# Anthropometric risk factors for ovarian cancer in the NIH-AARP Diet and Health Study

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## ABSTRACT

**Background**: Identifying potentially modifiable risk factors for ovarian cancer is essential for prevention because this cancer is predominantly detected at a late stage. Here we estimated the relations of general adiposity and measures reflecting body fat distribution to the risk of epithelial ovarian cancer.

**Methods:** We ascertained 683 ovarian epithelial cancers (344 high-grade serous) among 145,575 women, aged 50 to 72 years (median follow-up 12.6 years), from the National Institutes of Health - American Association of Retired Persons (NIH-AARP) Diet and Health Study. Using Cox models, we estimated confounder-adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for associations of overall ovarian cancer and high-grade serous carcinoma with body mass index, waist circumference, hip circumference, waist-hip ratio, waist-height ratio, body adiposity index, body shape index, and abdominal volume index.

**Results:** Anthropometric measures were unrelated to overall ovarian cancer and high-grade serous ovarian cancer. For example, the HR for overall ovarian cancer per standard deviation increment of body mass index at baseline was 0.97 (95% CI: 0.87 to 1.09). Similar associations were observed with measurements of body fat distribution.

**Conclusions:** These results do not indicate that adult adiposity is associated with ovarian cancer risk in post-menopausal women.

**Impact:** These findings provide little evidence that lowering obesity prevents ovarian cancer.


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## Introduction

Ovarian cancer is the fifth most common cause of cancer death in women in North America and western Europe (1). Meta-analyses and pooled observational studies suggest that obesity may be positively related to ovarian cancer risk (2-5). The World Cancer Research Fund/American Institute for Cancer Research concluded that the evidence for the link between obesity and increased ovarian cancer risk is probable (6), and an umbrella review graded the evidence as suggestive (3). A growing body of research further suggests that body composition plays an important role in site-specific cancer development (7-9). Previous studies indicate that anthropometric measures of general obesity and body fat distribution may be differentially related to ovarian cancer risk; however, results have been conflicting (4,5,10-12). We conducted a cohort study among post-menopausal women using data from the National Institutes of Health - American Association of Retired Persons (NIH-AARP) Diet and Health Study to provide further insights into the association between body fatness and subtype-specific epithelial ovarian cancer risk by comparing indicators of general obesity and body fat distribution.

## Methods

### *Study Population*

The NIH-AARP Diet and Health Study is a prospective cohort study of persons in the U.S. (13). At baseline (1995-1996), 3.5 million AARP members aged 50 to 71 years who resided in six states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia; and Detroit, Michigan) were invited to complete a questionnaire on demographic, diet, and lifestyle characteristics. Questionnaires were completed satisfactorily by 566,398 participants. Six months after completing the baseline questionnaire, a second questionnaire was mailed to living participants who did not have a self-reported colon, breast, or prostate cancer at baseline to collect additional information. Self-reported weight and height were collected on the baseline questionnaire. Self-reported waist circumference and hip circumference were assessed on the second questionnaire. We

excluded male participants (n= 339,666); those with unknown cancer or previous diagnosis of cancer other than non-melanoma skin cancer at baseline before completion of the second questionnaire (n=16,300); those with bilateral oophorectomy and unknown oophorectomy status (n=57,047); those with no information on height, weight, waist circumference, or hip circumference (n=95,764); and subjects with body mass index less than 18.5 $kg/m^2$ or more than 65 $kg/m^2$ (n=3,528). Our final analytical datasets included 145,575 women for the analysis on body mass index, 60,999 for waist circumference, 60,826 for hip circumference, 60,597 for waist-to-hip ratio, 60,999 for waist-to-height ratio, 60,826 for body adiposity index, 60,999 for body shape index, and 60,597 for abdominal adiposity index. The Special Studies Institutional Review Board of the U.S. National Cancer Institute approved the study (13). All participants gave informed consent by virtue of completing and returning the baseline questionnaire.

*Assessment of anthropometric measures*

Self-reported height and weight were obtained from the baseline questionnaire. Body mass index was calculated as weight (kg) divided by the square of height (in meters). In the second questionnaire, participants were instructed to measure their waist circumference and hip circumference using a tape measure to the nearest 0.25 inch while standing. Waist circumference was to be measured 1 inch above the navel if this was not the waistline. Hip circumference was defined as the largest circumference between the upper edge of the pelvis and the femur. Waist-hip ratio was calculated by dividing waist circumference (cm) by hip circumference (cm), and waist-height ratio was calculated as waist circumference (cm) / height (cm). The body adiposity index was calculated as $\text{hip circumference (cm)}/\text{height}^{1.5}\text{(m)}-18$ (14). The body shape index was based on $\text{waist circumference (cm)}/\text{BMI}^{\frac{2}{3}}\times\text{height}^{2}\text{(m)}$ (15). The abdominal volume index was also quantified:

$$2\text{cm}\times\text{waist circumference}^{2}\text{(cm)}+0.7\text{cm}\times\left(\text{waist circumference(cm)-hip circumference(cm)}\right)^{2}/1000$$

(16).

*Definition of cancer outcomes*

Diagnoses of ovarian cancer were ascertained through September 31, 2011, via linkage to state cancer registries of the eight recruitment areas where the study participants were most likely to relocate: Arizona, Nevada, and Texas. This approach has been estimated to yield a sensitivity of 90% and a specificity of nearly 100% (17). Newly diagnosed ovarian cancer cases were identified using the International Classification of Diseases for Oncology (ICD-O-3) topography (C56.9) and morphology codes (8441, 8460, 8461, 8470, 8471, 8480, 8481, 8380, 8381, 8560, 8570, 8310, 8313, 8010, 8020, 8021, 8050, 8070, 8120, 8140, 8255, 8260, 8323, 8440, 8450, 8562, 9000) (18). The high-grade serous group included all invasive serous cancers except low-grade (8461/3) (19).

*Baseline confounders*

We controlled for several baseline participant characteristics that were assumed to cause adiposity or ovarian cancer (3,5,20-22). We assumed that direct causes of the exposure or outcome, excluding possible instrumental variables, would identify a sufficient set of confounders (23). Potential confounding variables included age, education (no school degree/unknown, primary school, technical school/secondary, university), participants' self-reported information on race/ethnicity (none-Hispanic white, other), cigarette smoking (never, current <15 cigarettes per day, current ≥15 cigarettes/day, former < 10 years, former ≥10 years), alcohol consumption (in grams of pure alcohol per day), parity (0, 1, ≥2 children), age at menarche (≤12 years, > 12 years), family history of ovarian cancer, oral contraceptive use, and menopausal hormone therapy.

*Statistical Analysis*

Cox proportional hazards regression was used for estimating adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for overall ovarian cancer and ovarian cancer subtypes. Time of study entry was age at baseline (or second questionnaire) and exit time was age at cancer diagnosis or the last date at which follow-up was considered complete. After confirming that the linearity assumption was met by testing cubic spline transformations (24), HRs were estimated

per standard deviation (1-SD) increase in anthropometric measures. Models were stratified by five-year age groups to minimize departure from proportionality and adjusted for education, race, smoking, alcohol consumption, parity, age at menarche, family history of ovarian cancer, oral contraceptive use, and menopausal hormone therapy.

The improvement in predictive accuracy after adding anthropometric measures to a null model (including race, age, education, smoking, alcohol consumption, parity, family history of ovarian cancer, oral contraceptive use and menopausal hormone therapy) was evaluated in terms of explained variation ($R^2$) (25), the Bayes Information Criterion (BIC), and model discrimination using Harrel's C index (24) derived from flexible parametric models (26). *P* values for the difference between Harrel's C indices of models with and without anthropometric indicators were computed using the method proposed by Antolini et al. (27). We used 1,000 bootstrap replications to perform internal validations and to correct $R^2$, BIC, and Harrel's C indices for optimism (24).

In a sensitivity analysis, we used regression calibration for self-reported body mass index, waist circumference, and hip circumference to assess possible regression dilution bias (28). Because replicate measurements were not available, we applied published reliability coefficients (29-32), ranging from 0.5 to 0.9. A further threat to the validity of our estimates is potential unobserved confounding by undiagnosed ovarian cancer (often referred to as "reverse causation" (33)) if these conditions are symptomatic enough to induce a change in body weight. We, therefore, assumed a three year minimum latent period required for weight change due to unobserved disease to affect the outcome and excluded events that occurred during this time (34). The statistical analysis was performed using Stata 15.1.

**Results**

In the analytical sample of 145,575 women, the mean (SD) age at baseline was 61.8 (5.4) years. During a median follow-up time of 12.6 years, participants contributed 1,897,323 person-years and 683 ovarian cancer (343 high-grade serous) cases occurred. The baseline characteristics of the analytical are provided in Table 1.

Neither body mass index nor other anthropometric measurements were associated with the risk of ovarian cancer (Table 2). For example, HRs for overall ovarian cancer per 1-SD increment in body mass index, waist circumference, hip circumference, waist-hip ratio, waist-height-ratio were 0.97 (95% CI: 0.87-1.09), 1.07 (95% CI: 0.91-1.25), 1.05 (95% CI: 0.90-1.24), 1.03 (95% CI: 0.88-1.20), 1.07 (95% CI: 0.91-1.26), respectively. No associations were observed for high-grade serous carcinomas. The accuracy of models predicting ovarian cancer risk was not improved after adding anthropometric measures (Table 3).

Sensitivity analysis indicated that HRs could have been attenuated towards the null because of measurement error in self-reported anthropometric measurements. For example, the unadjusted HR for waist circumference and overall ovarian cancer was 1.07 (95% CI: 0.91-1.25), but after accounting for potential regression dilution bias, assuming an attenuation factor of 0.7, the HR was 1.09 (95% CI: 0.90-1.29) (Supplementary Table 1). The associations were virtually unchanged when events occurring during the first three years of follow-up were excluded (Supplementary Table 2).

**Discussion**

This study examined the association of indicators of general obesity and body fat distribution with ovarian cancer risk using a large U.S. prospective cohort study of post-menopausal women. We found no association of anthropometric measures with the risk of overall ovarian cancer. Overall, our analysis does not support the hypothesis that central adiposity or measures of body fat distribution improve the prediction of ovarian cancer risk.

A larger body of research examined the association between obesity and ovarian cancer risk. However, the findings of more than 30 epidemiologic studies have been weak and mixed (35). Several meta-analyses and pooled analyses reported weak positive associations between adult body mass index and ovarian cancer risk, noting substantial between-study heterogeneity with weaker associations in prospective than case-control studies (2,6,36). A systematic review from the World Cancer Research Fund and the American Institute for Cancer Research included 28 prospective studies on ovarian cancer and calculated a summary relative risk for a 5 unit increment in body mass index of 1.07 (95% CI: 1.03-1.11) (2,6). The effect size was similar in

the post-menopausal group but it was less precise (relative risk per 5 kg $m^{-2}$ = 1.07; 95% CI: 1.00-1.14). Results from the 2013 Ovarian Cancer Association Consortium (4) pooled analysis of case-control studies found that the positive association with body mass index was stronger in pre-menopausal women. The heterogeneity of findings reported here and previously could be explained by menopausal status and higher statistical efficacy of meta-analysis. Few studies have examined how different measures of body fat distribution are related to ovarian cancer and its subtypes (10-12). Existing cohort studies found no association of waist circumference and waist-hip ratio and ovarian cancer risk (2,6,10). Similar to previous studies (4,5), the present study found no notable differences between histotypes.

The present study has several limitations. It relied on self-reported anthropometric data and potential measurement error could have attenuated the observed associations. Our study also lacked updated information on anthropometric measurements during follow-up. Another drawback is the low number of cases by ovarian cancer subtype and a lack of statistical power to test for effect modification.

In summary, results from this prospective study of post-menopausal women does not support associations between measures of central obesity and body fat distribution and risk of ovarian cancer.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Author's Contribution**

**Conception and design:** Sebastian E. Baumeister, Inga Schlecht, Michael F. Leitzmann

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**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** Britton Trabert, Michael F. Leitzmann

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** Sebastian E. Baumeister, Inga Schlecht, Michael Nolde

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**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** Britton Trabert, Michael Nolde, Michael F. Leitzmann

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Table 1 Baseline characteristics of ovarian cancer cases among 145,575 women in the NIH-AARP Study

| | *All study subjects* | No ovarian cancer | Ovarian cancer | High-grade serous |
|---|---|---|---|---|
| Age (years) | 62.2 (57.4, 66.4) | 62.2 (57.4, 66.4) | 63.8 (58.1, 67.4) | 63.0 (57.6, 67.4) |
| Education (%) | | | | |
| <12 yrs | 5.8 | 8.6 | 5.3 | 3.1 |
| 12 yrs | 25.7 | 25.7 | 24.9 | 24.3 |
| >12 yrs | 68.5 | 68.5 | 69.8 | 72.6 |
| Race (%) | | | | |
| Non-hispanic white | 91.2 | 91.2 | 95.0 | 96.2 |
| Non-hispanic black | 8.1 | 5.3 | 2.6 | 1.1 |
| Hispanic/other | 5.3 | 3.5 | 2.4 | 2.7 |
| Body mass index | 25.8 (22.9, 29.3) | 25.7 (22.9, 29.3) | 25.6 (22.5, 29.7) | 25.1 (22.5, 29.0) |
| Waist circumference (cm) | 82.6 (74.9, 91.4) | 82.6 (74.9, 91.4) | 83.3 (74.3, 93.9) | 82.6 (74.3, 91.4) |
| Hip circumference (cm) | 101.6 (96.5, 109.2) | 101.6 (96.5, 109.2) | 101.6 (96.5, 112.4) | 101.6 (96.5, 109.2) |
| Waist-hip ratio | 0.81 (0.75, 0.86) | 0.81 (0.76, 0.86) | 0.81 (0.76, 0.87) | 0.81 (0.76, 0.86) |
| Waist -height ratio | 0.51 (0.46, 0.57) | 0.51 (0.46, 0.57) | 0.51 (0.46, 0.57) | 0.51 (0.46, 0.56) |
| Body adiposity index | 31.0 (28.0, 34.7) | 31.0 (28.0, 35.0) | 31.1 (28.3, 34.9) | 31.4 (28.2, 34.5) |
| Body shape index | 0.01 (0.01, 0.01) | 0.01 (0.01, 0.01) | 0.01 (0.01, 0.01) | 0.01 (0.01, 0.01) |
| Abdominal volume index | 13.9 (11.6, 17.2) | 14.0 (11.6, 17.2) | 14.5 (11.4, 17.8) | 13.9 (11.4, 17.2) |
| Smoking status (%) | | | | |
| Never smoked | 45.3 | 45.3 | 49.4 | 54.6 |
| Former smoker, ≤20 cigarettes per day | 27.6 | 27.6 | 27.8 | 23.7 |
| Former smoker, >20 cigarettes per day | 13.7 | 13.7 | 11.3 | 10.5 |
| Current smoker, ≤20 cigarettes per day | 10.5 | 10.5 | 8.8 | 8.9 |
| Alcohol consumption (grams/day) | 1.0 (0.3, 4.9) | 1.0 (0.3, 4.9) | 1.0 (0.4, 5.3) | 0.9 (0.1, 5.3) |
| Parity | | | | |
| Never had a child | 15.3 | 15.3 | 18.7 | 17.2 |

| | | | | |
|---|---|---|---|---|
| 1 child | 10.3 | 10.3 | 11.9 | 11.8 |
| 2 and more children | 74.4 | 74.4 | 69.4 | 70.1 |
| Age at menarche | | | | |
| ≤12 yrs | 48.6 | 48.6 | 49.5 | 52.2 |
| >12 yrs | 51.4 | 51.4 | 50.5 | 47.9 |
| Family history of ovarian cancer (%) | 6.1 | 6.1 | 7.3 | 6.2 |
| Ever oral contraceptive use (%) | 40.6 | 40.6 | 33.2 | 31.6 |
| Ever hormone replacement therapy (%) | 46.2 | 46.2 | 50.2 | 54.3 |

NIH-AARP, NIH-AARP Diet and Health Study. Entries are percent values for categorical variables and medians ($25^{th}$ percentile, $75^{th}$ percentile) for continuous variables.

Table 2 Association of general obesity and indicators of body fat distribution with ovarian cancer in NIH-AARP

| | Ovarian Cancer Risk | High-grade serous |
|---|---|---|
| **Body mass index** *(n=145,575),* | | |
| number of cases | *683* | *343* |
| HR per SD (95% CI) | 0.97 (0.87; 1.09) | 0.90 (0.76; 1.06) |
| **Waist circumference** | | |
| *(n=60,999),* number of cases | *295* | *151* |
| HR per SD (95% CI) | 1.07 (0.91; 1.25) | 0.98 (0.77; 1.23) |
| **Hip circumference** *(n=60,826),* | | |
| number of cases | *295* | *150* |
| HR per SD (95% CI) | 1.05 (0.90; 1.24) | 0.95 (0.75; 1.21) |
| **Waist-hip ratio** *(n=60,597),* | | |
| number of cases | *294* | *150* |
| HR per SD (95% CI) | *1.03 (0.88; 1.20)* | *1.01 (0.81; 1.27)* |
| **Waist-height ratio** *(n=60,999),* | | |
| number of cases | *295* | *151* |
| HR per SD (95% CI) | *1.07 (0.91; 1.26)* | *0.97 (0.77; 1.23)* |
| **Body adiposity index** | | |
| *(n=60,826),* number of cases | 294 | 150 |
| HR per SD (95% CI) | 1.06 (0.90; 1.25) | 0.95 (0.75; 1.21) |
| **Body shape index** | | |
| *(n=60,999)* , number of cases | 294 | 151 |
| HR per SD (95% CI) | 0.99 (0.84; 1.17) | 1.10 (0.87; 1.39) |
| **Abdominal volume index** | | |
| **(n=60,597)** , number of cases | 295 | 150 |
| HR per SD (95% CI) | 1.06 (0.90;1.24) | 0.95 (0.75; 1.21) |

NIH-AARP, NIH-AARP Diet and Health Study. HR (hazard ratio) from age-group stratified multivariable Cox model adjusted for education, race, smoking, alcohol consumption, parity, age at menarche, family history of ovarian cancer, oral contraceptive use, and menopausal hormone therapy.

Table 3 General obesity and indicators of body fat distribution for prediction of ovarian cancer

| | Baseline model | Body mass index | Waist circumference | Hip circumference | Waist-to-hip ratio | Waist-to-height ratio | Body adiposity index | Body shape index | Abdominal volume index |
|---|---|---|---|---|---|---|---|---|---|
| **Ovarian cancer** | | | | | | | | | |
| Adjusted $R^2$ | 0.060 | 0.059 | 0.071 | 0.067 | 0.066 | 0.071 | 0.068 | 0.069 | 0.067 |
| BIC | 16396.29 | 16408.11 | 6681.254 | 6659.244 | 6657.74 | 6681.033 | 6658.871 | 6682.416 | 6656.822 |
| | | 0.601 | 0.616 | 0.616 | 0.615 | 0.617 | 0.617 | 0.617 | 0.615 |
| Harrel's C-index (P) | 0.600 | (0.601) | (0.517) | (0.423) | (0.572) | (0.465) | (0.320) | (0.419) | (0.519) |
| **High-grade serous** | | | | | | | | | |
| Adjusted $R^2$ | 0.090 | 0.092 | 0.109 | 0.103 | 0.103 | 0.109 | 0.103 | 0.112 | 0.103 |
| BIC | 8303.135 | 8313.223 | 3492.481 | 3471.319 | 3470.144 | 3492.480 | 3471.347 | 3491.962 | 3470.177 |
| | | 0.627 | 0.648 | 0.645 | 0.645 | 0.648 | 0.645 | 0.648 | 0.645 |
| Harrel's C-index (P) | 0.624 | (0.146) | (0.255) | (0.287) | (0.296) | (0.255) | (0.281) | (0.256) | (0.276) |

Null model included the predictors age, education, race, smoking, alcohol consumption, physical activity, parity, family history of ovarian cancer, family history of breast cancer, hormone therapy.
Adjusted $R^2$: explained variation. BIC: Bayes Information Criterion. P: P Value for difference of Harrel's C vs null model.