Published in final edited form as:

Ann Epidemiol. 2015 October ; 25(10): 788–793. doi:10.1016/j.annepidem.2015.05.009.

A prospective analysis of diet quality and endometrial cancer among 84,415 postmenopausal women in The Women's Health Initiative

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Abstract

Purpose—Endometrial cancer is the most commonly diagnosed gynecological cancer, but no convincing dietary risk factors for this cancer have been identified. Among postmenopausal women, we examined how four key a-priori diet quality indices—the Healthy Eating Index-2010 (HEI), Alternative Healthy Eating Index-2010 (AHEI), alternate Mediterranean Diet (aMED), and Dietary Approaches to Stop Hypertension (DASH) are related to risk of endometrial cancer in the Women's Health Initiative Clinical Trials and Observational Study.

Methods—Our prospective cohort study included 84,415 postmenopausal women with a uterus who completed a food frequency questionnaire at enrollment. Cox proportional hazards models were used to estimate multivariate hazard ratios and 95% confidence intervals for endometrial cancer associated with increasing quintiles of diet quality index scores.

Results—During 13.3 years of follow-up, 1,392 endometrial cancer cases occurred. After adjustment for known risk factors, having better diet quality (Q5 vs. Q1) was not associated with risk of endometrial cancer, as evidenced using HEI (HR: 1.11, 95% CI: 0.93, 1.33), AHEI (HR: 0.98, 95% CI: 0.82, 1.17), aMED (HR: 0.98, 95% CI 0.82, 1.17), or DASH (HR: 1.00, 95% CI 0.84, 1.19).

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Conclusion—Diet quality was not associated with endometrial cancer risk in this large cohort of postmenopausal women.

Keywords

diet quality; endometrial cancer; prospective cohort study

INTRODUCTION

In 2015, it is expected that 54,870 women will be diagnosed with endometrial cancer, and most of these cases will be among women over age 60[1]. Endometrial cancer is the most commonly diagnosed gynecological cancer, and the American Institute for Cancer Research (AICR) and World Cancer Research Fund's (WCRF) Continuous Update Project (CUP) found convincing evidence that excess body weight is a cause of endometrial cancer. However, no convincing dietary risk factors for endometrial cancer were identified [2]. Higher glycemic load and lower consumption of coffee were identified as probable risk factors [2], but the evidence on how macro- and micro-nutrients relate to endometrial cancer are mixed.

Although it is important to understand the role of individual dietary constituents, foods are not consumed in isolation. There are inherent statistical limitations with the single-nutrient approach because intakes are often inter-correlated [3]. Diet quality indices address the complexity of the diet and the likely interaction between multiple diet components [4], preserve some of the multidimensional aspects of food. Further, they address the biological interaction between nutrients and have relevance for interventions and dietary guidance. To date, only two small case-control studies and one prospective study have examined the association of diet quality and endometrial cancer; one using factor analysis found lower odds of endometrial cancer associated with a plant-based dietary pattern [5]; another found no association between the Healthy Eating Index-2005 score and endometrial cancer [6]; and another found no association between the Recommended Food Score and endometrial cancer [7]. The Women's Health Initiative (WHI) presents a key and unique opportunity to study this relationship prospectively among postmenopausal women, strengthen the scientific evidence-base on diet quality and endometrial cancer, and inform the AICR/WCRF CUP. To build on our previous work on diet quality and other chronic disease outcomes in the Dietary Patterns Methods Project [8-10] and grow the evidence base on diet quality and endometrial cancer. Among postmenopausal women with a uterus in the WHI Clinical Trials (CT) and Observational Study (OS), we examined how four key commonly-used a-priori diet quality indices— the Healthy Eating Index-2010 (HEI) [11-13], Alternative Healthy Eating Index-2010 (AHEI) [14, 15], alternate Mediterranean Diet (aMED) [16], and Dietary Approaches to Stop Hypertension (DASH) [17], are related to risk of endometrial cancer.

METHODS

The WHI has been previously described in depth [18-20]. Briefly, between 1993 and 1998 through 40 clinical centers, postmenopausal women who were 50-79 years at study entry

were recruited into either a CT component (n=68,132) or the OS (n=93,676 women). The CT and OS were closed in 2004-2005 and the participants were invited to continue being followed in the WHI Extension Study I (2005-2010) which ended September 30, 2010. Participants consenting to joining the Extension Study 2 (2010-2015) continue to be followed. Written informed consent was obtained from all study participants. Procedures and protocols were approved by institutional review boards at all participating institutions. A standardized written protocol, centralized training of staff, and quality assurance visits by the Clinical Coordinating Center were used to ensure uniform data collection.

The present sample was drawn from the 161,808 women participating in the WHI CT and OS. Of these, we excluded women with a hysterectomy at baseline (n=67,868), history of cancer other than non-melanoma skin cancer (n=6242), implausible energy intake (<600 or >5000 kcal/day; n=2205), incomplete diet data (n=168), missing measured height and weight (n=765), or missing follow-up time (n=327), resulting in 84,415 women in our analytic sample..

At enrollment, participants self-reported age, demographic characteristics, health behaviors, postmenopausal estrogen plus progesterone hormone use (HT), and medical histories using self-administered standardized questionnaires. We categorized risk factors as follows: race/ethnicity (white, Black, Hispanic, other, missing); education (high school or below, some college, college, postgraduate, missing); Metabolic Equivalent of Task (MET) hours of physical activity/wk (0; 0.1-3; 3.1 to 8.9; 9+; missing); oral contraceptive use (ever, never); age at first live birth (nulliparous, <20 years, 20-29 years, 30+ years, missing); HT (never, former, current); and diabetes (no, yes).

At the clinic visit, trained staff measured each participant's weight and height using a standardized protocol. Body mass index (BMI) was calculated and we categorized BMI levels (<18.5; 18.5 to <25; 25 to <30; 30 to <35; >35 kg/m²).

Diet assessment

Diet was measured at enrollment using a self-administered food frequency questionnaire (FFQ) developed and validated specifically for WHI [21], adapted from the Health Habits and Lifestyle Questionnaire [22]. The WHI-FFQ was designed to capture foods relevant for multiethnic and geographically diverse population groups, and has been shown to produce reliable (r all nutrients=0.76) and comparable estimates to 8 days of dietary intake from four 24-hour dietary recalls and 4-day food records (r= 0.37, 0.62, 0.41, and 0.36 for energy intake, percent energy from fat, carbohydrate, and protein, respectively) [21]. The three sections of the WHI FFQ included 122 composite and single food line items asking about frequency of consumption and portion size, 19 adjustment questions related to type of fat intake, and 4 summary questions asking about the usual intake of fruits and vegetables and added fats for comparison with information gathered from the line items.

The nutrient database used to analyze the WHI-FFQ was derived from the Nutrition Data Systems for Research (NDS-R, version 2005, University of Minnesota, Minneapolis, MN) [23, 24]. NDS-R provides nutrient information for >140 nutrients and compounds including energy, saturated fat, and sodium. We measured diet quality with the following indices: 1)

HEI [11] which was created by the U.S. Department of Agriculture and the National Cancer Institute and aligns with the 2010 U.S. Dietary Guidelines for Americans [25]; 2) AHEI which was created based on dietary guidance with modification to include factors especially important for cardiovascular disease prevention [14]; 3) aMED which reflects adherence to a Mediterranean dietary pattern [16]; and 4) DASH [17] which is based on foods and nutrients emphasized or minimized in the DASH diet tested in two randomized controlled feeding trials [26, 27]. Details about components for the diet quality indices and their contributions to total scores have been previously reported in WHI [8].

We calculated index scores using diet data in units of MyPyramid equivalents by establishing a customized link [28] between NDSR and the MyPyramid Equivalents Database version 2 [29]. We then classified index scores into quintiles to best capture the comparison of individuals scoring highest vs. lowest on components of each diet quality index (Q5 vs Q1).

Outcome assessment

Outcome ascertainment for the WHI has been described elsewhere [30]. Clinical outcomes, including incident endometrial cancer diagnoses, were self-reported semi-annually in the CT and annually in the OS. Study physicians adjudicated self-reports of malignancy by reviewing medical records and pathology reports. Each case was centrally coded by tumor registry coders to determine grade and stage. Vital status of participants was collected through annual clinical center follow-up of participants and proxies, and periodic searches of the National Death Index were conducted.

Statistical analysis

Participants were followed from study enrollment until a diagnosis of endometrial cancer, death, loss to follow-up, or the end of follow-up on September 20, 2013. Participants who did not consent to the Extension Study 1 and were alive at study closeout on September 12, 2005 were censored on that date. Participants who did not consent to Extension Study 2 and were alive at the end of Extension Study 1 on September 30, 2010 were censored on that date.

Means, standard deviations, and frequencies of demographic and lifestyle characteristics of the study sample were calculated by quintiles of index scores. Cox proportional hazards models were fit to our data using person-years as the underlying time metric. We estimated multivariate hazard ratios (HR) and 95% confidence intervals (CI) for endometrial cancer associated with increasing quintiles of index scores, with the lowest quintile as the reference group.

In addition to age and energy, we adjusted for covariates previously demonstrated to be risk factors for endometrial cancer [2]. The final model included age at study entry, daily energy intake [31], BMI, diabetes, physical activity, smoking, parity, oral contraceptive use, HT, race/ethnicity, and education. Because HEI and DASH indices do not include a specific component for alcohol, those scores were also adjusted for alcohol. Only BMI, diabetes and physical activity acted as confounders altering HRs by 10% or more; other covariates were included for comparability with extant literature [32-36, 2]. Given obesity's potential role as

a mediator of the relationships we examined, we also chose to explore the effect of removing BMI from the final model.

Due to the difference in dietary inclusion criteria for the DM intervention arm where the participants were required to have a percent energy from fat >32% on a baseline FFQ, we also chose to also explore the associations in a sensitivity analysis excluding the women in the DM intervention arm. Given the documented relationships between BMI, HT, and endometrial cancer in WHI and extant literature [33, 37, 32, 38, 39], we also tested for interaction by BMI (normal, overweight, obese) and HT (never, former, current) using Wald chi-square tests.

All statistical analyses were conducted using SAS (version 9.3, Cary, NC). All tests were two-sided HR estimates with corresponding p-values < 0.05 were considered statistically significant.

Results

Across diet quality indices, women with a better vs. poor quality diet (Q5 vs. Q1) were older, had lower BMIs (although still overweight) and higher physical activity levels, were more likely to be current users of HT, college graduates, non-Hispanic White, and nulliparous, and less likely to have diabetes or be current smokers (**Table 1**).

During 13.3 (SD=4.4) years of follow up, 1392 endometrial cancer cases were documented. As shown in Table 2, in multivariate models, having better quality diet was not associated with a reduced risk of endometrial cancer, as evidenced using HEI (HR: 1.11, 95% CI: 0.93, 1.33), AHEI (HR: 0.98, 95% CI: 0.82, 1.17), aMED (HR: 0.98, 95% CI 0.82, 1.17), or DASH (HR: 1.00, 95% CI 0.84, 1.19). Hazard ratios in models without BMI as a covariate were also close to 1.0 and statistically non-significant. In a sensitivity analysis excluding women in the Intervention arm of the DM trial, results were similar (data not shown).

None of the tests for interactions by HT were statistically significant (data not shown). The test for interaction by BMI was statistically significant for DASH, but in stratified analyses, all HRs remained non-significant and with no clear pattern (normal: HR=0.88, 95% CI=0.63, 1.22; overweight: HR=1.23, 95% CI=0.87, 1.75; obese: HR=0.99, 95% CI=0.76, 1.29).

Discussion

In this study of 84,415 postmenopausal women, we did not observe an association between four recognized diet quality indices and risk of endometrial cancer. Obesity is a known, independent, and strong risk factor for endometrial cancer [2], especially among women who have never used postmenopausal HT [40]. Therefore, it is biologically plausible that diet quality alone, after menopause, may not independently influence endometrial cancer risk.

Our study is the largest to examine this etiologic relationship in a prospective design, and builds on work linking diet quality and other chronic disease outcomes in the Dietary

Patterns Methods Project [8, 9]. Additional advantages of the present study include long-term follow-up, large number of cases, high quality data on covariates including objectively measured height and weight, variation in diet quality scores, and the use of the multidimensional diet quality indices which capture the potentially synergistic nature of multiple important dietary components [41] and permit comparisons among study populations. Study limitations include measurement error inherent to the FFQ [42] and to other self-report measures of health behaviors.

Our study suggests that the consumption of a diet after menopause that is consistent with HEI, AHEI, aMED, and DASH may not be an independent risk factor for subsequent endometrial cancer.

Acknowledgments

This work was supported by the Division of Cancer Control and Population Sciences of the National Cancer Institute. The Women's Health Initiative study is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221.

We thank the Women's Health Initiative investigators, staff, and the trial participants for their outstanding dedication and commitment.

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Additional Information: A full list of all the investigators who have contributed to Women's Health Initiative science appears at <https://cleo.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf>.

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Table 1
Baseline Descriptive Characteristics of Participants in the Women's Health Initiative (1993-2013) Based on Lower (Q1) and Upper (Q5) Quintiles of Diet Quality Index Scores (n=84,415)

Characteristic	HEL-2010				AHEI-2010				aMED				DASH			
	Quintile 1		Quintile 5		Quintile 1		Quintile 5		Quintile 1		Quintile 5		Quintile 1		Quintile 5	
	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%
Total no. of subjects	16883		16883		16883		16883		14708		21413		19027		18817	
Age	61.7 (0.05)		64.2 (0.05)		62.2 (0.05)		63.3 (0.06)		62.6 (0.06)		63.1 (0.05)		61.7 (0.05)		63.9 (0.05)	
Energy intake (kcal)	1879 (6)		1471(4)		1753 (5)		1613 (4)		1392 (4)		1881 (4)		1574(5)		1740 (4)	
Alcohol (g)	5.3 (0.1)		5.2 (0.06) ^b		4.5 (0.09)		7.1 (0.07)		4.7 (0.09)		6.6 (0.07)		5.2 (0.08)		5.4 (0.07)	
MET-h/wk	7.1 (0.1)		14.5 (0.2)		6.8 (0.1)		15.5 (0.2)		7.6 (0.1)		14.0 (0.1)		7.0 (0.1)		15.2 (0.1)	
Body mass index	29.3 (0.05)		26.0 (0.04)		29.2 (0.05)		26.1 (0.04)		28.6 (0.05)		26.7 (0.04)		29.0 (0.05)		26.1 (0.04)	
Race/Ethnicity																
Non-Hispanic white	79		89		81		88		82		88		75		92	
Black	11		5		11		4		8		5		12		3	
Hispanic	6		2		5		2		5		2		6		2	
Other	4		4		3		6		4		4		6		3	
Education (% college graduate)	32		53		30		58		31		55		30		57	
E+P postmenopausal hormone therapy																
Never	67		58		67		56		66		57		66		58	
Former	9		10		9		9		9		10		9		9	
Current	25		32		24		34		25		33		25		32	
Diabetes (% yes)	14		10		15		10		13		11		15		10	
Oral contraceptive use (% ever)	44		40		42		43 ^b		41		44 ^a		44		41	
Current Smoker (%)	13		3		11		3		11		4		12		3	
Nulliparous (%)	13		14 ^a		12		14		12		14 ^a		12		14	
Participant in DM trial	44		16		39		21		36		26		42		18	

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Characteristic	HEI-2010					AHEI-2010					aMED					DASH				
	Quintile 1		Quintile 5		Mean (SE)	Quintile 1		Quintile 5		Mean (SE)	Quintile 1		Quintile 5		Mean (SE)	Quintile 1		Quintile 5		Mean (SE)
	%	%	%	%		%	%	%	%		%	%	%	%		%	%	%	%	
Participant in HT trial	22	16	22	14		22	16	21	16		21	16	22	16		22	22	15	15	
Participant in OS	43	71	46	67		46	71	49	62		49	62	44	62		44	44	70	70	
Healthy Eating Index (HEI-2010), Alternate Healthy Eating Index (AHEI-2010), alternate Mediterranean Diet Score (aMED), Dietary Approaches to Stop Hypertension (DASH). Range of index points for quintiles of indices were as follows: (HEI-2010: 17-56; 56-63; 63-68; 68-74; 74-96; AHEI: 15-44; 44-50; 50-55; 55-62; 62-96; aMED: 0-2; 3; 4; 5; 6-9; DASH: 8-20; 21-22; 23-25; 26-27; 28-38)																				
All p-values for continuous (test for trend) and categorical variables (chi-square) were statistically significant at p<0.0001 unless otherwise noted																				
^a p<0.0007																				
^b not statistically significant																				

TABLE 2
Risk of Endometrial Cancer According to Quintiles of Baseline Diet Quality Index Scores in WHI (n=84,415)

	N	Cases	Multivariate HR	95% CI	P-contrast _{Q5:Q1}	Multivariate HR	95% CI	P-contrast _{Q5:Q1}	Multivariate HR	95% CI	P-contrast _{Q5:Q1}
HEI ^b											
Q1	16883	272	1.00			1.00			1.00		
Q2	16883	312	1.16	0.99, 1.37		1.13	0.96, 1.33		1.17	0.99, 1.37	
Q3	16883	265	0.98	0.83, 1.17		0.95	0.80, 1.13		1.01	0.84, 1.20	
Q4	16883	263	0.98	0.83, 1.17		0.94	0.79, 1.13		1.02	0.85, 1.22	
Q5	16883	280	1.05	0.88, 1.25	0.577	1.00	0.83, 1.20	0.977	1.11	0.93, 1.33	0.256
AHEI											
Q1	16883	284	1.00			1.00			1.00		
Q2	16883	268	0.95	0.80, 1.12		0.94	0.80, 1.11		0.96	0.82, 1.14	
Q3	16883	302	1.06	0.90, 1.24		1.04	0.88, 1.22		1.09	0.93, 1.29	
Q4	16883	270	0.94	0.79, 1.11		0.91	0.77, 1.08		0.97	0.82, 1.15	
Q5	16883	268	0.92	0.80, 1.09	0.334	0.89	0.75, 1.06	0.197	0.98	0.82, 1.17	0.827
aMED											
Q1	14708	227	1.00			1.00			1.00		
Q2	15020	224	0.93	0.77, 1.11		0.92	0.76, 1.11		0.96	0.79, 1.15	
Q3	17088	296	1.03	0.86, 1.22		1.01	0.84, 1.20		1.05	0.88, 1.26	
Q4	16186	284	1.00	0.83, 1.19		0.97	0.81, 1.16		1.04	0.87, 1.25	
Q5	21413	361	0.91	0.77, 1.08	0.282	0.88	0.74, 1.05	0.154	0.98	0.82, 1.17	0.789
DASH ^b											
Q1	19027	286	1.00			1.00			1.00		
Q2	12306	192	1.00	0.83, 1.20		0.97	0.80, 1.16		0.99	0.83, 1.20	
Q3	21511	384	1.10	0.94, 1.28		1.05	0.89, 1.22		1.10	0.94, 1.28	
Q4	12754	224	1.05	0.88, 1.25		0.99	0.83, 1.19		1.07	0.89, 1.28	
Q5	18817	306	0.95	0.81, 1.12	0.562	0.89	0.75, 1.06	0.189	1.00	0.84, 1.19	0.994

^aModel 1 is adjusted for age, energy intake, ethnicity, education, MET-h/week leisure time physical activity, diabetes status, postmenopausal hormone replacement therapy use, oral contraceptive use, age at first birth, participant in Observational Study, participant in HT trial, participant in DM trial

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γ Additionally adjusted for alcohol because alcohol not included in diet quality score as a separate component

γ Model 2=Model 1 + body mass index (categorical)