Intentional Weight Loss and Endometrial Cancer Risk

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ABSTRACT

Purpose

Although obesity is an established endometrial cancer risk factor, information about the influence of weight loss on endometrial cancer risk in postmenopausal women is limited. Therefore, we evaluated associations among weight change by intentionality with endometrial cancer in the Women's Health Initiative (WHI) observational study.

Patients and Methods

Postmenopausal women (N = 36,794) ages 50 to 79 years at WHI enrollment had their body weights measured and body mass indices calculated at baseline and at year 3. Weight change during that period was categorized as follows: stable (change within $\pm 5\%$), loss (change $\geq 5\%$), and gain (change $\geq 5\%$). Weight loss intentionality was assessed via self-report at year 3; change was characterized as intentional or unintentional. During the subsequent 11.4 years (mean) of follow-up, 566 incident endometrial cancer occurrences were confirmed by medical record review. Multi-variable Cox proportional hazards regression models were used to evaluate relationships (hazard ratios [HRs] and 95% CIs) between weight change and endometrial cancer incidence.

Results

In multivariable analyses, compared with women who had stable weight ($\pm 5\%$), women with weight loss had a significantly lower endometrial cancer risk (HR, 0.71; 95% CI, 0.54 to 0.95). The association was strongest among obese women with intentional weight loss (HR, 0.44; 95% CI, 0.25 to 0.78). Weight gain (≥ 10 pounds) was associated with a higher endometrial cancer risk than was stable weight, especially among women who had never used hormones.

Conclusion

Intentional weight loss in postmenopausal women is associated with a lower endometrial cancer risk, especially among women with obesity. These findings should motivate programs for weight loss in obese postmenopausal women.

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INTRODUCTION

Endometrial cancer is the most common gynecologic cancer and the fourth most common cancer among women in the United States.¹ Although endometrial cancer is the cancer most strongly associated with obesity,² information about the effects of weight loss in postmenopausal women on subsequent endometrial cancer incidence is limited. Several observational studies have associated self-reported weight loss at some period during adult life with lower endometrial cancer risk.³⁻⁶ However, these reports have not focused on weight loss that occurred in postmenopausal women or on the potential influence of intentionality of weight loss on risk.

Unintentional weight loss is highly correlated with increased morbidity and may contribute to reverse causality.^{7,8} To our review, the issue of the influence of intentional weight loss on endometrial cancer risk has only been addressed in one prospective study—the Iowa Women's Health Study.³ In that study, women who experienced a previous episode, anytime during adult life, of intentional, self-reported weight loss of greater than 20 pounds and who were not currently overweight had endometrial cancer risks similar to those of nonoverweight women who never lost weight.

The Women's Health Initiative (WHI) observational study, which measured serial weights with an associated query about weight loss intentionality, provides a unique opportunity

ASSOCIATED CONTENT

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to evaluate the association of weight change and endometrial cancer risk by weight loss intentionality among an ethnically diverse population of postmenopausal women.

PATIENTS AND METHODS

WHI

The WHI was designed to address major causes of morbidity and mortality in postmenopausal women⁹ and included both a set of clinical trials and an observational study. Details of design and implementation of the WHI program have been published elsewhere.¹⁰⁻¹⁴ Briefly, 161,808 women ages 50 to 79 years with anticipated survival greater than 3 years were recruited at 40 clinical centers throughout the United States between September 1, 1993, and December 31, 1998. Participants in the observational study included 93,676 women who were ineligible or uninterested in participating in the clinical trials. The study was approved by institutional review boards at the clinical centers, and participants provided written informed consent.

Information on covariates of interest was collected from questionnaires administered at baseline. Information on menopausal hormone therapy use was collected during interviews that included a review of medication containers. Race/ethnicity was documented by self-report at baseline. Weight and height were measured by using a standardized approach at clinic visits, and body mass index (BMI) was calculated.

The following participants were excluded from the cohort for this analysis: women who had a history of cancer (except for non-melanoma skin cancer; $n = 10,197$) at baseline; women who were enrolled in the WHI but provided no follow-up information ($n = 422$); women who had undergone hysterectomy before enrollment ($n = 33,317$); women who had a missing value of exposures of interest and major confounders ($n = 11,081$); women whose BMI was less than 18.5 kg/m^2 (underweight; $n = 837$); and women who had an endometrial cancer diagnosis, had a hysterectomy, died, or were lost to follow-up between baseline and the year-3 visit ($n = 1,029$). After exclusions, 36,793 women remained for additional analysis.

Follow-Up and Ascertainment of Cases

Follow-up continued through the original specified completion date of March 31, 2005. Additional follow-up required two additional written consents, which were obtained in 78% of surviving participants.

All incident endometrial cancer occurrences diagnosed after the year-3 visit were the primary study outcome. Endometrial cancer occurrences were initially identified by self-report from questionnaires administered annually, confirmed by medical record review, and coded centrally at the clinical coordinating center according to the SEER guidelines. For these analyses, participants were observed from the year-3 visit to the first of either an endometrial cancer diagnosis, a date of hysterectomy, a date of death, loss to follow-up, or end of current follow-up (September 30, 2015).

Measurements

Weight change between baseline and year 3 was calculated from the measured weights and was grouped into three categories: stable weight, weight loss, or weight gain. The three categories were defined in two ways: on the basis of an actual change in body weight (stable weight, or change within ± 10 pounds; weight loss ≥ 10 pounds from baseline weight; and weight gain ≥ 10 pounds from baseline weight) and on the basis of percentage change in body weight (stable weight, or change within $\pm 5\%$; weight loss $\geq 5\%$ from baseline; and weight gain $\geq 5\%$ from baseline).

In addition, at the year-3 year follow-up, women were asked in a questionnaire “In the past 2 years, did you gain or lose 5 or more pounds?” and “Was the change intentional or unintentional?” The information was used to categorize weight loss as intentional or unintentional.

Covariates

We adjusted for the following potential confounders measured at baseline: age (< 55 , 55 to 59 , 60 to 64 , 65 to 69 , 70 to 74 , and ≥ 75 years), race/ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, Black, Hispanic/Latino, non-Hispanic white, and other), level of education (high school or less, some college/technical training, college or some postcollege, and master's degree or higher), smoking pack-years (never, < 10 , 10 to < 20 , 20 to < 30 , 30 to < 40 , and ≥ 40), recreational physical activity (total metabolic equivalent tasks [METs] per week: < 5 , 5 to < 10 , 10 to < 20 , 20 to < 30 , and ≥ 30), history of hormone therapy use (none, estrogen alone, estrogen and progestin, mixed), parity (never pregnant, never had term, $1, 2, 3, 4$, or ≥ 5), age of menarche (< 12 , 12 to 13 , 14 to 15 , or ≥ 16 years), age at first birth (never had term pregnant, < 20 , 20 to 29 , or ≥ 30 years), family history of endometrial cancer (yes or no), and BMI. Detailed information about the categorizations of each variable is listed in Table 1.

Table 1. HRs and 95% CIs for the Association Between Weight Change and Risk of Endometrial Cancer

Weight Change Between Baseline and Year 3	No. of Patients	Multivariable-Adjusted HR (95% CI)*
Change in pounds		
Stable weight (within ± 10)	425	Reference
Weight gain (≥ 10)	96	1.26 (1.00 to 1.57)
Weight loss (≥ 10)	45	0.70 (0.51 to 0.98)
Intentional	27	0.61 (0.40 to 0.92)
Unintentional	18	0.91 (0.56 to 1.46)
% weight change		
Stable weight (within ± 5)	384	Reference
Weight gain (≥ 5)	124	1.12 (0.92 to 1.38)
Weight loss (≥ 5)	58	0.71 (0.54 to 0.95)
Intentional	33	0.60 (0.42 to 0.86)
Unintentional	25	0.94 (0.62 to 1.41)

Abbreviation: HR, hazard ratio.

*Multivariable models adjusted for age at enrollment, race/ethnicity, education, smoking pack-years, recreational physical activity, history of hormone therapy use, parity, age of menarche, age at first birth, family history of endometrial cancer, and body mass index.

Statistical Analysis

χ^2 tests were used to evaluate differences for categorical covariates. An analysis of variance was used for continuous variables. Cox proportional hazards regression models were used to evaluate the relationship (hazard ratios [HRs] and 95% CIs) between weight change and incidence of endometrial cancer. We also performed analyses of relationships between weight change and endometrial cancer risk stratified by obesity status, hormone use, and age at baseline. In the final multivariate-adjusted models, potential confounders included these variables listed in the Covariates section. Because obesity reportedly has a greater effect on type I endometrial cancer (endometrioid adenocarcinoma, adenocarcinoma not otherwise specified, or adenocarcinoma with squamous differentiation) than on type II endometrial cancer (serous/papillary serous and mixed-cell adenocarcinoma),¹⁵ we restricted sensitivity analyses to type I tumors. Our primary study hypothesis was that intentional weight loss would be significantly associated with a lower risk of endometrial cancer. We conducted another sensitivity analysis to test whether women who intentionally lost weight and had a lower BMI at 3 years had the same risk of endometrial cancer as women who had the same lower stable BMI (at baseline and 3 years) by analyzing the changes of BMI between baseline and year 3. The change of BMI was categorized as low-stable BMI (BMI < 25 kg/m² at baseline and year-3 visit: reference group); weight gain or stay-high BMI group (BMI < 25 kg/m² at baseline and BMI $\geq$ 25 kg/m² at year-3 visit, or BMI $\geq$ 25 kg/m² at baseline and year-3 visit); and weight loss group (BMI $\geq$ 25 kg/m² at baseline and BMI < 25 kg/m² at year-3 visit). We then divided the weight loss group into intentional and unintentional.

RESULTS

During a mean 11.4 years of follow-up, 566 women developed endometrial cancer. Baseline characteristics by percentage of weight change categories from baseline to year 3 (stable weight [change within $\pm$ 5%]), weight loss $\geq$ 5%, and weight gain $\geq$ 5%) are listed in Appendix Table A1 (online only). Compared with women who

had stable weight, women who had weight gain were more likely to be younger, less physically active, black, less educated, and heavier smokers. They were also more likely to be hormone therapy users, have a younger age at menarche, have fewer term pregnancies, and have a younger age at first birth. Compared with women who had stable weight, women who had intentional weight loss were more likely to have a higher BMI, be less physically active, be black, be less educated, and be heavier smokers. They were also more likely to never have used hormone therapy, to have had a younger age at menarche, to have had a greater number of term pregnancies, and to have had a younger age at first birth (all $P < .05$).

After analyses were adjusted for baseline BMI and other potential confounders, women who had weight loss $\geq$ 5% had a significantly lower risk of endometrial cancer than women who had stable weight (HR, 0.71; 95% CI, 0.54 to 0.95; Table 1). This was observed for any weight loss, but the risk was even lower for obese women who had intentional weight loss (HR, 0.44; 95% CI, 0.25 to 0.78; Table 2). These results were similar regardless of weight change measured in pounds or percentage between baseline and year 3. Women with weight gain $\geq$ 10 pounds had a significantly higher risk of endometrial cancer ($P = .049$). Weight gain measured by percentage ($\geq$ 5%) was not associated with an endometrial cancer risk. Unintentional weight loss was not associated with a lower risk (Table 1).

We examined the associations between weight change and risk of endometrial cancer stratified by potential effect modifiers, including BMI (normal weight, overweight, and obese), menopausal hormone therapy use (never, ever estrogen alone users, or exclusively estrogen plus progestin users), and age at baseline (50 to 59, 60 to 69, $\geq$ 70 years). We observed a significantly lower risk of endometrial cancer associated with weight loss among women who were obese but not in women who were normal weight or overweight (Table 2). There was a 48% lower risk seen for obese women who lost weight intentionally when weight change was measured in pounds (HR, 0.52; 95% CI, 0.30 to 0.90), and a 56% lower risk when weight change was measured as a percentage (HR, 0.44; 95% CI, 0.25 to 0.78). The P value for the interaction test was .07 when weight change was measured in pounds and was .10 when weight change was measured as a percentage.

Table 2. Multivariable-Adjusted HRs and 95% CIs for the Association Between Weight Change and Endometrial Cancer Risk Stratified by BMI

Weight Change Between Baseline and Year 3	Normal Weight (BMI 18.5 to < 25 kg/m ²)		Overweight (BMI 25 to < 30 kg/m ²)		Obese (BMI $\geq$ 30 kg/m ²)	
	No. of Patients	HR (95% CI)*	No. of Patients	HR (95% CI)	No. of Patients	HR (95% CI)
Change in pounds						
Stable weight (within $\pm$ 10)	198	Reference	112	Reference	115	reference
Weight gain ($\geq$ 10)	25	1.08 (0.71 to 1.64)	30	1.49 (0.99 to 2.24)	41	1.29 (0.90 to 1.86)
Weight loss ($\geq$ 10)	5	0.59 (0.24 to 1.43)	18	1.36 (0.82 to 2.25)	22	0.53 (0.33 to 0.87)
Intentional	2	0.52 (0.13 to 2.08)	9	1.04 (0.52 to 2.05)	16	0.52 (0.30 to 0.90)
Unintentional	3	0.64 (0.21 to 2.02)	9	2.00 (1.01 to 3.96)	6	0.57 (0.25 to 1.33)
% weight change						
Stable weight (within $\pm$ 5% change)	164	Reference	100	Reference	120	Reference
Weight gain ($\geq$ 5%)	49	1.08 (0.78 to 1.49)	37	1.23 (0.84 to 1.80)	38	1.14 (0.78 to 1.65)
Weight loss ($\geq$ 5%)	15	0.80 (0.47 to 1.35)	23	1.16 (0.74 to 1.83)	20	0.47 (0.29 to 0.77)
Intentional	6	0.61 (0.27 to 1.38)	13	1.01 (0.57 to 1.81)	14	0.44 (0.25 to 0.78)
Unintentional	9	1.00 (0.51 to 1.97)	10	1.44 (0.75 to 2.78)	6	0.57 (0.25 to 1.30)

Abbreviations: BMI, body mass index; HR, hazard ratio.

*Multivariable models adjusted for age at enrollment, race/ethnicity, education, smoking pack-years, recreational physical activity, history of hormone therapy use, parity, age of menarche, age at first birth, family history of endometrial cancer, and BMI (measured continuously and included as a covariate only for the obese group).

We observed a higher risk of endometrial cancer associated with weight gain ≥ 10 pounds in women without a history of menopausal hormone use but not in women with a history of hormone use (Table 3). We also observed a lower risk of endometrial cancer associated with intentional weight loss measured in pounds or as a percentage in women with a history of estrogen plus progestin use exclusively but not in women without hormone use or with estrogen alone use (P for interaction test = .02 when weight change was measured in pounds; $P = .6$ when weight change was measured as a percentage). The association between weight change and endometrial cancer risk did not differ by age.

In a sensitivity analysis of weight loss and endometrial cancer subtypes, a stronger association was seen between intentional weight loss and risk of type I endometrial cancer compared with overall results. For example, compared with women who had stable weight ($\pm 5\%$), women who had intentional weight loss had a 52% lower risk of type I endometrial cancer (HR, 0.48; 95% CI, 0.30 to 0.76) overall; obese women who had intentional weight loss had a 74% lower risk compared with obese women with stable weight (HR, 0.26; 95% CI, 0.12 to 0.57). The results from the second sensitivity analysis showed that women who intentionally lost weight and had a normal BMI at 3 years (ie, $< 25 \text{ kg/m}^2$) had the same risk of endometrial cancer as women who maintained a stable normal BMI (Appendix Table A2, online only).

DISCUSSION

In this large prospective study of postmenopausal women, after analyses were adjusted for BMI and other potential confounders, intentional weight loss was associated with a lower risk of endometrial cancer, especially among obese women.

Previous studies³⁻⁶ that investigated the association between endometrial cancer and weight loss have considered weight change throughout adult life, without a focus on change during the postmenopausal period, and have been based on self-reported weights. One case-control study⁵ and one cohort

study⁴ have associated self-reported weight loss with lower endometrial cancer risk. One case-control study⁶ reported that women who had intentionally lost weight and maintained that weight loss were not at a higher endometrial cancer risk than women who maintained a normal weight throughout. A similar result was also reported in the Iowa Women's Health Study.³

To our knowledge, this study is the first to use measured baseline and follow-up weights with weight loss intentionality examined over a relatively short period to temporally link measured weight change in postmenopausal women. In this setting, modest weight loss was associated with a significantly lower risk of endometrial cancer. Additionally, although intentional weight loss was associated with a significantly lower risk of endometrial cancer, unintentional weight loss was not. These findings suggest that, in postmenopausal women, it may not be too late for weight loss to offer potential health benefits.

In our study population, the lower risk of endometrial cancer associated with weight loss was more pronounced in women who were obese at baseline. We are not aware of other studies in which the associations of weight loss and endometrial cancer risk were stratified by BMI. However, our finding is consistent with reports that sustained weight loss after bariatric surgery has been associated with lower endometrial cancer risk in severely obese women.¹⁶⁻¹⁸

Most previous studies that have examined the relationship between absolute weight gain during adulthood and endometrial cancer risk have reported positive associations.^{4-6,19-21} We observed a significant positive association between weight gain ≥ 10 pounds and endometrial cancer risk in women without hormone use. In the WHI randomized clinical trial on hormone therapy, estrogen plus progestin significantly reduced endometrial cancer incidence.²² In our current analyses, the lower risk of endometrial cancer associated with weight loss was more pronounced in women with estrogen plus progestin use. Somewhat in contrast, in several prior studies, postmenopausal hormone therapy use substantially attenuated the association between obesity and higher risk of endometrial cancer.^{20,23,24}

Table 3. Multivariable-Adjusted HRs and 95% CIs for the Association Between Weight Change and Endometrial Cancer Risk Stratified by Hormone Use

Weight Change Between Baseline and Year 3	Never Used Hormone		Ever Used Estrogen Alone		Exclusively Used Estrogen Plus Progestin	
	No. of Patients	HR (95% CI)*	No. of Patients	HR (95% CI)	No. of Patients	HR (95% CI)
Change in pounds						
Stable weight (within ± 10)	154	Reference	79	Reference	192	Reference
Weight gain (≥ 10)	42	1.48 (1.05 to 2.10)	11	0.92 (0.48 to 1.75)	43	1.21 (0.86 to 1.69)
Weight loss (≥ 10)	29	0.93 (0.60 to 1.44)	4	0.40 (0.14 to 1.14)	12	0.54 (0.30 to 0.99)
Intentional	19	0.85 (0.51 to 1.43)	2	0.35 (0.08 to 1.51)	6	0.39 (0.17 to 0.89)
Unintentional	10	1.10 (0.57 to 2.12)	2	0.45 (0.11 to 1.90)	6	0.87 (0.38 to 1.98)
% weight change						
Stable weight (within $\pm 5\%$ change)	151	Reference	67	Reference	166	Reference
Weight gain ($\geq 5\%$)	46	1.15 (0.83 to 1.61)	16	0.96 (0.55 to 1.67)	62	1.16 (0.87 to 1.56)
Weight loss ($\geq 5\%$)	28	0.70 (0.46 to 1.07)	11	0.90 (0.47 to 1.75)	19	0.64 (0.40 to 1.04)
Intentional	18	0.64 (0.39 to 1.07)	5	0.72 (0.28 to 1.84)	10	0.49 (0.26 to 0.94)
Unintentional	10	0.82 (0.43 to 1.57)	6	1.13 (0.48 to 2.66)	9	0.95 (0.48 to 1.86)

Abbreviation: HR, hazard ratio.

*Multivariable models adjusted for age at enrollment, race/ethnicity, education, smoking pack-years, recreational physical activity, parity, age of menarche, age at first birth, family history of endometrial cancer, and body mass index.

Strengths of this study include the large prospective design with long-term follow-up, centrally adjudicated endometrial cancer occurrences, detailed information on potential confounders, measured baseline and follow-up body weights, and determination of intentional or unintentional weight loss linked to the period of measured body weights. However, limitations deserve mention. Our findings are limited to postmenopausal women and did not account for weight change beyond 3 years of follow-up. If a woman lost weight between years 1 and 3 and then regained or even increased her weight, she was analyzed as a member of the weight loss group, a misclassification more likely to make our findings conservative.

In conclusion, intentional weight loss in postmenopausal women was associated with lower endometrial cancer risk, especially among women with obesity. These findings should motivate programs for weight loss in obese postmenopausal women.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Manuscript writing: All authors
Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No relationship to disclose

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No relationship to disclose

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Appendix

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Women's Health Initiative memory study (Wake Forest University School of Medicine, Winston-Salem, NC) investigator: Mark Espeland

For a list of all the investigators who have contributed to WHI science, please visit <https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf>.

Table A1. Baseline Characteristics of Participants by Percentage of Weight Change Between Baseline and Year 3

Characteristic	% Weight Change* (N = 36,793)									
	Stable Weight (within 5%)		Weight Gain (≥ 5%)		Weight Loss					
	No. of Patients (n = 24,863)	Mean or %	No. of Patients (n = 7,159)	Mean or %	≥ 5%		Unintentional		Intentional	
					No. of Patients (n = 4,771)	Mean or %	No. of Patients (n = 1,856)	Mean or %	No. of Patients (n = 2,915)	Mean or %
Mean age at screening, years		63.5		61.4		64.3		65.9		63.3
Mean BMI, kg/m ²		26.4		26.5		28.8		27.5		29.6
Total METs per week		15.2		14.4		13.3		12.3		13.9
Ethnicity										
American Indian or Alaskan Native	70	0.3	35	0.5	18	0.4	7	0.4	11	0.4
Asian or Pacific Islander	891	3.6	188	2.6	121	2.5	55	3.0	66	2.3
Black or African-American	1,221	4.9	395	5.5	304	6.4	122	6.6	182	6.2
Hispanic/Latino	702	2.8	223	3.1	140	2.9	51	2.7	89	3.1
White (not of Hispanic origin)	21,637	87.0	6,230	87.0	4,135	86.7	1,597	86.0	2,538	87.1
Other	342	1.4	88	1.2	53	1.1	24	1.3	29	1.0
Education	4,399	17.7	1,293	18.1	900	18.9	368	19.8	532	18.3
High school diploma or less										
Some college/technical training	8,127	32.7	2,462	34.4	1,748	36.6	676	36.4	1,072	36.8
College graduate or more	6,726	27.1	1,845	25.8	1,177	24.7	466	25.1	711	24.4
Masters degree or more	5,611	22.6	1,559	21.8	946	19.8	346	18.6	600	20.6
Pack-years of cigarette smoking	757	3.0	232	3.2	139	2.9	52	2.8	87	3.0
Missing										
Never smoking	12,864	51.7	3,385	47.3	2334	48.9	947	51.0	1,387	47.6
< 10	5,083	20.4	1,415	19.8	914	19.2	308	16.6	606	20.8
10 to < 20	2,166	8.7	707	9.9	387	8.1	155	8.4	232	8.0
20 to < 30	1,368	5.5	471	6.6	307	6.4	124	6.7	183	6.3
30 to < 40	1,121	4.5	380	5.3	241	5.1	87	4.7	154	5.3
≥ 40	1,504	6.0	569	7.9	449	9.4	183	9.9	266	9.1
Relative had endometrial cancer	13,838	55.7	3,993	55.8	2,654	55.6	1,043	56.2	1,611	55.3
Missing										
No	9,815	39.5	2,843	39.7	1,860	39.0	714	38.5	1,146	39.3
Yes	1,210	4.9	323	4.5	257	5.4	99	5.3	158	5.4
History of hormone therapy use	12,165	48.9	3,196	44.6	2,549	53.4	1010	54.4	1,539	52.8
Never HRT use										
Estrogen alone use	1,672	6.7	454	6.3	322	6.7	160	8.6	162	5.6
Estrogen plus progestin use	9,621	38.7	3,099	43.3	1,665	34.9	593	32.0	1,072	36.8
Estrogen alone and estrogen plus progestin use	1,405	5.7	410	5.7	235	4.9	93	5.0	142	4.9
Age at menarche, years	3,762	15.1	1,083	15.1	738	15.5	276	14.9	462	15.8
Missing										
< 12	2,625	10.6	848	11.8	545	11.4	183	9.9	362	12.4
12-13	9,784	39.4	2,818	39.4	1,927	40.4	780	42.0	1,147	39.3
14-15	5,721	23.0	1,539	21.5	1,014	21.3	387	20.9	627	21.5
≥ 16	2,971	11.9	871	12.2	547	11.5	230	12.4	317	10.9
No. of term pregnancies	2,686	10.8	799	11.2	582	12.2	232	12.5	350	12.0
Never pregnant										
Never had term pregnancy	663	2.7	228	3.2	135	2.8	56	3.0	79	2.7
1	2,115	8.5	646	9.0	432	9.1	157	8.5	275	9.4
2	6,562	26.4	2,019	28.2	1,216	25.5	456	24.6	760	26.1
3	6,141	24.7	1,693	23.6	1,090	22.8	404	21.8	686	23.5
4	3,602	14.5	982	13.7	670	14.0	283	15.2	387	13.3
≥ 5	3,094	12.4	792	11.1	646	13.5	268	14.4	378	13.0
Age at first birth, years	2,164	8.7	598	8.4	376	7.9	135	7.3	241	8.3
Missing										
Never had term pregnancy	3,349	13.5	1,027	14.3	717	15.0	288	15.5	429	14.7
< 20	1,813	7.3	721	10.1	439	9.2	186	10.0	253	8.7
20-29	15,187	61.1	4,240	59.2	2,781	58.3	1,074	57.9	1,707	58.6
≥ 30	2,350	9.5	573	8.0	458	9.6	173	9.3	285	9.8

Abbreviations: BMI, body mass index; HRT, hormone replacement therapy; METs, metabolic equivalents.

*P values for testing differences among stable weight, weight gain, and weight loss were less than .05, except for the category of relative had endometrial cancer.

Intentional Weight Loss and Endometrial Cancer

Table A2. HRs and 95% CIs for the Association Between BMI Change and Risk of Endometrial Cancer

BMI (kg/m ²) Change Between Baseline and Year 3	No. of Patients	Multivariable-Adjusted HR (95% CI)*
Low stable BMI†	186	Reference
Weight gain or stay high BMI‡	358	1.46 (1.22 to 1.75)
Weight loss§	22	0.97 (0.14 to 6.93)
Intentional	9	0.74 (0.38 to 1.44)
Unintentional	13	2.09 (1.19 to 3.67)

Abbreviations: BMI, body mass index; HR, hazard ratio.

*Multivariable models adjusted for age at enrollment, race/ethnicity, education, smoking pack-years, recreational physical activity, parity, age of menarche, age at first birth, family history of endometrial cancer, and BMI.

†BMI < 25 kg/m² at both baseline and year 3.

‡BMI < 25 kg/m² at baseline and BMI ≥ 25 kg/m² at year 3, or BMI ≥ 25 kg/m² at both baseline and year 3.

§BMI ≥ 25 kg/m² at baseline and BMI < 25 kg/m² at year 3.