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# Pre-diagnosis body mass index, physical activity and ovarian cancer mortality

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## HIGHLIGHTS

- Limited prospective data exists on the effect of pre-diagnosis obesity or physical activity on ovarian cancer mortality.
- Higher BMI is associated with increased overall and ovarian cancer mortality; physical activity level was not associated.
- Findings suggest that having a normal weight before ovarian cancer diagnosis confers survival advantage.

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## ABSTRACT

*Background.* Ovarian cancer is the deadliest gynecologic malignancy, yet the effects on survival of modifiable pre-diagnosis lifestyle factors, such as obesity and physical activity, remain largely unexplored. Our objective was to evaluate the effect of pre-diagnosis BMI and physical activity on ovarian cancer mortality using prospectively collected data.

*Methods.* Data on women who developed ovarian cancer after enrollment into the NIH-AARP Diet and Health Study were analyzed. Cancer incidence was ascertained through linkage state cancer registries and consisted of 741 cases of epithelial ovarian cancer.

*Results.* Higher pre-diagnosis BMI was associated with increased overall and ovarian cancer-specific mortality. Comparing women with BMI 25–29.9, 30–34.9 and ≥ 35 to normal weight women, the HRs of overall mortality were 1.18 (95%CI 0.96–1.45), 1.05 (0.82–1.36) and 1.59 (1.14–2.18, p-trend = 0.02). The findings were similar for ovarian cancer-specific mortality comparing women with BMI ≥ 35 to normal weight women (BMI <25) with a HR of 1.47 (95%CI 1.03–2.09, p-trend 0.08). Pre-diagnosis physical activity was not associated with mortality, with HRs for overall mortality of 1.06 (95%CI 0.79–1.43), 0.94 (0.72–1.23), 0.98 (0.76–1.25), and 0.98 (0.75–1.28, p-trend = 0.91), comparing women who engaged in vigorous physical activity 1–3 times/month, 1–2 times/week, 3–4 times/week and 5 times/week, respectively, with those who never/rarely engaged in such activity.

*Conclusions.* Women who were obese before developing ovarian cancer had increased mortality than those who were normal weight, but physical activity before diagnosis was not associated with mortality in this study population. These results suggest that maintaining a healthy weight is a powerful preventative tool.



## 1. Introduction

Ovarian cancer is one of the most lethal malignancies worldwide with approximately 295,000 new diagnoses and 185,000 deaths per year [1]. This year, in the United States alone, 22,530 women will be diagnosed, and 13,980 women will die of the disease [2]. Symptoms are

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non-specific, including bloating, appetite changes or vague abdominal pain. Hence, the majority (60%) of patients are diagnosed with advanced stage disease and distant metastases; 5-year survival rates are as low as 20% [3]. Although treatment and tumor characteristics are important determinants of prognosis, there is substantial variation even among patients with similar characteristics who receive the same treatment [4,5], indicating other factors, such as lifestyle, are involved. Nevertheless, there is very little data on the influence of modifiable pre-diagnosis lifestyle factors, such as obesity and physical activity.

Evidence suggests that obesity may increase the risk of ovarian cancer [6,7]. This risk may be limited to the less common, non-high-grade serous cancer subtype [8] or to those who have not previously used menopausal hormone replacement therapy [9]. However, additional analyses have demonstrated increased mortality with increased BMI. These studies used BMI as ascertained by patient recall or by measurement at the time of cancer diagnosis, so are inherently limited by the risk for recall bias and by the possible effect of occult or overt ovarian cancer on BMI, given its predisposition to cause large ascites and bulky tumor [10–14]. Prospectively assessed pre-diagnosis obesity has been associated with increased mortality in other cancers [15–19], but to the best of our knowledge, only the Women's Health Initiative (WHI) study has prospectively evaluated the association of pre-diagnosis obesity and ovarian cancer mortality and found none [20].

Obesity, however, does not exist in a vacuum. Sedentary behavior and lack of physical activity is inversely related to obesity and has been independently associated with an increased risk of several cancer types [21]. While a large prospective cohort study found no association between physical activity and ovarian cancer risk [22], only three studies have evaluated its association with survival [20,23,24]. Only one used prospectively collected data and found that women who engaged in the highest level of physical activity had no survival advantage over those who engaged in none, though there may be some benefit in any amount compared to none [20].

Because of the limited prospective data on these associations, we sought to investigate whether pre-diagnosis BMI and physical activity were associated with ovarian cancer mortality using prospectively collected data from the NIH-AARP Diet and Health Study.

## 2. Methods

The analysis was conducted among participants in NIH-AARP Diet and Health Study. The NIH-AARP study included 566,398 AARP members (339,666 men and 226,732 women), aged 50–71, residing in 6 states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, GA and Detroit, MI) who completed a baseline mailed questionnaire in 1995–1996 [25]. This questionnaire obtained data on dietary habits, family history of cancer, height, weight and lifestyle-related factors such as physical activity [25]. In 1996–1997, a second questionnaire, the risk factor questionnaire, was mailed to those who responded at baseline. We excluded the following women from our study population: those with (i) questionnaires completed by a proxy ($n = 15{,}760$), (ii) cancer at baseline ($n = 26{,}797$) or cancer diagnosis before entry ($n = 543$), and (iii) end-stage renal disease ($n = 284$), due to their higher risk of death at baseline.

Cancer incidence was ascertained through linkage to the eight original and three additional (AZ, NV and TX) state cancer registries [26]. The additional states were included in order to capture cancer cases among members who relocated during follow-up. A previous study validated that approximately 90% of cancer cases were identified through registry linkage [26]. The registries collected data on diagnosis date, cancer diagnosis, histology, grade, and stage. Primary epithelial ovarian cancer cases were identified using the International Classification of Diseases for Oncology, Third Edition (ICD—O). Cases were classified into serous (8441, 8460, 8461, 8450), endometrioid (8380, 8381, 8560, 8570), mucinous (8470, 8471, 8480, 8481), clear cell (8310, 8313), and other epithelial (8010, 8020, 8021, 8050, 8070, 8120, 8140, 8240, 8246, 8255, 8260, 8323, 8440, 8450, 8490, 8562) cancers. Our study population consisted of 741 cases of epithelial ovarian cancer. Vital status and causes of death were ascertained by linkage with the National Death Index Plus through December 31, 2011. We defined all-cause mortality and ovarian cancer specific mortality using ICD-9 and ICD-10 codes.

BMI was calculated using baseline self-reported weight and height as weight(kg)/height($m^2$) and categorized into 4 groups (<25 (normal), 25–29.99 (overweight), 30–34.99 (class I obesity), ≥35 kg/$m^2$ (classes II and III obesity)). We did not have a separate category for BMI < 18.5 kg/$m^2$ due to the small number of cases ($N = 11$). BMI <25.0 was the referent category for our analyses. We excluded 30 women with missing BMI and 3 women with BMI <17 kg/$m^2$; thus, our analytic set for BMI had 708 cases.

Vigorous physical activity over the preceding 12 months was assessed in the baseline questionnaire. Vigorous activities were defined as those that lasted ≥20 min and caused an increase in breathing or heart rate or worked up a sweat [25]. Physical activity frequency was defined as never, rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week, and ≥ 5 times/week. For this analysis, "never" ($n = 36$) and "rarely" ($n = 128$) were combined into one group and used as the referent category for analyses. The risk factor questionnaire assessed light and vigorous recreational and household physical activities over the last 10 years. These were defined as never, rarely, weekly but <1 h/week, 1–3 h/week, 4–7 h/week, and ≥ 7 h/week. As with the risk factor questionnaire, "never" and "rarely" were combined and used as the referent category for analyses. Ten women were excluded from the baseline physical activity analyses due to missing data. Therefore, 731 women were included in the final analyses of the baseline questionnaire. Of the women that completed the risk factor questionnaire, 489 of 741 included data on light and vigorous physical activity so were included in the analysis.

We compared baseline characteristics by BMI categories. The chi-square and Fisher's Exact tests were applied as appropriate for categorical variables. Follow-up for survival commenced on the date of ovarian cancer diagnosis and ended at death or end of follow-up (December 31, 2011), whichever came first. We evaluated associations of BMI and physical activity with overall survival and ovarian cancer-specific survival. For ovarian cancer-specific survival, deaths from other causes were considered as censored events.

Cox proportional hazard models, with age as the time metric and adjusted for confounders, were used to estimate the hazard ratios (HRs) and 95% confidence intervals (95%CIs). The proportional hazards assumption was examined by cumulative sums of martingale residuals for each variable using ASSESS statement and resampling method in SAS. This is a standard and robust method to evaluate whether a fitted Cox regression model adequately describes the data. The assumption was valid for all models. We included potential confounding variables in the Cox model if their inclusion changed the risk estimate for the BMI variable by ≥10%. We evaluated the associations of BMI or physical activity with ovarian cancer survival in model 1 which was adjusted for age at study entry and time from entry to cancer diagnosis, and model 2 adjusting for additional confounders such as alcohol use, hormone replacement therapy (HRT) use, cancer stage, race, and parity. In analyses for physical activity and ovarian cancer survival, we further adjusted for BMI and combined never and rarely physically active into one category (reference). Trend tests were performed using the median value of each category in a regression analysis.

We conducted sensitivity analyses excluding participants diagnosed with ovarian cancer within the first two years of study entry. Additionally, we conducted analyses stratified by histology subtype. A survival analysis was performed using the Kaplan-Meier method and the log-rank test to compare homogeneity of survival functions between BMI categories. All tests were two-sided and $p$-values <0.05 were considered statistically significant. Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

## 3. Results

Demographic pre-diagnosis characteristics of study participants are shown in Table 1. The mean age at study entry for ovarian cancer cases was 62.7 years, with no significant difference when stratified by BMI. The mean BMI was 26.7 kg/m$^2$. Five hundred and forty-nine deaths (representing 74.1% of total cases) occurred during follow-up. Compared to women with BMI ≥ 35, women with BMI <25 were less likely to consume no alcohol (25.1% non-drinkers vs. 41.1% non-drinkers) and more likely consume ≥10 g/day of alcohol (26.3% vs. 5.4%, *p*-value ≤0.01). Women with BMI <25 were also more likely to use menopausal hormone replacement therapy (HRT) (63.3% vs. 37.5%, p-value<0.01)

**Table 1**
Pre-diagnosis characteristics of women with ovarian cancer by body mass index (BMI kg/m$^2$) category ($N = 741$)[a].

| Characteristic | BMI < 25<br>$n = 327$ | BMI 25–29.99<br>$n = 206$ | BMI 30–34.99<br>$n = 119$ | BMI ≥ 35<br>$n = 56$ | p-Value |
|---|---|---|---|---|---|
| Age at enrollment (mean, SD) | 63.76 (5.33) | 63.09 (5.02) | 61.69 (5.95) | 63.39 (5.22) | $p = 0.22$ |
| Race | | | | | $p = 0.04$ |
| Non-Hispanic White | 307 (93.88%) | 194 (94.17%) | 112 (94.12%) | 47 (83.93%) | |
| Others | 20 (6.12%) | 12 (5.83%) | 7 (5.88%) | 9 (16.07%) | |
| Education | | | | | $p = 0.09$ |
| 12 years or less of school | 82 (25.08%) | 64 (31.07%) | 45 (37.82%) | 17 (30.36%) | |
| Post high school education (technical) | 32 (9.79%) | 22 (10.68%) | 12 (10.08%) | 3 (5.36%) | |
| Some college | 76 (23.24%) | 54 (26.21%) | 28 (23.53%) | 20 (35.71%) | |
| College graduate | 73 (22.32%) | 37 (17.96%) | 17 (14.29%) | 9 (16.07%) | |
| Post graduate | 51 (15.60%) | 25 (12.14%) | 15 (12.61%) | 3 (5.36%) | |
| Unknown | 13 (3.98%) | 4 (1.94%) | 2 (1.68%) | 4 (7.14%) | |
| Vigorous physical activity in the past year | | | | | $p < 0.01$ |
| Never/rarely | 57 (17.76%) | 40 (19.51%) | 33 (28.21%) | 25 (44.64%) | |
| 1–3 times/month | 48 (14.95%) | 28 (13.66%) | 20 (17.09%) | 6 (10.71%) | |
| 1–2 times/week | 56 (17.45%) | 40 (19.51%) | 28 (23.93%) | 11 (19.64%) | |
| 3–4 times/week | 82 (25.55%) | 63 (30.73%) | 27 (23.08%) | 9 (16.07%) | |
| ≥5 times/week | 78 (24.30%) | 34 (16.59%) | 9 (7.69%) | 5 (8.93%) | |
| Light physical activity in the past 10 years | | | | | p < 0.01 |
| Never/Rarely | 6 (2.70%) | 5 (3.70%) | 2 (2.82%) | 7 (18.92%) | |
| <1 h/week | 8 (3.60%) | 9 (6.67%) | 6 (8.45%) | 5 (13.51%) | |
| 1–3 h/ week | 29 (13.06%) | 24 (17.78%) | 24 (33.80%) | 8 (21.62%) | |
| 4–7 h/week | 79 (35.59%) | 43 (31.85%) | 16 (22.54%) | 7 (18.92%) | |
| ≥7 h/week | 100 (45.05%) | 54 (40.00%) | 23 (32.39%) | 10 (27.03%) | |
| Vigorous physical activity in the past 10 years | | | | | p < 0.01 |
| Never/Rarely | 27 (12.22%) | 16 (11.85%) | 16 (21.92%) | 8 (21.05%) | |
| <1 h/week | 12 (5.43%) | 19 (14.07%) | 13 (17.81%) | 11 (28.95%) | |
| 1–3 h/ week | 54 (24.43%) | 33 (24.44%) | 20 (27.40%) | 6 (15.79%) | |
| 4–7 h/week | 74 (33.48%) | 37 (27.41%) | 18 (24.66%) | 9 (23.68%) | |
| ≥7 h/week | 54 (24.43%) | 30 (22.22%) | 6 (8.22%) | 4 (10.53%) | |
| Smoking | | | | | $p = 0.15$ |
| Never smoked | 155 (47.40%) | 111 (53.88%) | 58 (48.74%) | 24 (42.86%) | |
| Former smoker | 115 (35.17%) | 77 (37.38%) | 45 (37.82%) | 25 (44.64%) | |
| Current Smoker | 51 (15.60%) | 16 (7.77%) | 12 (10.08%) | 5 (8.93%) | |
| Alcohol consumption (g/day) | | | | | p < 0.01 |
| 0 g | 82 (25.08%) | 61 (29.61%) | 37 (31.09%) | 23 (41.07%) | |
| <5 g | 132 (40.37%) | 104 (50.49%) | 64 (53.78%) | 26 (46.43%) | |
| 5–10 g | 27 (8.26%) | 12 (5.83%) | 7 (5.88%) | 4 (7.14%) | |
| ≥10 g | 86 (26.30%) | 29 (14.08%) | 11 (9.24%) | 3 (5.36%) | |
| Parity | | | | | $p = 0.003$ |
| 0 | 54 (16.51%) | 41 (19.90%) | 26 (21.85%) | 7 (12.50%) | |
| 1 | 44 (13.46%) | 27 (13.11%) | 13 (10.92%) | 6 (10.72%) | |
| 2 | 85 (25.99%) | 65 (31.55%) | 25 (21.01%) | 11 (19.64%) | |
| 3 | 119 (36.39%) | 62 (30.10%) | 41 (34.45%) | 18 (32.14%) | |
| ≥4 | 25 (7.65%) | 11 (5.34%) | 14 (11.76%) | 14 (25.00%) | |
| Age at first live birth | | | | | p = 0.04 |
| Nulliparous | 52 (16.00%) | 40 (19.61%) | 25 (21.55%) | 7 (12.73%) | |
| <20 | 39 (12.00%) | 38 (18.63%) | 21 (18.10%) | 12 (21.82%) | |
| 20–24 | 128 (39.38%) | 76 (37.25%) | 49 (42.24%) | 25 (45.45%) | |
| ≥25 | 106 (36.62%) | 50 (24.51%) | 21 (18.10.%) | 11 (20.00%) | |
| Hysterectomy status, ever | 90 (27.61%) | 68 (33.01%) | 43 (36.75%) | 19 (33.93%) | $p = 0.25$ |
| Menopausal hormone use, ever | 207 (63.30%) | 99 (48.06%) | 54 (45.38%) | 21 (37.50%) | p < 0.01 |
| Oral contraceptive use, ever | 114 (35.19%) | 56 (27.59%) | 40 (34.48%) | 14 (25.45%) | $p = 0.19$ |
| Cancer histology | | | | | $p = 0.18$ |
| Other epithelial | 93 (28.44%) | 60 (29.13%) | 56 (47.06%) | 26 (46.43%) | |
| Serous | 188 (57.49%) | 102 (49.51%) | 38 (31.93%) | 21 (37.50%) | |
| Endometrioid | 26 (7.95%) | 19 (9.22%) | 15 (12.61%) | 5 (8.93%) | |
| Mucinous | 12 (3.67%) | 14 (6.80%) | 9 (7.56%) | 2 (3.57%) | |
| Clear cell | 8 (2.45%) | 11 (5.34%) | 1 (0.84%) | 2 (3.57%) | |
| Cancer stage | | | | | $p = 0.10$ |
| Localized | 18 (5.50%) | 14 (6.80%) | 14 (11.76%) | 2 (3.57%) | |
| Regional[b] | 38 (11.62%) | 22 (10.68%) | 16 (13.45%) | 5 (8.93%) | |
| Distant metastases/systemic disease | 169 (51.68%) | 87 (42.23%) | 45 (37.82%) | 27 48.21%) | |
| Missing[c] | 102 (31.19%) | 83 (40.29%) | 44 (36.97%) | 22 (39.29%) | |

[a] Total number of participants, 741 who have epithelial ovarian cancer. For some characteristics, numbers may not add to 741 due to missing information.
[b] Regional by direct extension, regional to lymph nodes, regional by both, and regional NOS.
[c] Includes not abstracted and unknown stages.

and less likely to have ≥4 children (7.7% vs. 25%, p-value = 0.003). There were no statistically significant differences in stage at presentation between BMI groups.

The survival difference in ovarian cancer-specific mortality is demonstrated in the Kaplan-Meier curve, which showed a statistically significant decrease in survival among the BMI ≥35 group (Fig. 1, $p$ = 0.031). Higher pre-diagnosis BMI was associated with increased all-cause, overall mortality (Table 2), with a median survival of 3.92 years (95%CI 3.19–4.47), 3.12 years (2.55–3.88), 3.68 years (2.76–5.67), and 1.98 years (1.06–2.85) in women with BMI <25, 25–29.9, 30–34.9, and ≥ 35, respectively. In the analysis adjusted for age and time to cancer diagnosis, the HRs were 1.13 (95%CI 0.92–1.38), 0.95 (0.74–1.23), and 1.64-fold (1.20–2.24, p-trend = 0.04), respectively, comparing women with BMI 25–29.9, 30–34.9 and ≥ 35 to normal weight women. Further adjustment for alcohol use, menopausal HRT use, cancer stage, race and parity did not affect the estimates, with corresponding HRs of 1.18 (95%CI 0.96–1.45), 1.05 (0.82–1.36) and 1.59 (1.14–2.18, p-trend = 0.02). Survival advantage of lower BMI was maintained in the analysis of ovarian cancer-specific mortality, with a multivariable adjusted HR of 1.47 (95%CI 1.03–2.09, p-trend = 0.08) and a median survival of 2.85 years (95%CI 1.41–4.04) compared to 4.42 years (3.80–4.91), comparing women with BMI ≥35 to those with BMI <25.

A sensitivity analysis excluding women diagnosed within the first two years of study entry observed similar results (Table 2), with a median overall survival of 1.98 years (95%CI 0.96–2.98) versus 3.45 years (2.79–4.25) and ovarian cancer-specific survival of 2.98 years (1.41–4.07) versus 4.13 years (3.34–4.77), comparing women with BMI ≥35 to those with BMI <25. The multivariable adjusted HRs were 1.72 (95%CI = 1.21–2.42, p-trend<0.01) for overall mortality and 1.52 (95%CI 1.02–2.25, p-trend = 0.02) for ovarian cancer-specific mortality. These differences were not observed when stratified by histologic subtype (Supplemental Table S1).

Pre-diagnosis vigorous physical activity was not associated with ovarian cancer mortality (Table 3). In multivariable analyses comparing women who engaged in vigorous physical activity 1–3 times/month, 1–2 times/week, 3–4 times/week and 5 times/week with those who never/rarely did, the HRs for overall mortality by physical activity level were 1.06 (95%CI 0.79–1.43), 0.94 (0.72–1.23), 0.98 (0.76–1.25), and 0.98 (0.75–1.28, p-trend = 0.91), respectively. Similar null results were observed in analyses for ovarian cancer-specific mortality (Table 3), as well as in sensitivity analyses excluding women diagnosed within the first 2 years of study entry and analyses stratified by histologic subtype (data not shown). There remained no statistically significant association when we compared women who rarely/never engaged in vigorous physical activity vs. all others.

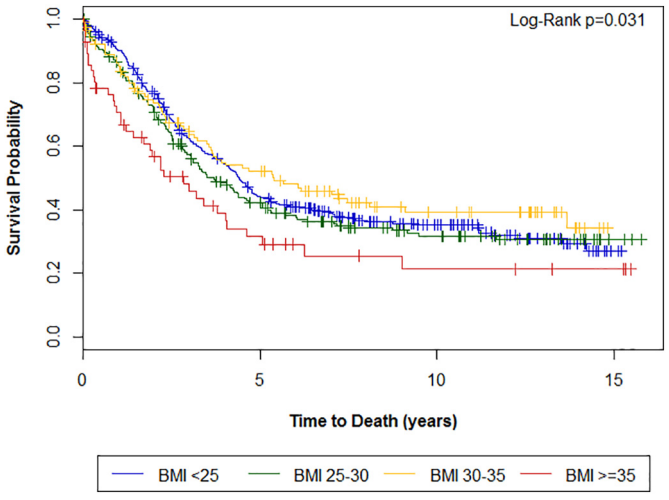


**Fig. 1.** Kaplan-Meier for Cancer-specific Analysis Survival Curves of Ovarian Cancer Patients by Body Mass Index Category (BMI) at Baseline Questionnaire.

In the subset of women who completed the risk factor questionnaire, there was no association with overall or ovarian cancer-specific mortality by either light or vigorous physical activity (Table 4). The HRs for overall mortality were 0.73 (95%CI 0.48–1.21), 0.87 (0.62–1.23), 0.67 (0.48–0.94), 0.92 (0.64–1.31, p-trend = 0.07), respectively, comparing women who engaged in <1 h/week, 1–3 h/ week, 4–7 h/week, or ≥ 7 h/week of vigorous physical activity to those who rarely/never did. Similar results were observed for ovarian cancer-specific mortality. Even a high level of light physical activity was not associated significantly with overall mortality (HR = 0.86, 95%CI 0.51–1.43, p-trend = 0.57) or ovarian cancer-specific mortality (HR = 0.84, 95%CI 0.48–1.47, p-trend = 0.50).

## 4. Discussion

In this study of >700 women with prospectively collected data on BMI and physical activity, higher pre-diagnosis BMI was associated with higher overall and ovarian cancer-specific mortality. There were no associations between physical activity and overall or ovarian cancer-specific mortality.

Prior clinical and case-control studies have reported varied associations between obesity and ovarian cancer mortality [10]. A pooled analysis by the Ovarian Cancer Association Consortium with 12,390 ovarian cancer cases and 6715 deaths found that mortality risk increased by 3% for every 5-unit increase in BMI over 18.5 kg/m$^2$ [11]. Likewise, meta-analyses of obesity and ovarian cancer survival have reported excess risks of mortality ranging from 17 to 40% among obese women compared with non-obese women [10,12]. However, because BMI-related and other information were collected before cancer diagnosis in our study, our findings provide important new context on these associations. Furthermore, the association found here between increased pre-diagnosis BMI and ovarian cancer mortality is consistent with research in other cancer types, including endometrial [15], pancreatic [27], prostate [28] and colorectal cancer [29].

Our findings do differ from the previous prospective study that reported no association of BMI with ovarian cancer mortality in the WHI [20]. The characteristics of our study population are very similar to the WHI population, including mean age at enrollment, mean BMI, and the proportion of women who have had a hysterectomy. Nevertheless, there are some notable differences. In our study, women with BMI < 25 kg/m$^2$ were less likely to be non-drinkers compared to women with BMI ≥ 35, and alcohol intake was associated with mortality (data not shown), suggesting that alcohol intake might confound the association of BMI with ovarian cancer mortality. Therefore, we adjusted for alcohol intake in our multivariable analyses, while the WHI study did not. Studies have demonstrated mixed associations between alcohol use and risk of ovarian cancer, but most have not analyzed the effect of obesity or examined recurrence rates or survival after diagnosis [30,31]. While there is a lack of research on the role of alcohol in outcomes of ovarian cancer, alcohol consumption of three to four drinks or more per week was found to increase the risk of breast cancer recurrence in the Life After Cancer Epidemiology (LACE) study. Interestingly, these risks were particularly notable in overweight or obese women [32].

Of note, our study found only a survival difference when comparing patients with the highest BMI with normal BMI patients. A p-trend of 0.08 in the ovarian cancer-specific mortality multivariable model 2 indicated no statistically significant linear association between survival and increasing BMI. It has been previously described in literature that the effect of obesity on many diseases, including cancer, may not be related to a linear "dose effect," but is instead referred to as the obesity paradox [29,33]. This is the observation that overweight and early obese patients (BMI 25–34.9 kg/m$^2$) may experience improved survival compared to their underweight or very obese counterparts, resulting in a "J" or "U" shaped curve when comparing BMI to the hazard ratio of survival [29,33]. This has generated discussions on the utility of BMI as the sole indicator of adiposity to predict survival [34].

**Table 2**
Hazard Ratios (HR) and 95% Confidence Intervals (CI) of ovarian cancer mortality by pre-diagnosis body mass index (BMI), kg/m$^2$ in women with ovarian cancer ($N = 708$).

| Body mass index, kg/m2 | <25 | 25–29.99 | 30–34.99 | ≥35 | *p*-Trend |
|---|---|---|---|---|---|
| Overall mortality | | | | | |
| No. of deaths/total cases | 239/327 | 159/206 | 81/119 | 47/56 | |
| Multivariable model[a] | 1.00 (ref) | 1.13 (0.92–1.38) | 0.95 (0.74–1.23) | 1.64 (1.20–2.24) | 0.04 |
| Multivariable model[b] | 1.00 (ref) | 1.18 (0.96–1.45) | 1.05 (0.82–1.36) | 1.59 (1.16–2.18) | 0.02 |
| Ovarian cancer-specific mortality | | | | | |
| No. of deaths/total cases | 201/327 | 129/206 | 65/119 | 37/56 | |
| Multivariable model[a] | 1.00 (ref) | 1.09 (0.87–1.36) | 0.91 (0.69–1.20) | 1.53 (1.07–2.17) | 0.19 |
| Multivariable model[b] | 1.00 (ref) | 1.15 (0.92–1.45) | 1.02 (0.77–1.35) | 1.47 (1.03–2.09) | 0.08 |
| Excluding women diagnosed with ovarian cancer within the first two years of study enrollment | | | | | |
| Overall mortality | | | | | |
| No. of deaths/total cases | 187/258 | 140/175 | 64/95 | 40/46 | |
| Multivariable model[a] | 1.00 (ref) | 1.17 (0.94–1.46) | 0.97 (0.73–1.29) | 1.74 (1.24–2.46) | 0.03 |
| Multivariable model[b] | 1.00 (ref) | 1.27 (1.01–1.58) | 1.12 (0.84–1.49) | 1.72 (1.21–2.42) | <0.01 |
| Ovarian cancer-specific mortality | | | | | |
| No. of deaths/total cases | 158/258 | 117/175 | 57/95 | 30/46 | |
| Multivariable model[a] | 1.00 (ref) | 1.17 (0.92–1.48) | 1.01 (0.75–1.37) | 1.54 (1.04–2.28) | 0.08 |
| Multivariable model[b] | 1.00 (ref) | 1.26 (0.99–1.61) | 1.19 (0.87–1.62) | 1.52 (1.02–2.25) | 0.02 |

[a] Multivariable model 1 adjusted for age at entry and time from entry to cancer diagnosis.
[b] Multivariable model 2 age at entry, time from entry to diagnosis, alcohol use, menopausal hormone use, cancer stage, race, parity.

Several plausible mechanisms, however, do support a biologic association between obesity and ovarian cancer outcomes. Adipose tissue is a metabolically active endocrine organ and is associated with chronic inflammation due to greatly augmented production of pro-inflammatory metabolic cytokines [35,36]. Pro-inflammatory cytokines are significantly elevated in ovarian cancer, and while research suggests an association between cytokine levels and chemotherapeutic sensitivity, a relationship between cytokine levels, BMI and cancer survival has not been observed [37]. Increased adiposity also promotes rapid tumor progression in obese mice with resultant genomic dysregulation [38] and enhances metastases by providing an energy reservoir for anchored tumor cells [39]. Furthermore, a preclinical study recently suggested that obesity influences ovarian cancer metastases through its effects on lipogenesis, lipid transport and enhanced vascularity [39].

Although there is limited data on the association of physical activity and ovarian cancer survival, our findings support previous publications in showing no association [14,20,23,24]. Nevertheless, the WHI study, which found no significant association when comparing highest to lowest levels of physical activity, reported a 24% reduction in mortality among women who reported any vigorous physical activity (MET h/week >0) compared to those who reported none (MET h/week = 0) [20]. When we conducted similar analyses by grouping study participants (never/rarely vs. all others), we did not observe any significant association between physical activity and ovarian cancer mortality. Two other case control studies with sizeable numbers of participants ($N =$ 635 and 638) did not observe an association between physical activity and ovarian cancer survival [23,24], although one of the studies reported an inverse association of physical activity at ages 18–30 with survival among women with stages I and II disease [24].

This study has several limitations. Primarily, data on ovarian cancer treatment was not collected and could therefore not be controlled for in the analysis. There is suggestion that obesity affects the concentration and potency of chemotherapy due to altered distribution and pharmacokinetics. Thus, the obese population is at risk of receiving substandard chemotherapy dose intensity, thereby compromising outcomes [40]. BMI has not been shown to impact the amount of residual disease in primary cytoreductive surgery [41] or to be associated with suboptimal debulking in secondary cytoreduction [42]. The NIH-AARP dataset, however, does not have information on treatment, including use of chemotherapy, surgery, or residual disease status, so we were not able to confirm these findings. Obesity is also associated with metabolic dysregulation, including development of diabetes mellitus, which has been shown to be associated with poorer outcomes in ovarian cancer [43]. The relationship between metabolic syndrome and ovarian cancer risk and mortality is not fully understood, thus future studies should control for this. We also lacked information on the hereditary risks of this population, the presence of which is emerging as a powerful prognostic tool, especially regarding BRCA 1 and 2 mutations. Future studies investigating the interaction of obesity and genetic predisposition on ovarian cancer mortality are needed. Moreover, stage, the most important predictor of ovarian cancer mortality, was missing for 36% of cases. However, the proportion of women with BMI < 25 kg/m$^2$ who had missing stage information was 31.2%, compared with 39.3% among women with BMI ≥ 35. Hence, there is no suggestion that missing stage information could impact study findings. While physical activity, height and weight were self-reported and are thus prone to measurement errors, because self-reporting took place prior to cancer diagnosis, any misclassification is likely to be non-differential. Finally, additional studies in other ethnic groups are needed for greater generalizability, as our study population was predominantly non-Hispanic White.

Despite these limitations, our study has several strengths. Because of its prospective nature, potentials for recall bias, a major limitation of

**Table 3**
Hazard Ratios (HR) and 95% Confidence Intervals (CI) of ovarian cancer mortality by pre-diagnosis vigorous physical activity level in women with ovarian cancer ($N = 731$).

| | Never/Rarely | 1–3 times/month | 1–2 times/week | 3–4 times/week | ≥5 times/week | *p*-Trend |
|---|---|---|---|---|---|---|
| Overall mortality | | | | | | |
| No. of deaths/total cases | 124/164 | 74/103 | 98/142 | 142/187 | 102/135 | |
| Multivariable model[a] | 1.00 (ref) | 0.93 (0.70–1.25) | 0.84 (0.64–1.09) | 0.97 (0.76–1.23) | 0.95 (0.73–1.24) | 0.44 |
| Multivariable model[b] | 1.00 (ref) | 1.06 (0.79–1.43) | 0.94 (0.72–1.23) | 0.98 (0.76–1.25) | 0.98 (0.75–1.28) | 0.91 |
| Ovarian cancer-specific mortality | | | | | | |
| No. of deaths/total cases | 94/164 | 58/103 | 89/142 | 116/187 | 84/135 | |
| Multivariable model[a] | 1.00 (ref) | 0.93 (0.67–1.30) | 0.95 (0.71–1.27) | 1.01 (0.77–1.32) | 0.99 (0.75–1.34) | 0.81 |
| Multivariable model[b] | 1.00 (ref) | 1.06 (0.76–1.48) | 1.06 (0.79–1.43) | 1.01 (0.77–1.33) | 1.03 (0.76–1.39) | 0.74 |

[a] Multivariable model 1 for age at entry and time from entry to cancer diagnosis.
[b] Multivariable model 2 age at entry, time from entry to diagnosis, alcohol use, menopausal hormone use, cancer stage, race, parity.

**Table 4**
Hazard Ratios (HR) and 95% Confidence Intervals (CI) of ovarian cancer mortality by pre-diagnosis light and vigorous physical activity level in the past 10 years in women with ovarian cancer ($N = 489$).

| | Never/rarely | <1 h/week | 1–3 h/ week | 4–7 h/week | ≥7 h/week | *p*-Trend |
|---|---|---|---|---|---|---|
| Overall mortality | | | | | | |
| Light physical activity | | | | | | |
| No. of deaths/total cases | 17/21 | 19/27 | 66/88 | 103/150 | 144/196 | |
| Multivariable model[a] | 1.00 (ref) | 0.69 (0.36–1.33) | 0.84 (0.49–1.44) | 0.74 (0.44–1.24) | 0.80 (0.48–1.32) | 0.28 |
| Multivariable model[b] | 1.00 (ref) | 0.79 (0.41–1.54) | 0.94 (0.54–1.61) | 0.86 (0.51–1.45) | 0.86 (0.51–1.43) | 0.57 |
| Vigorous physical activity | | | | | | |
| No. of deaths/total cases | 54/72 | 40/56 | 84/114 | 94/141 | 78/101 | |
| Multivariable model[a] | 1.00 (ref) | 0.83 (0.55–1.26) | 0.84 (0.59–1.18) | 0.74 (0.53–1.03) | 0.99 (0.70–1.41) | 0.15 |
| Multivariable model[b] | 1.00 (ref) | 0.73 (0.48–1.21) | 0.87 (0.62–1.23) | 0.67 (0.48–0.94) | 0.92 (0.64–1.31) | 0.07 |
| Ovarian cancer-specific mortality | | | | | | |
| No. of deaths/total cases | 14/21 | 17/27 | 50/88 | 84/150 | 122/196 | |
| Multivariable model[a] | 1.00 (ref) | 0.73 (0.36–1.48) | 0.77 (0.42–1.39) | 0.73 (0.41–1.28) | 0.82 (0.47–1.47) | 0.30 |
| Multivariable model[b] | 1.00 (ref) | 0.84 (0.41–1.71) | 0.83 (0.45–1.51) | 0.81 (0.45–1.44) | 0.84 (0.48–1.47 | 0.50 |
| Vigorous physical activity | | | | | | |
| No. of deaths/total cases | 46/72 | 35/56 | 66/114 | 72/141 | 69/101 | |
| Multivariable model[a] | 1.00 (ref) | 0.84 (0.54–1.31) | 0.77 (0.53–1.13) | 0.66 (0.45–0.95) | 1.01 (0.70–1.49) | 0.09 |
| Multivariable model[b] | 1.00 (ref) | 0.79 (0.50–1.25) | 0.81 (0.55–1.18) | 0.60 (0.41–0.87) | 0.95 (0.65–1.39) | 0.06 |

[a] Multivariable model 1 adjusted for age at entry and time from entry to cancer diagnosis.
[b] Multivariable model 2 adjusted age at entry, time from entry to diagnosis, alcohol use, menopausal hormone use, cancer stage, race, parity and BMI.

previous clinical and case-control studies, are absent. Furthermore, the large size of this study enabled robust analyses, including sensitivity analyses excluding cases diagnosed within the first two years of study enrollment, helping to minimize the likelihood that measurements were obtained while the women had occult ovarian cancer, a unique distinction in our study.

In summary, we observed that women who were obese before developing ovarian cancer had increased mortality than those of normal weight, but increasing levels of physical activity was not associated with mortality. Future research should explore the role of weight loss as well as increased physical activity within the obese population on ovarian cancer survival. Focusing on lifestyle interventions and BMI after cancer diagnosis is often emphasized. The GOG225 "LIVES" study, which is ongoing, randomizes women with ovarian cancer to 24 months of lifestyle interventions, including dietary changes and physical activity, to evaluate their effect on disease progression [44]. Our study, however, underscores the importance of maintaining a healthy weight throughout life as a powerful way to reduce ovarian cancer mortality.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.07.025.

## Declaration of Competing Interest

There are no additional conflicts of interest to disclose by any author.

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## Author contributions

Abigail Zamorano: Data interpretation, Drafting of manuscript, Critical review of manuscript, Final approval of manuscript.

Andrea Hagemann: Critical review of manuscript, Final approval of manuscript.

Leavitt Morrison: Data analysis, Final approval of manuscript.

Jung Ae Lee: Data analysis, Final approval of manuscript.

Linda Liao: Conception and design of the project, Critical review of manuscript, Final approval of manuscript.

Louise Brinton: Conception and design of the project, Critical review of manuscript, Final approval of manuscript.

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