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Estrogen Metabolites Are Not Associated with Colorectal Cancer Risk in Postmenopausal Women

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Abstract

Background: A potential protective role for estrogen in colon carcinogenesis has been suggested based on exogenous hormone use, but it is unclear from previous studies whether endogenous estrogens are related to colorectal cancer risk. These few prior studies focused on parent estrogens; none evaluated effects of estrogen metabolism in postmenopausal women.

Methods: We followed 15,595 women (ages 55–80 years) enrolled in the Breast and Bone Follow-up to the Fracture Intervention Trial (B∼FIT) who donated blood between 1992 and 1993 for cancer through December 2004. A panel of 15 estrogen metabolites (EM), including estradiol and estrone, were measured in serum from 187 colorectal cancer cases and a subcohort of 501 women not using exogenous hormones at blood draw. We examined EM individually, grouped by pathway (hydroxylation at the C-2, C-4, or C-16 position) and by ratios of the groupings using Cox proportional hazards regression models.

Results: No significant associations were seen for estrone ($HR_{Q4\ vs.\ Q1} = 1.15$; 95% CI, 0.69–1.93; $P_{trend} = 0.54$), estradiol ($HR_{Q4\ vs.\ Q1} = 0.98$; 95% CI, 0.58–1.64; $P_{trend} > 0.99$), or total EM (the sum of all EM; $HR_{Q4\ vs.\ Q1} = 1.35$; 95% CI, 0.81–2.24; $P_{trend} = 0.33$). Most metabolites in the 2-, 4-, or 16-pathway were unrelated to risk, although a borderline trend in risk was associated with high levels of 17-epiestriol.

Conclusion: Circulating estrogens and their metabolites were generally unrelated to colorectal cancer risk in postmenopausal women.

Impact: Additional studies are needed to understand how exogenous estrogen may prevent colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 24(9); 1419–22. ©2015 AACR.*

Introduction

Exogenous hormones are linked to colorectal cancer risk reduction (1, 2), yet risks associated with circulating estrogens are elevated (3, 4), or null (5). In normal colonic tissue, ERα enhances cell growth and is expressed at low levels, while the antiproliferative ERβ is abundant (6). In neoplastic colonic tissue, this is reversed. Estradiol binds to both receptors with comparably high affinity, but at least one estrogen metabolite (EM), 17-epiestriol, shows a binding preference for ERβ (7). We speculated that selective binding of EM to ERα or ERβ may influence colon carcinogenesis. Thus, we investigated the association between a panel of EM and colorectal cancer in the Breast and Bone Follow-up to the Fracture Intervention Trial (B∼FIT).

Materials and Methods

FIT, a randomized trial designed to test alendronate, screened 22,695 postmenopausal women ages 55 to 80 from 1992 to 1993, who provided a bone mineral density (BMD) scan, blood and information on demographic, lifestyle, and reproductive factors through a self-administered questionnaire. B∼FIT comprises 15,595 of the FIT screenees followed for incident cancer through December 2004. An additional questionnaire covering subsequent cancer diagnoses was sent to these participants (8).

Self-reported cancers were confirmed by medical records and/or cancer registries. Additional cases were identified from cancer registries. Vital status was determined by the National Death Index. All participants provided written informed consent, and Institutional Review Board approval was obtained from all clinical sites and the National Cancer Institute.

This analysis was part of a case–cohort study within B∼FIT examining EM in relation to colorectal cancer, breast, endometrial, and ovarian cancer (8). We studied 187 colorectal cancer cases (10 in the subcohort) and 501 subcohort women. Fifteen EM were measured in serum: estrone, estradiol, 2-hydroxyestrone, 2-methoxyestrone, 2-hydroxyestradiol, 2-methoxyestradiol,

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2-hydroxyestrone-3-methyl ether, 4-hydroxyestrone, 4-methoxyestrone, 4-methoxyestradiol, 16α-hydroxyestrone, estriol, 17-epiestriol, 16-ketoestradiol, and 16-epiestriol.

EM were examined individually, by pathway (C-2, C-4, or C-16 hydroxylation, with EM in each pathway summed), and by ratios of pathways. Cox proportional hazards regression models with robust variance adjustment were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). For cases not in the subcohort, follow-up began 6 months prior to colorectal cancer diagnosis and ended at diagnosis. For the subcohort, follow-up began at baseline and ended at colorectal cancer diagnosis for cases ($n = 10$), and death or end of the follow-up for noncases ($n = 491$). Covariates examined included body mass index (BMI), parity, smoking, postmenopausal hormone use, and ages at menarche, birth of the first child, and menopause. The final model adjusted for clinic site, trial participation status, age at blood collection, and total BMD. No adjustment was made for multiple comparisons.

Results

Descriptive characteristics and HR for lifestyle/reproductive risk factors are presented in Table 1. Compared with the subcohort, cases were older at study entry, followed for fewer years, and had

Table 1. Select characteristics and HRs[a] for lifestyle and reproductive/hormonal risk factors; colorectal cancer (CRC) case–cohort study, B∼FIT

Characteristics	CRC cases	Subcohort			*P*
Caucasian, *n* (%)	182 (97)	475 (95)			
Years follow-up, mean (SD)	5.4 (3.1)	10.2 (2.2)			<0.001
Age at blood draw, mean (SD)	69.8 (5.6)	67.3 (6.2)			<0.001
Years postmenopausal at blood draw, mean, (SD)	22.5 (8.2)	20.7 (8.8)			0.015
Bone mineral density, femoral neck g/cm, mean (SD)	0.74 (0.1)	0.77 (0.1)			0.030
	CRC cases	**Subcohort**	**HR**	**95% CI**	P_{trend}
Lifestyle risk factors					
BMI at blood draw (kg/m^2)					
<25	78	209	1.00	Referent	
25–29	72	157	1.18	(0.78–1.77)	
30–34	21	83	0.68	(0.39–1.21)	
35+	14	47	0.81	(0.40–1.65)	0.232
Regular exercise program, yes	72	228	0.98	(0.81–1.17)	0.975
Cigarette use					
Never	111	259	1.00	Referent	
Former	53	185	1.03	(0.86–1.25)	
Current	20	53	1.38	(1.06–1.81)	0.849
Recent alcohol consumption					
None (past 30 days)	95	210	1.00	Referent	
<3 days/week	50	138	0.97	(0.88–1.22)	
3–6 days/week	27	116	1.18	(0.95–1.46)	
Daily	15	37	1.13	(0.83–1.53)	0.127
Hormonal and reproductive risk factors					
Age at menarche					
<11	27	77	1.00	Referent	
12, 13	93	280	0.94	(0.55–1.61)	
14+	58	125	1.36	(0.77–2.42)	0.615
Age at first live birth					
Nulliparous	24	47	1.00	Referent	
<20	23	50	0.87	(0.41–1.85)	
20–24	71	216	0.66	(0.36–1.21)	
25–29	52	128	0.82	(0.44–1.52)	
30+	18	60	0.50	(0.24–1.07)	0.136
Parity					
Nulliparous	24	47	1.00	Referent	
1	15	60	0.35	(0.16–0.77)	
2	49	143	0.67	(0.35–1.26)	
3	47	115	0.86	(0.46–1.63)	
4+	52	136	0.75	(0.40–1.39)	0.564
Ever breastfeed, yes	103	274	1.04	(0.73–1.47)	0.984
Age at menopause					
<40	27	82	1.00	Referent	
40–44	27	81	1.23	(0.64–2.35)	
45–49	62	176	1.16	(0.65–2.08)	
50–54	60	145	1.48	(0.84–2.60)	
55+	11	17	2.51	(1.08–5.85)	0.064
Postmenopausal estrogen use					
Never	129	334	1.00	Referent	
<1 year	12	49	0.74	(0.37–1.47)	
1–4 years	30	64	1.25	(0.74–2.10)	
5–9 years	4	27	0.35	(0.12–1.04)	
10+ years	10	23	0.94	(0.41–2.15)	0.608

[a]HRs are adjusted for clinic, trial participation status, age at blood collection, and total BMD.

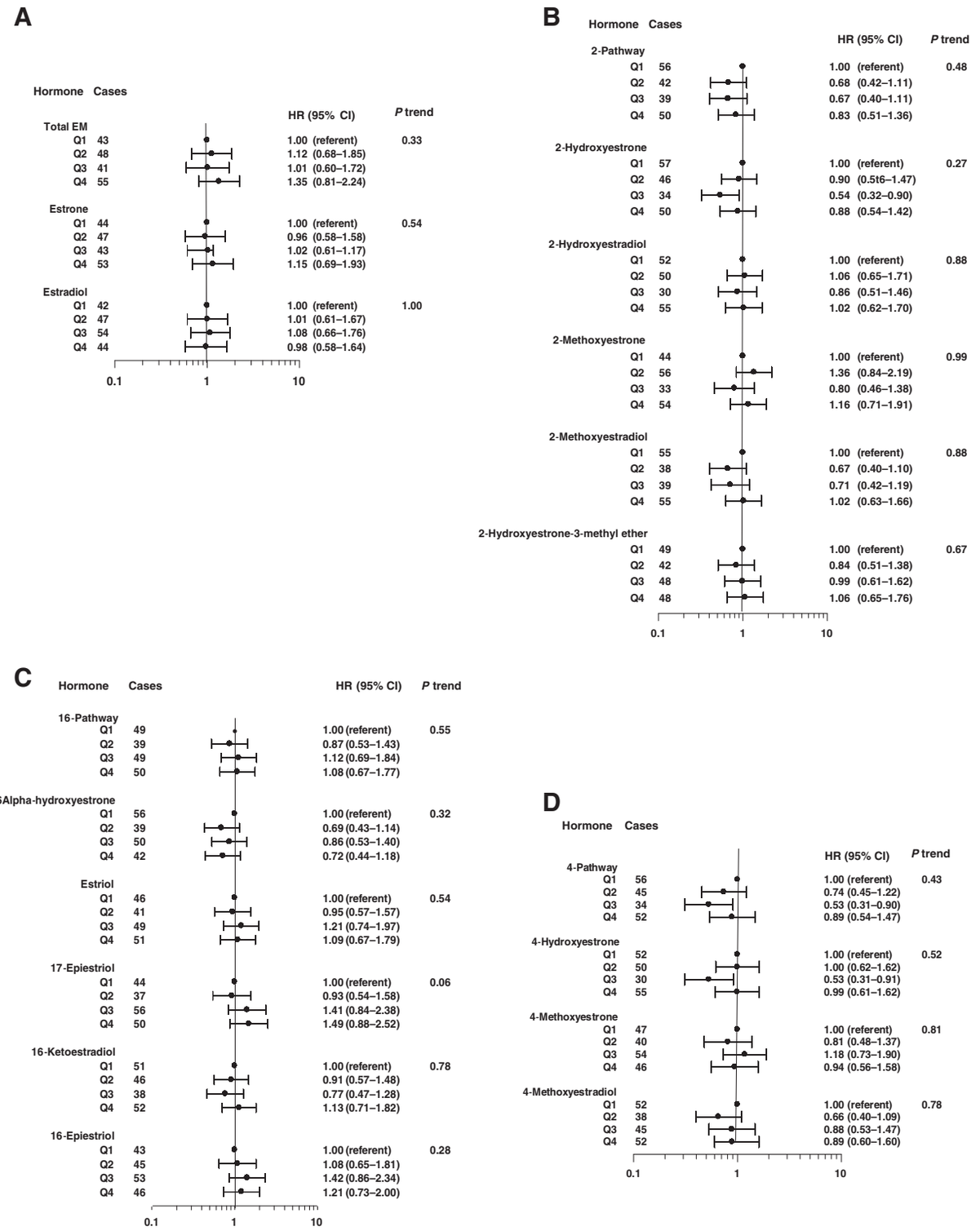

Figure 1.

A–D, HRs and 95% CIs, estrogen metabolites, and colorectal cancer [parent estrogens (A), 2-pathway (B), 16-pathway (C), and 4-pathway EM (D)]. Time scale for HR estimates is age at entry (baseline) through age at diagnosis or censoring (exit). For cases not in the subcohort, follow-up began 6 months prior to their colorectal cancer diagnosis. HRs are adjusted for clinic, age at blood draw, bone mineral density, and trial participation.

lower BMD at baseline. Current smokers experienced a 40% increased risk, and women with a late age at menopause had >2-fold excess risk, but HR for other factors were not statistically significant.

Women with higher total EM were not at elevated risk compared with those in the lowest quartile (Fig. 1A). HR for estrone and estradiol were not significant, and there was no evidence of dose response. HR and trends were not significant for 2- or 4-pathway metabolites, except for reduced risks for moderately high 2-hydroxyestrone ($HR_{Q3\ vs.\ Q1} = 0.54$; 95% CI, 0.32–0.90; Fig. 1B) and 4-hydroxyestrone ($HR_{Q3\ vs.\ Q1} = 0.53$; 95% CI, 0.31–0.91; Fig. 1D). For the 16-pathway, a trend of increasing risk with higher 17-epiestriol was suggested, but results for other metabolites were null (Fig. 1C). HR for quartiles of pathway ratios (2- vs. 4-pathway, 2- vs. 16-pathway, and 4- vs. 16-pathway) showed no association (results not shown).

Discussion

This first prospective study of EM and colorectal cancer risk found no evidence for associations with these hormones. There was a suggestion of a slight effect for 17-epiestriol, but this may have occurred by chance given the number of comparisons. Our lack of association is consistent with results from one study (5), but not others (3, 4), showing modest elevated risks for estradiol or estrone. Reasons for these disparate findings are not clear. Women in our study were older (mean age 67 vs. 60–64 in prior studies), but all involved postmenopausal women not using menopausal hormones at blood draw. The studies were of comparable size; however, unlike others, BMI was not associated with colorectal cancer in our study. Additionally, immunoassays for estrogens in prior studies may not detect the low levels in postmenopausal women.

Estrogen is not central to the etiology of colorectal cancer, but the change from predominantly ERβ expression in the healthy colon to ERα in neoplastic tissue suggests that it may afford protection in the healthy colon, but promote tumorigenesis once neoplastic changes occur. However, results from observational studies of endogenous and exogenous estrogens are not consistent (1, 2).

In summary, although our apparent lack of association between endogenous estrogens is at odds with findings of reduced risk associated with exogenous hormone use, additional well-powered studies are needed to improve our understanding of the exogenous hormone and colorectal cancer association.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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