Associations of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use with Colorectal Cancer Risk in the Women's Health Initiative

Theodore M. Brasky[1], Katrina F. Flores[2], Joseph C. Larson[3], Alison M. Newton[1], Aladdin H. Shadyab[2], Jonathan H. Watanabe[4], Dorothy S. Lane[5], Cynthia A. Thomson[6], and Andrea Z. LaCroix[2]

ABSTRACT

Background: Use of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) has been postulated to reduce cancer risk by inhibition of tumor progression, vascularization, and metastasis. The renin–angiotensin system is upregulated in colorectal cancers; however, the association of ACEi and ARB use with colorectal cancer risk is not well understood.

Methods: The study population was 142,812 Women's Health Initiative participants free of colorectal cancer who reported on ACEi and ARB use at baseline; 2,216 incident colorectal cancers were diagnosed during 10 years of follow-up. Cox regression models estimated adjusted HRs and 95% confidence intervals for associations relative to nonuse among normotensive women, untreated hypertensive women, and hypertensive women treated with other antihypertensive medications.

Results: HRs among women who used any ACEi or ARB compared with nonuse in the three referent groups ranged between 0.97 and 1.01. Findings were similar for increased ACEi/ARB duration and for medications examined as separate classes or individually.

Conclusions: In this large prospective study of women, no associations of ACEi or ARB use with colorectal cancer risk were observed.

Impact: Choice of drug in the large population of aging women who will be prescribed ACEi and ARB should be made without factoring in any benefit on colorectal cancer risk.

Introduction

Use of antihypertensive medications (AHM) has increased in the United States, with use among women consistently higher than that of men and angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) among the most commonly used medications (1).

Recent studies have suggested that renin–angiotensin system inhibitors—which include ACEi and ARB—may modify cancer risk via inhibition of tumor progression, vascularization, and metastasis (2). Importantly, angiotensin II has been shown to stimulate mitogenesis in intestinal epithelial cells (3). In addition, the renin–angiotensin system is upregulated in colorectal cancers (2), and data from experimental animal studies suggest that administration of ACEi or ARB may reduce colon tumorigenesis (4). Several epidemiologic studies have examined associations between use of ACEi or ARB and colorectal cancer risk (4–6), with mixed findings. However, prior studies have been plagued by limitations. Case–control studies have included normotensives or untreated hypertensives in their referent groups, and prospective studies—limited to record linkage analyses—had limited capacity to adjust for confounding factors. Few investigations have examined ACEi and ARB as separate classes and none has examined associations for individual medications within each class, nor estimated risks contrasted against several relevant comparison groups.

We comprehensively examined the association of ACEi and ARB use, separately and combined, with colorectal cancer risk leveraging robust data from the Women's Health Initiative (WHI), a large cohort of postmenopausal women.

Materials and Methods

Information about the WHI methods have been published previously (7). Between 1993 and 1998, 161,808 postmenopausal women, ages 50 to 79 years, were recruited into a set of four overlapping clinical trials or an observational study. Women were recruited directly into the observational study, and participation was offered to women who were screened for participation in the clinical trial but were subsequently ineligible or unwilling to participate. After the original WHI study ended in 2005, participants were invited to continue participation in three subsequent extension studies, which continued follow-up through 2020. Here, we excluded at baseline women with: prevalent (or missing) colorectal cancer (n = 1,075), indeterminate hypertension status (n = 3,643), no follow-up time (n = 651), and women missing baseline adjustment data (n = 13,627), leaving 142,812 women for analysis.

Incident, primary colorectal cancers were reported by questionnaire and confirmed by physician adjudicators after medical record review. After a median follow-up of 10.0 years, 2,185 colorectal cancers were confirmed. Normotensive and untreated hypertensive

[1]Division of Medical Oncology, The Ohio State University College of Medicine, Columbus, Ohio. [2]Division of Epidemiology, Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, California. [3]Women's Health Initiative, Fred Hutchinson Cancer Research Center, Seattle, Washington. [4]Department of Clinical Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, University of California Irvine, Irvine, California. [5]Department of Family, Population and Preventive Medicine, Renaissance School of Medicine at Stony Brook University, Stony Brook, New York. [6]The University of Arizona Cancer Center, Tucson, Arizona.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

T.M. Brasky and K.F. Flores contributed equally to this article.

Corresponding Author: Theodore M. Brasky, Division of Medical Oncology, The Ohio State University College of Medicine, 514B Tzagournis Research Facility, Columbus, OH 43210. Phone: 614-293-3772; E-mail: theodore.brasky@osumc.edu

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women at baseline who self-reported starting antihypertensive therapy during follow-up were right censored at the date of follow-up when this information was obtained. Participants were additionally censored from the analysis at the earliest date of the following occurrences: withdrawal from the study; death; loss of contact; end of the original follow-up (for participants not enrolled in the WHI extension studies); end of the extension studies; or March 1, 2019, the last available date of the WHI extension study outcome adjudication.

Women attended baseline screening visits and completed extensive baseline questionnaires. Height, weight, and blood pressure (see ref. 8) were measured by trained clinical staff. We defined untreated hypertension as no AHM use at baseline and either self-reported treatment of hypertension prior to baseline, or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at baseline. Women using AHM at baseline were considered to have treated hypertension, whereas women who did not meet these criteria and who were not using AHM were classified as normotensive. In-person medication inventories were obtained by review of participants' pill containers. This database classified brand and generic names, national drug codes, and therapeutic class codes. Information was collected on duration of current prescription medications by self-report; however, no information was collected on medications that had been discontinued prior to baseline.

In this study, use of ACEi and ARB was defined as any current use of an ACEi or ARB, including monotherapy and polytherapy with other antihypertensive medications. Separate variables were additionally created for ACEi and ARB use, and duration of their use was categorized as <1 year, 1–4.9 years, and ≥5 years (ACEi only). Because of their introduction to the U.S. market in 1995, baseline data for ARB were restricted to participants who were recruited between 1995 and 1998 and duration of use was restricted to <5 years.

Statistical analysis

To address the potential for hypertension to be an underlying contributor to colorectal cancer risk, and the potential for untreated hypertension to confound associations, we examined associations between ACEi/ARB use (n = 13,078) and colorectal cancer risk compared with nonuse in three comparison groups: (i) normotensive women (n = 78,108); (ii) untreated hypertensives women (n = 20,286); and (iii) hypertensive women treated with any other AHM (n = 31,340). Cox proportional hazards regression estimated associations between ACEi/ARB use and colorectal cancer risk relative to nonuse among referent categories. Models were adjusted *a priori* for colorectal cancer risk factors and correlates of hypertension/AHM use.

Results

Baseline characteristics of WHI participants, stratified on hypertension and treatment status, are given in Supplementary Table S1. Differences between hypertensive and normotensive women tended to be small. Untreated hypertensive women and hypertensive women treated with other AHM were generally similar with respect to their baseline characteristics.

Use of ACEi or ARB was not associated with colorectal cancer risk compared with nonuse among normotensives, untreated hypertensives, and hypertensives treated with other AHM medications (**Table 1**). Increased duration of any ACEi or ARB use or consideration of ACEi or ARB use as separate classes was also not associated with colorectal cancer risk. In a secondary analysis limited by use

Table 1. Associations of ACEi and ARB with colorectal cancer risk relative to nonuse among normotensive women, untreated hypertensive women, and hypertensive women treated with other antihypertensive medications in the WHI (n = 142,812).

		Reference population					
		Normotensive women (n = 78,108, n_{cases} = 1,051)		Untreated hypertensive women (n = 20,286, n_{cases} = 171)		Hypertensive women treated with any other AHM (n = 31,340, n_{cases} = 688)	
	n_{cases}	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
Any ACEi/ARB	275	1.05 (0.92–1.21)	1.00 (0.87–1.16)	1.03 (0.85–1.25)	1.01 (0.83–1.23)	1.00 (0.87–1.15)	0.97 (0.85–1.12)
Duration of use (years)							
<1	74	1.20 (0.95–1.52)	1.14 (0.90–1.45)	1.17 (0.89–1.54)	1.15 (0.87–1.52)	1.14 (0.90–1.45)	1.11 (0.87–1.41)
1–4.9	112	0.93 (0.77–1.14)	0.89 (0.73–1.09)	0.91 (0.72–1.16)	0.90 (0.70–1.14)	0.89 (0.73–1.09)	0.86 (0.71–1.05)
≥5	89	1.12 (0.90–1.39)	1.07 (0.85–1.33)	1.09 (0.84–1.41)	1.08 (0.83–1.39)	1.06 (0.85–1.33)	1.03 (0.83–1.29)
Any ACEi use	254	1.06 (0.93–1.22)	1.01 (0.88–1.17)	1.04 (0.85–1.26)	1.02 (0.84–1.24)	1.01 (0.88–1.17)	0.98 (0.85–1.13)
Duration of use (years)							
<1	61	1.21 (0.94–1.57)	1.15 (0.88–1.49)	1.18 (0.88–1.59)	1.16 (0.86–1.56)	1.15 (0.89–1.50)	1.11 (0.86–1.45)
1–4.9	104	0.95 (0.77–1.16)	0.90 (0.73–1.10)	0.92 (0.72–1.18)	0.91 (0.71–1.16)	0.90 (0.73–1.11)	0.87 (0.71–1.07)
≥5	89	1.13 (0.91–1.41)	1.08 (0.87–1.35)	1.11 (0.86–1.43)	1.09 (0.84–1.41)	1.08 (0.86–1.34)	1.05 (0.84–1.31)
Any ARB use	21	0.93 (0.60–1.43)	0.91 (0.59–1.41)	0.90 (0.57–1.43)	0.92 (0.58–1.45)	0.88 (0.57–1.36)	0.88 (0.57–1.36)
Duration of use (years)							
<1	13	1.11 (0.64–1.92)	1.10 (0.63–1.90)	1.08 (0.62–1.91)	1.11 (0.63–1.95)	1.05 (0.61–1.83)	1.06 (0.61–1.84)
1–4.9	8	0.81 (0.40–1.62)	0.79 (0.39–1.59)	0.79 (0.39–1.60)	0.80 (0.39–1.62)	0.77 (0.38–1.54)	0.77 (0.38–1.54)

Note: Baseline hazards are stratified on hysterectomy status, WHI Dietary Modification Trial arm (intervention, comparison, not randomized), study component (clinical trial, observational study), and WHI follow-up period (original study period, extension 1, extension 2, extension 3).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; AHM, antihypertensive medications; ARB, angiotensin receptor blockers.

[a]Adjusted for age, race/ethnicity, and education.

[b]Adjusted for age, race/ethnicity, education, diabetes, coronary heart disease, inflammatory bowel disease, colorectal cancer screening, family history of colorectal cancer, duration of estrogen-only hormone therapy, duration of combined hormone therapy, body mass index, physical activity, smoking, alcohol, nonsteroidal anti-inflammatory drug use, and red/processed meat intake.

Table 2. Associations of individual ACEi/ARB medications, monotherapy, and polytherapy with colorectal cancer risk in the WHI ($n = 142{,}812$).

		Reference population					
		Normotensive women ($n = 78{,}108$, $n_{cases} = 1{,}051$)		Untreated hypertensive women ($n = 20{,}286$, $n_{cases} = 171$)		Hypertensive women treated with any other AHM ($n = 31{,}340$, $n_{cases} = 688$)	
	n_{cases}	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
ACEi[c]							
Benazepril	23	0.98 (0.65–1.48)	0.93 (0.61–1.41)	0.95 (0.62–1.48)	0.94 (0.61–1.45)	0.93 (0.61–1.41)	0.90 (0.59–1.37)
Captopril	16	0.97 (0.59–1.59)	0.87 (0.53–1.43)	0.95 (0.57–1.58)	0.88 (0.52–1.47)	0.92 (0.56–1.52)	0.84 (0.51–1.38)
Enalapril	67	1.11 (0.86–1.42)	1.05 (0.81–1.35)	1.08 (0.81–1.44)	1.05 (0.79–1.40)	1.05 (0.82–1.35)	1.01 (0.79–1.30)
Fosinopril	15	1.23 (0.74–2.05)	1.15 (0.69–1.92)	1.20 (0.71–2.04)	1.16 (0.68–1.97)	1.17 (0.70–1.95)	1.11 (0.67–1.86)
Lisinopril	98	1.00 (0.81–1.23)	0.97 (0.79–1.20)	0.98 (0.76–1.26)	0.98 (0.76–1.26)	0.95 (0.77–1.18)	0.94 (0.76–1.16)
Quinapril	21	1.08 (0.70–1.66)	1.02 (0.66–1.58)	1.05 (0.67–1.66)	1.03 (0.65–1.63)	1.03 (0.66–1.58)	0.99 (0.64–1.53)
Ramipril	12	1.74 (0.99–3.08)	1.60 (0.91–2.84)	1.70 (0.95–3.06)	1.62 (0.90–2.91)	1.66 (0.94–2.93)	1.55 (0.88–2.75)
ARB[c]							
Losartan	21	1.03 (0.67–1.59)	1.01 (0.65–1.56)	1.01 (0.64–1.59)	1.02 (0.65–1.61)	0.98 (0.63–1.51)	0.98 (0.63–1.51)
Monotherapy							
Any ACEi/ARB Use	121	1.01 (0.83–1.22)	0.97 (0.80–1.17)	0.98 (0.78–1.24)	0.97 (0.77–1.23)	0.96 (0.79–1.16)	0.93 (0.77–1.14)
Polytherapy—ACEi/ARB use plus:							
Beta blockers	9	0.69 (0.36–1.34)	0.69 (0.35–1.32)	0.68 (0.35–1.33)	0.69 (0.35–1.35)	0.66 (0.34–1.27)	0.66 (0.34–1.28)
Calcium channel blockers	29	1.28 (0.89–1.86)	1.23 (0.84–1.78)	1.25 (0.84–1.86)	1.24 (0.83–1.84)	1.22 (0.84–1.77)	1.19 (0.82–1.72)
Diuretics	78	1.20 (0.95–1.51)	1.14 (0.90–1.44)	1.17 (0.90–1.54)	1.15 (0.87–1.50)	1.14 (0.90–1.44)	1.10 (0.87–1.39)
Multiple antihypertensive medication classes	38	1.01 (0.73–1.40)	0.95 (0.68–1.32)	0.98 (0.69–1.40)	0.96 (0.67–1.37)	0.96 (0.69–1.33)	0.92 (0.66–1.28)

Note: Baseline hazards are stratified on hysterectomy status, WHI Dietary Modification Trial arm (intervention, comparison, not randomized), study component (clinical trial, observational study), and WHI follow-up period (original study period, extension 1, extension 2, extension 3).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; AHM, antihypertensive medications.

[a]Adjusted for age, race/ethnicity, and education.

[b]Adjusted for age, race/ethnicity, education, diabetes, coronary heart disease, inflammatory bowel disease, colorectal cancer screening, family history of colorectal cancer, duration of estrogen-only hormone therapy, duration of combined hormone therapy, body mass index, physical activity, smoking, alcohol, nonsteroidal anti-inflammatory drug use, and red/processed meat intake.

[c]Moexipril, trandolapril, irbesartan, and valsartan are excluded from the analysis due to low frequencies.

frequencies and low case numbers, associations for individual mediations as well as monotherapy and polytherapy were generally similar to those observed for ACEi and ARB classes (**Table 2**).

Discussion

In this prospective cohort study of postmenopausal women, we found no association of ACEi or ARB use with colorectal cancer risk when compared with normotensive women and treated or untreated hypertensive women.

Several prior studies, including case–control and prospective record linkage studies have examined ACEi/ARB and colorectal cancer risk (4–6). Similar to our findings, neither case–control study reported a clear association between ACEi or ARB and colorectal cancer (4, 6). Our findings further agree with three prior record linkage studies (4, 5). Most recently, Htoo and colleagues (5), examined combined ACEi/ARB use among U.S. Medicare beneficiaries, and reported no association. In contrast, three prospective studies, including two from the same UK database, reported significant inverse associations for ACEi or ARB (4). The discrepancy between these findings may be due to confounding given these prior studies' limited ability to control for colorectal cancer risk factors and the inclusion of untreated hypertensives in the comparison group.

This study has several strengths, including its prospective design, long follow-up, physician confirmation of outcomes, robust consideration of potential confounders, and careful measurement of medication use. It is the first to examine associations for individual medications within ACEi and ARB classes. The study was limited in statistical power by stratifying referent groups, and lacked data on medications discontinued prior to baseline.

This study adds to a growing body of evidence that the use of ACEi and ARB for hypertension control in postmenopausal women is not associated with colorectal cancer risk. These findings suggest that choice of drug in the large population of aging women who will be prescribed AHM should be made without factoring in any benefit on risk of colorectal cancer.

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Authors' Contributions

T.M. Brasky: Conceptualization, formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **K.F. Flores:** Conceptualization, formal analysis, writing–original draft, writing–review and editing. **J.C. Larson:** Formal analysis, writing–original draft, writing–review and editing. **A.M. Newton:** Writing–review and editing. **A.H. Shadyab:** Writing–review and editing.

J.H. Watanabe: Writing–review and editing. **D.S. Lane:** Data curation, writing–review and editing. **C.A. Thomson:** Data curation, writing–review and editing. **A.Z. LaCroix:** Data curation, writing–review and editing.

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A short list of WHI Investigators:

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, MD) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller

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Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (University of Nevada, Reno, NV) Robert Brunner

Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Mark Espeland

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