Body Mass Index and Weight Change During Adulthood Are Associated With Increased Mortality From Liver Cancer: The JACC Study

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ABSTRACT

Background: We investigated the association of baseline body mass index (BMI) and weight change since age 20 years with liver cancer mortality among Japanese.

Methods: The data were obtained from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study). A total of 31 018 Japanese men and 41 455 Japanese women aged 40 to 79 years who had no history of cancer were followed from 1988 through 2009.

Results: During a median 19-year follow-up, 527 deaths from liver cancer (338 men, 189 women) were documented. There was no association between baseline BMI and liver cancer mortality among men or men with history of liver disease. Men without history of liver disease had multivariable hazard ratios (HR) of 1.95 (95%CI, 1.07–3.54) for BMI less than 18.5 kg/m² and 1.65 (1.05–2.60) for BMI of 25 kg/m² or higher, as compared with a BMI of 21.0 to 22.9 kg/m². BMI was positively associated with liver cancer mortality among women and women with history of liver disease. Weight change since age 20 years was positively associated with liver cancer mortality among women regardless of history of liver disease. Women with history of liver disease had a multivariable HRs of 1.96 (1.05–3.66) for weight gain of 5.0 to 9.9 kg and 2.31 (1.18–4.49) for weight gain of 10 kg or more, as compared with weight change of −4.9 to 4.9 kg.

Conclusions: Both underweight (BMI <18.5 kg/m²) and overweight (BMI ≥25 kg/m²) among men without history of liver disease, and weight gain after age 20 (weight change ≥5 kg) among women with history of liver disease, were associated with increased mortality from liver cancer.

Key words: weight change; body mass index; liver cancer; mortality; prospective study; epidemiology

INTRODUCTION

According to the World Health Organization, liver cancer was responsible for 700 000 deaths worldwide in 2008 and was the third leading cause of cancer death after lung cancer (1.4 million deaths) and stomach cancer (740 000 deaths).1 Meta-analyses2 and systematic reviews3,4 reported associations between excess body weight and higher risk of liver cancer among both men and women. However, few studies have examined the association of weight change with risk of liver cancer.5,6

In a population with a high prevalence of chronic infection with hepatitis C virus (HCV),7 it is important to determine whether body weight and weight change are associated with risk of liver cancer irrespective of viral infection (a major contributor to liver cancer).8 Thus, we chose to examine these associations in relation to the presence or absence of liver disease.

We conducted a prospective study of the associations of BMI at age 20 years, BMI at baseline, and weight change since age 20 years with mortality from liver cancer in a large cohort of Japanese men and women aged 40 to 79 years at baseline.
Methods

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study) was initiated during 1988–1990. Self-administered questionnaires with items on lifestyle and medical history of cancer, liver disease, gallbladder disease, diabetes mellitus, other diseases, and blood transfusion were completed by 110,588 people (46,398 men and 64,190 women) aged 40 to 79 years from 45 communities across Japan. Among them, 73,463 people (31,321 men and 42,142 women) provided self-reported data on weight and height at baseline and weight at age 20 years. We excluded 303 men and 687 women with a reported history of cancer at baseline, leaving 31,018 men and 41,455 women for the present analysis.

Mortality surveillance was conducted systematically by reviewing death certificates. Participants were followed-up until death or until they moved away from their original community, through the end of 2009 (follow-up of 4, 4, and 2 communities finished at the end of 1999, 2003, and 2008, respectively). The median follow-up period was 19.0 years. Underlying cause of death according to the International Classification of Diseases (ICD-10) was obtained centrally from the Ministry of Health and Welfare. Death from liver cancer was defined as ICD-10 codes C22.0 to C22.9. The present study was approved by the Ethical Committees of Nagoya University and Osaka University.

Variables

Weight (kg) and height (m) were self-reported at baseline. BMI was calculated as weight (kg) divided by height (m) squared and then divided into 5 categories (<18.5, 18.5–20.9, 21.0–22.9, 23.0–24.9, and ≥25 kg/m²); a BMI of 21.0–22.9 kg/m² served as the reference group. Weight change since age 20 years was calculated by subtracting weight at age 20 years from weight at baseline. Weight change was grouped into 5 categories (<10, –9.9 to –5.0, –4.9 to 4.9, 5.0 to 9.9, and ≥10 kg); stable weight (–4.9 to 4.9 kg) was used as the reference group. We asked the subjects, “Do you have a history of physician-diagnosed liver disease such as hepatitis?” Potential confounding variables were smoking status (never, former, current smoker of <20 cigarettes per day, and current smoker of ≥20 cigarettes per day), ethanol consumption (never, former, current [1–22, 23–45, 46–68, and ≥69 g per day]), hours of walking (<0.5, 0.5, 0.6–0.9, and ≥1.0 h per day), hours of exercise (<1, 1–2, 3–4, and ≥5 per week), frequency of coffee intake (seldom, 1–2 cups per month, 1–2 cups per week, 3–4 cups per week, and almost every day), frequency of fish intake (seldom, 1–2 times per month, 1–2 times per week, 3–4 times per week, and almost every day), education level (<10, 10–12, 13–15, and ≥16 years), area of residence (Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyushu regions), and histories of diabetes mellitus, gallbladder disease, and blood transfusion.

A positive history of liver disease, with or without present treatment, was also considered.

Statistical analyses

Sex-specific, age-adjusted means (SD) and proportions of potential confounding factors were calculated by a general linear model.

Cox proportional hazards models were used to calculate sex-specific age- and multivariable-adjusted hazard ratios (HRs) and 95% CIs for liver cancer mortality associated with BMI at baseline, BMI at age 20, and weight change since age 20 years. Multivariable-adjusted Cox modeling included continuous age at baseline, smoking status, ethanol consumption, hours of walking and exercise, frequencies of coffee and fish intake, education level, area of residence, and histories of diabetes mellitus, gallbladder disease, blood transfusion, and positive history of liver disease with or without present treatment. For the analysis of weight change, the model was further adjusted for height (continuous) and weight (continuous) at age 20. The P values for linear trends were calculated by assigning the median value of each category to corresponding individuals and treating it as a continuous variable in the model. Testing for trends was performed across the upper 3 categories of BMI (ie, ≥21.0 kg/m²) and weight change (≥–5 kg). Testing for overall trends was performed across all 5 categories of BMI and weight change. Multivariable-adjusted HRs were also calculated for a 5-kg increment of weight change if necessary. To identify effect modification of the association between body weight or weight change and risk of liver cancer, additional stratified analyses were conducted based on the presence or absence of history of liver disease at baseline in men and women.

Because lower body weight and weight loss could be due to preclinical liver cancer, and higher body weight or weight gain could be a consequence of ascites associated with liver cancer, we excluded early deaths from liver cancer (ie, those that occurred during the first 10 years after baseline) to reduce reverse causation in our analyses.

All analyses were conducted using SAS version 9.1.3 Service Pack 4 (SAS Institute, Cary, North Carolina, USA). Two-tailed probability values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Mean age at baseline, BMI at baseline, and weight change since age 20 years, in men and women, were 57.2 (10.2) and 56.8 (9.8) years, 22.7 (2.8) and 23.0 (3.2) kg/m², and 1.7 (8.9) and 2.7 (8.5) kg, respectively (Table 1). We identified 527 deaths (338 men, 189 women) from liver cancer during 1,168,909 follow-up person-years (486,745 in men, 682,164 in women).

There was no association between baseline BMI and mortality from liver cancer among men or men with liver
disease. In contrast, among men without a history of liver disease the association was U-shaped: as compared with a BMI of 21.0 to 22.9 kg/m², the multivariable HR (95% CI) was 1.95 (1.07–3.54) among those with a BMI less than 18.5 kg/m² and 1.65 (1.05–2.60) among those with a BMI of 25 kg/m² or higher. BMI was positively associated with mortality from liver cancer among women (P = 0.04 for overall trend) and women with a history of liver disease (P = 0.02 for overall trend), but not among women without a history of liver disease (P = 0.23 for overall trend) (Table 2).

No associations were found for BMI at age 20 in either sex (Table 3). Weight change since age 20 years was positively associated with mortality from liver cancer among women, women with a history of liver disease, and women without a history of liver disease (P = 0.01, 0.02, and 0.03, respectively). Among women with a history of liver disease, weight gain of 5.0 to 9.9 kg was associated with a multivariable HR of 1.96 (95% CI, 1.05–3.66) for mortality from liver cancer, and weight gain of 10 kg or more was associated with an HR of 2.31 (1.18–4.49), as compared with women with a weight change of −4.9 to 4.9 kg. The multivariable HRs associated with a 5-kg increment in weight were 1.11 (1.00–1.28), 1.14 (1.00–1.30), and 1.17 (1.00–1.36) among women, women with a history of liver disease, and women without a history of liver disease, respectively. There was no association between weight change and mortality from liver cancer in men (Table 4). The results of the analyses that excluded early deaths from liver cancer were essentially identical. Among overweight men without a history of liver disease the multivariable HR was 1.67 (0.90–3.12), versus a BMI of 21.0 to 22.9 kg/m². Analysis of the overall trend for BMI categories among women and women with and without a history of liver disease yielded P values of 0.009, 0.02, and 0.06, respectively, in the multivariable model. Analysis of overall trend for weight change in women, women with a history of liver disease, and women without a history of liver disease yielded P values of 0.007, 0.03, and 0.02, respectively (data not shown in table).

DISCUSSION

In this large-scale prospective study of Japanese men and women, we observed that overweight and underweight were associated with liver cancer mortality in men without liver disease and that weight change positively correlated with liver cancer mortality in women, regardless of history of liver disease.

Our results showing an excess risk of mortality from liver cancer in overweight men without a history of liver disease are in line with those from studies of men from the general populations of East Asian countries, European countries, and the United States. Among women, we found a weak positive association between BMI categories and liver cancer mortality, which supports previous findings for women from...
The positive association between BMI and liver cancer risk in the general populations of the United States\textsuperscript{12} and Korea.\textsuperscript{11} The positive association between BMI and liver cancer risk in women with a history of liver disease was in line with previous findings in patients with liver disease, namely, that a higher baseline BMI was predictive of incident liver cancer.\textsuperscript{13–19}

Two prospective studies investigated the association of weight change during adulthood with liver cancer risk.\textsuperscript{5,6} A study of 107 815 Swedish men with a small number of incident liver cancers ($n = 55$) reported no association between weight gain and risk of liver cancer, as compared with stable weight.\textsuperscript{5} Another study of 191 927 European men and women found a positive dose-dependent association between weight change after age 20 years and risk of incident liver cancer.\textsuperscript{6} However, in sex-specific analysis, there was a positive association only among men, perhaps due to the small number of incident liver cancers among women ($n = 54$). Nonetheless, we found a positive relationship between weight change and liver cancer mortality in women, regardless of history of liver disease, which confirms previous findings among men. Because the

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### Table 2. Sex-specific, age- and multivariable-adjusted hazard ratios and 95% CIs for mortality from liver cancer according to body mass index (BMI) categories at baseline (JACC study, 1988–2009)

| BMI at baseline (kg/m\(^2\)) | P for trend\(^a\) | P for overall trend\(^b\) |
|-----------------------------|---------------|---------------------|
| <18.5                       | 18.5–20.9     | 21.0–22.9           | 23.0–24.9 | ≥25.0 |

#### Men

| No. at risk | No. of person-years | Crude death rate\(^c\) | Age-adjusted HR (95% CI)\(^d\) | Multivariable HR (95% CI)\(^d\) |
|-------------|---------------------|-------------------------|-------------------------------|--------------------------------|
| 1669        | 7116                | 151                     | 1.87 (1.25–2.82)              | 1.42 (0.93–2.15)               |
| 21 231      | 107 857             | 76                      | 1.01 (0.74–1.37)              | 1.04 (0.76–1.42)               |

#### Women

| No. at risk | No. of person-years | Crude death rate\(^c\) | Age-adjusted HR (95% CI)\(^d\) | Multivariable HR (95% CI)\(^d\) |
|-------------|---------------------|-------------------------|-------------------------------|--------------------------------|
| 139         | 544                 | 49                      | 1.28 (0.90–1.82)              | 1.04 (0.74–1.47)               |
| 1376        | 7055                | 30                      | 1.02 (0.75–1.40)              | 0.82 (0.58–1.17)               |

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\(^a\)Test for trend refers to a baseline BMI of ≥21.0 kg/m\(^2\).

\(^b\)Test for overall trend refers to a baseline BMI of <18.5 kg/m\(^2\).

\(^c\)Mortality rate is expressed as rate per 100 000 person-years.

\(^d\)Multivariable adjustment: age, smoking status, alcohol consumption, hours of walking, hours of exercise, frequencies of coffee and fish intake, education level, area of residence, histories of diabetes mellitus, gallbladder disease, blood transfusion, and positive history of liver disease with or without present treatment.
numbers of deaths were relatively small in the first 2 weight-change groups (i.e., \( \leq -10.0 \) and \( -5.0 \) to \(-9.9 \) kg) in the analyses of women in the present study, we examined whether combining the first 2 weight-change groups would alter the results; however, the \( P \) values were very similar for overall trend. We found no association between weight change since age 20 years and risk of liver cancer in men.

The mechanism linking excess body weight or weight gain during adulthood with higher mortality from liver cancer may be mediated via progression of nonalcoholic fatty liver disease (NAFLD), a clinicopathologic condition that encompasses a wide spectrum of liver tissue changes, ranging from steatosis alone to nonalcoholic steatohepatitis, advanced fibrosis, cirrhosis, and, in the most severe cases, liver cancer.\(^20\) Level of obesity was found to be correlated with NAFLD development: a study of 39,151 Japanese adults reported that 12.8% of nonobese subjects (BMI < 25 kg/m\(^2\)), 51.4% of overweight subjects (25 \( \leq \) BMI < 30 kg/m\(^2\)), and 80.4% of highly obese subjects (BMI \( \geq 30 \) kg/m\(^2\)) had fatty liver disease, as determined by abdominal ultrasonography.\(^21\) In addition,

| Table 3. Sex-specific, age- and multivariable-adjusted hazard ratios and 95% CIs for mortality from liver cancer according to body mass index (BMI) categories at age 20 years (JACC study, 1988–2009) |

| BMI at age 20 (kg/m\(^2\)) | Men | Women |
|---------------------------|-----|-------|
| \(<18.5\)                  |     |       |
| No. at risk               | 1805| 4061  |
| No. of person-years       | 28079| 64,811|
| No. of deaths             | 14  | 4  |
| Crude death rate\(^a\)    | 50  | 366  |
| Age-adjusted HR (95% CI)\(^b\) | 0.78 (0.45–1.36) | 0.86 (0.41–1.82) |
| Multivariable HR (95% CI)\(^c\) | 0.74 (0.42–1.29) | 0.91 (0.42–1.97) |

| \(18.5–20.9\)              |     |       |
| No. of person-years       | 148,241 | 127,328 |
| No. of deaths             | 91  | 48  |
| Crude death rate\(^a\)    | 61  | 332  |
| Age-adjusted HR (95% CI)\(^b\) | 0.99 (0.75–1.30) | 0.83 (0.53–1.28) |
| Multivariable HR (95% CI)\(^c\) | 0.89 (0.68–1.18) | 0.68 (0.43–1.07) |

| \(21.0–22.9\)              |     |       |
| No. of person-years       | 164,069 | 141,043 |
| No. of deaths             | 115 | 57  |
| Crude death rate\(^a\)    | 70  | 40  |
| Age-adjusted HR (95% CI)\(^b\) | 1.00 (0.72–1.29) | 1.02 (0.65–1.61) |
| Multivariable HR (95% CI)\(^c\) | 0.92 (0.69–1.24) | 0.98 (0.61–1.56) |

| \(23.0–24.9\)              |     |       |
| No. of person-years       | 97,587 | 83,287 |
| No. of deaths             | 75  | 33  |
| Crude death rate\(^a\)    | 77  | 40  |
| Age-adjusted HR (95% CI)\(^b\) | 0.96 (0.72–1.29) | 1.02 (0.65–1.61) |
| Multivariable HR (95% CI)\(^c\) | 0.91 (0.61–1.56) | 0.75 (0.41–1.35) |

| \(\geq25.0\)                |     |       |
| No. of person-years       | 48,768 | 40,864 |
| No. of deaths             | 43  | 25  |
| Crude death rate\(^a\)    | 88  | 54  |
| Age-adjusted HR (95% CI)\(^b\) | 0.92 (0.72–1.29) | 0.85 (0.58–1.21) |
| Multivariable HR (95% CI)\(^c\) | 0.54 (0.34–0.83) | 0.36 (0.20–0.65) |

| P for trend\(^d\) |     |       |

\(P\) for trend refers to a baseline BMI of \( \geq 21.0 \) kg/m\(^2\).\(^a\)

\(P\) for overall trend refers to a baseline BMI of \(<18.5 \) kg/m\(^2\).\(^b\)

Mortality rate is expressed as rate per 100,000 person-years.\(^c\)

Multivariable adjustment: age, smoking status, ethanol consumption, hours of walking, hours of exercise, frequencies of coffee and fish intake, education level, area of residence, histories of diabetes mellitus, gallbladder disease, blood transfusion, and positive history of liver disease with or without present treatment.\(^d\)
Second, overweight (BMI ≥25 kg/m²) was associated with a 5-fold risk of fibrosis progression in liver during a 1-year period among people with HCV infection, which suggests that overweight increases the risk of liver cancer via progression of liver fibrosis.

Third, it is possible that overweight was confounded by hepatitis C infection. However, according to a nested case-control study of a JACC study subsample of approximately 12,000 adults, BMI tended to be inversely associated with HCV infection. For example, among men without liver disease, the proportion of those with HCV infection was 6.7% for a BMI of 23.0 to less than 25.0 kg/m², 6.9% for a BMI of 21.0 to less than 23.0 kg/m², and 4.7% for a BMI of 25.0 kg/m² or higher. Thus, it is unlikely that the excess risk of mortality from liver cancer in adults with a BMI of 25.0 kg/m² or higher was due to HCV

Table 4. Sex-specific, age- and multivariable-adjusted hazard ratios and 95% CIs for mortality from liver cancer according to categories of weight change since age 20 years to baseline (JACC study, 1988–2009)

| Weight change from age 20 to baseline (kg) | P for trend<sup>a</sup> | P for overall trend<sup>b</sup> |
|-----------------------------------------|-------------------------|-------------------------------|
| **Men**                                 |                         |                               |
| No. at risk                             | 2454                    | 4831                          | 12279                         | 5666                          | 5788  |
| No. of person-years                     | 30,812                  | 70,268                        | 197,516                       | 93,608                        | 94,540 |
| No. of deaths                           | 27                      | 76                            | 124                           | 55                            | 56    |
| Crude death rate<sup>c</sup>            | 88                      | 108                           | 63                            | 59                            | 59    |
| Age-adjusted HR (95% CI)                | 0.94 (0.61–1.43)        | 1.32 (0.99–1.77)              | 1.06 (0.77–1.46)              | 1.09 (0.80–1.50)              | 0.59  | 0.85 |
| Multivariable HR (95% CI)<sup>d</sup>   | 0.68 (0.43–1.08)        | 1.08 (0.80–1.46)              | 1.06 (0.77–1.47)              | 0.98 (0.70–1.37)              | 0.88  | 0.54 |
| **Men with liver disease**              |                         |                               |
| No. at risk                             | 193                     | 390                           | 882                           | 436                           | 537   |
| No. of person-years                     | 1942                    | 4895                          | 12,357                        | 6322                          | 7752  |
| No. of deaths                           | 11                      | 29                            | 49                            | 23                            | 26    |
| Crude death rate<sup>c</sup>            | 566                     | 592                           | 397                           | 364                           | 335   |
| Age-adjusted HR (95% CI)                | 1.09 (0.56–2.12)        | 1.26 (0.79–2.00)              | 1.03 (0.62–1.69)              | 0.97 (0.60–1.56)              | 0.89  | 0.48 |
| Multivariable HR (95% CI)<sup>d</sup>   | 0.59 (0.28–1.23)        | 0.93 (0.56–1.54)              | 1.08 (0.64–1.81)              | 1.03 (0.61–1.72)              | 0.63  | 0.33 |
| **Women**                               |                         |                               |
| No. at risk                             | 1908                    | 3880                          | 10,406                        | 4,818                         | 4,781 |
| No. of person-years                     | 24,969                  | 58,307                        | 171,105                       | 81,354                        | 80,327 |
| No. of deaths                           | 13                      | 33                            | 65                            | 28                            | 25    |
| Crude death rate<sup>c</sup>            | 52                      | 57                            | 38                            | 34                            | 31    |
| Age-adjusted HR (95% CI)                | 0.95 (0.52–1.73)        | 1.15 (0.75–1.76)              | 1.03 (0.66–1.61)              | 0.94 (0.59–1.50)              | 0.84  | 0.73 |
| Multivariable HR (95% CI)<sup>d</sup>   | 0.69 (0.36–1.34)        | 0.98 (0.64–1.52)              | 1.08 (0.69–1.70)              | 1.00 (0.61–1.61)              | 0.95  | 0.52 |
| **Women with liver disease**            |                         |                               |
| No. at risk                             | 2269                    | 5811                          | 16,186                        | 8,986                         | 8,203 |
| No. of person-years                     | 32,934                  | 92,910                        | 270,774                       | 150,616                       | 134,929 |
| No. of deaths                           | 10                      | 24                            | 62                            | 46                            | 47    |
| Crude death rate<sup>c</sup>            | 30                      | 57                            | 26                            | 23                            | 31    |
| Age-adjusted HR (95% CI)                | 0.77 (0.39–1.52)        | 0.82 (0.51–1.32)              | 1.44 (0.98–2.10)              | 1.60 (1.10–2.34)              | 0.01  | 0.0006 |
| Multivariable HR (95% CI)<sup>d</sup>   | 0.68 (0.34–1.40)        | 0.83 (0.51–1.35)              | 1.31 (0.89–1.94)              | 1.41 (0.94–2.11)              | 0.08  | 0.01 |
| **Women without liver disease**         |                         |                               |
| No. at risk                             | 135                     | 308                           | 789                           | 508                           | 564   |
| No. of person-years                     | 1750                    | 4400                          | 11,184                        | 7,488                         | 7,528 |
| No. of deaths                           | 3                       | 15                            | 21                            | 22                            | 22    |
| Crude death rate<sup>c</sup>            | 171                     | 341                           | 188                           | 294                           | 292   |
| Age-adjusted HR (95% CI)                | 0.67 (0.20–2.26)        | 1.56 (0.80–3.04)              | 1.64 (0.90–2.98)              | 1.70 (0.94–3.10)              | 0.06  | 0.11 |
| Multivariable HR (95% CI)<sup>d</sup>   | 0.55 (0.15–2.03)        | 1.47 (0.72–3.00)              | 1.96 (1.05–3.66)              | 2.31 (1.18–4.49)              | 0.02  | 0.02 |
| **Women without liver disease**         |                         |                               |
| No. at risk                             | 1812                    | 4880                          | 14,141                        | 7,720                         | 6,825 |
| No. of person-years                     | 27,205                  | 79,851                        | 241,627                       | 132,498                       | 116,006 |
| No. of deaths                           | 4                       | 6                             | 36                            | 22                            | 22    |
| Crude death rate<sup>c</sup>            | 15                      | 8                             | 15                            | 17                            | 19    |
| Age-adjusted HR (95% CI)                | 0.54 (0.19–1.52)        | 0.35 (0.15–0.84)              | 1.22 (0.72–2.08)              | 1.36 (0.80–2.30)              | 0.24  | 0.003 |
| Multivariable HR (95% CI)<sup>d</sup>   | 0.50 (0.17–1.49)        | 0.35 (0.15–0.85)              | 1.16 (0.68–1.99)              | 1.14 (0.65–2.00)              | 0.58  | 0.03 |

<sup>a</sup>Test for trend refers to weight change ≥−4.9 kg.
<sup>b</sup>Test for overall trend refers to weight change ≤−10.0 kg.
<sup>c</sup>Mortality rate is expressed as rate per 100,000 person-years.
<sup>d</sup>Multivariable adjustment: age, weight at age 20, height at age 20, smoking status, ethanol consumption, hours of walking, hours of exercise, frequencies of coffee and fish intake, education level, area of residence, histories of diabetes mellitus, gallbladder disease, blood transfusion, and positive history of liver disease with or without present treatment.

weight gain during an average of 414 days was found to be an independent risk factor for incident NAFLD in Japanese men and women.22
infection. However, the excess risk of mortality from liver cancer in those with a BMI less than 18.5 kg/m² could be confounded by HCV infection.

In the present study, men without liver disease and a baseline BMI less than 18.5 kg/m² had excess mortality from liver cancer as compared with those with a BMI of 21.0 to 22.9 kg/m², perhaps because underweight men without liver disease were in a preclinical disease state. Indeed, in our study the proportion of former drinkers was higher among underweight men without liver disease than among men with a BMI of 21.0 to 22.9 kg/m² (10% vs 5%). However, the associations were weaker in sensitivity analyses that excluded deaths from liver cancer within 10 years (n = 77) and former drinkers (n = 1277) from men without liver disease: the multivariable HRs were 1.80 (95% CI, 0.72–4.53) and 1.86 (95% CI, 0.96–3.58), respectively. Therefore, the increased risk of mortality from liver cancer associated with low BMI is unlikely to be due to reverse causation. The mechanisms responsible should be investigated in future studies.

Our study benefited from a long follow-up period and a large population-based sample, which allowed us to examine associations with liver cancer in narrow ranges of BMI and weight change in both men and women. However, some limitations of the present study should be discussed. First, the lack of information on HCV infection, a major risk factor for liver cancer, is a major limitation of the current study. Because most individuals with hepatitis virus infection are asymptomatic, the use of a questionnaire to exclude hepatitis would be insufficient. Second, we used mortality data rather than incidence data as an endpoint. However, the prognosis of liver cancer is generally poor: relative 5-year survival rates were 21.2% to 27.1% from 1993–1996 to 2000–2002, according to statistics by the Japan National Cancer Center, which means that most incident cases are detected as mortality cases. Third, weight and height were self-reported in the current study and were not validated by actual measurements. However, a previous validation study of a Japanese population indicated that self-reported weight and height strongly correlated with previously measured weight and height: the reported Pearson correlation coefficients for men and women were 0.979 and 0.998 for height and 0.961 and 0.959 for weight, respectively, i.e., the differences were immaterial. Fourth, weight at age 20 was also self-reported. However, a study found that long-term recall of past body weights was reasonably accurate in Japanese adults and that people who had experienced weight loss after age 25 years underestimated their past weights, whereas those with stable weight or weight gain overestimated them. Recall bias resulting in misclassification of weight changes would likely lead to overestimation of real associations. Fifth, only 70% of the present cases reported their weight at age 20 and at baseline. However, any selection bias caused by missing data is unlikely to affect the results because age (57.0 vs 58.2 years), baseline BMI (22.8 vs 22.7 kg/m²), and other baseline variables were similar between the included and excluded subjects.

In conclusion, underweight (BMI <18.5 kg/m²) and overweight (BMI ≥25 kg/m²) in men without liver disease, and weight gain (weight change ≥5 kg) after age 20 in women with liver disease, were associated with increased mortality from liver cancer. Higher BMI tended to be associated with higher mortality from liver cancer among women and women with a history of liver disease. Weight change was positively associated with increased risk of liver cancer mortality in women with or without liver disease.

**ONLINE ONLY MATERIAL**

Abstract in Japanese.

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Conflicts of interest: None declared.

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REFERENCES

1. World health organization report, 2008. Cancer. http://www.who.int/mediacentre/factsheets/fs297/en/. Retrieved Oct. 12, 2012.
2. Larsson SC, Wolk A. Overweight, obesity and risk of liver cancer: A meta-analysis of cohort studies. Br J Cancer. 2007;97:1005–8.
3. Saunders D, Seidel D, Allison M, Lyратзопулос Г. Systematic review: The association between obesity and hepatocellular carcinoma—epidemiological evidence. Aliment Pharmacol Ther. 2010;31:1051–63.
4. Tanaka K, Tsuji I, Tamakoshi A, Matsuo K, Ito H, Wakai K, et al. Obesity and liver cancer risk: An evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol. 2012;42:212–21.
5. Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni JF Jr. Relation of body mass index to cancer risk in 362,552 Swedish men. Cancer Causes Control. 2006;17:901–9.
6. Schlesinger S, Aleksandrova K, Pischon T, Fedirko V, Jenab M, Trepo E, et al. Abdominal obesity, weight gain during adulthood and risk of liver and biliary tract cancer in a European cohort. Int J Cancer. 2013;132(3):645–57.
7. Yano M, Yatsuhashi H, Inoue O, Inokuchi K, Koga M. Epidemiology and long term prognosis of hepatitis C virus infection in Japan. Gut. 1993;34(2 Suppl):S13–6.
8. Iki I, Arii S, Okazaki M, Okita K, Omata M, Kojiro M, et al. Report of the 17th nationwide follow-up survey of primary liver cancer in Japan. Hepatol Res. 2007;37:676–91.
9. Ohno Y, Tamakoshi A; JACC Study Group. Japan collaborative cohort study for evaluation of cancer risk sponsored by monbusho (JACC study). J Epidemiol. 2001;11:144–50.
10. Tamakoshi A, Yoshimura T, Inaba Y, Ito Y, Watanabe Y, Fukuda K, et al. Profile of the JACC study. J Epidemiol. 2005;15 Suppl 1:S4–8.
11. Jee SH, Yun JE, Park EJ, Cho ER, Park IS, Sull JW, et al. Body mass index and cancer risk in Korean men and women. Int J Cancer. 2008;123:1892–6.
12. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. Adults. N Engl J Med. 2003;348:1625–38.
13. Nair S, Mason A, Eason J, Loss G, Perrillo RP. Is obesity an independent risk factor for hepatocellular carcinoma in cirrhosis? Hepatology. 2002;36:150–5.
14. N’Kontchou G, Paries J, Har MT, Ganne-Carrie N, Costentin L, Grando-Lemaire V, et al. Risk factors for hepatocellular carcinoma in patients with alcoholic or viral C cirrhosis. Clin Gastroenterol Hepatol. 2006;4:1062–8.
15. Chen CL, Yang HI, Yang WS, Liu CJ, Chen PJ, You SL, et al. Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: A follow-up study in Taiwan. Gastroenterology. 2008;135:111–21.
16. Inoue M, Kurahashi N, Iwasaki M, Tanaka Y, Mizokami M, Noda M, et al. Metabolic factors and subsequent risk of hepatocellular carcinoma by hepatitis virus infection status: A large-scale population-based cohort study of Japanese men and women (JPHC study cohort II). Cancer Causes Control. 2009;20:741–50.
17. Ohki T, Tateishi R, Sato T, Masuzaki R, Inamura J, Goto T, et al. Obesity is an independent risk factor for hepatocellular carcinoma development in chronic hepatitis C patients. Clin Gastroenterol Hepatol. 2008;6:459–64.
18. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, et al. Overweight and obesity increase the risk for liver cancer in patients with liver cirrhosis and long-term oral supplementation with branched-chain amino acid granules inhibits liver carcinogenesis in heavier patients with liver cirrhosis. Hepatol Res. 2006;35:204–14.
19. Kurokasi M, Hosokawa T, Matsunaga K, Hirayama I, Tanaka T, Sato M, et al. Hepatic steatosis in chronic hepatitis C is a significant risk factor for developing hepatocellular carcinoma independent of age, sex, obesity, fibrosis stage and response to interferon therapy. Hepatol Res. 2010;40:870–7.
20. Marchesini G, Moscattiello S, Di Domenico S, Forlani G. Obesity-associated liver disease. J Clin Endocrinol Metab. 2008;93(11 Suppl 1):S74–80.
21. Kojima S, Watanabe N, Numata M, Ogawa T, Matsuzaki S. Increase in the prevalence of fatty liver in Japan over the past 12 years: Analysis of clinical background. J Gastroenterol. 2003;38:954–61.
22. Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. Ann Intern Med. 2005;143:722–8.
23. Ortiz V, Berenguer M, Rayón JM, Carrasco D, Berenguer J. Contribution of obesity to hepatitis C-related fibrosis progression. Am J Gastroenterol. 2002;97:2408–14.
24. Wakai K, Kurozawa Y, Shibata A, Fujita Y, Kofati K, Ogimoto I, et al. Liver cancer risk, coffee, and hepatitis C virus infection: A nested case-control study in Japan. Br J Cancer. 2007;97:426–8.
25. Japan National Cancer Center report, 2006. Statistics. http://ganjoho.jp/professional/statistics/statistics.html. Retrieved Oct. 29, 2012 (in Japanese).
26. Wada K, Tamakoshi K, Tsunekawa T, Otsuka R, Zhang H, Murata C, et al. Validity of self-reported height and weight in a Japanese workplace population. Int J Obes (Lond). 2005;29:1093–9.
27. Tamakoshi K, Yatsuya H, Kondo T, Hirano T, Hori Y, Yoshida T, et al. The accuracy of long-term recall of past body weight in Japanese adult men. Int J Obes Relat Metab Disord. 2003;27:247–52.