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【 Original Article 】

Health food intake and risk of overall death and cancer incidence in the general population of Amami Islands and mainland of Kagoshima, Japan

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Abstract

OBJECTIVES: Various health foods have been introduced and marketed on television and the internet; however, evidence of their efficacy and effects is often limited to in vitro and in vivo studies. To examine the relationship between health food intake, overall death and cancer incidence risk, we conducted a cohort study on the general population of the Kagoshima Prefecture.

METHODS: We recruited 7561 eligible participants (3136 men and 4425 women) from the general populations of Amami islands and mainland Kagoshima Prefecture, Japan. We estimated the hazard ratios and 95% confidence intervals for overall death and cancer incidence using Cox proportional hazard models, adjusting for confounding variables, for the total and nine types of health foods (black vinegar, glucosamine, chlorella, Agaricus, royal jelly, green juice, garlic, blueberry, and turmeric).

RESULTS: Black vinegar was the most commonly consumed health food (2.3% in men and 2.6% in women). In the baseline cross-sectional study, positive associations were found between black vinegar and hypertension, garlic and glucose intolerance, and other health foods and dyslipidemia. However, in the prospective study, no significant association was observed between the intake of total and nine-specific health foods and overall deaths and cancer incidence, except for green juice, in which HR for cancer incidence was increased (2.84, 1.15–7.04).

CONCLUSIONS: Health foods commonly consumed by the general population of Kagoshima were not significantly associated with the risk of overall death and cancer incidence, except green juice intake. Further study is required to clarify the potential increased risk of cancer with green juice intake.

Key words: health foods, death, cancer incidence, risk, cohort study

Footnote: The most parts of the present study were done, when Drs. Takumi AKAHO, Tomoko YASUDA and Kaede MIYAMOTO were medical students of the School of Medicine, Faculty of Medicine, Kagoshima University, Kagoshima.

Introduction

Japan has consistently ranked high globally in terms of average life expectancy and healthy life expectancy. However, due to the declining birth rate and aging population, an increase has been observed regarding the number of bedridden individuals and those requiring long-term care [1]. To address this issue, Health Japan 21 (the second term) was launched in 2012, aiming to extend healthy life expectancy, reduce health disparities, prevent lifestyle-related diseases, and promote healthy aging [2]. This national initiative has resulted in a growing public interest in health and an increased demand for health-related information and products, leading to the revitalization of health-related markets.

In Japan, health foods are widely used, and various products are marketed as "health foods" through the television and internet. According to recent surveys, approximately 60% of consumers use health foods, with the consumption rate increasing as consumers age [3]. People consume health foods for various reasons, such as filling nutritional gaps in their daily diets, promoting beauty and anti-aging effects, supporting overall health and wellness, and aiding in disease management based on their individual health conditions.

The Japanese Ministry of Health, Labour and Welfare defines health foods as "foods that contribute to the maintenance and promotion of health without legal provisions" [4]. Health foods are classified into two categories under the Health Claim Food System: health foods and foods with health claims [5]. Foods with health claims are further categorized into three groups: foods with function claims, foods with nutritional claims, and foods for specified health uses, which aid in maintaining and promoting health by performing functions such as "toning the stomach" and "moderating fat absorption". Since the establishment of functional claims in 2015, foods with functional claims can now be labeled with functionality related to the structure and function of the body; however, this label is provided under the responsibility of the business operator. Additionally, foods with nutritional function claims can be labeled with the functions of nutrients without obtaining permission from the government, leading to the production and sale of many different types of health foods.

Typical health foods that are widely consumed in Japan today include *Aojiru* (green juice), *Kurozu* (black vinegar), and blueberries. Distributors advertise the health benefits of these health foods by presenting their functionality. However, evidence of the efficacy and effects of health foods is often examined using *in vitro* and *in vivo* studies [6]. Several studies have reported the positive effects of green juice, such as improved bowel movements due to dietary fiber [7], a suppressed rise in blood sugar levels [8], and an antioxidant effect due to flavonoids [9]; however, studies on health foods have their limitations. Similarly, studies suggest that black vinegar has a hypotensive effect [10], blood glucose regulation effect [11], and fat synthesis suppression [12]. On the other hand, blueberries have an antioxidant effect due to anthocyanins [13], a blood glucose regulation effect [14], and a blood pressure improvement effect [15,16]. However, most studies have their limitations [6], and some have reported that black vinegar was not significantly associated with blood pressure, blood glucose levels, and body mass index (BMI) [17]. Additionally, other studies reported no association between blueberries and blood pressure improvement [18]. Epidemiological studies on supplementation and health risks often focus on specific components such as catechins, phenols [19], n3-PUFAs, vitamin D [20], and calcium [21].

Health foods often contain multiple ingredients despite their high specific ingredient content, and epidemiological studies regarding the intake and health risks of health foods are limited. Especially, the effects of these health foods on the risk of death and cancer, which are the most significant health events, have not been adequately examined. We conducted a cohort study of the general population of the Kagoshima Prefecture to examine the relationship between health food intake and the risks of overall death and cancer incidence.

Participants and Methods

Study population. Participants were selected from the general population of the Amami Islands and mainland Kagoshima Prefecture, Japan, as part of the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study, which has been described in detail elsewhere [22]. Briefly, the baseline survey was conducted in five Amami Islands between 2005 and 2008 and in three local cities on the mainland in 2012. The survey was conducted among individuals who underwent routine health checkups that were conducted by local government or private companies. A total of 5015 participants from Amami and 2623

participants from the mainland aged 35–69 years provided written consent and were enrolled in the study, resulting in a response rate of 69.8%. Among these participants, 42 and 35 participants were excluded due to insufficient information and lack of duration information on health food intake, respectively, and the final number of eligible participants was 7561 (3136 men and 4425 women). The Ethics Review Committee for Human Genome/ Gene Analysis Research at the Kagoshima University Graduate School of Medical and Dental Sciences approved the study (Nos. 16 and 382).

Follow-up. Information on participant mortality and migration was collected by obtaining data from the municipality and cross-referencing this data with the basic resident register. Cases where participants moved out of the municipality or were removed from the basic resident register were treated as censored cases. Information on the cause of death was obtained from death certificates and vital statistics data with permission from the Ministry of Health, Labour and Welfare. After obtaining authorized permission, information on cancer incidence was collected through periodic surveys of research collaborators by mail or face-to-face interviews, death certificates, secondary surveys (questionnaires), hospital-based cancer registry materials, and regional cancer registry materials of the Kagoshima Prefecture. Medical records were reviewed for additional information, and written informed consent was obtained from participants.

The baseline survey began in October 2005, and follow-up information was collected until December 2019, resulting in a follow-up period ranging from 0.06 to 14.2 years. During this period, 344 participants moved out of the area, and 341 died. Twelve dead cases who died within one year after the baseline were excluded from the analysis, and final dead cases for the analysis were 329. Cancer cases were defined as those who received a cancer diagnosis one year after their respective baseline dates and had no history of cancer at baseline. The total number of participants diagnosed with cancer was 332, of whom 16.0% (n = 53) information was obtained from death certificates (death certificate notification [DCN]: 16.0%).

Health food intake. The present health food consumers were defined as those who had consumed health foods once or more times per week for one or more years. For those who responded "yes", detailed information was collected on the type of health food consumed, the duration of intake, and the frequency of intake per week or day. The most commonly consumed health foods, in descending order, were black vinegar (*Kurozu*), glucosamine, chlorella, agaricus bisporus mushroom (*Agaricus*), royal jelly, green juice (*Aojiru*), garlic, blueberry, and turmeric. Other health foods were consumed infrequently.

Lifestyles and biochemical data. Information on various lifestyle factors including smoking history, alcohol intake, daily activities, exercise habits, medical and drug history, and health food intake was collected using a questionnaire. A food frequency questionnaire (FFQ) was also administered to collect information on the dietary intake of three staple foods (rice, bread, and noodles), 43 food items, and several local foods. Daily energy, carbohydrate and fat intakes were estimated using the FFQ and an alcohol intake questionnaire. The validity of the FFQ has been confirmed in two different regions, including Amami, and has demonstrated its usefulness for relative comparison among participants [23,24].

Clinical data were obtained from the Kagoshima Kouseiren Medical Health Care Center and Clinical Pathology Laboratory as part of the health examination information. The data included height, weight, systolic and diastolic blood pressures, total cholesterol levels, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and fasting blood glucose (FBG) levels after fasting for more than 10 hours. Blood pressure was measured in the sitting position using a standard mercury sphygmomanometer or an automated blood pressure measurement monitor. When the low-density lipoprotein cholesterol (LDL-C) examination was not included in the routine health checkup, LDL-C levels were calculated using the Friedewald formula when a TG level <400 mg/dL [25].

Statistical Analysis. Age was categorized into three groups (35–49, 50–59, and 60–69 years). Food and beverage intake was stratified into three groups with a similar number of participants. Total and specific health food intake were classified as "yes" or "no". Smoking and alcohol consumption were categorized as current, former, or never. BMI was categorized as <18.5 kg/m^2, 18.5–24.9 kg/m^2, and ≥25 kg/m^2. To estimate metabolic equivalents (METs) for habitual exercise and daily activity, the questionnaire data on intensity, frequency, and duration were considered [26]. The resulting METs)h/day values were

categorized into three groups with similar numbers of the subjects: <0.17, 0.17–2.17, and ≥2.18 for habitual exercise, and <7.0, 7.0–21.0, and ≥21.0 for daily activity. Energy-adjusted carbohydrate and fat intake were estimated using the residual method [27]. Carbohydrate and fat intake were also classified into three groups based on percentiles.

Hypertension was defined as having a systolic or diastolic blood pressure of ≥140 mmHg or ≥90 mmHg, respectively, or the use of antihypertensive medication. Dyslipidemia was defined as having a TG level ≥150 mg/dL, an LDL-C level ≥140 mg/dL, HDL-C level <40 mg/dL, or the use of lipid-lowering agents. Glucose intolerance was defined as having an FBG level ≥110 mg/dL or the use of antidiabetic medication. Obesity was defined as having a BMI ≥25.0 kg/m2.

Person-years were calculated from baseline date (October 12, 2005, for the first participant) to the date of death or cancer incidence, the date of relocation out of the region, or the last date of follow-up (December 31, 2019), whichever occurred first. The median follow-up period was 11.5 years (range: 0.06–14.2 years) for death events and 11.4 years (range: 0.06–14.2 years) for cancer incidence events. Cases of death and cancer incidence within one year after the baseline survey were excluded from the analysis to eliminate potential confounding factors due to the reverse causation. An unconditional logistic model was used to estimate the odds ratios (ORs) and their 95% confidence intervals (CIs) for hypertension, dyslipidemia, glucose intolerance, and obesity in the cross-sectional analysis at baseline. Hazard ratios (HRs) and their 95% CIs for death and cancer incidence according to health food intake were estimated using the Cox proportional hazards model. Both ORs and HRs were adjusted for confounding factors such as age; sex; region; smoking; drinking; daily activity; habitual exercise; BMI; hypertension; dyslipidemia; glucose intolerance; family history of cancer; intake of meat, fish, green vegetables, fruits, citrus, and green tea; energy-adjusted carbohydrates; and energy-adjusted fat. For sub-analyses of each type of health food intake, other health foods were also added to the adjusted variables.

The HRs and p for trends for death and cancer incidence were also estimated by intake duration (0, 1.0-2.9, ≥3.0 years) using median duration years among participants who took health foods every day to evaluate dose-response effects of intake duration. Subgroup analysis by cause of death and cancer site was not conducted due to the limited number of deaths and incident cancer cases. A comparison of the characteristics of the study participants by sex was performed using chi-square test.

Statistical significance was set at $p < 0.05$. All statistical analyses were performed using Stata software (version 16; Stata Corp., College Station, TX, USA).

Results

The characteristics of the study participants, except for region, and total and several health food intakes, varied by sex, as shown in Table 1. Women had a slightly higher proportion of total health food intake (10.6%) compared to men (9.6%), and 5.2% of men and 5.2% of women had been consuming health foods for more than 3 years, but these differences were not statistically significant. Black vinegar was the most frequently consumed health food, with an intake of 2.3% in men and 2.6% in women. The intake frequency differed by sex, with more men reporting consumption of turmeric compared to women and more women reporting consumption of royal jelly and other health foods compared to men.

Table 1. Characteristics of study participants by sex

	Men		Women		*P*
	N	(%)	N	(%)	
Age in years					
35–49	752	24.0	977	22.1	
50–59	722	23.0	1147	25.9	*0.009*
60–69	1662	53.0	2301	52.0	
Total	3136	100	4425	100	
Region					
Amami islands	2035	64.9	2916	65.9	*0.364*
Mainland	1101	35.1	1509	34.1	
Smoking (current & former)	1653	52.7	677	15.3	*<0.001*
Drinking (current & former)	2426	77.4	1769	40.0	*<0.001*
Daily activity (≥21.0 METs・h/day)	1254	40.0	1468	33.2	*<0.001*
Habitual exercise (≥2.18 METs・h/day)	1088	34.7	1523	34.4	*0.021*
BMI (≥25.0 kg/m^2)	1287	41.0	1375	31.7	*<0.001*
Hypertension	1703	54.3	2003	45.3	*<0.001*
Dyslipidemia	1757	56.0	2228	50.4	*<0.001*
Glucose intolerance	736	23.5	500	11.3	*<0.001*
Family history of cancer among parents	964	30.7	1473	33.3	*0.002*
Health food intake					
Yes (≥1 year)	300	9.6	471	10.6	*0.127*
Years of intake (1–2.5 years)	137	4.4	240	5.4	*0.114*
Years of intake (≥3.0 years)	163	5.2	231	5.2	
Frequency of intake (1-6 times/week)*	55	1.6	91	2.1	*0.474*
Frequency of intake (≥7 times/week)*	205	6.5	315	7.1	
Kinds of health foods†					
Black vinegar (*Kurozu*)	72	2.3	113	2.6	*0.475*
Glucosamine	35	1.1	36	0.8	*0.179*
Chlorella	27	0.9	34	0.8	*0.657*
Agaricus	24	0.8	34	0.8	*0.988*
Royal jelly	12	0.4	40	0.9	*0.007*
Green juice (*Aojiru*)	16	0.5	27	0.6	*0.569*
Garlic	22	0.7	26	0.6	*0.539*
Blueberry	14	0.5	20	0.5	*0.972*
Turmeric	21	0.7	6	0.1	*<0.001*
Others	102	3.3	202	4.6	*0.004*

BMI, body mass index; METs, metabolic equivalents.
* Frequency information was missing in 105 participants.
† Some of intakes were duplicated.

At the baseline, the cross-sectional analyses found no association between total health food intake and atherosclerosis-related factors, except glucose intolerance (Table 2). However, a kind-specific analysis revealed a positive association between garlic and glucose intolerance (OR: 2.59, 95% CI: 1.17–5.74).

In the prospective study, overall health food intake or specific type of health food intake was not associated with increased or decreased HRs for

Table 2. Odds ratios and 95% confidence intervals for atherosclerosis-related factors according to health food intake in the cross-sectional study at the baseline

	Hypertension			Dyslipidemia			Glucose intolerance			Obesity		
	Case/ctrl	OR‡	95% CI	Case/ctrl	OR‡	95% CI	Case/ctrl	OR‡	95% CI	Case/ctrl	OR‡	95% CI
Health food intake												
No	3,271/2,749	1.00	-	3,539/2,946	1.00	-	1,082/4,333	1.00	-	2,389/4,345	1.00	-
Yes*	435/228	0.95	0.77-1.17	446/308	1.06	0.91-1.25	154/409	1.19	0.95-1.49	273/494	1.15	0.97-1.36
Kinds of health foods†												
Black vinegar (*Kurozu*)	120/34	1.00	0.62-1.61	102/80	0.84	0.61-1.16	36/78	1.22	0.78-1.92	52/133	0.93	0.65-1.32
Glucosamine	44/9	0.87	0.39-1.95	46/25	1.33	0.79-2.25	14/27	0.93	0.45-1.92	21/50	1.14	0.66-1.96
Chlorella	37/21	1.08	0.57-2.03	34/25	0.88	0.51-1.53	16/34	1.75	0.89-3.43	30/31	1.45	0.84-2.52
Agaricus	30/26	1.33	0.74-2.40	31/26	0.92	0.53-1.60	14/41	1.40	0.70-2.78	29/26	1.35	0.76-2.41
Royal jelly	29/19	1.06	0.53-2.12	32/18	1.46	0.79-2.67	8/35	0.93	0.40-2.15	15/37	0.70	0.37-1.34
Green juice (*Aojiru*)	27/10	1.84	0.80-4.21	24/18	0.95	0.50-1.80	10/21	1.90	0.83-4.37	12/31	0.67	0.33-1.36
Garlic	30/11	0.82	0.34-1.97	32/16	1.15	0.61-2.16	16/17	2.59	1.17-5.74	18/30	1.39	0.73-2.62
Blueberry	19/8	0.60	0.20-1.80	13/19	0.48	0.23-1.01	4/13	0.67	0.18-2.56	10/24	1.08	0.50-2.33
Turmeric	12/14	0.59	0.24-1.45	16/11	1.25	0.55-2.83	8/17	1.68	0.68-4.15	13/14	1.18	0.52-2.67
Others	163/97	0.91	0.66-1.25	183/114	1.26	0.98-1.62	49/175	0.82	0.57-1.19	111/192	1.27	0.98-1.64

Ctrl, control; OR, odds ratio; CI, confidence interval.
* Adjusted for age; sex; region; smoking; drinking; daily activity; habitual exercise; body mass index; hypertension; dyslipidemia; glucose intolerance; intake of meat, fish, green vegetables, fruits except citrus, citrus, and green tea; energy-adjusted carbohydrate; and energy-adjusted fat.
† Some of intakes were duplicated.
‡ Adjusted for age; sex; region; smoking; drinking; daily activity; habitual exercise; body mass index; hypertension; dyslipidemia; glucose intolerance; intake of meat, fish, green vegetables, fruits except citrus, citrus, and green tea; energy-adjusted carbohydrate; energy-adjusted fat; and each health food.

Table 3. Hazard ratios and 95% confidence intervals for overall death and cancer incidence according to health food intake in the prospective study

	Overall death			Cancer incidence		
	Event / PY	HR‡	95% CI	Event / PY	HR§	95% CI
Health food intake						
No	300 / 72,270	1.00	-	295 /70,445	1.00	-
Yes*	29 / 7,321	0.91	0.61-1.34	37 /7,117	1.13	0.79-1.62
Kinds of health foods†						
Black vinegar (*Kurozu*)	7 / 1,516	1.30	0.60-2.82	9 / 1,480	1.52	0.74-3.14
Glucosamine	1 / 561	0.41	0.06-2.99	6 / 523	1.77	0.71-4.41
Chlorella	4 / 661	0.91	0.29-2.89	5 / 631	1.68	0.69-4.09
Agaricus	1 / 764	0.28	0.04-2.01	1 / 758	0.30	0.04-2.13
Royal jelly	3 / 512	1.44	0.45-4.67	1 / 505	0.43	0.06-3.15
Green juice (*Aojiru*)	3 / 425	1.42	0.45-4.50	5 / 379	2.84	1.15-7.04
Garlic	2 / 417	1.21	0.29-4.93	0 / 410	-	
Blueberry	0 / 270	-		0 / 264	-	
Turmeric	2 / 308	0.91	0.22-3.71	2 / 300	1.06	0.26-4.34
Others	10 / 2,866	0.91	0.48-1.71	13 / 2,819	1.11	0.63-1.94

PY, person-years; HR, hazard ratio; CI, confidence interval.
* Adjusted for age; sex; region; smoking; drinking; daily activity; habitual exercise; body mass index; hypertension; dyslipidemia; glucose intolerance; intake of meat, fish, green vegetables, fruits except citrus, citrus, and green tea; energy-adjusted carbohydrate; and energy-adjusted fat.
† Some of intakes were duplicated.
‡ Adjusted for age; sex; region; smoking; drinking; daily activity; habitual exercise; body mass index; hypertension; dyslipidemia; glucose intolerance; intake of meat, fish, green vegetables, fruits except citrus, citrus, and green tea; energy-adjusted carbohydrate; energy-adjusted fat; and each health food.
§ Adjusted for age; sex; region; smoking; drinking; daily activity; habitual exercise; body mass index; hypertension; dyslipidemia; glucose intolerance; family history of cancer; intake of meat, fish, green vegetables, fruits except citrus, citrus, and green tea; energy-adjusted carbohydrate; energy-adjusted fat; and each health food.

overall mortality (Table 3). Additionally, there was no association found between health food intake and increased or decreased HRs for cancer incidence, except for a positive association between green juice intake and HR (OR: 2.84, 95% CI: 1.15–7.04).

The *p* for trends on the HRs for death and cancer incidence according to health food intake duration were not statistically significant among those who took health foods every day, except blueberry intake which number of participants were too small to estimate HRs, although increased HR for overall death with green juice intake was observed in a relative shorter intake duration group (Table 4).

Site-specific analysis for increased HRs for cancer incidence with green juice intake showed significant increased HRs for stomach cancer in men and women (HR: 8.07, 95% CI: 1.05-61.9) and breast cancer in women (HR: 4.99, 95% CI: 1.11-22.5), although the number of events was very small (n = 1 and 2, respectively) (Table 5).

Discussion

This study investigated the impact of health foods on the risk of death and cancer incidence in a cohort study of the general population in the Kagoshima Prefecture. Our findings suggest that total health food intake did not have a significant impact on the risk of death or cancer incidence. While the cross-sectional analysis at baseline revealed positive associations between some health foods and arteriosclerosis-

Table 4. Hazard ratios and 95% confidence intervals for overall death and cancer incidence according to health food intake by intake duration among those who took every day

	Overall death						Cancer incidence					
	0 years	1.0-2.9 years		≥3 years		*P* for trends†	0 years	1.0-2.9 years		≥3 years		*P* for trends‡
	HR	HR†	95% CI	HR†	95% CI		HR	HR‡	95% CI	HR‡	95% CI	
Kinds of health food*												
Black vinegar	1.00	0.89	0.21-3.74	1.22	0.38-3.90	0.811	1.00	1.56	0.48-5.01	1.77	0.65-4.86	*0.192*
Glucosamine	1.00	-		-		1.000	1.00	2.00	0.49-8.16	1.96	0.47-8.18	*0.214*
Chlorella	1.00	-		1.34	0.18-10.1	0.890	1.00	-		2.74	0.68-11.2	*0.354*
Agaricus	1.00	-		-		-	1.00	-		-		-
Royal jelly	1.00	1.03	0.13-7.98	1.71	0.23-12.8	0.643	1.00	-		2.00	0.28-14.5	*0.981*
Green juice	1.00	4.13	1.01-16.9	-		0.814	1.00	2.45	0.34-17.7	1.21	0.17-8.83	*0.634*
Garlic	1.00	-		2.19	0.53-9.11	0.382	1.00	-		-		-
Blueberry	1.00	-		-		-	1.00	-		-		-
Turmeric	1.00	-		5.80	1.39-24.2	0.080	1.00	1.63	0.22-12.2	1.75	0.24-12.9	*0.481*
Others	1.00	1.09	0.35-3.42	0.79	0.25-2.48	0.749	1.00	0.89	0.29-2.81	1.24	0.51-3.03	*0.721*

HR, hazard ratio; CI, confidence interval.
* Some of intakes were duplicated.
† Adjusted for age; sex; region; smoking; drinking; daily activity; habitual exercise; body mass index; hypertension; dyslipidemia; glucose intolerance; intake of meat, fish, green vegetables, fruits except citrus, citrus, and green tea; energy-adjusted carbohydrate, energy-adjusted fat; and each health food.
‡ Adjusted for age; sex; region; smoking; drinking; daily activity; habitual exercise; body mass index; hypertension; dyslipidemia; glucose intolerance; family history of cancer; intake of meat, fish, green vegetables, fruits except citrus, citrus, and green tea; energy-adjusted carbohydrate, energy-adjusted fat; and each health food.

Table 5. Hazard ratios and 95% confidence intervals for specific-site cancer incidence according to green juice intake

	Green juice intake			
	Yes	No		
	Event / PY	Event / PY	HR*	95% CI
Stomach	1 / 378	48 / 77,184	8.07	1.05-61.9
Colon	0 / 378	39 / 77,184	-	
Lung	0 / 378	44 / 77,184	-	
Breast in women	2 / 261	78 / 45,461	4.99	1.11-22.5
Prostate in men	1 / 117	32 / 31,722	3.56	0.28-45.8

PY, person-years; HR, hazard ratio; CI, confidence interval.
* Adjusted for age; sex; region; smoking; drinking; daily activity; habitual exercise; body mass index; hypertension; dyslipidemia; glucose intolerance; family history of cancer; intake of meat; fish; green vegetables; fruits except citrus; citrus; green tee; energy-adjusted carbohydrate; energy-adjusted fat; and each food product/supplement.

related factors, the prospective study showed no association between health food intake and overall death or cancer incidence, except for a positive association between green juice intake and cancer incidence.

The popularity of health foods is driven by the desire to maintain and improve health, improve nutritional balance, and provide various other benefits such as fatigue recovery, joint health, beautiful skin and skin care, and nutritional support [3]. In this study, the most consumed health foods, in descending order, were black vinegar, glucosamine, chlorella, agaricus, royal jelly, green juice, garlic, blueberry, and turmeric. Each health food has unique properties that are associated with specific health benefits. For instance, black vinegar has been shown to reduce blood pressure [10], regulate blood glucose levels [11], and inhibit fat synthesis [12]. Glucosamine is known to improve joint health and reduce osteoarthritis symptoms in the knee and hip joints [28], while chlorella has been found to promote overall health and wellness [29]. Agaricus bisporus mushrooms are believed to have cancer-preventive properties [30], and royal jelly is associated with health longevity [31]. Green juice is a great source of antioxidants that can help improve bowel movements [7], decrease blood sugar levels [8], and protect against oxidative stress [9]. Garlic has been shown to improve cardiovascular function [32], boost the immune system, and reduce inflammation [33]. Anthocyanins, which are present in blueberries and other foods, can improve night vision [34], regulate blood glucose levels [14], lower blood pressure [15,16], and provide antioxidant and anti-inflammatory benefits [13]. Turmeric is known for its powerful antioxidant, anti-inflammatory, and anticancer properties [35]. However, the effects of these health foods on the risk of death and cancer, which are the most significant health events, have not been adequately examined.

In the current cross-sectional study, a reverse causality between health food intake and health events was assumed. As a result, positive associations were found between black vinegar and hypertension, garlic and impaired glucose tolerance, and other health foods and dyslipidemia.

The 14-year prospective study found that total health foods and the nine-specific health foods were not associated with overall deaths and cancer incidence, except for green juice that was associated with increased HR for cancer. There is no study reported a positive association between intake of green juice itself and increased cancer risk, as far as we know. Green juice (*Aojiru*) is a common health food in Japan made from young barley leaves, kale, Angelica keiskei (*Ashitaba*), moroheiya, and chlorella; green juice has been shown to improve bowel movements with dietary fiber [7], suppress the rise in blood glucose levels [8], and provide antioxidant effects with flavonoids [9]. The decrease in cancer risk due to green juice was expected; however, the opposite relationship observed in this study may be due to an accidental alpha-error, confounding with unknown factors such as ingestion by high-risk individuals, or the negative effects of antioxidant overdosing [36, 37]. As dose-dependent relationship between intake duration and the increased HRs with green juice intake was not observed in Appendix Table 1, the possibility of an accidental alpha-error cannot be rule out. Furthermore, cancer site-specific relationship was not observed in Appendix Table 2, and the specific cause of this relationship are currently unknown. Further study is required to clarify the potential increased risk of cancer with green juice intake.

One limitation of this study is that the number of participants who consumed health foods was relatively small, which may have increased the susceptibility to random errors. To address this limitation, the follow-up period was extended to 14 years to increase person-years. Additionally, the reasons why participants began consuming health foods are unknown; additionally, the phenomenon of reverse causality may not have been completely eliminated, even in a prospective study. To mitigate this effect, individuals who died or developed cancer within 1 year of the baseline survey were excluded from the analysis. Furthermore,

due to the relatively small number of participants who consumed health foods, statistical power may be small to analyze the dose-response effects of intake period as the sub-group analysis among every day consumers. Although definitive amount and duration of health food intake which involve in health effects is unclear, we defined the definition of health food intake as one or more times per week for one or more years with reference to the previous reports. In experiments using mice, each health food was administered for 4-12 weeks [7,10-12,14,29], and in intervention trials on humans, it was administered for 3-16 weeks [8,15,17,30,34], except glucosamine for 1-144

weeks [28]. In addition, the FFQ used in this study collected the information on the average dietary habit of the past one year. Another limitation is the variability in the raw materials and ingredients of health foods, which may affect their effectiveness, making it challenging to evaluate their effects accurately. As the study participants were recruited in Amami islands and mainland of Kagoshima, Japan, the study results reflected the characteristics of this region.

Conclusion

This study aimed to investigate the relationship between health food intake, and risks of death and cancer incidence in a general population cohort in Kagoshima Prefecture, Japan. In the baseline cross-sectional study, several health foods were found to be associated with arteriosclerosis-related factors, and reverse causality was observed. In this prospective study, health food intake was not associated with overall death or cancer incidence, except for green juice intake. In conclusion, the consumption of healthy foods by the general population in Amami Islands and mainland of Kagoshima, Japan did not have a significant impact on the risk of overall death or cancer incidence, except green juice intake. Further study is required to clarify the increased risk of cancer with green juice intake.

COI declaration

No conflicts of interest to be declared.

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鹿児島県の奄美群島と本土の一般集団における健康食品摂取と全死亡・がん罹患リスクに関する研究

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和文要約

【背景と目的】様々な健康食品がテレビやインターネットで紹介され，販売されているが，それらの有効性と効果の証拠は，多くの場合，in vitroおよびin vivo研究に限定されている．本研究では，健康食品摂取と全死亡とがん罹患リスクとの関連を検索するため，鹿児島県の一般人口を対象としたコーホート研究を行った．

【方法】研究対象者は奄美群島と鹿児島県本土の一般集団7,561人(男性3,136人，女性4,425人)である．健康食品全体および9種類の健康食品(黒酢，グルコサミン，クロレラ，アガリクス，ローヤルゼリー，青汁，ニンニク，ブルーベリー，ターメリック)について，Cox比例ハザードモデルを用いて交絡変数を調整し，全死亡およびがん発生のハザード比（HR）と95%信頼区間を見積もった．

【結果】健康食品の中で，最も高頻度に摂取されていたのは黒酢であった(男性で2.3%，女性で2.6%)．ベースライン時の横断的解析では，ニンニクと耐糖能異常との間に正の関連が見られた．しかし，前向き研究では，青汁摂取とがん罹患HR上昇(2.84，1.15-7.04)が認められた他には，健康食品全体および9種類それぞれの健康食品摂取と全死亡および，がん罹患との間に有意な関連は認められなかった．

【結論】鹿児島の一般集団が一般的に摂取している健康食品と全死亡およびがん罹患リスクとの間に有意な関連は，青汁摂取以外には認められなかった．青汁摂取に伴うがんリスク上昇の可能性に関しては，さらなる研究が必要である．