Weight change since age 20 and incident risk of obesity-related cancer in Japan: a pooled analysis of the Miyagi Cohort Study and the Ohsaki Cohort Study

Mano Wakamatsu, Yumi Sugawara, Shu Zhang, Fumiya Tanji, Yasutake Tomata and Ichiro Tsuji

Division of Epidemiology, Department of Health Informatics and Public Health, Tohoku University School of Public Health, Graduate School of Medicine, Sendai, Japan

It is unclear whether weight change during adulthood affects the risk of obesity-related cancers such as those of the esophagus, colorectum, pancreas, breast, endometrium, and kidney among Japanese, where obesity is less frequent and less severe. We examined the association between weight change during adulthood and the risk of obesity-related cancer among Japanese by conducting a pooled analysis of two prospective studies of residents in Miyagi Prefecture, Japan. A total of 78,743 persons (40,422 women and 38,321 men) aged 40–79 years participated in the Miyagi Cohort Study in 1990 and in the Ohsaki Cohort Study in 1994. Weight change since age 20 was divided into four categories (weight loss; stable weight; moderate weight gain; high weight gain). Cox proportional hazards regression analysis was used to estimate the multivariate hazard ratios (HRs) and 95% confidence intervals (CIs) for obesity-related cancer incidence. During 1,057,899 person-years of follow up, 4,467 cases of obesity-related cancer (women; 1,916 cases, men; 2,551 cases) were identified. In women, compared to the stable weight, weight gain was associated with an increased risk of obesity-related cancer (moderate weight gain; HRs = 1.10, 95%CIs: 0.97–1.26, high weight gain; HRs = 1.29, 95%CIs: 1.14–1.47). The results indicate that weight gain since age 20 was associated with a significantly increased risk of obesity-related cancer among Japanese women. By contrast, in men, our study found that weight change is not associated with the incidence of obesity-related cancer.

Introduction

Excess body weight and weight gain during adulthood pose an increased risk of major chronic diseases, including several cancers. A study conducted in the United States in 2014 found that excess body weight was associated with 10.9% of all incident cancers in women, and represented the second highest population-attributable fraction among major risk factors for cancer (PAF). Similarly, excess body weight was associated with 4.8% of all incident cancers in men, and represented the third highest PAF. Excess body weight and weight gain during adulthood are important public health problems that affect the incidence of cancer, and weight control during adulthood is effective for prevention of obesity-related cancer.

The association between weight change during adulthood and the risk of obesity-related cancers has been investigated mainly in western countries. One meta-analysis including a total of 50 previous studies reported that adult weight gain was associated with an increased risk of postmenopausal breast cancer and endometrial cancer, although it was unrelated to colon cancer in women. It is generally recognized that Asian women tend not to be as overweight or obese as western women, and one study has examined the association between weight change during adulthood and the risk of overall cancer and major site-specific cancer among Chinese women. That study concluded that weight gain since age 20 was associated with an increased risk of postmenopausal breast cancer and endometrial cancer.

Meanwhile, many of previous studies reported that adult weight gain became more strongly associated with a higher weight change, obesity-related cancer, Cohort, Japan, incidence

Key words: weight change, obesity-related cancer, Cohort, Japan, incidence

Additional Supporting Information may be found in the online version of this article.

Grant sponsor: the National Cancer Center Research and Development Fund; Grant numbers: 27-A-4; Grant sponsor: Research and Development; Grant sponsor: National Cancer Center; Grant sponsor: School of Medicine; Grant sponsor: Tohoku University

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

DOI: 10.1002/ijc.31743

History: Received 19 Feb 2018; Accepted 21 Jun 2018; Online 11 Jul 2018

Correspondence to: Yumi Sugawara, Division of Epidemiology, Department of Health Informatics and Public Health, Tohoku University School of Public Health, Graduate School of Medicine, Sendai, Japan, 2-1, Seiryo-machi, Aoba-ku, Sendai, Miyagi, 980-8575, Japan. Phone: +81-22-717-8123 Fax: +81-22-717-8125; E-mail: yumii1717@med.tohoku.ac.jp
risk of obesity-related cancer (colorectal, renal, pancreatic, and esophageal cancers) in men.4,8

However, compared to the number of previous studies conducted in western countries, relatively few studies have examined the association between weight change during adulthood and the risk of obesity-related cancer among Asian, and no study has examined these associations in Japanese. Therefore, the objective of our study was to examine the association between weight change since age 20 and the risk of obesity-related cancer, both overall and at individual sites, among Japanese.

**Methods**

**Study population**

We carried out a pooled analysis of two prospective cohort studies, the Miyagi Cohort Study and the Ohsaki Cohort Study, details of which have been described previously elsewhere.9–11 In brief, for the Miyagi Cohort Study, we distributed a self-administered questionnaire to all 51,921 subjects (26,642 women and 25,279 men) aged 40–64 years resident in 14 municipalities of Miyagi Prefecture, northeastern Japan, between June and August 1990. We collected eligible questionnaires from 24,769 (47.6%) of those subjects (response rate: 91.7%).9 For the Ohsaki Cohort Study, we distributed a self-administered questionnaire to all 54,996 subjects (28,515 women and 26,481 men) aged 40–79 years living in the catchment area of the Ohsaki Public Health Center, a local government agency that provides preventive health services for the residents of 14 municipalities in Miyagi Prefecture, between September and December 1994. We collected eligible questionnaires from 52,029 of those subjects (response rate: 94.6%).10

The study protocol was reviewed and approved by the Institutional Review Board of Tohoku University Graduate School of Medicine (approved number: 2014-1-838 for Miyagi, 2014-1-839 for Ohsaki). We considered the return of self-administered questionnaires signed by the participants to indicate their consent to participate in the study.

We excluded from our analysis 777 subjects who had moved from the study area before the start of follow-up and one woman whose date of cancer diagnosis was missing in the Ohsaki Cohort Study. Also, during the process of pooling the two cohorts, we identified 5,451 subjects who had participated in both of the cohort studies. Therefore, we eliminated data only for those subjects involved in the Ohsaki Cohort Study, for which the baseline followed that of the Miyagi Cohort Study. In addition, we excluded subjects who had a history of cancer at the baseline (n = 4,094) and those for whom data were missing with regard to weight at the baseline (n = 3,625), weight at age 20 (n = 5,544), and height at the baseline (n = 1,399). After these exclusions, 78,743 subjects (40,422 women and 38,321 men) were eligible for analysis.

**Exposure data**

We collected data at the baseline for each individual using a self-completed questionnaire inquiring about age, weight at the baseline, weight at age 20, height, medical history, level of education, smoking status, alcohol consumption, time spent walking, history of cancer in the family, number of births, age at menarche, menopausal status, and use of oral contraceptives.

Weight change since age 20 was calculated as the difference between weight at the baseline and weight at age 20. Weight change since age 20 was categorized into quartile values: women; weight loss (< −2.0 kg), stable weight (−2.0 to +4.0 kg), moderate weight gain (+4.1 to +9.0 kg), and high weight gain (> + 9.0 kg), men; weight loss (< −2.9 kg), stable weight (−2.9 to +3.0 kg), moderate weight gain (+3.1 to +8.0 kg), and high weight gain (> + 8.0 kg).

We evaluated the validity of self-reported body height and body weight. Among the study subjects in the Miyagi Cohort Study, 7,153 had had their body height and weight measured during health examinations provided by the local government in 1990. The Pearson’s correlation coefficient (r) for self-reported and measured values was 0.97 for body weight (p < 0.01) and 0.85 for body height (p < 0.01). On the other hand, among the study subjects in the Ohsaki Cohort Study, 14,883 had had their body height and weight measured during local government health examinations in 1995. The Pearson’s correlation coefficient for self-reported and measured values was 0.96 for body weight (p < 0.01) and 0.93 for body height (p < 0.01).12 Thus, the self-reported weight and height data obtained by these baseline questionnaires were considered to be sufficiently valid.

**Follow-up**

The follow-up period for the Miyagi Cohort Study was from 1 June 1990 to 31 December 2007, and that for the Ohsaki Cohort Study was from 1 January 1995 to 31 March 2008.
For both cohorts, we followed the incidence of cancer and residential status using the records of the Miyagi Prefectural Cancer Registry, one of the oldest and most accurate population-based cancer registries in Japan.13

The endpoints were incidence of obesity-related cancer and of cancer at individual sites, defined according to the International Classification of Diseases for Oncology, 3rd ed. (ICD-O-3). In our study, we defined thirteen cancers (esophageal cancer (C15), gastric cardia cancer (C16.0), colorectal cancer (C18-20), liver cancer (C22), gallbladder cancer (C23), pancreatic cancer (C25), multiple myeloma (C42.1), postmenopausal breast cancer (C50), endometrial cancer (C54), ovarian cancer (C56), kidney cancer (C64), meningioma (C70) and thyroid cancer (C73) for which the World Cancer Research Fund/American Institute for Cancer Research have judged to have a convincingly increased risk in relation to body fatness.14–16

During the follow-up period, the number of individuals lost to follow-up was 2,425 in the Miyagi Cohort Study (6.0% of the analyzed individuals) and 6,652 in the Ohsaki Cohort Study (17.7%). For each individual, we continued follow-up until diagnosis of obesity-related cancer, death, emigration from the study area, or the end of the observation period, whichever occurred first.

Statistical analysis
We prospectively counted the person-years of follow-up for each subject. Next, we used Cox proportional hazards regression analysis to estimate the multivariate-adjusted hazard ratio (HR) and 95% confidence intervals (95% CIs) for incidence of obesity-related cancer in relation to stable weight as the reference group in both men and women. Also, to consider the effect of reverse causality, we carried out sensitivity analysis excluding cases of obesity-related cancer that occurred in the first 3 years. The P-values for the test of linear trend (P for weight gain trend) were calculated using weight change category as a continuous variable. We considered the after variables to be potential confounders: age at the baseline (continuous variable), body mass index (BMI) at age 20 (continuous variable), history of diabetes mellitus (DM) (yes or no), level of education (junior high school, high school, college and university or more, or missing), smoking status (never, former, current smoker, or missing), alcohol consumption (never, former, current drinker, or missing), time spent walking per day (<0.5 h, 0.5–1.0 h, >1.0 h, or missing), history of any cancer in the family (yes or no). In women, we considered the after variables as additional potential confounders: number of births (0, 1, 2, ≥3, or missing), age at menarche (≤13 yr, 14–15 yr, ≥16 yr, missing), menopausal status (premenopausal, postmenopausal, or missing), and use of oral contraceptives (never, ever, or missing). BMI at age 20 was calculated as weight at age 20 divided by the square of height (kg/m²). Missing values for confounders were treated as an additional variable category, and included in the model.

To assess whether the association between weight change and the risk of obesity-related cancer differed between subjects who were of normal weight and overweight at age 20, we conducted stratified analysis according to BMI at age 20 (<25.0 kg/m², ≥25.0 kg/m²). Interaction between weight gain since age 20 and BMI at age 20 was tested through the addition of cross-product terms to the multivariate model.

All P values were two-sided, and differences at P < 0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results
Table 1 shows the baseline characteristics of the study participants according to the categories of weight change since age 20. In women, compared to the stable category, the high weight gain category tended to have higher proportions of women who were current smokers, current drinkers, and spent <0.5 h walking per day. Women in the weight loss category tended to be older, postmenopausal and more likely to be current smokers. In contrast, men with the high weight gain category more likely to be never or former smokers.

A total of 1,057,899 person-years were accrued, and 4,467 cases of obesity-related cancer (women; 1,916 cases, men; 2,551 cases) were documented. Also, 716 cases of obesity-related cancer (women; 305 cases, men; 411 cases) were documented within the first 3 years of follow-up. Table 2 shows the multivariate-adjusted HR and 95% CI for obesity-related cancer and cancer at individual sites according to the categories of weight change since age 20 in women. For women, after adjustment for confounding variables, weight gain was significantly associated with an increased risk of obesity-related cancer (moderate weight gain; HRs = 1.10, 95% CI: 0.97–1.26, high weight gain; HRs = 1.29, 95% CI: 1.14–1.47, P for weight gain trend <0.01). We also observed that weight gain was associated with an increased risk of colon cancer, postmenopausal breast cancer, and endometrial cancer. For high weight gain, the increased risk of associated colon cancer was significant (HRs = 1.31, 95% CI: 1.01–1.69).

For postmenopausal breast cancer, moderate and high weight gain were significantly associated with an increased risk (moderate weight gain; HRs = 1.62, 95% CI: 1.16–2.27, high weight gain; HRs = 1.88, 95% CI: 1.35–2.61). For endometrial cancer, high weight gain was significantly associated with an increased risk (HRs = 1.90, 95% CI: 1.09–3.32). Also, weight loss tended to be associated with a decreased risk of endometrial cancer (HRs = 0.46, 95% CI: 0.21–1.00). For esophageal cancer, both categories of weight gain and weight loss tended to be associated with an increased risk, but not to a significant degree (weight loss; HRs = 1.55, 95% CI: 0.67–3.55, moderate weight gain; HRs = 1.54, 95% CI: 0.68–3.47, high weight gain; HRs = 1.28, 95% CI: 0.55–2.98). Also, after exclusion of incident cases that occurred within the first 3 years of follow-up, these associations were not observed. For gallbladder cancer,
| Weight change since age 20 (kg) | loss | −2.0 to + 4.0 | +4.1 to + 9.0 | > 9.0 | P-value^a |
|-------------------------------|------|---------------|---------------|-------|-----------|
| **Women**                     |      |               |               |       |           |
| Range                         |      |               |               |       |           |
| Number of subjects            | 9,913| 11,161        | 9,586         | 9,762 |           |
| Age, year (mean ± SD)         | 59.2±10.5 | 54.5±9.8   | 54.9±9.3     | 55.4±9.1 | <0.01   |
| BMI at baseline^2 (kg/m^2)    | 21.5±2.5    | 22.4±2.4   | 24.3±2.4    | 26.9±3.1 | <0.01   |
| BMI at age 20^3 (kg/m^2)      | 24.5±4.1    | 22.0±2.4   | 21.4±2.3    | 20.7±2.4 | <0.01   |
| History of DM (%)             | 5.1           | 3.4         | 3.4         | 5.2     | <0.01   |
| Level of education (%)        |      |               |               |       |           |
| Junior high school            | 50.5         | 40.9        | 43.1        | 46.2    |           |
| High school                   | 35.4         | 42.9        | 41.6        | 39.6    | <0.01   |
| College / University or more  | 8.5           | 12.3        | 10.7        | 9.6     |           |
| Missing                       | 5.6           | 3.9         | 4.6         | 4.6     |           |
| Smoking status (%)            |      |               |               |       |           |
| Never                         | 66.2         | 71.5        | 70.4        | 68.5    |           |
| Former                        | 1.8           | 1.7         | 1.8         | 2.0     | <0.01   |
| Current                       | 8.1           | 6.6         | 5.9         | 7.6     |           |
| Missing                       | 23.9         | 20.2        | 21.9        | 21.9    |           |
| Alcohol consumption^a (%)     |      |               |               |       |           |
| Never                         | 59.3         | 59.9        | 59.1        | 56.4    |           |
| Former                        | 3.8           | 2.9         | 3.2         | 4.2     | <0.01   |
| Current                       | 17.9          | 21.7        | 20.7        | 22.3    |           |
| Missing                       | 19.1          | 15.6        | 17.0        | 17.1    |           |
| Time spent walking per day (%)|      |               |               |       |           |
| < 0.5 h                       | 25.7         | 26.4        | 27.2        | 29.2    |           |
| 0.5–1.0 h                     | 23.1         | 23.6        | 24.9        | 24.8    | <0.01   |
| ≥ 1.0 h                       | 41.8         | 42.3        | 39.8        | 37.1    |           |
| Missing                       | 9.5           | 7.7         | 8.1         | 8.9     |           |
| History of any cancer in the family (%) | 29.7 | 29.8 | 31.3 | 31.3 | <0.01 |
| Number of births              | 2.8±1.4       | 2.6±1.1     | 2.6±1.1     | 2.7±1.2 | <0.01   |
| Age at menarche (year)        | 15.2±2.0      | 14.8±1.9    | 14.9±2.0    | 14.9±2.1 | <0.01   |
| Menopausal status (%)         |      |               |               |       |           |
| Premenopausal                 | 21.6         | 36.3        | 32.2        | 30.2    |           |
| Postmenopausal                | 63.6         | 53.5        | 57.6        | 58.8    | <0.01   |
| Missing                       | 14.8          | 10.2        | 10.2        | 11      |           |
| Use of oral contraceptives (%)|      |               |               |       |           |
| Never                         | 80.2         | 82.7        | 82.4        | 81.4    |           |
| Ever                          | 3.8           | 5.0         | 5.0         | 5.0     | <0.01   |
| Missing                       | 16.0          | 12.3        | 12.6        | 13.6    |           |
| **Men**                       |      |               |               |       |           |
| Range                         |      |               |               |       |           |
| Number of subjects            | 10,361        | 10,237      | 8,439       | 9,284   |           |
| Age, year (mean ± SD)         | 60.5±9.7      | 53.9±9.8    | 53.0±9.5    | 52.6±9.2 | <0.01   |
| BMI at baseline^2 (kg/m^2)    | 21.7±2.5      | 22.3±2.2    | 24.0±2.1    | 26.2±2.7 | <0.01   |
| BMI at age 20^3 (kg/m^2)      | 24.5±3.6      | 22.2±2.2    | 21.8±2.0    | 21.1±2.2 | <0.01   |

(Continues)
weight gain tended to be associated with an increased risk (moderate weight gain; HRs = 1.41, 95% CI: 0.71–2.81, high weight gain; HRs = 1.90, 95% CI: 0.99–3.65). For kidney cancer, there was a positive association between the high weight gain category and the risk of cancer, but this was not significant (HRs = 1.54, 95% CI: 0.74–3.22). No statistically significant association was observed for gastric cardia cancer, rectal cancer, liver cancer, pancreatic cancer, multiple myeloma, ovarian cancer, meningioma and thyroid cancer. None of the above changed after exclusion of incident cases that occurred within the first 3 years of follow-up (Table 2).

In addition, we conducted sensitivity analysis excluding any observations that had missing values for confounders (n = 21,952), but the results remained unchanged (Appendix 1).

Table 3 shows the multivariate-adjusted HR and 95% CI for obesity-related cancer and cancers at individual sites according to the categories of weight change since age 20 in men. For men, after adjustment for confounding variables, weight gain was not associated with an increased risk of obesity-related cancer (moderate weight gain; HRs = 1.04, 95% CI: 0.91–1.18, high weight gain; HRs = 1.06, 95% CI: 0.94–1.21, P for weight gain trend = 0.23). Furthermore, we observed that weight gain tended to be associated with an increased risk of colon cancer and gallbladder cancer, although the association was not significant. For colon cancer, there was a positive association between the high weight gain category and the risk of cancer, but this was not significant (HRs = 1.22, 95% CI: 0.99–1.51). For gallbladder cancer, as well as for colon cancer, high weight gain was associated with an increased risk, but this was not significant (HRs = 1.53, 95% CI: 0.72–3.25). No statistically significant association was observed for esophageal cancer, gastric cardia cancer, rectal cancer, liver cancer, pancreatic cancer, multiple myeloma, kidney cancer, meningioma or thyroid cancer.

We further conducted stratified analysis according to BMI at age 20 to assess whether the association between weight change and the risk of obesity-related cancer differed between subjects who were of normal weight and overweight at age 20 in women. Table 4 shows the multivariate-adjusted HR for obesity-related cancer incidence according to BMI at age 20 and weight change categories in women. A positive association between weight gain and the risk of obesity-related cancer was consistently observed. In women whose BMI at age
Table 2. Multivariate-adjusted HRs and 95% CIs of obesity-related cancer according to weight change since age 20 among women (n = 40,422)

| Weight change since age 20 (kg) | Person years | Number of cases | Age adjusted HR (95% CI) | Multivariate-adjusted HR1 | Number of cases (excluding cases <3 years) | Multivariate-adjusted HR2 | Cancer at individual sites | Number of cases | Age adjusted HR (95% CI) | Multivariate-adjusted HR1 | Number of cases (excluding cases <3 years) | Multivariate-adjusted HR2 |
|--------------------------------|--------------|-----------------|--------------------------|--------------------------|---------------------------------------------|--------------------------|---------------------------|-----------------|--------------------------|--------------------------|---------------------------------------------|--------------------------|
| Loss <−2.0                    | 129,703      | 459             | 0.95 (0.83–1.08)         | 0.93 (0.81–1.07)         | 376                                         | 0.94 (0.81–1.09)         | Esophageal cancer       | 16              | 1.40 (0.63–3.11)         | 1.55 (0.67–3.55)         | 11                                          | 1.09 (0.44–2.70)         |
| Stable −2.0 to +4.0           | 154,128      | 463             | 1.10 (0.97–1.25)         | 1.00 (0.81–1.07)         | 392                                         | 1.00 (0.44–2.70)         | Gastric cardia cancer  | 9               | 0.85 (0.34–2.12)         | 0.91 (0.35–2.38)         | 10                                          | 1.09 (0.44–2.70)         |
| Moderate gain +4.1 to +9.0    | 133,144      | 450             | 1.29 (1.14–1.46)         | 1.28 (0.68–3.47)         | 389                                         | 1.39 (0.61–3.19)         | Colorectal cancer      | 168             | 1.02 (0.82–1.27)         | 1.01 (0.80–1.27)         | 146                                         | 0.79 (0.25–2.53)         |
| High gain > +9.0              | 134,763      | 544             | 1.29 (1.14–1.47)         | 1.28 (0.55–2.98)         | 454                                         | 0.95 (0.39–2.33)         | Colon cancer           | 122             | 1.01 (0.78–1.31)         | 0.97 (0.74–1.27)         | 108                                         | 0.79 (0.25–2.53)         |
|                                |              |                 |                          |                          |                                             |                          |                           |                 |                          |                          |                                             |                           |
| P for weight gain trend        |              |                 |                          | 0.01                     |                                             | 0.01                     |                           |                 | 0.64                     | 0.41                     |                                             | 0.98                     |

(Continues)
Table 2. Continued

| Weight change since age 20 (kg) | Multivariate-adjusted HR2 (95% CI) | Rectal cancer | Liver cancer | Gallbladder cancer | Pancreatic cancer | Multiple myeloma |
|--------------------------------|-----------------------------------|---------------|-------------|-------------------|-----------------|------------------|
| loss ≤ −2.0                   | 0.99 (0.74–1.31)                  | 1.00 (ref)    | 1.09 (0.82–1.44) | 1.31 (1.00–1.72) | 0.10            |
| stable −2.0 to +4.0            |                                   | 1.00 (ref)    | 1.09 (0.82–1.44) | 1.31 (1.00–1.72) | 0.10            |
| moderate gain +4.1 to +9.0     |                                   | 1.00 (ref)    | 1.09 (0.82–1.44) | 1.31 (1.00–1.72) | 0.10            |
| high gain > +9.0               |                                   | 1.00 (ref)    | 1.09 (0.82–1.44) | 1.31 (1.00–1.72) | 0.10            |
| P for weight gain trend        |                                   |               |              |                   |                 |
| Number of cases                | 48                                | 48            | 48          | 48                | 48              |
| Age adjusted HR (95% CI)       | 1.01 (0.67–1.50)                  | 1.00 (ref)    | 1.03 (0.69–1.53) | 1.22 (0.83–1.79) | 0.31            |
| Multivariate-adjusted HR1 (95% CI) | 1.10 (0.73–1.68)                 | 1.00 (ref)    | 0.99 (0.66–1.49) | 1.10 (0.74–1.63) | 0.56            |
| Number of cases (excluding cases 3 years) | 39 | 41 | 39 | 44 |                |
| Multivariate-adjusted HR2 (95% CI) | 1.19 (0.75–1.90)                 | 1.00 (ref)    | 1.03 (0.67–1.61) | 1.04 (0.67–1.61) | 0.79            |
| Number of cases                | 46                                | 42            | 24          | 45                |                 |
| Age adjusted HR (95% CI)       | 0.86 (0.57–1.32)                  | 1.00 (ref)    | 0.65 (0.39–1.08) | 1.17 (0.77–1.79) | 0.47            |
| Multivariate-adjusted HR1 (95% CI) | 0.79 (0.51–1.22)                 | 1.00 (ref)    | 0.65 (0.39–1.07) | 1.15 (0.75–1.76) | 0.62            |
| Number of cases (excluding cases 3 years) | 32 | 38 | 22 | 35 |                |
| Multivariate-adjusted HR2 (95% CI) | 0.69 (0.43–1.12)                 | 1.00 (ref)    | 0.65 (0.39–1.11) | 1.00 (0.63–1.58) | 0.87            |
| Number of cases                | 13                                | 15            | 18          | 25                |                 |
| Age adjusted HR (95% CI)       | 0.68 (0.32–1.45)                  | 1.00 (ref)    | 1.37 (0.69–2.71) | 1.82 (0.96–3.46) | 0.07            |
| Multivariate-adjusted HR1 (95% CI) | 0.62 (0.28–1.34)                 | 1.00 (ref)    | 1.41 (0.71–2.81) | 1.90 (0.99–3.65) | 0.04            |
| Number of cases (excluding cases 3 years) | 10 | 13 | 16 | 19 |                |
| Multivariate-adjusted HR2 (95% CI) | 0.56 (0.23–1.32)                 | 1.00 (ref)    | 1.45 (0.70–3.03) | 1.62 (0.63–1.58) | 0.14            |
| Number of cases                | 50                                | 50            | 51          | 42                |                 |
| Age adjusted HR (95% CI)       | 0.85 (0.57–1.26)                  | 1.00 (ref)    | 1.15 (0.78–1.70) | 0.91 (0.61–1.38) | 0.69            |
| Multivariate-adjusted HR1 (95% CI) | 0.77 (0.51–1.17)                 | 1.00 (ref)    | 1.16 (0.78–1.72) | 0.89 (0.58–1.34) | 0.66            |
| Number of cases (excluding cases 3 years) | 43 | 46 | 46 | 35 |                |
| Multivariate-adjusted HR2 (95% CI) | 0.76 (0.49–1.18)                 | 1.00 (ref)    | 1.14 (0.75–1.71) | 0.79 (0.51–1.24) | 0.47            |
| Number of cases                | 37                                | 23            | 17          | 28                |                 |
| Age adjusted HR (95% CI)       | 1.58 (0.93–2.68)                  | 1.00 (ref)    | 0.84 (0.45–1.57) | 1.34 (0.77–2.32) | 0.29            |
| Multivariate-adjusted HR1 (95% CI) | 1.53 (0.89–2.64)                 | 1.00 (ref)    | 0.84 (0.45–1.57) | 1.34 (0.77–2.32) | 0.23            |
| Number of cases (excluding cases 3 years) | 31 | 19 | 17 | 24 |                |
Table 2. Continued

| Weight change since age 20 (kg) | Multivariate-adjusted HR2 (95% CI) | P for weight gain trend |
|---------------------------------|-----------------------------------|-------------------------|
| loss < −2.0                    | 1.61 (0.89–2.92)                 | 0.24                    |
| stable −2.0 to +4.0             | 1.00 (ref)                       |                         |
| moderate gain +4.1 to +9.0      | 1.02 (0.53–1.96)                 |                         |
| high gain > +9.0               | 1.39 (0.76–2.56)                 |                         |

Breast cancer (Postmenopausal)

| Number of cases | Age adjusted HR (95% CI) | Multivariate-adjusted HR1 (95% CI) | Number of cases (excluding cases <3 years) |
|-----------------|--------------------------|-----------------------------------|-------------------------------------------|
| 48              | 0.79 (0.66–1.16)         | 0.78 (0.53–1.17)                  | 38                                        |
| 59              | 1.00 (ref)               | 1.00 (ref)                        | 52                                        |
| 83              | 1.60 (1.14–2.23)         | 1.62 (1.16–2.27)                  | 69                                        |
| 96              | 1.79 (1.29–2.47)         | 1.88 (1.35–2.61)                  | 82                                        |

Endometrioid cancer

| Number of cases | Age adjusted HR (95% CI) | Multivariate-adjusted HR1 (95% CI) | Number of cases (excluding cases <3 years) |
|-----------------|--------------------------|-----------------------------------|-------------------------------------------|
| 10              | 0.51 (0.24–1.08)         | 0.46 (0.21–1.00)                  | 7                                         |
| 21              | 1.00 (ref)               | 1.00 (ref)                        | 17                                        |
| 24              | 1.30 (0.72–2.34)         | 1.36 (0.76–2.45)                  | 20                                        |
| 33              | 1.74 (1.01–3.01)         | 1.90 (1.09–3.32)                  | 31                                        |

Ovarian cancer

| Number of cases | Age adjusted HR (95% CI) | Multivariate-adjusted HR1 (95% CI) | Number of cases (excluding cases <3 years) |
|-----------------|--------------------------|-----------------------------------|-------------------------------------------|
| 29              | 1.52 (0.87–2.64)         | 1.62 (0.91–2.90)                  | 23                                        |
| 23              | 1.00 (ref)               | 1.03 (0.56–1.87)                  | 17                                        |
| 20              | 1.01 (0.55–1.84)         | 1.39 (0.73–2.66)                  | 17                                        |
| 30              | 1.49 (0.87–2.57)         | 2.15 (1.18–3.94)                  | 31                                        |

Kidney cancer

| Number of cases | Age adjusted HR (95% CI) | Multivariate-adjusted HR1 (95% CI) | Number of cases (excluding cases <3 years) |
|-----------------|--------------------------|-----------------------------------|-------------------------------------------|
| 13              | 0.98 (0.45–2.14)         | 0.94 (0.42–2.10)                  | 11                                        |
| 13              | 1.00 (ref)               | 1.00 (ref)                        | 11                                        |
| 8               | 0.70 (0.29–1.68)         | 0.73 (0.30–1.75)                  | 7                                         |
| 17              | 1.43 (0.70–2.95)         | 1.54 (0.74–3.22)                  | 15                                        |

Meningioma

| Number of cases | Age adjusted HR (95% CI) | Multivariate-adjusted HR1 (95% CI) | Number of cases (excluding cases <3 years) |
|-----------------|--------------------------|-----------------------------------|-------------------------------------------|
| 3               | 1.69 (0.28–10.26)        | 2.35 (0.36–15.37)                 | 3                                         |
| 2               | 1.00 (ref)               | 1.00 (ref)                        | 2                                         |
| 7               | 3.99 (0.83–19.20)        | 3.89 (0.80–18.91)                 | 7                                         |
| 2               | 1.12 (0.16–7.93)         | 1.02 (0.14–7.36)                  | 2                                         |

Number of cases (excluding cases <3 years)

| Multivariate-adjusted HR2 (95% CI) | (Continues) |

Obesity-related cancer in Japan

Int. J. Cancer: 144, 967–980 (2019) © 2018 The Authors. International Journal of Cancer published by John Wiley & Sons Ltd on behalf of UICC
20 had been <25.0 kg/m², high weight gain was significantly associated with an increased risk of obesity-related cancer (moderate weight gain; HRs = 1.08, 95% CI: 0.94–1.23, high weight gain; HRs = 1.25, 95% CI: 1.10–1.43). Similarly, we found that weight gain was associated with an increased risk of obesity-related cancer in women whose BMI at age 20 had been ≥25.0 kg/m² (moderate weight gain; HRs = 1.24, 95% CI: 0.79–1.95, high weight gain; HRs = 1.28, 95% CI: 0.76–2.17). However, no statistically significant effect modifications between weight gain since age 20 and BMI at age 20 were observed (p-value for weight gain interaction = 0.42).

### Discussion

Our study of Japanese women demonstrated an association between weight gain since age 20 and an increased risk of obesity-related cancer both generally, and for colon cancer, postmenopausal breast cancer, and endometrial cancer. Moreover, weight loss since age 20 tended to be associated with a decreased risk of endometrial cancer. No statistically significant association was observed for esophageal cancer, gastric cardia cancer, rectal cancer, liver cancer, gallbladder cancer, pancreatic cancer, multiple myeloma, ovarian cancer, kidney cancer, meningioma and thyroid cancer. By contrast, our study found that weight change since age 20 was not significantly associated with the incidence of obesity-related cancer among Japanese men.

Many previous studies of obesity-related cancer have shown that weight gain during adulthood was associated with an increased risk of cancers, such as postmenopausal breast cancer and endometrial cancer in women, and the present findings were consistent with those studies. An association between weight gain during adulthood and ovarian cancer, kidney cancer, pancreatic cancer, and esophageal cancers in women has also been reported. However, our results were not consistent with those previous findings. Meanwhile, in men, many previous studies have reported an association between weight gain and the risk of obesity-related cancers, such as esophageal, gastric cardia, colorectal, pancreatic, and kidney cancer. We found that weight gain tended to be associated with an increased risk of colon cancer and gallbladder cancer among men, although this was not significant. Furthermore, stratified analysis according to BMI at age 20 suggested that weight gain since age 20 was associated with an increased risk of obesity-related cancer for any of the categories of BMI at age 20 in women.

Our study suggested that weight gain since age 20 may also affect an increased risk of obesity-related cancer in Japanese women who have less severe and a low incidence of obesity than western women. In our study, we also observed a significant association for obesity-related cancer at several sites, such as postmenopausal breast cancer and endometrial cancer. A meta-analysis including total of 50 studies reported an association between weight gain during adulthood and the risk of 10 adiposity-related cancers, and weight gain was associated with an increased risk of postmenopausal breast cancer and endometrial cancer. With regard to both postmenopausal breast cancer and endometrial cancer, many previous studies of Japanese and Chinese women have already demonstrated a positive association between weight gain during adulthood and the risk of cancer, and the present results are consistent.
Table 3. Multivariate-adjusted HRs and 95% CIs of obesity-related cancer according to weight change since age 20 among men (n = 38,321)

| Weight change since age 20 (kg) | Number of subjects | Obesity-related cancer | Number of cases | Age adjusted HR (95% CI) | Multivariate-adjusted HR1 (95% CI) | Number of cases (excluding cases <3 years) | Multivariate-adjusted HR2 (95% CI) | Cancer at individual sites |
|--------------------------------|--------------------|------------------------|----------------|--------------------------|-----------------------------------|------------------------------------------|-----------------------------------|----------------------------|
| < −2.9                         | 10,361             | Person years           | 124,378        | 1.03 (0.92–1.14)         | 0.98 (0.88–1.09)                  | 671                                      | 0.99 (0.88–1.12)                 | Esophageal cancer             |
| −2.9 to +3.0                   | 10,237             |                        | 137,811        | 1.00 (ref)               | 1.00 (ref)                        | 535                                      | 1.04 (0.91–1.18)                | Number of cases              |
| moderate gain                  | 8,439              |                        | 115,948        | 1.02 (0.91–1.14)         | 1.03 (0.91–1.15)                  | 444                                      | 1.06 (0.94–1.21)                | Age adjusted HR              |
| high gain                      | 9,284              |                        | 128,024        | 1.03 (0.92–1.15)         | 1.03 (0.91–1.15)                  | 490                                      | 0.23                             | Multivariate-adjusted HR     |
| P for weight gain trend        |                    |                        |                |                          |                                   |                                          |                                   |                            |

(Continues)
Table 3. Continued

| Weight change since age 20 (kg) | P for weight gain trend |
|-------------------------------|-------------------------|
| Number of cases (excluding cases <3 years) | Rectal cancer |
| 172 147 134 167 | 0.88 (0.70–1.12) 1.00 (ref) 1.13 (0.89–1.43) 1.31 (1.04–1.64) 0.01 |
| Multivariate-adjusted HR1 (95% CI) | 0.80 (0.60–1.05) 1.00 (ref) 1.06 (0.81–1.39) 0.86 (0.65–1.15) 0.38 |
| Number of cases (exceeding cases <3 years) | 94 92 77 78 |
| Multivariate-adjusted HR2 (95% CI) | 0.87 (0.64–1.19) 1.00 (ref) 1.03 (0.76–1.40) 0.95 (0.70–1.30) 0.78 |
| Liver cancer |
| 138 86 74 95 | 1.29 (0.98–1.70) 1.00 (ref) 1.08 (0.79–1.47) 1.29 (0.96–1.72) 0.09 |
| Multivariate-adjusted HR1 (95% CI) | 1.14 (0.86–1.52) 1.00 (ref) 1.06 (0.77–1.44) 1.27 (0.95–1.71) 0.12 |
| Number of cases (excluding cases <3 years) | 98 68 63 83 |
| Multivariate-adjusted HR2 (95% CI) | 1.11 (0.80–1.54) 1.00 (ref) 1.13 (0.80–1.59) 1.39 (1.00–1.93) 0.04 |
| Gallbladder cancer |
| 29 13 10 16 | 1.56 (0.80–3.04) 1.00 (ref) 0.99 (0.43–2.25) 1.51 (0.72–3.13) 0.25 |
| Multivariate-adjusted HR1 (95% CI) | 1.56 (0.78–3.11) 1.00 (ref) 1.01 (0.44–2.32) 1.53 (0.72–3.25) 0.32 |
| Number of cases (excluding cases <3 years) | 26 11 7 14 |
| Multivariate-adjusted HR2 (95% CI) | 1.65 (0.79–3.46) 1.00 (ref) 0.83 (0.32–2.16) 1.59 (0.71–3.57) 0.29 |
| Pancreatic cancer |
| 83 62 43 49 | 1.04 (0.74–1.45) 1.00 (ref) 0.87 (0.59–1.29) 0.93 (0.64–1.36) 0.72 |
| Multivariate-adjusted HR1 (95% CI) | 1.08 (0.76–1.53) 1.00 (ref) 0.86 (0.58–1.27) 0.90 (0.61–1.33) 0.82 |
| Number of cases (excluding cases <3 years) | 75 56 39 43 |
| Multivariate-adjusted HR2 (95% CI) | 1.12 (0.77–1.62) 1.00 (ref) 0.86 (0.57–1.30) 0.87 (0.57–1.30) 0.67 |
| Multiple myeloma |
| 49 36 25 22 | 1.10 (0.71–1.71) 1.00 (ref) 1.28 (0.81–2.03) 0.71 (0.81–2.03) 0.28 |
| Multivariate-adjusted HR1 (95% CI) | 1.12 (0.70–1.77) 1.00 (ref) 1.23 (0.77–1.95) 0.66 (0.39–1.14) 0.11 |

(Continues)
with those findings. In addition, our study found that weight loss since age 20 tended to be associated with a decreased risk of endometrial cancer, and this association was observed even after exclusion of incident cases that occurred within the first 3 years of follow-up. Dougan et al. have reported that weight loss is associated with a return to normal sex hormone-binding globulin levels, suggesting that the converse is true for weight gain. Our findings suggest that weight loss during adulthood is effective for prevention of endometrial cancer.

For colon cancer, a meta-analysis of 10 prospective cohort studies and two case-control studies failed to find a significant association between weight gain and the risk of colon cancer. A previous study of Chinese women also found that there was no significant association. Unlike those studies, our study observed an association between weight gain since age 20 and an increased risk of colon cancer. A protective effect of exogenous estrogens, such as oral contraceptives and postmenopausal hormone therapy, against colorectal cancer has been pointed out previously. Japanese women are less affected by exogenous estrogens because fewer use oral contraceptives and hormone replacement therapy than women in Western countries, and this may have accounted for the increased risk of colon cancer found in the present study.
In view of the paucity of data for Asian populations, further studies of the association between weight gain during adulthood and the risk of colon cancer will be needed. In addition, studies of the association between weight gain during adulthood and the risk of renal cancer and endometrial cancer.

Adipokines, which are hormones produced from adipose tissue, are reported to play a role in the association between obesity and cancer incidence; for example, an increased serum level of leptin has been associated with the risk of colorectal cancer, breast cancer and prostate cancer. For postmenopausal breast cancer and endometrial cancer, obesity leads to increased serum levels of estradiol through the action of aromatase in adipose tissue, thus affecting the risk of these cancers.

Our study had several strengths. First, it had a prospective design and a long follow-up period. Second, we adjusted for various potential confounders, including lifestyle habits, history of disease and hormonal factors. Third, using stratified analysis, we assessed whether the risk of obesity-related cancer associated with weight change differed between subjects who were of normal weight, and those who were overweight.

Our study also had several limitations. First, data on weight were self-reported. In our data, correlations between measured values and self-reported values of weight at baseline were high. On the other hand, since there were no data for measured values of weight at age 20, we were unable to evaluate the validity of those data. Second, there may have been residual confounding due to factors that were not measurable, for example genomic data and estrogen receptor status. Finally, in the analysis of esophageal cancer and kidney cancer, the number of cases was lower than for other obesity-related cancers, and thus the statistical power was insufficient.

Our study has shown that weight gain since age 20 was associated with an increased risk of obesity-related cancer among this cohort of Japanese women. These results provide

### Table 4. Multivariate-adjusted HRs and 95% CIs of obesity-related cancer according to weight change since age 20 stratified by BMI at age 20 in women

| Weight change since age 20 (kg) | BMI at age 20 | Number of cases | Number of subjects | Multivariate-adjusted HR (95% CI) | P for weight gain trend | P for weight gain interaction |
|-------------------------------|--------------|----------------|-------------------|----------------------------------|------------------------|-----------------------------|
| Loss (~2.0)                  | < 25.0 kg/m² | 285            | 6,305             | 0.96 (0.83–1.12)                  | 0.10                   | 0.99                        |
| Stable (~2.0 to +4.0)        |              | 416            | 10,130            | 1.00 (ref)                        | 0.94                   | 0.99                        |
| Moderate gain (+4.1 to +9.0) | ≥ 25.0 kg/m² | 418            | 9,035             | 1.08 (0.94–1.23)                  | 1.25 (1.10–1.43)       | <0.01                       |
| High gain (> +9.0)           |              | 524            | 9,427             | 1.25 (1.10–1.43)                  | 1.43 (1.28–1.61)       | <0.01                       |

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; ref, reference.

1. Multivariate-adjusted HR: adjusted for age (continuous variable), history of diabetes mellitus (yes, no), level of education (junior high school or less, high school, and college or higher, missing), smoking status (never, former, current, missing), alcohol consumption (never, former, current, missing), time spent walking per day (<0.5 h, 0.5–1.0 h, >1.0 h, or missing), history of any cancer in the family (yes, no), number of birth (0, 1, 2, 3, missing), age at menarche (≤13 yr, 14–15 yr, ≥16 yr, missing), menopausal status (premenopausal, postmenopausal, missing), use of oral contraceptives (never, ever, missing), and any significant, risk. A previous study of Chinese women has reported that each 5-kg increase in body weight was associated with an increased risk of esophageal cancer, which may have been residual confounding due to factors that were not measurable, for example genomic data and estrogen receptor status. Finally, in the analysis of esophageal cancer and kidney cancer, the number of cases was lower than for other obesity-related cancers, and thus the statistical power was insufficient.

Our study has shown that weight gain since age 20 was associated with an increased risk of obesity-related cancer among this cohort of Japanese women. These results provide
additional evidence to indicate an association between weight change during adulthood and the incidence of obesity-related cancers in a population of Asian women, who are known to have less severe, and a lower incidence of, obesity than women in western populations. These results also suggest the importance of maintaining a standard body weight for prevention of obesity-related cancers among Japanese women.

Acknowledgements
The authors gratefully acknowledged the assistance of Yoshiko Nakata and Mami Takahashi, Tohoku University Graduate School of Medicine.

Funding
Our study was supported by the National Center Cancer Research and Development Fund (27-A-4).

References
1. Zheng Y, Manson JE, Yuan C, et al. Associations of Weight Gain From Early to Middle Adulthood With Health Outcomes Later in Life. JAMA 2017;318:255–69.
2. Kyrぎou M, Kalliaίa I, Markozannes G, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ 2017; 356:j477.
3. Islami F, Godin Sauer A, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin 2018;68:31–54.
4. Kuem N, Greenwood DC, Lee DH, et al. Adult Weight Gain and Adiposity-Related Cancers: A Dose-Response Meta-Analysis of Prospective Observational Studies. J Natl Cancer Inst 2015; 107:dx0088.
5. Parr CL, Batty GD, Lam TH, et al. Body-mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: Pooled analyses of 424 519 participants. Lancet Oncol 2010;11: 741–52.
6. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016;387:1377–96.
7. Liu Y, Warren Andersen S, Wen W, et al. Prospective cohort study of general and central obesity, weight change trajectory and risk of major cancers among Chinese women. Int J Cancer 2016;139:1461–70.
8. de Mutsert R, Sun Q, Willet WC, et al. Overweight in early adulthood, adult weight change, and risk of type 2 diabetes, cardiovascular diseases, and certain cancers in men: a cohort study. Am J Epidemiol 2014;179:1353–650.
9. Fukao A, Tsuibo Y, Komatsu S, et al. A Cohort Study on the Relation of Lifestyle, Personality and Biologic Markers to Cancer in Miyagi, Japan: Study Design, Response Rate and Profiles of the Cohort Subjects. J Epidemiol 1995;5:153–7.
10. Tsujo I, Nishino Y, Ohkubo T, et al. A prospective cohort study on National Health Insurance beneficiaries in Ohsaki, Miyagi Prefecture, Japan: study design, profiles of the subjects and medical cost during the first year. J Epidemiol 1998;8: 258–63.
11. Sugiyama K, Sugawara Y, Tomata Y, et al. The association between coffee consumption and bladder cancer incidence in a pooled analysis of the Miyagi Cohort Study and Ohsaki Cohort Study. Eur J Cancer Prev 2017;26:125–30.
12. Kuriyama S, Tsuji I, Ohkubo T, et al. Medical care expenditure associated with body mass index in Japan: the Ohsaki Study. Int J Obes Relat Metab Disord 2002;26:1069–74.
13. Forman D, Bray F, Brewster DH, Gomez Mbalawa C, Kohler B, Piñeros M, Stelsonova-Foucher E, Swaminathan R, Ferlay J. Cancer incidence in five continents, vol. X, Lyon: International Agency for Research on Cancer, 2014. 1365p.
14. World Cancer Research Fund / American Institute for Cancer Research. Diet, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective, Washington, DC: AICR, 2007:p. 517.
15. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body Fatness and Cancer—Viewpoint of the IARC Working Group. N Engl J Med 2016;375: 794–8. https://doi.org/10.1056/NEJMe1606602.
16. Kyrぎou M, Kalliaίa I, Markozannes G, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ 2017; 356:j477.
17. Suzuki R, Iwasaki M, Inoue M, et al. Body weight at age 20 years, subsequent weight change and breast cancer risk defined by estrogen and progesterone receptor status—the Japan public health center-based prospective study. Int J Cancer 2011; 129:124–24.
18. Suzuki S, Kojima M, Tokudome S, et al. Obesity / Weight Gain and Breast Cancer Risk: Findings From the Japan Collaborative Cohort Study for the Evaluation of Cancer Risk. J Epidemiol 2013; 23:139–45.
19. Nitta J, Nojima M, Ohnishi H, et al. Weight gain and alcohol drinking associations with breast cancer risk in Japanese postmenopausal women - results from the Japan collaborative cohort (JACC) study. Asian Pacific J Cancer Prev 2016;17:1437–43.
20. World Cancer Research Fund / American Institute for Cancer Research. Diet, nutrition, physical activity and breast cancer 2017. 2017 120p, http://www.aicr.org/continuous-update-project/reports/breast-cancer-report-2017.pdf
21. Dougan MM, Hankinson, SE, De Vl, et al. Prospective study of body size throughout the life-course and the incidence of endometrial cancer among premenopausal and postmenopausal women. Int J Cancer 2015;137: 625–37.
22. Schlesinger S, Lieb W, Koch M, et al. Body weight gain and risk of colorectal cancer A systematic review and meta-analysis of observational studies. Obes Rev 2015;16:607–19.
23. Chen Q, Wang J, Yang J, et al. Association between adult weight gain and colorectal cancer: A dose-response meta-analysis of observational studies. Int J Cancer 2015;136:2880–9.
24. Chlebowski RT, Wactawski-Wende J, Itensbaugh C, et al. Estrogen plus Progestin and Colorectal Cancer in Postmenopausal Women. N Engl J Med 2004;350:991–1004.
25. Nelson HD, Humphrey LL, Nygren P, et al. Postmenopausal Hormone Replacement Therapy: scientific review. JAMA 2002;288: 872–81.
26. Song M, Hu FB, Spiegelman D, et al. Adulthood Weight Change and Risk of Colorectal Cancer in the Nurses’ Health Study and Health Professionals Follow-up Study. Cancer Prev Res (Phila) 2015:8: 620–7.
27. Steins Bischop CN, van Gil CH, Emaus MJ, et al. Weight change later in life and colon and rectal cancer risk in participants in the EPIC-PANACEA study. Am J Clin Nutr 2014;99: 139–47.
28. Aleksandrova K, Pischon T, Buijse B, et al. Adult weight change and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition. Eur J Cancer; 2013; 49:3526–36.
29. Ozr I, Matsuo K, Waki K, et al. Alcohol Drinking and Esophageal Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence Among the Japanese Population. Ipn J Clin Oncol 2011;41:877–92.
30. van Kruisjijk RC, van der Wall E, Visseren FL. Obesity and cancer: The role of dysfunctional adipose tissue. Cancer Epidemiol Biomarkers Prev 2009;18:2569–78.
31. Basen-Engquist KI, Chang M. Obesity and Cancer Risk: Recent Review and Evidence. Curr Oncol Rep 2011; 13: 71–6.
32. De Pergola G, Silvestris F. Obesity as a major risk factor for cancer. J Obes 2013;2013:291546.