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ORIGINAL RESEARCH ARTICLE

Epidemiological analysis of obesity-related comorbidities and mortality among postmenopausal women with endometrial cancer: Findings from the Women's Health Initiative randomized controlled trials and observational study

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Abstract

Introduction: Obesity is a well-established risk factor for endometrial cancer (EC). Postmenopausal women with EC frequently present with obesity-related comorbidities or develop them after diagnosis, which may impact survival.

Objectives: This study aimed to identify modifiable comorbidities (diabetes, cardiovascular disease, hypertension, and fractures) among postmenopausal EC survivors and evaluate the relationship between obesity-related comorbidities and all-cause mortality after an EC diagnosis.

Design: Prospective cohort analysis of overall mortality risk in relation to obesity-related comorbidities in women diagnosed with EC.

Population and Setting: Postmenopausal women recruited across 40 clinical sites within the Women's Health Initiative (WHI) observational and clinical trials and experiencing a new diagnosis of EC.

Methods: Adjusted Cox proportional hazards regression models were used to evaluate the relationship between comorbidities and all-cause mortality among women with incident EC.

Results: A total of 1,661 incident cases of EC were identified. The overall mortality rate was 55.5%. The prevalence of each comorbidity increased from baseline to 18 years of follow-up. Regression analyses for incident EC indicated that severe obesity (hazard ratio [HR] = 2.13; 95% confidence interval [CI]: 1.52–2.97), cardiovascular disease (HR = 1.50; 95% CI: 1.26–1.78), and fracture (HR = 1.17; 95% CI: 1.07–1.27) were associated with greater overall mortality.

Conclusion: Obesity-associated comorbidities are common and associated with higher mortality in postmenopausal women diagnosed with EC. Interventions to reduce the risk of comorbidity among EC survivors may improve survival and should be evaluated (ClinicalTrial.gov identifier: NCT00000611).

Keywords: Obesity; Endometrial cancer; Women's Health Initiative; Risk; Comorbidity

1. Introduction

Endometrial cancer (EC) is the most common gynecological cancer diagnosed in women in the United States; an estimated 86% of new cases occur in postmenopausal women, with a mean age of onset of 60 years.[1] Rates have increased steadily by 0.6% annually since 2010 in the United States,[2] corresponding to a parallel increase in obesity rates. Risk estimates suggest that obesity is associated with an overall 85% greater risk of EC, with an even higher risk observed among women with severe obesity.[3-5] Survival after a diagnosis is considered good, with an estimated 83.6% of women still alive 5 years after their diagnosis.[2] However, age-adjusted mortality for EC has increased by 1.7% annually since 2010—more than twice the rate of increase in incidence.[2] Among the modifiable risk factors that have been postulated in relation to mortality after an EC diagnosis are obesity-associated comorbidities.

Mechanistically, obesity and obesity-related comorbidities influence several of the hallmarks of cancer, including tumor cell proliferative signaling, immune modulation, evasion of growth suppression, activation of invasive pathways, enhancement of genomic instability, and deregulation of cell energetics.[6] Adipose serves as a source of unopposed estrogen in postmenopausal women, which may promote DNA damage and contribute to carcinogenesis.[7] Mesenchymal stem cells originating from adipose tissue can support tumor growth and proliferation, and adipokines from visceral fat, common in obesity-related comorbid disease, promote inflammation and insulin resistance,[8] all of which may alter survival.

Literature substantiating the relationship between obesity, obesity-related comorbidities, and EC survival is evolving. A 2004 report evaluating EC survival among 415 women suggested that a concurrent diagnosis of diabetes was associated with a 2.79-fold (95% confidence interval: 1.63–4.78) higher risk for overall mortality.[9] Similarly, an analysis of 490 EC cases in Utah showed that a diagnosis of hypertension and diabetes in EC patients was associated with a 70% higher risk of death over 4.5 years of follow-up.[10] Analyses from Australia and Norway showed that comorbidities at the time of diagnosis, including obesity and diabetes, were associated with a two- to three-fold higher all-cause mortality.[11,12] A single-center analysis of 2,519 women with EC applying the Adult Comorbidity Evaluation-27[13] suggested more than a twofold risk of mortality or EC recurrence in women with an elevated comorbidity score.[14]

While these earlier analyses suggested that comorbidities may influence EC survival outcomes, replication in a larger United States cohort, particularly for older women who experience a greater burden of comorbid disease, is needed. The Women's Health Initiative (WHI), the most extensive study of postmenopausal women ever undertaken in the United States, provides fertile ground for expanding knowledge in this area. Specifically, this analysis aims to describe the prevalence and incidence of modifiable obesity-related comorbidities among postmenopausal women diagnosed with EC and examine the association between obesity-related comorbidities and mortality following EC diagnosis. Our overall goal is to determine if comorbidities, which are potentially modifiable through lifestyle

interventions and/or medications, are associated with survival after an EC diagnosis in postmenopausal women.

2. Methods

2.1. Study design and population

This study employed an prospective cohort design registered under ClinicalTrial.gov identifier NCT00000611. The sample was drawn from the WHI, a large prospective research program comprising three overlapping randomized controlled clinical trials (Hormone Therapy, Diet Modification, and Calcium and Vitamin D) and an observational study. Details of the WHI study population have been previously described.[15] Briefly, postmenopausal women aged 50–79 were recruited from 40 clinical sites across the United States. During enrollment, women free of active cancer were considered eligible, while those with a history of cancer but not under active treatment could also participate if their life expectancy exceeded 3 years. Enrollment occurred between 1993 and 1998, involving 161,808 women. All participants provided written informed consent, and the study protocol was approved by the Human Subjects' Committee Internal Review Board at each clinical site, in accordance with the Declaration of Helsinki. From the WHI cohort, our analytic sample included all women who were diagnosed with incident EC after baseline and up to February 28, 2021.[16] Incident EC was defined as having an adjudicated case of EC after enrollment in WHI. Women without complete data for the outcome or independent variables, and those diagnosed with EC posthumously, were excluded. A total of 1,853 incident cases of EC were identified.

2.2. Data sources

2.2.1. Eligibility assessment

Women from the WHI cohort—including participants from both the clinical trials and the observational study[16]—who self-reported EC during the biannual mailed follow-up questionnaire were included in this analysis. All reported incident EC cases were adjudicated using medical record reviews of clinical and pathology documentation by trained physician adjudicators, as previously described.[16]

2.2.2. Outcome assessments

The primary outcome of interest was all-cause mortality. Mortality and changes in health status were assessed every 6 months through mailed questionnaires, with follow-up telephone contacts for non-respondents. Women from the WHI cohort reported health status on the standardized, protocol-specified questionnaire. Surrogates identified by WHI participants at baseline provided follow-up data for women who were unable or declined to complete the form or who had died during the observational period. Death was verified by medical record review, and death ascertainment was supplemented with an annual review of the National Death Index[11] to update mortality status and cause of death.

An exploratory outcome was the incidence of obesity-related cancers after EC diagnosis. Obesity-related cancers following EC diagnosis included cancers of the esophagus, breast, colorectum, gallbladder, kidney, liver, ovary, pancreas, and thyroid, as well as meningioma and multiple myeloma.

2.2.3. Comorbid conditions

The modifiable/treatable comorbidities of interest included obesity (defined by body mass index [BMI] category), type 2 diabetes, cardiovascular disease (CVD; angina, coronary artery bypass, carotid artery occlusion, congestive heart failure, myocardial infarction, peripheral vascular disease, percutaneous transluminal coronary angioplasty, and stroke), hypertension, and the number of incident fractures. New onset of CVD and hypertension was verified through review of medical records. CVD and fracture events/diagnoses were adjudicated by trained physician adjudicators throughout the study.[16] Incident diabetes was self-reported and verified through medication inventories documenting prescribed antidiabetic medications, a method previously shown to have high validity.[17]

These comorbidities were modeled as time-varying, except for BMI, which was fixed at the measured value from the WHI baseline clinic visit. Accordingly, the dataset captured each interval during which a participant was diagnosed with a new comorbidity or sustained an additional fracture. Once diagnosed, each comorbidity was considered to persist throughout the follow-up period.

2.2.4. Covariates

Additional independent variables included potential confounders: stage at EC diagnosis, smoking status (never, former, current), energy intake (kcal), hormone therapy (HT) use (never, former, current), aspirin or non-steroidal anti-inflammatory drug use at baseline, alcohol consumption (never, ≤1 drink/day, ≥1 drink/day), physical activity (min/week), race and ethnicity, income, formal education, and parity.

2.3. Statistical analyses

Descriptive statistics were calculated for variables of interest, including participant characteristics, prevalent and incident comorbidities, and the exploratory incidence of obesity-related cancers after EC diagnosis. To evaluate the association between mortality and modifiable comorbidities, Cox proportional hazard regressions were used, and models

were fitted separately for women with incident EC. The time origin was the age at the time of EC diagnosis. We first fitted an unadjusted model including only the modifiable comorbidities as predictors, followed by a fully adjusted model incorporating the covariates. We adjusted for the WHI trial arm and treatment assignment because participants eligible for randomization to the clinical trials were generally healthier than those enrolled in the observational study. In addition, the treatments received in the clinical trials (HT, dietary modification, & calcium + vitamin D supplementation) may have affected the outcomes of interest. For the primary analyses, a two-sided p-value < 0.05 was used to indicate statistical significance. All analyses were conducted using Statistical Analysis System version 9.4 and Stata 18.[18]

3. Results

A total of 1,661 participants were diagnosed with EC following enrollment in the study and provided complete covariate data. Table 1 shows the demographic and clinical characteristics of the analytical sample. The mean age at EC diagnosis was 72.2 years, while the mean age at death, among those who died during follow-up, was 81.2 years. Most participants with EC were non-Hispanic White, had vocational or college education, were non-smokers with minimal alcohol intake, and were diagnosed with Surveillance, Epidemiology, and End Results (SEER) stage 2 disease (78.7%).

3.1. Incident comorbidities in EC survivors

The prevalence of obesity-related comorbidities increased over 18 years of follow-up across all evaluated conditions. This included an estimated 30% increase in hypertension (40.4% to 69.1%), 12% increase in CVD (26.7% to 38.9%), and a doubling in incidence of diabetes (9.7% to 18.6%). Overweight/obesity was the most common comorbidity; on average, an estimated one-third of the sample had normal BMI (Table 2). Overall, hypertension was common; 40.4% of women had prevalent hypertension, and an additional 28.7% developed hypertension during follow-up (after baseline enrollment in WHI). CVD was prevalent in 26.7% of participants, and 12.2% experienced at least one CVD event. Diabetes was the least common comorbidity, with 9.7% of women with prevalent diabetes and 8.9% with incident diabetes during a mean 17.8 years of follow-up. Incident fractures were common; 21.9% of women experienced one fracture, 7.8% had two fractures, and 3.6% had three or more fractures during the follow-up period.

The evaluated comorbidities primarily comprised obesity-related conditions, which frequently overlapped in this cohort, where above-normal BMI values were prevalent. Furthermore, hypertension was frequent and thus demonstrated higher overlap with other

Table 1. Sample characteristics of incident endometrial cancer cases in the Women's Health Initiative (n=1,661)

Characteristics	Data
Age at baseline (years), mean (SD)	62.7 (6.9)
Age at last observation (years), mean (SD)	82.1 (6.9)
Age at death for those who died (years), mean (SD)	81.2 (8.1)
Age at last observation among those surviving (years), mean (SD)	82.8 (5.7)
Age at diagnosis (years), mean (SD)	72.2 (7.8)
Total daily energy intake (kcal), mean (SD)	1722.3 (667.7)
Physical activity (min/week), mean (SD)	187.2 (182.1)
Race and ethnicity	
Non-Hispanic White	1,505 (90.6%)
Black	83 (5.0%)
Hispanic	23 (1.4%)
American Indian or Alaskan Native	23 (1.4%)
Asian or Pacific Islander	2 (0.1%)
Other race	20 (1.2%)
Not reported	5 (0.3%)
Formal education	
Less than high school	44 (2.6%)
High school or General Educational Development completed	239 (14.4%)
Vocational training, technical, or college	537 (32.3%)
College degree	207 (12.5%)
Post-graduate or professional school	245 (14.8%)
Graduate degree	378 (22.8%)
Missing	11 (0.7%)
[a]Income	
Less than $20,000	188 (11.3%)
$20,000 to $34,999	332 (20.0%)
$35,000 to $49,999	311 (18.7%)
$50,000 to $74,999	351 (21.1%)
$75,000 and greater	358 (21.6%)
Missing or unknown	121 (7.3%)
Smoking status at baseline	
Never smoked	881 (53.0%)
Formerly smoked	702 (42.3%)
Currently smoking	78 (4.7%)
Alcohol intake	
Does not drink alcohol	139 (8.4%)
Drank alcohol in the past	258 (15.5%)
Minimal (<1 drink/week)	597 (35.9%)
Moderate (1–7 drinks/week)	440 (26.5%)
Heavy (7+drinks/week)	227 (13.7%)

(*Contd...*)

Table 1. (*Continued*)

Characteristics	Data
Parity	
Never pregnant	205 (12.3%)
Never had a term pregnancy	56 (3.4%)
1	157 (9.5%)
2	428 (25.8%)
3	420 (25.3%)
4	215 (12.9%)
5+	174 (10.5%)
Missing	6 (0.4%)
Menopausal hormone therapy	
Never used	767 (46.2%)
Formerly used	236 (14.2%)
Currently using	656 (39.5%)
NSAID use	
Using NSAIDs	329 (19.8%)
Not using NSAIDs	1,332 (80.2%)
SEER stage (in incident endometrial cancer)	
1	15 (0.9%)
2	1,308 (78.7%)
3	238 (14.3%)
4	81 (4.9%)
Unknown stage	19 (1.1%)

Note: Data presented as n (%), unless stated otherwise. [a]Income stated in United States Dollars.
Abbreviations: NSAID: Non-steroidal anti-inflammatory drug; SD: Standard deviation; SEER: Surveillance, Epidemiology, and End Results.

comorbidities, notably diabetes, obesity-related cancers, CVD, and fractures (Figure S1).

3.2. All-cause mortality

During follow-up, 717 (43.2%) women with incident EC succumbed to death. In adjusted models (Table 3), severe obesity, CVD, and fracture were each associated with greater mortality, with a more than twofold higher risk in women with severe obesity, 50% higher for CVD, and 17% higher for fracture among women with EC. Adjusting for covariates showed little attenuation of unadjusted hazard ratios (HRs) (Table 3). Evaluating the relationships between comorbidity burden and mortality as a function of age (Figure S2) illustrated increasing HRs for all-cause mortality across comorbidities with advancing age.

3.3. Incident obesity-related cancers

The proportion of incident obesity-related cancer was 8.97% among EC survivors (Table 4). The most common obesity-related cancer in our sample was breast cancer (5.42%), followed by colorectal cancer (1.63%). The mean time to diagnosis for these additional obesity-related cancers was 14.1 years from EC diagnosis (data not shown). The number of events was small, precluding robust multivariable evaluation, including analyses of associations with comorbidity status.

Table 2. Obesity-related comorbidities among postmenopausal women with endometrial cancer from the Women's Health Initiative cohort (*n*=1,661)

[a]Variable	*n*	%
Body mass index category at baseline		
Underweight (< 18.5)	14	0.73
Normal (18.5–24.9)	605	31.76
Overweight (25.0–29.9)	628	32.97
Obesity I (30.0–34.9)	371	19.48
Obesity II (35.0–39.9)	164	8.61
Severe obesity III (≥ 40)	123	6.46
Prevalence of diabetes	185	9.71
Incidence of diabetes	169	8.87
Prevalence of cardiovascular disease[b]	508	26.67
One incident event	233	12.23
Two incident events	49	2.57
Three incident events	8	0.42
Prevalence of hypertension	769	40.37
Incidence of hypertension	546	28.66
Incident fractures		
One fracture	418	21.94
Two fractures	150	7.87
Three or more fractures	69	3.61

Notes: [a]Incident comorbidities developed after EC diagnosis. [b]Cardiovascular disease is defined as angina, coronary artery bypass, carotid artery occlusion, congestive heart failure, myocardial infarction, peripheral vascular disease, percutaneous transluminal coronary angioplasty, and stroke.

4. Discussion

The key finding from this analysis is that obesity-related comorbidities are strongly associated with higher mortality following an EC diagnosis in postmenopausal women. Despite high short-term survival, severe obesity was the strongest driver of overall mortality, more than twice the risk compared to women with a normal BMI.

Within our sample, obesity-related comorbidities known to drive EC risk were common. Over 34% of EC survivors were obese, 26% had prevalent CVD, an estimated 18.58% had diabetes, and 40% were diagnosed with hypertension. These prevalence estimates are lower than

Table 3. Hazard ratios for all-cause mortality among women with incident endometrial cancer from the Women's Health Initiative cohort

Comorbidities	Unadjusted		Adjusted	
	Hazard ratio	95% confidence interval	Hazard ratio	95% confidence interval
Body mass index category at baseline				
Underweight (<18.5 kg/m^2)	0.76	0.24–2.40	0.68	0.21–2.18
Overweight (25.0–29.9 kg/m^2)	1.12	0.91–1.37	1.10	0.89–1.36
Obesity I (30.0–34.9 kg/m^2)	1.18	0.94–1.48	1.19	0.94–1.51
Obesity II (35.0–39.9 kg/m^2)	1.57	1.22–2.03	1.62	1.22–2.15
Severe obesity III (≥40 kg/m^2)	1.91	1.42–2.57	2.13	1.52–2.97
Diabetes	1.33	1.10–1.60	1.19	0.97–1.46
Cardiovascular disease	1.45	1.23–1.71	1.50	1.26–1.78
Hypertension	0.95	0.80–1.13	0.95	0.80–1.14
Number of incident fractures	1.19	1.09–1.29	1.17	1.07–1.27

Note: Cox proportional hazards regression models were fitted for the incident cases of endometrial cancer. Reference groups included individuals with a normal BMI (18.5–24.9 kg/m^2), the absence of cardiovascular disease, diabetes, hypertension, and no incident fractures. Diabetes, cardiovascular disease, hypertension, and the number of incident fractures in the model were time-varying. Covariates for adjusted models were study arm, education, income, race/ethnicity, current smoker, minutes per week of exercise, total energy (kcal) consumed, alcohol intake, current hormone therapy use at baseline, former hormone therapy use at baseline, non-steroidal anti-inflammatory drug or aspirin use at baseline, metformin use at baseline, and parity.

Table 4. Incident of obesity-related cancers among women with endometrial cancer

Variable	*n*	%
Obesity-related cancers: Incident	149	8.97
Breast cancer	90	5.42
Colorectal cancer	27	1.63
Gallbladder cancer	1	0.06
Kidney cancer	9	0.54
Liver cancer	3	0.18
Ovarian cancer	25	1.51
Pancreatic cancer	8	0.48
Thyroid cancer	2	0.12
Meninges cancer	0	0.00
Multiple myeloma	1	0.06
Esophageal cancer	3	0.18

national estimates for obesity (43.3%)[19] and cardiovascular disease (78.2%),[20] but comparable to nationally reported rates of diabetes (16–20%).[19] Cumulative hypertension prevalence reached 69%, higher than national estimates of 39.7%[20] and the Utah EC cohort, which reported estimated rates of 47%.[10] The variance from national averages likely reflects the higher educational attainment, lower poverty rates, and greater access to healthcare and screening services among women in the WHI cohort.

The results showed that CVD was associated with a 50% greater adjusted overall mortality risk in women with EC. An earlier report from the WHI suggested that women with EC did not have a higher risk of CVD events compared with those without cancer.[21] Our findings complement those of Ward *et al.*,[22] who analyzed invasive EC cases from the SEER database (N = 33,232) and reported that CVD was the leading cause of death following an EC diagnosis.

Diabetes and hypertension were not associated with mortality after EC diagnosis. However, a study of 337 EC cases in Norway showed that diabetes was associated with a 214% greater all-cause mortality.[12] In this study, diabetes was not significantly associated with cancer-specific mortality, contrary to results from Nagle *et al.*[11] and Folsom *et al.*,[9] which reported a more than two-fold increase in cancer-specific mortality risk among EC survivors with concurrent diabetes.[9,11] Only one earlier analysis specifically evaluated hypertension; in that cohort of 490 patients, hypertension was associated with a 66% higher risk for overall mortality. Hypertension has been linked to malignant transformation of endometrial polyps, a condition identified in approximately 30% of women.[23]

While literature has suggested that obese women are marginally protected from fracture, when fractures were reported, they were associated with an elevated risk for all-cause mortality in our sample, a finding not previously reported in the literature. Notably, over 65% of our sample were not obese and had normal or overweight BMI. The small subgroup sizes, however, limited our ability to evaluate these associations across specific types of fractures. Fractures, particularly hip fractures in older adults, in

general, carry high morbidity and mortality.[15] In addition, fracture in older women is commonly associated with lower physical activity levels, and reductions in physical activity with age are associated with elevated overall mortality. These factors, along with physical inactivity, may partially explain the observed associations.

Obesity's role in carcinogenesis is well established but remains poorly communicated to patients with EC. Ekelund *et al.*[24] showed that over one-third of EC patients had no awareness of the association between obesity and EC.[24] Encouragingly, EC survivors tend to hold positive beliefs about the benefits of exercise. Lukowski *et al.*[25] surveyed 106 cancer survivors and found that most believed that exercise is very or extremely likely to make them feel physically and emotionally better, aid in weight maintenance, improve sleep, and reduce the risk of chronic diseases, though notably, not cancer.[25] These results imply the potential benefit of providing post-EC lifestyle interventions to support this at-risk group.

A novel finding of this study was that 8.97% of EC survivors developed at least one additional obesity-related cancer after EC diagnosis. Literature suggests that rates of second primary cancers vary widely among cancer patients overall (2–17%);[26] therefore, the 9% observed in our cohort represents a noteworthy proportion.

Strengths of these analyses include the use of a comprehensive dataset with a large sample of women with over 25 years of follow-up data. Our regression approach adjusted for numerous confounders, using the largest United States sample reported to date. Limitations exist, including the definition of EC to encompass all histopathological case types, given the limited information available regarding EC subtype classifications. WHI includes a highly educated sample with higher-than-average access to care, which may suggest that our findings have greater applicability to EC survivors who are regularly monitored within the healthcare system. Our sample was underpowered to rigorously evaluate cancer-specific mortality, and we could identify only breast, colorectal, liver, ovarian, and thyroid cancers as obesity-related cancers in baseline data sources. Finally, we were unable to confirm the clinical effectiveness of treatment for the various comorbidities, such as blood pressure and blood glucose control, that likely influenced cancer risk and mortality, as well as other causes of death.

These data underscore the importance of systematically assessing comorbidities in EC survivors and rigorously evaluating lifestyle behaviors. They also emphasize the need for supportive interventions that promote weight loss and prevent or manage comorbid conditions. The findings suggest that reducing the burden of obesity-related comorbidity could improve mortality following an EC diagnosis among postmenopausal women.

5. Conclusion

In summary, obesity-related comorbidities are common following an EC diagnosis, and many women experience multiple concurrent conditions. Interventions to address obesity are likely to reduce both individual morbidities and mortality in EC survivors. Given the national rise in mortality among EC survivors over the past decade, these data provide important targets for clinical intervention to potentially improve long-term survival outcomes.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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Ethics approval and consent to participate

The study was approved by the Human Subjects' Committee Internal Review Board at Fred Hutchinson Cancer Center, as required by the Declaration of Helsinki. All enrolled participants provided written informed consent.

Consent for publication

Written consent was obtained from participants to publish their data.

Availability of data

Eligible researchers may download the data directly at the WHI inline resource (www.whi.org). Other researchers may download the publicly available data through BioLINCC in accordance with NHLBI BioLINCC guidelines.

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