Received: 17 December 2020 | Revised: 25 February 2021 | Accepted: 25 February 2021

DOI: 10.1111/cas.14870

ORIGINAL ARTICLE

Cancer Science WILEY

Long-term antihypertensive drug use and risk of cancer: The Japan Public Health Center-based prospective study

Satoshi Matsui[1] | Tomotaka Sobue[1] | Ling Zha[1] | Tetsuhisa Kitamura[1] | Norie Sawada[2] | Motoki Iwasaki[2] | Taichi Shimazu[2] | Shoichiro Tsugane[2]

[1]Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, Suita, Japan

[2]Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan

Correspondence
Tomotaka Sobue, Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, F1 2-2 Yamadaoka, Suita 565-0871, Japan.
Email: tsobue@envi.med.osaka-u.ac.jp

Funding information
Food Safety Commission, Cabinet Office, Government of Japan, Grant/Award Number: 1503; the National Cancer Center Research and Development Fund; Ministry of Health, Labor and Welfare of Japan

Abstract

Antihypertensive drugs have been reported as both promotors and suppressors of cancers and this relationship has been known for several decades. We examined a large-scale prospective cohort study in Japan to assess the relationship between long-term antihypertensive drug use, for 10 y, and carcinogenesis. We divided participants into 4 categories according to the period of antihypertensive drug use, and calculated the hazard ratios (HRs), 95% confidence intervals (CIs), and *P* trends using the Cox proportional hazard model. In all cancers, there was a significant difference in the medication period and the adjusted HR, as well as a significant difference in the *P* trend. Furthermore, more than 10 y use of antihypertensive drugs significantly increased the adjusted HR in colorectal cancer (multivariable HR: 1.18, 95% CI: 1.01-1.37 in the >10 y use group; *P* for trend = .033) and renal cancer (multivariable HR: 3.76, 95% CI: 2.32-6.10 in the 5-10 y use group; multivariable HR: 2.14, 95% CI: 1.29-3.56 in the >10 y use group; *P* for trend < .001). The highest adjusted HR in renal cancer among antihypertensive drug users was observed in the analysis performed on patients in which the outcomes were calculated from 3 y after the 10-y follow-up survey and by sex. A large-scale cohort study in Japan suggested that long-term use of antihypertensive drugs may be associated with an increased incidence of colorectal and renal cancer.

KEYWORDS

cancer risk, carcinogenesis, cohort, long-term drug use, prospective study

1 | INTRODUCTION

It has been suggested that several drugs can either prevent or promote cancer, as well as their intended effect. For antihypertensive drugs, the relationship with cancer has been known for several decades.[1] Coleman et al[2] in a 2008 meta-analysis with an average observation period of 3.3 y reported no substantial association between cancer development and antihypertensive drugs. However, in 2010, Sipahi et al[3] suggested that ARB increased the risk of developing cancer and, conversely, the results of Bangalore et al[4] reported in 2011 that they were unrelated. In recent studies on various cancers and antihypertensive drugs, it has been reported

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AT1R, angiogenesis II type-1 receptor; AT2R, angiogenesis II type-2 receptor; CI, confidence interval; HR, hazard ratio; JPHC, Japan Public Health Center; PHC, public health center; RAS, renin-angiotensin system.

that angiotensin-converting enzyme inhibitor (ACE-I) and ARB are associated with a decrease in the incidence of colorectal cancer,[5] while for lung cancer, there have been reports that ACE-I is associated with increased cancer incidence.[6] Moreover, for breast cancer, it has been reported that antihypertensive drugs (ARB, ACE-I, Ca blocker, β-blocker, diuretics) are either associated with an increase in cancer incidence[7,8] or are not related.[9] In other words, the association between antihypertensive drug use and cancer is controversial. Furthermore, these previous studies vary in terms of their data source, duration of drug use, and study design, while there remain limited studies from Asian countries.

In this study, we investigated the relationship between the long-term use of antihypertensive drugs and the occurrence of various cancers in a large-scale prospective cohort study in Japan.

2 | MATERIALS AND METHODS

2.1 | Study cohort and participants

The Japan Public Health Center-Based prospective study (JPHC study) is a cohort study that mainly investigated cancer and cardiovascular diseases. The study comprised 2 cohorts; the first was initiated in 1990 (Cohort I), and the second in 1993 (Cohort II). The participants were identified by population registries maintained by local municipalities. In total, in this study, 140 420 residents participated from 11 public health centers (PHCs), of which, there were 61 595 participants in Cohort I (aged 40-59 y at the time of their first survey) who were identified in the areas supervised by 6 PHCs. Additionally, there were 78 825 participants in Cohort II (aged 40-69 y at the time of their first survey) who were identified in the areas supervised by 5 PHCs. The questionnaire was distributed mostly by hand, and the 5-y and 10-y follow-up surveys were conducted to update the information. The study design has been reported in detail previously.[10] The JPHC study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan. The present study was approved by the Ethical Review Board of Osaka University, Osaka, Japan. Figure 1 shows the flowchart for the selection of eligible patients for the analysis. In this study, the subjects from 2 public health center areas (Katsushika in the Tokyo prefecture and Suita in the Osaka prefecture) were excluded (N = 23 524) because the incidence data for cancer were unavailable and the selection of subjects differed from those in other PHCs. We also excluded participants who had cancer (N = 28 787), died, or moved out of the study area, and those who were lost to follow-up before the 10-y follow-up survey (N = 2997). In addition, we further excluded participants who did not answer the baseline, 5-y follow-up, or 10-y follow-up surveys (N = 17 150). For the final analysis, the number of eligible participations was 67 962.

2.2 | Exposure assessment

The participants were divided into the following 4 antihypertensive drug-use categories; participants who could not be categorized into any category were excluded (N = 2876). As a result, 65 086 subjects were analyzed.

- no, participants who took no antihypertensive drugs at the baseline, 5-y follow-up, or 10-y follow-up survey
- <5 y, participants who took antihypertensive drugs at the 10-y follow-up survey, but not at the baseline and 5-y follow-up surveys
- 5-10 y, participants who took antihypertensive drugs at the 5-y follow-up and 10-y follow-up surveys, but not at the baseline survey
- >10 y, participants who took antihypertensive drugs at the baseline, 5-y follow-up, and 10-y follow-up surveys

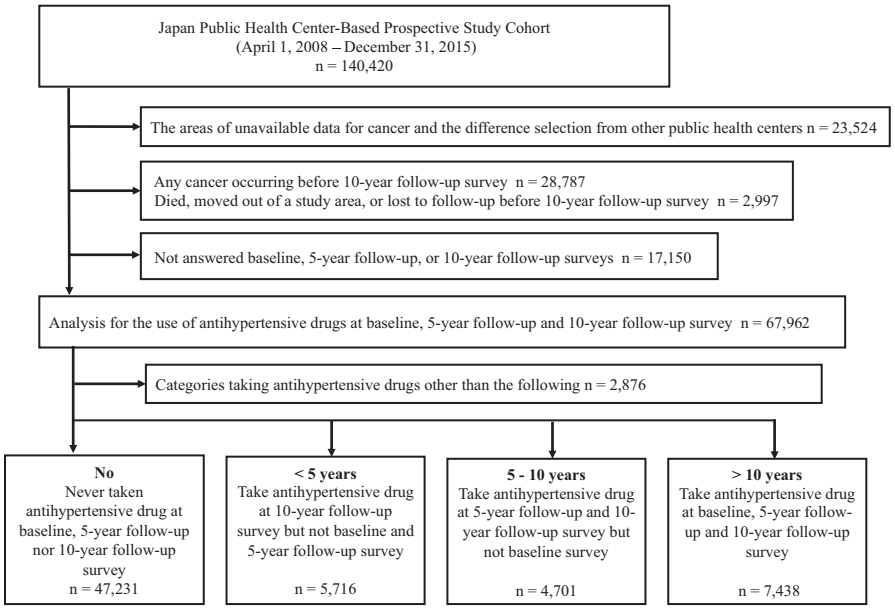

FIGURE 1 Patient selection flow chart

2.3 | Follow-up and cancer incidence

The follow-up was performed using information on residential status and survival collected from the residential registers from each municipality in the study area. Death certificates were coded in accordance with the requirements of the Japanese Ministry of Health, Labor, and Welfare. Cancer incidence was mainly identified from 2 data sources: active patient notification from major local hospitals in the study area; and population-based cancer registries. In this study, we selected the most common cancer sites in Japan and renal cancer as the population to be analyzed. The common cancer sites were decided by the national cancer registration in Japan[11] and a previous study;[12] lung, stomach, colorectal, liver, pancreatic, prostate, and breast cancers were selected in our analyses. In addition, as renal cancer has been known to be associated with the use of antihypertensive drugs in the preceding studies,[13,14] we selected this cancer. The site of origin was coded using the International Classification of Diseases for Oncology, Third Edition, with lung cancer as C34; stomach cancer as C16; colorectal cancer as C18, C19, and, C20; liver cancer as C22; renal cancer as C64; pancreatic cancer as C25; prostate cancer as C61; and breast cancer as C50. If a participant was diagnosed with more than 1 cancer, the cancer that had the earliest diagnosis was used for the analysis.

2.4 | Statistical analyses

The survey consisted of a self-administered questionnaire that included questions on various lifestyle factors, including personal and family medical histories, smoking habits, and alcohol drinking frequency. The questions on cigarette smoking included the starting and quitting age, current smoking situation, and the number of cigarettes smoked per day. The smoking index (SI) was used as an index of smoking intensity. The baseline questionnaire on alcohol consumption included drinking frequency and the weekly ethanol consumption was calculated[15] and used to approximate the amount of ethanol intake.

The number of person-years for the follow-up was calculated from the date of the 10-y follow-up survey until the end of the follow-up, which was the earliest date of any of the following events: moving out of the study area, lost to follow-up, death, diagnosis of any cancer, or the last date of the follow-up period (December 31, 2012). The participants who were lost to follow-up were censored at the last confirmed date of their presence in the study area. The incidence rate was calculated by dividing the number of cases by the person-years of follow-up.

The participant characteristics were compared across the 4 categories of antihypertensive drug use (No, <5 y, 5-10 y, and >10 y) using analysis of variance for numerical variables and chi-square test for categorical variables. The HRs, 95% CIs, and *P* trends for all cancers and each cancer among the 4 categories were estimated using the Cox proportional hazards model with an adjustment for potential confounders.

This multivariate analysis model was adjusted for the following potential confounders from baseline survey that were biologically a priori and/or were considered to be associated with general/specific cancer risk[16-18]: age (continuous); study area (9 PHC areas); sex (men/women); body mass index (<25, ≥25 kg/m^2); smoking status (never, former, 0 < SI < 400, 400 ≤ SI < 600, 600 ≤ SI < 800, 800 ≤ SI < 1000, 1000 ≤ SI < 1200, 1200 ≤ SI, unknown); alcohol drinking status (never, former, 0 < and < 150, 150 ≤ and < 299, 300 ≤ and <449, ≥450 g/wk, unknown); history of diabetes mellitus (no/yes). Additionally, we used the following factors for analysis of each specific cancer: history of chronic hepatitis or cirrhosis (no/yes) for liver cancer analysis; salt intake (continuous) for stomach cancer analysis; and history of parous (no/yes) for breast cancer analysis. Moreover, only for renal cancer analysis, we also readjusted for blood pressure classification (systolic blood pressure [sBP] < 120 or diastolic blood pressure [dBP] < 80, 120 ≤ sBP <130 or 80 ≤ dBP <85, 130 ≤ sBP <140 or 85 ≤ dBP <90, 140 ≤ sBP < 160 or 90 ≤ dBP < 100, 160 ≤ sBP < 180 or 100 ≤ dBP < 110, sBP ≥ 180 and dBP ≥ 110) in addition to above confounding factors. The blood pressure data were from self-reporting in 10-y follow-up surveys. In this analysis, 19 460 subjects were excluded because they did not have blood pressure data. We analyzed the ordinal variables as dummy variables, and we performed the same analysis as above for patients in which the outcomes were calculated from 3 y after the 10-y follow-up survey and by sex.

All *P* values were two-sided, and the significance level was set at $P < .05$. All statistical analyses were performed using Stata MP version 15.0 software (StataCorp LP).

3 | RESULTS

Table 1 shows the baseline characteristics according to the antihypertensive drug-use category. The participants who took antihypertensive drugs for longer tended to be older, and the proportion tended to be higher in females and those who had a body mass index ≥ 25 kg/m^2. With regards to smoking status (6 categories in Table 1, unlike the classification used as a covariate), participants who did not smoke tended to take antihypertensive drugs for longer, and participants who took antihypertensive drugs for longer tended to have a smaller SI. In terms of alcohol consumption, participants who never drunk alcohol tended to take antihypertensive drugs for longer.

The HRs and 95% CIs for cancer incidence according to antihypertensive drug-use categories are shown in Table 2. The duration of antihypertensive drug use was significantly associated with an increased risk of all cancers (multivariable HRs: 1.08, 95% CI: 1.01-1.16 in the >10 y group; *P* for trend = .009), colorectal cancer (multivariable HRs: 1.18, 95% CI: 1.01-1.37 in the >10 y group; *P* for trend = .033) and renal cancer (multivariable HRs: 3.76, 95% CI: 2.32-6.10, in 5-10 y group; multivariable HRs: 2.14, 95% CI: 1.29-3.56 in >10 y group; *P* for trend < .001). For the other cancers, there

TABLE 1 Characteristics according to antihypertensive drug-use categories, Japan Health Centered-based Prospective Study

	Total (N = 65 086)	No (N = 47 231)	<5 y (N = 5716)	5-10 y (N = 4701)	>10 y (N = 7438)	
Female, n (%)	36 022 (55.4)	25 917 (54.9)	3139 (56.4)	2649 (56.4)	4317 (58.0)	<.001
Age in years, mean (SD)	62.3 (7.7)	61.1 (7.4)	63.9 (7.7)	65.0 (7.6)	67.3 (6.9)	<.001
Body mass index ≥ 25 kg/m^2, n (%)[a]	19 426 (30.6)	12 259 (26.6)	2137 (38.2)	1909 (41.5)	3121 (43.1)	<.001
Smoking, n (%)						
Never	41 698 (64.1)	29 918 (63.3)	3685 (64.5)	3082 (65.6)	5013 (67.4)	<.001
Former	9143 (14.1)	6114 (12.9)	993 (17.4)	801 (17.0)	1235 (16.6)	
0 ≤ SI < 600	3730 (5.7)	2950 (6.2)	263 (4.6)	205 (4.4)	312 (4.2)	
600 ≤ SI < 1000	5850 (9.0)	4697 (9.9)	403 (7.1)	318 (6.8)	432 (5.8)	
1000 ≤ SI	3063 (4.7)	2439 (5.2)	238 (4.2)	165 (3.5)	221 (3.0)	
Unknown	1602 (2.5)	1113 (2.4)	134 (2.3)	130 (2.8)	225 (3.0)	
Drinking, n (%)						
Never	33 469 (51.4)	24 037 (50.9)	2953 (51.7)	2467 (52.5)	4012 (53.9)	<.001
Former	2335 (3.6)	1508 (3.2)	274 (4.8)	199 (4.2)	354 (4.8)	
0 < Alcohol (g/wk) < 149	8116 (12.5)	6466 (13.7)	593 (10.4)	466 (9.9)	591 (8.0)	
150 ≤ Alcohol (g/wk) < 299	3463 (5.32)	2519 (5.3)	298 (5.2)	260 (5.5)	386 (5.2)	
300 ≤ Alcohol (g/wk) < 449	2377 (3.65)	1726 (3.7)	212 (3.7)	173 (3.7)	266 (3.6)	
450 ≤ Alcohol (g/wk)	2822 (4.3)	2032 (4.3)	270 (4.7)	239 (5.1)	281 (3.8)	
Unknown	12 504 (19.2)	8943 (18.9)	1116 (19.5)	897 (19.1)	1548 (20.8)	
Blood pressure, n (%)[b]						
sBP < 120 or dBP < 80	7165 (15.7)	6865 (22.1)	131 (2.9)	78 (2.0)	91 (1.5)	<.001
120 ≤ sBP < 130 or 80 ≤ dBP < 85	9523 (20.9)	8184 (26.4)	492 (10.7)	367 (9.6)	480 (7.7)	
130 ≤ sBP < 140 or 85 ≤ dBP < 90	13 416 (29.4)	9036 (29.1)	1379 (30.1)	1248 (32.5)	1753 (28.3)	
140 ≤ sBP < 160 or 90 ≤ dBP < 100	13 412 (29.4)	6176 (19.9)	2114 (46.1)	1832 (47.8)	3290 (53.1)	
160 ≤ sBP < 180 or 100 ≤ dBP < 110	2098 (4.6)	744 (2.4)	463 (10.1)	310 (8.1)	581 (9.4)	
sBP ≥ 180 and dBP ≥ 110	12 (0.0)	4 (0.0)	3 (0.1)	1 (0.0)	4 (0.1)	
Diabetes mellitus	3984 (6.1)	2324 (4.9)	440 7.7)	443 (9.4)	777 (10.5)	
Salt intake (g), mean (SD)	12.24 (7.82)	12.45 (7.9)	11.81 (8.20)	11.70 (7.77)	11.64 (7.11)	<.001
Chronic hepatitis/cirrhosis	723 (1.1)	449 (1.0)	78 (1.4)	96 (2.0)	100 (1.3)	<.001
Non parous, n (%)[c]	1920 (5.7)	1410 (5.8)	158 (5.4)	141 (5.8)	211 (5.3)	.549

Note: No, never taken antihypertensive drug at baseline, 5-y follow-up nor 10-y follow-up survey; <5 y, take antihypertensive drug at 10-y follow-up survey but not baseline and 5-y follow-up survey; 5-10 y, take antihypertensive drug at 5-y follow-up and 10-y follow-up survey but not baseline survey; >10 y, take antihypertensive drug at baseline, 5-y follow-up and 10-y follow-up survey.

Abbreviations: CI, confidence interval; dBP diastolic blood pressure; sBP, systolic blood pressure; SD, standard deviation; SI, smoking index.

[a]The number of missing values is 1646.; [b]The number of missing values is 19 460.; [c]The number of missing values among women is 2461.

were no significant differences in the multivariable HRs of the antihypertensive drug-use categories and the *P* for trend.

In the relationship between antihypertensive drug use and renal cancer, in which blood pressure was also added as a confounding factor, multivariable HRs in <5 y group, 5-10 y group, and >10 y group were 1.11 (95% CI: 0.51-2.44), 3.59 (95% CI: 2.05-6.30), and 1.90 (95% CI: 1.04-3.48) respectively, and *P* for trend was <.001.

In the analysis of patients in which outcomes were calculated from 3 y after the 10-y follow-up survey (Table 3), we found a significant difference in the multivariable HRs and *P* for trend in all cancers (multivariable HR: 1.12, 95% CI: 1.02-1.23 in 5-10 y

TABLE 2 Hazard ratios for major sites of cancer according to antihypertensive drug-use categories

	No	<5 y	5-10 y	>10 y	*P* for trend
Person, y (n = 716 198), n	5 27 777	61 650	50 357	76 413	
All cancers					
Cases (n = 8256), n	5659	802	674	1121	
Age, gender and area adjusted HRs (95% CI)	Reference	1.07 (0.99-1.15)	1.07 (0.99-1.16)	1.07 (1.005-1.15)	.011
Multivariable HRs (95% CI)[a]	Reference	1.07 (0.996-1.16)	1.06 (0.98-1.16)	1.08 (1.01-1.16)	.009
Lung cancer					
Cases (n = 1031), n	756	79	70	126	
Age, gender and area adjusted HRs (95% CI)	Reference	0.74 (0.58-0.93)	0.76 (0.59-0.97)	0.80 (0.66-0.97)	.003
Multivariable HRs (95% CI)[a]	Reference	0.81 (0.64-1.07)	0.87 (0.67-1.11)	0.94 (0.77-1.14)	.262
Stomach cancer					
Cases (n = 1391), n	981	117	105	188	
Age, gender and area adjusted HRs (95% CI)	Reference	0.92 (0.76-1.12)	1.02 (0.83-1.25)	1.04 (0.88-1.22)	.719
Multivariable HRs (95% CI)[b]	Reference	0.93 (0.77-1.13)	0.97 (0.79-1.20)	1.06 (0.90-1.24)	.679
Colorectal cancer					
Cases (n = 1584), n	1070	155	129	230	
Age, gender and area adjusted HRs (95% CI)	Reference	1.12 (0.94-1.32)	1.10 (0.91-1.32)	1.21 (1.05-1.40)	.008
Multivariable HRs (95% CI)[a]	Reference	1.12 (0.94-1.33)	1.07 (0.88-1.29)	1.18 (1.01-1.37)	.033
Liver cancer					
Cases (n = 355), n	216	47	38	54	
Age, gender and area adjusted HRs (95% CI)	Reference	1.60 (1.17-2.20)	1.53 (1.08-2.17)	1.26 (0.93-1.72)	.022
Multivariable HRs (95% CI)[c]	Reference	1.45 (1.04-2.02)	1.31 (0.92-1.88)	1.18 (0.86-1.62)	.141
Renal cancer					
Cases (n = 120), n	61	10	25	24	
Age, gender and area adjusted HRs (95% CI)	Reference	1.29 (0.66-2.54)	3.81 (2.37-6.14)	2.25 (1.37-3.68)	<.001
Multivariable HRs (95% CI)[a]	Reference	1.29 (0.66-2.54)	3.76 (2.32-6.10)	2.14 (1.29-3.56)	<.001
Pancreas cancer					
Cases (n = 318), n	210	37	22	49	
Age, gender and area adjusted HRs (95% CI)	Reference	1.31 (0.92-1.87)	0.91 (0.58-1.41)	1.20 (0.87-1.65)	.355
Multivariable HRs (95% CI)[a]	Reference	1.30 (0.91-1.87)	0.94 (0.60-1.47)	1.20 (0.86-1.68)	.338
Prostatic cancer					
Cases (n = 907), n	617	87	66	137	
Age, gender and area adjusted HRs (95% CI)	Reference	1.02 (0.82-1.28)	0.94 (0.72-1.21)	1.23 (1.02-1.48)	.100
Multivariable HRs (95% CI)[a]	Reference	0.99 (0.79-1.25)	0.87 (0.67-1.14)	1.16 (0.95-1.41)	.370
Breast cancer					
Cases (n = 462), n	336	48	34	44	
Age, gender and area adjusted HRs (95% CI)	Reference	1.27 (0.94-1.73)	1.07 (0.75-1.53)	0.91 (0.66-1.26)	.880
Multivariable HRs (95% CI)[d]	Reference	1.21 (0.88-1.67)	1.00 (0.69-1.46)	0.73 (0.51-1.05)	.180

Note: No, never taken antihypertensive drug at baseline, 5-y follow-up nor 10-y follow-up survey; <5 y, take antihypertensive drug at 10-y follow-up survey but not baseline and 5-y follow-up survey; 5-10 y, take antihypertensive drug at 5-y follow-up and 10-y follow-up survey but not baseline survey; >10 y, take antihypertensive drug at baseline, 5-y follow-up and 10-y follow-up survey.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Adjusted for gender, age, area, body mass index, smoking status, drinking status, and history of diabetes mellitus.; [b]Adjusted for gender, age, area, body mass index, smoking status, drinking status, history of diabetes mellitus, and salt intake.; [c]Adjusted for gender, age, area, body mass index, smoking status, drinking status, history of diabetes mellitus, and hepatic status.; [d]Adjusted for gender, age, area, body mass index, smoking status, drinking status, history of diabetes mellitus, and parous status.

group; multivariable HRs: 1.11, 95% CI: 1.02-1.20 in >10 y group; *P* for trend = .001) and renal cancer (multivariable HRs: 3.89, 95% CI: 2.30-6.58 in 5-10 y group; multivariable HRs: 2.29, 95% CI: 1.33-3.97 in >10 y group; *P* for trend < .001), although there was no significant difference in the multivariable HRs and *P* for trend for colorectal cancer.

TABLE 3 Hazard ratios for major sites of cancer according to antihypertensive drug-use categories on cases in which outcomes were calculated from the date of the 3 y after the 10-y follow-up survey

	No	<5 y	5-10 y	>10 y	*P* for trend
All cancers					
Cases (n = 6771), n	4642	661	564	904	
Multivariable HRs (95% CI)[a]	Reference	1.10 (1.01-1.20)	1.12 (1.02-1.23)	1.11 (1.02-1.20)	.001
Lung cancer					
Cases (n = 824), n	608	63	59	94	
Multivariable HRs (95% CI)[a]	Reference	0.83 (0.63-1.08)	0.93 (0.71-1.23)	0.95 (0.76-1.19)	.300
Stomach cancer					
Cases (n = 1115), n	780	94	88	153	
Multivariable HRs (95% CI)[b]	Reference	0.96 (0.77-1.19)	1.05 (0.83-1.32)	1.13 (0.94-1.35)	.231
Colorectal cancer					
Cases (n = 1293), n	882	126	107	178	
Multivariable HRs (95% CI)[a]	Reference	1.11 (0.92-1.35)	1.09 (0.88-1.34)	1.12 (0.94-1.33)	.142
Liver cancer					
Cases (n = 275), n	162	38	28	47	
Multivariable HRs (95% CI)[c]	Reference	1.56 (1.08-2.27)	1.29 (0.85-1.95)	1.41 (0.9975-2.01)	.031
Renal cancer					
Cases (n = 103), n	52	9	21	21	
Multivariable HRs (95% CI)[a]	Reference	1.41 (0.69-2.89)	3.89 (2.30-6.58)	2.29 (1.33-3.97)	<.001
Pancreas cancer					
Cases (n = 267), n	176	34	19	38	
Multivariable HRs (95% CI)[a]	Reference	1.49 (1.01-2.18)	1.02 (0.63-1.66)	1.19 (0.82-1.73)	.330
Prostatic cancer					
Cases (n = 765), n	527	71	56	111	
Multivariable HRs (95% CI)[a]	Reference	0.99 (0.77-1.28)	0.94 (0.71-1.24)	1.15 (0.93-1.42)	.363
Breast cancer					
Cases (n = 378), n	274	41	29	34	
Multivariable HRs (95% CI)[d]	Reference	1.27 (0.89-1.80)	1.06 (0.70-1.60)	0.81 (0.55-1.19)	.509

Note: No, never taken antihypertensive drug at baseline, 5-y follow-up nor 10-y follow-up survey; <5 y, take antihypertensive drug at 10-y follow-up survey but not baseline and 5-y follow-up survey; 5-10 y, take antihypertensive drug at 5-y follow-up and 10-y follow-up survey but not baseline survey; >10 y, take antihypertensive drug at baseline, 5-y follow-up and 10-y follow-up survey.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Adjusted for gender, age, area, body mass index, smoking status, drinking status, and history of diabetes mellitus.; [b]Adjusted for gender, age, area, body mass index, smoking status, drinking status, history of diabetes mellitus, and salt intake.; [c]Adjusted for gender, age, area, body mass index, smoking status, drinking status, history of diabetes mellitus, and hepatic status.; [d]Adjusted for gender, age, area, body mass index, smoking status, drinking status, history of diabetes mellitus, and parous status.

In the analysis performed by sex (Table 4), there were significant differences in multivariable HRs and in the *P* for trend only in women (multivariable HRs: 1.30, 95% CI: 1.04-1.61 in >10 y group; *P* for trend = .040) in colorectal cancer, but in renal cancer there were significant differences in multivariable HRs and in the *P* for trend in both men (multivariable HRs: 3.47, 95% CI: 1.88-6.40 in 5-10 y group; multivariable HRs: 2.01, 95% CI: 1.04-3.88 in >10 y group; *P* for trend = .002) and women (multivariable HRs: 4.48, 95% CI: 2.03-9.88 in 5-10 y group; multivariable HRs: 2.44, 95% CI: 1.08-5.52 in >10 y group; *P* for trend = .003).

4 | DISCUSSION

This study was a large-scale cohort study that investigated the relationship between long-term antihypertensive drug use for 10 y. In our study, long-term use of antihypertensive drugs increased the risk of developing all cancers, colorectal cancers, and renal cancers, and there were no cancers in which antihypertensive drug use reduced the risk.

There are various reports on the mechanism by which antihypertensive drugs promote carcinogenesis. Sipahi et al[3] described that both angiogenesis II type-1 receptor (AT1R) blockade with an

TABLE 4 Hazard ratios for major sites of cancer according to antihypertensive drug-use categories by sex

	No	<5 y	5-10 y	>10 y	*P* for trend
Men					
All cancers					
Cases (n = 5023), n	3464	471	410	678	
Multivariable HRs (95% CI)[a]	Reference	1.03 (0.93-1.13)	1.08 (0.97-1.20)	1.13 (1.04-1.23)	.003
Lung cancer					
Cases (n = 717), n	542	49	46	80	
Multivariable HRs (95% CI)[a]	Reference	0.75 (0.56-1.01)	0.84 (0.61-1.14)	0.92 (0.72-1.17)	.202
Stomach cancer					
Cases (n = 933), n	645	79	76	133	
Multivariable HRs (95% CI)[b]	Reference	0.95 (0.75-1.21)	1.08 (0.84-1.39)	1.20 (0.99-1.46)	.083
Colorectal cancer					
Cases (n = 889), n	615	90	74	110	
Multivariable HRs (95% CI)[a]	Reference	1.12 (0.89-1.41)	1.12 (0.88-1.44)	1.08 (0.87-1.34)	.310
Liver cancer					
Cases (n = 239), n	153	29	21	36	
Multivariable HRs (95% CI)[c]	Reference	1.35 (0.89-2.04)	1.15 (0.71-1.86)	1.28 (0.87-1.89)	.172
Renal cancer					
Cases (n = 75), n	40	7	15	13	
Multivariable HRs (95% CI)[a]	Reference	1.36 (0.61-3.07)	3.47 (1.88-6.40)	2.01 (1.04-3.88)	.002
Pancreas cancer					
Cases (n = 160), n	100	23	11	26	
Multivariable HRs (95% CI)[a]	Reference	1.81 (1.13-2.89)	1.08 (0.57-2.03)	1.58 (0.99-2.50)	.054
Prostatic cancer					
Cases (n = 907), n	617	87	66	137	
Multivariable HRs (95% CI)[a]	Reference	0.99 (0.79-1.25)	0.87 (0.67-1.14)	1.16 (0.95-1.41)	.370
Women					
All cancers					
Cases (n = 3233), n	2195	331	264	443	
Multivariable HRs (95% CI)[a]	Reference	1.16 (1.03-1.31)	1.05 (0.92-1.20)	1.03 (0.92-1.15)	.385
Lung cancer					
Cases (n = 314), n	214	30	24	46	
Multivariable HRs (95% CI)[a]	Reference	0.98 (0.66-1.47)	0.97 (0.63-1.49)	1.03 (0.73-1.45)	.945
Stomach cancer					
Cases (n = 458), n	336	38	29	55	
Multivariable HRs (95% CI)[b]	Reference	0.90 (0.64-1.26)	0.78 (0.53-1.15)	0.81 (0.60-1.10)	.099
Colorectal cancer					
Cases (n = 695), n	455	65	55	120	
Multivariable HRs (95% CI)[a]	Reference	1.12 (0.86-1.45)	1.00 (0.75-1.34)	1.30 (1.04-1.61)	.040
Liver cancer					
Cases (n = 116), n	63	18	17	18	
Multivariable HRs (95% CI)[c]	Reference	1.58 (0.91-2.74)	1.53 (0.88-2.67)	1.06 (0.61-1.87)	.463
Renal cancer					
Cases (n = 45), n	21	3	10	11	
Multivariable HRs (95% CI)[a]	Reference	1.14 (0.33-3.88)	4.48 (2.03-9.88)	2.44 (1.08-5.52)	.003

(Continues)

TABLE 4 (Continued)

	No	<5 y	5-10 y	>10 y	*P* for trend
Pancreas cancer					
Cases (n = 158), n	110	14	11	23	
Multivariable HRs (95% CI)[a]	Reference	0.87 (0.49-1.56)	0.80 (0.43-1.51)	0.90 (0.56-1.46)	.533
Breast cancer					
Cases (n = 458), n	333	48	34	43	
Multivariable HRs (95% CI)[d]	Reference	1.21 (0.88-1.67)	1.00 (0.69-1.46)	0.73 (0.51-1.05)	.180

Note: No, never taken antihypertensive drug at baseline, 5-y follow-up nor 10-y follow-up survey; <5 y, take antihypertensive drug at 10-y follow-up survey but not baseline and 5-y follow-up survey; 5-10 y, take antihypertensive drug at 5-y follow-up and 10-y follow-up survey but not baseline survey; >10 y, take antihypertensive drug at baseline, 5-y follow-up and 10-y follow-up survey.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Adjusted for gender, age, area, body mass index, smoking status, drinking status, and history of diabetes mellitus.; [b]Adjusted for gender, age, area, body mass index, smoking status, drinking status, history of diabetes mellitus, and salt intake.; [c]Adjusted for gender, age, area, body mass index, smoking status, drinking status, history of diabetes mellitus, and hepatic status.; [d]Adjusted for gender, age, area, body mass index, smoking status, drinking status, history of diabetes mellitus, and parous status.

ARB and direct stimulation of angiogenesis II type-2 receptor (AT2R) could stimulating tumor angiogenesis in vivo, however the relevance of these observations to human malignancy is largely unknown. Li et al described that antihypertensive drugs have a broad spectrum of physiologic effects. With respect to calcium-channel blockers, some have hypothesized that they may inhibit apoptosis by increasing intracellular calcium levels, although evidence supporting this effect is lacking.[7] Colt et al[14] hypothesized that certain diuretics could be converted in the stomach to a mutagenic nitroso derivative that could cause carcinogenic effects.

Conversely, there have been reports that these drugs also suppress carcinogenesis. Indeed, studies have demonstrated that high doses of calcium-channel blockers can be used to potentiate the antitumor effect of some antineoplastic agents, and have been implicated in the regulation of cell proliferation and calcium influx, thereby inhibiting the proliferation of calcium-dependent neoplastic cells.[4] Moreover, RAS inhibitors might exert an inhibitory effect on tumor angiogenesis by reducing the expression of vascular endothelial growth factor, promoting cancer cell apoptosis, and disrupting the tumor microenvironment.[19]

The current study showed the highest adjusted HR in renal cancer among antihypertensive drug users. This was observed in the analysis performed for patients for whom outcomes were calculated 3 y after 10-y follow-up survey and by sex. The adjusted HR was higher in the 5-10 y group than in the >10 y group, but the reason for this difference is unknown. Due to the small number of cases of renal cancer, further case accumulation is needed to explain this difference. In this study, we also added blood pressure classification as a confounding factor, and the results showed that significant differences remained. Because hypertension patients have a high risk of chronic kidney disease and have a higher chance of detected renal cancer because of clinical follow-up by ultrasonography, there have been several studies that have reported antihypertensive drug-use increased renal cancer incidence.[13,14]

Although antihypertensive drugs have been associated with a significant increase in colorectal cancer incidence in terms of adjusted HRs in this study, there have been reports that ACE-Is and ARB reduced preneoplastic lesions in the colon of mice[20] and that RAS inhibitors also prevented colorectal cancer by reducing chronic inflammation of the colonic mucosa.[21] Furthermore, ACE-Is and ARB have also been shown to suppress liver metastasis of colon cancer and improve survival in colon cancer patients.[22,23] Moreover, in a systematic review and meta-analysis, Dai et al concluded that ACE-Is/ARBs might be associated with a reduced risk of colorectal cancer.[19] However, as this meta-analysis was on the basis of research in Europe and America, the differences may be as the result of factors that were not considered in this study, such as the type of antihypertensive drugs and race. For example, in the 1990s when exposure factors were investigated in the JPHC study, ARB was not available in Japan[24] and it is possible that antihypertensive drugs other than RAS inhibitors might be associated with the development of colorectal cancer. Conversely, the overdiagnosis of colorectal cancer among hypertension patients might be observed in the short-term period by colonoscopy during clinically follow-up. However, polypectomy would reduce the risk of colorectal cancer incidence in the long-term period because the procedure is performed in the process of early detection.

The strength of this study is its long-term observation of antihypertensive drug use, however this study has several limitations. First, the types of antihypertensive drugs taken by the participants are unknown. However, given that, in the real world, many patients take several types of antihypertensive drugs at the same time, and some may change medication during long-term use, this study still provides useful information. Second, although participants who indicated that they took oral medicine every 5 y are considered 'to continue', it is unclear whether they actually did so. However, because antihypertensive drugs are rarely completed in a short period of time, it seems reasonable to consider that participants who answered that they are taking them every 5 y continued to take them. Third, there may be an effect of unmeasured variables and residual confounding, although the statistical model was adjusted for as many variables as possible.

In conclusion, a large-scale cohort study in Japan suggested that long-term use of antihypertensive drugs may be associated with

increased incidence of all cancers, colorectal cancers, and renal cancers. This finding suggests the possibility that we should pay close attention to patients with long-term use of antihypertensive drugs. Moreover, further detailed research on each antihypertensive drug is needed in Asia in the future.

ACKNOWLEDGMENTS

This study was supported by a grant from Food Safety Commission, Cabinet Office, Government of Japan (Research Program for Risk Assessment Study on Food Safety, No. 1503; the principal investigator is TS), the National Cancer Center Research and Development Fund (since 2011; the principal investigator is ST), and a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare of Japan (from 1989 to 2010; the principal investigator from 1997 to 2010 is ST). JPHC members are listed at the following site (as of September 2019): https://epi.ncc.go.jp/en/jphc/781/8390.html. We are indebted to the Aomori, Akita, Iwate, Ibaraki, Niigata, Osaka, Kochi, Nagasaki, and Okinawa Cancer Registries for providing their incidence data.

DISCLOSURE

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

For information on how to apply to gain access to JPHC data, please follow the instruction at https://epi.ncc.go.jp/en/jphc/805/8155.html.

ORCID

Satoshi Matsui https://orcid.org/0000-0001-6240-2011
Tomotaka Sobue https://orcid.org/0000-0003-2817-3483
Norie Sawada https://orcid.org/0000-0002-9936-1476
Motoki Iwasaki https://orcid.org/0000-0003-3319-4131

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How to cite this article: Matsui S, Sobue T, Zha L, et al. Long-term antihypertensive drug use and risk of cancer: The Japan Public Health Center-based prospective study. *Cancer Sci*. 2021;112:1997–2005. https://doi.org/10.1111/cas.14870