Body Mass Index in Relation to Ovarian Cancer Survival

Min Zhang,[1,2] Xing Xie,[3] Andy H. Lee,[2] Colin W. Binns,[2] and C. D'Arcy J. Holman[1]

[1]School of Population Health, The University of Western Australia and [2]School of Public Health, Curtin University of Technology, Perth, Western Australia, Australia; and [3]Women's Hospital, School of Medicine, Zhejiang University, P.R. China

Abstract

Evidence for an association between indicators of adiposity and survival after ovarian cancer has been inconsistent. A prospective cohort study was conducted in China to examine the relationship between ovarian cancer survival and body mass index (BMI). From the 214 patients recruited in 1999 to 2000 with histopathologically confirmed invasive epithelial ovarian cancer, 207 patients or their close relatives (96.7% of cases) were traced and followed to 2003. Deaths were recorded and Cox proportional hazards regression was used to obtain hazard ratios (HR) and 95% confidence intervals (95% CI) from multivariate models. Reduced survival was observed among patients with BMI $\geq$ 25 kg/m^2 at 5 years before diagnosis (P = 0.001). There were 98 (59.8%) of 164 patients with BMI <25 kg/m^2 survived to the time of interview compared with only 15 women (34.9%) among the 43 patients whose BMI was $\geq$25 kg/m^2. The HRs significantly increased with higher BMI at 5 years before diagnosis but not at diagnosis nor at age 21 years. The adjusted HR was 2.33 (95% CI, 1.12-4.87) for BMI of $\geq$25 versus <20 kg/m^2, with a significant dose-response relationship. The HR was 3.31 (95% CI, 1.26-8.73) among patients who had been overweight or obese at age 21 years, but a linear dose-response was not found. We conclude that premorbid BMI may have independent prognostic significance in ovarian cancer. (Cancer Epidemiol Biomarkers Prev 2005;14(5):1307–10)

Introduction

Obesity have been reported to be associated with increased mortality from all cancers combined and from cancers of the breast, uterus, cervix, and ovary in women (1-3). Higher body mass index (BMI) is independent and well-established prognostic factors for mortality from several hormone-related cancers, such as breast and endometrial cancer (4-6). As a hormone-dependent cancer, ovarian cancer, however, has been linked inconsistently to obesity (2, 7).

Ovarian cancer is a major cause of mortality in women because of its typically insidious onset and consequential late diagnosis (8). Due to lack of effective screening programs and the high proportion of diagnoses at advanced stages, ovarian cancer survival is low with the highest fatality-to-case ratio of all gynecologic malignancies (9). Furthermore, ovarian cancer tends to recur, even in the patients who achieve a remission following primary treatment with surgery and chemotherapy (10).

To investigate whether obesity has an adverse effect on ovarian cancer survival, a prospective cohort study was conducted in China. The associations between survival from the cancer and BMI at diagnosis, at 5 years before diagnosis, and at age 21 years were assessed.

Materials and Methods

Study Design and Participants. The cohort comprised 214 patients with ovarian cancer, who had originally participated in our case-control study conducted in 1999 to 2000 in Hangzhou, China (11). The inclusion criteria for the participants were women under 75 years of age, who had been residents of Zhejiang Province for at least 10 years and who had been histopathologically diagnosed with invasive epithelial ovarian cancer after surgery within the past 3 years. Diagnostic categories were based on the International Histological Classification of Ovarian Tumors recommended by the Fesddration Internationale des Gynaecologistes et Obstetristes (12). A total of 215 patients were identified and only one patient did not participate in the study (99.5% response).

After a minimum of 3 years of follow-up, the patients were traced to determine their vital status post-diagnosis between March and June 2003. We attempted to contact all patients in the cohort using their telephone numbers and addresses recorded when they were first recruited to the study. Those participants who had changed their telephone numbers were traced in the community with the assistance of local community and village committees, which in Zhejiang Province maintain a register of individual residents and their personal details such as date of birth and death and contact telephone numbers. Those patients without a home telephone were contacted using the office telephone of a local community and village committee. However, four patients were lost to follow-up because they had moved out of the province, and another three patients had changed their place of residence within the province, but their new addresses and telephone numbers were unavailable. Thus, a total of 207 subjects were located and available for analyses, representing a follow-up fraction of 96.7%.

Questionnaire and Interview. An initial face-to-face interview was conducted after obtaining the informed consent of the participants. Information on self-reported past body height and weight at three time points during adulthood was collected using a structured questionnaire. Subjects were asked to recall their adult height (in cm) and weight (in kg) at diagnosis as well as their body weight at 5 years before diagnosis and at age 21 years. The collected information also included demographic characteristics, tobacco smoking, alcohol consumption, usual diet, reproductive history, factors relevant to hormonal status, and family history of cancer.

Received 7/13/04; revised 1/19/05; accepted 2/21/05.

Grant support: Cancer Council of Western Australia and National Health and Medical Research Council of Australia, Public Health Postdoctoral Fellowship grant APP ID 303292 (M. Zhang).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Min Zhang, School of Population Health The University of Western Australia 35 Stirling Highway, Crawley, WA 6009 Australia. Phone: 61-8-6488-8175; Fax: 61-8-6488-1188. E-mail: minzhang@sph.uwa.edu.au

The structured questionnaire was based on the Hawaii Cancer Research Survey (13), with additional questions taken from the Australian Health Survey (14). Details on its validity and reliability were described in Zhang et al. (11). To assess the reliability of self-reported past body height and weight, 41 patients from the cohort was interviewed twice within 11.3 weeks (SD 6.2). Intraclass correlations were 0.97 for body height and 0.98, 0.95, and 0.96 for body weight at diagnosis, at 5 years before diagnosis, and at age 21 years respectively, confirming the reliability of these measures.

The vital status of the patients was determined by follow-up telephone contact. A structured follow-up questionnaire was used to collect individual information on survival status, date and cause of death (if deceased), and medication taken post-diagnosis. Of the 207 patients followed-up in this study, 113 women were interviewed in person. For the remaining 94 cases, their next of kin were interviewed instead because the patients were deceased. These 94 proxies comprised husbands (68%), children (21%), siblings (4%), parents (1%), and other relatives (5%). All telephone interviews were conducted by the first author and took about 10 to 15 minutes. To ascertain all ovarian cancer-related deaths, information was sought from hospital medical records and/or community registration files. Data on the following variables were retrieved from medical records in the corresponding hospitals: Fesddration Internationale des Gynaecologistes et Obstetristes stage, histologic type, grade of differentiation, cytology of ascites, residual disease after surgery, and regime and frequency of chemotherapy.

Statistical Analysis. The data were coded and analyzed using the SPSS package (15). Survival time was calculated from the date of diagnosis to the date of death (event) or date of interview (censored). The Kaplan-Meier technique was applied to compare the survival experiences between the patients who had BMI of <25 and ≥25 kg/m^2 at 5 years before diagnosis. This premorbid BMI was chosen as a proxy for overweight and obesity in adulthood to minimize the bias due to ''inverse causation'' effects on body weight resulting from the presence of ovarian cancer.

BMI was calculated using the Quetelet's index expressed in kg/m^2 and categorized as follows: <20, 20-22.4, 22.5-24.9, and ≥25 kg/m^2 to facilitate analysis. The lowest categories were regarded as the reference groups. The BMI cut points corresponded to those proposed by the WHO for underweight (<18.5), normal weight (18.5-24.9), overweight (25-29.9), and obese (≥30; ref. 16). Because only a few patients (<2%) could be classified as obese, those women with BMI ≥ 25 kg/m^2 were pooled together as one group.

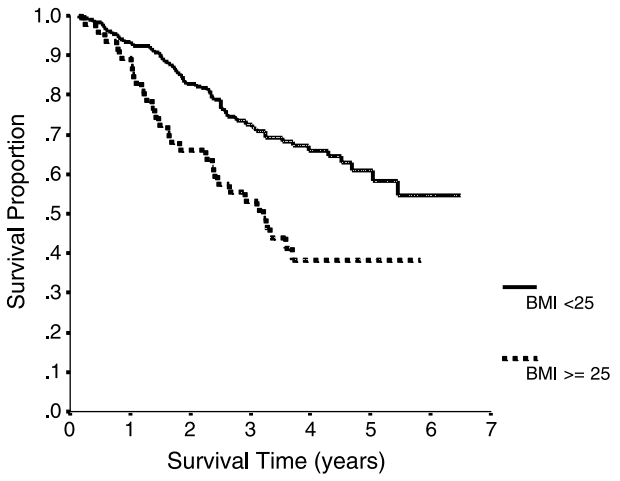

Figure 1. Survival curves by BMI at 5 years before diagnosis.

Table 1. Selected characteristics of ovarian cancer patients by survival status (*n* = 207)

Selected characteristics	Alive (*n* = 113), *n* (%)	Dead (*n* = 94), *n* (%)
Age at diagnosis (y), mean (SD)*	46.7 (12.7)	51.6 (8.8)
<40	34 (30.1)	7 (7.4)
40-49	33 (29.2)	39 (41.5)
50-59	27 (23.9)	29 (30.9)
≥60	19 (16.8)	19 (20.2)
Body height (cm), mean (SD)	158.2 (4.9)	158.1 (5.1)
Body weight (kg), mean (SD)		
At diagnosis	55.5 (7.9)	56.9 (8.7)
5 y ago*	54.8 (7.8)	58.2 (7.7)
At age 21 y†	51.7 (6.6)	53.3 (6.4)
Body mass index (kg/m^2), mean (SD)		
At diagnosis	22.2 (2.9)	22.7 (3.1)
5 y ago*	21.9 (2.7)	23.3 (2.7)
At age 21 y†	20.7 (2.4)	21.3 (2.3)
Tobacco smoking		
Never	111 (98.2)	92 (97.9)
Ever	2 (1.8)	2 (2.1)
Alcohol consumption		
Never	79 (69.9)	58 (61.7)
Ever	34 (30.1)	36 (38.3)
Menopausal status		
Premenopause	74 (65.5)	50 (53.2)
Postmenopause	39 (34.5)	44 (46.8)
Hormone replacement therapy		
Never	110 (97.3)	93 (98.9)
Ever	3 (2.7)	1 (1.1)
Oral contraceptive use		
Never	88 (77.9)	72 (76.6)
Ever	25 (22.1)	22 (23.4)
Ovarian cancer in first-degree relatives		
No	110 (97.3)	91 (96.8)
Yes	3 (2.7)	3 (3.2)
Fesddration Internationale des Gynaecologistes et Obstetristes stage*		
I	62 (54.9)	3 (3.2)
II	14 (12.4)	1 (1.1)
III	35 (30.9)	78 (82.9)
IV	2 (1.8)	12 (12.8)
Histopathologic grade*		
Well differentiated	43 (38.1)	4 (4.2)
Moderately differentiated	16 (14.2)	20 (21.3)
Poorly differentiated	30 (26.5)	61 (64.9)
Not available	24 (21.2)	9 (9.6)
Ascites*		
No	53 (46.9)	2 (2.1)
Yes	60 (53.1)	92 (97.9)
Residual lesions* (cm)		
<2	100 (88.5)	22 (23.4)
≥2	13 (11.5)	72 (76.6)
Chemotherapy		
No	3 (2.7)	4 (4.3)
Yes	110 (97.3)	90 (95.7)

NOTE: Differences between alive and dead patients were assessed using a χ^2 test for categorical variables and a *t* test for continuous variables.
*$P < 0.01$.
†$P < 0.05$.

Univariate analysis was first undertaken to screen for potentially significant variables to be used in a subsequent multivariate analysis. Separate Cox regression models were fitted to each anthropometric variable and the corresponding linear trend test were done. The effects of anthropometric variables on ovarian cancer survival were estimated by hazard ratios (HR) and associated 95% confidence intervals (95% CI), adjusting for age at diagnosis (in years, continuous), total energy intake (kcal, continuous), menopausal status (premenopause, postmenopause), Fesddration Internationale des Gynaecologistes et Obstetristes stage (I, II, III, and IV), grade of differentiation (well, moderately, poorly differentiated, not available), ascites (no/yes), residual lesions after debulking

surgery (<2 and ≥2 cm), and chemotherapeutic status (no/yes). These variables had been reported to influence ovarian cancer survival (17, 18) or were significant confounders according to our univariate results.

Results

After a minimum of 3 years of follow-up, 94 of the 207 cases in the original cohort were deceased. All deaths included in the analysis were due to ovarian cancer–related causes. Most of them died from recurrence of the disease, except for two patients whose deaths were recorded as being related to the side effects of chemotherapy. The survival experience was significantly different between patients with BMI of <25 and ≥25 kg/m^2 at 5 years before diagnosis, according to the log-rank test (P = 0.001). There were 98 (59.8%) of 164 patients whose BMI was <25 kg/m^2 and survived to the time of interview compared with only 15 women (34.9%) still alive among the 43 patients with BMI ≥ 25 kg/m^2. A significantly reduced survival time was observed for those patients with BMI ≥ 25 kg/m^2. The mean survival time were 4.5 years (95% CI, 4.2-4.9) among patients with BMI < 25 kg/m^2 and 3.2 years (95% CI, 2.6-3.8) among women with BMI ≥ 25 kg/m^2. The crude survival curves for BMI at 5 years before diagnosis are presented in Fig. 1.

Selected characteristics of ovarian cancer patients by survival status are shown in Table 1. Compared with the survivors, the deceased patients were older and heavier and had a higher BMI at all three time points. A larger proportion of the deceased patients was diagnosed at an advanced stage, with ascites, a poorly differentiated histopathologic grade and had residual lesions of ≥2 cm after surgery. There was no significant difference between the living and deceased patients in terms of body height, smoking, alcohol consumption, menopausal status, hormone replacement therapy, oral contraceptive use, family history of ovarian cancer, and chemotherapy status. No significant association was found between cancer stage and BMI ≥ 25 kg/m^2 at the three time points.

Table 2 gives crude and adjusted HR of epithelial ovarian cancer death for BMI after fitting separate Cox regression models. The HRs increased with higher BMI at 5 years before diagnosis but not at diagnosis nor at age 21 years. The adjusted HRs was 2.33 (95% CI, 1.12-4.87) for BMI of ≥25 versus <20 kg/m^2, with a significant dose-response relationship. The HR was 3.31 (95% CI, 1.26-8.73) among patients with BMI ≥ 25 kg/m^2 at age 21 years, but the corresponding linear trend was not significant.

Discussion

This prospective cohort study examined the relationship between ovarian cancer survival and BMI at three different time points during adulthood in Chinese women. We found a significant inverse association between survival time and BMI ≥ 25 kg/m^2 at 5 years before diagnosis but not at diagnosis nor at age 21 years. The dose-response relationships were significant. The findings are generally consistent with previous prospective studies that suggested a positive relationship between overweight and obesity and ovarian cancer mortality (1-3). To the best of our knowledge, this study provides the first epidemiologic evidence that premorbid overweight and obesity are associated with a higher case fatality separately from the association with incidence.

The association between BMI and ovarian cancer mortality has not been consistently reported in previous studies, although most of which were conducted in countries with an obesity epidemic (2, 7). The inconsistency may be due to the presence of ovarian cancer or ascites at diagnosis. In this study, there was no difference in BMI at diagnosis between the surviving and deceased patients. Because no significant relationship was found between cancer stage and BMI ≥ 25 kg/m^2 at the three time points, premorbid BMI seems independently associated with ovarian cancer survival.

Some strengths and limitations of the study should be considered when interpreting our findings. The strengths include the prospective design and characteristics of the sample. Selection bias was minimal due to the low number of refusals and a high follow-up fraction of 97%. The majority of patients were recently diagnosed, whereas the recruitment and identification procedures ensured that ascertainment of the patients was maximized and complete. The vital status of each patient was confirmed by independent sources. Another strength was the effort made to seek detailed information on body weight at different time points in adulthood. Moreover, the effects of BMI on ovarian cancer survival were assessed after adjusting for known prognostic factors (17, 18). The usage

Table 2. Crude and adjusted HRs of epithelial ovarian cancer death according to anthropometric variables (n = 207)

Anthropometric variables	No. cases	% Dead	Crude HR (95% CI)	Adjusted HR (95% CI)
BMI at diagnosis (kg/m^2)				
<20.0	40	45	1.0	1.0
20.0-22.4	75	36	0.79 (0.44-1.44)	0.60 (0.32-1.14)
22.5-24.9	53	53	1.23 (0.68-2.23)	0.65 (0.34-1.24)
≥25.0	39	54	1.15 (0.61-2.17)	0.76 (0.38-1.52)
χ_1^2 for trend*			0.84 (P = 0.36)	0.52 (P = 0.47)
BMI at 5 y before diagnosis (kg/m^2)				
<20.0	46	28	1.0	1.0
20.0-22.4	64	45	1.99 (1.04-3.85)	1.79 (0.90-3.55)
22.5-24.9	54	44	1.78 (0.91-3.50)	1.71 (0.84-3.46)
≥25.0	43	65	3.32 (1.72-6.42)	2.33 (1.12-4.87)
χ_1^2 for trend*			11.39 (P < 0.01)	6.13 (P = 0.01)
BMI at age 21 years (kg/m^2)				
<20.0	68	38	1.0	1.0
20.0-22.4	87	44	1.28 (0.78-2.11)	0.99 (0.59-1.69)
22.5-24.9	42	57	1.83 (1.05-3.19)	1.03 (0.56-1.89)
≥25.0	10	60	2.60 (1.07-6.33)	3.31 (1.26-8.73)
χ_1^2 for trend*			5.37 (P = 0.02)	1.54 (P = 0.22)

NOTE: Estimates from Cox regression models included terms for age at diagnosis (in y, continuous), total energy intake (kcal, continuous), menopausal status (premenopause and postmenopause), Fesddration Internationale des Gynaecologistes et Obstetristes stage (I, II, III, and IV), histopathologic grade of differentiation (well, moderately, poorly differentiated, and not available), ascites (no/yes), residual lesions (<2 and ≥2 cm), and chemotherapy (no/yes).
*Quantity of anthropometric variables was tested for linear trend.

of premorbid weight was also pertinent since the disease could result in weight change, making it difficult to determine the direction of the relationship (19).

With regard to limitations, anthropometric variables were not directly measured, but relied upon self-reported body weight and height. Nevertheless, previous studies showed that reported and measured height and weight values were generally highly correlated, and the reported values were still reliable among older persons (20, 21). The high intraclass correlations observed in our test-retest study have confirmed a lack of volatility in self-reported past body height and weight among the participants. Given the lack of public information on the relationship between overweight and obesity and ovarian cancer survival in China and the blindness of the participants regarding the study purpose, information bias was unlikely. However, because of the small sample size and relatively short follow-up period, further investigations are needed to confirm the observed associations in this study.

Obesity, resulting from major changes in lifestyle, represents a rapidly growing threat to the health of populations because it is a predisposing factor for many chronic diseases (22, 23). This study provides epidemiologic evidence that premorbid BMI may have independent prognostic influence on ovarian cancer. These results underscore the importance of maintaining moderate weight throughout adult life.

Acknowledgments

We thank the participation of the subjects, the collaboration received from the participating hospitals and their staff, and Associate Chief Doctor W.G. Lu and Chief Pathologist X.D. Chen (Women's Hospital, School of Medicine, Zhejiang University) for their kind assistance.

References

1. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–38.
2. Rodriguez C, Calle EE, Fakhrabadi-Shokoohi D, Jacobs EJ, Thun MJ. Body mass index, height, and the risk of ovarian cancer mortality in a prospective cohort of postmenopausal women. Cancer Epidemiol Biomarkers Prev 2002;11:822–8.
3. Zhao L, Zhou B, Wu Y, Li Y, Yang J. A prospective study on body mass index and mortality. Zhonghua Liu Xing Bing Xue Za Zhi 2002; 23:24–7.
4. McTiernan A, Rajan KB, Tworoger SS, et al. Adiposity and sex hormones in postmenopausal breast cancer survivors. J Clin Oncol 2003;21:1961–6.
5. Daling JR, Malone KE, Doody DR, et al. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. Cancer 2001;92:720–9.
6. Ballard-Barbash R, Swanson CA. Body weight: estimation of risk for breast and endometrial cancers. Am J Clin Nutr 1996;63:437–641S.
7. Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. J Natl Cancer Inst 1998; 90:1774–86.
8. Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. CA Cancer J Clin 2000;50:7–33.
9. Holschneider HC, Berek SJ. Ovarian cancer: epidemiology, biology, and prognostic factors. Semin Surg Oncol 2000;19:3–10.
10. Kristensen GB, Trope C. Epithelial ovarian carcinoma. Lancet 1997;349: 113–7.
11. Zhang M, Binns CW, Lee AH. Tea consumption and ovarian cancer risk: a case-control study in China. Cancer Epidemiol Biomarkers Prev 2002;11: 713–8.
12. Cotran RS, Kumar V, Collins T, editors. Robbins pathologic basis of disease. Philadelphia: W.B. Saunders Company; 1999. p. 1067.
13. Goodman MT, Hankin JH, Wilkens LR, et al. Diet, body size, physical activity, and the risk of endometrial cancer. Cancer Res 1997;57:5077–85.
14. Australian Bureau of Statistics. National health survey 1995: summary of results. Canberra: Australian Bureau of Statistics; 1995.
15. SPSS for windows. SPSS Incorporation. Release 10. 2000.
16. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO expert committee. World Health Organ Tech Rep Ser 1995;854: 1–452.
17. Brun JL, Feyler A, Chene G, Saurel J, Brun G, Hocke C. Long-term results and prognostic factors in patients with epithelial ovarian cancer. Gynecol Oncol 2000;78:21–7.
18. Clark TG, Stewart ME, Altman DG, Gabra H, Smyth JF. A prognostic model for ovarian cancer. Br J Cancer 2001;85:944–52.
19. Vatten LJ, Foss OP, Kvinnsland S. Overall survival of breast cancer patients in relation to preclinically determined total serum cholesterol, body mass index, height and cigarette smoking: a population-based study. Eur J Cancer 1991;27:641–6.
20. Nakamura K, Hoshino Y, Kodama K, Yamamoto M. Reliability of self-reported body height and weight of adult Japanese women. J Biosoc Sci 1999;31:555–8.
21. Casey VA, Dwyer JT, Berkey CS, Coleman KA, Gardner J, Valadian I. Long-term memory of body weight and past weight satisfaction: a longitudinal follow-up study. Am J Clin Nutr 1991;53:1493–8.
22. James PT, Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. Obes Res 2001;4:228–33S.
23. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. (WHO Technical Report Series). Geneva: WHO; 2000.

Body Mass Index in Relation to Ovarian Cancer Survival

Min Zhang, Xing Xie, Andy H. Lee, et al.

Cancer Epidemiol Biomarkers Prev 2005;14:1307-1310.