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Original Contribution

Associations of a Healthy Lifestyle Index With the Risks of Endometrial and Ovarian Cancer Among Women in the Women's Health Initiative Study

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Lifestyle-related factors influence risk of endometrial and ovarian cancers, but few studies have examined their joint associations with risk of these cancers. Using multivariable Cox regression models, we assessed the association of a healthy lifestyle index (HLI—a composite score (range, 0–20) involving diet, alcohol consumption, physical activity, body mass index, and smoking; higher scores represent healthier behavior) with risk of endometrial and ovarian cancers among 108,136 postmenopausal women who were recruited in the US Women's Health Initiative study between 1993 and 1998. After a median follow-up of 17.9 years, 1,435 endometrial cancer cases and 904 ovarian cancer cases had been ascertained. Women in the highest quintile of the HLI score had a lower risk of overall, type I, well-differentiated, moderately differentiated, poorly differentiated, and localized endometrial cancer than those in the lowest quintile (for quintile 5 vs. quintile 1, hazard ratio (HR) = 0.61 (95% CI: 0.51, 0.72), HR = 0.60 (95% CI: 0.49, 0.72), HR = 0.66 (95% CI: 0.46, 0.96), HR = 0.69 (95% CI: 0.52, 0.90), HR = 0.49 (95% CI: 0.34, 0.72), and HR = 0.61 (95% CI: 0.50, 0.74), respectively). The HLI score had a weak positive association with risk of serous ovarian cancer. Our findings underscore the potential importance of a healthy lifestyle in lowering endometrial cancer risk among postmenopausal women.

alcohol intake; BMI; diet score; endometrial cancer; healthy lifestyle index score; ovarian cancer; physical activity; smoking

Abbreviations: BMI, body mass index; CI, confidence intervals; HLI, healthy lifestyle index; HR, hazard ratio; HT, hormone therapy; WHI, Women's Health Initiative.

Epidemiologic evidence suggests that specific lifestyle-related factors might influence risk of endometrial cancer (1–4). Obesity, in particular, has been strongly associated with increased risk of endometrial cancer (1, 2), possibly through its effects on levels of circulating estrogens and inflammatory factors (5–9). Further, some studies have suggested that foods with high glycemic load might be associated with increased risk of this cancer (1, 2), while lifestyle-related risk factors with antiestrogenic and/or antioxidant properties, such as physical activity and smoking, might be associated with lower risk (1, 3, 4, 10, 11).

It has not been well-established whether lifestyle-related factors are associated with ovarian cancer, but recent findings from the World Cancer Research Fund Continuous Update Report suggest that obesity might be associated with increased risk of ovarian cancer, particularly mucinous invasive ovarian cancer and low-grade serous ovarian cancer (12, 13). Moreover, in the Women's Health Initiative (WHI) cohort, we provided evidence indicating that a low-fat dietary pattern might be inversely associated with ovarian cancer risk (14), and, in some studies, carotenoids and phytoestrogens have also been associated with a reduced risk of ovarian cancer (15–17). A few studies have also shown an inverse association between physical activity and ovarian cancer risk, although the associations were weak (3, 4, 12).

An individual's lifestyle habits typically cluster (18, 19). In this respect, existing evidence purports that, in combination, lifestyle-related factors might contribute to a greater increase/decrease in risk of chronic diseases (e.g., cardiovascular diseases) than that associated with each factor individually (18, 19). However, only a few studies, using various lifestyle indices, have assessed the combined association of lifestyle-related

risk factors—namely diet, alcohol consumption, physical activity, obesity, and smoking—with risk of cancers of the endometrium and ovary. Irrespective of the lifestyle index used, studies have consistently associated an overall healthy lifestyle with a reduced risk of endometrial cancer (20–23), but no associations have been observed for ovarian cancer (20–23). Differences between the associations of individual lifestyle-related factors and risk of endometrial and ovarian tumor subtypes have also been reported (6, 24, 25). However, to our knowledge, no study has investigated the combined association of these risk factors with histopathological subtypes of these cancers.

To advance our knowledge of the joint association of lifestyle-related factors with risk of endometrial and ovarian cancers, we examined the association of a healthy lifestyle index (HLI) with the risk of endometrial and ovarian cancers among women in the WHI cohort.

METHODS

Study population and design

Details of the WHI trial design and primary results have been previously published (26). Briefly, the WHI study comprised 161,808 postmenopausal women, aged 50–79 years, from major racial/ethnic groups, who were recruited at 40 US clinical centers between 1993 and 1998 (26). The WHI included an Observational Study and 4 overlapping clinical trials, including 2 hormone-therapy trials (estrogen alone or estrogen plus progesterone), a low-fat dietary modification trial, and a calcium and vitamin D supplementation trial (26). Since the completion of the original study in 2005, WHI Extension Studies (2005–2010, 2010–2020) have been initiated to gather follow-up data. All participants provided written informed consent. The study was approved by human subject review committees at the participating institutions.

For the present study, all women in the intervention group of the dietary modification arm ($n = 19{,}541$) were excluded because they were required to make dietary changes (i.e., reduce their intake of energy-dense foods while increasing their intake of fruits and vegetables and grain products), which would have skewed the diet score estimates (27). Participants were also excluded if they: 1) had implausible energy intake (i.e., <600 kcal or >5,000 kcal; $n = 4{,}543$) or 2) did not have information on follow-up time ($n = 409$). For analyses focused on endometrial cancer, we additionally excluded women who had history of hysterectomy ($n = 52{,}534$) or endometrial cancer ($n = 4{,}658$) at enrollment, leaving a total of 80,123 women available for analyses. For analyses of ovarian cancer, women with a history of bilateral oophorectomy ($n = 26{,}866$) or ovarian cancer ($n = 3{,}266$) at enrollment were additionally excluded, leaving a total of 107,183 women available for analyses.

Exposure and covariate ascertainment

Information on sociodemographic characteristics, menstrual and reproductive history, exogenous hormone use, anthropometric characteristics, family history, medical history, lifestyle factors, and dietary factors was collected at enrollment. A 122-item self-administered food frequency questionnaire was used to evaluate the participants' dietary intake (28). Participants were required to record their usual frequency of intake (from "never or less than once per month" to "2+ per day" for foods and "6+ per day" for beverages) and portion size (small, medium, or large compared with the stated medium portion size). The food frequency questionnaire has been shown to be reliable, with intraclass correlation coefficients of 0.67 for retinol, vitamin C, and vitamin B12; 0.82 for fiber; 0.84 for magnesium; 0.92 for alcohol; and 0.74 for percentage of energy from fat (mean intraclass correlation coefficient = 0.76) (28). With respect to history of cigarette smoking, current and former smokers reported the age at smoking initiation, number of cigarettes smoked daily, and years of smoking; former smokers additionally reported age at quitting smoking. Weight and height were measured by trained staff at baseline. Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared and categorized according to the World Health Organization's criteria (29). Physical activity was summarized in metabolic equivalent-hours/week by multiplying the number of hours per week of leisure-time physical activity by the metabolic equivalent value of the activity and summing over of all types of activities (30).

Healthy lifestyle index

The HLI was developed based on existing scientific knowledge and on public health guidelines for cancer prevention (21, 31–35). The score is a combination of 5 common lifestyle-related factors—including diet, alcohol consumption, physical activity, BMI, and smoking—that have been associated with risk of chronic diseases including cancer (21, 31–35). For the dietary component, energy-adjusted deciles of 6 dietary components (cereal fiber, red and processed meat, the ratio of polyunsaturated to saturated fat, trans-fats, glycemic load, and fruits and vegetables) were created using the residual method (34, 36). The deciles were scored from 0 (lowest decile) to 9 (highest decile) (and vice-versa for red/processed meat, trans-fat, and glycemic load). The individual scores were then summed and categorized into quintiles (37). The healthy lifestyle index score was then constructed by summing the scores of diet (5th quintile = 4, 4th quintile = 3, 3rd quintile = 2, 2nd quintile = 1, 1st quintile = 0) and other lifestyle factors (smoking: never smoked = 4, former smoker ≤15 pack years = 3, former smoker >15 pack years = 2, current smoker ≤15 pack years = 1, current smoker >15 pack years = 0; alcohol intake: <6.0 g/day = 4, 6.0–11.9 g/day = 3, 12.0–24.9 g/day = 2, 24.0–59.9 g/day = 1, ≥60 g/day = 0; physical activity based on metabolic equivalent tasks: 5th quintile = 4, 4th quintile = 3, 3rd quintile = 2, 2nd quintile = 1, 1st quintile = 0; and BMI: <25.0 = 4, 25.0–29.9 = 3, 30.0–34.9 = 2, 35.0–39.9 = 1, ≥40.0 = 0). The final score ranged from 0 to 20, with 20 being the healthiest behaviors. The healthiest behavior was characterized by consuming a healthy diet (5th quintile), avoidance of smoking, avoidance of alcohol, high physical activity level (5th quintile), and a normal BMI (<25).

Outcome ascertainment

The outcomes were primary invasive endometrial and ovarian cancers. Information on endometrial and ovarian cancers was collected semiannually in the clinical trials groups and

annually in the Observational Study group, using in-person, mailed, or telephone questionnaires. Cancer diagnoses and tumor characteristics (histological subtype, grade, and stage) were then adjudicated centrally by trained physicians, who reviewed medical records and pathology reports. Endometrial and ovarian cancer histological subtypes were defined in accordance with International Classification of Diseases for Oncology, Third Edition. For endometrial cancer, type I tumors included adenocarcinoma (not otherwise specified) or endometrioid adenocarcinoma, while type II tumors included papillary, clear cell, and serous adenocarcinomas, as well as carcinosarcomas. Histological subtypes for ovarian cancer included serous tumors and nonserous tumors, namely endometrioid, clear cell, mucinous, and other-epithelial subtypes. Tumor grade and stage were coded using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) coding system (38). Tumor grade was classified as well, moderately, or poorly differentiated. Due to the small number of well-differentiated ovarian tumors (n = 25), this group was not included in the subtype analyses. Tumor stage was classified as localized or regional/distant metastatic. Vital status was collected through follow-up with participants and proxies and linkage to the National Death Index.

Statistical analyses

Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals for the associations between the HLI score (categorized by quintiles; participants who did not have complete information on the individual components were excluded from analyses involving the HLI) and risk of invasive endometrial and ovarian cancers. Women were followed up from their date of enrollment until the date of diagnosis of endometrial or ovarian cancer, and noncases contributed person-time from their date of enrollment until date of death, date of withdrawal from the study, date of hysterectomy (for endometrial cancer analyses), or until the end of follow-up (September 30, 2016), whichever came first. Participants were censored (noncases) if they died, withdrew from the study before the end of follow-up or had a hysterectomy during follow-up (for endometrial cancer analyses), or did not develop endometrial or ovarian cancer by the end of follow-up. After a median follow-up time of 17.9 years (interquartile range, 9.0–19.4), 1,435 endometrial cancer cases and 904 ovarian cancer cases had been diagnosed. Regression models were adjusted for age at baseline (continuous), ethnicity (white, black, Hispanic, other), education (high school or less, postsecondary or some college, graduate school or some graduate school), nonalcohol energy intake (continuous), age (years) at menarche (>12, 12–13, ≥14), parity (never been pregnant or no term pregnancy, 1, 2, 3, ≥4), combined estrogen and progestin therapy (never, former, current), unopposed estrogen therapy (never, former, current), oral contraceptive use (yes/no), age (years) at menopause (>45, 45–54, ≥55), and family history of endometrial or ovarian cancer (yes/no). The association of the HLI score with overall risk of endometrial and ovarian cancer among the subgroup of women with available clinicopathological information was also examined. For the subgroup analyses, we censored subtypes that were not in the event group of interest. Joint Cox proportional hazards models were created to simultaneously compare hazard ratios for the association between the HLI score and risk of endometrial or ovarian cancer subtypes, and the difference in these associations across subtype was assessed using a Wald test (39).

Given that hormone therapy (HT) use is a risk factor for endometrial and ovarian cancers (6, 40), we also performed analyses stratified by baseline HT status to determine whether HT use is an effect modifier for the association between the HLI score and risk of endometrial and ovarian cancers. For the stratified analyses, the stratification variable was excluded from the multivariable models. P values for interaction were computed by introducing an interaction term in the regression models and testing its coefficient with the Wald test.

In analyses involving the individual components of the HLI score, the models adjusted for the aforementioned covariates as well as the other individual components of the score.

P values for trend were calculated including the ordinal HLI variable as a continuous variable in the regression models. Use of Schoenfeld residuals showed that the proportional hazards assumption was not violated. In sensitivity analyses to assess the possibility of reverse causation, women who developed endometrial or ovarian cancer within 2 years of enrollment were excluded.

All P values were 2-sided. All statistical analyses were performed using Stata, version 14.1 (StataCorp LLC, College Station, Texas).

RESULTS

Table 1 provides a summary of the study population's characteristics. Women with an HLI in the healthiest behavior category were slightly older, were more likely to have postcollege education and be current HT users, and had lower energy intake than those in the other HLI categories.

Table 2 shows the association between the HLI score and risk of endometrial cancer overall and according to clinicopathological characteristics. Compared with women in the lowest category of the HLI score (≤10), women in the highest quintile (≥16) had a 39% lower risk of endometrial cancer overall (hazard ratio (HR) = 0.61, 95% confidence interval (CI): 0.51, 0.72). Similarly, the uppermost quintile of the HLI score was inversely associated with risk of type 1 (HR = 0.60, 95% CI: 0.49, 0.72), well-differentiated (HR = 0.66, 95% CI: 0.46, 0.96), moderately differentiated (HR = 0.69, 95% CI: 0.52, 0.90), poorly differentiated (HR = 0.49, 95% CI: 0.34, 0.72), and localized (HR = 0.61, 95% CI: 0.50, 0.74) tumors. These associations were also observed when considering the continuous HLI score. Inverse but statistically nonsignificant associations were also observed for risk of type II or regional/distant tumors. There was no evidence to suggest heterogeneity in the associations of the score with the clinicopathological characteristics.

Exclusion of obesity from the HLI score attenuated the association between the score and risk of endometrial cancer. However, there was still a tendency towards a reduced risk of endometrial cancer (i.e., overall, type 1, high grade, localized and, to a lesser extent, intermediate tumors) with higher HLI (Web Table 1, available at https://academic.oup.com/aje).

In analyses restricted to women who had never used HT, we observed an even stronger inverse association between the HLI score and risk of endometrial cancer than that seen in the overall

Table 1. Characteristics of Study Population According to Healthy Living Index Score, Women's Health Initiative Study, United States, 1995–2016

Characteristic	Healthy Living Index Score									
	≤10		11–12		13		14–15		≥16	
	No.	%	No.	%	No.	%	No.	%	No.	%
Age at entry, years[a]	62 (57–68)		63 (57–69)		63 (58–69)		64 (58–69)		64 (57–70)	
Ethnicity										
White (not of Hispanic origin)	22,316	83.8	19,174	84.8	10,273	85.1	18,410	84.6	15,565	83.0
Black or African-American	2,699	10.1	1,823	8.1	820	6.8	1,391	6.4	999	5.3
Other	1,573	5.9	1,552	6.8	946	7.8	1,904	8.7	2,130	11.4
Missing	51	0.2	50	0.2	36	0.3	61	0.3	59	0.3
Postcollege education	6,026	22.6	6,163	27.3	3,467	30.2	7,330	33.7	7,280	38.8
Age at menarche of <12 years	6,496	24.4	4,782	21.2	2,542	21.1	4,355	20.0	3,734	19.9
Nulliparous	2,970	11.2	2,603	11.5	1,415	11.7	2,637	12.1	2,258	12.0
Age at menopause of ≥55 years	3,054	11.5	2,855	12.6	1,549	12.8	2,877	13.2	2,527	13.5
WHI enrollment										
OS group	15,610	58.6	14,279	63.2	8,049	66.7	15,424	70.9	14,583	77.8
CT group	11,026	41.4	8,320	36.8	4,026	33.3	6,342	29.1	4,170	22.2
HT status										
Never user	14,425	54.2	11,257	49.9	5,823	48.3	10,067	46.3	8,489	45.3
Former user	4,023	15.1	3,352	14.8	1,813	15.0	3,243	14.9	2,733	14.6
Current user	8,179	30.7	7,973	35.3	4,426	36.7	8,440	38.8	7,514	40.1
Oral contraceptives	11,902	44.7	9,517	42.1	5,026	41.6	8,988	41.3	7,398	39.5
Nonalcohol energy intake, kcal/day[a]	1,766.2 (1,370.0–2,239.4)		1,586.3 (1,234.1–2,003.0)		1,495.6 (1,167.5–1,891.7)		1,420.0 (1,112.4–1,787.4)		1,308.8 (1,032.1–1,634.4)	

Abbreviations: CT, clinical trial; HT, hormone therapy; OS, observational study; WHI, Women's Health Initiative.
[a] Values are expressed as median (interquartile range).

Table 2. Associations Between Healthy Lifestyle Score and Risk of Endometrial Cancer Among Women From the Women's Health Initiative Study, United States, 1993–2016

Cancer Type	Healthy Living Index Score													*P* for Trend	*P* for Heterogeneity	Continuous, per Unit Increase in Score	
	≤10[a]	11–12			13			14–15			≥16						
	No. of Cases	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI			HR	95% CI
Overall	431	276	0.70	0.60, 0.82	171	0.79	0.66, 0.95	262	0.65	0.55, 0.76	217	0.61	0.51, 0.72	<0.01		0.94	0.93, 0.96
Type 1	338	216	0.70	0.59, 0.83	122	0.72	0.68, 0.98	210	0.66	0.55, 0.79	168	0.60	0.49, 0.72	<0.01		0.94	0.92, 0.96
Type II	64	44	0.75	0.51, 1.11	32	1.01	0.66, 1.56	41	0.70	0.47, 1.05	39	0.76	0.50, 1.16	0.17	0.97	0.97	0.93, 1.02
Grade																	
Well-differentiated	84	47	0.60	0.42, 0.86	32	0.72	0.48, 1.10	51	0.62	0.43, 0.88	51	0.66	0.46, 0.96	0.04		0.94	0.90, 0.98
Moderately differentiated	160	103	0.72	0.56, 0.92	70	0.90	0.68, 1.20	109	0.76	0.59, 0.98	86	0.69	0.52, 0.90	0.02		0.97	0.94, 0.99
Poorly differentiated	100	52	0.56	0.40, 0.79	29	0.57	0.37, 0.86	52	0.55	0.39, 0.77	42	0.49	0.34, 0.72	<0.01	0.75	0.92	0.89, 0.96
Stage																	
Localized	338	216	0.70	0.59, 0.83	136	0.80	0.65, 0.98	210	0.66	0.55, 0.79	173	0.61	0.50, 0.74	<0.01		0.94	0.93, 0.96
Regional/distant metastatic	78	50	0.71	0.49, 1.01	32	0.83	0.55, 1.27	50	0.71	0.49, 1.02	43	0.70	0.47, 1.03	0.08	0.46	0.97	0.93, 1.01

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Reference category was score of ≤10; adjusted for age at entry, education, nonalcohol energy intake, ethnicity, age at menarche, parity, combined estrogen and progesterone therapy, unopposed estrogen therapy, oral contraceptive use, family history of endometrial cancer, and age at menopause.

Table 3. Associations Between the Healthy Lifestyle Index Score and Risk of Endometrial Cancer According to Hormone-Therapy Status Among Women From the Women's Health Initiative Study, United States, 1993–2016

HT Status	Healthy Living Index Score													*P* for Trend	*P* for Heterogeneity	Continuous, per Unit Increase in Score	
	≤10[a]	11–12			13			14–15			≥16						
	No. of Cases	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI			HR	95% CI
Overall																	
Never user	246	129	0.63	0.51, 0.78	74	0.69	0.53, 0.89	98	0.52	0.40, 0.66	77	0.46	0.35, 0.60	<0.01		0.92	0.89, 0.93
Former user	69	33	0.53	0.35, 0.80	22	0.61	0.38, 0.99	47	0.72	0.49, 1.06	37	0.67	0.44, 1.03	0.11		0.96	0.91, 1.00
Current user	116	114	0.94	0.73, 1.22	75	1.10	0.82, 1.48	116	0.85	0.65, 1.11	102	0.83	0.63, 1.10	0.17	<0.01	0.98	0.96, 1.01
Combined estrogen and progesterone therapy[b]																	
Never user	286	150	0.63	0.52, 0.77	87	0.67	0.53, 0.86	126	0.56	0.45, 0.69	102	0.51	0.40, 0.65	<0.01		0.92	0.90, 0.94
Former user	41	24	0.63	0.38, 1.05	21	0.99	0.58, 1.70	33	0.85	0.53, 1.37	25	0.70	0.42, 1.19	0.46		0.97	0.92, 1.02
Current user	104	102	0.91	0.69, 1.20	63	1.00	0.73, 1.38	102	0.81	0.61, 1.07	90	0.79	0.58, 1.06	0.07	0.01	0.98	0.96, 1.01
Unopposed estrogen therapy[c]																	
Never user	363	227	0.69	0.58, 0.82	141	0.80	0.66, 0.97	211	0.64	0.53, 0.76	171	0.59	0.49, 0.71	<0.01		0.94	0.92, 0.96
Former user	56	37	0.65	0.43, 0.99	18	0.52	0.30, 0.88	37	0.58	0.38, 0.89	33	0.56	0.35, 0.88	0.01		0.93	0.99, 0.98
Current user	12	12	1.42	0.63, 3.21	12	2.30	1.02, 5.17	14	1.42	0.64, 3.17	12	1.25	0.53, 2.93	0.56	0.23	1.04	0.95, 1.13

Abbreviations: CI, confidence interval; HR, hazard ratio; HT, hormone therapy.

[a] Reference category was score of ≤10; adjusted for age at entry, education, nonalcohol energy intake, ethnicity, age at menarche, parity, oral contraceptive use, family history of endometrial cancer, and age at menopause.

[b] Also adjusted for unopposed estrogen.

[c] Also adjusted for combined estrogen and progesterone therapy.

Table 4. Associations Between Healthy Lifestyle Score and Risk of Ovarian Cancer Among Women From the Women's Health Initiative Study, United States, 1995–2016

Cancer Type	Healthy Living Index Score												*P* for Trend	*P* for Heterogeneity	Continuous, per Unit Increase in Score	
	≤10[a]	11–12			13			14–15			≥16					
	No. of Cases	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI			HR	95% CI
Overall	143	133	0.88	0.72, 1.07	173	0.93	0.73, 1.19	168	1.01	0.82, 1.23	141	0.96	0.77, 1.19	0.84		1.00	0.98, 1.03
Nonserous	50	48	0.79	0.55, 1.11	71	1.02	0.70, 1.49	60	0.99	0.71, 1.37	47	0.93	0.65, 1.32	0.87		1.00	0.97, 1.04
Serous	58	60	1.00	0.74, 1.46	76	1.30	0.69, 1.46	82	1.30	0.96, 1.75	75	1.28	0.93, 1.76	0.04	0.41[b]	1.03	0.99, 1.07
High-grade serous	30	31	0.94	0.59, 1.51	17	0.89	0.50, 1.59	38	1.13	0.71, 1.78	28	1.00	0.61, 1.65	0.73		1.01	0.95, 1.06
Grade																	
Intermediate	30	31	1.48	0.77, 2.88	17	1.84	0.88, 3.87	38	1.97	1.03, 3.77	28	1.04	0.47, 3.77	0.43		1.05	0.98, 1.13
High	50	48	1.04	0.71, 1.52	17	1.22	0.79, 1.88	38	1.24	0.85, 1.80	28	1.18	0.79, 1.76	0.25	0.55	1.02	0.98, 1.07
Stage																	
Localized	26	17	1.54	0.95, 2.49	34	0.83	0.41, 1.67	24	1.21	0.71, 2.05	19	1.08	0.61, 1.93	0.91		1.00	0.94, 1.06
Regional/distant metastatic	97	93	0.89	0.69, 1.13	132	1.08	0.82, 1.43	123	1.17	0.92, 1.47	116	1.19	0.93, 1.53	0.03	0.15	1.03	1.00, 1.06

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Reference category was score of ≤10; adjusted for age at entry, education, nonalcohol energy intake, ethnicity, age at menarche, parity, combined estrogen and progesterone therapy, unopposed estrogen therapy, oral contraceptive use, family history of ovarian cancer, and age at menopause.

[b] *P* for heterogeneity between serous and nonserous tumors (excluding high-grade serous tumors).

Table 5. Associations Between the Healthy Lifestyle Index Score and Risk of Ovarian Cancer According to Hormone-Therapy Status Among Women From the Women's Health Initiative Study, United States, 1993–2016

HT Status	Healthy Living Index Score													*P* for Trend	*P* for Heterogeneity	Continuous, per Unit Increase in Score	
	≤10[a]	11–12			13			14–15			≥16						
	No. of Cases	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI			HR	95% CI
Overall																	
Never user	104	78	0.93	0.69, 1.25	43	0.99	0.69, 1.42	68	0.89	0.65, 1.22	56	0.87	0.62, 1.22	0.86		0.98	0.94, 1.01
Former user	31	23	0.81	0.47, 1.40	14	0.91	0.48, 1.72	29	1.01	0.60, 1.71	25	0.99	0.57, 1.74	0.76		1.02	0.96, 1.09
Current user	77	71	0.87	0.63, 1.20	43	0.92	0.63, 1.34	103	1.11	0.82, 1.51	86	1.02	0.74, 1.42	0.39	0.05	1.02	0.99, 1.06
Combined estrogen and progesterone therapy[b]																	
Never user	160	116	0.84	0.66, 1.06	68	0.91	0.68, 1.21	129	0.97	0.76, 1.23	109	0.96	0.74, 1.24	0.94		0.99	0.96, 1.02
Former user	18	18	1.01	0.52, 1.95	8	0.80	0.34, 1.86	20	1.10	0.57, 2.13	16	0.99	0.49, 2.03	0.90		1.03	0.96, 1.10
Current user	34	38	1.01	0.64, 1.61	24	1.13	0.67, 1.92	51	1.17	0.75, 1.83	42	1.03	0.64, 1.66	0.69	0.60	1.02	0.97, 1.08
Unopposed estrogen therapy[c]																	
Never user	142	121	0.95	0.75, 1.22	73	1.08	0.81, 1.44	125	0.99	0.77, 1.27	97	0.88	0.67, 1.16	0.54		0.99	0.96, 1.02
Former user	28	18	0.69	0.38, 1.25	8	0.53	0.24, 1.18	23	0.83	0.47, 1.47	26	1.05	0.59, 1.86	0.72		1.03	0.96, 1.10
Current user	42	33	0.78	0.50, 1.24	19	0.78	0.45, 1.35	52	1.13	0.74, 1.72	44	1.09	0.69, 1.70	0.30	0.05	1.02	0.97, 1.08

Abbreviations: CI, confidence interval; HR, hazard ratio; HT, hormone therapy.

[a] Reference category was score of ≤10; adjusted for age at entry, education, nonalcohol energy intake, ethnicity, age at menarche, parity, oral contraceptive use, family history of ovarian cancer, and age at menopause.

[b] Also adjusted for unopposed estrogen.

[c] Also adjusted for combined estrogen and progesterone therapy.

Table 6. Associations Between Healthy Lifestyle Score Index Components and Risk of Endometrial and Ovarian Cancers[a] Among Women From the Women's Health Initiative Study, United States, 1993–2016

HLI Component	Endometrial Cancer			Ovarian Cancer		
	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
Diet score quintiles						
≤20	330	1.00		158	1.00	
21–25	364	0.97	0.83, 1.13	211	1.15	0.93, 1.43
26–29	245	0.79	0.66, 0.94	184	1.21	0.96, 1.52
30–34	263	0.85	0.71, 1.02	177	1.16	0.92, 1.47
>34	233	0.81	0.67, 0.98	174	1.26	0.99, 1.62
P for trend			0.01			0.11
Alcohol, g/day						
<0.0	251	1.00		150	1.00	
0.1–4.9	733	1.01	0.84, 1.27	453	1.06	0.86, 1.30
5.0–9.9	153	0.87	0.71, 1.07	119	1.18	0.91, 1.51
10.0–19.9	170	0.79	0.64, 0.98	104	1.05	0.81, 1.37
>19.9	128	0.93	0.79, 1.09	78	1.22	0.92, 1.63
P for trend			0.54			0.20
Physical activity quintiles, MET-hours/week						
≤1.5	302	1.00		155	1.00	
1.6–6.0	260	0.94	0.80, 1.17	175	1.21	0.98, 1.51
6.1–12.0	282	0.91	0.77, 1.07	174	1.10	0.88, 1.37
12.1–21.5	263	0.91	0.77, 1.08	180	1.22	0.98, 1.52
>21.5	273	0.84	0.71, 0.99	182	1.10	0.88, 1.37
Missing	55			38		
P for trend			0.06			0.44
BMI[b]						
<25.0	454	1.00		354	1.00	
25.0–29.9	391	1.05	0.91, 1.21	302	0.99	0.85, 1.17
30.0–34.9	305	1.73	1.44, 2.06	157	1.10	0.91, 1.34
35.0–39.9	159	2.40	1.89, 3.05	52	1.01	0.75, 1.36
≥40	115	3.18	2.28, 4.42	33	1.29	0.89, 1.86
Missing	11			6		
P for trend			<0.01			0.25
Smoking						
Never	737	1.00		445	1.00	
Former smoker, ≤15 pack years	359	0.99	0.87, 1.12	236	1.03	0.87, 1.20
Former smoker, >15 pack years	258	0.90	0.77, 1.05	164	1.13	0.94, 1.36
Current smoker, ≤15 pack years	23	0.93	0.61, 1.42	17	0.88	0.54, 1.43
Current smoker, >15 pack years	44	0.72	0.53, 0.98	33	1.14	0.80, 1.64
Missing	14			9		
P for trend			0.03			0.31

Abbreviations: BMI, body mass index; CI, confidence interval; HLI, health living index; HR, hazard ratio; MET, metabolic equivalent.

[a] Adjusted for age at entry, education, nonalcohol energy intake, ethnicity, age at menarche, parity, combined estrogen and progesterone therapy, unopposed estrogen therapy, oral contraceptive use, family history of endometrial or ovarian cancer, age at menopause, diet, physical activity, alcohol consumption, BMI, and smoking unless included as main exposure.

[b] Weight (kg)/height $(m)^2$.

study population (Table 3). Among nonusers of combined estrogen and progesterone therapy and nonusers and former users of unopposed estrogen therapy, the associations were also inverse. There was evidence for heterogeneity in the associations between the HLI score and risk of endometrial cancer by HT status overall and combined estrogen and progesterone therapy status (Table 3).

There was also a tendency towards an increased risk of serous and metastatic ovarian tumors with increasing HLI score. However, no associations were observed with risk of ovarian cancer overall or with risk of the remaining clinicopathological characteristics (Table 4). The association between the HLI and ovarian cancer risk also did not vary by HT use (Table 5).

Table 6 shows that among the individual components of the HLI score, diet, physical activity, and smoking score were inversely associated with risk of endometrial cancer, while being obese was positively associated with risk. None of the individual components was associated with risk of ovarian cancer.

Exclusion of women with an endometrial cancer diagnosis within 2 years of enrollment did not alter the association of the HLI score with risk of endometrial cancer overall, or with risk of type 1, poorly differentiated, and localized endometrial cancer (Web Table 2). With respect to ovarian cancer, the associations of the HLI with risk of serous and metastatic ovarian tumors disappeared (Web Table 3).

DISCUSSION

The results of this large prospective study of postmenopausal women suggest that a healthy lifestyle is associated with reduced risk of endometrial cancer overall, as well as of type 1, well-differentiated, moderately differentiated, poorly differentiated, and localized tumors. Similar inverse associations were seen among women who never used HT, as well as among nonusers and former users of opposed estrogen therapy. Diet, physical activity, and smoking were also inversely associated with risk of endometrial cancer while obesity was positively associated with risk. Further, there was a suggestion of a positive association between the HLI score and risk of serous and metastatic ovarian tumors.

To date, only 4 studies have explored the joint association between lifestyle-related risk factors and endometrial cancer (20–23). In the E3N cohort study, which used an HLI similar to that in the present study, having a high HLI score was associated with a 54% reduction in the risk of endometrial cancer (HR = 0.45, 95% CI: 0.29, 0.71) (23). Previously in the WHI cohort, using a lifestyle index based on the American Cancer Society/Cancer Prevention Guidelines, we also demonstrated an inverse association between an overall healthy lifestyle and risk of endometrial cancer (21). Other prospective studies using lifestyle indices based on the American Cancer Society guidelines (20) and on World Cancer Research Fund/American Institute for Cancer Research guidelines (22) also observed that women with the strongest adherence to the guidelines had a 23% and 60% lower risk of endometrial cancer (respectively, HR = 0.77, 95% CI: 0.62, 0.94; and HR = 0.40, 95% CI: 0.34, 0.46). Our findings also suggested that an overall healthy lifestyle might reduce risk of all endometrial cancer histopathological subtypes, although the associations were statistically nonsignificant for some subtypes.

Exogenous hormone use has been shown to alter the risk of endometrial cancer (6, 41). However, it is unknown whether HT use modulates the association between a healthy lifestyle and risk of endometrial cancer. Interestingly, in the present study, we found evidence to suggest that the associations might be modified by HT use, because the inverse associations were strongest among women who had never used any form of HT. However, more studies are needed to confirm our findings.

Epidemiologic evidence to support an association of diet with endometrial cancer is limited (1), but, in agreement with our study, several recent studies reported that a healthy dietary pattern, characterized by high intake of antioxidant-rich foods, was inversely associated with risk of endometrial cancer (42, 43). Similar to our study, others have also indicated that being physically active (1) and smoking are inversely associated with risk of endometrial cancer (44, 45). Previous studies have, however, largely failed to observe an association of alcohol consumption with risk of endometrial cancer (44, 46–48). Our study also confirmed the findings of previous studies that documented a strong positive association between obesity and risk of endometrial cancer (1). Given the strong association between obesity and endometrial cancer, it is not surprising that the results of our sensitivity analyses indicated that the association between the HLI and risk of endometrial cancer was mostly explained by level of adiposity. Nevertheless, there was still evidence to suggest that the remaining modifiable risk factors might collectively influence risk of endometrial cancer, particularly type 1 endometrial cancer.

The observed inverse association between the lifestyle-related risk factors and risk of endometrial cancer might involve a complex interaction between several biological mechanisms. Briefly, excess body fat, diets low in antioxidant-rich foods, relatively high alcohol consumption, and physical inactivity might contribute to several metabolic changes such as increased estrogen levels resulting from enhanced aromatase activity, hyperinsulinemia, increased levels of bioavailable insulin-like growth factor 1, and increased production of inflammatory markers (5–9), which might promote carcinogenesis by inducing oxidative stress, deoxyribonucleic acid damage, and mutagenesis; by inhibiting apoptosis; and by other processes that can foster tumor cell growth, proliferation, and migration (5–9). The mechanisms underlying the inverse association between smoking and endometrial cancer remain unclear, but studies have indicated that smoking might lower risk of endometrial cancer through its antiestrogenic effect (11, 44, 45).

With respect to ovarian cancer, the observed null association between the HLI score and risk of this cancer is consistent with that of the E3N study (23) and with those of studies that used scores based on adherence to the American Cancer Society and/or the World Cancer Research Fund/American Institute for Cancer Research guidelines (21, 22). In the present study, we also observed weak positive associations between the HLI and risk of serous and metastatic ovarian tumors. Unexpectedly, positive but nonsignificant associations were also observed for 2 components of the HLI: diet and physical activity. The positive associations suggest that the beneficial influence of some components of a healthy lifestyle on risk of ovarian cancer (including some subtypes) might be obscured by the influence of other components. Nevertheless, our findings might not be a true estimation of the associations between the HLI index or its components with risk of ovarian cancer, given the heterogeneity in the associations of the component risk factors across and within the various ovarian cancer subtypes (13, 25, 49–51). For example, among the nonserous and serous subtypes, obesity has been associated with risk of mucinous invasive ovarian cancer and low-grade

serous ovarian cancer, respectively (13, 50). Further, cigarette smoking has been shown to be inversely associated with risk of clear cell subtypes but positively associated with risk of mucinous subtypes (25, 51).

This study has several strengths, including its large sample size, standardization of the procedures used to collect risk factor information, limited loss to follow-up, and central adjudication of pathology reports. This is also, to our knowledge, the only study to date that has explored whether the association between an overall healthy lifestyle and endometrial or ovarian cancer differs by histopathological subtypes. There are also several limitations that require consideration. Aside from height and weight, the HLI components were self-reported and therefore subject to nondifferential measurement errors. Such error might have precluded us from observing small associations with ovarian cancer risk. Moreover, we were unable to assess how change in exposure status over time influences risk of the outcomes. We also lacked information on oophorectomy during follow-up, which might have contributed to misclassification of follow-up time for individuals who had oophorectomy after baseline. Finally, the number of events for some ovarian cancer subtypes was small. Therefore, our study might not have been adequately powered to assess heterogeneity in the associations between the HLI score and these subtypes.

In conclusion, our study underscores the potential importance of maintaining an overall healthy lifestyle to lower risk of endometrial cancer. However, further studies should be conducted to substantiate our findings; these results might be useful in developing intervention strategies for the primary prevention of endometrial cancer.

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