Anthropometric measures and epithelial ovarian cancer risk among Chinese women: results from the Shanghai Women's Health Study

X Ma[1,2], A Beeghly-Fadiel*[,1], X-O Shu[1], H Li[3], G Yang[1], Y-T Gao[3] and W Zheng[1]

[1]Division of Epidemiology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA; [2]Department of Epidemiology, College of Preventive Medicine, Third Military Medical University, Chongqing, China and [3]Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China

Background: Studies of anthropometric measures and ovarian cancer risk have predominantly included women of European descent with mixed findings.

Methods: Data from the prospective Shanghai Women's Health Study (SWHS) were used to evaluate associations between anthropometric measures and risk of epithelial ovarian cancer (EOC). Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by Cox proportional hazards regression.

Results: A total of 152 EOC cases occurred among 70 258 women. Increasing quartiles of weight, hip circumference, and weight gain during adulthood were associated with significantly increased EOC risks. Body mass index (BMI) was also associated; overweight ($25 \leqslant BMI < 29.99$) and obese women ($BMI \geqslant 30.0$) had significantly increased risks (HR: 1.49, 95% CI: 1.05, 2.13, and HR: 2.42, 95% CI: 1.37, 4.28, respectively). No significant associations were observed for height, waist circumference, waist-to-hip ratio (WHR), and waist-to-height ratio (WHER).

Conclusion: Results from this large prospective study of Chinese women support the hypothesis that general adiposity contributes to the aetiology of ovarian cancer.

Anthropometric measures include markers of general adiposity, such as weight and body mass index (BMI) and markers of central adiposity, such as hip or waist circumference. Associations between these measures and ovarian cancer risk have been inconsistent. Except for two case–control studies conducted among Chinese women (Zhang et al, 2005; Su et al, 2012) and three small cohort studies of Japanese women (Kuriyama et al, 2005; Niwa et al, 2005; Weiderpass et al, 2012), the majority of investigations conducted to date have predominantly included women of European descent. For example, a recent large pooled analysis from the Ovarian Cancer Association Consortium (OCAC) found that high BMI was associated with increased risks of less-common ovarian cancers (Olsen et al, 2013); however, only 3% of the study population was Asian.

Associations of anthropometric measures with ovarian cancer risk may differ by ethnicity. One large study conducted meta-analyses for cancer risks associated with 5 unit increases in BMI; the risk of ovarian cancer seemed to be higher among Asian women than among European or North American women (Renehan et al, 2008). Another large collaborative project included data from 47 studies and found that increasing height and BMI were both associated with increased risks of ovarian cancer; however, in analyses among non-Caucasian women, associations were imprecise and non-significant (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012). Notably, both of these two large collaborative efforts included only two studies each that were conducted among Asian women. Given that

Caucasian and Asian women may differ in many regards, including reproductive characteristics, dietary habits, and genetic architecture, and that the relationship between anthropometric measures and ovarian cancer risk among Asian women is not well defined, this study was undertaken in order to evaluate associations between anthropometric measures and ovarian cancer risk among a large prospective study of Chinese women.

MATERIALS AND METHODS

Study participants. The SWHS is a prospective cohort study of 74 942 adult women from Shanghai, China. Enrolment occurred from 1996 to 2000, and included women aged 40–70. Study methods and rationale have been previously reported (Zheng *et al*, 2005). Briefly, all included participants completed baseline surveys and their anthropometric measurements were recorded. Follow-up was conducted by in-person interviews, coupled to annual linkage to the Shanghai Cancer and Vital Statistics Registries. In this analysis, outcome data were censored on 31 December 2009. Cancer diagnoses were verified via medical chart review. Epithelial ovarian cancer cases were determined according to International Classification of Diseases for Oncology. Study participants were excluded from the current analysis if they had a previous diagnosis of any cancer ($N = 1578$), prior oophorectomy ($N = 2869$), were missing BMI or WHR measures ($N = 30$), had extreme BMI values (< 15.0 or > 45.0; $N = 46$), were lost to follow-up ($N = 14$), had unverified cancer diagnoses ($N = 58$), or were missing information on cancer diagnosis date ($N = 89$). Histological subtypes of ovarian cancer were classified according to International Classification of Diseases for Oncology (ICD-O) codes as serous (8441, 8460, and 8462), endometrioid (8380 and 8381), mucinous (8470, 8471, 8472, 8473, and 8480), clear cell (8310), other epithelial (8140, 8260, 8440, 8450, and 9000), and unspecified (8000 and 8010). All participants provided written informed consent. Institutional Review Board (IRB) approval was obtained from appropriate institutions in both China and the United States.

Anthropometric measures and classification. Anthropometric measurements were taken by trained study personnel at cohort enrolment, and included weight, height, waist circumference, and hip circumference. Weight and height at age 20 were collected by self-report; BMI and BMI at age 20 were calculated as weight (kg) divided by height (m) squared, and categorised using the World Health Organization (WHO) classifications: underweight ($< 18.5 \, \text{kg} \, \text{m}^{-2}$), normal weight ($18.5–24.99 \, \text{kg} \, \text{m}^{-2}$), overweight ($25–29.99 \, \text{kg} \, \text{m}^{-2}$), and obese ($\geqslant 30 \, \text{kg} \, \text{m}^{-2}$). Weight gain from age 20 to cohort enrolment was calculated by subtraction; waist-to-hip ratio (WHR) and waist-to-height ratio (WHER) were calculated by division. Other than BMI, measures were categorised using quartile distributions of participants.

Statistical analyses. Cox proportional hazards regression was used to evaluate association between anthropometric measurements and EOC risk; hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Age was the underlying time variable, with entry and exit times defined as age at recruitment and age at cancer diagnosis or censoring date (death or age at the last follow-up), respectively. All models included adjustment for age (as a continuous variable) and education (as a dichotomous variable); models for weight gain also included adjustment for weight at age 20. Additional adjustment for family income, occupation, energy intake, physical activity, age at menarche, menopausal status, years of menstruation, regular ovulatory cycles, oral contraceptive use, live birth history, fibroadenoma history, hormone replacement therapy, smoking exposure, alcohol consumption, tea consumption, family history of any cancer, and family history of breast or ovarian cancer was also considered. Lowest categories or quartiles

of anthropometric measurements were used as reference groups, except when evidence of a J-shaped curve was present. Exploratory analyses included stratification by histologic subtype of ovarian cancer, dichotomized as serous or non-serous EOC. All statistical tests were two-sided and significance was defined by a P-value ⩽ 0.05. Analyses were conducted using SAS, v9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Among 70 258 Chinese women with a total of 761 389 person-years of follow-up (average 10.84, s.d.: 1.85), 152 EOC cases were diagnosed (Table 1). Women who did and did not develop EOC were found to significantly differ with regards to age at natural

Table 1. Characteristics of participants in the Shanghai Women's Health Study (SWHS), by epithelial ovarian cancer (EOC) status

Characteristics	EOC cases[a]	Non-EOC cases	P-value[b]
Participants (N)	152	70 106	—
Person-years	891.45	760 497.86	—
Age at interview	52.91 ± 8.75	52.46 ± 9.07	0.547
Age at menarche	14.91 ± 1.71	14.94 ± 1.74	0.834
Postmenopausal	78 (51.32%)	33 431 (47.70%)	0.372
Age at menopause[c]	50.22 ± 3.21	49.23 ± 3.71	**0.022**
Hormone replacement therapy	2 (1.32%)	1153 (1.64%)	0.750
Parous	145 (95.39%)	67 885 (96.83%)	0.313
Total years of menstruation	30.28 ± 4.76	29.43 ± 4.95	**0.036**
Ever oral contraceptive use	31 (20.39%)	14 327 (20.44%)	0.990
Irregular ovulatory cycles	4 (2.63%)	4692 (6.69%)	**0.045**
Education (college and above)	17 (11.18%)	9319 (13.30%)	0.444
Ever drank regularly	5 (3.29%)	1585 (2.26%)	0.394
Ever smoked regularly	9 (5.92%)	1943 (2.77%)	**0.018**
Passive smoke exposure	126 (82.89%)	56 417 (80.47%)	0.452
Ever drank tea	47 (30.92%)	20 947 (29.88%)	0.779
Family history of any cancer	46 (30.26%)	18 452 (26.32%)	0.270
Family history of breast or ovarian cancer	3 (1.97%)	1472 (2.10%)	0.914
History of fibroadenomas	4 (2.63%)	2307 (3.29%)	0.649
Occupation (manual workers)	77 (50.66%)	35 539 (50.69%)	0.993
Family income (high)	50 (32.89%)	23 379 (33.35%)	0.906
Regular physical activity	55 (36.18%)	24 390 (34.79%)	0.719
Physical activity units[d]	1.76 ± 1.71	1.94 ± 2.10	0.520
Energy intake	1700.20 ± 386.10	1675.90 ± 405.80	0.461

Abbreviation: EOC = epithelial ovarian cancer.
[a]Incident EOC cases diagnosed during follow-up.
[b]Continuous variables: mean values ± standard deviation, P-values from t-tests; categorical variables: numbers and percentages, P-values from χ^2 test and Fisher's exact test; P-values in bold denote significance at ⩽ 0.05.
[c]Age at natural menopause for postmenopausal women; not including 2106 women with surgical or other non-natural causes of menopause.
[d]Units of physical activity defined as MET-h day^{-1} year^{-1}; only available for participants with regular physical activity.

Table 2. Anthropometric measures by epithelial ovarian cancer (EOC) status, the SWHS

Measures	EOC cases (N = 152)[a]				Non-EOC cases (N = 70 106)				P-value[b]
	Mean ± s.d.	25th	Median	75th	Mean ± s.d.	25th	Median	75th	
Weight	61.40 ± 9.71	55.25	61	67.25	59.56 ± 8.89	53.5	59	65	**0.011**
Height	157.95 ± 5.67	154.5	158	162	157.53 ± 5.55	154	158	161	0.352
BMI	24.62 ± 3.76	22.17	24.6	26.47	24.00 ± 3.41	21.63	23.71	26.06	**0.027**
Waist circumference	79.50 ± 9.23	73	79	85	77.83 ± 8.79	72	77	83	**0.019**
Hip circumference	97.23 ± 8.49	92	97	102	95.91 ± 7.60	90	95	100	**0.033**
Waist-to-hip ratio	0.82 ± 0.06	0.78	0.82	0.85	0.81 ± 0.05	0.77	0.81	0.84	0.173
Waist-to-height ratio	0.50 ± 0.06	0.46	0.49	0.54	0.49 ± 0.06	0.45	0.49	0.53	0.057
Weight at age 20[c]	49.74 ± 6.64	45	50	55	49.57 ± 6.59	45	49	54	0.764
BMI at age 20[d]	19.59 ± 2.48	17.65	19.4	21.19	19.60 ± 2.45	17.8	19.33	21.11	0.957
Weight gain from age 20[e]	12.03 ± 9.57	6	11	17	9.94 ± 9.14	4	10	15.5	**0.008**

Abbreviations: BMI = body mass index; EOC = epithelial ovarian cancer.
[a]Incident EOC cases diagnosed during follow-up.
[b]P-value from t-tests; bold values denote significance at ⩽0.05.
[c]Self-reported weight at age 20 was unavailable for 7298 participants (including 17 cases).
[d]Data for BMI at age 20 was unavailable for 10 418 participants (including 20 cases).
[e]Weight gain from age 20 to SWHS enrolment.

menopause, total years of menstruation, irregular ovulatory cycles, and smoking history. In regards to anthropometric measurements, women with EOC had significantly higher distributions for weight, BMI, waist circumference, hip circumference, and weight gain from age 20 to cohort enrolment (Table 2). Among the women who developed ovarian cancer, histologic subtypes included serous (N = 50, 32.9%), endometrioid (N = 19, 12.5%), clear cell (N = 15, 9.9%), mucinous (N = 14, 9.2%), other (N = 33, 21.7%) and unspecified (N = 22, 14.5%). As >90% of ovarian tumours arise from the surface epithelium, unspecified cases were included as ovarian cancers of other epithelial histologic types.

Cox proportional hazards regression was used to evaluate associations with EOC risk (Table 3). Significant trends were found for increasing quartiles of weight, hip circumference, weight gain from age 20, and BMI categories as defined by the WHO. Women in the highest quartiles or categories of these anthropometric measures had significantly increased EOC risks; the smallest was for weight (HR: 1.71, 95% CI: 1.08–2.71), and the largest was for BMI (HR: 2.42, 95% CI: 1.37–4.28). Only two women had a BMI of ⩾25 at age 20 and so risk estimates for this measurement were unstable and not shown. All regression models included adjustment for age and education; weight at age 20 was also included for weight gain from age 20 to cohort enrolment. Additional adjustment for a variety of factors was considered; none resulted in altered risk estimates (⩾10%) when included. In mutually adjusted models, no anthropometric measures remained significantly associated with ovarian cancer risk after adjustment for BMI. The significance of the association for BMI was attenuated when waist circumference, hip circumference, or WHR was included in the regression model.

The robustness of these findings was evaluated by sensitivity analyses. When women diagnosed with EOC within the first year of follow-up (N = 14) were excluded, the results were materially unaltered. When ovarian cancer cases of unspecified type (N = 22) were excluded, significance was attenuated for weight (P-value = 0.070) and hip circumference (P-value = 0.052). When smokers (N = 1952) were excluded, significance was attenuated for hip circumference (P-value = 0.089).

Exploratory analyses were conducted to evaluate if associations between anthropometric characteristics and EOC risk differed by histologic subtype of ovarian cancer (data not shown); owing to our sample size, histologic type was classified as either serous or non-serous subtypes. Weight, BMI, hip circumference, and weight gain from age 20 to cohort enrolment were all significantly associated with an increased risk of non-serous ovarian cancers. No associations with anthropometric characteristics were evident for serous ovarian cancer risk, possibly due to the limited sample size (N = 50).

DISCUSSION

In this large, population-based prospective cohort study of 70 258 Chinese women, during which 152 incident cases of EOC occurred, weight, BMI, hip circumference, and weight gain from age 20 to cohort enrolment were found to be significantly associated with increased EOC risk. Height, waist circumference, WHR, WHER, and weight at age 20 were not significantly associated with EOC risk. To the best of our knowledge, this is the first prospective study of anthropometric measures and ovarian cancer risk among Chinese women, and the largest such study conducted among Asian women.

Although it is generally accepted that measurements of general adiposity, such as weight and BMI, are associated with increased risks of many cancers (Calle and Kaaks, 2004), such measures have had inconsistent associations with ovarian cancer risk in prior epidemiologic studies. Only five studies have been conducted among Asian women (Kuriyama et al, 2005; Niwa et al, 2005; Zhang et al, 2005; Su et al, 2012; Weiderpass et al, 2012). In two hospital-based case–control studies of Chinese women, weight and BMI were associated with increased ovarian cancer risk (Zhang et al, 2005; Su et al, 2012). A small cohort study of Japanese women also found a positive association between BMI and ovarian cancer risk (Niwa et al, 2005), whereas two others found no association (Kuriyama et al, 2005; Weiderpass et al, 2012). In the current study, EOC risk increased linearly with weight, whereas a J-shaped

Table 3. Anthropometric measures and epithelial ovarian cancer (EOC) risk, the SWHS

Anthropometric measures	N cases (152 total)	EOC Risk[a] HR (95% CI)	P-value
Weight (kg, quartiles)			
<53.50	28	Referent	**0.018**
53.50–58.99	33	1.22 (0.74, 2.02)	
59.00–64.99	39	1.37 (0.84, 2.23)	
≥65.00	52	**1.71 (1.08, 2.71)**	
Height (cm, quartiles)			
<154.00	30	Referent	0.09
154.00–157.99	36	1.13 (0.69, 1.85)	
158.00–160.99	40	1.55 (0.95, 2.54)	
≥161.00	46	1.43 (0.87, 2.35)	
BMI (kg m^{-2}, WHO categories)			
<18.50	7	1.73 (0.80, 3.75)	**0.008**
18.50–24.99	75	Referent	
25.00–29.99	55	**1.49 (1.05, 2.13)**	
≥30.00	15	**2.42 (1.37, 4.28)**	
Waist circumference (cm, quartiles)			
<72.00	27	Referent	0.061
72.00–76.99	34	1.36 (0.82, 2.26)	
77.00–82.99	41	1.50 (0.92, 2.46)	
≥83.00	50	1.61 (0.98, 2.64)	
Hip circumference (cm, quartiles)			
<90.50	28	1.57 (0.92, 2.69)	**0.024**
90.50–94.99	25	Referent	
95.00–99.99	39	**1.70 (1.03, 2.82)**	
≥100.00	60	**2.14 (1.33, 3.45)**	
WHR (cm/cm, quartiles)			
<0.77	24	Referent	0.358
0.77–0.81	43	1.13 (0.69, 1.87)	
0.81–0.84	35	1.28 (0.76, 2.16)	
≥0.84	50	1.25 (0.76, 2.07)	
WHER (cm/cm, quartiles)			
<0.45	31	Referent	0.138
0.45–0.49	37	1.20 (0.74, 1.94)	
0.49–0.53	38	1.22 (0.75, 1.99)	
≥0.53	46	1.49 (0.90, 2.47)	
Weight at age 20 (kg, quartiles)[b]			
<45.00	29	1.24 (0.74, 2.08)	0.453
45.00–48.99	29	Referent	
49.00–53.99	36	1.19 (0.73, 1.94)	
≥54.00	41	1.39 (0.86, 2.23)	
Weight gain from age 20 (quartiles)[c]			
<4.00	37	Referent	**0.005**
4.00–9.99	35	**1.83 (1.05, 3.21)**	
10.00–15.99	36	**1.97 (1.12, 3.46)**	
≥16.00	44	**2.33 (1.33, 4.06)**	

Abbreviations: BMI = body mass index; WHER = waist-to-height ratio; WHR = waist-to-hip ratio.
[a]Cox proportional hazards regression among 70 258 SWHS participants, adjusted for age (continuous) and education (high vs low); P-values from tests for trends, bold values denote significance at ⩽0.05.
[b]Data for weight at age 20 was unavailable for 7298 participants (including 17 cases).
[c]Weight gain from age 20 to SWHS enrolment; adjusted for weight at age 20, age and education.

curve was evident for BMI. Weight gain from age 20 to cohort enrolment was also associated with an increased risk. These findings indicate that weight and BMI during later adulthood are likely to contribute to ovarian cancer aetiology among Chinese women. Possible biological mechanisms for this association include insulin resistance, increased steroid hormone bioavailability from adipose tissue, and inflammation (Calle and Kaaks, 2004). Our findings are consistent with a large meta-analysis that found a positive association with increasing BMI among never-users of hormone therapy (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012). Notably, the use of hormone therapy in our study population was very low (1.64%).

Prior epidemiologic studies that evaluated measures of central adiposity in relation to ovarian cancer risk have also had mixed findings; positive (Dal Maso et al, 2002; Hoyo et al, 2005; Delort et al, 2009; Canchola et al, 2010; Lahmann et al, 2010) and null associations (Anderson et al, 2004; Chionh et al, 2010) have been reported. No studies of central adiposity have been previously conducted among Asian women. In the current study, the highest quartile of hip circumference was significantly associated with increased EOC risk. Neither waist circumference, WHR, nor WHER, a suggested better indicator of central adiposity (Ashwell et al, 1996), were significantly associated with EOC risk in the current study.

Only one prior study has evaluated height in relation to ovarian cancer risk among Asian women; no association was found (Weiderpass et al, 2012). A pooled analysis of primary data from 12 prospective cohort studies among Caucasian women found a significant association between increasing height and ovarian cancer risk (Schouten et al, 2008). A recent meta-analysis of 47 studies also found a significant increase in ovarian cancer risk associated with each 5-cm increase in height (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012). Height has been proposed to influence ovarian cancer risk mostly through increased levels of circulating growth factors (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012). In the current analysis, although there was a trend towards increasing risk as a factor of height, this association was not statistically significant.

Strengths of the current study include its prospective design, long duration of follow-up time, large sample size, and measured anthropometric characteristics from cohort enrolment (except for measures at age 20 which were self-reported). Collecting anthropometric measurements as well as self-reported data prior to disease occurrence minimised the possibility of associations being inflated by recall or information bias. One limitation of our study is that only 152 ovarian cancer cases were included, because of the low incidence rate of ovarian cancer among Chinese women. Another limitation is that this study lacked power for analyses stratified by histologic type. However, exploratory analyses were conducted by dichotomizing our cases into serous or non-serous histologic types; all associations from our main findings were present for non-serous but not for serous ovarian cancer risk; this is in agreement with a recent large pooled project that found significant associations for BMI with endometrioid and mucinous ovarian cancers but not with serous ovarian cancers among a primarily Caucasian study population (Olsen et al, 2013).

In summary, results from this large prospective study support associations between increasing weight, BMI, hip circumference, and weight gain during adulthood and increased EOC risk among Chinese women. The effects of these anthropometric measures on EOC risk could not be fully disentangled using models with mutual adjustment; however, our data indicate that general adiposity may have a larger role than central adiposity in ovarian cancer risk among Chinese women. Our data also suggest that these associations may be specific to non-serous ovarian cancer types, but further research is needed in order to investigate possible

heterogeneous effects with respect to specific histological subtypes among Asian women, and to incorporate biomarker measurements in order to help elucidate potential causal mechanisms.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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