Brief communication

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

Stephanie M. George PhD, MPH, MA [a,*], Rachel Ballard MD, MPH [a], James M. Shikany DrPH, PA-C [b], Tracy E. Crane MS, RD [c,d,e], Marian L. Neuhouser PhD, RD [f]

[a] Office of Disease Prevention, National Institutes of Health, Bethesda, MD
[b] Division of Preventive Medicine, School of Medicine, University of Alabama at Birmingham, Birmingham
[c] Department of Nutritional Sciences, University of Arizona, Tucson
[d] University of Arizona Cancer Center, University of Arizona, Tucson
[e] Mel & Enid Zuckerman College of Public Health, University of Arizona, Tucson
[f] Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

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ABSTRACT

Purpose: Endometrial cancer is the most commonly diagnosed gynecologic 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, Alternative Healthy Eating Index-2010, alternate Mediterranean Diet, and Dietary Approaches to Stop Hypertension are related to the 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 (HRs) and 95% confidence intervals (CIs) for endometrial cancer associated with increasing quintiles of diet quality index scores.
Results: During 13.3 years of follow-up, 1392 endometrial cancer cases occurred. After adjustment for known risk factors, having better diet quality (Q5 vs. Q1) was not associated with the risk of endometrial cancer, as evidenced using Healthy Eating Index-2010 (HR: 1.11, 95% CI: 0.93–1.33), Alternative Healthy Eating Index-2010 (HR: 0.98, 95% CI: 0.82–1.17), alternate Mediterranean Diet (HR: 0.98, 95% CI: 0.82–1.17), or Dietary Approaches to Stop Hypertension (HR: 1.00, 95% CI: 0.84–1.19).
Conclusions: Diet quality was not associated with endometrial cancer risk in this large cohort of postmenopausal women.

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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 more than the age of 60 years [1]. Endometrial cancer is the most commonly diagnosed gynecologic cancer, and the American Institute for Cancer Research and World Cancer Research Fund's Continuous Update Project 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 macronutrients and micronutrients relate to endometrial cancer is 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 intercorrelated [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. Furthermore, 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

* Corresponding author. Office of Disease Prevention, National Institutes of Health. 6100 Executive Blvd, Suite 2B03, Bethesda, MD 20982. Tel.: +1-301-451-9416; fax: +1-240-276-7906.
E-mail address: stephanie.george@nih.gov (S.M. George).

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 American Institute for Cancer Research and World Cancer Research Fund's Continuous Update Project. To build on our previous work on diet quality and other chronic disease outcomes in the Dietary Patterns Methods Project [8—10], 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 the 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 1 (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 nonmelanoma skin cancer ($n = 6242$), implausible energy intake (<600 or >5000 kcal/d; $n = 2205$), 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 (hormone therapy [HT]), and medical histories using self-administered standardized questionnaires. We categorized risk factors as follows: race and/or ethnicity (white, black, Hispanic, other, and missing); education (high school or below, some college, college, postgraduate, and missing); metabolic equivalent of task hours of physical activity per week (0, 0.1—3, 3.1—8.9, ≥ 9, and missing); oral contraceptive use (ever and never); age at first live birth (nulliparous, <20 years, 20—29 years, ≥ 30 years, and missing); HT (never, former, and current); and diabetes (no and 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, and >35 kg/m^2).

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 four 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 (NDSR, version 2005; University of Minnesota, Minneapolis, MN) [23,24]. NDSR provides nutrient information for more than 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 versus 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 semiannually 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 (HRs) and 95% confidence intervals (CIs) for endometrial cancer associated with increasing