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# Health management in cancer survivors: Findings from a population-based prospective cohort study—the Yamagata Study (Takahata)

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**Key words**

Health behavior, lifestyle risk reduction, preventive health services, second cancer, survivors

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**The number of cancer survivors is increasing; however, optimal health management of cancer survivors remains unclear due to limited knowledge. To elucidate the risk of non-communicable diseases, and the effect of lifestyle habits on risk of non-communicable diseases, we compared cancer survivors and those who never had cancer (non-cancer controls) using a population-based prospective cohort study. The baseline survey of 2292 participants was carried out from 2004 to 2006, and the follow-up survey of 2124 participants was carried out in 2011. We compared the baseline characteristics and the risk of non-communicable diseases between cancer survivors and non-cancer controls. Analyzed participants included 124 cancer survivors (men/women, 57/67), and 2168 non-cancer controls (939/1229). Several lifestyle factors and nutritional intake significantly differed between survivors and non-cancer controls, although smoking status did not differ between the groups ($P = 0.30$). Univariate logistic regression analysis showed increased risk of death (odds ratio [OR], 3.64; 95% confidence interval [CI], 2.19–6.05) and heart disease (OR, 2.60; 95% CI, 1.06–6.39) in cancer survivors. Increased risk of heart disease was also significant (OR, 2.95; 95% CI, 1.05–8.26; $P = 0.04$) in the multivariate analysis of the smoking-related cancer subgroup. Current smoking significantly increased risk of death (OR, 2.42; 95% CI, 1.13–5.18). Specific management should be implemented for cancer survivors. More intense management against smoking is necessary, as continued smoking in cancer survivors may increase the risk of second primary cancer. Moreover, cancer survivors are at a high risk of heart disease; thus, additional care should be taken.**

The number of cancer survivors is increasing in accordance with an ageing population and owing to recent progress in earlier cancer diagnosis and improved cancer treatment.[1–3] Health management (reducing modifiable risk factors for non-communicable diseases, including second primary cancer) for cancer survivors is a crucial issue not only for oncologists, but also for primary care physicians, who play an important role. Such management should aim at prevention of non-communicable diseases, including second primary cancer.[3–5]

Healthy lifestyle habits, including physical activity, healthy diet, healthy weight, and smoking cessation, are related with better health outcomes and quality of life.[6,7] However, guidelines for health management in cancer survivors remain relatively general, as there is still only limited knowledge of detailed effects or risks of lifestyle habits on health outcomes.[6–9] For example, cancer survivors are considered to be at a high risk of non-communicable diseases such as cardiovascular disease, diabetes, dyslipidemia, or stroke compared with those who never had cancer,[6] but the effect of lifestyle habits on the actual risk for non-communicable diseases is unknown.[6] Therefore, health management and prevention of non-communicable diseases for cancer survivors remain unclear.[5,6] Considering that prognosis of cancer survivors is adversely affected by comorbid non-communicable diseases,[10,11] there is a need to clarify whether the current non-specific strategy is sufficient. Two facts suggest that specific guidance for cancer survivors is needed: (i) adhering to a healthy lifestyle decreases the risk of recurrence and mortality in specific cancers;[7] and (ii) the risk of second primary cancer and its lesions differs depending on the primary cancer.[12,13]

Specific guidance for health management and prevention of non-communicable diseases in cancer survivors has not yet been established, owing to limited evidence regarding the effect of lifestyle habits on non-communicable diseases in cancer survivors and the risk of non-communicable diseases in cancer survivors. To elucidate the risk of non-communicable diseases, including second primary cancer, and the effect of lifestyle habits on risk of non-communicable diseases, we

compared cancer survivors and those who never had cancer using a prospective cohort study of healthy participants. These data will provide important information for primary care practitioners and oncologists to conduct good health management and patient education.

## Materials and Methods

**Study population.** The Yamagata Study (Takahata) is a population-based cohort study of the general Japanese population aged over 40 years. Takahata City is 300 km north of Tokyo, Japan; in 2010, 15 244 of its inhabitants were over 40 years old. The study design has been described elsewhere.[14,15] In brief, the baseline survey of 2292 participants was carried out from 2004 to 2006. Of these, 2124 participants completed the follow-up survey in 2011. The study profile is shown in Figure 1. Both surveys were carried out in conjunction with a health check-up, at which anthropometric traits and data from blood chemical tests were obtained. Japanese universal health coverage is based upon either residence-based, or employment-based insurance. Participants of this study were recruited at health check-ups for those who were covered by residence-based insurance, run by the local government (Takahata City). Medical history of cancer and other lifestyle-related diseases and information on lifestyle such as nutrition, physical activity, and smoking status were obtained using a self-administered questionnaire. This study was approved by the Ethics Committee of the Yamagata University School of Medicine (Yamagata, Japan), and written informed consent was obtained from all participants.

**Assessment of cancers.** Participants with a medical history of cancer at baseline were defined as cancer survivors, and those who had never had cancer were defined as non-cancer controls. Cancer incidence and information regarding death from any cause from 2006 to 2008 was provided by the Yamagata Prefectural Cancer Registry, which was sufficient in quality; in 2008, the rates of death certificate notification and death certificate only were 14.2% and 3.5%, respectively.[16] History of cancer was classified into stomach, lung, breast, colorectal, liver, hematopoietic, or other; of these, stomach, lung, breast, colorectal, and liver cancer were defined as smoking-related cancers.[17,18] The cancer registry before the baseline survey was also included as cancer survivors.

**Data collection of non-communicable diseases.** Data on incidence of diabetes, hypertension, heart disease (heart failure and angina pectoris), dyslipidemia, and stroke (intracranial hemorrhage, subarachnoid hemorrhage, and cerebral infarction) were obtained at the follow-up survey in 2011 based on a known diagnosis. Moreover, undiagnosed participants at baseline and at the follow-up survey were included as having these conditions according to the following criteria: diabetes was defined as either fasting plasma glucose ≥126 mg/dL, postprandial glucose ≥200 mg/dL, glycosylated hemoglobin (HbA1c) ≥6.5%, or those on treatment for diabetes; hypertension was defined as either systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or those on treatment for hypertension; and dyslipidemia was defined as either triglyceride ≥150 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, or those on treatment for dyslipidemia.[14,19,20] Participants who had corresponding disease at baseline were excluded. Incidence of death was determined by reviewing death certificates through to January 3, 2012.

**Assessment of lifestyle factors.** Weight and height were measured by an examiner and used to calculate body mass index (BMI; kg/m$^2$). Blood pressure was measured using a mercury manometer. Smoking status was assessed as never-smoker (participants who had never smoked), former smoker (participants who smoked in the past but had already quit smoking at baseline), or current smoker (participants who smoked at baseline). Daily nutritional intake status was assessed using the brief self-administered diet history questionnaire.[21] Physical activity status was assessed using the Japan Arteriosclerosis Longitudinal Study Physical Activity Questionnaire, which allows total energy and activity-specific energy to be quantified in metabolic equivalents–hours per day (METs-h/day).[22] We converted Japan Diabetic Society HbA1c values to that of the National Glycohemoglobin Standardization Program by adding 0.4% to the Japan Diabetic Society value.[19] Other methods in collection of the data in the Yamagata Study (Takahata) have been described in detail elsewhere.[14,15]

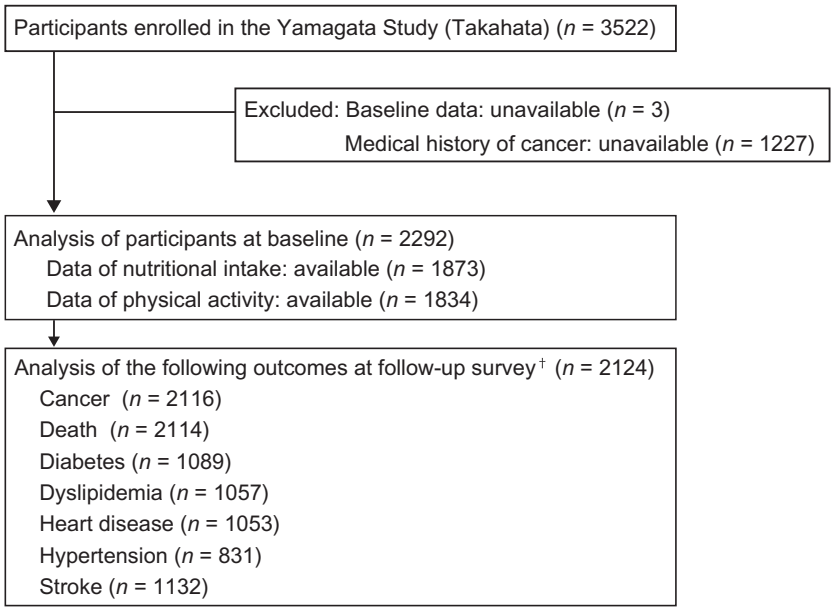


**Fig. 1.** Flowchart showing selection of participants for this study. Participants with a medical history of the following conditions at baseline were excluded from the corresponding analysis: diabetes ($n$ = 151), hypertension ($n$ = 676), heart disease ($n$ = 231), dyslipidemia ($n$ = 188), and stroke ($n$ = 66). †Numbers of participants whose medical history of cancer was available.

**Statistical analysis.** Continuous data were compared between cancer survivors and non-cancer controls using F-test followed by Student's *t*-test. If a *P*-value >0.20 was observed, then Welch's *t*-test was used. Categorical data were compared using Pearson's $\chi^2$-test with Yates' continuity correction. When any category's expected values were <5, Fisher's exact test was carried out. We conducted a logistic regression analysis to calculate the odds ratio (OR) of the outcomes by comparing cancer survivors and non-cancer controls. Multivariate models included possible confounders as covariates, based on the known risk factors for non-communicable diseases: age, sex, BMI, physical activity, smoking status, fruit and vegetable intake, red meat intake, alcohol intake, and salt intake.[5,23] As there were few outcome events, models for several diseases were over-fitted; thus, interaction terms were not added to the model for a reliable analysis. We graphically checked that continuous variables were linear on the logit using a generalized additive model with a smoothing spline with the *gam* function from the mgcv package using R software version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Any variable that could not achieve linearity on the logit as a continuous variable was categorized in the corresponding analysis (Fig. S1). Age was categorized into quarters (40–55, 56–63, 64–71, 72–87 years), BMI was categorized into three groups (<18.5, 18.5–24.99, ≥25 kg/m$^2$), physical activity was categorized into quarters (25.8–32.0, 32.0–35.2, 35.2–39.3, 39.3–46.0 METs-h/day), intake of fruit and vegetable was categorized into two groups (<400, ≥400 g/day), intake of red meat was categorized into two groups (<500, ≥500 g/day), alcohol intake was categorized into three groups (0, <150, ≥150 g/week), and salt intake was categorized into two groups (<6, ≥6 g/day).[5,23] Multicollinearity was assessed using the variance inflation factor (VIF) with the *vif* function from the DAAG package in R, and the largest VIF value was 4.4, indicating that there was no collinearity in the models. Available participants with no missing data were included in each analysis. We also carried out the same analysis for logistic regression models, after excluding outliers using the Smirnov–Grubbs test. All reported *P*-values are two-sided; a *P*-value <0.05 was considered to be statistically significant. Statistical analyses were carried out with R software.

## Results

The number of cancer survivors and non-cancer controls at the baseline survey was 124 (men/women; 57/67) and 2168 (939/1229), respectively. Lesions of the primary cancers were as follows: gastrointestinal (GI) cancer ($n$ = 50), smoking-related cancer ($n$ = 81), and others ($n$ = 46). Six cases were included as they were registered to the cancer registry before the baseline survey. Multiple primary cancer was seen in six cases.

The baseline characteristics are shown in Tables 1 and S1. Smoking status did not differ between the groups ($P$ = 0.16). We also compared blood chemical values at the baseline survey between cancer survivors and non-cancer controls (Table S2). Gamma-glutamyl transferase ($P$ = 0.01), cholinesterase ($P$ = 0.03), iron ($P$ = 0.03), albumin ($P$ = 0.02), total cholesterol ($P$ = 0.003), and low-density lipoprotein cholesterol ($P$ = 0.04) were significantly lower in the cancer survivor group compared to the non-cancer controls.

The ORs of the outcomes comparing cancer survivors and non-cancer controls are shown in Table 2. The outcomes included deaths (172), onset of cancer (95), diabetes (95), hypertension (452), heart disease (50), dyslipidemia (623), and stroke (43) during the follow-up period. The risk of death (OR, 3.64; 95% confidence interval [CI], 2.19–6.05) and heart disease (OR, 2.60; 95% CI, 1.06–6.39) in cancer survivors was unfavorable compared to non-cancer controls. In multivariate models, the association between being a cancer survivor and death (OR, 1.23; 95% CI, 0.50–3.05) and the onset of cancer (OR, 1.54; 95% CI, 0.67–3.56) was not significant. Current smoking significantly increased the risk of death (OR, 2.42; 95% CI, 1.13–5.18; data not shown). These results did not differ even after excluding the outliers. The OR of each lifestyle factor is shown in Table 3.

Information regarding smoking status and cancer onset was available for 2000 of the 2165 non-cancer controls; cancer onset was observed for 4.1% (68/1661) of never or former smokers and 5.3% (18/339) of current smokers. In contrast, information regarding smoking status and cancer onset was available for 116 of the 124 cancer survivors; cancer onset was observed in 6.7% (7/104) of never or former smokers and 16.7% (2/12) of current smokers. Of the nine cases of second primary cancer, seven cases were smoking-associated: six cases were in never or former smokers, and one case was in a current smoker. The relative risk of second primary cancer caused by current smoking was 2.48 (95% CI, 0.58–10.59) in cancer survivors, and 1.30 (95% CI, 0.78–2.15) in non-cancer controls.

We also compared the characteristics and outcomes of non-communicable diseases according to the lesions of the primary cancer (Tables 4, S3). Survivors of GI cancer and smoking-related cancer were older than non-cancer controls ($P$ < 0.001 for both). Smoking status significantly differed only in GI cancer survivors ($P$ = 0.02); however, there was no difference in the proportion between cancer survivors and non-cancer controls (GI cancer, $P$ = 0.46; smoking-related cancer, $P$ = 0.12; cancer of other lesions, $P$ = 0.37), when current smokers were compared with never and former smokers. Alcohol intake status did not differ between GI cancer survivors and non-cancer controls ($P$ = 0.41). Increased risk of second primary cancer (OR, 2.26; 95% CI, 1.01–5.06) and heart disease (OR, 3.37; 95% CI, 1.25–9.07) was observed in smoking-related cancer survivors. Increased risk of heart disease was also significant in the multivariate analysis (OR, 2.95; 95% CI, 1.05–8.26; $P$ = 0.04).

## Discussion

In this population-based study, we investigated differences in lifestyle and the risk of non-communicable diseases, including the onset of cancer, between cancer survivors and non-cancer controls. The current results may indicate that smoking cessation is not emphasized enough for cancer survivors, although cancer survivors have been reported to be at high risk for the development of second primary cancers. We also suggest that being a cancer survivor *per se* is a possible risk factor for some non-communicable diseases.

We believe that intense management against smoking is necessary for cancer survivors. Smoking is a major cause of cancer, and it increases the risk of smoking-related cancers up to approximately 3–5-fold in cancer survivors.[24] The increased risk caused by smoking in cancer survivors in our study (relative risk, 2.48) is comparable to those in previous studies.[24,25] Our results and previous studies showed that smoking increases the risk of primary cancer in non-cancer controls by 1.5-fold;[25] thus, it is reasonable to conclude that the risk of

**Table 1. Characteristics compared between cancer survivors and non-cancer controls**

| Characteristics† | All participants | Non-cancer controls | Cancer survivors | *P*-value |
|---|---|---|---|---|
| General characteristics | (*n* = 2292) | (*n* = 2168) | (*n* = 124) | |
| Age, years | 62.4 (0.2) | 62.2 (0.2) | 66.8 (0.8) | <0.001 |
| Sex | | | | |
| Men | 996 (43.5%) | 939 (43.3%) | 57 (46.0%) | 0.626 |
| Women | 1296 (56.5%) | 1229 (56.7%) | 67 (54.0%) | |
| METs,‡ METs-h/day | 36.1 (0.1) | 36.2 (0.1) | 35.2 (0.5) | 0.066 |
| BMI, kg/m$^2$ | 23.5 (0.1) | 23.5 (0.1) | 23.3 (0.3) | 0.485 |
| <18.5 | 122 (5.3%) | 113 (5.2%) | 9 (7.3%) | 0.429 |
| ≥18.5, <25 | 1488 (64.9%) | 1405 (64.8%) | 83 (66.9%) | |
| ≥25 | 682 (29.8%) | 650 (30.0%) | 32 (25.8%) | |
| Blood pressure, kPa | | | | |
| Systolic | 17.84 (0.04) | 17.84 (0.05) | 17.91 (0.18) | 0.717 |
| Diastolic | 10.57 (0.03) | 10.57 (0.03) | 10.60 (0.11) | 0.807 |
| Smoking status | | | | |
| Never | 1588 (69.3%) | 1497 (69.0%) | 91 (73.4%) | 0.155 |
| Former | 322 (14.0%) | 302 (13.9%) | 20 (16.1%) | |
| Current | 382 (16.7%) | 369 (17.0%) | 13 (10.5%) | |
| Nutritional intake§ | (*n* = 1873) | (*n* = 1766) | (*n* = 107) | |
| Total energy, kJ/day | 9336.6 (65.7) | 9328.4 (68.1) | 9471.1 (240.8) | 0.570 |
| Carbohydrate | 322.5 (2.2) | 322.5 (2.3) | 329.8 (9.0) | 0.412 |
| % of total energy | 58.5 (0.2) | 58.6 (0.2) | 58.4 (0.6) | 0.883 |
| Sugar | 21.2 (0.2) | 21.1 (0.2) | 22.3 (1.0) | 0.249 |
| Protein | 76.7 (0.7) | 76.4 (0.7) | 81.7 (2.8) | 0.092 |
| % of total energy | 13.6 (0.1) | 13.6 (0.1) | 14.4 (0.3) | 0.004 |
| Animal protein | 39.3 (0.5) | 39.1 (0.6) | 42.8 (2.2) | 0.107 |
| % of total energy | 6.9 (0.1) | 6.9 (0.1) | 7.5 (0.3) | 0.022 |
| Vegetable protein | 37.5 (0.3) | 37.4 (0.3) | 38.9 (1.1) | 0.204 |
| % of total energy | 6.7 (0.02) | 6.7 (0.02) | 6.8 (0.1) | 0.285 |
| Fat | 57.3 (0.5) | 57.1 (0.6) | 60.6 (1.9) | 0.087 |
| % of total energy | 22.9 (0.1) | 22.9 (0.1) | 24.1 (0.4) | 0.008 |
| Animal fat | 23.4 (0.3) | 23.3 (0.3) | 25.4 (1.1) | 0.070 |
| % of total energy | 9.3 (0.1) | 9.2 (0.1) | 10.2 (0.4) | 0.012 |
| Vegetable fat | 33.8 (0.3) | 33.8 (0.3) | 35.2 (1.2) | 0.289 |
| % of total energy | 13.6 (0.1) | 13.6 (0.1) | 13.9 (0.3) | 0.362 |
| Saturated fatty acid | 14.0 (0.1) | 14.0 (0.1) | 14.9 (0.5) | 0.093 |
| % of total energy | 5.6 (0.04) | 5.6 (0.04) | 6.0 (0.2) | 0.018 |
| Monounsaturated fatty acid | 20.0 (0.2) | 19.9 (0.2) | 21.1 (0.7) | 0.110 |
| % of total energy | 8.0 (0.05) | 7.9 (0.05) | 8.4 (0.2) | 0.016 |
| Polyunsaturated fatty acid | 15.9 (0.1) | 15.9 (0.1) | 16.7 (0.5) | 0.141 |
| % of total energy | 6.4 (0.04) | 6.4 (0.04) | 6.6 (0.1) | 0.118 |
| Cholesterol, g × 10$^{-3}$/day | 330.7 (4.1) | 329.1 (4.2) | 356.8 (16.4) | 0.114 |
| Fiber | 15.0 (0.1) | 14.9 (0.1) | 16.3 (0.6) | 0.025 |
| Soluble fiber | 3.3 (0.04) | 3.3 (0.04) | 3.6 (0.1) | 0.027 |
| Insoluble fiber | 10.8 (0.1) | 10.8 (0.1) | 11.8 (0.4) | 0.017 |
| Alcohol | 12.2 (0.6) | 12.6 (0.6) | 5.9 (1.4) | <0.001 |
| 0 g/week | 1009 (53.9%) | 941 (53.3%) | 68 (63.6%) | 0.013 |
| <150 g/week | 496 (26.5%) | 466 (26.4%) | 30 (28.0%) | |
| ≥150 g/week | 368 (19.6%) | 359 (20.3%) | 9 (8.4%) | |
| Salt | 12.8 (0.1) | 12.8 (0.1) | 13.3 (0.4) | 0.177 |
| <6 | 44 (2.3%) | 41 (2.3%) | 3 (2.8%) | 0.737 |
| ≥6 | 1829 (97.7%) | 1725 (97.7%) | 104 (97.2%) | |
| Sodium, g × 10$^{-3}$/day | 5083.6 (37.2) | 5071.2 (38.3) | 5288.0 (150.7) | 0.176 |
| Potassium, g × 10$^{-3}$/day | 2724.8 (25.8) | 2711.0 (26.6) | 2952.9 (103.5) | 0.029 |
| Calcium, g × 10$^{-3}$/day | 616.5 (6.4) | 613.3 (6.6) | 669.8 (27.1) | 0.040 |
| Magnesium, g × 10$^{-3}$/day | 292.5 (2.5) | 291.5 (2.6) | 309.9 (9.9) | 0.088 |
| Phosphorus, g × 10$^{-3}$/day | 1158.3 (10.7) | 1153.7 (11.1) | 1233.7 (42.2) | 0.083 |
| Iron, g × 10$^{-3}$/day | 9.2 (0.1) | 9.1 (0.1) | 10.0 (0.3) | 0.019 |
| Zinc, g × 10$^{-3}$/day | 9.4 (0.1) | 9.4 (0.1) | 10.0 (0.3) | 0.049 |
| Copper, g × 10$^{-3}$/day | 1.5 (0.01) | 1.4 (0.01) | 1.5 (0.04) | 0.044 |

**Table 1 (continued)**

| Characteristics† | All participants | Non-cancer controls | Cancer survivors | *P*-value |
|---|---|---|---|---|
| Manganese, g × $10^{-3}$/day | 4.2 (0.03) | 4.2 (0.03) | 4.5 (0.1) | 0.047 |
| Beta-carotene, g × $10^{-6}$/day | 4117.5 (61.1) | 4092.8 (63.0) | 4525.3 (250.9) | 0.101 |
| Vitamin A, g × $10^{-6}$/day | 765.9 (15.6) | 758.1 (15.5) | 894.1 (94.7) | 0.160 |
| Retinol, g × $10^{-6}$/day | 420.3 (13.9) | 414.6 (13.7) | 514.4 (89.3) | 0.272 |
| Vitamin D | 16.2 (0.3) | 16.0 (0.3) | 17.8 (1.2) | 0.161 |
| Vitamin E, tocopherol, g × $10^{-3}$/day | 8.0 (0.1) | 8.0 (0.1) | 8.6 (0.3) | 0.071 |
| Vitamin K, g × $10^{-6}$/day | 473.2 (5.4) | 471.0 (5.6) | 508.9 (24.4) | 0.106 |
| Vitamin B1, g × $10^{-3}$/day | 0.8 (0.01) | 0.8 (0.01) | 0.9 (0.03) | 0.014 |
| Vitamin B2, g × $10^{-3}$/day | 1.5 (0.01) | 1.4 (0.01) | 1.6 (0.06) | 0.013 |
| Niacin, g × $10^{-3}$ NE/day | 17.5 (0.2) | 17.4 (0.2) | 18.4 (0.8) | 0.253 |
| Pantothenic acid, g × $10^{-3}$/day | 7.3 (0.1) | 7.3 (0.1) | 7.8 (0.3) | 0.030 |
| Vitamin B6, g × $10^{-3}$/day | 1.4 (0.01) | 1.4 (0.01) | 1.5 (0.1) | 0.100 |
| Folic acid, g × $10^{-3}$/day | 386.9 (4.0) | 384.5 (4.1) | 426.4 (17.2) | 0.014 |
| Vitamin B12, g × $10^{-6}$/day | 10.7 (0.2) | 10.7 (0.2) | 11.8 (0.8) | 0.138 |
| Vitamin C, g × $10^{-3}$/day | 116.5 (1.4) | 115.5 (1.5) | 132.5 (5.9) | 0.005 |
| Fruits and vegetables | 216.5 (3.4) | 214.5 (3.5) | 249.2 (13.6) | 0.017 |
| Fruits | 84.2 (1.9) | 82.7 (1.9) | 109.9 (8.9) | 0.004 |
| Vegetables | 132.3 (2.1) | 131.9 (2.1) | 139.3 (8.0) | 0.407 |
| Meat | 37.3 (0.7) | 37.1 (0.7) | 41.1 (2.7) | 0.167 |

BMI, body mass index; METs, metabolic equivalents. †Standard errors are shown within parentheses unless otherwise specified. ‡Data were available for 1834 participants (1732 non-cancer controls and 102 survivors) pa. §Units are in grams per day unless otherwise specified.

**Table 2. Logistic regression analysis for death, second primary cancer, and non-communicable diseases in cancer survivors and non-cancer controls**

| Outcomes | Univariate analysis† | | Multivariate analysis‡ | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | *P*-value | Odds ratio (95% CI) | *P*-value |
| Death | | | | |
| Non-cancer controls | Reference | – | Reference | – |
| Cancer survivors | 2.05 (1.07–3.95) | 0.03 | 1.23 (0.50–3.05) | 0.65 |
| Cancer onset | | | | |
| Non-cancer controls | Reference | – | Reference | – |
| Cancer survivors | 1.87 (0.92–3.82) | 0.09 | 1.54 (0.67–3.56) | 0.31 |
| Diabetes | | | | |
| Non-cancer controls | Reference | – | Reference | – |
| Cancer survivors | 1.11 (0.46–2.64) | 0.82 | 0.97 (0.40–2.36) | 0.95 |
| Dyslipidemia | | | | |
| Non-cancer controls | Reference | – | Reference | – |
| Cancer survivors | 0.97 (0.57–1.65) | 0.92 | 0.95 (0.55–1.64) | 0.86 |
| Heart disease§ | | | | |
| Non-cancer controls | Reference | – | Reference | – |
| Cancer survivors | 2.60 (1.06–6.39) | 0.04 | 2.05 (0.80–5.22) | 0.13 |
| Hypertension | | | | |
| Non-cancer controls | Reference | – | Reference | – |
| Cancer survivors | 0.75 (0.41–1.39) | 0.36 | 0.56 (0.29–1.08) | 0.08 |
| Stroke¶ | | | | |
| Non-cancer controls | Reference | – | Reference | – |
| Cancer survivors | 1.22 (0.37–4.06) | 0.74 | 0.88 (0.25–3.09) | 0.84 |

†Number of participants was 2114 (non-cancer controls/survivors, 1998/116) for death, 2116 (2000/116) for cancer onset, 1089 (1026/63) for diabetes, 1057 (997/60) for dyslipidemia, 1053 (993/60) for heart disease, 831 (787/44) for hypertension, and 1132 (1066/66) for stroke. ‡Number (non-cancer controls/survivors) of participants were 1556 (1467/89) for death, 1558 (1469/89) for cancer onset, 1089 (1026/63) for diabetes, 1057 (997/60) for dyslipidemia, 1053 (993/60) for heart disease, 831 (787/44) for hypertension, and 1132 (1066/66) for stroke. §Heart disease includes heart failure and angina pectoris. ¶Stroke includes intracranial hemorrhage, subarachnoid hemorrhage, and cerebral infarction.

cancer onset is exacerbated more by smoking in cancer survivors compared to non-cancer controls, although the small sample size precludes a definitive conclusion. Therefore, more intense management promoting smoking cessation should be provided for cancer survivors to help prevent second primary cancer.

However, the smoking rate of cancer survivors and non-cancer controls was similar, indicating that smoking cessation

**Table 3. Odds ratios of covariates in multivariate logistic regression analysis of cancer survivors and non-cancer controls**

| | Death ($n$ = 1556) | | Cancer onset ($n$ = 1558) | | Diabetes ($n$ = 1089) | | Dyslipidemia ($n$ = 1057) | | Hypertension ($n$ = 831) | | Heart disease† ($n$ = 1053) | | Stroke‡ ($n$ = 1132) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Odds ratio (95% CI) | $P$-value | Odds ratio (95% CI) | $P$-value | Odds ratio (95% CI) | $P$-value | Odds ratio (95% CI) | $P$-value | Odds ratio (95% CI) | $P$-value | Odds ratio (95% CI) | $P$-value | Odds ratio (95% CI) | $P$-value |
| Age, years | 1.12 (1.08–1.16) | <0.001 | – | – | – | – | – | – | – | – | 1.05 (1.01–1.09) | 0.01 | 1.08 (1.03–1.12) | <0.001 |
| ≥40, <56 | – | – | Reference | | Reference | | Reference | | Reference | | – | – | – | – |
| ≥56, <64 | – | – | 1.85 (0.82–4.15) | 0.139 | 2.66 (1.36–5.22) | 0.004 | 1.24 (0.89–1.72) | 0.20 | 1.81 (1.27–2.58) | 0.001 | – | – | – | – |
| ≥64, <72 | – | – | 3.30 (1.52–7.15) | 0.002 | 2.48 (1.22–5.04) | 0.012 | 1.21 (0.85–1.72) | 0.30 | 3.12 (2.05–4.77) | <0.001 | – | – | – | – |
| ≥72, <88 | – | – | 3.54 (1.53–8.18) | 0.003 | 3.67 (1.62–8.30) | 0.002 | 0.94 (0.60–1.49) | 0.81 | 6.72 (3.49–12.97) | <0.001 | – | – | – | – |
| Sex | | | | | | | | | | | | | | |
| Men | Reference | | Reference | | Reference | | Reference | | Reference | | Reference | | Reference | |
| Women | 0.38 (0.18–0.80) | 0.01 | 0.77 (0.41–1.47) | 0.43 | 0.72 (0.41–1.28) | 0.27 | 1.08 (0.77–1.53) | 0.65 | 0.77 (0.52–1.16) | 0.21 | 0.69 (0.33–1.44) | 0.32 | 0.77 (0.31–1.93) | 0.58 |
| Smoking status | | | | | | | | | | | | | | |
| Never | Reference | | Reference | | Reference | | Reference | | Reference | | Reference | | Reference | |
| Former | 1.59 (0.78–3.26) | 0.20 | 1.59 (0.79–3.18) | 0.19 | 0.94 (0.48–1.82) | 0.85 | 0.86 (0.58–1.29) | 0.47 | 0.78 (0.48–1.29) | 0.34 | 0.56 (0.21–1.49) | 0.25 | 1.07 (0.41–2.79) | 0.89 |
| Current | 2.42 (1.13–5.18) | 0.02 | 1.65 (0.82–3.33) | 0.16 | 0.92 (0.45–1.86) | 0.81 | 1.12 (0.75–1.68) | 0.57 | 0.71 (0.45–1.13) | 0.15 | 0.91 (0.36–2.32) | 0.84 | 6.63 (0.22–2.00) | 0.47 |
| Metabolic equivalents, METs-h/day | – | – | – | – | 1.00 (0.96–1.04) | 0.96 | 1.00 (0.98–1.02) | 0.83 | 1.00 (0.97–1.03) | 0.94 | 1.00 (0.95–1.05) | 0.88 | 1.05 (1.01–1.11) | 0.03 |
| ≥25.8, <32.0 | Reference | | Reference | | – | – | – | – | – | – | – | – | – | – |
| ≥32.0, <35.2 | 0.39 (0.18–0.85) | 0.02 | 0.62 (0.33–1.17) | 0.14 | – | – | – | – | – | – | – | – | – | – |
| ≥35.2, <39.3 | 0.45 (0.21–0.95) | 0.02 | 0.54 (0.28–1.05) | 0.07 | – | – | – | – | – | – | – | – | – | – |
| ≥39.3, <46.0 | 0.74 (0.37–1.47) | 0.39 | 0.55 (0.28–1.09) | 0.09 | – | – | – | – | – | – | – | – | – | – |
| | | | | | | | | | | | | | – | – |
| BMI, kg/m$^2$ | – | – | 0.94 (0.87–1.02) | 0.14 | 1.09 (1.02–1.17) | 0.02 | – | – | – | – | 1.16 (1.06–1.27) | 0.002 | 1.00 (0.91–1.11) | 0.94 |
| <18.5 | Reference | | – | – | – | – | Reference | | Reference | | – | – | – | – |
| ≥18.5, <25 | 0.48 (0.20–1.15) | 0.10 | – | – | – | – | 0.98 (0.56–1.72) | 0.94 | 2.23 (1.17–4.25) | 0.01 | – | – | – | – |
| ≥25 | 0.50 (019–1.30) | 0.15 | – | – | – | – | 1.78 (0.98–3.25) | 0.06 | 3.80 (1.91–7.56) | <0.001 | – | – | – | – |
| Fruits and vegetables, 10 g/day | 1.00 (0.98–1.02) | 0.81 | 0.98 (0.96–1.00) | 0.03 | 1.00 (0.98–1.02) | 0.68 | 1.00 (0.99–1.01) | 0.73 | – | – | 0.99 (0.97–1.01) | 0.42 | – | – |
| <400 g/day | – | – | – | – | – | – | – | – | Reference | | – | – | Reference | |
| ≥400 g/day | – | – | – | – | – | – | – | – | 1.45 (0.54–3.91) | 0.46 | 0.46 | – | 0.18 (0.03–1.20)§ | 0.99 |
| Meat, 10 g/day | – | – | 0.98 (0.89–1.08) | 0.72 | 0.96 (0.87–1.06) | 0.37 | 0.96 (0.91–1.01) | 0.09 | 0.97 (0.92–1.02) | 0.26 | 1.00 (0.89–1.11) | 0.94 | 1.00 (0.98–1.01) | 0.50 |
| <500 g/day | Reference | | – | – | – | – | – | – | – | – | – | – | – | – |
| ≥500 g/day | 0.87 (0.38–2.03) | 0.75 | – | – | – | – | – | – | – | – | – | – | – | – |
| Salt, g/day | – | – | – | – | 0.97 (0.90–1.05) | 0.47 | 1.02 (0.98–1.07) | 0.39 | – | – | – | – | – | – |
| <6 g/day | Reference | | Reference | | – | – | – | – | Reference | | Reference | | Reference | |
| ≥6 g/day | 0.18 (0.05–0.69) | 0.01 | 0.79 (0.17–3.61) | 0.76 | – | – | – | – | 0.35 (0.10–1.22) | 0.10 | 0.74 (0.09–6.26) | 0.79 | 2.35 (0.22–25.6)§ | 0.99 |
| Alcohol, g/day | 1.00 (0.99–1.01) | 0.73 | 1.00 (0.99–1.01) | 0.74 | 1.00 (0.99–1.01) | 0.82 | 0.99 (0.99–0.99) | 0.01 | – | – | 1.00 (0.98–1.01) | 0.76 | – | – |
| 0 g/week | – | – | – | – | – | – | – | – | Reference | | – | – | Reference | |
| <150 g/week | – | – | – | – | – | – | – | – | 0.85 (0.60–1.22) | 0.38 | – | – | 0.33 (0.12–0.92) | 0.03 |
| ≥150 g/week | – | – | – | – | – | – | – | – | 1.94 (1.21–3.12) | 0.01 | – | – | 0.98 (0.39–2.50) | 0.97 |

BMI, body mass index; METs-h/day, metabolic equivalents-hours per day. †Heart disease includes heart failure and angina pectoris. ‡Stroke includes intracranial hemorrhage, subarachnoid hemorrhage, and cerebral infarction. §Odds ratio and 95% confidence interval (CI) was derived with logistf function from the logistf package in R software.

**Table 4. Subgroup analysis of cancer lesions in cancer survivors and non-cancer controls**

| | Non-cancer controls | GI cancer survivors† | *P*-value | Smoking-related cancer survivors‡ | *P*-value | Cancer survivors of other lesions§ | *P*-value |
|---|---|---|---|---|---|---|---|
| Characteristics¶ | (*n* = 2168) | (*n* = 50) | | (*n* = 81) | | (*n* = 43) | |
| Age, years | 62.2 (0.2) | 69.4 (1.0) | <0.001 | 68.3 (0.9) | <0.001 | 64.1 (1.5) | 0.20 |
| Sex | | | | | | | |
| Men | 939 (43.3%) | 37 (74.0%) | <0.001 | 44 (54.3%) | 0.053 | 14 (30.4%) | 0.11 |
| Women | 1229 (56.7%) | 13 (26.0%) | | 37 (45.7%) | | 32 (69.6%) | |
| METs, METs-h/day | 36.2 (0.1) | 35.2 (0.9) | 0.306 | 35.0 (0.7) | 0.097 | 35.7 (0.6) | 0.43 |
| BMI,‡‡ kg/m$^2$ | 23.5 (0.1) | 22.7 (0.4) | 0.086 | 23.3 (0.3) | 0.668 | 23.4 (0.5) | 0.85 |
| <18.5 | 133 (5.2%) | 4 (8.0%) | 0.350 | 6 (7.4%) | 0.327 | 3 (6.5%) | 0.84 |
| ≥18.5, <25 | 1405 (64.8%) | 35 (70.0%) | | 56 (69.1%) | | 29 (63.0%) | |
| ≥25 | 650 (30.0%) | 11 (22.0%) | | 19 (23.5%) | | 14 (30.4%) | |
| Univariate logistic regression analysis‡‡ | | OR (95% CI) | | OR (95% CI) | | OR (95% CI) | |
| Death | Reference | 4.02 (1.83–8.84) | 0.001 | 2.97 (1.48–5.95) | 0.002 | 0.47 (0.06–3.43) | 0.45 |
| Second primary cancer | Reference | 2.07 (0.73–5.90) | 0.173 | 2.26 (1.01–5.06) | 0.048 | 1.09 (0.26–4.56) | 0.91 |
| Diabetes | Reference | 1.44 (0.42–4.89) | 0.563 | 0.88 (0.26–2.91) | 0.830 | 1.32 (0.39–4.46) | 0.66 |
| Hypertension | Reference | 0.83 (0.31–2.22) | 0.705 | 0.83 (0.38–1.80) | 0.632 | 0.60 (0.24–1.51) | 0.28 |
| Heart disease§§ | Reference | 3.08 (0.89–10.72) | 0.077 | 3.37 (1.25–9.07) | 0.016 | 2.81 (0.81–9.73) | 0.10 |
| Dyslipidemia | Reference | 0.39 (0.17–0.89) | 0.026 | 0.89 (0.47–1.67) | 0.714 | 1.00 (0.43–2.37) | 0.99 |
| Stroke¶¶ | Reference | 1.03 (0.14–7.76) | 0.980 | 1.28 (0.30–5.49) | 0.737 | 0.99 (0.13–7.45) | 0.99 |

BMI, body mass index; CI, confidence interval; METs, metabolic equivalents; OR, odds ratio. †Cancer survivors of stomach and colorectal cancer. Non-cancer controls and gastrointestinal (GI) cancer survivors were compared. ‡Cancer survivors of stomach, lung, breast, colorectal, liver, and prostate cancer. Non-cancer controls and smoking-related cancer survivors were compared. §Survivors of cancer other than GI or smoking-related cancer. Non-cancer controls and cancer survivors of other regions were compared. ¶Standard errors are shown within parentheses unless otherwise specified. ††Data were available for 1834 (non-cancer controls/GI/smoking-related/others, 1732/40/66/39) participants. ‡‡Number (non-cancer controls/GI/smoking-related/other) of participants was 2114 (1998/47/76/43) for death, 2116 (2000/47/76/43) for cancer onset, 1089 (1026/25/39/27) for diabetes, 1057 (997/25/41/22) for dyslipidemia, 1053 (993/24/37/26) for heart disease, 831 (787/16/26/19) for hypertension, and 1132 (1066/26/42/27) for stroke. §§Heart disease includes heart failure and angina pectoris. ¶¶Stroke includes intracranial hemorrhage, subarachnoid hemorrhage, and cerebral infarction.

support was insufficient for cancer survivors. This is one of the biggest problems in cancer prevention for cancer survivors. Insufficient support of smoking cessation for the cancer survivors would be in part due to the lack of knowledge in general physicians, resulting from the limited research on health management for cancer survivors. In Japan, there is no nationwide smoking cessation program specific for cancer survivors. The prevalence of smoking in the general population is approximately 15% in the USA, with the 20% rate in Japan about 10–15 years behind.[26] The USA began taking antismoking measures prior to Japan, and many medical societies support smoking cessation; moreover, services such as Quitline are available. In Japan, the environment for smoking cessation is not as well maintained. Notwithstanding, smoking prevalence in cancer survivors is similar in Japan and the USA. This is due to the paucity of smoking cessation services specific for cancer survivors in both countries: only approximately 70–80% of designated cancer hospitals provide smoking cessation services,[27,28] and clinicians possibly lack knowledge to support smoking cessation and feel reluctant to even carry out the initial evaluation.[29,30] Smoking cessation is a big challenge for cancer survivors.[29] Therefore, support for smoking cessation should be widely provided in clinical practice, and its benefits should be clarified in future research.

In addition to support for smoking cessation, the current results show that the following health management targets may be necessary for cancer survivors. First, the risk of heart disease was higher in cancer survivors compared to non-cancer controls. This implies a need for additional care for heart disease among cancer survivors. Smoking is a mutual risk factor for heart disease and cancer, and chemotherapy may be cardiotoxic or increase cardiac load in relevant cases;[31–33] hence, survivors would be at risk of heart disease. Second, subgroup analysis showed an excess risk of cancer onset among smoking-associated cancer survivors. Cancer survivors also need management for prevention of second primary cancer. Furthermore, most of the second primary cancers in smoking-associated cancer survivors were also smoking-associated. This reinforces the need to support smoking cessation, especially in smoking-associated cancer survivors, given that the prevalence of smoking was comparable between smoking-related cancer survivors and non-cancer controls. As cancer survivors would be more likely to die before the cancer onset because of comorbid conditions or complications[24] and with the effect of confounding factors like age, increased risk of cancer onset was scarcely detectable only in smoking-associated cancer survivors. Risk of second primary cancer and its lesions differs depending on the primary cancer;[12,13] thus, the effect of smoking on those risks needs to be elucidated. For this, a larger study with sufficient statistical power is needed.

Baseline characteristics differed between cancer survivors and non-cancer controls. Cancer survivors abstained from alcohol, indicating that current management regarding alcohol consumption is providing sufficient results. However, 5/41 (12.2%) of GI cancer survivors still consumed more than 150 g alcohol per week. Physicians should be aware of this population and continue to emphasize alcohol abstinence, as alcohol is an established risk factor for GI cancer.[5,23] In addition, cancer survivors tended to be malnourished, as indicated by cholinesterase, albumin, total cholesterol, and low-density lipoprotein levels (Table S2), especially in GI cancer survivors.

Malnutrition in cancer survivors arises from causes other than nutritional intake,[34] as energy intake (Tables 1, S3) and energy intake per body weight (data not shown) did not differ between cancer survivors and non-cancer controls. Dietary management is generally directed toward limiting intake (often caloric) or endorsing frugal meals, although some survivors need the opposite and should be encouraged to have sufficient nutrition to avoid malnourishment. We could not infer the cause of other differences observed in food and nutritional intake or blood chemical values, thus we were unable to determine whether these differences between cancer survivors and non-cancer controls result from the cancer *per se*; the potential causal relationship needs to be addressed in a larger population-based or interventional study. We emphasize the importance of this study, because the general public wants to know what kind of foods they should eat or avoid in order to reduce the risk of non-communicable diseases. At present, recommendations and management of dietary habits for cancer survivors is the same as that for the general public for factors other than those revealed in the present study.

The strength of this study was that detailed information regarding lifestyle was obtained after the onset of cancer for cancer survivors. Also, the onset of non-communicable diseases, including the onset of second cancer after the baseline survey, was prospectively obtained. These allowed us to investigate the risk of non-communicable diseases caused by being a cancer survivor. We observed an increased risk of death, cancer onset, and heart disease for cancer survivors; although statistical power was insufficient, an increased risk was verified in multivariate analysis for heart disease. Conversely, our results indicated that known risk factors, such as age, smoking, and unknown confounding factors had a larger effect than being a cancer survivor on the risk of non-communicable diseases, especially in diseases other than heart disease; for example, age was significantly higher in cancer survivors. Note that for stroke, although intracranial and subarachnoid hemorrhages were included, due to the lack of information in the questionnaire, it could not be differentiated whether these strokes were caused by cerebrovascular disease or by another cause. This is highly important, because smoking is an evident risk factor for cerebrovascular disease. In addition, the influence of GI cancer history should also be considered, as its incidence was greatest (40.3%). Another limitation is that we could not compare the difference in the risk of each lifestyle factor between cancer survivors and non-cancer controls, due to the number of participants and events that were available. Selection bias exists for cancer survivors in this study as survivors included those who had survived for a certain period of time and could come to the health check-up. In other words, survivors who had an undesirable course after the diagnosis of cancer were unable to participate in this study. Therefore, participants who had an undesirable course might be more likely not to have adhered to a healthy lifestyle than those who participated in this study. Moreover, we could not take into account the time period of being a cancer survivor, as it was not obtained in the questionnaire. Self-reported history of cancer at baseline and the short follow-up period were also limitations of this study.

Our population-based cohort study in a Japanese general population was consistent with the results of previous studies. Specific health management for cancer survivors as suggested above may also apply to other developed nations in Europe and North America, but this needs to be verified in future studies. In addition, information regarding differences in lifestyle and risk of non-communicable diseases between cancer survivors and non-cancer controls is limited in the Asian population. The current results suggest that a large study in an Asian population would be worthwhile. We are now advancing a prospective cohort study of approximately 20 000 people, with detailed information of lifestyles, aiming in part to validate the results of the current study.

In conclusion, the current study indicates that smoking, known but undetermined lifestyle habits, and other unknown factors are associated with the risk of non-communicable diseases in cancer survivors. These data are valuable in that they elucidate the need to establish specific health management for cancer survivors with a focus on the prevention of non-communicable diseases, including second primary cancer. The need for smoking cessation is commonly accepted, although cancer survivors need more intense management against smoking. In addition, cancer survivors should receive additional care for heart disease.

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## Disclosure Statement

The authors have no conflict of interest.

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## Supporting Information

Additional supporting information may be found in the online version of this article:

**Fig. S1.** Checking linearity assumption of each logistic regression using smoothing spline.

**Table S1.** Food intake according to brief self-administered diet history questionnaire (BDHQ) compared between cancer survivors and non-cancer controls.

**Table S2.** Odds ratio of covariates in multivariate logistic regression analysis.

**Table S3.** Characteristics of subgroups according to cancer lesions.