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TITLE PAGE

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ABSTRACT

Purpose. Questions remain on how the excess risk of breast cancer associated with menopausal hormone therapy (MHT) evolves after treatment stops.

Methods. We investigated that issue in the E3N cohort, with 3678 invasive breast cancers identified between 1992 and 2008 among 78 353 women (881 290 person-years of postmenopausal follow-up). Exposure to MHT was assessed through biennial self-administered questionnaires and classified by type of progestagen component (progesterone or dydrogesterone; other progestagen), duration (short-term ≤5 years; long-term >5 years) and time since last use (≤5, 5-10, 10+ years). Hazard ratios (HR) and confidence intervals (CI) were estimated with Cox models.

Results. Among short-term users, only those currently using estrogens associated with a progestagen other than progesterone/dydrogesterone had a significantly elevated breast cancer risk (HR 1.70, 95% CI 1.50-1.91, compared with never users). Long-term use of this type of MHT was associated with a HR of 2.02 (1.81-2.26) when current and of 1.36 (1.13-1.64), 1.34 (1.04-1.73) and 1.52 (0.87-2.63) when stopped ≤5, 5-10, and 10+ years earlier, respectively.

Conclusions. Our results suggest residual increases in breast cancer risk several years after MHT cessation, which are restricted to long-term treatments. Whether increases persist more than 10 years after cessation deserves continuing investigation.

Keywords: menopausal hormone therapy; cohort study; breast cancer; estrogens; progestagens

INTRODUCTION

Recent exposure to menopausal estrogen-progestagen therapy (EPT) is a recognized risk factor for breast cancer [1]. A dramatic decline in the use of menopausal hormone therapy (MHT) followed the publication of the results of the Women's Health Initiative (WHI) trial [2] and of the Million Women Study cohort [3]. It was paralleled, in many countries, by a decrease in breast cancer incidence [4, 5], the two phenomena being probably linked [6].

We aimed at evaluating how the risk of breast cancer evolves after MHT discontinuation in an epidemiological study based on individual data. This requires: 1) distinguishing between EPT and estrogen-only therapy; 2) separating out the effects of duration of use and time since last use; 3) accurately measuring time since last use. Indeed, users of estrogen-only as well as users of short-term EPT are far more common among past than among recent MHT users in the available epidemiologic studies, and they have a lower breast cancer risk than do long-term EPT users [7]. The third requirement cannot be fulfilled with a single "past-user" category or when time since last use is assessed only at baseline in cohort studies. To our knowledge, the single published study that complies with these 3 principles is an analysis of the post-intervention phase of the WHI trial, in which the relatively short period following treatment discontinuation precluded any assessment of the risk of breast cancer more than 2.5 years after treatment stop [8].

In the large French E3N cohort study, we previously found that the excess risk of breast cancer associated with EPT was less elevated when it contained micronized progesterone or dydrogesterone (frequently used in France) rather than other progestagens [9]. The high rate of MHT discontinuation after 2002 now gives us the opportunity to investigate in that cohort how the excess risk of breast cancer associated with MHT evolves after treatment stops, using detailed and regularly updated data on MHT use.

MATERIALS AND METHODS

The E3N cohort

E3N is a prospective cohort comprising 98 995 women born between 1925 and 1950 and insured by a national health insurance fund that mainly covers teachers and their family members. It enrolled women who replied to a questionnaire mailed out in 1990. They thereafter received questionnaires every 2-3 years for follow-up. The questionnaire mailed in June 2008 is the last used for this analysis. Response rates were ≥75% for each follow-up questionnaire.

Ethics statement

The E3N cohort was approved by the French National Commission for Data Protection and Privacy. Participants provided written informed consent.

Identification of breast cancer cases

Occurrence of breast cancer was identified mainly from self-reports in the questionnaires; a few additional cases came from next-of-kin reports and the national cause-of-death registry. Pathology reports were retrieved for 94% of the incident cases.

Data on 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.

MHT included any nonvaginal use of estrogens (except estriol) or tibolone. Following our previous findings that associations with breast cancer risk vary across different EPT [9], exposure was classified as: i) estrogen-only (mainly estradiol); ii) estrogen+progesterone or dydrogesterone; iii) estrogen+other progestagen; iv) tibolone; v) other (ie, MHT containing an androgen, or intramuscularly administered, or with no specified formulation).

Study population and follow-up

The study population was restricted to postmenopausal women. Menopausal status and date of menopause were determined from regularly updated data on menstrual periods, hysterectomy, oophorectomy, MHT use, self-reported menopausal status, and menopausal symptoms, as detailed elsewhere [10].

Follow-up started either at the date the 1992 questionnaire was returned for already postmenopausal women, or at the date menopause was first reported. Follow-up ended at the date of diagnosis of any cancer, the date of the last completed questionnaire, or June 2008, whichever occurred first. Of the 98 995 E3N cohort women, we excluded those still premenopausal (n=6233), with no follow-up at all (n=4902), diagnosed with cancer (other than a basal cell carcinoma) before follow-up started (n=6574), or who did not respond to the 1992 questionnaire about lifetime MHT use (n=2933). Accordingly, analysis included 78 353 women.

Statistical analysis

Hazard ratios (HR) of invasive breast cancer and their 95% confidence intervals (CI) were estimated with Cox proportional hazards models for left-truncated and right-censored data, with age as the time scale.

Exposure was a time-varying variable in our statistical models, starting from the first questionnaire answered after menopause and updated at the date of answer of each follow-up questionnaire: the exposure reported in questionnaires n and earlier was used to categorize participants for the period between completion of questionnaires n and n+1. When a woman did not respond to a questionnaire, her MHT exposure was classified as unknown for the period between its mailing date and the next questionnaire that she answered. At each questionnaire, a woman was considered a past user of each type of MHT when she reported any use ever but none in the preceding 3 months. 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 successively took different types of MHT, she simultaneously contributed to each of the relevant categories (eg, current user of estrogen-only and past user of estrogen+progesterone/dydrogesterone).

All analyses were adjusted for the variables listed in Table 1 (using the same categories). Body mass index and data on whether a mammogram had been performed recently, updated during follow-up, as well as recency of use of oral contraceptives and progestagens alone, were included in the models as time-varying variables.

When values were missing for ≤5% of any given covariate, they were imputed to the median (for continuous variables) or mode (for discrete variables). When the proportion of missing values was higher, we created a category of unknown values (as shown in Table 1).

Model parameters were estimated and compared with likelihood methods and Wald tests. Tests of statistical significance were two-sided, and significance set at the 0.05 level. SAS software, version 9.3 (SAS Institute, Inc., Cary, NC) was used to perform the analyses.

RESULTS

A total of 3678 first primary invasive breast cancers were diagnosed during 881 290 person-years of follow-up (mean, 11.2 years). Table 1 summarizes the participants' characteristics.

Many women used more than one type of MHT: of those who ever used estrogen-only, 72% also ever used EPT; of those who ever used estrogen+progesterone/dydrogesterone, 57% also used estrogen+other progestagen or estrogen-only, and of those who ever used estrogen+other progestagen, 54% also used estrogen+progesterone/dydrogesterone or estrogen-only. We verified that the association between current use of a given MHT type and the risk of breast cancer was not modified by past use of any other type of MHT ($.43 \leq P$ for interaction $\leq .91$).

In EPT but not estrogen-only users, the risk of breast cancer was significantly lower for past than for current use, with or without adjustment for duration of use (Table 2).

Compared with never users, current and past users of tibolone had HRs of 1.24 (95% CI, 0.91-1.69; n=43 breast cancer cases among exposed women) and 1.23 (0.84-1.79; n=28 cases), respectively.

Adding any of the covariates listed in Table 1 to the age-adjusted model did not alter HRs associated with the different MHT categories by more than 10%, and supplementary analyses showed that alcohol consumption, osteoporosis history, and bisphosphonate use were also not confounders (data not shown).

For each type of MHT, the longer the time since last use, the shorter the duration of use. For example, the mean duration of EPT among cases was 6.1 years among current users, and 4.7, 3.4, and 2.4 among women who had stopped treatment 3 months to 5 years earlier, 5-10 years earlier, and more than 10 years earlier, respectively. We therefore chose to present analyses stratified by duration of use (short-term use, defined as ≤5 years, compared with long-term use, >5 years) so as to assess the effect of time since last use for sufficiently homogeneous durations of use (Table 3).

Compared with never users, the only short-term users with a significantly elevated breast cancer risk were those currently using estrogen+other progestagen (HR 1.70, 95% CI 1.50-1.91). Other estimates, including those for past use, were close to unity (Table 3). In particular, short-term estrogen+other progestagen that stopped less 3 months to 5 years earlier was associated with a HR of 1.08 (95% CI, 0.92-1.25) (Table 3), and additional stratification of the first years following cessation yielded HRs of 1.12 (95% CI, 0.81-1.55; 38 breast cancer cases among exposed women), 1.08 (0.80-1.46; 44 cases), 1.10 (0.85-1.44; 58 cases), and 1.01 (0.77-1.33; 54 cases) for treatments stopped 3 months to 2 years, 2-3 years, 3-4 years, and 4-5 years earlier, respectively.

Among women with long-term use, compared with never users, significant increases in risk were observed for estrogen-only that stopped more than 10 years earlier, current use of estrogen+progesterone/dydrogesterone, current use of estrogen+other progestagen, and estrogen+other progestagen that stopped less than 5 years and 5-10 years earlier (Table 3).

Stratification by BMI

Stratification by BMI showed that HRs for current use were systematically higher among women with a BMI <25 kg/m^2 than among women with a BMI ≥25 kg/m^2 (Table 4); the *P*-value for heterogeneity between the two BMI strata reached borderline statistical significance for current short-term use of estrogen-only (*P* = 0.06), current short-term use of estrogen+progesterone/dydrogesterone (*P* = 0.02), and current short-term use of estrogen+other progestagen (*P* = 0.06). For past use of MHT, no clear difference was apparent between HRs in the two BMI strata (Table 4).

Sensitivity analyses

We performed a sensitivity analysis where women began contributing person-years in our models at the time they had reported in two consecutive questionnaires having recently (ie, during the preceding follow-up cycle) a mammogram, indicating regular mammographic surveillance. The corresponding results are shown in Table 5. Based on these results, our conclusions would remain unchanged.

We previously found that the timing of MHT initiation modulated the risk of breast cancer [11]. We therefore performed another sensitivity analysis that included only women whose interval between menopause and treatment was ≤3 years (n=66 372; 3083 breast cancer cases). This analysis did not modify our conclusions (data not shown).

DISCUSSION

Our results suggest that when MHT is used for less than 5 years, any MHT-associated excess risk of breast cancer disappears during the 5-year period after treatment stops. However, this may not be the case for longer exposures, since we found significant increases in risk among past long-term users of estrogen-only and of EPT containing progestagens other than progesterone or dydrogesterone.

It should be noted that the majority of our cohort participants have a BMI <25 kg/m^2: MHT-associated increases in breast cancer risk have been found to be attenuated in overweight or obese women in several observational studies [3, 12-19], which is consistent with our own results regarding current MHT use. Although this is unlikely to limit the generalizability of our findings [3], it should

also be noted that, in our study, the estrogen component of MHT consisted almost exclusively in estradiol compounds, frequently administered through the skin [20].

Our estimates for past use (regardless of how recent or old) of MHT, which showed weak associations, if any, with breast cancer risk, are in line with those from previous epidemiological studies [3, 8, 12, 16, 17, 21]. However, when time since last use was split into more detailed categories and different durations of use were taken into account, residual increases in risk emerged among some groups of past users.

In particular, we found that long-term (>5 years) use of EPT containing progestagens other than progesterone or dydrogesterone was associated with significant increases in risk, even many years after treatment cessation. Very few epidemiological studies have assessed the breast cancer risk associated with former (overall) long-term EPT use, and only one with treatment that stopped years before. In the Million Women Study cohort, the risk of breast cancer increased slightly among former long-term MHT users, but the authors did not examine the separate effects of estrogen-only and EPT [3]. A case-control study found no increased risk among former long-term users of EPT, but it was based on only 29 breast cancer cases among the exposed women [21]. In the American Cancer Prevention Study II Nutrition cohort [16], which regularly updated data on exposure, long-term use of EPT (48 breast cancer cases) was associated with a HR of ductal breast cancer of 2.38 (95% CI, 1.50-3.78) for women who had ceased use within the past 2 years and 1.20 (0.80-1.81) for those who stopped earlier.

Our study further suggests that long-term use of estrogen-only can be associated with an increased breast cancer risk more than 10 years after treatment cessation, although this association was based on only 12 cases. Previous observational studies have yielded heterogeneous results. Some found no significant increase in breast cancer risk associated with former long-term use of estrogen-only, but reported no results for treatment that had stopped over 10 years earlier [12, 16]. Others found no significant increase in risk among distant past users of estrogen-only, but did not report results according to duration of use [14, 22]. Finally, one population-based case-control study showed a

significant increase in risk for treatment (predominantly estrogen-only therapy) that had stopped more than 10 years earlier (OR 2.57, 95% CI 1.28-5.15, based on 25 breast cancer cases diagnosed among exposed women), although not among women with last use 1 to 10 years prior to index date (OR 1.22, 95% CI 0.72-2.08, based on 28 cases) [13].

We already discussed in a previous paper our finding of a lower breast cancer risk associated with estrogen+progesterone/dydrogesterone than with estrogen+other progestagen [9]. This could be due to a lower progestagenic effect or an insufficient dose of progesterone/dydrogesterone, as suggested by an increased endometrial cancer risk as compared to other progestagens [23].

From a pathophysiological point of view, our results do not support the hypothesis that EPT only accelerates the growth of breast tumours that would otherwise have appeared later, at least when it is used for 5 years or longer. Indeed, breast cancer incidence increased among past users of long-term EPT containing progestagens other than progesterone/dydrogesterone, compared with never users. Combined with the increased breast cancer risk in current long-term users, this would translate into additional breast cancer cases among women who ever used long-term treatment. Use of EPT may therefore be able to promote the growth of pre-existing breast tumours that would otherwise not have evolved. The increase in breast cancer risk observed with long-term use of estrogen-only that stopped more than 10 years earlier, however based on a limited number of breast cancer cases, suggests that an initiating effect could also exist, perhaps due to the known mutagenic effects of some estradiol metabolites [24]. Finally, our observation that the ≈70% increase in breast cancer risk associated with current short-term use of EPT disappeared less than 5 years after treatment cessation indicates either that EPT intervenes only at late stages of breast carcinogenesis or that stopping MHT may allow MHT-promoted preclinical breast tumors to stop their progression or even to regress.

Strengths of our study include its large size and long follow-up. We however lacked statistical power among users of long-term MHT who stopped treatment more than 10 years earlier, so that, for example, the HR of 0.98 (95% CI 0.46-2.06) associated with long-term use of estrogen+progesterone/dydrogesterone does not exclude the possibility of an increased risk.

Another strength of our study lies on the regular updates of exposure, which limited classification bias and allowed to account for possible changes over time in the types of hormones used by a woman, by adjusting our models simultaneously for the different MHT types she could have ever used. Hence it is unlikely that our results on a given MHT type are in fact due to the previous or subsequent use of other types of MHT. Although self-reports of MHT use lead to recall bias, previous studies have shown a good agreement between self-reported MHT exposure and prescription data, especially for recent use [25, 26]. Furthermore, recall bias is probably limited since data on MHT use were updated every 2-3 years. We must acknowledge our limited ability to describe with precision the risks of breast cancer within a 2-year period after stopping treatment. This limitation is due mainly to the prospective design of our analysis: women who stopped MHT recently are considered to be current users until the first questionnaire after treatment stops is completed. As a consequence, breast cancer cases classified in the 3 months-5 years since last use category were mainly cases diagnosed several years after treatment stopped (3.2 years on average).

A screening bias may be feared because hormone users have generally mammograms more frequently than non-users, and because women may be less inclined to undergo regular mammograms if they stop taking MHT. However, adjustment for recent mammogram ("mammogram performed in the preceding follow-up period [yes/no]", as a time-varying variable) did not alter our risk estimates. When we restricted our analysis to women who reported in two consecutive questionnaires having recently performed a mammogram, as a proxy of regular mammographic surveillance, our conclusions also remained unaltered. Furthermore, the proportion of women who had recently undergone a mammogram is high in our cohort, and at the end of follow-up it was very similar for current and past MHT users (Table 1). Finally, we did not consider in situ breast cancers, more frequently detected through mammography than invasive breast cancers.

In conclusion, our results suggest that the excess breast cancer risk associated with MHT, when used for more than 5 years, does not simply dissipate in the 5 years after treatment stops. Whether increases in breast cancer risk persist more than 10 years after treatment cessation, which would support an initiating effect, deserves continuing investigation.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Table 1. Characteristics of Participants according to MHT Exposure Status, at the End of Follow-Up. E3N Study, 1992 to 2008.

		MHT never users (n=21 601)	MHT past users (n=31 223)	MHT current users (n=17 986)
Age at end of follow-up, years (mean ± SD)		67.1 ± 7.8	67.0 ± 5.8	63.1 ± 5.5
Age at menopause, years (mean ± SD)		51.2 ± 3.9	50.2 ± 3.7	50.3 ± 3.6
Year of birth	1925-1929	15.6%	4.8%	2.4%
	1930-1934	18.5%	12.0%	7.7%
	1935-1939	15.5%	23.6%	17.4%
	1940-1944	15.2%	29.9%	28.8%
	1945-1950	35.2%	29.7%	43.7%
Years of schooling	<13	15.3%	11.5%	9.4%
	13-16	69.2%	72.2%	69.9%
	17+	15.5%	16.3%	20.8%
Parity and age at first birth	Nulliparous	13.7%	10.4%	11.2%
	First child before age 30 years, 1 or 2 children	45.4%	51.7%	53.0%
	First child before age 30 years, 3 or more children	29.6%	28.2%	25.3%
	First child after age 30 years	11.3%	9.7%	10.5%
Body mass index (kg/m^2)	<18.5	4.1%	3.3%	3.3%
	18.5-22.9	38.7%	44.1%	50.0%
	23.0-24.9	21.0%	22.7%	22.5%
	25.0-29.9	26.2%	24.0%	20.1%
	30+	10.0%	6.0%	4.0%
Type of menopause	Natural	92.9%	91.4%	91.4%

	Artificial	7.1%	8.6%	8.6%
Age at menarche, years	<13	44.7%	44.6%	45.5%
	13+	55.3%	55.4%	54.5%
Pap smear frequency (assessed in 1990)	Never or irregular	24.7%	10.3%	8.5%
	Every 4-5 years	5.0%	2.8%	2.3%
	Every 2-3 years	26.1%	26.4%	25.9%
	Every year	37.1%	55.1%	58.5%
	Unknown	7.1%	5.4%	4.9%
History of breast cancer in first-degree relatives	None	87.1%	88.8%	89.0%
	One relative	11.6%	10.4%	10.1%
	More than one relative	1.2%	0.9%	0.9%
History of breast cancer in other relatives	None	77.8%	78.8%	77.9%
	At least one relative	15.5%	15.3%	15.9%
	Unknown	6.7%	5.9%	6.2%
Personal history of benign breast disease[a]	No	74.2%	72.1%	70.9%
	Yes	25.8%	27.9%	29.1%
Mammogram in the previous follow-up period	No	22.4%	7.5%	5.0%
	Yes	75.0%	91.7%	88.5%
	Unknown	2.6%	0.8%	6.5%
Use of oral contraceptives before menopause	Never	55.9%	43.2%	35.8%

	Ever, less than 5 years ago	0.3%	0.0%	0.4%
	Ever, more than 5 years ago	27.9%	37.1%	42.1%
	Ever, unknown time since last use	15.9%	19.7%	21.8%
Use of progestagens alone before menopause	Never	67.2%	43.8%	42.5%
	Ever, less than 5 years ago	3.7%	2.3%	6.6%
	Ever, more than 5 years ago	26.7%	48.9%	46.5%
	Ever, unknown time since last use	2.5%	5.0%	4.3%

Note: at the end of follow-up, 7543 women were in the "unknown" MHT exposure category.
[a] as assessed at the time closest to menopause onset.

Table 2. Hazard Ratios of Invasive Breast Cancer Associated with Different Types and Times Since Last Use of MHT. E3N Study, 1992 to 2008.

Time since last use		Estrogen-only	Estrogen + progesterone/dydrogesterone	Estrogen + other progestagen[a]
Current use	Hazard Ratio (95% CI) [b]	1.17 (0.99-1.38)	1.22 (1.11-1.35)	1.87 (1.71-2.04)
	No. of cases	169	638	931
	Mean duration of use[c]	5.1	6.1	6.1
Past use	Hazard Ratio (95% CI)[b]	1.06 (0.95-1.19)	0.96 (0.87-1.06)	1.12 (1.02-1.23)
	No. of cases	374	552	708
	Mean duration of use[c]	2.2	3.5	3.9
	Mean time since last use[c]	7.8	5.9	5.9
***P* for homogeneity between current and past use**		0.30	< 0.001	< 0.001
***P* for homogeneity between current and past use with further adjustment for duration of use[d]**		0.78	0.03	< 0.001

Abbreviations: CI, confidence interval; MHT, menopausal hormone therapy.

Note: 890 cases were diagnosed among MHT never users, 253 among women with unknown exposure status, 260 among women ever exposed to an "other" MHT (ie, MHT containing an androgen/intramuscularly administered MHT/MHT with no specified formulation), 71 among ever users of tibolone, and 76 among women whose time since last use was unknown. The total number of breast cancer cases exceeds 3678 because a woman can contribute person-years to several categories of exposure simultaneously (eg, current use of estrogen-only and past use of estrogen+progesterone/dydrogesterone).

[a] Chlormadinone acetate, cyproterone acetate, demegestone, dienogest, drospirenone, ethynodiol acetate, gestodene, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, megestrol acetate, nomegestrol acetate, norethisterone acetate, and promegestone.

[b] Adjusted for age (time scale), all variables listed in Table 1, and all categories of MHT exposure described in this Table. Reference category: never use of the considered MHT.

[c] Years, among cases.

[d] Categorized as ≤ 2 / 2-5 / 5-7 / 7-10 / over 10 years of use, for each MHT type.

Table 3. Hazard Ratios of Invasive Breast Cancer Associated with Different Types, Durations, and Times Since Last Use of MHT. E3N Study, 1992 to 2008.

Time since last use of the considered MHT	Mean duration of use[a]	No. cases	HR (95% CI)[b]	Mean duration of use[a]	No. cases	HR (95% CI)[b]
	Estrogen-only, 5 years or less of use (short-term)			**Estrogen-only, more than 5 years of use (long-term)**		
Current use	2.8	87	1.11 (0.89-1.38)	7.8	76	1.22 (0.96-1.54)
3 months-5 years since last use	1.6	110	1.10 (0.91-1.33)	7.9	14	0.79 (0.46-1.34)
5-10 years since last use	1.3	122	1.11 (0.92-1.33)	7.5	15	1.54 (0.92-2.57)
> 10 years since last use	1.3	88	0.92 (0.74-1.15)	9.1	12	1.81 (1.02-3.22)
	Estrogen + progesterone/dydrogesterone, 5 years or less of use (short-term)			**Estrogen + progesterone/dydrogesterone, more than 5 years of use (long-term)**		
Current use	3.0	284	1.13 (0.99-1.29)	8.7	335	1.31 (1.15-1.48)
3 months-5 years since last use	2.1	175	0.96 (0.82-1.12)	7.8	98	1.15 (0.93-1.42)
5-10 years since last use	2.0	133	0.85 (0.71-1.01)	7.3	45	1.08 (0.80-1.46)
> 10 years since last use	1.6	82	1.14 (0.91-1.44)	6.9	7	0.98 (0.46-2.06)
	Estrogen + other progestagen[c], 5 years or less of use (short-term)			**Estrogen + other progestagen[c], more than 5 years of use (long-term)**		
Current use	3.2	397	1.70 (1.50-1.91)	8.4	513	2.02 (1.81-2.26)
3 months-5 years since last use	2.2	194	1.08 (0.92-1.25)	8.2	139	1.36 (1.13-1.64)
5-10 years since last use	1.8	197	1.13 (0.97-1.31)	8.0	67	1.34 (1.04-1.73)
> 10 years since last use	1.6	76	0.87 (0.68-1.10)	6.8	13	1.52 (0.87-2.63)

Abbreviations: CI, confidence interval; HR, hazard ratio; MHT, menopausal hormone therapy.

[a] Years; mean among cases.

[b] Adjusted for age (time scale), all variables listed in Table 1, and all categories of MHT exposure described in this Table. Reference category: never use of the considered MHT.

[c] Chlormadinone acetate, cyproterone acetate, demegestone, dienogest, drospirenone, ethynodiol acetate, gestodene, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, megestrol acetate, nomegestrol acetate, norethisterone acetate, and promegestone.

Table 4. Hazard Ratios of Invasive Breast Cancer Associated with MHT Use, Stratified by Body Mass Index. E3N Study, 1992 to 2008.

Time since last use of the considered MHT	BMI <25 kg/m^2 [a]				BMI ≥25 kg/m^2 [a]			
	No. cases	HR (95% CI)[b]	No. cases	HR (95% CI)[b]	No. cases	HR (95% CI)[b]	No. cases	HR (95% CI)[b]
	Estrogen-only, short-term use		**Estrogen-only, long-term use**		**Estrogen-only, short-term use**		**Estrogen-only, long-term use**	
Current use	74	1.22 (0.96-1.56)	64	1.33 (1.02-1.72)	13	0.73 (0.42-1.28)	12	0.88 (0.49-1.57)
3 months-5 years since last use	92	1.14 (0.92-1.40)	8	0.58 (0.29-1.17)	18	0.93 (0.58-1.49)	6	1.54 (0.68-3.49)
5-10 years since last use	103	1.14 (0.93-1.40)	14	1.81 (1.07-3.08)	19	0.98 (0.61-1.55)	1	0.52 (0.07-3.75)
> 10 years since last use	70	0.91 (0.71-1.16)	9	1.71 (0.88-3.32)	18	0.99 (0.61-1.61)	3	2.49 (0.78-7.90)
	Estrogen + progesterone/dydrogesterone, short-term use		**Estrogen + progesterone/dydrogesterone, long-term use**		**Estrogen + progesterone/dydrogesterone, short-term use**		**Estrogen + progesterone/dydrogesterone, long-term use**	
Current use	248	1.25 (1.08-1.44)	281	1.36 (1.19-1.57)	36	0.71 (0.50-1.01)	54	1.16 (0.86-1.56)
3 months-5 years since last use	144	0.99 (0.83-1.18)	79	1.15 (0.91-1.45)	31	0.88 (0.61-1.27)	19	1.24 (0.77-1.99)
5-10 years since last use	106	0.85 (0.70-1.04)	39	1.15 (0.83-1.60)	27	0.86 (0.58-1.27)	6	0.83 (0.36-1.88)
> 10 years since last use	66	1.13 (0.88-1.46)	7	1.21 (0.57-2.56)	16	1.20 (0.71-2.01)	0	-
	Estrogen + other progestagen[c], short-term use		**Estrogen + other progestagen[c], long-term use**		**Estrogen + other progestagen[c], short-term use**		**Estrogen + other progestagen[c], long-term use**	
Current use	331	1.77 (1.55-2.02)	439	2.11 (1.86-2.38)	66	1.43 (1.08-1.89)	74	1.75 (1.34-2.28)
3 months-5 years since last use	163	1.11 (0.94-1.31)	119	1.38 (1.13-1.69)	31	0.93 (0.64-1.35)	20	1.28 (0.81-2.04)
5-10 years since last use	164	1.16 (0.98-1.37)	57	1.36 (1.03-1.79)	33	1.00 (0.69-1.44)	10	1.34 (0.71-2.55)
> 10 years since last use	59	0.81 (0.62-1.06)	9	1.27 (0.66-2.47)	17	1.14 (0.69-1.89)	4	2.98 (1.09-8.12)

Abbreviations: BMI, body mass index; CI, confidence interval; E, estrogen-only; HR, hazard ratio; MHT, menopausal hormone therapy.
[a] closest record to menopause onset.
[b] Adjusted for age (time scale), all variables listed in Table 1, and all categories of MHT exposure described in this Table. Reference category: never use of the considered MHT.
[c] Chlormadinone acetate, cyproterone acetate, demegestone, dienogest, drospirenone, ethynodiol acetate, gestodene, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, megestrol acetate, nomegestrol acetate, norethisterone acetate, and promegestone.

Table 5. Hazard Ratios of Invasive Breast Cancer Associated with Different Types, Durations, and Times Since Last Use of MHT, among women with regular mammographic surveillance (n = 59 818). E3N Study, 1992 to 2008.

Time since last use of the considered MHT	No. cases	HR (95% CI)[a]	No. cases	HR (95% CI)[a]
	Estrogen-only, 5 years or less of use		**Estrogen-only, more than 5 years of use**	
Current use	51	1.02 (0.77-1.36)	58	1.16 (0.88-1.52)
3 months-5 years since last use	74	1.02 (0.81-1.29)	12	0.78 (0.44-1.39)
5-10 years since last use	95	1.13 (0.92-1.40)	14	1.76 (1.03-2.99)
> 10 years since last use	71	0.92 (0.72-1.17)	10	2.04 (1.09-3.83)
	Estrogen + progesterone/dydrogesterone, 5 years or less of use		**Estrogen + progesterone/dydrogesterone, more than 5 years of use**	
Current use	166	1.09 (0.92-1.30)	262	1.31 (1.13-1.51)
3 months-5 years since last use	132	1.00 (0.83-1.20)	85	1.12 (0.89-1.41)
5-10 years since last use	102	0.81 (0.66-1.00)	42	1.09 (0.80-1.50)
> 10 years since last use	69	1.10 (0.85-1.41)	6	0.88 (0.39-1.97)
	Estrogen + other progestagen[b], 5 years or less of use		**Estrogen + other progestagen[b], more than 5 years of use**	
Current use	208	1.72 (1.46-2.03)	378	1.98 (1.73-2.26)
3 months-5 years since last use	133	1.08 (0.89-1.30)	118	1.32 (1.08-1.61)
5-10 years since last use	154	1.09 (0.91-1.30)	61	1.34 (1.03-1.76)
> 10 years since last use	65	0.84 (0.65-1.08)	11	1.41 (0.77-2.58)

Abbreviations: CI, confidence interval; HR, hazard ratio; MHT, menopausal hormone therapy.

[a] Adjusted for age (time scale), all variables listed in Table 1, and all categories of MHT exposure described in this Table. Reference category: never use of the considered MHT.

[b] Chlormadinone acetate, cyproterone acetate, demegestone, dienogest, drospirenone, ethynodiol acetate, gestodene, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, megestrol acetate, nomegestrol acetate, norethisterone acetate, and promegestone.