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ORIGINAL PAPER

The Influence of Menopausal Hormone Therapy and Potential Lifestyle Interactions in Female Cancer Development—a Population-Based Prospective Study

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Abstract

The past decades have seen contradictory research results on the health benefits and risks of menopausal hormone therapy (HT). In particular, long-term associations with overall cancer incidence and the potential interplay with other lifestyle factors remain undetermined. In a population-based prospective cohort, 29,152 women aged 50–64 years at entry (1993–1997) were followed through 2013 for incidence of cancer (99% complete follow-up). Cox' proportional hazards models were used to estimate cancer incidence according to baseline HT alone and in combination with lifestyle factors including alcohol intake, BMI, physical activity, diet, and smoking. Among 5484 women diagnosed with cancer, baseline HT was associated with an overall higher risk of cancer (HR 1.28; 95%CI, 1.21–1.36)—in particular, a higher risk of breast (HR 1.77; 95%CI, 1.61–1.95), ovarian (HR 1.68; 95%CI, 1.26–2.26), and endometrial (HR 1.86; 95%CI, 1.45–2.37) cancer. Combination with other lifestyle risk factors largely displayed additive associations. The risk of colorectal cancer was significantly lower (HR 0.79; 95%CI, 0.66–0.95). However, in the interaction analysis, only "healthy" subgroups of women using HT had a lower risk of colorectal cancer. With an overall higher risk of cancer among women on HT, this study underlined the importance of considering all female cancer risks in menopausal treatment guidelines. The largely additive associations between HT and the investigated lifestyle factors support the notion that high levels of hormones in itself play an important etiological role in female reproductive cancers, whereas the possible protective impact in colorectal cancer might be limited to women with an otherwise healthy lifestyle.

Abbreviations

95%CI	95% confidence interval
BMI	Body mass index
HR	Hazard ratio
HT	Hormone therapy

Introduction

Menopausal symptoms affect a large proportion of middle-aged women resulting in impaired quality of life [1] and substantial use of health resources [2]. Even though hormone therapy (HT) is undisputedly the most effective treatment for menopausal symptoms [3], the past decades have seen contradictory research results and recommendations as to its use and effects on major health outcomes including common female cancers. Menopausal HT has consistently been associated with a higher risk of breast cancer [4, 5] with different associations for combined and estrogen alone treatment [6]. Except for the association between unopposed estrogen and a higher risk of endometrial cancer [7], the evidence on HT and risk of other female cancers is considered not yet conclusive [8, 9], although recent publications also indicate statistically significant associations between HT and higher risk of both endometrial [7] and ovarian cancer [10, 11]. In contrast, a seemingly protective effect of hormone therapy on colorectal cancer incidence has been reported [12].

Conjointly, contemporary professional guidelines for the treatment of menopausal symptoms state that HT can be used

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to treat severe symptoms for a short period of time (< 5 years) around menopause [8, 9]. The most conservative of recommendations is the European Code Against Cancer, "which recommends limiting – or avoiding when possible the use of HT" [4].

The importance of an individual risk assessment when making decisions on appropriate HT is evident, and this is being advocated especially for individual cancers and for cardiovascular disease risk [13]. Several other modifiable lifestyle factors have also been convincingly associated with the cancers in questions including alcohol intake, adiposity, diet, physical activity, and smoking [14, 15]. These factors are thought, at least partly, to affect female cancer risk via affecting levels of circulating female sex hormones [16]. Thus, it is relevant to study more closely if and how these other factors might interact in the associations between HT and cancer outcomes. A better understanding of combined effects might help determine appropriateness of treatment depending on individual lifestyle risk profile while shedding light on possible etiological differences that could be relevant for risk prediction and prevention more generally.

Using data from a large prospective population-based cohort with long and near complete follow-up, we studied the association between menopausal HT and female cancer incidence. Particular attention was given to possible interaction between established lifestyle factors and HT and cancer risk.

Materials and Methods

Population

The Diet, Cancer, and Health cohort is a large population-based study established in Denmark between 1993 and 1997. Eighty thousand nine hundred ninety-six men and 79,729 women aged 50–64, born in Denmark, and without a previous cancer diagnosis were invited to participate. Twenty-nine thousand eight hundred seventy-five women (37% response), corresponding to approximately 7% of the Danish female population in the given age group, accepted the invitation. A more detailed description of the cohort has been published previously [17]. Each participant was followed from baseline (the date of first study clinic visit) until either date of cancer diagnosis, date of death, date of emigration, or December 31, 2013, whichever came first.

Exposure and Outcome Assessment

Participants completed two self-administered, previously validated [18, 19], questionnaires at baseline including a food frequency questionnaire (FFQ) and a lifestyle questionnaire. Anthropometric measurements, including participant height and weight, were obtained by professional staff members at a study clinic visit, where various biological specimens were also sampled from participants.

Outcomes

Cancer diagnoses were ascertained through record linkage with the Danish Cancer Registry using participants' unique national personal identification numbers (linkage 99.8%) [20]. In patients with more than one cancer diagnosis (n = 511), the first cancer diagnosis determined their outcome and exit time. Cancer diagnoses were further divided into breast (ICD10 C50), colorectal (ICD C18–20), lung (ICD10 C34), ovarian (ICD10 C56), endometrial (ICD10 C54.0–C54.1, C54.3–C54.6, C54.8–C54.9 (C55.9)), and others (all other ICD10 C-diagnoses). In the analyses of endometrial cancer risk, all hysterectomized women (according to self-report) were excluded (n = 4365). Likewise, all women with previous bilateral oophorectomy (n = 1882) were excluded in analysis of ovarian cancer risk. Figure 1 gives an overview of study in, and exclusions and final sample size.

Main Exposure

In the lifestyle questionnaire, women gave information about hormone therapy (HT) (never/previous/current use at baseline). Baseline users also provided the brand name of the therapy they currently used. Based on this, the type of HT was divided into "estrogen alone," "combination therapy" (estrogen and progestogen) or "unspecified and previous use" if no brand name was given. From women who indicated either previous or current hormone use, information on duration and route of administration (tablets/injections/skin depot/skin patch/vaginal) was used for further analysis. Women with ≤ 6 months of use were categorized as "triers" and the remaining users categorized into ≤ 5 years and > 5 years of use. The route of administration was categorized as "oral" (incl. any

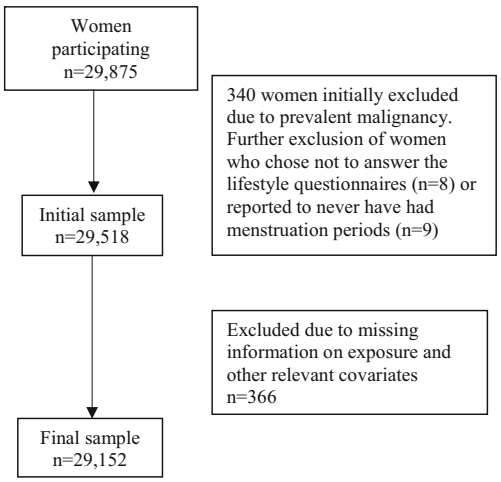


Fig. 1 Women included in the study and development of cancer outcome

combination with others); "other systemic" (all non-oral HT); and "only local" (only vaginal treatment). Serum sex hormone measurements previously conducted in a subsample of the cohort showed good correlation between self-reported HT and serum sex hormone blood levels [21].

Covariates and Interaction Variables

The following variables were considered as possible confounders and included in the regression analyses: age at menarche ("early" < 13 years, normal 13–15; "late" > 15 years), adult attained height (continuous variable measured in cm), parity and age at first childbirth combined ("nulliparous or > 35 years"; "1–2 kids and 30–35 years; 1–2 kids and 25–30 years; < 25 or ≥ 3 kids and < 35 years); education level based on duration of schooling (short ≤ 7 years; medium 8–10 years; long ≥ 10 years) was used as an indirect measure for socioeconomic position. Oral contraceptive pill use (ever; never), baseline alcohol intake ("abstainers"; ≤ 1 unit (1–10 g) per day; > 1 unit (10 g) per day). Smoking; recorded as "never," "previous," or "current" at baseline. Physical activity; recorded as leisure time activity and divided into "active" vs. "inactive." BMI was divided into four categories according to WHO definitions (< 18.5 "underweight"; 18.5–24.99 "normal weight"; 25–29.99 "overweight", ≥ 30 "obesity" [22]. Intake of whole grains, dietary fiber, red, and processed meat was assessed from the FFQ and measured in g/day. A combined, ordered, categorical dietary variable was created ("high fibre-wholegrain – low meat"; "low fibre-wholegrain – low meat"; "high fibre-wholegrain – high meat"; "low fibre-wholegrain – high meat"). Categories of high and low intake were based on the distribution of the continuous estimates.

Possible interaction in the association between HT and cancer risk according to other lifestyle factors believed to affect hormone levels was explored by creating new four-level composite variables between binary categories of HT (never and previous vs. baseline users) and all other variables [23]. The binary categories used were smoking (never vs previous/baseline), alcohol (moderate "<=1 unit(10 g)/day" vs "all others" (including abstainers $n = 787$)), BMI ("normal (18.5–25)" vs "all others" (368 women had BMI < 18.5)), diet (healthy (low meat/high dietary fiber-whole grains vs. unhealthy (all others)), and physical activity (active vs inactive).

Statistical Methods

The associations between HT and cancer incidence were assessed using Cox' proportional hazards models with age as the underlying time scale. For all outcomes, we created separate models for each modality of hormone exposure (overall, type, duration, and route). "Never users" was the reference group.

In the interaction analyses, we created separate models for each of the composite exposure variables (composite of HT (overall measure) and the other lifestyle factors), and calculated HRs for each category, while adjusting for potential confounders as in the models considering HT alone. No hormone use combined with the lowest risk category of the other variable was the reference category (except for analyses of colorectal cancer, see later). Possible interaction was evaluated by graphically presenting separate associations for both exposures as well as joint associations relative to no exposure [24]. In addition, relative excess risk due to interaction (RERI) estimates were calculated to allow for evaluation of interaction in the Cox' (multiplicative) models on an additive scale [25]. The RERI measure and test for interaction is only interpretable when the associations for the primary exposures are in the same direction. Since the association between HT and colorectal cancer was in the opposite direction, for the interaction analysis and calculation of RERI for this cancer, the reference category was hormone use combined with the lowest risk category of the other risk factor. The STATA *ic* (interaction contrast) program was used to calculate (RERI) incl. 95% confidence intervals [26]. All tests were based on log likelihood ratio test statistic and confidence intervals calculated with Wald's test and performed with STATA v14.

Ethics

The "Diet, Cancer and Health" study has been approved by the relevant Scientific Ethical Committees and the Danish Data Protection Agency. Informed consent was obtained from all participants to search information from medical registries.

Results

A total of 5484 women were diagnosed with cancer during a median follow-up of 15.9 years. Of these, as first cancer diagnosis, 1992 women were diagnosed with breast, 642 with colorectal, 694 with lung, 315 with endometrial, 222 with ovarian, and 1619 with other cancers. The baseline characteristics of the participating women are summarized in Table 1.

Cancer Incidence

After adjustment for relevant demographic and lifestyle risk factors, baseline HT was associated with statistically significantly higher hazards of breast (HR 1.77 (95%CI, 1.61 to 1.95)), ovarian (HR 1.68 (95%CI, 1.26 to 2.26), and endometrial (HR 1.86 (95%CI, 1.45 to 2.37) cancer. Reversely, the HR for colorectal cancer was statistically significantly lower (HR 0.79 (95%CI, 0.66 to 0.95). No association with lung (HR 0.99 (95%CI, 0.83 to 1.17) or other cancers (HR 0.98 (95%CI, 0.88 to 1.10) was seen. When considering all cancers

Table 1 Overview of demographic and lifestyle factors by menopausal hormone use in 29,152 women included in the Danish Diet, Cancer, and Health cohort between 1993 and 1997 and followed through December 31, 2013

	Hormone use	All	%	Never	%	Previous	%	Baseline	%
n	Level	29,152		15,895	54.5	4515	15.5	8742	30.0
Age at menarche	early < 13 years	6561	22.5	3465	21.8	1025	22.7	2071	23.7
	13–15 years	18,230	62.5	9950	62.6	2808	62.2	5472	62.6
	> 15 years	3335	11.4	1855	11.7	526	11.7	954	10.9
	Unknown	1026	3.5	625	3.9	156	3.5	245	2.8
Education level	Short (≤ 7 years)	9106	31.2	4967	31.3	1621	35.9	2518	28.8
	Medium (8–10 years)	14,642	50.2	7953	50.0	2195	48.6	4494	51.4
	Long (≥ 10 years)	5404	18.5	2975	18.7	699	15.5	1730	19.8
Oral contraceptive use (ever)	No	12,082	41.4	6897	43.4	1918	42.5	3267	37.4
	Yes	16,854	57.8	8890	55.9	2568	56.9	5396	61.7
	Missing	216	0.7	108	0.7	29	0.6	79	0.9
Parity and age at first childbirth	Nulliparous or > 35	3805	13.1	2066	13.0	554	12.3	1185	13.6
	1–2 kids 30–35 years	1232	4.2	723	4.6	166	3.7	343	3.9
	1–2 kids 25–30	4766	16.4	2699	17.0	648	14.4	1419	16.2
	or > =3 kids and < 35 years)	19,115	65.6	10,273	64.6	3105	68.8	5737	65.6
	Unknown	234	0.8	134	0.8	42	0.9	58	0.7
Family history of cancer	No	13,099	44.9	7214	45.4	1983	43.9	3902	44.6
	Yes	12,378	42.5	6666	41.9	1958	43.4	3754	42.9
	Unknown	3675	12.6	2015	12.7	574	12.7	1086	12.4
Age at baseline	Median (5–95%)	56 (50–64)		55 (50–64)		57 (51–64)		56 (50–64)	
Adult attained height	Median (5–95%)	164 (155–174)		164 (155–174)		164 (154–174)		164 (155–174)	
BMI	Median (5–95%)	25 (20–34)		25 (20–34)		25 (20–34)		24 (20–32)	
	Underweight < 18.5	368	1.3	198	1.3	48	1.1	122	1.4
	Normal 18.5–24.99	14,451	49.6	7714	48.5	1953	43.3	4784	54.7
	Overweight 25–29.99	10,169	34.9	5420	34.1	1783	39.5	2966	33.9
	Obese > 30	4164	14.3	2563	16.1	731	16.2	870	10.0
Smoking	Never	12,741	43.7	7426	46.7	1737	38.5	3578	40.9
	Previous	6855	23.5	3559	22.4	1109	24.6	2187	25.0
	Baseline	9556	32.8	4910	30.9	1669	37.0	2977	34.1
Alcohol intake at baseline	g/day median (5–95%)	10 (1–42)		9 (1–41)		10 (1–43)		11 (1–43)	
	No baseline intake	521	1.8	275	1.7	106	2.4	140	1.6
	<=1 unit (10 g)/day	14,403	49.4	8088	50.9	2252	49.9	4063	46.5
	1–2 units/day	7862	27.0	4246	26.7	1165	25.8	2451	28.0
	> 2 units/day	6100	20.9	3123	19.7	951	21.1	2026	23.2
	lifetime abstainers	266	0.9	163	1.0	41	0.9	62	0.7
Physical activity	Inactive	11,856	40.7	6566	41.3	1901	42.1	3389	38.8
	Active	17,035	58.4	9182	57.8	2583	57.2	5270	60.3
	Missing	261	0.9	147	0.9	31	0.7	83	1.0
Whole grain intake	g/day median, 5–95%	34 (11–76)		34 (10–76)		34 (10–76)		34 (11–76)	
Dietary fiber	g/day median, 5–95%	20 (11–33)		20 (11–33)		20 (11–33)		20 (11–33)	
Red meat	g/day median, 5–95%	63 (27–120)		64 (26–122)		63 (27–120)		63 (27–118)	
Processed meat	g/day median, 5–95%	18 (4–50)		18 (4–51)		18 (4–50)		17 (4–48)	
Diet index	Low red and processed meat-high dietary fiber and whole grains	5782	19.8	3080	19.4	901	20.0	1801	20.6
	Low red and processed meat-low dietary fiber and whole grains	3630	12.5	1950	12.3	575	12.7	1105	12.6
	High red and processed meat-high dietary fiber and whole grains	12,617	43.3	6970	43.9	1912	42.4	3735	42.7
	High red and processed meat-low dietary fiber and whole grains	7123	24.4	3895	24.5	1127	25.0	2101	24.0

together, the overall HR was 1.28 (95%CI, 1.21 to 1.36) (Fig. 2). The higher hazard was only obvious among users of HT at baseline and not statistically significant for previous users (see Table 2).

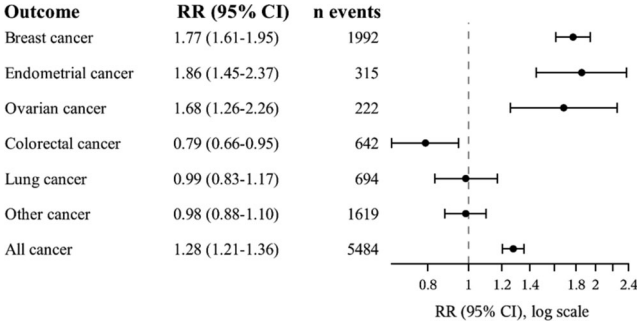


Fig. 2 Female cancer incidence in baseline hormone users compared to never users

When dividing HT into estrogen alone and combined therapy, the hazard of breast cancer was statistically significantly higher with combined therapy (HR 1.98 (95%CI, 1.78 to 2.21), than with estrogen alone (HR 1.40 (95%CI, 1.21 to 1.63). The opposite was seen for endometrial and ovarian cancer with higher hazard estimates among estrogen alone users (HR 2.38 (95%CI, 1.50 to 3.76 and 1.96 (95%CI, 1.26 to 3.04, respectively) than among combined therapy users (1.86 (95%CI, 1.42 to 2.43 and 1.69 (95%CI, 1.21 to 2.37), although these estimates were rather imprecise due to lower power. The HRs for colorectal cancer were in the same direction when divided into estrogen alone and combined therapy but not statistically significantly different.

When looking at duration of hormone use, most estimates were similar, although also less precise as a result of the stratification. However, the risk estimates for both breast, ovarian, and endometrial cancer were highest among women with longer duration of HT (see Table 2). The estimates for colorectal cancer were similar regardless of duration, but also here less precise and not statistically significant (≤ 5 years HR 0.77 (95%CI, 0.58 to 1.02) and > 5 years HR 0.83 (95%CI, 0.68–1.02)).

As can be seen in the estimates of route of HT, most women in the cohort took HT as oral medication (86% 11,517/13,257), which hindered meaningful comparisons of different routes of administration.

Interaction Analyses

When looking at combined associations for HT and other lifestyle risk factors, alcohol intake alone was associated with a statistically significantly higher hazard of breast cancer (HR 1.25 (95%CI, 1.11 to 1.41), as was HT use alone (HR 1.84 (95%CI, 1.62 to 2.11). The interaction test suggested additive associations for the two exposures with a combined measure of association of (2.11 (95%CI, 1.85 to 2.39) and RERI of 0.01 (95%CI, − 0.28 to 0.31).

A high BMI alone was associated with a higher hazard of breast cancer (HR 1.20 (95%CI, 1.06 to 1.35)) as was HT alone 2.00 (95%CI, 1.76 to 2.26). However, the combined association for HT and high BMI was lower than expected if assuming additive effects of the two exposures (HR 1.81 (95%CI, 1.58 to 2.08), RERI − 0.38 (95%CI, − 0.68. to − 0.08), $p = 0.01$ and therefore a possible interaction present here.

No statistically significant associations were seen between physical activity, diet, or smoking and breast cancer (see Fig. 3a).

A high BMI alone exerted a significantly higher hazard of endometrial cancer (HR 2.07 (95%CI, 1.52 to 2.82)), as did HT alone (2.76 (95%CI, 1.95 to 3.91)). The combined association for HT and high BMI compared to no exposure was 2.30 (95%CI, 1.56 to 3.39), and test for interaction indicated departure from additivity with an RERI of − 1.53 (95%CI, − 2.72 to − 0.35), $p = 0.01$. Physical inactivity, alcohol intake, and diet alone showed no significant associations. A markedly lower hazard was seen among smokers not using hormones (HR 0.46 (95%CI, 0.34 to 0.62)), and HT was associated with a higher hazard only among non-smokers (HR 1.46 (95%CI, 1.07 to 1.99)) but not among smokers (HR 1.01 (95%CI, 0.74 to 1.39) (see Fig. 3b).

HT alone was associated with higher hazard of ovarian cancer. None of the remaining lifestyle risk factors alone were associated with ovarian cancer. Due to the low number of outcomes ($n = 222$), most estimates were rather imprecise and hence power for the interaction analyses was limited (see Fig. 3c).

For the interaction analyses of colorectal cancer due to the opposite association between HT and cancer risk, using hormones was considered the low risk reference. Again, largely additive effects were seen between other lifestyle risk factors and "not using hormones" with no significant departure from additivity (RERI ≈ 0). Only physical inactivity was associated with a higher hazard of colorectal cancer, tendency of higher hazard was seen in women using hormones (HR 1.36 (95%CI, 0.90 to 2.06). Only the combined associations for high-risk lifestyle (high BMI, inactivity, unhealthy diet, and smoking) and "no hormone use" resulted in statistically significantly higher hazards of colorectal cancer (see suppl. Table 1 & Fig. 3d).

Discussion

In this study, HT was associated with a higher hazard of breast, endometrial, and ovarian cancer. Combination with other known lifestyle risk factors largely displayed additive effects. Reversely, HT appeared to be associated with a lower hazard of colorectal cancer but significant associations were only seen in combination with other healthy lifestyle parameters.

This study was conducted in a large, population-based cohort with long and almost complete follow-up on cancer outcomes and with detailed and validated information on

Table 2 Hazard ratios and 95% confidence intervals of the association between hormone therapy and cancer incidence in 29,152 Danish women followed from 1993 to 1997 through 2013 in the Danish Diet, Cancer, and Health cohort

Outcome Hormone therapy (HT)	All cancers Adjusted[3] HR (95%CI)	Breast Adjusted[3] HR (95%CI)	Colorectal Adjusted[3] HR (95%CI)	Lung Adjusted[3] HR (95%CI)	Ovarian[1] Adjusted[3] HR (95%CI)	Endometrial[2] Adjusted[3] HR (95%CI)
N outcomes		1992	642	694	222	315
Overall Hormone Therapy						
Never	1.00	1.00	1.00	1.00	1.00	1.00
Previous	1.02 (0.94–1.10)	1.05 (0.91–1.20)	0.82 (0.66–1.03)	0.96 (0.78–1.18)	1.00 (0.66–1.51)	1.32 (0.96–1.82)
Baseline	1.28 (1.21–1.36)	1.77 (1.61–1.95)	0.79 (0.66–0.95)	0.99 (0.83–1.17)	1.68 (1.26–2.26)	1.86 (1.45–2.37)
Type of Hormone Therapy						
No HT use	1.00	1.00	1.00	1.00	1.00	1.00
Estrogen only	1.15 (1.05–1.26)	1.40 (1.21–1.63)	0.77 (0.57–1.03)	1.07 (0.83–1.38)	1.96 (1.26–3.04)	2.38 (1.50–3.76)
Combined	1.39 (1.30–1.49)	1.98 (1.78–2.21)	0.86 (0.69–1.07)	0.96 (0.78–1.19)	1.69 (1.21–2.37)	1.86 (1.42–2.43)
Unspecified incl. previous users	1.03 (0.96–1.11)	1.16 (1.03–1.32)	0.77 (0.62–0.95)	0.94 (0.77–1.14)	1.00 (0.68–1.48)	1.31 (0.97–1.77)
Duration of Hormone Therapy						
Never	1.00	1.00	1.00	1.00	1.00	1.00
Triers (< 6 months)	1.12 (1.03–1.22)	1.28 (1.11–1.47)	0.81 (0.62–1.05)	0.96 (0.75–1.22)	1.21 (0.79–1.86)	1.27 (0.89–1.83)
≤ 5 years	1.13 (1.04–1.24)	1.40 (1.22–1.61)	0.77 (0.58–1.02)	0.77 (0.58–1.01)	1.21 (0.77–1.90)	1.55 (1.09–2.22)
> 5 years	1.28 (1.20–1.37)	1.78 (1.60–1.98)	0.83 (0.68–1.02)	1.10 (0.92–1.31)	1.71 (1.24–2.37)	2.07 (1.58–2.71)
Route of Hormone Therapy						
Never	1.00	1.00	1.00	1.00	1.00	1.00
Oral	1.21 (1.14–1.28)	1.57 (1.43–1.72)	0.81 (0.69–0.96)	1.02 (0.87–1.18)	1.46 (1.11–1.93)	1.75 (1.39–2.20)
Other systemic	1.09 (0.95–1.26)	1.24 (0.99–1.57)	0.75 (0.49–1.17)	0.70 (0.45–1.09)	1.05 (0.49–2.26)	1.24 (0.66–2.36)
Only local	0.92 (0.75–1.13)	1.12 (0.81–1.56)	0.66 (0.35–1.24)	0.65 (0.32–1.31)	1.50 (0.66–3.43)	0.72 (0.27–1.94)

[1] 1.633 women who reported having both ovaries removed (or answered unknown ($n = 249$)) were excluded from the analyses on ovarian cancer

[2] 4.365 women who reported previous hysterectomy (8 were unknown) were excluded from the analyses on endometrial cancer

[3] Adjusted for age (underlying timescale), age at menarche; parity and age at first childbirth, history of oral contraceptive pill use; adult attained height, education level; baseline alcohol intake, BMI; physical activity, smoking and diet (whole grains, dietary fiber, red and processed meat)

exposures of interest and potential confounders. Further, the population is very homogenous in terms of diagnoses and treatment of diseases because of the single, public healthcare system providing free, universal healthcare coverage in Denmark.

An important limitation of the current study is the self-reported, single point measurement of hormone use rendering changes in use after baseline unknown. Other limitations include the possible influence of residual confounding and confounding by factors associated with the symptoms leading women to take hormones. Also, "healthy users" selection is unavoidably introduced when excluding women with prior relevant morbidity outcomes or when susceptible women dying before potential recruitment could not be included. However, this is true for any study of hormone therapy including RCTs where women with previous hormone use are also allowed to enter. This type of selection most likely bias the associations towards the null-hypothesis. The interaction analyses were done by using composite variables of binary categorizations of main exposure (HT) and lifestyle factors and then investigating departure from additivity. This approach optimizes power and eases interpretability of the interaction models. However, it also limits the ability to study more than one level of interaction.

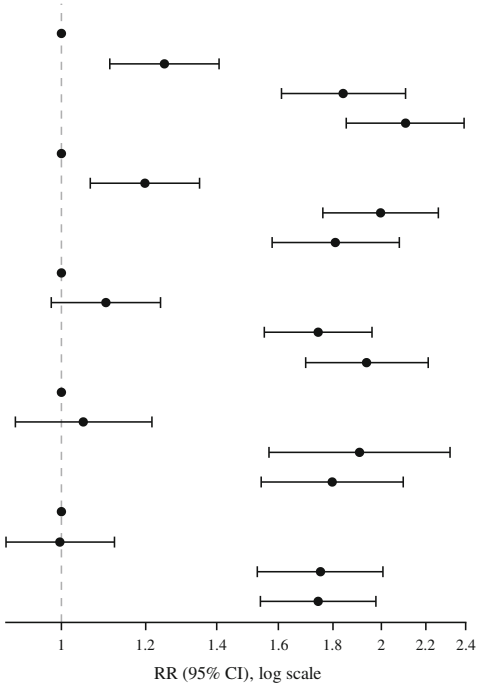
In the evaluation of possible interaction, it should be noted that the RERI measure only is interpretable if the associations for the individual exposures are in the same direction. It is also important to note that test parameters obtained in interaction analyses of subgroups in studies where the strength of the overall associations are not very large should be done with caution [24].

The overall higher risk of cancer seen in women on HT is in concordance with a very recent large Swedish nationwide registry study, which found similar associations between HT and higher risks of breast, ovarian, and endometrial cancer. They also found a lower risk for gastrointestinal cancers; however, the overall cancer risk was still slightly higher among ever hormone therapy users SIR 1.09 (95%CI, 1.07 to 1.11) [27]. In contrast to our study, where no association was found, they found a higher risk of lung cancer; however, insufficient adjustment for smoking could be a likely explanation as suggested by the authors. In fact, in our population, there were more smokers among hormone users compared to never users, which further supports this possibility.

a

Breast cancer

Exposure		RR (95% CI)
HT & Alcohol intake	No HT-low alcohol	Ref.
	No HT-high alcohol	1,25 (1,11, 1,41)
	HT-low alcohol	1,84 (1,61, 2,11)
	HT-high alcohol	2,11 (1,85, 2,39)
HT & BMI	No HT-normal	Ref.
	No HT-high	1,20 (1,06, 1,35)
	HT-normal	2,00 (1,76, 2,26)
	HT-high	1,81 (1,58, 2,08)
HT & Physical activity	No HT-active	Ref.
	No HT-inactive	1,10 (0,98, 1,24)
	HT-active	1,74 (1,55, 1,96)
	HT-inactive	1,94 (1,70, 2,21)
HT & Diet	No HT-healthy	Ref.
	No HT-unhealthy	1,05 (0,90, 1,22)
	HT-healthy	1,91 (1,57, 2,32)
	HT-unhealthy	1,80 (1,54, 2,10)
HT & smoking	No HT-non smoking	Ref.
	No HT-smoking	1,00 (0,89, 1,12)
	HT-nonsmoking	1,75 (1,53, 2,01)
	HT-smoking	1,74 (1,54, 1,98)



b

Endometrial cancer

Exposure		RR (95% CI)
HT & Alcohol intake	No HT-low alcohol	Ref.
	No HT-high alcohol	0,91 (0,69, 1,21)
	HT-low alcohol	1,58 (1,14, 2,19)
	HT-high alcohol	1,74 (1,27, 2,40)
HT & BMI	No HT-normal	Ref.
	No HT-high	2,07 (1,52, 2,82)
	HT-normal	2,76 (1,95, 3,91)
	HT-high	2,30 (1,56, 3,39)
HT & Physical activity	No HT-active	Ref.
	No HT-inactive	1,06 (0,79, 1,40)
	HT-active	1,87 (1,39, 2,50)
	HT-inactive	1,64 (1,14, 2,36)
HT & Diet	No HT-healthy	Ref.
	No HT-unhealthy	0,75 (0,54, 1,04)
	HT-healthy	0,90 (0,51, 1,59)
	HT-unhealthy	1,53 (1,08, 2,16)
HT & smoking	No HT-non smoking	Ref.
	No HT-smoking	0,46 (0,34, 0,62)
	HT-nonsmoking	1,46 (1,07, 1,99)
	HT-smoking	1,01 (0,74, 1,39)

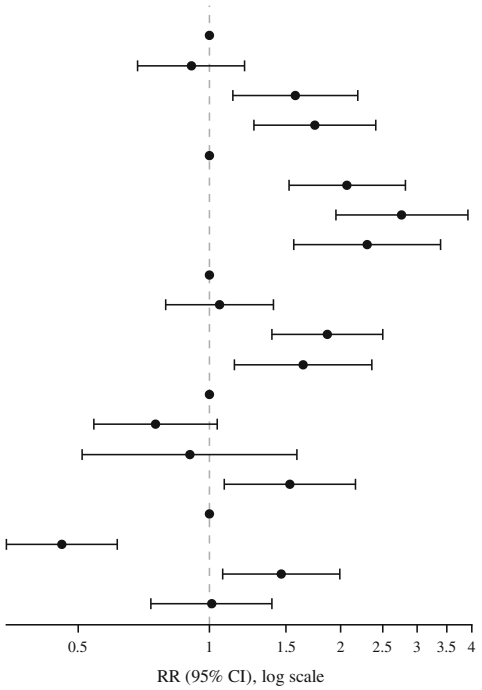
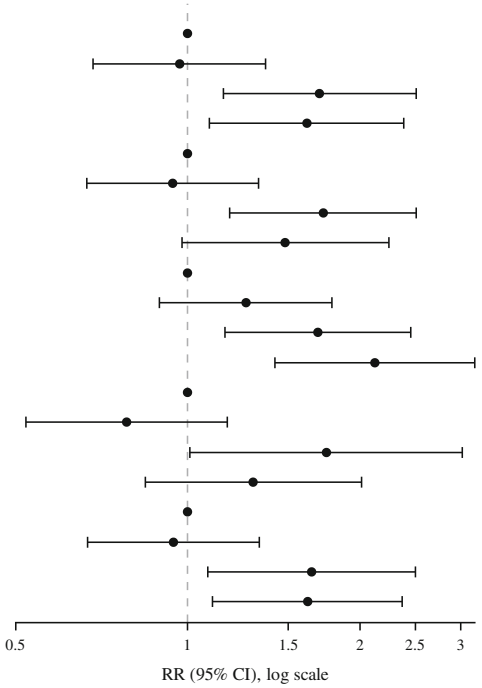


Fig. 3 Incidence of selected female cancers by combinations between hormone therapy and other modifiable risk factors. **a** Breast cancer. **b** Endometrial cancer. **c** Ovarian cancer. **d** Colorectal cancer. All analyses were adjusted for age at menarche, parity and age at first childbirth, adult attained height, history of oral contraceptive pill use, and education level, and the remaining lifestyle variables not combined with HT. No hormone use combined with the lowest risk category of the other variable was the reference category except for colorectal cancer where hormone use combined with the lowest risk category of the other variable was the reference category

c

Ovarian cancer

Exposure		RR (95% CI)
HT & Alcohol intake	No HT-low alcohol	Ref.
	No HT-high alcohol	0,97 (0,68, 1,37)
	HT-low alcohol	1,70 (1,15, 2,51)
	HT-high alcohol	1,61 (1,09, 2,39)
HT & BMI	No HT-normal	Ref.
	No HT-high	0,94 (0,66, 1,33)
	HT-normal	1,72 (1,18, 2,51)
	HT-high	1,48 (0,98, 2,25)
HT & Physical activity	No HT-active	Ref.
	No HT-inactive	1,26 (0,89, 1,79)
	HT-active	1,69 (1,16, 2,45)
	HT-inactive	2,12 (1,42, 3,18)
HT & Diet	No HT-healthy	Ref.
	No HT-unhealthy	0,78 (0,52, 1,17)
	HT-healthy	1,75 (1,01, 3,02)
	HT-unhealthy	1,30 (0,84, 2,01)
HT & smoking	No HT-non smoking	Ref.
	No HT-smoking	0,94 (0,67, 1,33)
	HT-nonsmoking	1,65 (1,08, 2,50)
	HT-smoking	1,62 (1,10, 2,37)



d

Colorectal cancer

Exposure		RR (95% CI)
HT & Alcohol intake	HT-low alcohol	Ref.
	No HT-low alcohol	1,19 (0,93, 1,53)
	HT-high alcohol	0,95 (0,70, 1,29)
	No HT-high alcohol	1,18 (0,91, 1,52)
HT & BMI	HT-normal	Ref.
	No HT-normal	1,28 (0,99, 1,67)
	HT-high	1,30 (0,96, 1,77)
	No HT-high	1,52 (1,18, 1,96)
HT & Physical activity	HT-active	Ref.
	No HT-active	1,37 (1,07, 1,75)
	HT-inactive	1,41 (1,04, 1,92)
	No HT-inactive	1,48 (1,15, 1,91)
HT & Diet	HT-healthy	Ref.
	No HT-healthy	1,51 (0,98, 2,32)
	HT-unhealthy	1,36 (0,90, 2,06)
	No HT-unhealthy	1,58 (1,07, 2,34)
HT & smoking	HT-nonsmoking	Ref.
	No HT-non smoking	1,31 (0,99, 1,75)
	HT-smoking	1,21 (0,88, 1,67)
	No HT-smoking	1,40 (1,06, 1,85)

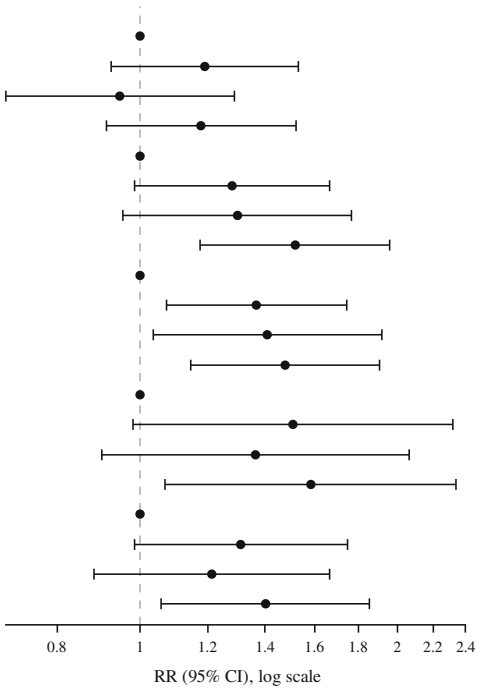


Fig. 3 (continued)

The current evidence base for guidelines on menopausal HT is largely dominated by the Women's Health Initiative (WHI) early stopped, primary prevention trials, which found no overall increase in cancer incidence during the

interventions [28, 29] nor after additional observational follow-up, where the overall IRR for all cancers was 1.02 (95%CI, 0.91 to 1.15). The only two cancers that were statistically significantly associated with HT (and only for combined estrogen and progestin therapy) were breast (1.24 (95%CI, 1.01 to 1.53)), and colorectal cancer (0.62 (95%CI, 0.43 to 0.89) [30]. It should be noted that the incidence of ovarian cancer in the combined treatment group was markedly higher than in the placebo group ($n = 24$ vs 16), although the difference not statistically significant. No follow-up of this outcome has been reported from the WHI [6]. However, with less than 2000 cancer cases (in both trials together), the WHI was not well powered to analyze risks for less common cancers. Further, it can be argued that even though contemporary observational studies have shortcomings, they more correctly illustrate the effect of various types of HT used to treat menopausal symptoms rather than single regimens used as primary prevention. A Danish nationwide register study on hormone use similar to the one from Sweden also found a higher risk of both ovarian [31] and endometrial cancer [32] as well as lower risk of colorectal cancer [33].

The lower risk of colorectal cancer has been reported rather consistently across both randomized and observational studies [34, 35]. However, as argued, the absolute risk reduction is small compared to the absolute increase in reproductive cancers [12]. Adding to that is our observation that the lower colorectal cancer risk was only visible in the "healthy" subgroups of women using hormones, which overall suggests a lesser influence of exogenous hormones in colorectal cancer etiology as compared to other lifestyle influences.

When looking at the combined associations for HT and the other lifestyle factors, the generally additive associations we saw between HT & alcohol and breast cancer are in line with most previous reports ([36]; eAppendix 4). Several previous studies have reported the effect of adiposity on female cancers to differ between women using hormones and never users including two recent comprehensive meta-analyses that both found positive associations between measures of adiposity and risks of breast, endometrial and ovarian cancer and with the strongest associations among women not on HT [37, 38]. However, these stratified analyses with different baseline hazards make the measures of association not directly comparable. From a public health perspective, departure from additivity is the most relevant approach when trying to determine whether interaction is likely present [39].

As mentioned above, the possible interaction we saw between HT and BMI in breast and endometrial cancer should be interpreted with caution given the modest overall associations seen. However, it does seem biologically plausible that in women on HT, the effect of adiposity on cancer risk might be attenuated by the fact that there is already a high level of bioavailable hormones and consequently the contribution from peripheral fat tissue, which is otherwise the main source of estrogen after menopause, has a lesser impact.

The only clearly visible diverging association we observed between HT and lifestyle was the seemingly protective effect of smoking on endometrial cancer, which has also been reported in most prospective studies [40]. Although smoking is known to affect the level of bioavailable estrogen (through a combination of influences on weight, elevated hepatic clearance, and hydroxylation of estradiol into less potent forms of estrogen [41]), the fact that the effect was selectively seen in endometrial cancer and not in breast and ovarian cancer is paradoxical. Although, animal studies have found exposure to tobacco smoke to increase the expression of endometrial progesterone receptors, resulting in increased cell differentiation and tumor suppression [42] as a possible explanation of a tissue specific effect.

In addition to the direct effects of sex hormones in the target tissues are those mechanisms that indirectly influence circulating sex hormone levels. Alcohol intake and adiposity are known to increase estrogen hormone levels [43, 44], whereas physical exercise reduces them [45]. Overall, these indirect effects all seem like plausible explanations to the associations found in this study with largely additive risks between HT and factors that raise estrogen levels and attenuation by factors that lower them.

Conclusion

With an overall higher risk of cancer among women on HT, this study underlined the importance of considering all potential female cancer risks in menopausal treatment guidelines. Information on individual lifestyle risk profile has limited additional value when determining appropriateness of treatment and cancer risk in women on HT. Our results support the notion that high levels of hormones in itself play an etiological role in female reproductive cancers, whereas the possible protective impact in colorectal cancer might be limited to women with an otherwise healthy lifestyle.

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