Adiposity, adult weight change and breast cancer risk in postmenopausal Japanese women: the Miyagi Cohort Study

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BACKGROUND: The role of adult weight change in breast cancer (BC) risk is unclear in Japanese women.

METHODS: A total of 10,106 postmenopausal women aged 40–64 years (the Miyagi Cohort) were followed from 1990 to 2003, and 108 BC cases were identified. Hazard ratios (HRs) were estimated according to body mass index (BMI) at the current age and at the age of 20 years, and weight change since age 20 years.

RESULTS: Higher current BMI was associated with an increased risk of BC (P for trend = 0.02), whereas higher BMI at the age 20 years was inversely associated with this risk (P for trend = 0.002). There was a significant association between weight change since age 20 years and BC risk (P for trend = 0.0006). Compared with stable weight, HR was 0.35 for weight loss of 5 kg or more (P for weight loss trend = 0.04) and 1.55 for weight gain of 12 kg or more (P for weight gain trend = 0.05).

CONCLUSION: Adiposity at younger and current age has differential effects on BC risk among postmenopausal women; weight gain in adulthood being associated with an increased, and weight loss with a decreased risk.

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The incidence of breast cancer (BC) shows variations among countries and although Japan has a lower risk of BC than Western countries, its age-standardised incidence is the highest among female cancers, and it is increasing (Matsuda et al., 2008). The increase of BC incidence may be attributed to a change in the proportion of women in the population who have reproductive and anthropometric risk factors (Minami et al., 2004). Among such risk factors, the associations between adiposity and BC risk have been extensively investigated, mainly in the Western countries (Lahmann et al., 2004; Morimoto et al., 2002; Reeves et al., 2007).

We therefore conducted a population-based cohort study, in which we evaluated the association of adiposity in different periods, that is, at current age and at age 20 years, with BC risk and examined the change in risk resulting from body weight gain and loss since the age of 20 years among postmenopausal Japanese women.

MATERIALS AND METHODS

Our analysis used the Miyagi Cohort Study, whose design has been described in detail elsewhere (Fukao et al., 1995; Kawai et al., 2010). Briefly, 25,279 men and 26,642 women aged 40–64 years living in 14 municipalities, selected randomly from among the 62 municipalities in Miyagi Prefecture, Northeastern Japan, were entered into a cohort on 1 June 1990. A self-administered questionnaire on various health aspects was delivered to these subjects between June and August 1990. Usable questionnaires were returned by 22,836 men (90.3%) and 24,769 women (93.0%). After excluding men, women with a history of cancer (n = 705), who were premenopausal (n = 9131), with undefined menopausal status (n = 642) and for whom data on menopausal status were missing (n = 2927), 11,364 postmenopausal women remained (Kawai et al., 2010). After further excluding women with missing data or extreme values for current height or current weight or weight at age 20 years (n = 1258), 10,106 postmenopausal women contributed to this study. The study protocol was approved by the institutional review board of Tohoku University School of Medicine. We considered the return of self-administered questionnaires signed by the subjects to imply their consent to participate in the study.
The questionnaire covered personal history including current height (centimeters) and weight (kilograms) and weight at age 20 years and details of general lifestyle including menstrual and reproductive histories. The self-reported current height and weight data were highly correlated with measured data (correlation coefficient: 0.82 for height and 0.97 for weight) in a subsample of postmenopausal women (n = 2921), although we were unable to validate the data for weight at age 20 years.

As a measure of adiposity, body mass index (BMI) was used. The BMI at the current age and at age 20 years, calculated as weight divided by the square of current height (kg m⁻²), respectively. To analyze BC risk for adiposity in the different periods, the study women were categorised using quartile points of BMI at age 20 years, respectively: < 20.5, 20.5–< 22.0, ≥ 22.0–< 23.8 and ≥ 23.8. Subjects with a current BMI of 23.8 and higher were further divided into two groups on the basis of median value in the range between 23.8 and the largest current BMI, as the BMI at the current age was skewed towards a higher value than at age 20 years. Finally, women were categorised as follows: current BMI < 20.5, ≥ 20.5–< 22.0, ≥ 22.0–< 23.8, ≥ 23.8–< 25.9 and ≥ 25.9; BMI at age 20 < 20.5, ≥ 20.5–< 22.0, ≥ 22.0–< 23.8 and ≥ 23.8. Weight change from age 20 years to the current age was calculated as the difference between current weight and weight at age 20. Subjects were also categorised into seven groups as follows: weight loss of ≤ – 5 and > – 5 ≤ – 2, stable weight of > – 2 to < + 2, and weight gain of ≥ + 2 to < + 5, ≥ 5 to < + 8, ≥ 8 to ≥ + 12 and ≥ + 12. The categorisation of weight loss was based on the median value, and that of weight gain was determined using quintile values.

Women were followed from the start of the study (1 June 1990) until 31 December 2003. The end point of our analysis was BC diagnosis at age 20 years and that of weight gain was determined using a follow-up because of emigration.

RESULTS

The characteristics of the study subjects are presented in Tables 1 and 2. The subjects with a higher current BMI were less likely to smoke, whereas the subjects with a higher BMI at age 20 years tended to be older and to have a shorter period of education (Table 1). A total of 64.8% of the subjects had gained more than 2 kg since age 20 years (Table 2). The subjects who lost weight were heavier at age 20 years.

During 129,891 person-years of follow-up, 108 BC cases were documented. Table 3 shows the HRs and 95% CIs according to current BMI and BMI at age 20 years. After adjustment for confounding variables, current BMI was marginally associated with an increased BC risk (P for trend in multivariate-adjusted model 1 = 0.07). The BMI at age 20 years was inversely associated with risk (P for trend in multivariate-adjusted model 1 = 0.01). Postmenopausal women with a BMI of ≥ 23.8 at age 20 years showed half the risk (multivariate-adjusted HR = 0.44, 95% CI: 0.24–0.81) of women with a BMI of < 20.5. Multivariate analysis adjusting for both BMI s each other demonstrated a stronger inverse association for BMI at age 20 years (P for trend in multivariate-adjusted model 2 = 0.002). The association of current BMI with risk was statistically significant (P for trend = 0.02).

Weight change since the age of 20 years was significantly associated with the risk (multivariate-adjusted P for trend = 0.0086) (Table 4). Compared with women whose weight had been stable (lost or gained ≤ 2 kg), those who lost 5 kg or more were at a lower risk (multivariate-adjusted HR 0.35, 95% CI: 0.11–1.10). Women with a weight gain of 12 kg or more appeared to have a higher risk (HR 1.55, 95% CI: 0.70–3.45). According to weight loss and gain, weight loss was associated with a decreased risk (P for weight loss trend = 0.04), and weight gain with an increased risk (P for weight gain trend = 0.05). Although the data are not shown in the table, stratified analysis by the BMI at age 20 years revealed a clearer inverse association with weight loss among women who were heavier at age 20 years (BMI at age 20 years ≥ 23.8; P for weight loss trend = 0.01).

DISCUSSION

In this population-based cohort study, we found associations between adulthood adiposity and weight change and BC risk among postmenopausal women. Risk differed for BMI between that at current age and that at age 20 years. Weight change from age 20 to current age was significantly associated with risk. These results provide some insight into the significance of adiposity and weight change in terms of BC risk in postmenopausal Japanese women.

This study found a positive association of current BMI with postmenopausal BC risk consistent with previous prospective studies (Iwasaki et al, 2007; Kuriyama et al, 2005; Lahmann et al, 2004; Morimoto et al, 2002; Reeves et al, 2007), and the fact that postmenopausal obese women have more oestrogens than lean women (Potischman et al, 1996), has a central role in BC aetiology. After menopause, oestrogen is synthesised mainly by aromatase in adipose tissue (Bulun et al, 2005). Another mechanism is that obese women may be in a state of hyperinsulinaemia, insulin being a growth factor for BC cells. Insulin-like growth factor I may also affect risk among heavier women (Mutlu et al, 2002). On the other...
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Table 1  Characteristics of study population according to body mass index (BMI)

| Current BMI | < 20.5 | 20.5 ≤ < 22.0 | 22.0 ≤ < 23.8 | 23.8 ≤ < 25.9 | ≤ 25.9 |
|---|---|---|---|---|---|
| Number of subjects | 1209 | 2335 | 2516 | 2549 | 2801 |
| Age (mean, years) | 57.2 ± 4.5 | 57.0 ± 4.4 | 57.1 ± 4.3 | 57.2 ± 4.3 | 57.5 ± 4.2 |
| Occupation (no occupation/housewife, %) | 15.4 | 17.3 | 16.6 | 17.1 | 11.7 |
| Educational level (college/university or higher, %) | 12.4 | 12.8 | 12.5 | 11.7 | 10.3 |
| Alcohol drinking (drinkers, %) | 19.5 | 18.6 | 18.6 | 19.1 | 18.8 |
| Smoking (smokers, %) | 10.3 | 7.6 | 5.9 | 4.6 | 1.1 |
| Family history of breast cancer in mother or sisters (%) | 1.8 | 1.7 | 2.3 | 2.0 | 2.0 |
| Age at menopause (mean, years) | 54.7 ± 5.5 | 51.3 ± 5.2 | 51.3 ± 6.1 | 51.3 ± 6.1 | 51.4 ± 6.1 |
| BMI at age 20 years | 20.2 | 19.6 | 19.4 | 19.2 | 19.0 |
| Number of subjects | 2801 | 758 | 6547 | 2475 | 2549 |
| Age (mean, years) | 56.9 ± 4.4 | 57.3 ± 4.3 | 57.6 ± 4.2 | 57.6 ± 4.2 | 57.6 ± 4.2 |
| Occupation (no occupation/housewife, %) | 19.0 | 16.3 | 14.0 | 14.0 | 14.0 |
| Educational level (college/university or higher, %) | 14.0 | 10.8 | 9.5 | 9.5 | 9.5 |
| Alcohol drinking (drinkers, %) | 20.0 | 18.6 | 19.6 | 19.6 | 19.6 |
| Smoking (smokers, %) | 7.3 | 6.0 | 6.1 | 6.8 | 6.8 |
| Walking status (< 1 h per day, %) | 48.7 | 45.6 | 47.0 | 44.7 | 44.7 |
| Family history of breast cancer in mother or sisters (%) | 2.3 | 2.1 | 2.0 | 2.0 | 2.0 |
| Age at menopause (mean, years) | 49.3 ± 3.7 | 49.5 ± 3.5 | 49.6 ± 3.6 | 49.6 ± 3.6 | 49.6 ± 3.6 |
| Parity (nulliparous, %) | 3.7 | 2.0 | 2.0 | 1.8 | 1.8 |
| Parity number among parous women (mean) | 2.6 ± 1.0 | 2.7 ± 1.0 | 2.7 ± 1.1 | 2.8 ± 1.1 | 2.8 ± 1.1 |
| Exogenous female hormone use (users, %) | 11.6 | 9.9 | 10.2 | 10.1 | 10.1 |
| Height (mean, cm) | 152.4 ± 6.7 | 151.7 ± 5.2 | 151.5 ± 5.0 | 151.5 ± 4.9 | 150.7 ± 5.3 |

Table 2  Characteristics of study population according to weight change from age 20 to the current age

| Characteristics | Weight lossa | Stable weightb | Weight gainb |
|---|---|---|---|
| Number of subjects | 2801 | 758 | 6547 |
| Age (mean, years) | 57.4 ± 4.3 | 57.1 ± 4.4 | 57.2 ± 4.3 |
| Occupation (no occupation/housewife, %) | 14.6 | 16.1 | 17.5 |
| Educational level (college/university or higher, %) | 10.6 | 13.6 | 120.0 |
| Alcohol drinking (drinkers, %) | 19.4 | 18.2 | 18.9 |
| Smoking (smokers, %) | 8.0 | 6.3 | 6.0 |
| Walking status (< 1 h per day, %) | 43.5 | 44.7 | 48.1 |
| Family history of breast cancer in mother or sisters (%) | 1.6 | 3.2 | 2.0 |
| Age at menopause (mean, years) | 15.4 ± 2.0 | 15.1 ± 1.9 | 15.2 ± 2.0 |
| Age at menopause (16 years ≤, %) | 37.9 | 30.0 | 34.3 |
| Age at natural menopause (mean, years) | 49.5 ± 3.6 | 49.3 ± 3.4 | 49.5 ± 3.6 |
| Parity (nulliparous, %) | 2.2 | 3.0 | 2.4 |
| Parity number among parous women (mean) | 2.7 ± 1.0 | 2.7 ± 1.0 | 2.7 ± 1.0 |
| Exogenous female hormone use (users, %) | 10.2 | 12.4 | 10.3 |
| Height (mean, cm) | 150.8 ± 5.5 | 151.3 ± 5.2 | 151.7 ± 5.3 |
| Weight at 20 years (mean, kg) | 54.7 ± 6.2 | 51.3 ± 6.1 | 49.0 ± 5.4 |
| Current body mass index (mean) | 21.6 ± 2.3 | 22.4 ± 2.4 | 25.2 ± 2.9 |

Weight change was evaluated for subjects with complete data for height. aWeight loss ≥ 2 kg. bWeight gain or loss < 2 kg. cWeight gain ≥ 2 kg.

hand, a higher BMI at age 20 years was significantly associated with a decreased postmenopausal risk. This inverse association, which has also been observed in the Western countries (Ahn et al, 2007; Morimoto et al, 2002; Sellers et al, 1992; van den Brandt et al, 1997), was independent of the effect of current BMI. The Nurses’ Health Study recently reported the independent protective effect of body fatness at young age using a pictogram (Baer et al, 2010). Although the mechanisms explaining this inverse association are poorly understood, lower serum oestriadiol and progesterone levels and anovulation among young obese women may reduce BC risk after menopause (Potischman et al, 1996).

There was a significant association between weight change since age 20 and postmenopausal risk. Weight gain was associated with an increased risk, and weight loss with a decreased risk.
Table 3: Hazard ratio (HR) and 95% confidence interval (CI) of breast cancer according to current body mass index (BMI) at age 20 years.

| BMI at age 20 years | Person-years | Cases | HR   | 95% CI | HR   | 95% CI | HR   | 95% CI |
|---------------------|--------------|-------|------|--------|------|--------|------|--------|
| <20.5               | 15 327       | 8     | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| 20.5 ≤ <22.0        | 19 121       | 15    | 1.50 | 0.64 – 3.54 | 1.51 | 0.64 – 3.36 | 1.63 | 0.69 – 3.86 |
| 22.0 ≤ <23.8        | 29 835       | 24    | 1.54 | 0.69 – 3.43 | 1.55 | 0.70 – 3.46 | 1.74 | 0.78 – 3.90 |
| 23.8 ≤ <25.9        | 32 575       | 27    | 1.59 | 0.72 – 3.49 | 1.64 | 0.74 – 3.61 | 1.86 | 0.84 – 4.12 |
| 25.9 ≤ <27.0        | 33 033       | 34    | 1.97 | 0.91 – 4.25 | 2.04 | 0.94 – 4.41 | 2.54 | 1.16 – 5.55 |
| P for trend          |              |       | 0.09 |        | 0.07 |        | 0.02 |        |

Table 4: Hazard ratio (HR) and 95% confidence interval (CI) of breast cancer according to weight change from age 20 years to the current age.

| Weight change (kg) | Person-years | Cases | Age-adjusted model | Multivariate-adjusted model 1* | Multivariate-adjusted model 2 |
|-------------------|--------------|-------|--------------------|-------------------------------|-------------------------------|
| ≤−5               | 19760        | 5     | 0.31               | 0.10 – 0.94                   | 0.35                          |
| −5 ≤ <−2          | 16128        | 13    | 0.98               | 0.41 – 2.36                   | 0.95                          |
| −2 ≤ < +2         | 9714         | 8     | 1.00 (Reference)   | 1.00 (Reference)              | 1.00 (Reference)              |
| +2 ≤ < +5         | 18765        | 11    | 0.71               | 0.29 – 1.77                   | 0.70                          |
| +5 ≤ < +8         | 22857        | 21    | 1.12               | 0.49 – 2.52                   | 1.09                          |
| +8 ≤ < +12        | 20100        | 19    | 1.15               | 0.50 – 2.62                   | 1.10                          |
| +12 ≤ +20         | 22567        | 31    | 1.67               | 0.77 – 3.63                   | 1.55                          |
| P for trend        |              |       | 0.003              | 0.003                         | 0.003                         |
| P for weight loss  |              |       | 0.03               | 0.04                          | 0.05                          |
| P for weight gain  |              |       | 0.02               | 0.002                         | 0.002                         |

*Adjusted for age (continuous variable), alcohol drinking (ever, never), smoking (ever, never), occupation (permanent, no occupation/housewife), walking (<1 h per day, longer than 1 h per day), education level (junior high school or less, high school, college/university or higher), age at menarche (13, 14, 15, 16, 17), age at menopause (47, 48, 49, 50, 51, 52, 53, 54, 55), parity number (0, 1, 2, 3, 4, 5), family history of breast cancer (present, absent) and history of exogenous female hormone use (ever, never). Additionally adjusted for BMI at age 20 years (<20.5, 20.5 ≤ <22.0, 22.0 ≤ <23.8, 23.8 ≤ <25.9, 25.9 ≤ <27.0).
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Conflict of interest

The authors declare no conflicts of interest.

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