**Weight Gain During Adulthood and Body Weight at Age 20 Are Associated With the Risk of Endometrial Cancer in Japanese Women**

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Received February 14, 2011; accepted June 21, 2011; released online October 8, 2011

**ABSTRACT**

**Background:** Current obesity is an established risk factor for endometrial cancer; however, the roles of weight gain during adulthood and obesity in early adulthood have not been elucidated. Here, we conducted a case-control study comprising 222 histologically diagnosed incident endometrial cancer cases and 2162 age- and menstrual-status matched non-cancer controls.

**Methods:** Information on current body weight, weight and height at age 20 years, and lifestyle/environmental factors was obtained from a self-administered questionnaire. Subjects were classified into 3 groups according to change in body mass index (BMI, kg/m²) from age 20 years to enrollment (≤0 [reference], 0–3, and >3 kg/m²). The effects of adult BMI change and obesity in early adulthood were evaluated using an unconditional logistic regression model adjusted for potential confounders.

**Results:** A high BMI at age 20 (BMI ≥25, BMI <25 as reference) was significantly positively associated with endometrial cancer risk ($P$ = 0.005), as was a BMI increase during adulthood (0–3 BMI change, multivariate odds ratio [OR] = 1.28, 95% confidence interval [CI] = 0.88–1.87; >3 BMI change, OR = 2.02, 95% CI = 1.38–2.96; $P$-trend < 0.001). Parity and BMI at age 20 appeared to modify the effect of weight gain on cancer risk, albeit without statistical significance. This positive association of weight gain with risk was observed only for endometrioid adenocarcinoma.

**Conclusions:** The results show that endometrial cancer is positively associated with obesity at age 20 and weight gain during adulthood among Japanese women.

**Key words:** endometrial cancer; weight gain; case-control study

**INTRODUCTION**

Endometrial cancer is an increasingly common gynecologic cancer in Japanese women; the age-standardized incidence rate increased from 1.4 to 7.3 between 1975 and 2005.¹ Interestingly, a marked difference in age-specific incidence has been observed among women older than 50 years.¹ Obesity is an important established risk factor for endometrial cancer,²,³ with many studies showing that current obesity is associated with increased risk for endometrial cancer due to the effect of adiposity on the synthesis and bioavailability of endogenous sex steroid hormones, mainly estrogens.⁴–⁸

Although the overall prevalence of overweight (body mass index [BMI] ≥25 [kg/m²]) in Japanese women has not changed during the last 20 years, there has been a heterogeneous trend in BMI change across generations: BMI in Japanese women older than 50 years has increased, whereas mean BMI in women aged 20 to 39 has decreased.⁹,¹⁰ These trends in age-specific incidence and age-specific BMI suggest a potential association between weight gain during adulthood and endometrial cancer. Although several epidemiologic
studies have reported a positive association with weight gain, the interaction between weight gain during adulthood and various potential confounders, such as parity and physical activity, has remained unclear.

Here, we conducted a hospital-based, case-control study to examine the association of endometrial cancer risk with BMI at age 20 and weight gain from age 20 years. We also investigated whether these associations differed with regard to possible confounding factors.

METHODS

Subjects

The cases comprised 222 patients who had received a new histologic diagnosis of endometrial carcinoma between January 2001 and November 2005 at Aichi Cancer Center Hospital (ACCH) in Japan. With regard to histologic subtype, 177 cases were endometrioid adenocarcinoma (79.7%), 31 were other adenocarcinomas (14.0%), and 14 were unknown (6.3%). Mixed epithelial and mesenchymal tumors were excluded due to insufficient information on tumor etiology. Controls (n = 2162) were randomly selected and matched by age (±4 years) and menstrual status (premenopause, perimenopause, or postmenopause) to cases at a 1:10 case-control ratio from 11,814 women who were free of cancer (58 cases were matched with 9 instead of 10 controls each). All subjects were enrolled using the framework of the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), as described elsewhere. Briefly, using a self-administered questionnaire we collected information on lifestyle factors from all first-visit outpatients aged 20 to 79 years at ACCH who were recruited for HERPACC between January 2001 and November 2005. Patients were also asked about their lifestyle when healthy or before their current symptoms developed. We did not enroll apparently ill patients who had subjective difficulty in answering the questionnaire. A trained interviewer checked responses. Approximately 90% of eligible subjects responded to the questionnaire. Outpatients were also asked to provide blood samples. Our previous study indicated that the lifestyle patterns of first-visit outpatients conformed with those of a randomly selected sample of the general population of Nagoya City. The data were loaded into the HERPACC database and routinely linked with the hospital-based cancer registry system to update data on cancer incidence. We obtained informed consent from all participants, and the Institutional Ethical Committee of Aichi Cancer Center approved this study.

Assessment of anthropometric factors and other exposure data

The HERPACC questionnaire includes anthropometric factors as well as other lifestyle factors, body weight when healthy or before current symptoms developed, height, and body weight at age 20. In the questionnaire, respondents were asked: “current (pre-illness) weight?” and “weight at around age 20?” BMI at enrollment was calculated as weight in kilograms divided by the square of height in meters (kg/m²) from self-reported height and weight. Change in body weight and BMI from age 20 years to enrollment was calculated as: (current body weight – body weight at age 20) and (current BMI) – (BMI at age 20), respectively. Weight change per year from age 20 to enrollment was calculated as [(current body weight in kg)– (body weight at age 20 in kg)]/ (age at enrollment – 20). This variable was designed to investigate the association between velocity of weight change and endometrial cancer risk.

In our previous study, we assessed the validity of self-reported values versus measured values for 100 patients randomly selected from among 173 patients with thyroid cancer by comparing current height, weight, and BMI on the HERPACC questionnaire with the respective values measured and recorded in the medical record by hospital staff on admission to ACCH. Self-recorded and measured values for current height, weight, and BMI were highly correlated, with Pearson’s correlation coefficients of 0.978, 0.910, and 0.913 for women, respectively.

Smoking and drinking habits were categorized into 3 categories: never, former, and current. Former smokers and drinkers were defined as ever-smokers and ever-drinkers and included with current smokers and drinkers, respectively, in the analysis. Menstrual status was classified as premenopausal, perimenopausal, or postmenopausal, and premenopausal and perimenopausal women were included in the premenopausal group for the analysis. Postmenopausal was defined as the absence of a menstrual cycle for at least 1 year.

Statistical analysis

To evaluate the strength of associations between body weight change and risk of endometrial cancer, odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using unconditional logistic models adjusted for potential confounders. To improve statistical efficiency in stratified analysis, we used unconditional logistic models after confirming the consistency of results from the conditional and unconditional models. For subgroup analysis, subjects were classified by BMI change into 3 groups (<25 or ≥3 kg/m²). Change in body weight per year from age 20 to enrollment was also divided into 3 groups (<0, 0–0.19, 0.19–3.50 kg/year, based on median values among controls who had experienced weight gain during adulthood). The potential confounders that were adjusted for in the multivariate analyses were age, smoking habit (never or ever), drinking habit (never or ever), regular exercise (yes or no), age at menarche (<12, 13–14, or ≥15 years), duration of menstruation (years, tertile), parity (0, 1–2, ≥3), and a history of diabetes (yes or no), contraceptive use (yes or no), and hormone replacement therapy (yes or no). Current BMI and BMI age at 20 were classified into 2 groups (<25 or ≥25 kg/m²).
≥25 kg/m²) based on our previous study.\textsuperscript{15} We defined overweight as a BMI of 25 kg/m² or higher. Missing values for any covariate were treated as dummy variables in the logistic model. Differences in categorized demographic variables between cases and controls were assessed by the chi-square test. Age, age at menarche, current BMI, BMI at age 20, duration of menstruation, and parity were compared in cases and controls by the Mann-Whitney test. To estimate risks for subgroups, we conducted analysis stratified by menstrual status, regular exercise, parity (0 or ≥1), BMI at age 20 (<25 or ≥25 kg/m²), and histologic subtype (endometrioid or other carcinoma). A P value less than 0.05 was considered to indicate statistical significance. We used STATA version 10.1 (Stata Corp., College Station, TX, USA) for all analyses.

RESULTS

The baseline characteristics of the 222 endometrial cancer patients and 2162 controls are shown in Table 1. Median age was 56.0 years for both cases and controls. Smoking status did not differ between groups: the prevalence of ever-smokers among cases and controls was 14.9% and 18.9%, respectively. Not differ between groups: the prevalence of ever-smokers among cases and controls was 14.9% and 18.9%, respectively. A drinking habit was significantly less common among cases than among controls (P = 0.002). Current BMI and BMI at age 20 were higher among cases than among controls (P < 0.001). Regarding reproductive factors, low parity was more prevalent (P < 0.001) and duration of menstruation was longer among cases than among controls (P < 0.001). A history of diabetes was more common in cases. There was no difference between groups in regular exercise, age at menarche, history of hypertension, history of oral contraceptive use, or history of hormone replacement therapy use.

Table 2 shows the association of endometrial cancer risk with current BMI and BMI at age 20. A higher current BMI and a higher BMI at age 20 were associated with increased risk: as compared with women with a BMI less than 25, the multivariate OR of women with a current BMI of 25 or greater was 2.22 (95% CI = 1.59–3.09, P < 0.001), while that of women with a BMI of 25 or greater at age 20 was 2.30 (1.29–4.11, P = 0.005). Table 3 shows the associations of endometrial cancer risk with BMI and body weight change from age 20 to study enrollment. Regarding BMI change, women who had a BMI increase of 0 to 3 kg/m² or greater than 3 kg/m² had a higher risk of endometrial cancer than did those with no BMI increase, with ORs of 1.28 (95% CI = 0.88–1.87) and 2.02 (1.38–2.96), respectively (P-trend < 0.001). A significant positive association with greater body weight change per year was consistently observed from age 20 to enrollment (P-trend = 0.001) and was not changed by adjustment for BMI or body weight at age 20 (P-trend < 0.001). However, after adjusting for current BMI, these positive associations were attenuated.

Table 4 shows the joint effect of BMI change on analysis stratified by potential confounders. The positive association between BMI and endometrial cancer risk remained generally consistent after stratification by menstrual status, regular exercise, parity, and BMI at age 20. The multivariate OR of nulliparous women with a BMI change of 0 to 3 kg/m² was 1.80 (95% CI = 0.91–3.57); among those with a change greater than 3 kg/m², it was 3.75 (1.67–8.37). However, the P value for interaction was not significant (interaction P = 0.090). With regard to BMI at age 20, women with a BMI of 25 or greater at age 20 had higher ORs (0–3 kg/m² BMI change: multivariate OR = 2.50, 95% CI = 0.19–33.10; >3 kg/m² BMI change: 8.02, 0.95–67.51) than did those with a BMI less than 25 (0–3 kg/m² BMI change: 1.29, 0.86–1.91; >3 kg/m² BMI change: 1.97, 1.31–2.95). However, the interactions between BMI change and BMI at age 20 were not statistically significant (interaction P = 0.216). On analysis by histologic subtype, positive associations were observed only among patients with endometrioid carcinoma (0–3 kg/m² BMI change: OR = 1.46, 95% CI = 0.95–2.25; >3 kg/m² BMI change: 2.50, 1.62–3.85).

Table 5 shows the combined effect of BMI at age 20 and current BMI on endometrial cancer risk. As shown in Table 4, obesity at both age 20 and study enrollment increased endometrial cancer risk (OR = 3.45, 95% CI = 1.72–6.92). However, the interaction between BMI at age 20 and BMI at study enrollment was not significant (interaction P = 0.704).

DISCUSSION

We found that both BMI at age 20 and current BMI were associated with a significantly increased risk of endometrial cancer. In addition, weight gain from age 20 to study enrollment was associated with a positive risk of endometrial cancer. Further, nulliparous women, or women who were obese at age 20, who had increased body weight during adulthood were likely to have higher ORs, although the interactions between weight gain and these variables were not statistically significant. These positive associations were observed only among cases of endometrioid cancer.

Table 2 shows that current obesity (BMI ≥25) and obesity at age 20 were associated with an increased risk of endometrial cancer. This finding for current obesity is consistent with those of other studies.\textsuperscript{2,5,15} In premenopausal women, obesity causes insulin resistance, which has important effects on ovarian androgen synthesis, anovulation, and chronic progesterone deficiency.\textsuperscript{2,7} Postmenopausal obese women are thought to have higher levels of estrogens derived from extraglandular conversion of androgens.\textsuperscript{2,7} Furthermore, obese women are more likely to have lower levels of sex hormone-binding globulin (SHBG).\textsuperscript{2,3,22} As a consequence, increased levels of bioavailable estrogen might induce development of endometrial cancer among currently
### Table 1. Characteristics of subjects

| Characteristic                      | Cases (%) | Controls (%) | P value |
|-------------------------------------|-----------|--------------|---------|
| Number                              | 222       | 2162         |         |
| Histology                           |           |              |         |
| Endometrioid (%)                    | 177 (79.7)|              |         |
| Other carcinoma (%)                 | 31 (14.0) |              |         |
| Unknown (%)                         | 14 (6.3)  |              |         |
| Age, years (median [min–max])       | 56.0 (25–79)| 56.0 (20–79)| 0.771   |
| <40 (%)                             | 37 (16.8) | 297 (13.7)   | 0.306   |
| 40–54 (%)                           | 56 (25.2) | 631 (29.2)   |         |
| ≥55 (%)                             | 129 (58.1)| 1234 (58.1)  |         |
| Smoking status                      |           |              |         |
| Ever (%)                            | 33 (14.9) | 1751 (18.9)  | 0.153   |
| Never (%)                           | 187 (84.2)| 409 (81.0)   |         |
| Unknown (%)                         | 2 (0.9)   | 2 (0.1)      |         |
| Drinking status                     |           |              |         |
| Ever (%)                            | 61 (27.5) | 1331 (38.4)  | 0.002   |
| Never (%)                           | 159 (71.6)| 830 (61.6)   |         |
| Unknown (%)                         | 2 (0.9)   | 1 (0.1)      |         |
| Current body mass index (median [min–max]) | 23.1 (13.4–40.9) | 21.6 (13.3–40.9) | <0.001 |
| <25 kg/m² (%)                       | 152 (68.5)| 1804 (83.4)  | <0.001  |
| ≥25 kg/m² (%)                       | 65 (29.3) | 342 (15.8)   |         |
| Unknown (%)                         | 5 (2.3)   | 16 (0.7)     |         |
| Body mass index at age 20 (median [min–max]) | 20.8 (14.8–34.3) | 20.3 (14.9–34.2) | 0.001   |
| <25 kg/m² (%)                       | 196 (88.3)| 2043 (94.5)  |         |
| ≥25 kg/m² (%)                       | 17 (7.7)  | 70 (3.2)     |         |
| Unknown (%)                         | 9 (4.1)   | 49 (2.3)     |         |
| Regular exercise                    |           |              |         |
| No (%)                              | 69 (31.1) | 618 (28.6)   | 0.440   |
| Yes (%)                             | 150 (71.6)| 1512 (69.9)  |         |
| Unknown (%)                         | 3 (1.4)   | 32 (1.5)     |         |
| Menstrual status                    |           |              |         |
| Premenopausal (%)                   | 78 (35.2) | 738 (34.1)   | 0.709   |
| Postmenopausal (%)                  | 141 (63.5)| 1410 (65.2)  |         |
| Unknown (%)                         | 3 (1.4)   | 14 (0.7)     |         |
| Age at menarche, years (median [min–max]) | 13.0 (9–19) | 14.0 (9–22) | 0.241   |
| ≤12 (%)                             | 62 (27.9) | 555 (25.7)   | 0.340   |
| 13–14 (%)                           | 106 (47.8)| 997 (46.1)   |         |
| ≥15 (%)                             | 47 (21.2) | 556 (25.7)   |         |
| Unknown (%)                         | 7 (3.2)   | 54 (2.5)     |         |
| Duration of menstruation, years (median [min–max]) | 36.0 (11–47) | 35.0 (6–60) | <0.001  |
| ≤32 (%)                             | 57 (25.7) | 732 (33.9)   |         |
| 33–37 (%)                           | 69 (31.1) | 780 (36.1)   |         |
| >37 (%)                             | 83 (37.4) | 574 (26.6)   |         |
| Unknown (%)                         | 13 (5.9)  | 76 (3.5)     |         |
| Parity (median [min–max])           |           |              |         |
| 0 (%)                               | 63 (28.4) | 347 (16.1)   | <0.001  |
| 1–2 (%)                             | 123 (55.4)| 1318 (61.0)  |         |
| ≥3 (%)                              | 32 (14.4) | 488 (22.6)   |         |
| Unknown (%)                         | 4 (1.8)   | 9 (0.4)      |         |
| Diabetes history                    |           |              |         |
| No (%)                              | 207 (93.2)| 2080 (96.2)  | 0.033   |
| Yes (%)                             | 15 (6.8)  | 82 (3.8)     |         |
| Hypertension history                |           |              |         |
| No (%)                              | 186 (83.8)| 1889 (87.4)  | 0.129   |
| Yes (%)                             | 36 (16.2) | 273 (12.6)   |         |
| History of contraceptive use        |           |              |         |
| No (%)                              | 208 (93.7)| 2011 (93.0)  | 0.295   |
| Yes (%)                             | 8 (3.6)   | 114 (5.3)    |         |
| Unknown (%)                         | 6 (2.7)   | 37 (1.7)     |         |
| History of hormone replacement therapy |        |              |         |
| No (%)                              | 198 (89.2)| 1963 (90.8)  | 0.401   |
| Yes (%)                             | 20 (9.0)  | 161 (7.5)    |         |
| Unknown (%)                         | 4 (1.8)   | 38 (1.8)     |         |
obese women. In contrast, premenopausal obese women are likely to have anovulatory cycles and decreased levels of progesterone. In particular, obese women are exposed to prolonged unopposed estrogens during early adulthood and, as a result, they might have an increased risk of endometrial cancer. The mechanism underlying the association of BMI as a result, they might have an increased risk of endometrial cancer. The mechanism underlying the association of BMI with a 3-fold increased risk.5,8,12

Table 2. Impact of current BMI and BMI at age 20 years on endometrial cancer risk

| Category | Case/control | Age-adjusted OR (95% CI) | Multivariate OR (95% CI) | BMI at age 20 years (kg/m²) | Case/control | Age-adjusted OR (95% CI) | Multivariate OR (95% CI) |
|----------|--------------|--------------------------|--------------------------|-----------------------------|--------------|--------------------------|--------------------------|
| Current BMI (kg/m²) | | | | <25 kg/m² | 152/1804 | 1.00 (Reference) | 1.00 (Reference) |
| ≥25 kg/m² | 65/342 | 2.26 (1.65–3.10) | 2.22 (1.59–3.09) |
| Unknown | 5/16 | P for trend | <0.001 | <0.001 |
| BMI at age 20 years (kg/m²) | | | | <25 kg/m² | 196/2043 | 1.00 (Reference) | 1.00 (Reference) |
| ≥25 kg/m² | 17/70 | 2.53 (1.46–4.40) | 2.30 (1.29–4.11) |
| Unknown | 9/49 | P for trend | 0.001 | 0.005 |

4Multivariate models adjusted for age, smoking, drinking, regular exercise, age at menarche, duration of menstruation, parity, diabetes history, history of oral contraceptive use, and history of hormone replacement therapy.

Table 3. Odds ratios and 95% CI for endometrial cancer stratified according to BMI change and body weight change from age 20 to enrollment

| Category | Case/control | Age-adjusted OR (95% CI) | Multivariate OR (95% CI) | BMI change from age 20 to enrollment (kg/m²) | Case/control | Age-adjusted OR (95% CI) | Multivariate OR (95% CI) | Body weight change per year from age 20 to enrollment (kg/year) | Case/control | Age-adjusted OR (95% CI) | Multivariate OR (95% CI) |
|----------|--------------|--------------------------|--------------------------|---------------------------------------------|--------------|--------------------------|--------------------------|------------------------------------------------------------------|--------------|--------------------------|--------------------------|
| s0 | 57/719 | 1.00 (Reference) | 1.00 (Reference) | 0.0 | 59/720 | 1.00 (Reference) | 1.00 (Reference) | 0.19 | 63/685 | 1.10 (0.75–1.60) | 1.18 (0.80–1.76) |
| 0–3 | 73/804 | 1.15 (0.80–1.65) | 1.28 (0.88–1.87) | 0.9 | 93/701 | 1.62 (1.15–2.29) | 1.84 (1.28–2.64) | 0.19–3.50 | 93/701 | 1.62 (1.15–2.29) | 1.84 (1.28–2.64) |
| >3 | 82/581 | 2.02 (1.38–2.96) | 2.22 (1.50–3.28) | 3.09 | 7/56 | 0.005 | 0.001 | 0.20 | 63/685 | 1.10 (0.75–1.60) | 1.18 (0.80–1.76) |
| Unknown | 10/58 | P for trend | 0.001 | 0.001 | | | | | | | |

4Multivariate models adjusted for age, smoking, drinking, regular exercise, age at menarche, duration of menstruation, parity, diabetes history, history of oral contraceptive use, and history of hormone replacement therapy.

4Multivariate models adjusted for age, smoking, drinking, regular exercise, BMI at age 20 years, age at menarche, duration of menstruation, parity, diabetes history, history of oral contraceptive use, and history of hormone replacement therapy.

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J Epidemiol 2011;21(6):466-473
### Table 4. Effect of BMI change according to age, menstrual status, exercise, parity, BMI at age 20, and histology on endometrial cancer risk

| Category                              | BMI change from age 20 to enrollment (kg/m²) | P for trend |
|---------------------------------------|---------------------------------------------|-------------|
|                                       | ≤0   | 0–3 | >3  |                |              |
| Total (case/control)³                  | 57/719 | 73/804 | 82/581 |                |              |
| Age-adjusted OR (95% CI)              | 1.00 (Reference) | 1.15 (0.80–1.65) | 1.79 (1.25–2.56) | 0.001 |
| Multivariate OR (95% CI)²             | 1.00 (Reference) | 1.28 (0.88–1.87) | 2.02 (1.38–2.96) | <0.001 |
| Menstrual status interaction          | P = 0.334 |
| Premenopausal (case/control)          | 20/274 | 35/283 | 21/166 |                |              |
| Multivariate OR (95% CI)²             | 1.00 (Reference) | 2.10 (1.11–3.98) | 2.16 (1.02–4.55) | 0.036 |
| Postmenopausal (case/control)         | 35/437 | 38/518 | 60/412 |                |              |
| Multivariate OR (95% CI)²             | 1.00 (Reference) | 0.89 (0.54–1.46) | 1.82 (1.15–2.88) | 0.006 |
| Unknown (case/control)                | 2/8 | 0/3 | 1/3 | interaction P = 0.910 | interaction P = 0.383 |
| Regular exercise interaction          | P = 0.0875 |
| No (case/control)                     | 17/215 | 26/217 | 23/167 |                |              |
| Multivariate OR (95% CI)²             | 1.00 (Reference) | 1.55 (0.79–3.05) | 1.83 (0.90–3.72) | 0.097 |
| Yes (case/control)                    | 40/494 | 46/578 | 57/404 |                |              |
| Multivariate OR (95% CI)²             | 1.00 (Reference) | 1.16 (0.73–1.85) | 2.08 (1.31–3.31) | 0.002 |
| Unknown (case/control)                | 0/10 | 1/9 | 2/10 | interaction P = 0.376 | interaction P = 0.953 |
| Parity interaction                    | P = 0.090 |
| 0 (case/control)                      | 19/177 | 24/113 | 18/48 |                |              |
| Multivariate OR (95% CI)²             | 1.00 (Reference) | 1.80 (0.91–3.57) | 3.75 (1.67–8.37) | 0.001 |
| ≥1 (case/control)                     | 37/537 | 49/690 | 61/532 |                |              |
| Multivariate OR (95% CI)²             | 1.00 (Reference) | 1.01 (0.64–1.60) | 1.49 (0.96–2.32) | 0.058 |
| Unknown (case/control)                | 1/5 | 0/1 | 3/1 | interaction P = 0.129 | interaction P = 0.077 |
| BMI at age 20 interaction              | P = 0.216 |
| <25 (case/control)                    | 49/663 | 70/799 | 77/573 |                |              |
| Multivariate OR (95% CI)²             | 1.00 (Reference) | 1.29 (0.86–1.91) | 1.97 (1.31–2.95) | 0.001 |
| ≥25 (case/control)                    | 3/56 | 3/5 | 5/8 |                |              |
| Multivariate OR (95% CI)²             | 1.00 (Reference) | 2.50 (0.19–33.10) | 8.02 (0.95–67.51) | 0.056 |
| Unknown (case/control)                | 1/5 | 0/1 | 3/1 | interaction P = 0.164 | interaction P = 0.263 |
| Histology Not assessed                 | P = 0.90 |
| Endometrioid (case/control)           | 42/719 | 59/804 | 69/581 |                |              |
| Multivariate OR (95% CI)²             | 1.00 (Reference) | 1.46 (0.95–2.25) | 2.50 (1.62–3.85) | <0.001 |
| Other carcinoma (case/control)        | 13/719 | 9/804 | 7/581 |                |              |
| Multivariate OR (95% CI)²             | 1.00 (Reference) | 0.50 (0.20–1.26) | 0.54 (0.20–1.44) | 0.179 |
| Unknown (case/control)                | 2/719 | 5/804 | 6/581 |                |              |

³10 cases and 58 controls were excluded from the analyses due to lack of information on BMI.

²Multivariate models adjusted for age, smoking, drinking, regular exercise, age at menarche, duration of menstruation, parity, diabetes history, history of oral contraceptive use, and history of hormone replacement therapy.

### Table 5. Combined effect of BMI at age 20 and current BMI on endometrial cancer

| Category                              | BMI at age 20 (kg/m²) | BMI at enrollment (kg/m²) | Case/control | Age-adjusted OR (95% CI) | Multivariate OR (95% CI)²³ |
|---------------------------------------|------------------------|---------------------------|--------------|--------------------------|-----------------------------|
|                                       | <25                    | <25                       | 145/1738     | 1.00 (Reference)         | 1.00 (Reference)            |
|                                       | ≥25                    | <25                       | 3/33         | 1.10 (0.33–3.67)         | 1.25 (0.37–4.34)            |
|                                       | <25                    | ≥25                       | 51/297       | 2.07 (1.46–2.92)         | 2.07 (1.44–2.97)            |
|                                       | ≥25                    | ≥25                       | 13/96        | 4.33 (2.25–8.35)         | 3.45 (1.72–6.92)            |
| P for trend                           | interaction P <0.001  | 0.369                     |              |                          | 0.704                       |

³10 case and 58 controls were excluded from the analyses due to lack of information on BMI.

²Multivariate models adjusted for age, smoking, drinking, regular exercise, age at menarche, duration of menstruation, parity, diabetes history, history of oral contraceptive use, and history of hormone replacement therapy.
statistically significant interaction, several factors were suggestive in terms of mechanism. First, nulliparous women who had weight gain during adulthood were likely to have higher ORs as compared with multiparous women. Second, the impact of BMI change was greater in obese women at age 20 than in nonobese women at that age. In addition, this association was evident only in cases of endometrioid cancer. These findings may be of value in future epidemiologic and biologic studies.

There are several potential limitations in our study that should be considered. First, we used self-reported height and body weight. Previous validity studies of body size among Japanese women have reported that women tend to overestimate height and underestimate weight. However, correlation coefficients in our validity study were high and considered acceptable. Second, self-reported body weight at age 20 may be inaccurate. However, the fact that obesity at age 20 is not generally regarded as a risk factor for endometrial cancer likely precludes the possibility of recall bias regarding body size. Third, case-control studies are subject to information bias, although the HERPACC system is less vulnerable to this bias than are typical hospital-based studies, because data for most or all patients are collected before diagnosis. Fourth, because the study was conducted under a hospital-based case-control design, the possibility of inadequate comparability between cases and controls depended on whether the control population was the source population from which the cases arose. However, we selected cases and controls from the same hospital, and almost all these patients live in the Tokai area of central Japan. Validity in the HERPACC study was confirmed in our previous study. Finally, our study had a modest sample size; thus, replication of our findings in other studies is required.

In conclusion, this case-control study suggests that weight gain in adulthood increases the risk of endometrial cancer among Japanese. Further, a similar association was observed after stratification by potential confounders. This higher risk of endometrial cancer with increased adult weight might be exacerbated in women who were already obese at age 20, although this effect was not statistically significant in the present research. To prevent endometrial cancer, our findings support the importance of weight control starting in early adulthood. Further investigation of these findings is warranted.

ACKNOWLEDGMENTS

The authors are grateful to the staff of the Division of Epidemiology and Prevention at Aichi Cancer Center Research Institute for their support of this study. This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, Culture and Technology of Japan, by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan, and by a Grant-in-Aid for the Third-Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare of Japan.

Conflicts of interest: None declared.

REFERENCES

1. Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T; Japan Cancer Surveillance Research Group. Cancer incidence and incidence rates in Japan in 2005: based on data from 12 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCJ) project. Jpn J Clin Oncol. 2011;41:139–47.
2. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet. 2005;366:491–505.
3. Fader AN, Arriba LN, Frasure HE, von Gruenigen VE. Endometrial cancer and obesity: epidemiology, biomarkers, prevention and survivorship. Gynecol Oncol. 2009;114:121–7.
4. Kuriyama S, Tsutono Y, Hozawa A, Shimazu T, Suzuki Y, Koizumi Y, et al. Obesity and risk of cancer in Japan. Int J Cancer. 2005;113:148–57.
5. Friedenreich C, Cust A, Lahnmann PH, Steindorf K, Boutron-Ruault MC, Clavel-Chapelon F, et al. Anthropometric factors and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. Cancer Causes Control. 2007;18:399–413.
6. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371:569–78.
7. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomarkers Prev. 2002;11:1531–43.
8. Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry, physical activity, and endometrial cancer risk: results from the Netherlands Cohort Study. J Natl Cancer Inst. 2004;96:1635–8.
9. Yoshiike N, Seino F, Tajima S, Arai Y, Kawano M, Furuhata T, et al. Twenty-year changes in the prevalence of overweight in Japanese adults: the National Nutrition Survey 1976–95. Obes Rev. 2002;3:183–90.
10. Funatogawa I, Funatogawa T, Nakao M, Karita K, Yano E. Changes in body mass index by birth cohort in Japanese adults: results from the National Nutrition Survey of Japan 1956–2005. Int J Epidemiol. 2009;38:83–92.
11. Park SL, Goodman MT, Zhang ZF, Kolonel LN, Henderson BE, Setiawan VW. Body size, adult BMI gain and endometrial cancer risk: the multiethnic cohort. Int J Cancer. 2010;126:490–9.
12. Chang SC, Lacey Jv Jr, Brinton LA, Hartge P, Adams K, Mouw T, et al. Lifetime weight history and endometrial cancer risk by type of menopausal hormone use in the NIH-AARP diet and health study. Cancer Epidemiol Biomarkers Prev. 2007;16:723–30.
13. Trentham-Dietz A, Nichols HB, Hampton JM, Newcomb PA. Weight change and risk of endometrial cancer. Int J Epidemiol. 2006;35:151–8.
14. Xu WH, Xiang YB, Zheng W, Zhang X, Ruan ZX, Cheng JR, et al. Weight history and risk of endometrial cancer among Chinese women. *Int J Epidemiol.* 2006;35:159–66.

15. Hirose K, Tajima K, Hamajima N, Kuroishi T, Kuzuya K, Miura S, et al. Comparative case-referent study of risk factors among hormone-related female cancers in Japan. *Jpn J Cancer Res.* 1999;90:255–61.

16. Terry P, Baron JA, Weiderpass E, Yuen J, Lichtenstein P, Nyren O. Lifestyle and endometrial cancer risk: a cohort study from the Swedish Twin Registry. *Int J Cancer.* 1999;82:38–42.

17. Tajima K, Hirose K, Inoue M, Takezaki T, Hamajima N, Kuroishi T. A Model of Practical Cancer Prevention for Outpatients Visiting a Hospital: the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). *Asian Pac J Cancer Prev.* 2000;1:35–47.

18. Hamajima N, Matsuo K, Saito T, Hirose K, Inoue M, Takezaki T, et al. Gene-environment Interactions and Polymorphism Studies of Cancer Risk in the Hospital-based Epidemiologic Research Program at Aichi Cancer Center II (HERPACC-II). *Asian Pac J Cancer Prev.* 2001;2:99–107.

19. Hosono S, Matsuo K, Kajiyama H, Hirose K, Suzuki T, Hiraki A, et al. Reduced risk of endometrial cancer from alcohol drinking in Japanese. *Cancer Sci.* 2008;99:1195–201.

20. Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, Kuroishi T, et al. Epidemiological features of first-visit outpatients in Japan: comparison with general population and variation by sex, age, and season. *J Clin Epidemiol.* 1997;50:69–77.

21. Suzuki T, Matsuo K, Hasegawa Y, Hiraki A, Kawase T, Tanaka H, et al. Anthropometric factors at age 20 years and risk of thyroid cancer. *Cancer Causes Control.* 2008;19:1233–42.

22. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer.* 2004;4:579–91.

23. Stoll BA. Teenage obesity in relation to breast cancer risk. *Int J Obes Relat Metab Disord.* 1998;22:1035–40.

24. Stoll BA, Vatten LJ, Kvinsland S. Does early physical maturity influence breast cancer risk? *Acta Oncol.* 1994;33:171–6.

25. Weiderpass E, Persson I, Adami HO, Magnusson C, Lindgren A, Baron JA. Body size in different periods of life, diabetes mellitus, hypertension, and risk of postmenopausal endometrial cancer (Sweden). *Cancer Causes Control.* 2000;11:185–92.

26. 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.