

RESEARCH COMMUNICATION

Body Mass Index and its Change in Adulthood and Breast Cancer Risk in China

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Abstract

Objective: To investigate the association between the risk of breast cancer and body mass index (BMI) and its change in adulthood. **Methods:** A population-based case-control study was conducted in China from 2008 to 2009. The study sample included 643 cases with pathologically-confirmed breast cancer and 590 controls. Information on adult height and weight at diagnosis, at five years before diagnosis, and at age 21 years was collected by face-to-face interview using a structured questionnaire. Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained using unconditional logistic regression analyses. **Results:** There was an increased risk of breast cancer associated with overweight or obesity in adulthood in Chinese women. Compared with the women who never had overweight or obesity in their adulthood, the adjusted ORs of breast cancer were 1.99 (1.42-2.79) for a BMI ≥ 25.0 at age 21 and just before diagnosis. This rose to 3.04 (1.18-7.86) if, in addition, BMI ≥ 25.0 was also present five years before diagnosis. **Conclusion:** Weight gain throughout adulthood is associated with an increased risk of breast cancer in Chinese women.

Keywords: Body mass index - body weight - case-control study - breast cancer - obesity

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Introduction

Breast cancer is the second most common cancer in the world and the most common cancer in women in both developing and developed countries (Key et al., 2001). It is also the primary cause of cancer death in women worldwide, responsible for about 375,000 deaths in the year 2000 (Kamangar et al., 2006). Incidence rates of breast cancer are increasing in most countries, and the changes are usually greatest where rates were previously low. Since 1990, there has been an overall increase in incidence rates of about 0.5% annually. At this rate of increase, there would be around 1.4 million new cases in 2010. However, the most rapid rises are seen in developing countries, where breast cancer risk has historically been low relative to developed countries. Cancer registries in China are recording annual increases in incidence of 3% to 4% (Parkin et al., 2005). Breast cancer shows the biggest proportional increase in the number of new cancer cases in women during the most recent five-year period, and remains the leading cancer of women in China (Yang et al., 2005).

Increases in breast cancer in developing countries are often viewed as the result of the 'Westernisation' of lifestyles (Yang et al., 2003). China has made rapid progress towards industrialization during the past three

decades, bringing with it changes towards a more Western lifestyle. It is possible that increased Westernization of lifestyle may be responsible for the rising incidence of breast cancer in China. One common consequence of a Western lifestyle is the development of excessive body weight and obesity (World Cancer Research Fund, 1997).

A number of studies have investigated the relationship between breast cancer and BMI. An extensive systematic review, including 84 reports on the association of body weight or BMI with breast cancer risk, concluded that in most but not all prospective cohort and case-control studies, obesity has been found to be associated with an increased risk of breast cancer in postmenopausal women, but unrelated to or associated with a reduced risk of breast cancer risk in premenopausal women (Carmichael and Bates, 2004). The majority of published results concerning the association between anthropometric indices and breast cancer risk were based on studies conducted in Western countries where the prevalence of obesity is high (Taioli et al., 1995; Wenten et al., 2002; Eng et al., 2005; Colditz et al., 2006; Ahn et al., 2007). Only a limited number of studies have been conducted in populations in which a vast majority of women are classified as relatively lower or of normal weight according to cut points of anthropometric indices proposed by the WHO (WHO, 1995; Shu et al., 2001; Gao et al., 2009). The prevalence

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of overweight and obesity varies by age and race (James et al., 2001). Chinese women also have a low prevalence of obesity, thus providing an opportunity to evaluate the association of anthropometric variables with breast cancer risk in women of relatively lower or normal weight. We therefore conducted a case-control study in China to assess the effects of BMI, and its changes during adulthood on breast cancer risk.

Materials and Methods

Study participants

A hospital-based case-control study was conducted in Shenyang, capital of Liaoning Province, during Jan 2008 to July 2009. All cases were recruited at the First Hospital of China Medical University; their pathological diagnoses had been reviewed and confirmed by pathologists in the hospital. The hospital is a public teaching hospital with around 2500 beds, and receives patients from all over the Province. There were about 5,000 outpatients daily and 50,000 inpatients annually (China Medical University, 2010).

The cases were women under 75 years of age, who had been residents of Liaoning Province for at least one year. Pathological diagnoses were based on the 1993 WHO classification of breast cancer (Cotran et al., 1999). To ensure complete ascertainment of eligible cases, all medical records and laboratory pathology reports were screened daily during the study period. A total of 643 patients with breast cancer were identified and only one patient did not participate in the study (non-response rate 0.2%). The average time between diagnosis and interview was about six months, and all the cases were recent patients recruited within 6 months from pathology diagnosis.

Controls were women with no history of cancer in the same catchment areas as cases. During the same period, 590 controls were recruited and interviewed. The controls were matched to cases by 5-years age group. The selected control group consisted of 88 hospital visitors (of whom two declined interview; non-response, 2.3%) recruited from the same hospital where the cases were identified and 502 women (9 declined interview; non-response, 1.8%) recruited from the community. The project was approved by the hospital human research ethics committee.

Information on self-reported past body height and weight was collected by face-to-face interview using a structured questionnaire after obtaining informed consent from the participants. Subjects were unaware of specific hypotheses of the study, and exposures were assessed according to the three time points. The participants were asked to report their adult height (in cm) and weight (in kg) at diagnosis for cases and interview for controls. In addition, recalled body weight at five years before diagnosis in cases and five years before interview in controls and at age 21 years were elicited. All subjects could report their adult height and weight at the three time points, except five cases and one control who could not provide the information on their weight at age at 21 years, and four cases and one control who could not provide the information on their weight five years before interview. Information was also sought on demographic

characteristics, tobacco smoking, alcohol consumption, usual diet, physical activity, reproductive history, factors relevant to hormonal status, and family history of cancer.

The structured questionnaire was based on the Hawaii Cancer Research Survey (Goodman et al., 1997), with additional questions taken from the Australian Health Survey (Australian Bureau of Statistics, 1995). Both instruments have been validated and used extensively for cancer or health surveys in large multi-ethnic populations, including Chinese immigrants. The questionnaire was first pre-tested on 51 adult Chinese women who recently migrated to Perth, Australia, to assess the feasibility, face and content validity. The feedback from the participants indicated that they could answer the required information without difficulty, confirming that the concepts in the questionnaire could be successfully translated into Mandarin and accommodated the Chinese lifestyle. A test-retest study was then undertaken to assess the volatility of self-reported past body height and weight. A sample of 41 women residing in Hangzhou was interviewed twice within 11.3 weeks (SD=6.2). Intraclass correlations were 0.97, 0.98, 0.95, and 0.96 for body height, body weight at diagnosis, at five years before diagnosis, and at age 21 years, respectively. All study participants were interviewed in person by trained interviewers and took between 30 and 40 minutes.

Statistical analysis

All data were checked for completeness at the end of each interview. The data were coded and analyzed using the SPSS package. BMI was calculated from reported body height and weight using the formula for Quetelet's index (expressed in kg/m²) and categorized as follows: <18.5, 18.5-22.9, 23.0-24.9, and ≥25.0. We used BMI 18.5-22.9 as the reference group for analyses. The categories of BMI corresponded to cut points proposed by the WHO (1995) for underweight <18.5, normal range 18.5-24.9, and overweight 25.0-29.9. Since few women (3.6%) in the participants fell into the category of obese (BMI ≥30.0), the women who had BMI ≥25.0 remained as one group. Based on the cut point of BMI ≥25.0, the participants were also classified into eight groups, named as 'never', 'only at age 21 years', 'only five years ago', 'only now', 'at age 21 years and five years ago', 'at age 21 years and now', 'five years ago and now', and 'at age 21 years, five years ago, and now', to assess the effects of changes in BMI during adulthood in Chinese women on breast cancer risk.

Univariate analysis was undertaken to screen potential explanatory variables for subsequent multivariate analysis. Odds ratios (OR) and associated 95% confidence intervals (CI) for the anthropometric variables were computed using unconditional logistic regression models. Each fitted regression equation included terms adjusting for age at interview, education, residential area, passive smoking, alcohol consumption, parity, menopausal status, oral contraceptive use, and biopsy-confirmed benign breast diseases. Each quantitative or ordinal anthropometric variable was also subjected to a linear trend test in breast cancer risk. Finally, model adequacy was assessed using the Hosmer and Lemeshow goodness-of-fit statistic.

Results

The selected characteristics of cases with breast cancer and controls are contrasted in Table 1. There were statistically significant differences in age at interview, education, locality, passive smoking, alcohol consumption, parity, oral contraceptive use, menopausal status, and biopsy-confirmed benign breast diseases. There was no statistically significant difference between cases and controls in tobacco smoking, tea consumption, age at menarche ≤ 12 years, hormone replacement therapy, and breast cancer in first degree relatives.

Table 2 reports the means of BMI, numbers and percents of BMI < 25 and ≥ 25.0 at age 21 years, five

years ago, and the time of interview. Compared with controls, patients with breast cancer consistently had a higher average of BMI and higher percentage in BMI ≥ 25.0 at age 21 years, five years ago, and the time of interview with statistically significant difference. There was a significant difference of BMI ≥ 25.0 category during adulthood between cases and controls.

Table 3 presents the adjusted ORs and 95% confidence interval of breast cancer for BMI during adulthood after fitting separate logistic regression models. The risk of breast cancer increased with BMI ≥ 25.0 during adulthood in Chinese women. Compared with the women having BMI 18.5-22.9, the adjusted ORs of breast cancer were 2.20 (95% 1.13-4.32), 1.90 (1.37-2.62), and 1.53 (1.14-

Table 1. Selected Characteristic of Cases with Breast Cancer and Controls

Selected characteristics	Cases (n=643)	Controls (n=590)	P value ^a
Age at interview (years)	50.4 \pm 10.1	48.0 \pm 8.6	<0.001
<40	81 (12.6)	104 (17.6)	
40-49	234 (36.4)	256 (43.4)	
50-59	226 (35.2)	179 (30.3)	
60-69	71 (11.0)	37 (6.3)	
≥ 70	31 (4.8)	14 (2.4)	
Education			0.001
No formal education	6 (0.9)	14 (2.4)	
Primary	86 (13.4)	59 (10.0)	
Secondary	422 (65.6)	355 (60.2)	
Tertiary	129 (20.1)	162 (27.4)	
Resident in rural area	29 (4.5)	58 (9.8)	<0.001
Tobacco smoking	46 (7.2)	32 (5.4)	0.21
Passive smoking	384 (59.7)	301 (51.0)	<0.01
Alcohol consumption	125 (19.4)	245 (41.5)	<0.001
Tea consumption	159 (24.7)	163 (27.6)	0.25
Age at menarche ≤ 12 years	28 (4.4)	14 (2.4)	0.06
Parity ^b	1.4 \pm 0.9	1.3 \pm 0.8	<0.01
Oral contraceptive use (ever)	80 (12.4)	27 (4.6)	<0.001
Hormone replacement therapy (ever)	4 (0.6)	3 (0.5)	0.79
Menopausal women	310 (48.2)	204 (34.6)	<0.001
Biopsy-confirmed benign breast diseases ^b	109 (17.0)	39 (6.6)	<0.001
Breast cancer in first degree relatives	19 (3.0)	10 (1.7)	0.15

Values expressed as mean \pm SD or number (percent). ^aTwo-sided; t-test for continuous variables and chi-square test for categorical variables. ^bData was missing one case.

Table 2. Changes in BMI during Adulthood in Chinese Women

Anthropometric variables	Cases (n=643)	Controls (n=590)	P value ^a
BMI (21 years old, kg/m ²) ^b	21.2 \pm 2.4	20.7 \pm 1.9	<0.001
<25	602 (94.4)	574 (97.5)	
≥ 25	36 (5.6)	15 (2.5)	
BMI (five years ago, kg/m ²) ^c	23.4 \pm 3.1	22.7 \pm 2.6	<0.001
<25	456 (71.4)	497 (84.4)	
≥ 25	183 (28.6)	92 (15.6)	
BMI (now, kg/m ²)	24.0 \pm 3.5	23.3 \pm 2.5	<0.001
<25	415 (64.5)	461 (78.1)	
≥ 25	228 (35.5)	129 (21.9)	
BMI ≥ 25 in adulthood (kg/m ²) ^c			<0.001
Never	388 (60.7)	438 (74.4)	
Only at age 21 years	9 (1.4)	7 (1.2)	
Only five years ago	12 (1.9)	13 (2.2)	
Only now	57 (8.9)	52 (8.8)	
At age 21 years and five years ago	4 (0.6)	2 (0.3)	
At age 21 years and now	2 (0.3)	0 (0)	
At 5-years ago and now	146 (22.8)	71 (12.1)	
At age 21 years, five years ago & now	21 (3.3)	6 (1.0)	

Values expressed as mean \pm SD or number (percent). ^aTwo-sided; t-test for continuous variables and chi-square test for categorical variables. ^bData was missing for five cases and one control. ^cData was missing for four cases and one control.

Table 3. Adjusted Odds Ratios and 95% Confidence Intervals for Breast Cancer for BMI during Adulthood in Chinese Women

Variables	Cases (n=643)	Controls (n=590)	Odds ratio (95% CI) ^a
BMI at age 21 years (kg/m ²)			
<18.5	70	67	1.17 (0.79-1.73)
18.5-22.9	446	463	1.00 ^b
23.0-24.9	86	44	1.75 (1.16-2.65)
≥25.0	36	15	2.20 (1.13-4.32)
P _{trend} ^c			<0.01
BMI five years ago (kg/m ²)			
<18.5	26	14	1.99 (0.97-4.12)
18.5-22.9	288	338	1.00 ^b
23.0-24.9	142	145	1.02 (0.76-1.39)
≥25.0	183	92	1.90 (1.37-2.62)
P _{trend} ^c			<0.01
BMI now (kg/m ²)			
<18.5	19	10	1.42 (0.61-3.32)
18.5-22.9	258	269	1.00 ^b
23.0-24.9	138	182	0.75 (0.55-1.01)
≥25.0	228	129	1.53 (1.14-2.07)
P _{trend} ^c			<0.01

^aEstimates from multivariate logistic regression models included terms for age at interview (years, <40, 40-49, 50-59, 60-69, ≥70), education (none, primary, secondary, tertiary), residential area (urban, rural), passive smoking (no/yes), alcohol consumption (never, ever), parity (full-term pregnancy; continuous), menopausal status (no, yes), oral contraceptive use (never, ever), and biopsy-confirmed benign breast diseases (no, yes); ^bReference category.; ^cTwo-sided test for trend across quantitative or ordinal quantitative variables.

2.07) in those women who had BMI ≥ 25.0 at age 21 years, five years ago, and the time of interview respectively, with a significant dose response relationship. For the women with BMI 23.0-24.9 at age 21 years, the ORs of breast cancer was 1.75 (1.16-2.65) with statistically significant difference, compared with those who had BMI 18.5-22.9 at that time.

Table 4 shows the effects of changes in BMI during adulthood by the cut point of BMI ≥25.0. We found that an increased risk factor of breast cancer was associated with consistent overweight or obesity in adulthood in Chinese women. Compared with the women who never had overweight or obesity in their adulthood, the adjusted ORs of breast cancer were 1.99 (1.42-2.79) and 3.04 (1.18-

7.86) for BMI ≥25.0 at age 21 years and five years, and for at age 21 years, five years ago and now, with statistically significant relationship. The Hosmer and Lemeshow goodness-of-fit statistic indicated no lack of fit for the logistic regression models.

Discussion

With the case-control design, causality can only be suggestive, because subjects already had the outcome of interest and reflected back in time to report their level of potentially harmful exposures. This population-based case-control study examined the relationship between breast cancer and BMI, and its change during adulthood in Chinese women, a population experiencing a relatively low, but increasing occurrence of both breast cancer and obesity. The study assessed the associations at three time points during adulthood by menopausal status. A significant, positive association between breast cancer risk and excessive body weight and BMI was found at age 21 years, five years ago, and the time of interview. Our data from Chinese women are consistent with the results from other studies showing strong associations in Asia-Pacific populations between increased BMI and breast cancers risk (Key et al., 2003; Li et al., 2006; Renehan et al., 2008; Gao et al., 2009; Jung et al., 2009).

In the present study there was an overall increased risk of breast cancer associated with increasing body weight. The findings indicate that the relations of adult weight gain to breast cancer are evident throughout the adulthood rather than being limited to a specific time in life. To our knowledge, this is the first study to show significant increased risk in relation to multiple adult stages of life across a broad range of BMI change in Chinese women. Wenten et al., (2002) in their study also found that adult weight gain was a risk factor in Hispanic women in the combined menopausal group. This suggests that weight gain is an important risk factor for breast cancer. Because weight gain during adulthood mainly suggests the deposition of fat mass rather than lean body mass, weight gain potentially represents age-related metabolic change that may be important in breast cancer development (Ballard-Barbash et al., 1997).

Several plausible mechanisms might explain the observed associations between excess body weight and

Table 4. Adjusted Odds Ratios and 95% Confidence Intervals for Breast Cancer for Change in BMI during Adulthood in Chinese Women

Anthropometric variables	Cases (n=643)	Controls (n=590)	Odds ratio (95% CI) ^a
BMI ≥25 in adulthood (kg/m ²)			
Never	388	438	1.00 ^b
Only at age 21 years	9	7	1.48 (0.46-4.74)
Only five years ago	12	13	0.75 (0.31-1.81)
Only now	57	52	1.09 (0.71-1.67)
At age 21 years & five years ago	4	2	1.37 (0.23-8.14)
At age 21 years & now	146	71	1.99 (1.42-2.79)
At age 21 years, five years ago & now	21	6	3.04 (1.18-7.86)
P _{trend} ^c			0.001

^aEstimates from multivariate logistic regression models included terms for age at interview (years, <40, 40-49, 50-59, 60-69, ≥70), education (none, primary, secondary, tertiary), residential area (urban, rural), passive smoking (no/yes), alcohol consumption (never, ever), parity (full-term pregnancy; continuous), menopausal status (no, yes), oral contraceptive use (never, ever), and biopsy-confirmed benign breast diseases (no, yes); ^bReference category.; ^cTwo-sided test for trend across quantitative or ordinal quantitative variables.

BMI and breast cancer risk, and alterations in hormonal metabolism including estrogen, androgens, insulin, and insulin-like growth factor-1 (IGF-1) in breast carcinogenesis (Bianchini et al., 2002). Sex steroids are known to regulate the balance between cellular differentiation, proliferation, and apoptosis, and may also favour the selective growth of preneoplastic and neoplastic cells (Bianchini et al., 2002). Insulin and IGF-1 also strongly stimulate cell proliferation, inhibit apoptosis, and can enhance angiogenesis (Khandwala et al., 2000; Singletary, 2003). In this study, a significant increased risk of breast cancer with increasing body weight and BMI was observed in both pre- and postmenopausal women, which has also been reported by others (Key et al., 2003; Li et al., 2006; Renehan et al., 2008; Gao et al., 2009; Jung et al., 2009). This is of special importance in pre- and postmenopausal women because accumulation of body fat in this age group is usually abdominal, and abdominal obesity is strongly associated with hyperinsulinemia, a risk factor for breast cancer (Singletary, 2003). Obesity has multiple effects on the hormonal status of pre- and postmenopausal women. In premenopausal women, it lowers sex hormone binding globulin and increases the serum levels of IGF-1, but it does not influence levels of estrogens and androgens significantly, because the ovaries produce more steroids than the peripheral fat tissue (Siiteri, 1987). Since adipose tissue is the major source of endogenous estrogen after menopause, circulating levels of estrogen are higher in postmenopausal women who are obese (Siiteri, 1987). In the large cohort study of nurses, Huang et al., (1997) found that the weight gain and postmenopausal breast cancer association was confined to women who never used estrogen replacement therapy. In this study, the participants had low exposure (0.6%) to hormone replacement therapy after menopause.

Several limitations of the study should be considered when interpreting the findings. Participants were not weighted or measured, and their height and weight were self-reported. However, most results of methodological research evaluating the validity of reported compared with measured height and weight show that they are highly correlated, that the reported values are reliable even in older persons (Klipstein-Grobusch et al., 1998; Nakamura et al., 1999), and that there is no evidence that self reported measures are biased between cases and controls (Casey et al., 1991). High intraclass correlations in our test-retest study confirmed a lack of volatility of self-reported past body height and weight among the participants. This study assessed body weight in Chinese women during their adulthood by three time points and the breadth of this age range complicates the comparison of body weight because obesity and weight gain tend to increase with age (Flegal et al., 1998). As far as potential sources of biases were concerned, selection bias was minimal in view of the low number of refusals. All cases were recently diagnosed, while the recruitment and identification procedures ensured that ascertainment of cases was maximized and complete.

Furthermore, the controls were randomly selected from the same hospital from which the cases arose, and most of the controls were recruited from the community

which indicates that the association of increased breast cancer risk with higher weight and BMI was not a spurious association confounded by social-economic status or access to medical care. In the hospital control sample, it was possible that their reported body height and weight may not have been representative of the Liaoning female population. Consequently, another sample of community women was recruited, and the self-reported anthropometric measurements were found to be similar to the hospital controls. Given the lack of public information on the relationship between overweight and obesity and breast cancer risk in China, and the blindness of the participants regarding the study purpose, information bias in the responses of cases was unlikely.

Overweight and obesity, resulting from major changes in lifestyle, represent a rapidly growing threat to the health of populations in an increasing number of countries because it is a predisposing factor for many chronic diseases (WHO, 2000; James et al., 2001). This study provides additional evidence that overweight and obesity are associated with an increasing risk of breast cancer in a population, in which a majority of women are relatively lower but increasing in weight. The results from the study may at least partly explain the recent increase in the incidence rate of breast cancer in China, although other co-contributing factors cannot be ruled out. Because body size is one of the few risk factors for breast cancer that can be modified throughout life, health promotion programs should pay attention to the avoidance of overweight and obesity in the prevention of the cancers in countries across the world, including China.

In summary, we found that weight gain throughout adulthood was associated with increased breast cancer risk. Relations with weight gain were not limited to specific periods in life. Women should avoid weight gain throughout adult life. The finding may reinforce public health recommendations for the maintenance of a healthy weight throughout adulthood as a means of breast cancer prevention.

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