ACTA ONCOLOGICA
2021, VOL. 60, NO. 7, 881–887
https://doi.org/10.1080/0284186X.2021.1909747

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ORIGINAL ARTICLE

Prediagnostic use of estrogen-only therapy is associated with improved colorectal cancer survival in menopausal women: a Swedish population-based cohort study

Johanna Simin[a,b], Qing Liu[a,b], Xinchen Wang[a], Katja Fall[c,d], Cecilia Williams[e,f], Steven Callens[g], Lars Engstrand[a,b] and Nele Brusselaers[a,b,h,i]

[a]Department of Microbiology, Tumor and Cell Biology, Centre for Translational Microbiome Reseaarch (CTMR), Stockholm, Sweden; [b]Science for Life Laboratory (SciLifeLab), Stockholm, Sweden; [c]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [d]Clinical Epidemiology and Biostatistics School of Medical Sciences, Örebro University, Örebro, Sweden; [e]Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden; [f]Department of Protein Science, SciLifeLab, KTH Royal Institute of Technology, Solna, Sweden; [g]Department of General Internal Medicine, Ghent University Hospital, Gent, Belgium; [h]Global Health Institute, Antwerp University, Antwerp, Belgium; [i]Department of Head and Skin, Ghent University, Ghent, Belgium

ABSTRACT

Background: Menopausal hormone therapy (MHT) reduces the risk of developing colorectal cancer (CRC), yet it is largely unclear whether it could also influence survival in women with CRC. Therefore, we aimed to investigate the influence of prediagnostic MHT use on CRC-specific and all-cause mortality in women with CRC.

Methods: This nationwide nested cohort study, within a large population-based matched cohort, included all women diagnosed with incident CRC between January 2006 and December 2012 (N = 7814). A total of 1529 women had received at least one dispensed prescription of systemic MHT before CRC diagnosis, and 6285 CRC women with CRC did not receive MHT during the study period, as ascertained from the Swedish Prescribed Drug Registry. Multivariable Cox regression models provided adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for CRC-specific mortality and all-cause mortality.

Results: Past use of prediagnostic estrogen-only therapy (E-MHT) was associated with lower CRC-specific (HR = 0.67, 95%CI 0.44–0.99) and all-cause mortality (HR = 0.68, 95%CI 0.59–0.93). However, all-cause mortality (HR = 1.23, 95%CI 1.02–1.48) was elevated among current prediagnostic E-MHT users who were 70+ years at diagnosis. Current estrogen combined progestin therapy (EP-MHT) was associated with higher CRC-specific mortality (HR = 1.61, 95%CI 1.06–2.44) in older women, but no association was shown for all-cause mortality.

Conclusions: Our findings suggest that E-MHT, but not EP-MHT use, might be associated with improved CRC survival, indicating a potential role of estrogens in sex hormone-related cancers. However, association of MHT use with grade of cancer remains unclear.

Abbreviations: CI: Confidence interval; CRC: Colorectal cancer; E-MHT: Estrogen-only therapy; EP-MHT: Estrogen combined progestin therapy; HR: Hazard ratio; MHT: Menopausal hormone therapy

ARTICLE HISTORY
Received 3 February 2021
Accepted 23 March 2021

KEYWORDS
Colorectal cancer; survival; prognostic outlook; estrogens; progestins; menopausal hormone therapy

Introduction

Despite enhanced treatment possibilities during the past few decades, colorectal cancer (CRC) remain a major health threat accounting for 9% of all cancer-related deaths globally [1–3]. In Sweden, CRC is the third most common cancer among women, and the age-standardized incidence (40/100,000 women in 2015) is unsurprisingly lower compared with men, as male sex is a risk factor for this malignancy [1,3]. Worrisomely, half of the individuals are expected to develop metastases at some time point (unfavorably to liver, lungs, and even bone marrow) [3], underscoring the demand for preventive measures to lower the incidence and even mortality from CRC.

In addition to lower incidence among women, CRC-mortality is one-fourth lower among women than men, indicating for a potential role of sex hormones (and particularly estrogens) in CRC progression [1,3,4]. Two nuclear receptors, estrogen receptor alpha (ERα) and beta (ERβ) mediate effects of estrogen. ERβ in normal colon epithelia has been experimentally shown to play a role in the prevention of a tumor formation in mouse models, by reducing inflammation of the gut [5]. Furthermore, *in-vivo* mice-models suggest exogenous estrogens impacting inflammatory markers and reducing

CONTACT Johanna Simin johanna.simin@ki.se Department of Microbiology, Tumor and Cell Biology, Centre for Translational Microbiome Research (CTMR), Karolinska Institutet, Biomedicum, Quarter 8A, Solnavägen 9, Solna SE-171 64, Sweden

Supplemental data for this article can be accessed here.

proliferation of the crypt [5,6], and changing gut microbiota diversity in CRC-induced males [7]. As this posed link of estrogens with gut inflammation and microbiome might be modifiable, it could contribute to a reduced CRC risk [7], and potentially improved survival.

Menopausal hormone therapy (MHT) might reduce CRC risk with 30–40% [8,9]. Here, we hypothesized that MHT use before CRC diagnosis could lead to an improved CRC survival [4,10–13], however, the association of MHT with CRC mortality is largely understudied and inconclusive [4,9,11,14–17]. Therefore, we aimed to investigate if prediagnostic use of MHT might influence CRC-specific or all-cause mortality in women with CRC, by means of a nationwide study based on the Swedish Prescribed Drug Registry.

Material and methods

Study design

This was a nationwide cohort study within a large Swedish population-based matched-cohort, which has been extensively used to investigate the association of MHT use on the risk of breast [18], ovary [19], biliary tract [20], pancreatic [21], gastro-esophageal [22], and CRC [23]. The initial source cohort included virtually all Swedish MHT users, identified through the Prescribed Drug Registry and group-level matched (1:3) to MHT non-users, between 1 July 2005 and 31 December 2012, and it has been described in great detail elsewhere [18]. In brief, the unique Swedish personal identity number enabled an unambiguous data linkage between the Swedish Prescribed Drug Registry and other national high-quality registries supervised by the Swedish National Board of Health and Welfare [24,25]. The ethical application was approved by the Regional Ethical Review Board in Stockholm (2014/1291-31/4), and informed consent was not required.

From the source cohort, we identified all women diagnosed with incident CRC between 1 January 2006 and 31 December 2012, to ensure data availability of prediagnostic exposure (as the Swedish Prescribed Drug Registry was established in July 2005). CRC diagnoses were classified using the International Classification of Diseases (ICD) 10th edition, as ascertained from the Swedish Cancer Registry (ICD-codes: C18-C20). In addition, the TNM system was used to classify the stage of cancer (0–I, II, III, and IV) based on the Swedish guidelines [3]. Clinical data and information on surgical procedures were ascertained on discharge diagnoses, as recorded in the Swedish Patient Registry (in- and outpatient care) [26]. CRC surgeries, from 1 year before CRC diagnosis until the end of study period, were identified according to Nomesco-coding with codes JFB (partial excision of intestine), JFH (total colectomy), and JGB (excision of rectum) [27]. Supplementary Table 1 provides a complete list of the included codes.

Exclusion criteria

To exclude premenopausal women, the source cohort included only women who were 40 years or older at first MHT prescription.

Exposure ascertainment

MHT use was ascertained from the Swedish Prescribed Drug Registry, which is >99% complete for prescribed and dispensed outpatient care drugs using anatomical and therapeutic chemical (ATC) classification codes (Supplementary Table 2) [24,28]. Women, who received at least one dispensed prescription of MHT before their CRC diagnosis between 1 July 2005 and 31 December 2012, were considered as prediagnostic MHT users ($n = 1529$). Women with CRC, who did not receive MHT prescriptions during the study period, were considered as non-users ($n = 6285$). Furthermore, MHT users were classified as ever, current, and past users. Women who received at least one dispensed prescription during the last 6 months before their CRC diagnosis were classified as current users, and all other women as past users. In Sweden, the maximum of prescription coverage is 3 months, and MHT is not sold over-the-counter [18,29].

To ensure homogenous groups and strictly separating estrogen-only therapy (E-MHT) only users from women exposed to progestins, we classified women who received one or more progestin prescriptions during the study period as EP-MHT users. Estradiol (i.e., 17β-estradiol) accounted for 99% of the estrogenic component in the EP-MHT prescriptions. To evaluate the influence of only systemic MHT (i.e., oral or cutaneous) we excluded preparations with local effects (i.e., vaginal creams), because they are unlikely to have systemic effects [30]. Injectable MHT is not prescribed in Sweden [18].

Outcome ascertainment

The primary outcome was CRC-specific death (ICD codes: C18-C20), and the secondary outcome was all-cause mortality (ICD codes: A00-Z99). The Swedish Causes of Death Registry was used to ascertain the cause and date of death, with data for CRC-specific death until 31 December 2013, and for all-cause mortality until 31 December 2014 (with 100% coverage).

Statistical analyses

Multivariable proportional hazards Cox regression models compared MHT users to non-users, providing hazards ratios (HRs) with 95% confidence intervals (CIs) for CRC-specific and all-cause mortality. The analyses were adjusted for factors that may be related to MHT prescription (i.e., hysterectomy, parity, and thrombotic events), age at diagnosis, osteoporosis (confounding by indication), main comorbidities (i.e., smoking- and alcohol-related diseases, obesity, and diabetes), site (colon or rectum), and stage of cancer (0 + I, II, III, and IV).

Women were sub-grouped by age at diagnosis (<60, 60–69, and ≥70 years), and analyses were stratified by MHT type, and by ever, current, and past MHT use. Further analyses assessed the risk of colon and rectal cancer among MHT ever-users as compared with MHT non-users (Table 1). Women were followed from the incident CRC diagnosis until death from CRC, all-cause or end of study period (December

Table 1. Descriptive characteristics of the study included women, who were diagnosed with primary colorectal cancer (CRC) between 2006 and 2012.

	MHT ever-users Number of patients (%)	MHT non-users Number of patients (%)
Characteristics		
All MTH ever-users	1529 (100.0)	6285 (100.0)
Pre-diagnostic current users[a]	829 (54.2)	
Pre-diagnostic past users[b]	700 (45.8)	
Age at diagnosis		
<60 years	279 (18.3)	1282 (20.4)
60–69 years	529 (34.6)	1820 (29.0)
≥70 years	721 (47.2)	3183 (50.6)
Cancer site		
Colon	1061 (69.4)	4368 (69.5)
Rectum	468 (30.6)	1917 (30.5)
Site of cancer		
0 + I	207 (13.4)	742 (11.9)
II	351 (23.0)	1441 (22.9)
III	359 (23.7)	1437 (22.8)
IV	250 (16.3)	1126 (17.9)
Unknown	362 (23.6)	1539 (24.5)
Year of diagnosis		
2006–2009	829 (54.2)	3544 (56.4)
2010–2012	700 (45.8)	2741 (43.6)
Type of MHT therapy		
Estrogen-only	787 (51.5)	
Tibolone only	98 (6.4)	
Estrogens combined progestins	644 (42.1)	
Clinical factors		
Ever parous (in-hospital delivery)	373 (24.4)	1620 (25.8)
Thrombotic events	370 (24.2)	1533 (24.4)
Hysterectomy	393 (25.7)	1953 (30.8)
Diabetes Mellitus	155 (10.1)	600 (9.5)
Obesity	30 (2.0)	106 (1.7)
Alcohol-related disorders	30 (2.0)	134 (2.1)
Smoking-related disorders	128 (8.4)	492 (7.8)
Osteoporosis	61 (4.0)	258 (4.1)
History of colorectal surgery		
Yes	1529 (100.0)	6285 (100.0)

MHT: menopausal hormone therapy.
[a]Women who received at least one dispensed prescription of menopausal hormone therapy (MHT) during the last 6 months before incident CRC diagnosis were considered as current prediagnostic MHT users.
[b]All other women were considered as past users of prediagnostic MHT.

2014). Interaction by age was modeled additive on the linear prediction (i.e., log hazard scale), and a Wald test with p value $<.05$ was considered indicative of significance. To evaluate the robustness of our results sensitivity analyses were performed by postponing the start of the study, including only women diagnosed with CRC from 1 January 2007 and onwards. We also evaluated the effect of the different estrogen formulations and EP-MHT regimens separately, excluding women switching therapy type during the study period. All Analyses were performed on STATA MP4 15 (Stata Corporation, College Station TX, USA).

Results

Cohort characteristics

A total of 0.5% MHT users (1529 of 290,186) of the source cohort developed CRC, and 0.7% of the MHT non-users (6285 of 870,165) developed CRC during the study period of this cohort study (Table 1). Of all MHT users, the majority (54.2%) had received MHT within 6 months before their CRC diagnosis (i.e., current users), and 45.8% were past MHT users. Estrogen-only therapy (51.5%) was more common than EP-MHT (42.1%), and 6.4% had received tibolone.

Clinical factors were similarly distributed between the cohorts, apart from hysterectomy, which was more frequent among non-users (30.8%) than MHT users (25.7%). The median age at diagnosis was 70 years, and fewer prediagnostic MHT users were diagnosed before the age of 60 years (18.3%), as compared with non-users (20.4%). After a median follow-up time of 3 years (range 1–8 years), 27.3% of MHT users diagnosed with CRC and, respectively, 29.0% of non-users had died due to CRC. Altogether, 40.8% of MHT users and 42.0% of non-users died during the follow-up.

Past estrogen-only therapy associated lower CRC-specific mortality

Compared with MHT non-users, no association was shown for overall prediagnostic ever-use with CRC-specific mortality (HR = 1.05, 95%CI 0.93–1.18) (Table 2). However, we found important differences by MHT types, and current versus past use. Estrogen-only therapy was associated with a 33% lower CRC-specific mortality among past users (HR = 0.67, 95%CI 0.44–0.99), whilst current use of E-MHT was not associated with lower CRC-specific mortality (HR = 1.15, 95%CI 0.82–1.55). Among EP-MHT users, current use was associated with a 61% higher CRC-specific mortality among women

Table 2. Association of prediagnostic menopausal hormone therapy (MHT) use with colorectal cancer (CRC) specific mortality, among women diagnosed with CRC between 2006 and 2012.

	Number of patients/number of deaths MHT users	Number of patients/Number of deaths MHT non-users	Multivariable adjusted HR (95% CI)[a]				p for inter-action by age[b]
			All women	<60 years	60–69 years	≥70 years	
All MHT ever-users							
All MHT	1529/418	6285/1820	1.05 (0.93–1.18)	0.90 (0.66–1.24)	0.99 (0.80–1.23)	1.07 (0.82–1.38)	<.001
Estrogen-only	787/224		1.09 (0.92–1.29)	0.87 (0.44–1.72)	0.91 (0.61–1.36)	1.16 (0.95–1.41)	<.001
Tibolone only	98/28		0.82 (0.53–1.28)	1.07 (0.47–2.44)	0.72 (0.39–1.31)	1.22 (0.39–3.80)	<.001
Estrogen + progestin	644/166		1.06 (0.89–1.25)	0.89 (0.61–1.28)	1.08 (0.84–1.40)	1.34 (0.98–1.83)	<.001
Current users							
All MHT	829/ 224		1.15 (0.93–1.43)	1.26 (0.85–1.85)	1.06 (0.79–1.43)	**1.31 (1.05–1.65)**	<.001
Estrogen-only	467/ 134		1.15 (0.82–1.55)	1.95 (0.91–4.19)	0.86 (0.50–1.48)	1.25 (0.88–1.77)	<.001
Tibolone only	43/9		0.57 (0.24–1.38)	1.19 (0.38–3.75)	0.33 (0.08–1.34)	–	<.001
Estrogen + progestin	319/81		1.25 (0.98–1.59)	1.12 (0.70–1.79)	**1.61 (1.06–2.44)**	1.26 (0.57–2.70)	<.001
Past users							
All MHT	700/194		0.93 (0.79–1.09)	0.63 (0.39–1.02)	0.93 (0.70–1.22)	1.10 (0.87–1.39)	<.001
Estrogen-only	320/90		**0.67 (0.44–0.99)**	0.29 (0.07–1.19)	0.69 (0.53–1.62)	0.71 (0.42–1.18)	<.001
Tibolone only	55/19		0.98 (0.58–1.63)	0.98 (0.31–3.10)	1.00 (0.51–1.96)	1.23 (0.39–3.84)	<.001
Estrogen + progestin	325/85		0.93 (0.73–1.16)	0.69 (0.39–1.20)	0.91 (0.64–1.28)	1.34 (0.90–1.95)	<.001
Anatomical location of the tumor							
Colon	1061/312	4368/1284	1.04 (0.90–1.19)	0.98 (0.66–1.44)	1.01 (0.79–1.28)	1.14 (0.93–1.38)	<.001
Rectum	468/106	1917/536	1.09 (0.84–1.40)	0.82 (0.48–1.42)	0.89 (0.53–1.48)	1.38 (0.97–1.96)	<.001

HR: hazard ratio, 95%CI: 95% confidence interval.
Statistically significant 95% CIs are marked in bold.
[a]Multivariable analyses were adjusted for age at colorectal cancer diagnosis, hysterectomy, thrombotic events, smoking- and alcohol-related diseases, obesity, diabetes, osteoporosis, tumor location, and stage of cancer.
[b]Interaction by age was modeled additive on the linear prediction (i.e., log hazard scale), and a Wald test with p value <.05 was considered indicative of significance.

aged 60–69 years at diagnosis (HR = 1.61, 95%CI 1.06–2.44). In contrast, past EP-MHT use was not associated with CRC-specific mortality(HR = 0.93, 95%CI 0.73–1.16). No apparent association was found for tibolone (HR = 0.82, 95%CI 0.53–1.28), based on smaller groups. Analyses by anatomical location of the tumor showed no association.

Past estrogen-only therapy associated with lower all-cause mortality

Overall, prediagnostic MHT ever-use was not associated with all-cause mortality (HR = 1.03, 95%CI 0.93–1.14) (Table 3). However, past use of E-MHT only was associated with a 32% lower mortality (HR = 0.68%, 95%CI 0.59–0.93), compared with MHT non-users. Among current E-MHT only users, 23% higher all-cause mortality was shown, particularly among women 70+ years at diagnosis (HR = 1.23, 95%CI 1.02–1.48). No apparent overall association with EP-MHT (HR = 1.06, 95%CI 0.91–1.22) was shown, whilst current use of tibolone was associated with lower mortality risk (HR = 0.44, 95%CI 0.18–0.99).

Further analyses by anatomical location of the tumor suggested a marginal association with colon cancer among MHT users who were 70+ years at diagnosis (HR = 1.16, 95% CI 1.00–1.36), as compared with MHT non-users (Table 3).

Sensitivity analyses

We found no apparent effects by estrogen formulations or EP-MHT regimens on the risk of mortality (Supplementary Table 3). Furthermore, the association remained the similar in sensitivity analyses restricted to women diagnosed with CRC from January 2007 and onwards, yet with wider CIs (Supplementary Table 4).

Discussion

This population-based cohort study shows that past E-MHT use before CRC diagnosis is associated with over 30% lower CRC-specific mortality and all-cause mortality, as compared with women with CRC who did not receive MHT. However, elevated all-cause mortality was noted among older women (at diagnosis) who had received E-MHT within 6 months before their CRC diagnosis. Among EP-MHT users, current prediagnostic use was associated with higher CRC-specific mortality among women diagnosed at older age, whereas no association with all-cause mortality was shown. These findings support the role and chemopreventive effects of particularly estrogens in development of CRC, as prediagnostic use of E-MHT was associated with lower mortality. Furthermore, current use of tibolone is suggested for lower risk of all-cause mortality, based on smaller groups.

The main strength of this study is the well-designed methodology based on a population-based approach including all women exposed to MHT. The unique Swedish personal identification number ensured a valid data linkage between the high-quality Swedish health data registries, with high overall coverage and completeness of follow-up [25,31]. The exposure was ascertained from the highly complete (>99%) Swedish Prescribed Drug Registry and we included only dispensed MHT prescriptions. Misclassification of exposure due to over-the-counter drug use is unlikely, as systemic

Table 3. Association of prediagnostic menopausal hormone therapy (MHT) use with all-cause mortality, among women diagnosed with colorectal cancer (CRC) between 2006 and 2012.

	Number of patients/ Number of deaths in MHT ever-users	Number of patients/ Number of deaths in MHT non-users	Multivariable adjusted HR (95% CI)[a]				
			All women	<60 years	60–69 years	≥70 years	*p* for inter-action by ageb
All MHT ever-users							
All MHT	1529/624	6285/ 2635	1.03 (0.93–1.14)	0.96 (0.73–1.28)	0.95 (0.78–1.16)	1.14 (0.99–1.30)	<.001
Estrogen-only	787/359		1.06 (0.92–1.21)	0.95 (0.52–1.76)	0.89 (0.62–1.27)	1.10 (0.95–1.28)	<.001
Tibolone only	98/31		0.70 (0.46–1.09)	1.08 (0.47–2.46)	0.57 (0.32–1.02)	1.04 (0.33–3.23)	<0.001
Estrogen + progestin	644/234		1.06 (0.91–1.22)	0.95 (0.69–1.32)	1.06 (0.85–1.33)	1.28 (0.99–1.65)	<.001
Current users							
All MHT	829/346		**1.16 (1.01–1.32)**	1.19 (0.83–1.70)	1.06 (0.82–1.37)	**1.21 (1.02–1.45)**	<.001
Estrogen-only	467/225		**1.23 (1.04–1.46)**	1.83 (0.89–3.74)	0.98 (0.63–1.57)	**1.23 (1.02–1.48)**	<.001
Tibolone only	43/12		**0.44 (0.18–0.99)**	1.22 (0.39–3.86)	**0.26 (0.08–0.81)**	–	<.001
Estrogen + progestin	319/109		1.16 (0.94–1.43)	1.06 (0.68–1.62)	1.37 (0.98–1.85)	1.14 (0.75–1.76)	<.001
Past users							
All MHT	700/278		**0.88 (0.79–0.99)**	0.76 (0.50–1.16)	0.85 (0.66–1.10)	1.06 (0.88–1.28)	<.001
Estrogen-only	320/134		**0.68 (0.59–0.93)**	0.41 (0.13–1.29)	0.78 (0.46–1.29)	0.94 (0.74–1.19)	<.001
Tibolone only	55/19		0.94 (0.56–1.56)	0.96 (0.30–3.02)	0.96 (0.49–1.87)	1.07 (0.34–3.34)	<.001
Estrogen + progestin	325/125		0.97 (0.80–1.18)	0.85 (0.52–1.37)	0.86 (0.63–1.17)	1.36 (0.99–1.85)	<.001
Anatomical location of the tumor							
Colon	1061/463	4368/ 1876	1.04 (0.90–1.19)	0.98 (0.66–1.44)	1.01 (0.78–1.20)	1.16 (1.00–1.36)	<.001
Rectum	468/161	1917/ 759	0.98 (0.79–1.21)	0.73 (0.44–1.22)	0.82 (0.52–1.28)	1.10 (0.82–1.46)	<.001

HR: hazard ratio, 95%CI: 95% confidence interval
Statistically significant 95% CIs are marked in bold.
[a]Multivariable analyses were adjusted for age at colorectal cancer diagnosis, hysterectomy, thrombotic events, smoking- and alcohol-related diseases, obesity, diabetes, osteoporosis, tumor location, and stage of cancer.
[b]Interaction by age was modeled additive on the linear prediction (i.e., log hazard scale), and a Wald test with p value $< .05$ was considered indicative of significance.

MHT is only available on prescription in Sweden. However, some prediagnostic MHT users might have continued use after CRC diagnosis. Yet, we did not include incident post-diagnostic MHT users, which should be less common considering the cellular proliferation promoting properties of estrogens in various tissues [8,32], and the association of MHT use with other solid tumors [18].

A recent Swedish cohort study showed that postdiagnostic use of EP-MHT was not associated with mortality [4], whilst here current EP-MHT use was associated with elevated CRC-specific mortality among women who were 70+ years at diagnosis. This discrepancy could be explained by post-diagnostic systemic EP-MHT being favored among healthier women, possibly with lower dose, given the association of progestins promoting other cancer types [18,19]. Also, our study did not find an association between current use of EP-MHT and higher overall mortality.

This study has also some limitations. Healthy user bias cannot be excluded. Although access to healthcare in Sweden should be equal to all, a link between MHT use, higher socioeconomic status and potentially better survival is possible [4,29]. To alleviate these concerns, analyses were stratified by different MHT types, and by current versus past use. The fact that we found a better survival for E-MHT among past users, but not among current users, nor past or current EP-MHT users, argues against an impact of socioeconomic factors. Furthermore, a closer clinical follow-up might be favored among MHT users who are at an increased risk of CRC. If these women undergo clinical examinations more frequently, it could result in earlier detection of polyps, cancer or fatal disease selectively among MHT users, possibly leading to under or overestimation of the mortality. However, the discrepant findings for different MHT types suggest that such bias should not explain the observed associations. Moreover, no population-level screening programs for CRC were available during the study period in Sweden.

Another limitation is a potential left censoring, as the Swedish Prescribed Drug Registry was established in July 2005, and women may have received MHT before 2005. Yet, any potential misclassification of exposure would likely be at random between the groups, and it should not explain the differences shown between the MHT types. Whereas we lacked data on previous use of oral contraceptives the majority of Swedish oral contraceptive users are teenagers and young adults, making this group of women very young in relation to CRC occurrence [33]. However, residual confounding may have influenced our results, as data on non-surgical treatment, first-degree familial history of CRC, and dietary factors were unavailable.

Compared with other studies, our results are in line with a recent screening trial, which found that MHT use lowers CRC-specific and all-cause mortality [10]. Here, however, we investigated the different MHT types and timing of MHT use (i.e., current versus past use of MHT). Our data suggest that past E-MHT use is associated with lower CRC-specific and all-cause mortality, whereas all-cause mortality was elevated among E-MHT users who were 70+ years at diagnosis. One possible explanation could be that past E-MHT users had received MHT for longer duration than women who received E-MHT within 6 months before their diagnosis. However, we lacked data to investigate duration of use more in detail. Furthermore, we cannot exclude the possibility of reverse causality with certainty, particularly among current users and women who were older at the diagnosis, as these groups of

women could have had symptoms that would call for MHT treatment. On the other hand, as estrogens stimulate cellular proliferation in various tissues, they could contribute and partly explain the here shown higher all-cause mortality among older current E-MHT users [8,32]. Moreover, in a recent meta-analysis of five cohort studies, CRC-mortality was 29% lower among current MHT users and the overall mortality was respectively 26% lower [13]. However, any direct comparison is hampered by discrepancies in definitions of current *versus* past use, and considered confounders.

The Swedish guidelines for MHT use were updated in 2019, and they list a reduced risk of CRC cancer as one possible beneficial health outcome [34,35]. Our findings indicate that prediagnostic E-MHT use might improve survival from CRC, whilst EP-MHT may increase CRC-specific mortality. Although this study assessed CRC mortality, and MHT was not evaluated as adjuvant therapy, it is plausible that the group of women receiving past E-MHT might have developed tumors later, potentially of a lower-stage and/or slower progressing type of tumors and exhibited a lower mortality as a result of the CRC-protective effects of estrogens. However, comparisons to support this hypothesis are challenging to make considering the information on cancer stage (from the Swedish Cancer Registry) has important limitations. The cancer stages reflect a mixture of different TNM-classifications, which may be clinically challenging to interpret. Nonetheless, the analyses were, however, adjusted for stage of cancer. Whereas this study cannot investigate the underlying mechanisms, ERβ related pathways are likely involved in the underlying pathophysiology. ERβ promotes pro-apoptotic signaling (particularly in colon), inhibits inflammatory signaling, and CRC progression is associated with loss of ERβ expression [10,36]. It is noteworthy that colorectal tumors themselves also do not express ERα or the progesterone receptor (PR). Any effect of current MHT use on tumor characteristics or survival should therefore represent an indirect effect. The higher CRC-specific mortality noted for EP-MHT current users, but not for E-MHT current users, could thus be an indirect effect of progestins. Both estrogens and progestins are implicated in modifying the immune system. Animal models further suggest that estrogens alter the composition of gut microbiota, which could partly contribute to the protective effect and lower mortality among E-MHT users [7]. Evidence suggests that gut microbiota, and dysbiosis, may play a pivotal role in CRC promotion. Especially *Fusobacterium nucleatum* has been associated with CRC and even higher CRC mortality [37]. However, this association requires further clarification, and a potential link between drug-microbiome interactions is understudied.

Conclusions

In conclusion, our findings indicate that the influence of prediagnostic use of MHT on CRC -specific and all-cause mortality varies between past and current use, and by the different MHT treatment options in women diagnosed with primary CRC. This novel study showed that particularly past estrogen-only use, but not use of estrogen combined progestin therapy, is associated with lower CRC-specific mortality.

Acknowledgments

We wish to express our most sincere gratitude toward all the thousands of women, clinicians, and healthcare staff members who contributed to the data collection, and the Swedish National Board of Health and Welfare for collecting the data.

Author contributions

All authors designed the study (JS, QL, XW, KF, CW, SC, LE, and NB). NB and JS had full access to all the data in the study. JS performed the statistical analyses and takes complete responsibility for the accuracy of the data analysis. JS wrote the original draft of the manuscript, which was thoroughly reviewed, edited and approved by all other authors (JS, QL, XW, KF, CW, SC, LE, and NB). JS and NB take complete responsibility for the integrity of the data.

Disclosure statement

The authors report no conflicts of interest. All authors designed the study (JS, QL, XW, KF, CW, SC, LE, and NB). NB and JS had full access to all the data in the study. JS performed the statistical analyses and takes complete responsibility for the accuracy of the data analysis. JS wrote the original draft of the manuscript, which was thoroughly reviewed, edited and approved by all other authors (JS, QL, XW, KF, CW, SC, LE, and NB). JS and NB take complete responsibility for the integrity of the data.

Funding

The research was partly funded by Swedish Cancer Society (Cancerfonden CAN 2018/596) (CW), Swedish Research Council 2020-01058 (NB), and by China Scholarship Council (CSC, Grant 201700260302) (QL).

ORCID

Johanna Simin http://orcid.org/0000-0003-1611-139X
Nele Brusselaers http://orcid.org/0000-0003-0137-447X

Data availability statement

The dataset from this study is held securely in coded form at Karolinska Institutet, yet it belongs to the National Board of Health and Welfare (Socialstyrelsen). Data sharing agreements prohibit making the dataset publicly available, but the data will be made available upon reasonable request to the corresponding author (JS) after relevant ethical and data-sharing approval is obtained. The underlying analysis plan is available from the corresponding author (JS) upon request.

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