Lifetime Weight History and Endometrial Cancer Risk by Type of Menopausal Hormone Use in the NIH-AARP Diet and Health Study

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Abstract

Obesity and menopausal estrogen therapy are established risk factors for endometrial cancer. However, the joint effects of obesity and menopausal hormone therapy on endometrial cancer risk are incompletely understood. We addressed this issue in a cohort of 103,882 women ages 50 to 71 years at baseline in 1995 to 1996. During a median of 4.6 years, which contributed to a total of 455,304 person-years of follow-up through 2000, 677 cases of endometrial cancer were ascertained. Both baseline body mass index (BMI) and adult weight gain were associated with increased endometrial cancer risk. The multivariate relative risk (RR) comparing obese with normal weight women (BMI >30 versus <25 kg/m^2) was 3.03 [95% confidence interval (95% CI), 2.50-3.68]. Compared with women with stable weight (gained or lost <5 kg) between age 18 and baseline, women who gained ≥20 kg had a RR of 2.75 (95% CI, 1.96-3.86). Menopausal hormone therapy significantly modified the relations of BMI ($P_{interaction}$ < 0.001) and adult weight gain ($P_{interaction}$ = 0.004) to endometrial cancer risk. Compared with normal weight, the RRs for obesity were 5.41 (95% CI, 4.01-7.29) among women who never used menopausal hormone therapy, 2.53 (95% CI, 1.21-5.30) among former menopausal hormone therapy users, and 1.44 (95% CI, 1.00-2.05) among current users. Compared with a stable weight between age 18 and baseline, the RRs for weight gain of ≥20 kg among never users and ever users of menopausal hormone therapy were 5.35 (95% CI, 3.01-9.52) and 1.43 (95% CI, 0.96-2.15), respectively. We conclude that both current adiposity and adult weight gain are associated with substantial increases in the risk of endometrial cancer, with relations particularly evident among never users of menopausal hormone therapy. (Cancer Epidemiol Biomarkers Prev 2007;16(4):723–30)

Introduction

High body mass is an important risk factor for endometrial cancer (1). In postmenopausal women, adiposity is thought to enhance endometrial cancer risk through the mitogenic effects of excess endogenous estrogens that are produced in the adipose tissue through aromatization of androgens (2). In addition, obesity is accompanied by increased bioavailable estrogen as a result of decreased sex hormone binding globulin concentrations (3).

Menopausal hormone therapy in the form of unopposed estrogens is also known to be a risk factor for endometrial cancer because it provides exogenous estrogen (4). The proliferative effects of estrogen on the endometrium can be counteracted by the use of formulations that contain estrogen plus progestin (5, 6).

The relationship between current body mass index (BMI; kg/m^2) and endometrial cancer risk has been extensively investigated (1, 7-10). Studies have generally reported 2- to 5-fold increases in endometrial cancer risk with current obesity (1, 7-10), and obesity has been estimated to account for at least 40% of the observed incidence of endometrial cancer (11). However, the relations of body mass at different time periods in life and weight change over time to endometrial cancer risk are less well understood. Specifically, it is unclear whether body mass that is acquired during adolescence and that which is gained throughout adulthood represent two independent risk factors for endometrial cancer after taking current adiposity into account. Only two studies (12, 13) have found a statistically significant positive association between BMI at an early age and subsequent endometrial cancer risk after adjustment for current BMI, and only one study (10) has reported a positive association with adult weight gain that remained statistically significant after controlling for current BMI.

Moreover, despite consistent epidemiologic evidence linking both excess body mass (1) and estrogen-only menopausal hormone therapy (4) to increased endometrial cancer risk, very few epidemiologic investigations have specifically addressed whether the effect of body mass on risk for endometrial cancer differs by menopausal hormone therapy. Available data are limited to two studies (10, 14). One study (14) reported a stronger association between BMI and endometrial cancer among never users than ever users of estrogen. Another study (10) reported that the relation of body mass to endometrial cancer risk was modified by menopausal hormone use. However, no clear patterns of risk were observed, with the results not shown.

Therefore, in a large cohort of women enrolled in the NIH-AARP (formerly known as American Association of Retired Persons) Diet and Health Study, we prospectively examined the association between lifetime weight history and endometrial cancer risk. We explored in detail whether relations differed by menopausal hormone therapy.

Patients and Methods

The NIH-AARP Diet and Health Study Cohort. Subjects in this study were women who participated in the NIH-AARP

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Diet and Health Study, a prospective cohort study designed to address the effects of dietary and lifestyle factors on cancer risk. The rationale for and design of the study have been detailed elsewhere (15). Briefly, in 1995 to 1996, a 16-page questionnaire was sent to 3.5 million AARP members aged 50 to 71 years who resided in one of six states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) or two metropolitan areas (Atlanta, GA and Detroit, MI). Selection of these sites was based on their having high-quality cancer registries, adequate minority representation, and large AARP memberships. A total of 617,119 men and women returned the baseline questionnaire, with 567,169 of them satisfactorily completed. This baseline questionnaire requested information on diet, current weight and height, menopausal hormone therapy, reproductive factors, history of oral contraceptive use, physical activity, medical history, smoking status, and familial and personal history of cancer. In late 1996, an additional questionnaire was mailed to the baseline questionnaire respondents to obtain information on some factors that could not be accommodated in the baseline questionnaire. Specifically, the additional questionnaire requested information on body weight at ages 18, 35, and 50; type, duration, and dose of menopausal hormone therapy; and more detailed information on family history of cancer. A total of 334,910 persons responded to the additional questionnaire.

Study Population. Among the baseline questionnaire respondents, we excluded 179 questionnaires with duplicate representation in our database, 1 person who withdrew from the study, 582 persons who moved out of the study area or were found to have died before their questionnaire was returned, and 15,760 records that were not completed by the intended respondent, leaving 225,471 women and 325,176 men in the cohort. Our analysis included only women, of whom the following reasons resulted in further exclusions: previous diagnosis of cancer (excluding nonmelanoma skin cancer, n = 23,974); died of endometrial cancer through National Death Index record but not ascertained as incident during follow-up (n = 5); estimated total energy consumption >2 interquartile ranges above the 75th percentile or below the 25th percentile of the population distribution (n = 857); missing data on menopausal hormone therapy (n = 164); missing data on baseline weight or height; and implausible values for BMI <12 or >80 kg/m^2 (n = 3,745). We also excluded women who reported a hysterectomy before baseline (n = 85,030) or who were premenopausal at enrollment (n = 7,814). After these exclusions, 103,882 women remained for our current analysis. Of these, 66,935 responded to the more detailed second questionnaire, after we further excluded proxy respondents and subjects who were diagnosed with cancer before completing this second questionnaire.

Assessment of Body Weight, Height, and BMI. Body weight at enrollment was obtained in the baseline questionnaire and weight at ages 18, 35, and 50 years was requested in the second questionnaire. We calculated BMI by dividing weight in kilograms by the square of height in meters. Information on height at 18 years of age was additionally requested in the second questionnaire, allowing derivation of BMI at age 18 years.

Assessment of Menopausal Hormone Therapy. Menopausal hormone therapy use was assessed at enrollment by asking participants the following questions: ''Are you currently taking replacement hormones?'' with possible answers ''yes and no'' and ''How many years have you taken replacement hormones?'' with possible answers ''never, <5 years, 5-9 years, and >10 years.'' Women who reported ''no'' in the first question and ''never'' in the latter question were considered nonusers. Current users were defined as those who responded ''yes'' in the first question, whereas those who answered ''no'' to that question but provided information on duration of hormone therapy use were considered former users.

More detailed information on menopausal hormone therapy was collected in the second questionnaire, allowing us to identify the type of hormones used. Separate questions were asked regarding estrogen and progestin use. Women who reported ever using estrogen or progestin pills were asked to further specify whether they were still taking them, the date of first and last use, total duration of use, regimen, usual dose, and name of the pill they took for the longest period of time. Women were considered to be exclusive estrogen users if they reported ever using estrogen but not progestin. For women who reported ever using both estrogen and progestin pills, if the difference of reported date of first use between estrogen and progestin pills was <90 days, they were considered combined estrogen plus progestin users. In addition, if the reported date of first use of either estrogen or progestin was missing, but they reported the same duration of use for both estrogen and progestin, they were also considered combined estrogen plus progestin users. We further divided use of combined estrogen plus progestin into sequential and continuous regimens. The sequential regimen included estrogen plus progestin used for <15 days per cycle, and the continuous regimen included estrogen plus progestin used for ≥15 days per cycle.

Ascertainment and Classification of Endometrial Cancer Cases. Incident endometrial cancer cases, through December 31, 2000, were identified through linkage of the NIH-AARP cohort database to state cancer registries. All state cancer registries (for the six states and two metropolitan areas) met the quality standard (i.e., 95% case ascertainment within 18 months) defined by the North American Association of Central Cancer Registries (16). Deaths from endometrial cancer were additionally identified through the National Death Index. A validation study of cancer ascertainment in the NIH-AARP Diet and Health Study indicated that the registries included in the NIH-AARP cohort have about 90% sensitivity with a 4-year lag period between the end of the period of interest and the reporting from cancer registries (17), which is close to the completeness of the Surveillance, Epidemiology, and End Results program registries.

Statistical Analysis. Relative risks (RR) and 95% confidence interval (95% CI) for endometrial cancer were obtained using age-adjusted and multivariate Cox proportional hazards regression, with age as the underlying time metric (18). Person-time was calculated from the age of return of the baseline questionnaire (for the main analyses) or the second questionnaire (for the analyses involving the more detailed information on menopausal hormone therapy) until the age at diagnosis of endometrial cancer, death, or the age at the end of study in December 31, 2000, whichever occurred first. The covariates selected were those associated with endometrial cancer in the age-adjusted model and also related to BMI. Unless otherwise specified, multivariate models included race (White, Black, Hispanic, combined Asian, Pacific Islander, or American Indian/Alaskan Native), personal history of diabetes (yes/no), age at menarche (≤10, 11-12, >13 years), parity (0, 1, 2, >3 live births), self-reported history of oral contraceptive use (yes/no, further adjustment for duration did not affect risks), age at menopause (<44, 45-49, 50-54, >55 years), menopausal hormone therapy use at baseline (never, former, and current use), smoking (never, former, and current), and physical activity level (low, medium, and high).

We computed age-standardized incidence rates of endometrial cancer to compare the NIH-AARP rates with Surveillance, Epidemiology, and End Results rates. Internal comparisons were applied to examine age-standardized incidence rates of endometrial cancer across increasing categories of BMI within

strata of menopausal hormone therapy use, reproductive factors, and smoking.

Tests for linear trend were conducted by applying continuous variables in the model. To test for statistical interaction, we entered into the appropriate multivariate model the main effect terms for BMI on a continuous scale and the covariate of interest along with a term for their product, the coefficient for which was evaluated by the Wald test. For all comparisons, *P*s were two sided, and $\alpha < 0.05$ indicated statistical significance. SAS statistical software, version 8.2 (SAS Institute, Inc., Cary, NC) was used for all analyses.

Results

We identified 677 incident cases of endometrial cancer among 103,882 women during 455,304 person-years of follow-up. The age-adjusted incidence rate of endometrial cancer in the cohort, 82.3 per 100,000 woman years, was slightly higher than Surveillance, Epidemiology, and End Results rates (76.8 per 100,000 woman years).

Age-standardized baseline characteristics of the cohort by categories of BMI at study enrollment and the magnitude of their age-adjusted RR associated with endometrial cancer risk are summarized in Table 1. Women with a higher baseline BMI tended to be younger at menarche than women with a lower BMI. In addition, heavy women were more likely to be older at menopause, and they were less likely to have used menopausal hormones or oral contraceptives than lean women. Endometrial cancer risk was positively associated with age, age at menopause, and current use of menopausal hormone therapy. The RR of endometrial cancer risk for current versus never users of menopausal hormones was 1.25 (95% CI, 1.06-1.48). Endometrial cancer risk was inversely associated with age at onset of menarche, parity, and history of oral contraceptive use.

Baseline BMI was associated with a significant increase in risk of endometrial cancer. Women with a baseline BMI ≥ 30 kg/m^2 had a multivariate RR of 3.03 (95% CI, 2.50-3.68) compared with women with a BMI < 25 kg/m^2 (Table 2). Risk among 64% of women who responded to the second questionnaire was consistent with that in the entire population. BMI at age 18 years was also associated with increased endometrial cancer risk in the multivariate model, but the association disappeared after additional adjustment for baseline BMI. The association between BMI at age 35 years and endometrial cancer risk remained positive, but it became statistically nonsignificant after additionally controlling for baseline BMI. In contrast, BMI at age 50 years was positively related to risk of endometrial cancer after additionally controlling for baseline BMI. The multivariate RR for women with a BMI at age 50 of >30 kg/m^2 compared with <25 kg/m^2 was 1.59 (95% CI, 1.09-2.32).

We also investigated weight gain between age 18 years and baseline in relation to risk of endometrial cancer (Table 2). After multivariate adjustment including control for weight at age 18, the magnitude of risk for weight gain from age 18 years to baseline in relation to endometrial cancer was similar to that of baseline BMI, with a multivariate RR of 2.75 (95% CI, 1.96-3.86; $P_{trend} < 0.001$) for women who gained $\geq$20 kg compared with women with a stable weight (gain/loss < 5 kg) during that time period. When we adjusted for weight at baseline instead of weight at age 18, the association was attenuated and became marginally statistically significant (RR, 1.48; 95% CI, 0.99-2.21; $P_{trend} = 0.102$).

We observed a statistically significant interaction between BMI and menopausal hormone therapy ($P_{interaction} < 0.001$; Table 3). Among nonusers of menopausal hormones, the multivariate RR for a baseline BMI ≥ 30 versus < 25 kg/m^2 was 5.41 (95% CI, 4.01-7.29; $P_{trend} < 0.001$). Risk among women who responded to the second questionnaire was consistent with that in the baseline population; obese women had a RR of 5.07 (95% CI, 3.42-7.52; $P_{trend} < 0.001$) compared with normal-weight women. The comparable risk was considerably weaker among former users of menopausal hormones (RR, 2.53; 95% CI, 1.21-5.30; $P_{trend} = 0.009$), and it became marginally statistically significant among current users of menopausal hormones (RR, 1.44; 95% CI, 1.00-2.05; $P_{trend} = 0.023$). We also investigated the joint effect of BMI and menopausal hormone

Table 1. Selected characteristics of study participants in relation to BMI at study enrollment

Characteristic	Categories of BMI (kg/m^2) at enrollment			Age-adjusted RRs of endometrial cancer
	<25 (n = 48,128)	25-29.9 (n = 32,969)	≥30 (n = 22,785)	
Baseline BMI (kg/m^2)	22.3	27.2	35.0	
Baseline age (y)				
<55	11.9	10.3	12.6	1.0
55-59	23.6	23.2	25.1	1.36 (0.99-1.87)
60-64	28.4	29.7	29.3	1.59 (1.18-2.16)
≥65	36.2	36.8	33.1	1.85 (1.37-2.48)
Age at menarche, % (y)				
<10	4.4	6.2	9.5	1.0
11-12	38.3	41.8	46.3	0.82 (0.61-1.10)
≥13	57.3	52.0	44.2	0.65 (0.49-0.87)
Parity (%)				
0	17.9	16.3	17.5	1.0
1-2	38.5	35.7	32.4	0.80 (0.66-0.99)
≥3	43.6	48.1	50.1	0.66 (0.54-0.81)
Age at menopause, % (y)				
<44	11.7	12.2	12.9	1.0
45-49	28.1	27.0	26.1	1.30 (0.95-1.76)
50-54	50.2	49.9	48.8	1.59 (1.20-2.11)
≥55	10.0	10.9	12.2	2.07 (1.50-2.87)
Menopausal hormone therapy (%)				
Never	53.3	61.3	71.3	1.0
Former	8.3	8.6	7.4	1.00 (0.75-1.34)
Current	38.4	30.1	21.3	1.25 (1.06-1.48)
History of oral contraceptive use (%)				
Never	59.0	61.6	65.6	1.0
Ever	41.0	38.4	34.4	0.71 (0.60-0.85)

NOTE: All values (except age) are standardized, using direct standardization, to the age distribution of the study population.

Table 2. BMI at different ages and weight change between age 18 and study enrollment in relation to endometrial cancer risk

	BMI categories (kg/m^2)			P_{trend}
	<25	25.0-29.9	≥ 30	
Baseline BMI				
Baseline population				
Cases/person-years*	200/211,538	181/144,664	296/99102	
Multivariate RR†	1.0	1.31 (1.07-1.61)	3.03 (2.50-3.68)	<0.0001
With detailed RFQ information				
Cases/person-years*	131/123,544	111/81,706	165/53,662	
Age-adjusted RR	1.0	1.27 (0.99-1.64)	2.94 (2.34-3.70)	<0.0001
Multivariate RR†	1.0	1.29 (1.00-1.66)	2.88 (2.25-3.68)	<0.0001
BMI at age 50				
Cases/person-years*	184/160,935	118/61,628	92/27,884	
Age-adjusted RR	1.0	1.72 (1.36-2.16)	3.20 (2.49-4.13)	<0.0001
Multivariate RR‡	1.0	1.29 (0.99-1.67)	1.59 (1.09-2.32)	0.172
BMI at age 35				
Cases/person-years*	279/208,534	67/28,707	40/10,063	
Age-adjusted RR	1.0	1.78 (1.36-2.32)	3.21 (2.30-4.47)	<0.0001
Multivariate RR‡	1.0	1.14 (0.85-1.53)	1.35 (0.89-2.04)	0.117
BMI at age 18				
Cases/person-years*	329/211,881	36/12,687	11/3,730	
Age-adjusted RR	1.0	1.87 (1.33-2.64)	1.98 (1.09-3.62)	0.003
Multivariate RR‡	1.0	1.21 (0.84-1.73)	0.94 (0.50-1.76)	0.400

	Weight change (kg)					P_{trend}
	Less than −5	−5 to +4.9	5-9.9	10-19.9	≥20	
Age 18 to baseline						
Cases/person-years*	12/8,910	44/46,397	42/38,136	98/67,556	184/71,437	
Age-adjusted RR	1.41 (0.75-2.68)	1.0	1.16 (0.76-1.78)	1.53 (1.07-2.18)	2.75 (1.98-3.82)	<0.0001
Multivariate RR§	1.19 (0.61-2.33)	1.0	1.20 (0.78-1.83)	1.58 (1.11-2.27)	2.75 (1.96-3.86)	<0.0001

*Total cases and person-years are different across BMI at different ages and weight change categories due to missing data on BMI at earlier ages.
†Adjusted for age, physical activity, personal history of diabetes, menopausal hormone therapy, age at menarche, parity, age at menopause, history of oral contraceptives use, smoking, and race.
‡Adjusted for age, physical activity, personal history of diabetes, menopausal hormone therapy, age at menarche, parity, age at menopause, history of oral contraceptive use, smoking, race, and baseline BMI.
§Adjusted for age, physical activity, personal history of diabetes, menopausal hormone therapy, age at menarche, parity, age at menopause, history of oral contraceptive use, smoking, race, and weight at age 18.

therapy (Table 3). Current or former use of menopausal hormone therapy did not further increase risk of endometrial cancer among obese women.

We examined whether risk of endometrial cancer associated with higher BMI differed according to hormone therapy formulation. More than 75% of hormone therapy users reported exclusively using estrogen plus progestin. Among these women, the RR for obese women compared with normal-weight women was 1.52 (95% CI, 0.91-2.53; P_{trend} = 0.12). When we further divided the estrogen plus progestin use into sequential and continuous regimens, risk of endometrial cancer for obese women compared with normal-weight women was significantly increased in women who used a sequential regimen (RR, 2.20; 95% CI, 1.01-4.82; P_{trend} = 0.04) but not in women who used a continuous regimen (RR, 1.37; 95% CI, 0.66-2.82; P_{trend} = 0.90). Only 15% of women who reported hormone therapy use exclusively used unopposed estrogen, and among these, >90% were former users. Among unopposed estrogen users, the RR of endometrial cancer for obesity compared with normal weight was 1.63 (95% CI, 0.69-3.83; P_{trend} = 0.56).

We investigated whether the risk associated with weight gain from age 18 years to baseline differed according to adiposity at age 18 and by menopausal hormone therapy (Table 4). Compared with women who were normal weight at age 18 years and had a weight gain of <5 kg from age 18 to baseline, the greatest risk was found for women who were overweight at age 18 years and had gained ≥20 kg between age 18 and baseline (RR, 4.99; 95% CI, 2.91-8.55). Comparing women who gained >20 kg between age 18 and baseline with women who maintained a stable weight during that time period, the RRs of endometrial cancer among hormone therapy never users and ever users of menopausal hormones were 5.29 (95% CI, 2.97-9.42) and 1.48 (95% CI, 0.98-2.24), respectively. Risk among women who were both overweight at age 18 years and had gained ≥20 kg between age 18 and baseline was greater among those who had never used menopausal hormones (RR, 12.3; 95% CI, 5.54-27.5) than among those who had ever used menopausal hormones (RR, 1.77; 95% CI, 0.66-4.81).

We calculated age-adjusted incidence rates for endometrial cancer across increasing categories of adiposity and within subgroups of women defined by menopausal hormone therapy, reproductive factors, and smoking (Fig. 1). Among women who never used menopausal hormone therapy, the incidence rate of endometrial cancer was much higher in obese (328.7 per 100,000 woman years) than normal-weight women (52.8 per 100,000 woman years). Differences were less pronounced among former users. The incidence rates among current menopausal hormone therapy users were similar regardless of body size (rate in obese versus normal weight women: 229.7 versus 177.6 per 100,000 women years). We found no statistical interaction between BMI and reproductive factors or smoking status in relation to endometrial cancer. However, the highest incidence rates of endometrial cancer were observed among obese women who reported never using oral contraceptives, who were nulliparous, who had an early menarche or late menopause, or who were never smokers.

Discussion

In this large prospective study, both baseline BMI and weight gain between age 18 and baseline were strong predictors of

Table 3. BMI in relation to endometrial cancer risk according to menopausal hormone therapy in the baseline population, and in the baseline population with detailed information on menopausal hormone therapy

	BMI category (kg/m^2)			P_{trend}
	<25	25.0-29.9	≥30	
Baseline population				
Stratification by menopausal hormone therapy status				
Never use				
Cases/person-years	59/112,988	98/89,459	231/70,228	
Multivariate RR*	1.0	1.98 (1.43-2.74)	5.41 (4.01-7.29)	<0.0001
Former use				
Cases/person-years	14/17,503	19/12,429	19/7,350	
Multivariate RR*	1.0	1.81 (0.90-3.63)	2.53(1.21-5.30)	0.009
Current use				
Cases/person-years	127/81,047	64/42,777	46/21,524	
Multivariate RR*	1.0	0.96 (0.71-1.31)	1.44 (1.00-2.05)	0.023
Joint effect of BMI and menopausal hormone therapy status				
Never use				
Multivariate RR*	1.0	2.02 (1.46-2.80)	5.74 (4.28-7.70)	
Former use				
Multivariate RR*	1.63 (0.91-2.92)	3.07 (1.83-5.16)	4.82 (2.86-8.12)	
Current use				
Multivariate RR*	3.40 (2.49-4.65)	3.14 (2.20-4.50)	4.26 (2.88-6.31)	
Baseline population with detailed information on menopausal hormone therapy†				
Never use				
Cases/person-years	35/56,784	59/43,628	111/33,203	
Multivariate RR*	1.0	2.14 (1.41-3.26)	5.07 (3.42-7.52)	<0.001
Unopposed estrogen exclusively				
Cases/person-years	14/8,669	10/6,187	10/3,969	
Multivariate RR*	1.0	1.01 (0.44-2.28)	1.63 (0.69-3.83)	0.563
Estrogen plus progestin exclusively				
Cases/person-years	52/45,356	29/14,734	24/12,528	
Multivariate RR*	1.0	1.00 (0.63-1.59)	1.52 (0.91-2.53)	0.116

*Adjusted for age, physical activity, personal history of diabetes, age at menarche, parity, age at menopause, oral contraceptive use, smoking, and race.
†Women who reported mixed use of exclusive unopposed estrogen and exclusive estrogen plus progestin or unknown use are not included.

endometrial cancer risk. In addition, consistent adiposity throughout adulthood was associated with increased risk of endometrial cancer beyond that related to current adiposity. The relations of BMI and adult weight gain to endometrial cancer were significantly modified by menopausal hormone therapy; risks were more pronounced among never users of menopausal hormone therapy than among former or current users.

Current BMI and Endometrial Cancer. Our finding of a significantly positive association between current BMI and endometrial cancer risk is consistent with those from previous studies. The relationship between current BMI and endometrial cancer risk has been evaluated in at least 29 epidemiologic studies (1, 7-10). The magnitudes of RRs comparing extreme categories of BMI that have been reported in these previous studies have generally ranged between 2 and 5.

Table 4. Weight change from age 18 to baseline in relation to risk of endometrial cancer according to BMI at age 18

Weight gain (kg) between age 18 and study enrollment	BMI at age 18		Total women
	<25	≥25	
All women*			
<5 kg	1.0	0.70 (0.28-1.72)	1.0
Cases/person-years	50/46,739	6/7,554	56/54,293
5-20 kg	1.18 (0.85-1.65)	3.03 (1.63-5.61)	1.37 (0.99-1.88)
Cases/person-years	124/99,556	15/4,274	139/103,830
≥20 kg	2.24 (1.61-3.11)	4.99 (2.91-8.55)	2.48 (1.81-3.40)
Cases/person-years	155/65,586	26/4,589	181/70,175
Women never using menopausal hormone therapy†			
<5 kg	1.0	1.46 (0.39-5.53)	1.0
Cases/person-years	11/21,125	3/4,186	14/25,311
5-20 kg	1.77 (0.91-3.41)	8.00 (3.31-19.3)	2.21 (1.21-4.02)
Cases/person-years	47/47,948	11/2,599	58/50,547
≥20 kg	4.56 (2.42-8.60)	12.3 (5.54-27.5)	5.29 (2.97-9.42)
Cases/person-years	98/37,560	21/3,136	119/40,696
Women ever using menopausal hormone therapy†			
<5 kg	1.0	0.43 (0.12-1.55)	1.0
Cases/person-years	39/25,614	3/3,368	42/28,982
5-20 kg	1.03 (0.70-1.52)	1.13 (0.39-3.32)	1.11 (0.76-1.63)
Cases/person-years	77/51,608	4/1,676	81/53,284
≥20 kg	1.35 (0.89-2.06)	1.77 (0.66-4.81)	1.48 (0.98-2.24)
Cases/person-years	57/28,025	5/1,453	62/29,478

NOTE: $P_{interaction}$ with menopausal hormone therapy is 0.004.
*Adjusted for age, physical activity, personal history of diabetes, menopausal hormone therapy, age at menarche, parity, age at menopause, oral contraceptive use, smoking, race and weight at age 18.
†Adjusted for age, physical activity, personal history of diabetes, age at menarche, parity, age at menopause, oral contraceptive use, smoking, race and weight at age 18.

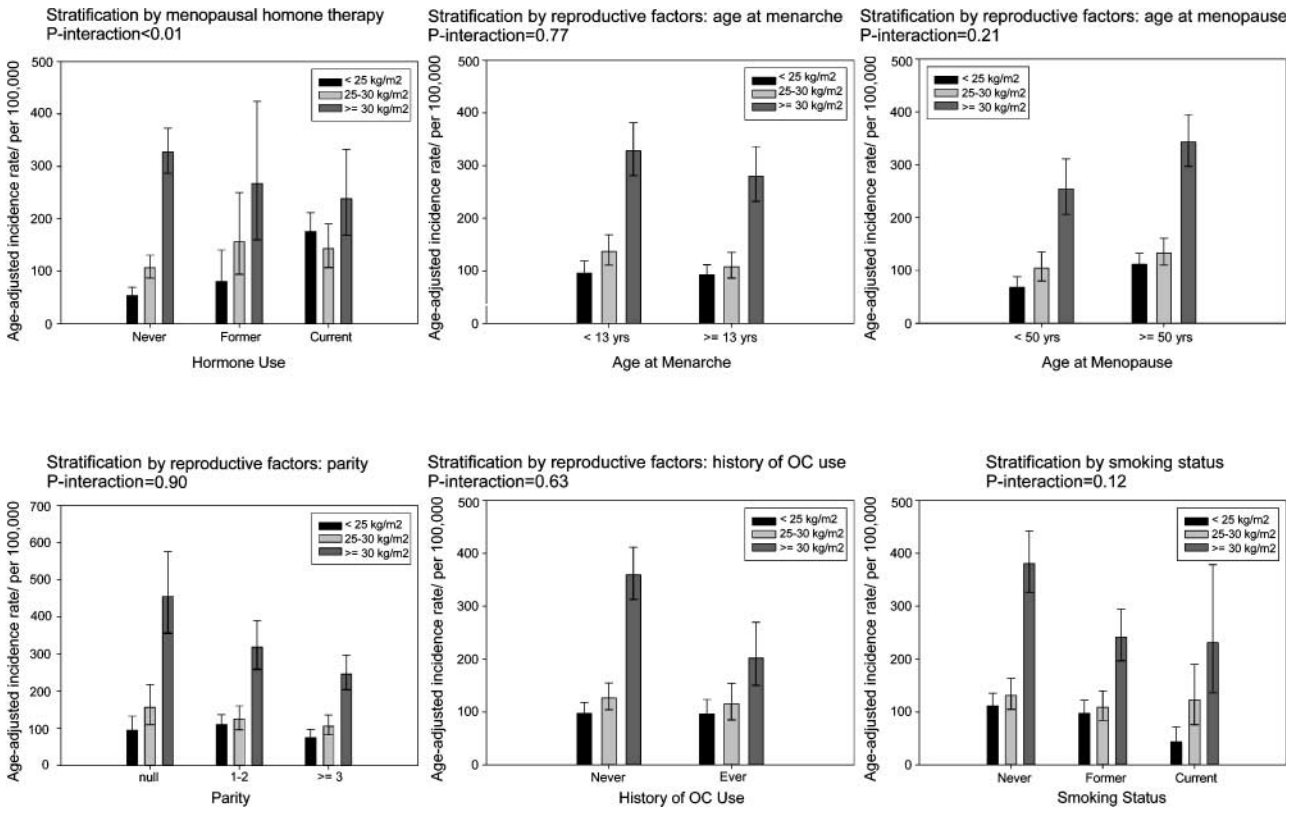

Figure 1. Age-adjusted incidence rates of endometrial cancer for increasing categories of BMI in subgroups according to menopausal hormone therapy, reproductive factors, and smoking status.

Adult Weight Gain and Endometrial Cancer. Several studies reported a statistically significant (7, 9, 10, 12, 19-21) or marginally significant (22) positive relation between adult weight gain and endometrial cancer risk, showing a 2- to 6-fold increased risk with increasing level of weight gain. Adult weight gain has not always been consistently defined in these studies but has generally encompassed weight gain from age 18 years to current ages. Three investigations on weight gain (10, 12, 21) adjusted for current BMI, which resulted in subsequent attenuated or null associations in two studies (12, 21). The findings from our and those studies (12, 21) suggest that weight gain is positively associated with endometrial cancer risk, but that part of the relation observed with weight gain is explained by current BMI. In contrast, one recent study (10) found a positive association with adult weight gain that remained statistically significant after adjustment for current BMI.

We found that women who were overweight at age 18 years and subsequently gained ≥20 kg between age 18 years and baseline showed greater endometrial cancer risk than those who were normal weight at age 18 years and had a similar weight gain. One study (19) showed that risk was greatest among those who fell into the highest category of BMI as a teenager (age 16 years) and subsequently gained the most weight during adulthood. Another study (23) reported that women who consistently weighed >10 lbs. above average from age 25 to 29 years to age 50 to 59 years had an increased risk of endometrial cancer compared with women who maintained the population average weight during that time.

BMI at Different Life Stages and Endometrial Cancer. Previous studies that have examined BMI at different life periods in relation to endometrial cancer risk have tended to focus on weight at early ages (usually ages 18-20 years). Most studies (12, 13, 21, 24-26) showed a statistically significant positive association between BMI at an early age and subsequent endometrial cancer risk. However, the association remained evident after adjustment for current BMI in only two studies (12, 13). Our findings regarding BMI at age 18 years are consistent with data from the remaining studies (21, 24-26) reporting that the association with early age BMI is either no longer statistically significant (24-26) or null (21) after adjustment for baseline BMI. Additional four studies (7, 9, 19, 22) showed a nonsignificant positive association, but those studies did not adjust for current BMI.

In our study, both BMI at ages 35 and 50 years were positively related to endometrial cancer risk, although only BMI at age 50 remained statistically significant after control for baseline BMI. These results are largely consistent with three (9, 25, 27) previous studies showing that BMI at ages 30 to 50 are positively associated with endometrial cancer risk, one (25) of which adjusted for current BMI, and two (9, 27) that did not. That we observed positive relations not only of adult weight gain but also of BMI at age 35 years and BMI at age 50 years to endometrial cancer risk suggests that the effect of adiposity on endometrial carcinogenesis is a continuous and cumulative process throughout the entire life.

Joint Effect of Baseline BMI and Menopausal Hormone Therapy in Relation to Endometrial Cancer. Most of the limited available research on the joint effects of BMI and menopausal hormone therapy on endometrial cancer risk (28-31) has focused on menopausal hormone therapy but not BMI as the main exposure variable. For example, one prospective study (30) reported that the excess RR per year of unopposed estrogen therapy was considerably higher among normal weight women (excess RR, 0.92) than among overweight women (excess RR, 0.31), and it was essentially null among obese women (excess RR, 0.05). Recently, the Million Women Study (31) reported that compared with nonusers of menopausal hormone therapy, the adverse effect

of unopposed estrogen therapy use was greatest in normal-weight women (RR, 2.99; 95% CI, 2.08-4.30) and least in obese women (RR, 1.09; 95% CI, 0.67-1.75), whereas the inverse association with estrogen plus progestin was greatest in obese women (RR, 0.28; 95% CI, 0.14-0.55) and least in normal-weight women (RR, 1.07; 95% CI, 0.73-1.56).

In our study, the increased risk of endometrial cancer with higher BMI was very strong in women who never used menopausal hormone therapy; risk associated with adiposity was attenuated in former users, and it became marginally statistically significant among current users. La Vecchia et al. (14) were the first to report a stronger association between BMI and endometrial cancer among never users of estrogen than among ever users. In contrast, a recent study (10) found no clear effect modification of the BMI-endometrial cancer association by menopausal hormone therapy. Any observed gradient in risk across categories of menopausal hormone therapy use would suggest that adiposity increases endometrial cancer risk largely through its estrogenic effects. In support of a role of estrogen, one study (32) showed that the positive association between BMI and endometrial cancer was substantially attenuated after adjustment for circulating levels of estrogen. Another study (33), however, found no evidence that the BMI and endometrial cancer relation is mediated by estrogens.

The relationship between BMI and endometrial cancer risk could be further modified by the type of menopausal hormone therapy because the effect of exogenous estrogen may vary by the level of progestin added in the regimen. We observed a slightly lower risk associated with adiposity in women using a continuous versus sequential estrogen plus progestin regimen. This finding is consistent with that from the Million Women Study (31) suggesting that the relationship between BMI and endometrial cancer is modified by the number of days per month that progestins are added to the regimen. These data raise the possibility that the progestins contained in combined formulations have the potential to counter endometrial proliferation from both exogenous estrogen and endogenous estrogen that arises from aromatization of androgens in the adipose tissue.

Baseline BMI, Other Reproductive Factors, and Endometrial Cancer. As expected, the incidence rates of endometrial cancer in our study were high among women with an increased lifetime exposure to estrogens (i.e., women with an early age at menarche, a later age at menopause, a lower parity, and no history of oral contraceptive use). In contrast, among obese women but not normal-weight women, we noted an apparent paradoxical lower incidence rate of endometrial cancer among women using menopausal hormone therapy compared with those not using menopausal hormone therapy. A similar pattern was also reported in the Million Women Study (31). One possible reason for the observation of such interaction is that exogenous estrogens supplied by menopausal hormones fail to add further to the high background levels of endogenous estrogens among obese women (31). However, chance or other health characteristics associated with both hormone therapy use and BMI might have contributed to the results observed in our study. The possibility of a certain threshold level of obesity-associated endogenous estrogens beyond which exogenous estrogens have little additional effect on endometrial cancer risk requires further research, especially if endogenous estrogens and exogenous estrogens affect endometrial carcinogenesis through similar pathways.

Strengths and Limitations. Our study has several important strengths, including the large size of the cohort with many incident cases and the availability of information on numerous known or suspected risk factors for endometrial cancer, which enabled us to minimize potential confounding. The validity of self-reported height and weight in our study should not be a concern because self-reported height and weight are highly accurate. The correlation coefficients between self-reported versus measured height and weight are typically >0.9, and recalled weight from 28 years earlier among elderly individuals has been reported to have a correlation of >0.8 with measured weight at that time (34). The relatively low prevalence of overweight and obesity during adolescence and early adulthood before the 1980s may have limited the statistical power of contemporary studies, including ours, to fully capture the association between obesity at earlier ages and subsequent endometrial cancer risk. The self-reported menopausal hormone therapy information in our study was likely to be accurate, with previous validation research showing >95% agreement between self-reported data and prescriptions for menopausal hormones (35). However, results on BMI-endometrial cancer associations by specific type of hormone therapy regimen are based on small numbers. These findings should be interpreted with caution.

Summary. In summary, we found that high BMI at baseline and adult weight gain were associated with increased endometrial cancer risk. In addition, consistent overweight or obesity during adulthood was associated with greater risk of endometrial cancer than being overweight or obese only in later adult life. Menopausal hormone therapy was independently associated with increased risk of endometrial cancer, and the relationships of both BMI and adult weight gain to endometrial cancer risk were stronger among nonusers than among current or former users of menopausal hormones. Taken together, our findings suggest that obesity and menopausal hormones increase endometrial cancer risk through common etiologic pathways.

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