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 al2 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 al3 suggested that ARB increased the risk of developing cancer and, conversely, the results of Bangalore et al4 reported in 2011 that they were unrelated. In recent studies on various cancers and antihypertensive drugs, it has been reported

1Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, Suita, Japan
2Epidemiology 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
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 investigates 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- and 10-year 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-year follow-up survey (N = 2,997). In addition, we further excluded participants who did not answer the baseline, 5-year follow-up, or 10-year 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 = 28,787). As a result, 65,086 subjects were analyzed.

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

![FIGURE 1 Patient selection flow chart](image-url)
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 Japan11 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 calculated15 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 risk16-18: age (continuous); study area (9 PHC areas); sex (men/women); body mass index (<25, ≥25 kg/m²); 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/m². 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
were no significant differences in the multivariable HRs of the anti- 
hypertensive 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 con- 
founding 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 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)      |
| 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)       |
| Body mass index ≥ 25 kg/ m², n (%)<sup>a</sup> | 19 426 (30.6) | 12 259 (26.6) | 2137 (38.2) | 1909 (41.5)       | 3121 (43.1)      |

**Smoking, n (%)**

|                | No (N = 47 231) | <5 y (N = 5716) | 5-10 y (N = 4701) | >10 y (N = 7438) |
|----------------|-----------------|-----------------|-------------------|------------------|
| Never          | 41 698 (64.1)   | 29 918 (63.3)   | 3685 (64.5)       | 3082 (65.6)      | 5013 (67.4)      |
| Former         | 9143 (14.1)     | 6144 (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 (%)**

|                 | No (N = 47 231) | <5 y (N = 5716) | 5-10 y (N = 4701) | >10 y (N = 7438) |
|-----------------|-----------------|-----------------|-------------------|------------------|
| Never           | 33 469 (51.4)   | 24 037 (50.9)   | 2953 (51.7)       | 2467 (52.5)      | 4012 (53.9)      |
| 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 (%)<sup>b</sup>**

|                 | No (N = 47 231) | <5 y (N = 5716) | 5-10 y (N = 4701) | >10 y (N = 7438) |
|-----------------|-----------------|-----------------|-------------------|------------------|
| sBP < 120 or dBP < 80 | 7165 (15.7)   | 6865 (22.1)     | 131 (2.9)         | 78 (2.0)         | 91 (1.5)         |
| 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)     |
| Chronic hepatitis/cirrhosis | 723 (1.1)    | 449 (1.0)       | 78 (1.4)          | 96 (2.0)         | 100 (1.3)        |

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.

<sup>a</sup>The number of missing values is 1646.;<sup>b</sup>The number of missing values is 19 460.;<sup>c</sup>The number of missing values among women is 2461.
### 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** | 527 777 | 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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.

aAdjusted for gender, age, area, body mass index, smoking status, drinking status, and history of diabetes mellitus.; bAdjusted for gender, age, area, body mass index, smoking status, drinking status, history of diabetes mellitus, and salt intake.; cAdjusted for gender, age, area, body mass index, smoking status, drinking status, history of diabetes mellitus, and hepatic status.; dAdjusted 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).

### 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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) | 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) | Reference | 1.14 (0.33-3.88) | 4.48 (2.03-9.88) | 2.44 (1.08-5.52) | .003 |

(Continues)
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\(^\text{14}\) 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.\(^8\) 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.\(^9\)\(^\text{19}\)

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.\(^13\)\(^\text{14}\)

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\(^\text{20}\) and that RAS inhibitors also prevented colorectal cancer by reducing chronic inflammation of the colonic mucosa.\(^\text{21}\) Furthermore, ACE-Is and ARB have also been shown to suppress liver metastasis of colon cancer and improve survival in colon cancer patients.\(^\text{22}\)\(^\text{23}\) Moreover, in a systematic review and meta-analysis, Dai et al\(^\text{24}\) concluded that ACE-Is/ARBs might be associated with a reduced risk of colorectal cancer.\(^\text{19}\) 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\(^\text{24}\) 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

REFERENCES
1. Grossman E. Antihypertensive therapy and the risk of malignancies. Eur Heart J. 2001;22:1343-1352.
2. Coleman CI, Baker WL, Kluger J, White CM. Antihypertensive medication and their impact on cancer incidence: a mixed treatment comparison meta-analysis of randomized controlled trials. J Hypertens. 2008;26:622-629.
3. Sipahi I, Debane SM, Rowland DY, Simon DI, Fang JC. Angiotsin receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncol. 2010;11:627-636.
4. Bangalore S, Kumar S, Kjeldsen SE, et al. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324 168 participants from randomised trials. Lancet Oncol. 2011;12:65-82.
5. Dierssen-Sotos T, Gómez-Acebo I, Palazuelos C, et al. Relationship between drugs affecting the renin-angiotensin system and colorectal cancer: the MCC-Spain study. Prev Med. 2017;99:178-184.
6. Hicks BM, Filion KB, Yin H, Sakr L, Udell JA, Azoulay L. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. BMJ. 2018;363:k4209.
7. Li CI, Daling JR, Tang MT, Haugan KL, Porter PL, Malone KE. Use of antihypertensive medications and breast cancer risk among women aged 55 to 74 years. JAMA Intern Med. 2013;173:1629-1637.
8. Coleman WB, Gómez-Acebo I, Dierssen-Sotos T, et al. the use of antihypertensive medication and the risk of breast cancer in a case-control study in a Spanish population: the MCC-Spain study. PLoS One. 2016;11(8):e0159672.
9. Devore EE, Kim S, Ramin CA, et al. Antihypertensive medication use and incident breast cancer in women. Breast Cancer Res Treat. 2015;150:219-229.
10. Tsugane S, Sawada N. The JPHC study: design and some findings on the typical Japanese diet. Jpn J Clin Oncol. 2014;44:777-782.
11. The Portal Site of Official Statistics of Japan. Statistics of Japan. https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=04450173&tstat=000011133323&cycle=1&year=20170&month=0&tclass1=00000111333363&tclass2=000001133366&result_back=1&classval=0. Accessed January 21, 2021.
12. Goto A, Yamaji T, Sawada N, et al. Diabetes and cancer risk: a Mendelian randomization study. Int J Cancer. 2020;146:712-719.
13. Xie Y, Xu P, Wang M, et al. Antihypertensive medications are associated with the risk of kidney and bladder cancer: a systematic review and meta-analysis. Aging. 2020;22:1545-1562.
14. Colt JS, Hofmann JN, Schwartz K, et al. Antihypertensive medication use and risk of renal cell carcinoma. Cancer Causes Control. 2017;28:289-297.
15. Tsugane S, Fahey MT, Sasaki S, Baba S, the JPHC Study Group. Alcohol consumption and all-cause and cancer mortality among middle-aged Japanese men: seven-year follow-up of the JPHC Study Cohort I. Am J Epidemiol. 1999;150:1201-1207.
16. Coughlin SS, Celle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol. 2004;159:1160-1167.
17. Wang XQ, Terry PD, Yan H. Review of salt consumption and stomach cancer risk: epidemiological and biological evidence. World J Gastroenterol. 2009;15:2204-2213.
18. Amir E, Freedman OC, Seruga B, Evans DG. Assessing women at high risk of breast cancer: a review of risk assessment models. J Natl Cancer Inst. 2010;102:680-691.
19. Dai YN, Wang JH, Zhu JZ, Lin JQ, Yu CH, Li YM. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers therapy and colorectal cancer: a systematic review and meta-analysis. Cancer Causes Control. 2015;26:1245-1255.
20. Kubota M, Shimizu M, Sakai H, et al. Renin-angiotensin system inhibitors suppress azoxymethane-induced colonic preneoplastic lesions in C57BL/KsJ-db/db obese mice. Biocem Biophys Res Commun. 2011;410:108-113.
21. Shirakami Y, Shimizu M, Kubota M, et al. Chemoprevention of colorectal cancer by targeting obesity-related metabolic abnormalities. World J Gastroenterol. 2014;20:8939-8946.
22. Luo Y, Ohmori H, Shimmoto M, et al. Anti-angiotensin and hypoglycemic treatments suppress liver metastasis of colon cancer cells. Pathobiology. 2011;78:285-290.
23. Wen SW, Ager EL, Neo J, Christophi C. The renin angiotensin system regulates Kupffer cells in colorectal liver metastases. Cancer Biol Ther. 2013;14:720-727.
24. Aoki M, Ogwara T. Etiology of hypertension and history of antihypertensive therapy. Nippon Rinsho. 2014;72:7-13.

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