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Reproductive and hormonal factors and mortality among women with colorectal cancer in the NIH-AARP Diet and Health Study

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Background: Although use of menopausal hormone therapy (MHT) and some reproductive factors have been associated with colorectal cancer (CRC) risk, relations between these factors and survival after CRC diagnosis are unclear.

Methods: Among 2053 post-menopausal women diagnosed with incident CRC in the NIH-AARP Diet and Health Study, we calculated hazard ratios (HRs) and 95% confidence intervals (CIs) using multivariable Cox proportional hazards regression to test associations between oral contraceptive (OC) use, menarche age, age at first birth, parity, menopausal age, and MHT use with all-cause and CRC-specific mortality.

Results: There were 759 deaths (332 CRC-related deaths) over a median follow-up of 7.7 years. We observed no statistically significant associations between OC use, menarche age, age at first birth, parity, menopausal age, and mortality. Compared with never MHT use, former use was not associated with mortality, but we found an inverse association among baseline current users, for both all-cause (HR = 0.79, 95% CI 0.66–0.94) and CRC mortality (0.76, 0.59–0.99).

Conclusion: Future studies should further focus on the mechanisms by which exogenous oestrogen exposure might affect tumour progression and CRC survival.

There were an estimated 624,340 female colorectal cancer (CRC) survivors in the United States in 2014 (American Cancer Society, 2014). This number is projected to grow to over 771,000 by 2024, making female survivors of CRC the second largest group of female cancer survivors in the United States (American Cancer Society, 2014). CRC rates are lower among women in the United States than among men (Brenner et al., 2007), and use of menopausal hormone therapy (MHT) has been associated with a 30–40% lower risk of CRC, prompting research into the role of oestrogen in carcinogenesis (Grodstein et al., 1999).

In addition to the well-established association between MHT use and lower CRC risk (Writing Group for the Women’s Health Initiative I, 2002), previous literature has explored the hypotheses of exogenous oestrogen exposure and better survival after a CRC diagnosis (Persson et al., 1996; Slattery et al., 1999; Mandelson et al., 2003; Chan et al., 2006; Ritenbaugh et al., 2008;...
Hormones and colorectal cancer survival

RESULTS

The median time from baseline questionnaire to diagnosis was 5.3 years and median follow-up time was 7.7 years. Women who died were more likely to have regional/distant stage tumours, poorly differentiated tumours, and to have received chemotherapy as first course of treatment (Table 1). Women who died were also more likely to be physically inactive, current smokers at baseline, and report worse health status. A greater percentage of women who died reported never use of MHT and history of diabetes.

We observed a suggested, but not statistically significant, lower risk of all-cause mortality among women who were 13 + years old

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Mean age at diagnosis, years (s.d.) 70.0 (5.1) 69.1 (5.6)
Pre-diagnosis, baseline characteristics

Menstrual factors

Table 1. Tumour and baseline characteristics of women with colorectal cancer in the NIH-AARP Study (n = 2053)

<table>
<thead>
<tr>
<th>Tumour characteristics</th>
<th>Deaths</th>
<th>Non-deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer site, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>561 (73.9)</td>
<td>967 (74.7)</td>
</tr>
<tr>
<td>Rectal</td>
<td>198 (26.1)</td>
<td>327 (25.3)</td>
</tr>
<tr>
<td>Mean age at diagnosis, years (s.d.) 70.0 (5.1) 69.1 (5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour summary stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localised</td>
<td>168 (22.1)</td>
<td>459 (35.5)</td>
</tr>
<tr>
<td>Regional/distant</td>
<td>286 (37.7)</td>
<td>353 (27.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>305 (40.2)</td>
<td>482 (37.3)</td>
</tr>
<tr>
<td>Tumour grade at diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>80 (10.5)</td>
<td>167 (12.9)</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>416 (55.1)</td>
<td>763 (59.0)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>156 (20.8)</td>
<td>160 (12.4)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>8 (1.1)</td>
<td>11 (0.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>95 (12.5)</td>
<td>193 (14.9)</td>
</tr>
<tr>
<td>First course of treatment, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>611 (80.5)</td>
<td>1126 (87.0)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>256 (33.7)</td>
<td>308 (23.8)</td>
</tr>
<tr>
<td>Radiation</td>
<td>77 (11.8)</td>
<td>87 (6.2)</td>
</tr>
</tbody>
</table>
| Pre-diagnosis, baseline characteristics

Race/ethnicity, n (%)  
Non-Hispanic White | 690 (90.9) | 1125 (86.9) |
Afro-Caribbean | 43 (5.7) | 92 (7.1) |
Other | 14 (1.8) | 43 (3.3) |
Missing | 12 (1.6) | 34 (2.6) |

Body mass index, kg/m², n (%)  
18.5 to <25 | 266 (35.1) | 487 (37.6) |
25 to <30 | 225 (29.6) | 445 (34.4) |
30+ | 205 (27.0) | 298 (23.0) |
Missing | 63 (8.3) | 64 (5.0) |

Physical activity, n (%)  
Never/rarely | 226 (29.8) | 303 (23.4) |
1–3 times per month | 109 (14.4) | 178 (13.8) |
1–2 times per week | 149 (19.6) | 284 (22.0) |
3+ times per week | 258 (34.0) | 512 (39.6) |
Missing | 17 (2.2) | 19 (1.3) |

Smoking history, n (%)  
Never | 275 (36.2) | 574 (44.4) |
Former | 305 (40.2) | 504 (39.0) |
Current | 150 (19.8) | 173 (13.4) |
Missing | 29 (3.8) | 43 (3.3) |

Education level, n (%)  
< High school | 269 (35.4) | 480 (37.1) |
Some college | 269 (35.4) | 432 (33.4) |
College or graduate school | 181 (23.9) | 335 (25.9) |
Missing | 40 (5.3) | 47 (3.6) |

Self-reported health, n (%)  
Excellent/very good | 332 (43.7) | 652 (50.4) |
Good | 271 (35.7) | 486 (37.6) |
Fair | 119 (15.7) | 114 (8.8) |
Poor | 19 (2.5) | 19 (1.5) |
Missing | 18 (2.4) | 23 (1.8) |

History of colorectal polyps, n (%) | 66 (8.7) | 99 (7.7) |

Parity, n (%)  
Nulliparous | 111 (14.6) | 187 (14.5) |
1 | 71 (9.4) | 134 (10.4) |
2 | 182 (24.0) | 321 (24.8) |
3+ | 382 (50.3) | 639 (49.4) |
Missing | 13 (1.7) | 13 (1.0) |

Age at first birth, n (%)  
Never pregnant | 103 (13.6) | 179 (13.8) |
< 20 years | 128 (16.9) | 215 (16.6) |
20–29 years | 449 (59.2) | 806 (62.3) |
30+ years | 58 (7.6) | 77 (6.0) |
Missing | 21 (2.8) | 17 (1.3) |

Table 1. (Continued)

Deaths | Non-deaths |
|--------|------------|

Menopausal hormone therapy use, n (%)  
Never | 457 (60.2) | 721 (55.7) |
Former | 87 (11.5) | 114 (8.8) |
Current | 214 (28.2) | 456 (35.2) |
Missing | 1 (0.1) | 3 (0.2) |

Oral contraceptive use ever, n (%) | 229 (30.2) | 424 (32.8) |

Family history of colon cancer, n (%) | 73 (9.6) | 139 (10.7) |

Diabetes history, n (%) | 121 (15.9) | 104 (8.0) |

Mean alcohol intake, g per day (s.d.)  
6.8 (19.1) | 6.8 (23.0) |

Abbreviation: s.d. = standard deviation.

at menarche compared with women who were ≤12 years old (HR = 0.88, 95% CI 0.76–1.01); No overall associations were found for age at menopause (regardless of hysterectomy/oophorectomy status), age at first live birth, parity, or OC use (Table 2). For CRC mortality, we found no associations between these five reproductive or menstrual factors in our analysis. Additional analyses comparing nulliparous to parous women showed no significant associations with mortality.

Compared with women who reported never use of MHT, former MHT use was not associated with all-cause mortality (HR = 1.13, 95% CI 0.89–1.43). We also found no association with CRC-specific death among former MHT users (HR = 0.98, 95% CI 0.68–1.43) compared with never MHT users. However, among women who reported current MHT use at baseline, we observed a 21% lower risk of all-cause death (HR = 0.79, 95% CI 0.66–0.94) and a 24% lower risk of CRC death (HR = 0.76, 95% CI 0.59–0.99).

Analyses of OC use, age at menarche, age at first birth, parity, and age at menopause stratified by never, former, or current MHT use showed no statistically significant interactions with all-cause or CRC-specific death (all P-values >0.1; Figures 1 and 2). Interaction terms were also not significant regardless of whether nulliparous women were included in the models.

In analyses stratified by cancer site (colon or rectum), none of the P-interaction values for the examined exposures were significant at a P<0.05 level (Table 3). However, for women with colon cancer, stratified models suggested a non-statistically significant increased risk of CRC-specific death (HR = 1.58, 95% CI 0.92–2.70) comparing women age 30+ years at first birth with women who gave birth before 20 years of age. This association was inverse, but not statistically significant, among women with rectal cancer (HR = 0.38, 95% CI 0.10–1.40).

There also appeared to be differences in associations by cancer site for MHT use and mortality. Among women with colon cancer, former and current use compared with never use were not associated with mortality. However, among women with rectal cancer, compared with never users, we found no association for former users, but among current users, we observed a significant, 39% lower risk of all-cause death (HR = 0.61, 95% CI 0.43–0.87).
and a 52% lower risk of CRC death (HR = 0.48, 95% CI 0.25–0.92). However, multiplicative interaction was not statistically significant by cancer site ($P_{\text{interaction}} = 0.980$ for all-cause mortality and $P_{\text{interaction}} = 0.531$ for CRC mortality).

Among the subset of women with information on MHT preparation, the inverse associations appeared to be stronger among women using oestrogen only compared with women using combined oestrogen–progestin therapy, although smaller numbers
may have led to a lack of statistical significance (Table 4). To assess whether tumour stage and grade differed by MHT usage status, we cross-tabulated the factors and found that the percentage of never, former, and current MHT users were similar by both tumour stage and grade.

We did not find evidence of interaction by median diagnosis age (69.8 years), median BMI (26.2 kg m⁻²), status of ovaries, or natural menopause status (all \(P\)-values > 0.1).

**DISCUSSION**

In this study of 2053 women with CRC, reproductive and menstrual factors were not associated with mortality, while current, but not former, baseline MHT use was associated with lower all-cause and CRC mortality risks.

A previous analysis in this cohort that examined reproductive history and CRC incidence reported increased risks with older age at menopause (55+ vs <40 years old, HR = 1.50, 95% CI 1.23–1.85) and age at first birth (30+ vs ≤19 years old, HR = 1.26, 95% CI 1.01–1.58); an inverse association between age at menarche (15+ vs 11–12 years old, HR = 0.73, 95% CI 0.57–0.94) and lower risk of CRC was observed only among those women with no history of MHT use (Zervoudakis et al, 2011). We did not find evidence of these patterns for mortality overall or due to CRC. The previous findings in this cohort, in combination with other prospective studies on age at first birth and CRC risk, are equivocal, as two previous studies showed no association (Tamakoshi et al, 2004; Lin et al, 2007), and a third study showed a statistically significant increased risk of developing CRC with older age at first birth (Martinez et al, 1997). One hypothesis for the observed association between reproductive factors and CRC risk is that pregnancy reduces bile acid synthesis, which affects carcinogenesis (McMichael and Potter, 1980). To our knowledge, previous studies have not examined these reproductive factors and mortality among CRC survivors.

Previous studies on MHT and CRC survival have reported variable results. Some studies have shown a ~30% lower mortality risk among women reporting oestrogen-only therapy, but not among women using combined oestrogen plus progestin therapy (Persson et al, 1996; Chan et al, 2006). The Nurses’ Health Study found 36% lower risk among current as opposed to never users, which differed by duration of use; current use <5 years was associated with a mortality HR (95% CI) of 0.59 (0.23–0.67), whereas current use for 5+ years was nonsignificant (0.83, 0.58–1.18; Persson et al, 1996).
Chan et al., 2006). Approximately 75% of the NIH study population reported use of oestrogen alone, whereas 25% reported oestrogen plus progestin use, but MHT type-stratified analyses were not presented. Two other studies without information on type of MHT have shown an ~40% lower risk of mortality among MHT users compared with non-users (Slattery et al., 1999; Mandelson et al., 2003). In contrast, a study in the Women’s Health Initiative (111 CRC cases) showed no association between conjugated equine oestrogen use and CRC mortality (Ritenbaugh et al., 2008). Our findings on MHT use and survival are generally consistent with those found in the Nurses’ Health Study, suggesting that use of MHT is associated with lower CRC mortality. Still, it is possible that lower mortality among MHT users could be due to better health surveillance of these women.

Mechanistic data support a role for endogenous oestrogen in CRC tumorigenesis and prognosis (Sato et al., 2009). In vitro studies have shown that oestrogen affects cell growth in colon cancer cell lines (Singh et al., 1994), and that oestrogen receptor-β (ER-β) protein expression is lower in malignant colon tissue (Foley et al., 2000; Barzi et al., 2013). A review of oestrogen-related molecular pathways and CRC suggested that the loss of ER-β expression during tumorigenesis can be countered by oestrogen ligands, MHT, or soy products, which perhaps may explain the importance of recent timing of hormone use in the protective association with CRC survival (Barzi et al., 2013). Previous studies in humans have also shown increased insulin sensitivity in response to oral equine oestrogens or transdermal E2 patches (Lindheim et al., 1994).

Strengths of this study include the prospective collection of data, which minimises recall bias. Our large sample size permitted separate examination of colon and rectal cancers to identify whether associations with these hormonal and menstrual factors differed by cancer site. We also had information on numerous other CRC risk and prognostic factors, as well as CRC tumour characteristics and treatment data. Limitations of this study include that only a subset of the cohort had detailed information on type of MHT, precluding detailed analyses of both type and duration of use. Also, in our study, we had only a single assessment of MHT use, which may have changed over the follow-up period.

Future studies may seek to further differentiate between mortality risk associated with specific MHT preparations, and further focus on the mechanisms through which recent oestrogen exposures may have a role in colorectal tumour progression.

Table 4. Menopausal hormone therapy and mortality risk among women with colorectal cancer by preparation (n=1245)

| Variable   | Overall mortality | | | CRC mortality | | |
|------------|-------------------|-----------------|-----------------|-----------------|-----------------|
|            | No. deaths/total | Multivariable-adjusted HR (95% CI)* | No. deaths | Multivariable-adjusted HR (95% CI)* |
| Never users | 246/642 | 1.00 | | 43/125 | 0.75 (0.52–1.08) |
| Estrogen only | 104/325 | 0.82 (0.65–1.04) | 43/125 | 0.75 (0.52–1.08) |
| Sequential EPT | 21/51 | 1.14 (0.72–1.81) | 10/51 | 1.03 (0.52–2.04) |
| Continuous EPT | 27/99 | 0.77 (0.51–1.15) | 12/99 | 0.64 (0.35–1.17) |
| Unknown type | 40/128 | 0.86 (0.61–1.21) | 20/128 | 0.91 (0.55–1.49) |

Abbreviations: CI = confidence interval; HR = hazard ratio

*Multivariable-adjusted models were adjusted for years from questionnaire to diagnosis (continuous), body mass index (18.5–25, 25–30, 30+ kg m−2), marital status (married or living as married, yes/no), smoking status (never, former, current), diabetes (yes/no), physical activity (never/rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5+ times/week), tumour stage, tumour grade (well differentiated, moderately differentiated, poorly differentiated), chemotherapy (yes/no), radiation (yes/no), and surgery (yes/no).

The authors declare no conflict of interest.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Hormones and colorectal cancer survival

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