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Original Contribution

Endometrial Cancer Risk Factors by 2 Main Histologic Subtypes

The NIH-AARP Diet and Health Study

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On the basis of clinical and pathologic criteria, endometrial carcinoma has been distinguished as Types I (mainly endometrioid) and II (nonendometrioid). Limited data suggest that these subtypes have different risk factor profiles. The authors prospectively evaluated risk factors for Types I ($n = 1,312$) and II ($n = 138$) incident endometrial carcinoma among 114,409 women in the National Institutes of Health (NIH)-AARP Diet and Health Study (1995–2006). For individual risk factors, relative risks were estimated with Cox regression by subtype, and $P_{heterogeneity}$ was assessed in case-case comparisons with Type I as the referent. Stronger relations for Type I versus Type II tumors were seen for menopausal hormone therapy use (relative risk (RR) of 1.18 vs. 0.84; $P_{heterogeneity} = 0.01$) and body mass index of ≥30 vs. <30 kg/m^2 (RR of 2.93 vs. 1.83; $P_{heterogeneity} = 0.001$). Stronger relations for Type II versus Type I tumors were observed for being black versus white (RR of 2.18 vs. 0.66; $P_{heterogeneity} = 0.0004$) and having a family history of breast cancer (RR of 1.93 vs. 0.80; $P_{heterogeneity} = 0.002$). Other risk factor associations were similar by subtype. In conclusion, the authors noted different risk factor associations for Types I and II endometrial carcinomas, supporting the etiologic heterogeneity of these tumors. Because of the limited number of Type II cancers, additional evaluation of risk factors will benefit from consortial efforts.

endometrial cancer; endometrioid; histology; nonendometrioid; prospective study

Abbreviations: CI, confidence interval; ICD-O-3, *International Classification of Diseases for Oncology*, Third Edition; NIH, National Institutes of Health; RR, relative risk; SD, standard deviation.

Endometrial carcinoma is the most common and the second most lethal gynecologic cancer in the United States, causing over 8,000 deaths annually (1). The majority of these tumors are low-grade, endometrioid carcinomas that present with stage 1 disease and portend an excellent prognosis (2). However, nonendometrioid carcinomas are important because they often present with late-stage disease and are fatal (3, 4). As suggested initially by Bokhman (5), and subsequently by others (6–8), endometrial carcinomas may be divisible into 2 major types, differing in clinical and pathologic characteristics. Type I endometrial carcinomas are mostly endometrioid adenocarcinomas, which seem to develop from abnormal glandular proliferations (i.e., endometrial hyperplasia) driven by hormonal mechanisms. In contrast, Type II endometrial carcinomas often display serous or clear cell histology and arise from atrophic endometrium in a less hormonally dependent manner. Furthermore, subtypes of these carcinomas are characterized by distinctive molecular alterations, and endometrioid carcinomas are more clearly linked to elevated levels of sex-steroid hormones and expression of hormone receptors (9, 10).

Despite barriers to understanding the etiology of Type II carcinomas, including the lack of pathologic data and

Table 1. Select Baseline Characteristics of Endometrial Carcinoma Cases Among 114,409 Women in the NIH-AARP Diet and Health Study, 1995–2006[a]

	All Subjects		Noncases ($n = 112,918$)		All Cases ($n = 1,491$)		Subtypes			
							Type I ($n = 1,312$)		Type II ($n = 138$)	
	Person-Years	%	No.	%	No.	%	No.	%	No.	%
Race										
White	963,756	95	102,135	95	1,380	96	1,228	96	115	89
Black	49,988	5	5,218	5	63	4	47	4	14	11
Age, years										
<55	175,961	16	18,033	16	178	12	159	12	15	11
55–59	253,344	24	26,386	23	350	23	310	24	29	21
60–64	288,968	27	30,643	27	404	27	353	27	41	30
65–69	314,507	29	34,084	30	508	34	443	34	49	36
≥70	34,059	3	3,772	3	51	3	46	4	4	3
Stage at diagnosis										
In situ/localized					792	80	617	83	35	53
Regional/distant metastases					196	20	124	17	31	47
Grade at diagnosis										
Grade I					652	47	633	51	11	10
Grade II					479	35	446	36	25	22
Grades III–IV					253	18	159	13	77	68

Abbreviation: NIH, National Institutes of Health.
[a] Numbers may not add up to total because of missing data.

limited power in most epidemiologic studies, amassing evidence supports the view that endometrial carcinoma is etiologically heterogeneous. In a population-based incident case-control study of 328 endometrioid and 26 serous cases and controls, high body mass index and use of menopausal hormone therapy were associated with higher risk for endometrioid as compared with serous carcinomas (9). Similarly, when 53 serous and 18 clear cell cancers were compared with 509 endometrioid tumors, women with serous cancers, compared with endometrioid cancers, were more commonly black and less commonly menopausal hormone therapy users and diabetics (11). A recent comparison of Type I ($n = 1,576$) and Type II ($n = 176$) carcinomas of clinical case series revealed that women with Type II carcinomas were older, more frequently nonwhite, and less obese than women with Type I carcinomas (12).

Overall evidence suggests that there are etiologic differences between Types I and II endometrial carcinomas, but conclusions are limited by small sample sizes and the lack of prospective data. Accordingly, we analyzed questionnaire data from the large, prospective National Institutes of Health (NIH)-AARP Diet and Health Study to assess relations between risk factors and endometrial carcinomas by pathologic characteristics. In addition, Type I and Type II case definitions have not been clearly established (e.g., whether some endometrioid carcinomas represent Type II cases); thus, as a sensitivity analysis, we have used various definitions of Types I and II carcinomas in our examination of the risk associations.

MATERIALS AND METHODS

Study population

The NIH-AARP Diet and Health Study design and methodology have been described in detail elsewhere (13). In brief, the NIH-AARP Diet and Health Study was established in 1995–1996 by inviting 3.5 million AARP members in 6 states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) to complete a baseline questionnaire. A total of 617,119 self-administered questionnaires were returned, of which 566,399 were nonduplicate and satisfactory responses. The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute.

Exposure assessment

The baseline questionnaire ascertained self-reports of demographic factors, anthropometric measures, lifestyle factors, and personal and family medical history. We calculated body mass index on the basis of self-reported weight in kilograms and height in meters squared and dichotomized the results as nonobese (<30 kg/m^2) versus obese (≥ 30 kg/m^2). Female study participants were additionally asked to provide information on reproductive and menstrual history and basic information (ever/never and duration)

Table 2. Adjusted Relative Risks and 95% Confidence Intervals for Type I and Type II Endometrial Carcinoma in Relation to Hormonal and Reproductive Factors in the NIH-AARP Diet and Health Study, 1995–2006

	No. of Noncases	Subtypes					
		Type I (n = 1,312)			Type II (n = 138)		
		No.	RR[a]	95% CI	No.	RR[a]	95% CI
Age at menarche, years							
<13	53,393	681	1	Referent	74	1	Referent
13–14	48,277	527	0.92	0.82, 1.03	55	0.84	0.59, 1.20
≥15	10,852	102	0.82	0.67, 1.01	8	0.53	0.25, 1.10
				$P_{heterogeneity}$[b] = 0.22			
Age at menopause, years							
<45	12,110	101	1	Referent	12	1	Referent
45–49	28,674	271	1.20	0.96, 1.51	28	1.05	0.53, 2.07
50–54	49,660	590	1.45	1.17, 1.79	64	1.32	0.71, 2.46
≥55	11,115	203	2.06	1.63, 2.63	16	1.40	0.66, 2.97
				$P_{heterogeneity}$[b] = 0.40			
Menopausal hormone therapy							
Never user	67,831	787	1	Referent	93	1	Referent
Ever user	45,087	525	1.18	1.05, 1.32	45	0.84	0.57, 1.22
				$P_{heterogeneity}$[b] = 0.01			
Duration of MHT use, years							
Never user	67,831	787	1	Referent	93	1	Referent
<5	22,549	183	0.81	0.69, 0.95	20	0.76	0.46, 1.25
5–9	13,336	160	1.23	1.03, 1.47	10	0.62	0.33, 1.22
≥10	9,072	182	2.09	1.77, 2.48	15	1.33	0.75, 2.36
				$P_{heterogeneity}$[b] = 0.01			
Oral contraceptive use							
Never user	66,327	901	1	Referent	100	1	Referent
Ever user	45,792	405	0.73	0.64, 0.83	37	0.63	0.42, 0.95
				$P_{heterogeneity}$[b] = 0.12			

Table continues

about any oral contraceptive and menopausal hormone therapy use. To determine whether study participants were menopausal, they were asked at what age they had their last menstrual period, and, if periods had stopped, whether menopause was natural or due to surgery or radiation/chemotherapy. Female participants were also asked whether they had a hysterectomy or surgery that involved removal of one or both ovaries.

Cohort follow-up

Cohort members were followed through the US Postal Service national database of address changes and for updated vital status through the US Social Security Administration Death Master File and the National Death Index Plus. Follow-up time was defined as the time from study baseline (between 1995 and 1996) until diagnosis of any cancer, date of death, date moved out of the registry ascertainment area, or last follow-up (December 31, 2006).

Analytical population

We excluded study participants who used proxy respondents (n = 15,760), were male (n = 325,172), or self-reported a previous diagnosis of cancer other than nonmelanoma skin cancer (n = 23,957). Additional exclusion criteria included participants who had a history of hysterectomy (n = 82,107), unknown hysterectomy status (n = 2,927), menstrual periods that stopped because of surgery (n = 1,830) or radiation or chemotherapy (n = 117); died or moved out of the study area before study entry (n = 12); or developed nonepithelial endometrial cancer during follow-up (n = 108). The resulting cohort consisted of 114,409 women.

Incident endometrial cancer ascertainment

Incident endometrial carcinomas were identified by probabilistic linkages with cancer registries in the original recruitment areas and 2 common states of relocation (Arizona

Table 2. Continued

	No. of Noncases	Subtypes					
		Type I ($n = 1,312$)			Type II ($n = 138$)		
		No.	RR[a]	95% CI	No.	RR[a]	95% CI
Duration of oral contraceptive use, years							
Never user	66,327	901	1	Referent	100	1	Referent
1–4	19,885	176	0.74	0.62, 0.87	20	0.78	0.47, 1.29
5–9	14,197	142	0.83	0.69, 1.00	10	0.56	0.29, 1.10
≥10	11,710	87	0.61	0.49, 0.77	7	0.47	0.21, 1.02
				$P_{heterogeneity}$[b] = 0.05			
Parous							
Nulliparous	19,717	302	1	Referent	31	1	Referent
Parous	92,745	1,002	0.69	0.60, 0.78	107	0.76	0.50, 1.14
				$P_{heterogeneity}$[b] = 0.83			
Age at first birth, years							
Nulliparous	19,717	302	1	Referent	31	1	Referent
<20	15,441	164	0.69	0.56, 0.83	18	0.72	0.40, 1.30
20–<25	46,930	513	0.70	0.60, 0.81	59	0.82	0.53, 1.27
25–<30	22,186	254	0.74	0.62, 0.87	23	0.67	0.39, 1.15
≥30	8,180	76	0.61	0.47, 0.78	7	0.54	0.24, 1.23
				$P_{heterogeneity}$[b] = 0.43			
Parity, no. of previous births							
Nulliparous	19,717	302	1	Referent	31	1	Referent
1	12,254	139	0.78	0.64, 0.95	13	0.71	0.37, 1.36
2	29,626	330	0.75	0.64, 0.88	37	0.85	0.53, 1.38
≥3	50,865	533	0.64	0.55, 0.73	57	0.68	0.43, 1.06
				$P_{heterogeneity}$[b] = 0.86			

Abbreviations: CI, confidence interval; MHT, menopausal hormone therapy; NIH, National Institutes of Health; RR, relative risk.

[a] Adjusted for age (continuous), oral contraceptive use (ever/never), MHT use (ever/never), parity (nulliparous, 1, 2, ≥3 births), body mass index (<30 vs. ≥30 kg/m^2), menarche (<13, 13–14, ≥15 years), age at menopause (premenopausal, <45, 45–49, 50–54, ≥55 years), race (white/nonwhite), and smoking status (never, former, current smoker). Unknown/missing was set as a separate category within each factor.

[b] *P* value from logistic regression of case-only analysis comparing each risk factor.

and Texas). The completeness of case ascertainment in this cohort has been reported previously, with an estimated sensitivity of approximately 90% and specificity of 99.5% with respect to identification of cases by cancer registry linkage (14). Of the 114,409 women available for analysis, 1,491 were diagnosed with incident epithelial endometrial carcinoma. Using histology codes from the *International Classification of Diseases for Oncology*, Third Edition (ICD-O-3) (15), we classified endometrial carcinoma (code 54) into Type I and II cases. Type I histologies included endometrioid, mucinous, tubular, adenocarcinoma not otherwise specified, and adenocarcinoma with squamous differentiation (codes 8380, 8382, 8383, 8480–8482, 8210, 8140, 8560, 8570). Inclusion of adenocarcinoma not otherwise specified in Type I is justified because endometrioid adenocarcinoma is the most common type of endometrial adenocarcinoma. Type II histologies included serous, clear cell, mixed cell, small cell, and squamous cell (codes 8440, 8441, 8460, 8461, 8310, 8323, 8041, 8070, 8071, 8076). Forty-one cases of other histologic subtypes were not categorized into either type (codes 8000, 8010, 8012, 8020–8022, 8050, 8255, 8260, 8320).

As a sensitivity analysis, we restricted our definition of the case subtypes. Type I ($n = 864$) cases were limited to endometrioid, mucinous, and adenocarcinoma with squamous differentiation (ICD-O-3 codes 8380, 8382, 8383, 8480–8482, 8560, 8570), and Type II ($n = 90$) cases were limited to serous and clear cell pathology (codes 8440, 8441, 8460, 8461, 8310). As an additional sensitivity analysis, we classified grade 3 or worse endometrioid and adenocarcinoma not otherwise specified as Type II cases ($n = 153$). Some endometrial cancer risk factors have been shown to differ in risk associations by stage. Thus, we limited our analysis to cases with stage information (Type I, $n = 741$; Type II, $n = 66$) and performed an evaluation stratified by stage.

Statistical analysis

We used Cox proportional hazards regression to estimate relative risks and 95% confidence intervals with age as the

time metric. We built a parsimonious regression model by adding endometrial cancer risk factors that were considered a priori important potential confounders. Multivariable models included the following covariates: age (continuous), race (white/nonwhite), oral contraceptive use (ever/never), menopausal hormone therapy use (ever/never), parity (nulliparous, 1, 2, ≥3), body mass index (<30 vs. ≥30 kg/m^2), age at menarche (<13, 13–14, ≥15 years), age at menopause (premenopausal, <45, 45–49, 50–54, ≥55 years), and smoking status (never, former, current smoker). Although detailed information on the formulation of both exogenous hormones was captured in a follow-up questionnaire in our study, case numbers in particular for Type II cases were too small to examine formula-specific associations. For covariates with missing data, women were coded into a separate category. Adjustment for other factors, including calendar time, did not change the results.

We constructed 2 Cox models for each exposure of interest by comparing risk factor associations for each case subtype with those for the entire noncase group. We used the same multivariable model for Types I and II endometrial carcinomas to ease interpretation. To test for heterogeneity in associations between risk factors and endometrial carcinoma subtypes, we conducted a case-only analysis using logistic regression models that treated histologic type as the response variable, with Type I carcinomas as the reference category. In these logistic regression models, we adjusted for the same covariates included in our multivariable proportional hazards models and additionally adjusted for person-years to account for duration in the cohort. In the models to calculate $P_{\text{heterogeneity}}$, we entered any categorical variables as a single continuous parameter, rather than dummy variables for each category separately. We present this $P_{\text{heterogeneity}}$ as the main analysis, but we also applied a method used to account for competing risks when there is more than one type of outcome (16). For the latter method of assessing heterogeneity, we created 2 duplicate data sets to produce 1 record for each subtype and treated the outcome of 1 of the 2 records as a nonevent. We used the likelihood ratio test to determine the significance of heterogeneity by subtypes for each potential endometrial cancer risk factor.

For all analyses, $P < 0.05$ was considered statistically significant. All tests of statistical significance were 2 sided. Analyses were performed by using SAS, release 9.1.3, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

A total of 114,409 women contributed 1,066,839 person-years, including an average period of 5.2 years from enrollment to diagnosis for cases and 9.4 years of observation time for noncases. The mean ages at enrollment were 62.3 (standard deviation (SD), 5.3) years for cases versus 61.6 (SD, 5.5) for noncases; ages at exit were 67.4 (SD, 5.8) years and 71.0 (SD, 5.9) years, respectively. Characteristics of the study population and of the cases by histologic subtypes are presented in Table 1. Most women were white and were postmenopausal at the time of study entry. Of the 1,491 endometrial carcinoma cases, 1,312 (88%) were Type I and 138 (9%) were Type II tumors. The mean ages at enrollment were similar for both types of endometrial carcinoma: 62.2 (SD, 5.3) years for Type I and 62.5 (SD, 5.2) years for Type II. Women with Type I endometrial carcinoma were more likely diagnosed with localized, low-grade tumors than were Type II cases.

Table 2 presents the associations between hormonal and reproductive factors and endometrial carcinoma by subtype. The risk association for menopausal hormone therapy was significantly different between Types I and II endometrial carcinoma risk ($P_{\text{heterogeneity}} = 0.01$), with increased risk for Type I cases (relative risk (RR) = 1.18, 95% confidence interval (CI): 1.05, 1.32) and nonsignificant decreased risk for Type II (RR = 0.84, 95% CI: 0.57, 1.22) tumors. We noted similar subtype-specific decreased risk associations with respect to use of oral contraceptives ($P_{\text{heterogeneity}} = 0.12$). Years of menopausal hormone therapy use were significantly different and years of oral contraceptive use were borderline significantly different between Types I and II endometrial carcinoma risk ($P_{\text{heterogeneity}} = 0.01$ and 0.05, respectively), although confidence limits for Types I and II overlapped. We did not identify significant differences with respect to age at menarche or menopause or parity-related risk factors between the 2 tumor subtypes (all $P_{\text{heterogeneity}} \geq 0.22$).

Table 3 presents the associations for demographic and lifestyle factors and endometrial carcinoma by subtype. We observed significant differences in subtype-specific risk according to race and obesity ($P_{\text{heterogeneity}} \leq 0.001$). Black women compared with white women were at decreased risk for Type I carcinomas (RR = 0.66, 95% CI: 0.49, 0.88) but at increased risk for Type II (RR = 2.18, 95% CI: 1.24, 3.84) tumors. In addition, the increased risk associated with being obese (body mass index = ≥ 30 kg/m^2) was stronger for Type I (RR = 2.93, 95% CI: 2.62, 3.28) compared with Type II (RR = 1.83, 95% CI: 1.27, 2.63). Both tumor types showed similar inverse associations with increased frequency of vigorous physical activity and smoking and were not significantly associated with level of education or alcohol consumption.

Table 4 presents the associations between personal and family medical history and endometrial carcinoma by subtype. First-degree family history of breast cancer was inversely associated with Type I (RR = 0.80, 95% CI: 0.67, 0.96) but positively associated with Type II (RR = 1.93, 1.27, 2.93) cancers ($P_{\text{heterogeneity}} = 0.002$). We observed similar subtype-specific risk estimates with respect to self-reported personal history of diabetes and first-degree family history of other cancers ($P_{\text{heterogeneity}} \geq 0.25$).

As a sensitivity analysis, we applied a model based on competing risk to assess $P_{\text{heterogeneity}}$ among the subtypes. The competing risk approach gave similar results, although the $P_{\text{heterogeneity}}$ was borderline significant for menopausal hormone therapy ($P_{\text{heterogeneity}} = 0.09$; data not shown for other risk factors). As an additional sensitivity analysis, we examined different definitions of Types I and II endometrial cancer cases. We found similar relations between risk factors and endometrial carcinoma types when we reanalyzed our data using narrower definitions of Type I (endometrioid, mucinous, and adenocarcinoma with squamous differentiation) and Type II (serous and clear cell) tumors (Web Table 1 available at http://aje.oxfordjournals.org/).

Table 3. Adjusted Relative Risks and 95% Confidence Intervals for Type I and Type II Endometrial Carcinoma in Relation to Demographic and Lifestyle Factors in the NIH-AARP Diet and Health Study, 1995–2006

	No. of Noncases	Subtypes					
		Type I (n = 1,312)			Type II (n = 138)		
		No.	RR[a]	95% CI	No.	RR[a]	95% CI
Race/ethnicity							
White	102,135	1,228	1	Referent	115	1	Referent
Black	5,218	47	0.66	0.49, 0.88	14	2.18	1.24, 3.84
Other	5,565	37	0.57	0.41, 0.79	9	1.35	0.68, 2.67
				$P_{heterogeneity}$[b,c] = 0.0004			
				$P_{heterogeneity}$[b,d] = 0.0004			
Education							
Less than high school	33,895	395	1	Referent	46	1	Referent
High school or more	75,863	883	1.04	0.92, 1.17	86	0.91	0.63, 1.31
				$P_{heterogeneity}$[b] = 0.20			
Body mass index[e]							
<30	85,613	708	1	Referent	86	1	Referent
≥30	23,763	570	2.93	2.62, 3.28	47	1.83	1.27, 2.63
				$P_{heterogeneity}$[b] = 0.001			
Frequency of vigorous physical activity							
Never/rarely	24,611	362	1	Referent	37	1	Referent
<2 times/week	39,757	464	0.85	0.74, 0.98	58	1.03	0.68, 1.57
≥3 times/week	47,304	469	0.78	0.68, 0.90	41	0.62	0.39, 0.97
				$P_{heterogeneity}$[b] = 0.06			
Alcohol intake, g/day							
0	31,311	401	1	Referent	41	1	Referent
>0–<12	64,669	735	0.96	0.85, 1.09	86	1.21	0.83, 1.77
12–<24	10,284	113	1.09	0.88, 1.35	8	0.83	0.39, 1.80
≥24	6,654	63	0.97	0.74, 1.28	3	0.52	0.16, 1.69
				$P_{heterogeneity}$[b] = 1.0			
Smoking status							
Never smoker	49,360	657	1	Referent	79	1	Referent
Ever smoker	60,258	627	0.89	0.80, 0.99	54	0.65	0.46, 0.91
				$P_{heterogeneity}$[b] = 0.20			

Abbreviations: CI, confidence interval; NIH, National Institutes of Health; RR, relative risk.

[a] Adjusted for age (continuous), oral contraceptive use (ever/never), menopausal hormone therapy use (ever/never), parity (nulliparous, 1, 2, ≥3 births), body mass index (<30 vs. ≥30 kg/m^2), menarche (<13, 13–14, ≥15 years), age at menopause (premenopausal, <45, 45–49, 50–54, ≥55 years), race (white/nonwhite), and smoking status (never, former, current smoker). Unknown/missing was set as a separate category within each factor.

[b] P value from logistic regression of case-only analysis comparing each risk factor.

[c] White, black, and other.

[d] White and black.

[e] Body mass index: weight (kg)/height (m)^2.

We also obtained similar results when we categorized grades 3 and 4 endometrioid tumors as Type II carcinomas (Web Table 2), although we also found a statistically significant difference in subtype risk estimate for diabetes ($P_{heterogeneity}$ = 0.04), with an increased risk restricted to Type II cases (RR = 1.80, 95% CI: 1.28, 2.55). Compared with the main analysis, these 2 sensitivity analyses were observed to have a similar magnitude of risk factor associations for Type I endometrial carcinoma cases, with estimates attenuating the most for race. Risk estimates for Type II cases were less consistent. Regardless of the definition used for subtype cases, we observed different risk associations for Type I and Type II endometrial carcinoma for menopausal hormone therapy use, obesity, race, and first-degree family history of breast cancer, in accordance with those observed for the main analysis.

Table 4. Adjusted Relative Risks and 95% Confidence Intervals for Type I and Type II Endometrial Carcinoma in Relation to Personal and Family Medical History in the NIH-AARP Diet and Health Study, 1995–2006

Self-reported (yes)	No. of Noncases	Subtypes					
		Type I (n = 1,312)			Type II (n = 138)		
		No.	RR[a]	95% CI	No.	RR[a]	95% CI
Diabetes	7,491	137	1.24	1.03, 1.49	18	1.67	1.00, 2.79
				$P_{heterogeneity}$[b] = 0.25			
First-degree family history of breast cancer	13,590	130	0.80	0.67, 0.96	28	1.93	1.27, 2.93
				$P_{heterogeneity}$[b] = 0.002			
First-degree family history of other cancer	39,072	466	1.01	0.90, 1.14	53	1.24	0.87, 1.75
				$P_{heterogeneity}$[b] = 0.52			

Abbreviations: CI, confidence interval; NIH, National Institutes of Health; RR, relative risk.

[a] Adjusted for age (continuous), oral contraceptive use (ever/never), menopausal hormone therapy use (ever/never), parity (nulliparous, 1, 2, ≥3 births), body mass index (<30 vs. ≥30 kg/m^2), menarche (<13, 13–14, ≥15 years), age at menopause (premenopausal, <45, 45–49, 50–54, ≥55 years), race (white/nonwhite), and smoking status (never, former, current smoker). Unknown/missing was set as a separate category within each factor.

[b] P value from logistic regression of case-only analysis comparing each risk factor.

Results in our stage-stratified analysis showed that subtype heterogeneity may be restricted to in situ/localized for race and family history of breast cancer and to metastases/distant for menopausal hormone therapy use (Web Table 3), but this analysis was based on smaller numbers of Type II cancers after stratification by stage.

DISCUSSION

On the basis of clinicopathologic observations, Bokhman (5) proposed a dualistic model of endometrial carcinogenesis in which Type I tumors were considered largely estrogen dependent and Type II tumors as relatively estrogen independent in development and growth. Consistent with that view, our analysis of expanded follow-up data from the NIH-AARP Diet and Health Study demonstrated that endometrial carcinoma risk factor associations differ between Type I and Type II carcinomas. Specifically, we showed that Type I carcinomas are more strongly related to menopausal hormone therapy use and obesity than were Type II carcinomas, whereas Type II versus Type I carcinomas showed stronger relations for being black relative to being white. In addition, Type II carcinomas were more strongly associated with a first-degree family history of breast cancer. Other factors proposed to reflect cumulative exposure to sex-steroid hormones, such as younger age at menarche, nulliparity, and older age at menopause (17–21), showed relatively homogeneous associations with Type I and Type II carcinomas in our analysis.

We found that menopausal hormone therapy use was a stronger risk factor for Type I than Type II tumors, as shown in previous studies (9, 11). The specific association between menopausal hormone therapy use and Type I carcinomas provides evidence for the greater importance of sex hormones in the etiology of Type I as compared with Type II carcinomas. Although formulation was captured in a follow-up questionnaire in our study, case numbers, in particular for Type II cases, were too few to examine formula-specific associations. We recognize that estrogens alone are associated with much higher relative risks than estrogen-plus-progestin formulations (22), and future pooled analyses may inform this question.

Obesity is a strong, modifiable risk factor for endometrial carcinoma, which is implicated in approximately 40% of cases (23). We and others have found that obesity is a stronger risk factor for Type I as opposed to Type II carcinomas, but some increase for the latter has been noted (24–26). Postmenopausal obesity is consistently linked to increased circulating levels of estrogens, which likely accounts for part of the excess endometrial cancer risk among heavier women (20, 27, 28). However, obesity is also related to diabetes, metabolic syndrome, and a proinflammatory state, which could contribute to endometrial carcinogenesis via elevated exposure to growth factors and other nonestrogenic mechanisms (20). In addition, given that progesterone induces endometrial maturation and lowers endometrial cancer risk (29), deficiency of this hormone relative to estrogen may represent a critical factor that needs to be assessed. Furthermore, the limited number of Type II carcinomas in this analysis precluded our evaluation of interactions between exogenous hormone use and body mass index, although obesity is a well-established endometrial cancer risk factor, particularly among nonusers of hormones (25, 30–33).

Our finding of greater risk of Type II carcinomas among black women compared with white women is consistent with prior data (34, 35). Despite the consistent demonstration of higher rates of serous and clear cell carcinomas among black women (36), the reasons for this association remain unclear. Although inequalities in health care may partly explain the differences between races, there is also evidence to suggest that biologic differences, such as the presence of p53 mutations (37) and *ERBB2* (formerly *HER2* or *HER2/neu*) overexpressions (38), which are genetic changes associated more commonly with Type II carcinomas, may be more common in blacks than in whites (36).

We also noted a relation between a first-degree family member with breast cancer and Type II endometrial carcinomas, although this result was based on limited numbers of events. Although endometrial and breast cancers share some of the same reproductive and hormonal risk factors, most studies have not assessed the relation between family history of breast cancer and endometrial cancer risk according to tumor subtype (39–42). In support of our finding, a recent study has reported that *BRCA* mutations may be common among uterine papillary serous cancers (43). Although an inherited factor could explain the association between breast cancer family history and Type II endometrial carcinoma, nongenetic causes are also possible. For example, use of tamoxifen may increase risk for serous carcinomas (44), and tamoxifen use may have been greater among women at higher risk for breast carcinoma. In addition, the association may reflect a chance finding or differential recall bias by tumor type, suggesting the need for further study.

In our analysis, the percentage of Type II carcinomas ranged from 6.0% to 19.5% of the endometrial carcinoma cases, depending on the definition used. Our results were generally similar, irrespective of which definition of Type II was used. Various definitions of Type I and Type II cancers have been used across studies, which adds complexity to the interpretation of our results with respect to prior reports. In particular, some investigators have argued for inclusion of grade 3 endometrioid carcinomas in the Type II category (6, 45), because poorly differentiated endometrioid tumors resemble prognostic and molecular characteristics typical of Type II tumors (46, 47). Supporting this notion, most high-grade endometrioid carcinomas have been observed to display weak estrogen receptor and/or progesterone receptor expression (10). In addition, a percentage of serous carcinomas seems to arise secondarily from preexisting endometrioid carcinomas to produce carcinomas of mixed histology (48). Thus, a percentage of tumors classified as serous carcinomas, as well as many grade 3 endometrioid carcinomas that arise from grade 1 carcinomas, may arise via Type I hormonal pathways, thus blurring the etiologic distinction between the subtypes.

In our analysis, Types I and II endometrial carcinoma distinctions were made on the basis of histology, which may be too simplistic. Etiologic heterogeneity may exist within endometrioid carcinoma given that hyperplasia is not identified in a significant portion of these Type I tumors (8). Currently, efforts are being made to establish molecularly based classification, which may aid in understanding the difference in biology and clinical outcome between the subtypes (49, 50). Other limitations of our study include the limited number of Type II carcinomas and, as with any study based on cancer registry data, the lack of centralized pathology review, which may have led to misclassification and nonspecific classification of some carcinomas, such as adenocarcinoma not otherwise specified. Another limitation is that our population was limited to older women, which would have a much greater effect on reducing Type I carcinomas as opposed to Type II carcinomas (11, 12, 51, 52). We were also limited in our ability to examine menopausal hormone therapy formulation and family history of endometrial or ovarian cancer independently as we did for family history of breast cancer.

Despite these limitations, our study had several strengths as a large, prospective investigation. We had the ability to examine Type I and Type II cases according to various definitions and calculate subtype-specific risks associated with each risk factor of interest. Additionally, our analysis was based on a single cohort with risk factors assessed in the same manner and with cases accrued over a relatively short period of time (approximately 5 years), limiting secular trends of histology terminology and prevalence of risk factors.

In summary, we noted different risk factor associations for Types I and II endometrial carcinomas, supporting the etiologic heterogeneity of these tumors. Pooling efforts will likely be needed to further characterize the etiology of Type II carcinomas, given their relative rarity. Given the poor prognosis of many Type II carcinomas and their disproportionately greater impact in black women, further studies are warranted in an effort to reduce the incidence of these carcinomas through prevention and treatment efforts.

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