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Body mass index, physical activity, and mortality in women diagnosed with ovarian cancer: Results from the Women's Health Initiative

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Abstract

Background—Ovarian cancer is often diagnosed at late stages and consequently the 5-year survival rate is only 44%. However, there is limited knowledge of the association of modifiable lifestyle factors, such as physical activity and obesity on mortality among women diagnosed with ovarian cancer. The purpose of our study was to prospectively investigate the association of (1) measured body mass index (BMI), and (2) self-reported physical activity with ovarian cancer-

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specific and all-cause mortality in postmenopausal women enrolled in the Women's Health Initiative (WHI).

Methods—Participants were 600 women diagnosed with primary ovarian cancer subsequent to enrollment in WHI. Exposure data, including measured height and weight and reported physical activity from recreation and walking, used in this analysis were ascertained at the baseline visit for the WHI. Cox proportional hazard regression was used to examine the associations between BMI, physical activity and mortality endpoints.

Results—Vigorous-intensity physical activity was associated with a 26% lower risk of ovarian cancer specific-mortality (HR=0.74; 95% CI: 0.56–0.98) and a 24% lower risk of all-cause mortality (HR=0.76; 95% CI: 0.58–0.98) compared to no vigorous-intensity physical activity. BMI was not associated with mortality.

Conclusions—Participating in vigorous-intensity physical activity, assessed prior to ovarian cancer diagnosis, appears to be associated with a lower risk of ovarian cancer mortality.

Keywords

ovarian cancer; obesity; weight; physical activity; exercise; prognosis; mortality; survival

Introduction

Over 20,000 women are diagnosed with ovarian cancer in the United States each year[1]. Despite efforts to improve early detection and treatment, ovarian cancer is the most fatal gynecologic cancer with a 44% five-year survival rate[1]. Genetic and clinical factors including having a family history of ovarian cancer and a BRCA1/2 mutation have been shown to be associated with higher risk of ovarian cancer[1]. In addition, lifestyle factors including physical activity and obesity may play a role in ovarian cancer risk and mortality[2, 3].

Studies that have examined associations between obesity and mortality in women diagnosed with ovarian cancer have yielded inconsistent results. To our knowledge, seventeen studies have examined the association between obesity and mortality[4–20]. Eleven observed no association between obesity and mortality[10–20], one study suggested that obesity was associated with lower risk of mortality[9], and five studies observed that obesity was associated with higher risk of mortality[4–8]. Fourteen of these studies were included in a recent meta-analysis that showed a slightly higher mortality rate among obese women with ovarian cancer compared to non-obese women with ovarian cancer (HR=1.17, 95% CI: 1.03–1.34)[21]. Another meta-analysis published in 2011 included 10 observational studies[22]. While no association was found for BMI at diagnosis and all-cause mortality, BMI in early adulthood (HR=1.60, 95% CI: 1.10–2.34) and pre-diagnosis (HR=1.45, 95% CI: 1.09–1.93) were associated with mortality in patients with ovarian cancer[22]. Despite the number of studies that have examined obesity and ovarian cancer mortality, none were prospective studies with measured BMI. Thus, there is a possibility of misclassification of obesity status when based on BMI derived from reported heights and weights. Furthermore, most of the studies were of limited sample size (<500 women) and often had a short follow-up period (<5 years).

Physical activity is another putative factor for ovarian cancer incidence and mortality. With mounting evidence that physical activity may help to reduce both the incidence and associated mortality of certain cancers, such as breast cancer, it is relevant to public health and clinical medicine to investigate whether ovarian cancer survivors would also obtain survival benefit from increased levels of physical activity[3, 23]. Few studies have examined the association between physical activity and ovarian cancer mortality[6, 10, 24]. Two studies used retrospective self-report of physical activity collected after ovarian cancer diagnosis[6, 24]. One study collected self-reported physical activity from healthy women who were followed for ovarian cancer outcomes [10]. No significant associations between physical activity before diagnosis and ovarian cancer mortality were found [6, 10, 24]. However, these studies were limited by retrospective physical activity data after cancer diagnosis and small sample sizes (<80 women).

The paucity of prospective, well-powered studies examining obesity, physical activity, and ovarian cancer mortality warrants further research. The purpose of our study was to examine the prospective associations among obesity status based on measured BMI, self-reported physical activity and ovarian cancer mortality in a large sample of well-characterized postmenopausal women enrolled in the Women's Health Initiative (WHI) Study that were subsequently diagnosed with ovarian cancer post-enrollment.

Methods

Study population

Detailed enrollment methods have been published[25]. Briefly, the study enrolled 93,646 women into the WHI Observational Study (OS) and 61,132 women into the WHI Clinical Trials (CT), for a total of 161,808 women enrolled between October 1993 and December 1998 from 40 different centers across the United States. Postmenopausal women of all races and socioeconomic backgrounds, between the ages of 50 and 79 were recruited. Institutional review boards at all centers approved the study protocol and participants provided informed consent.

A total of 927 WHI women were diagnosed with ovarian cancer between October 1993 and September 2012. Women were included in this analysis if they: 1) had histology confirmed ovarian cancer (n=35 with histology codes that indicated non-ovarian cancer were excluded); 2) did not have any previous cancer diagnosis (n=67 with previous cancers were excluded); 3) were diagnosed with invasive epithelial ovarian cancer (n=5 with in-situ ovarian cancer were excluded); 4) had clinical data associated with their ovarian cancer diagnosis (n=130 diagnosed at death and/or had missing disease stage information were excluded); 5) had complete physical activity, BMI and covariate data (n=33 with missing data were excluded); 6) were able to walk for one block (n=7 unable to walk one block were excluded); 7) were alive one year following enrollment into WHI (n=1 died within one year of enrollment was excluded); 8) had a date of last contact that was after diagnosis of ovarian cancer (n=6 with censor date prior to date of diagnosis were excluded); and 9) had ovarian cancer diagnoses at least one year following enrollment into WHI (n=43 were diagnosed within one year of enrollment were excluded) (Figure 1). Thus, 600 women (65% of 927 women diagnosed with invasive ovarian cancer subsequent to WHI enrollment) were included in this analysis of BMI and physical activity on mortality.

Exposure Assessment

Data collection was completed at each WHI center using a standardized protocol. Participants completed questionnaires on health and reproductive history, lifestyle factors and diet at enrollment. Height and weight were measured to the nearest one-tenth of a centimeter or kilogram. Height was measured using a wall-mounted stadiometer and weight was measured using either a calibrated balance beam or digital scale.

Physical activity was assessed during the baseline visit by asking participants how often they were currently participating in different types of physical activity (walking, light, moderate, and vigorous) and the frequency and duration of each exercise session. Examples of moderate-intensity included biking outdoors, exercise machine use, calisthenics and easy swimming, and examples of high-intensity included jogging, aerobics, tennis and swimming. Participants were asked to check categories on a Likert-type scale that ranged from never to ≥5 days/week. Duration categories included <20 minutes, 20–39 minutes, 40–59 minutes and ≥one hour. Walking outside the home for >10 minutes was measured separately. Speed categories for walking were: <2 mph (strolling), 2–3 mph (average/normal walking), 3–4 mph (fairly fast walking), and >4 mph (very fast walking) [41]. In addition, participants were asked to report the hours of sedentary activity per day including activities such as sitting, sleeping or lying down.

Midpoint values for ranges of frequency and duration of exercise sessions were calculated. Duration was multiplied by frequency to create a variable “hour/week” (hr/wk). Metabolic equivalent task (MET) values were assigned for walking (average 3 METs; fast 4 METs; and very fast 4.5 METs), moderate-intensity recreational (4 METs) and vigorous-intensity recreational (7 METs) activities. MET levels were then multiplied by hr/wk to compute a variable that summarized the average amount of both moderate and vigorous-intensity physical activity the participant reported doing per week (MET hr/wk). A second variable was created to only include vigorous-intensity physical activities reported by the participant (i.e. Activities with 7 METs).

Ascertainment of outcomes

All participants completed health assessment questionnaires annually (OS) or semi-annually (CT) regarding self-reported health outcomes including cancer. Centrally trained physician adjudicators verified all reported ovarian cancer outcomes at the clinical centers after medical record and pathology report review. Cases were coded according to National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) guidelines [26]. Vital status was collected periodically through follow-up of participants and surrogates by each clinical center. Systematic searches of the National Death Index were also conducted every two years with the most recent completed in 2012. Clinical adjudicators determined causes of death through medical record and death certificate review. Causes of death codes were assigned at the coordinating center. The National Death Index was also used to confirm cause of death or otherwise unreported deaths for participants who were lost to follow-up.

Statistical Analysis

Pre-diagnosis BMI and physical activity assessed at the baseline visit were used in the analyses. Baseline characteristics of all WHI women included in the analysis were compared by BMI and physical activity categories. Cox proportional hazard regression models were used to compare all-cause mortality and ovarian cancer-specific mortality between the different BMI and physical activity exposure categories while adjusting for relevant covariates. Person- years for the models were calculated using date of ovarian cancer diagnosis to date of death or date of administrative censoring at the end of follow-up on September 17, 2012. Separate unadjusted models for BMI and physical activity as continuous variables and as specific *a priori* categories were examined. Multivariate models were built assessing all of the variables in Table 1 as possible covariates and confounders as well as other variables including time from enrollment into WHI to ovarian cancer diagnosis and participants' status in the observational study or clinical trials. The models were also stratified by disease stage, age and histology. Two-sided p-values of <0.05 were considered statistically significant. All analyses were performed using SAS version 9.3 (SAS Institute, NC).

Results

Among the 600 WHI women diagnosed with ovarian cancer at least one year after study enrollment, there were 346 deaths, 301 of them from ovarian cancer. The distribution of baseline characteristics by BMI and physical activity categories are shown in Tables 1a and 1b respectively. The average time from pre-diagnosis assessments of BMI and physical activity to diagnosis of invasive ovarian cancer was 7.0±3.8 years. The average times from baseline to death or censor date and ovarian cancer diagnosis to death or censor date were 10.9±4.2 years and 3.9±3.4 years, respectively. All-cause mortality across disease stages differed greatly with 13%, 39% and 73% ovarian cancer mortality in women with SEER stage localized, regional and distant respectively.

Pre-diagnosis BMI measured categorized into underweight BMI<18.5 kg/m^2, normal 18.5≤BMI<25 kg/m^2, overweight 25≤BMI<30kg/m^2 and obese BMI≥30 kg/m^2 was not associated with all-cause or ovarian cancer specific mortality (Table 2). Analysis of other BMI categories was also performed and no significant associations were seen (results not shown). The fully adjusted model included age at baseline, time from study enrollment to ovarian cancer diagnosis, cancer disease stage, histology, hormone therapy use status, smoking status, physical activity, history of diabetes and status in the calcium and vitamin D trial, dietary modification trial, hormone therapy trials, and/or observational study.

Pre-diagnosis moderate- and vigorous-intensity physical activity was not found to be associated with all-cause or ovarian cancer specific mortality (Table 3). This variable summed the moderate (3–5 METs) and vigorous-intensity (≥6 METs) self-reported recreational physical activity collected at baseline enrollment. Multivariate analysis of vigorous-intensity physical activity alone demonstrated that women who reported any vigorous-intensity exercise had a 24% (HR=0.76, 95% CI: 0.58–0.96, p=0.0360) and 26% (HR=0.74, 95% CI: 0.56–0.98, p=0.0369) lower risk of all-cause and ovarian cancer specific mortality, respectively, compared to women who reported no vigorous-intensity physical activity (Table 4).

Disease stage stratified models were also examined for both BMI and physical activity exposures. Stage did not modify the association between BMI, physical activity and mortality (results not shown). Analysis of combined BMI (BMI<25 and BMI≥25 kg/m^2) and moderate- and vigorous- intensity physical activity (PA>9 and PA≤9 MET hr/wk) were examined with no significant associations between the combined effect of BMI and physical activity on mortality (results not shown).

Discussion

In this large population-based prospective study of WHI women diagnosed with ovarian cancer, we found that women who were participating in vigorous-intensity physical activity (ie. activities with 7 METs or greater) before diagnosis had a 26% lower risk of ovarian cancer specific mortality and a 24% lower risk of all-cause mortality compared to women who reported no vigorous-intensity physical activity. However, pre-diagnosis BMI measured at enrollment into the WHI was not associated with mortality. With 600 women and an average follow-up period of 10.9 years (±4.2 years), our study is one of the largest to examine the association between BMI, physical activity and ovarian cancer mortality using prospectively collected pre-diagnosis measured BMI and physical activity.

Only three other studies have examined the relationship between physical activity and ovarian cancer mortality[6, 10, 24]. Two studies, one from the U.S. and the other from Sweden, followed women previously enrolled in a case-control study for mortality endpoints. Both examined the association of self-reported physical activity at various ages in the women’s lifetimes and mortality, however, no significant associations were found[6, 24]. The third study is a small prospective cohort study of diet and exercise from Japan. After an average follow-up period of 13 years, self-reported physical activity collected at baseline and categorized seldom or ≥ 1–2 hours/week was not found to be associated with mortality among the 77 women who died from ovarian cancer[10].

Thus, the results from our study that suggest that women who reported vigorous-intensity exercise before ovarian cancer diagnosis had lower risk of ovarian cancer mortality differs from the limited published studies. Our study is the largest to use prospectively collected physical activity, which helps to eliminate recall bias that may have occurred in the two studies that enrolled women who had already been diagnosed with ovarian cancer. A study of breast cancer survivors enrolled in the Nurses’ Health Study found that moderate levels (9–14.9 MET hr/wk) of physical activity showed the greatest survival benefit when compared to none or higher levels (15–23.9 and ≥24 MET hr/wk) of physical activity[27]. A review physical activity and all-cause mortality indicated a possible inverse dose-response between physical activity volume and mortality, however, the role of intensity was uncertain [28]. We postulate that there could be a threshold effect of exercise benefiting ovarian cancer mortality and that vigorous-intensity physical activity is necessary to obtain the survival benefits of physical activity. Similarly, results from the Harvard Alumni Study found that vigorous-intensity activity was associated with all-cause mortality and nonvigorous exercise was not [29]. Vigorous-intensity physical activity is also easier to recall than moderate intensity physical activity, leading to more accurate classification of women into physical activity categories[30].

A recent meta-analysis of obesity and ovarian cancer mortality pooled results from 14 published studies found that obese women with ovarian cancer had slightly higher mortality than non-obese women (Pooled HR=1.17; 95% CI: 1.03–1.34)[21]. Obesity measures from each study varied, including pre-diagnosis, at diagnosis and/or during chemotherapy. However, the pooled HR did not vary appreciably when the analyses were restricted to only include studies with BMI from each of these time periods. These results differ from our study findings. BMI measured on average seven years prior to ovarian cancer diagnosis was not associated with mortality in this WHI cohort.

In our study, overweight (i.e., BMI 25–29.9 kg/m^2) was borderline associated with a lower mortality rate. A recent review of BMI and all-cause mortality among healthy individuals found a similar U-shaped trend where overweight adults had the lowest risk of all-cause mortality compared to both normal and obese adults[31]. The review presents earlier clinical presentation of overweight patients, cardioprotective metabolic effects of increased body fat, greater likelihood of receiving optimal medical treatment and benefits of higher metabolic reserves as possible explanations for the finding. This phenomenon has also been seen in patients undergoing percutaneous coronary interventions and was termed the “obesity paradox”[32]. In our study, BMI was measured on average 7 years prior to diagnosis, and all women included in this analysis were enrolled at least one year prior to diagnosis, thus, weight loss that may have occurred due to undetected ovarian cancer is an unlikely reason for our borderline association between overweight and lower risk of mortality. However, a finding of overweight being protective against ovarian cancer mortality may be due to the fact that BMI is not a completely accurate measure of body fat, especially in older women where loss of lean and bone mass and increases in body fat lead to some overweight (i.e., high body fat levels) women being classified as normal BMI (i.e., BMI<25 kg/m^2). Furthermore, there may be some limitations in using BMI to measure obesity as it does not account for other aspects, such as abdominal adiposity that has been shown to be associated with increased risk of mortality[33]. Future studies should examine body fat assessed via dual energy X-ray absorptiometry and ovarian cancer outcomes.

Limitations of our study include the self-reported nature of physical activity used. A social desirability bias exists when reporting physical activity because women may over-report their physical activity levels, in turn, misclassifying them as active, resulting in an underestimation of the association between physical activity and ovarian cancer mortality. Using more objective measures of physical activity, such as accelerometers, may lead to more accurate categorization of physical activity. Another study limitation was that 130 ovarian cancer diagnoses were ascertained through death certificates, and information on disease stage was missing. This limited our analyses that examined associations stratified by disease stage. Lastly, this study is a subgroup analysis of the WHI study that was designed for other purposes and we should be mindful of this when interpreting the findings. However, strengths of our study include all weight and height data used were measured by research staff and both BMI and physical activity was examined prospectively whereas most other studies used self-reported BMI measures collected retrospectively.

Overall, our findings demonstrate an association between vigorous-intensity physical activity and lower risk of ovarian cancer mortality in postmenopausal women diagnosed with ovarian cancer. Furthermore, there is definitive evidence of physical activity favorably affecting other cancer outcomes such as quality of life indices and other important clinical outcomes in breast cancer survivors. Specifically, exercise has been shown to improve cancer-related fatigue, anxiety, depression, risk of cardiovascular disease, risk of breast and colorectal cancer mortality, and overall quality of life, as well as other physical side effects including lymphedema[34–36]. Few studies have been conducted in women at high risk for poor quality of life, in particular, women diagnosed with ovarian cancer; yet an NCI-funded study is in progress to examine the effect of exercise vs. control on quality of life and biomarkers in women diagnosed with ovarian cancer (personal communication, Melinda Irwin, R01-CA138556). In conclusion, our WHI findings suggest that vigorous-intensity physical activity before diagnosis of ovarian cancer is associated with a reduced risk of ovarian cancer mortality. To more fully understand the potential roles that weight and physical activity have on ovarian cancer prognosis, future studies should examine associations between post-diagnosis BMI and physical activity on ovarian cancer outcomes including quality of life, biomarkers and disease free survival.

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Research Highlights

- Association of BMI, exercise and mortality among women diagnosed with ovarian cancer
- Women with pre-diagnosis vigorous exercise showed lower risk of mortality

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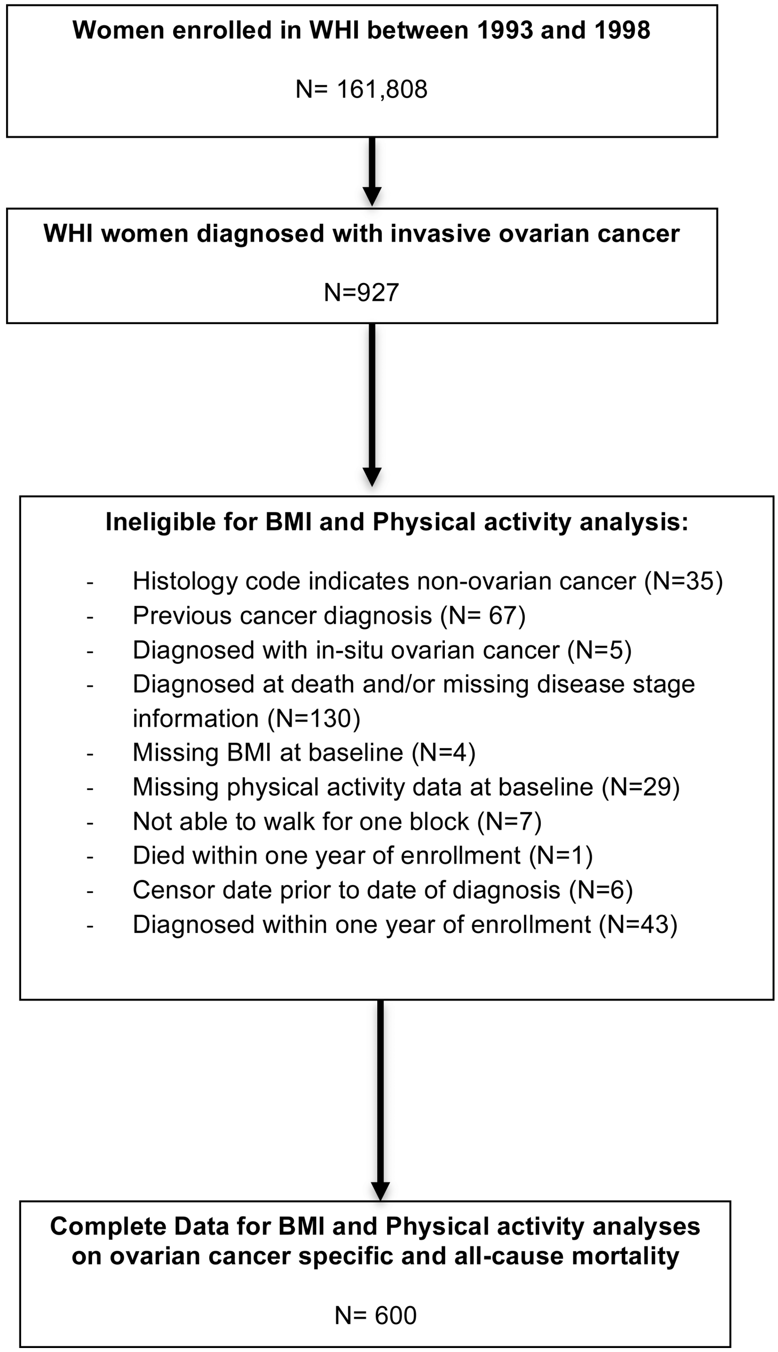

Figure 1.

Eligibility criteria for women in WHI included into the analysis of BMI and physical activity on ovarian cancer specific and all-cause mortality.

Table 1

a: Baseline characteristics by Pre-diagnosis BMI categories of Women Diagnosed with Ovarian Cancer after Enrollment into WHI

		Pre-Diagnosis BMI at Enrollment, kg/m^2			
	Total (N=600)	**BMI<18.5 (N=13)**	**18.5 ≤BMI<25 (N=217)**	**25≤BMI<30 (N=199)**	**BMI≥30 (N=171)**
Age, mean (years)	63.0	63.7	63.4	63.2	62.2
Years from baseline to ovarian cancer diagnosis*, mean	7.0	7.8	7.2	6.8	6.9
BMI, mean (kg/m^2)**	27.5	17	22.5	27.3	34.8
Physical activity[1], mean (MET hr /wk)*	9.8	16.2	13	9.7	5.2
Vigorous-Intensity Physical Activity, mean (MET hr /wk)	3.8	6.0	5.0	3.7	2.1
Ethnicity*, % White	88.8	84.6	93.1	90.5	81.9
Education, % with high school education or greater**	95.8	100	98.6	98.5	88.8
Cancer Stage (SEER Stage), %					
Localized	17.0	7.7	17.1	13.6	21.6
Regional	14.8	7.7	12.4	17.6	15.2
Distant	68.2	84.6	70.5	68.8	63.2
Disease Histology, %					
Serous	59.3	69.1	64.5	58.8	52.6
Undifferentiated	16.0	15.4	13.4	16.6	18.7
Endometriod	9.7	0	8.3	9.6	12.3
Mucinous	6.2	0	5.1	8.0	5.9
Clear-Cell	5.5	7.7	5.5	3.0	8.2
Other[2]	3.3	7.7	3.2	4.0	2.3
Age at Menarche*, % <12 yrs old	23.0	7.7	15.2	26.6	29.8
Oral Contraceptive Use, % Ever used	40.8	38.5	41.5	41.2	39.8
Hormone Therapy Use*, % Current	44.0	38.5	52.1	44.7	33.3
Parity, % ≥ 1 term pregnancy	86.1	84.6	88.4	87.9	81.2
Had Hysterectomy, %	30.4	30.8	26.3	36.9	28.1
Ovary removed, % None	86.8	92.3	88.5	85.9	85.2

a: Baseline characteristics by Pre-diagnosis BMI categories of Women Diagnosed with Ovarian Cancer after Enrollment into WHI

		Pre-Diagnosis BMI at Enrollment, kg/m^2			
	Total (N=600)	**BMI<18.5 (N=13)**	**18.5 ≤BMI<25 (N=217)**	**25≤BMI<30 (N=199)**	**BMI≥30 (N=171)**
First-degree relative with ovarian cancer, %	4.6	20.0	1.9	4.8	7.0
History of Type II Diabetes****, %**	5.3	0	1.9	2.5	13.5
Smoking, % Ever	50.7	46.2	45.3	55.8	51.8

b: Baseline characteristics by Pre-diagnosis Physical Activity Categories of Women Diagnosed with Ovarian Cancer after Enrollment into WHI

	Pre-Diagnosis Physical Activity$^{\pm}$ at Enrollment, MET hr/wk			
	PA=0 (N=209)	**0<PA<9 (N=163)**	**9≤PA<15 (N=73)**	**PA≥15 (N=155)**
Age, mean (yrs)	63.3	63.2	64.4	61.8
Years from baseline to ovarian cancer diagnosis, mean	6.9	7.4	6.7	6.8
BMI***, mean (kg/m**^{2}**)**	29.0	27.9	27.7	24.8
Physical activity^{1}**, mean (MET hr /wk)****	0	4.1	11.4	28.1
Vigorous-Intensity Physical Activity****, mean (MET hr /wk)**	0	0.6	3.2	12.4
Ethnicity***, % White**	83.7	89.6	87.7	95.5
Education***, % with high school education or greater**	93.2	95.0	97.3	99.4
Cancer Stage (SEER Stage), %				
Localized	17.7	15.3	24.6	14.2
Regional	16.3	17.8	11.0	11.6
Distant	66.0	66.9	64.4	74.2
Histology				
Serous	56.5	57.7	46.6	71.0
Undifferentiated	19.6	14.1	20.6	11.0
Endometriod	10.1	10.4	15.1	5.8
Mucinous	5.7	8.6	9.6	2.6
Clear-Cell	4.8	5.5	4.1	7.1
Other^{2}	3.4	3.7	4.1	2.6
Age at Menarche, % <12 yrs old	23.0	25.8	21.9	20.7

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b: Baseline characteristics by Pre-diagnosis Physical Activity Categories of Women Diagnosed with Ovarian Cancer after Enrollment into WHI

	Pre-Diagnosis Physical Activity± at Enrollment, MET hr/wk			
	PA=0 (N=209)	**0<PA<9 (N=163)**	**9≤PA<15 (N=73)**	**PA≥15 (N=155)**
Oral Contraceptive Use*, % Ever used	39.2	32.5	46.6	49.0
Hormone Therapy Use*, % Current	41.6	47.5	52.8	57.8
Parity, % ≥ 1 term pregnancy	83.7	85.7	83.6	91.0
Had Hysterectomy, %	31.6	31.9	32.9	26.0
Ovary removed, % None	81.2	89.6	93.2	88.3
First-degree relative with ovarian cancer, %	4.6	4.2	0	7.3
History of Type II Diabetes, %	4.3	8.6	9.6	1.3
Smoking, % Ever	48.5	49.4	50.7	54.9

Abbreviations: BMI, body mass index; MET, metabolic equivalent task; SEER, surveillance epidemiology and end results

[1] Moderate- to vigorous-intensity physical activity presented

[2] Other histology includes Mixed and Brenner

* P<0.05 for Levene's Test for homogeneity or Chi-square

** P<0.0001 Levene's Test for homogeneity or Chi-square

Abbreviations: PA, Physical Activity; BMI, body mass index; MET, metabolic equivalent task; SEER, surveillance epidemiology and end results

[1] Moderate- to vigorous-intensity physical activity presented

[2] Other histology includes Mixed and Brenner

* P<0.05

** P<0.0001

Table 2

Associations between ovarian cancer outcomes and pre-diagnosis BMI

	Pre-Diagnosis BMI, kg/m^2			
	BMI <18.5 (N=13)	**18.5 ≤BMI<25 (N=217)**	**25≤BMI<30 (N=199)**	**BMI≥30 (N=171)**
Total Deaths	n=8	n=131	n=113	n=94
Age-Adjusted HR (95% CI)	1.44 (0.71–2.95)	1.00	0.91 (0.71–1.17)	1.00 (0.77–1.30)
Multivariate Adjusted HR* (95% CI)	1.14 (0.55–2.40)	1.00	0.77 (0.59–1.01)	0.95 (0.70–1.29)
Ovarian Cancer Deaths	n=6	n=115	n=100	n=80
Age-Adjusted HR (95% CI)	1.22 (0.54–2.77)	1.00	0.92 (0.70–1.20)	0.97 (0.73–1.29)
Multivariate Adjusted HR* (95% CI)	0.90 (0.39–2.11)	1.00	0.79 (0.59–1.05)	0.95 (0.69–1.32)

Abbreviations: BMI, body mass index; MET, metabolic equivalent task; HR, Hazard Ratio

* Multivariate Model adjusted for age, stage, histology, time from study enrollment to ovarian cancer diagnosis, physical activity, hormone therapy use, smoking, history of diabetes and status in calcium and vitamin D trial, diet modification trial, hormone therapy trial and observational study.

Table 3

Associations between ovarian cancer and moderate- to vigorous-intensity physical activity

	Pre-Diagnosis Physical Activity± at Enrollment, MET hr/wk			
	PA=0 (N=209)	**0<PA<9 (N=163)**	**9≤PA<15 (N=73)**	**PA≥15 (N=155)**
Total Deaths	n=121	n=97	n=41	n=87
Age-Adjusted HR (95% CI)	1.00	1.15 (0.88–1.50)	0.89 (0.62–1.27)	0.98 (0.75–1.30)
Multivariate Adjusted HR* (95% CI)	1.00	1.09 (0.82–1.44)	0.76 (0.52–1.10)	0.87 (0.64–1.17)
Ovarian Cancer Deaths	n=105	n=84	n=32	n=80
Age-Adjusted HR (95% CI)	1.00	1.14 (0.85–1.52)	0.79 (0.53–1.52)	1.04 (0.77–1.39)
Multivariate Adjusted HR* (95% CI)	1.00	1.07 (0.79–1.44)	0.68 (0.45–1.03)	0.89 (0.65–1.23)

Abbreviations: BMI, body mass index; PA, Physical Activity; HR, Hazard Ratio

± Moderate- to vigorous-intensity physical activity presented

* Multivariate Model adjusted for age, stage, histology, time from study enrollment to ovarian cancer diagnosis, BMI, hormone therapy use, smoking, history of diabetes and status in calcium and vitamin D trial, diet modification trial, hormone therapy trial and observational study.

Table 4

Associations between ovarian cancer outcomes and vigorous- intensity physical activity

	Pre-Diagnosis Vigorous-Intensity Physical Activity (MET hr/wk)	
	Vigorous PA = 0 (N=439)	**Vigorous PA>0 (N=161)**
Total Deaths	n= 260	n=86
Age-Adjusted HR (95% CI)	1.00	0.83 (0.65–1.06)
Multivariate Adjusted HR* (95% CI)	1.00	0.76 (0.58–0.98)1
Ovarian Cancer Deaths (n)	n=228	n=73
Age-Adjusted HR (95% CI)	1.00	0.80 (0.61–1.04)
Multivariate Adjusted HR* (95% CI)	1.00	0.74 (0.56–0.98)[1]

Abbreviations: PA, Physical Activity; HR, Hazard Ratio

*Multivariate Model adjusted for age, stage, histology, time from study enrollment to ovarian cancer diagnosis, BMI, hormone therapy use, smoking, history of diabetes and status in calcium and vitamin D trial, diet modification trial, hormone therapy trial and observational study.

[1] $p<0.05$