Effects of daily aspirin on cancer incidence and mortality in the elderly Japanese

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Effects of daily aspirin on cancer incidence and mortality in the elderly Japanese

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Abstract

Background: Long-term follow-up of studies to investigate preventive effects of aspirin on arterial thrombosis indicate that aspirin reduces the incidence and mortality of some cancers in Western populations.

Objectives: To explore the effects of aspirin on cancer incidence and mortality in the elderly Japanese.

Patients/Methods: Patients aged 60 to 85 years, presenting with hypertension, dyslipidemia, or diabetes mellitus (n = 14 601, 7297 in the aspirin group and 7304 in the no-aspirin group) participated the Japanese Primary Prevention Project (JPPP), a

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multicenter, open-label, randomized, parallel-group trial. A subanalysis of JPPP was performed to analyze the incidence of newly diagnosed cancer and death related to cancer.

Results: The cumulative incidence of newly diagnosed cancer was 5.60% (4.65-6.64%) in the aspirin group and 4.14% (3.67-4.66%) in the no-aspirin group. The hazard ratio for newly diagnosed cancer was 1.24 (1.06-1.46), and the cancer incidence was significantly higher in the aspirin group. The cumulative cancer mortality was 1.96% (1.65-2.31%) in the aspirin group and 1.87% (1.56-2.22%) in the no-aspirin group, with no statistically significant difference. The Fine and Gray model suggested that the difference in the incidence of newly diagnosed cancer between the two groups decreased year by year.

Conclusions: Low-dose aspirin use did not reduce the cancer incidence or cancer mortality during a 5-year-average study period in the elderly Japanese. The cancer incidence in the aspirin group might decrease, however, to less than that in the no-aspirin group after the study period. Aspirin use might have led to earlier cancer diagnosis in our study.

KEYWORDS

aspirin, cancer, elderly, incidence, Japanese

Essentials

- The effects of aspirin on cancer incidence and mortality in the elderly Japanese are not clear.
- We analyzed cancer incidence and mortality in the Japanese Primary Prevention Project (JPPP).
- Low-dose aspirin for 5 years did not reduce cancer incidence or cancer mortality in the JPPP.
- Cancers might be diagnosed earlier in the aspirin group.

1 | INTRODUCTION

Aspirin is a widely used anti-platelet drug. Numerous studies have demonstrated the effects of aspirin on the secondary prevention of arterial thrombosis[1] and several studies have investigated the effects of aspirin use for the primary prevention of atherosclerotic diseases.[2-7] Long-term follow-up of these studies established that regular daily aspirin use reduces the incidence, distant metastasis, and mortality of some cancers after approximately 5 years.[8-11] Several case-control studies and cohort studies also revealed similar long-term effects of aspirin.[12-18] The evidence for the long-term inhibitory effects of aspirin on cancer incidence and cancer-related death is most prominent for gastrointestinal cancer, including colorectal cancer (CRC),[19] and recently the US Preventive Services Task Force recommended initiating low-dose aspirin use for the primary prevention of cardiovascular disease and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year cardiovascular disease risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin for at least 10 years.[20] However, cancer incidence and mortality increases with advancing age, and the incidence and mortality of cancer is 10 times and 16 times greater in older adults, respectively, than in those younger than 65.[21] Cancer is the leading cause of death in Japan, and

according to the Japanese Cancer Institute registry data, 1 014 000 patients were estimated to be newly diagnosed with cancer, and 378 000 patients were estimated to die from cancer in 2017.[22] Approximately half of Japanese people suffer from cancer during their lifetime, and one-third die from cancer. Therefore, it is crucial to assess the effects of aspirin on cancer incidence and mortality in the elderly Japanese, and the current evidence is insufficient.

We previously reported the results of the Japanese Primary Prevention Project (JPPP), which examined the inhibitory effects of aspirin on vascular events in the elderly Japanese population (age 60-85 years, mean ± SD, 70.6 ± 6.2 years) with no previous history of arterial thrombosis.[23] We performed a subanalysis of the JPPP to explore the effects of aspirin on cancer incidence and mortality in older Japanese by analyzing the in-trial cancer incidence and mortality of patients participating in the JPPP.

2 | METHODS

2.1 | Patients

The JPPP was a multicenter, open-label, randomized, parallel-group trial. Patients aged 60 to 85 years presenting with hypertension, dyslipidemia, or diabetes mellitus, and having no history of

atherosclerotic disease, were recruited by primary care physicians at 1007 clinics in the 47 prefectures of Japan between March 2005 and June 2007 (clinicaltrials.gov Identifier: NCT00225849). The study was approved by the institutional review board of each participating center, and written informed consent was obtained from all participants. We randomized the patients to receive a 100-mg tablet of enteric-coated aspirin once daily or not, and followed them for up to 6.5 years with the last follow-up exam in May 2012. The primary outcome was a composite of death from cardiovascular causes (myocardial infarction, stroke, and other cardiovascular causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal myocardial infarction.[23] Secondary endpoints included cause-specific mortality. Collection of the detailed clinical information of the patients and annual reports of adverse events, including cancer, were mandatory for registered physicians. The diagnosis of cancer was assessed centrally and annually by experts comprising a multidisciplinary event adjudication committee that was blinded to treatment based on the reports of adverse events. We analyzed the incidence and mortality of newly diagnosed cancer (ie, excluding recurrences of prerandomization cancers) in this population to evaluate the effect of aspirin on cancer in the elderly Japanese.

2.2 | Statistical analyses

The cumulative incidence rate was estimated by Gray's nonparametric approach which treated deaths without cancer as competing events.[24] The difference between two groups was tested by Gray's test, and hazard ratio (HR) was estimated by Fine and Gray model. The time dependency of proportional hazard assumption was also assessed by Fine and Grey model which included a log (time) term. SAS version 9.4 (SAS Institute, Cary, NJ, USA) was used for all statistical analyses. Statistical tests were two-sided with an alpha level of .05.

3 | RESULTS

3.1 | Patients

A total of 14 688 patients were randomized to the aspirin group (n = 7323) or the no-aspirin group (n = 7335). Of the 7323 patients randomized to the aspirin group, 26 were excluded, and of 7335 patients randomized to the no-aspirin group, 31 were excluded from the analysis because they never visited the registered physician after randomization. Finally, 7297 in the aspirin group and 7304 in the no-aspirin group were included in analysis (Figure 1). Both groups were well balanced in terms of the male-to-female ratio, age, underlying diseases (ie, hypertension, dyslipidemia, diabetes), body mass index, and current smoking habit (Table 1). The median follow-up period was similar in the aspirin and no-aspirin groups (5.01 years for the aspirin group and 5.02 years for the no-aspirin group).[23]

3.2 | Cancer incidence and mortality

Cancer was newly diagnosed in 332 (aspirin group) and 271 (no-aspirin group) patients.

The cumulative incidence of newly diagnosed cancer was 5.60% (4.65-6.64%) in the aspirin group and 4.14% (3.67-4.66%) in the no-aspirin group. In the aspirin group, the HR for newly diagnosed cancer was 1.24 (1.06-1.46) compared to the no-aspirin group, and the incidence of newly diagnosed cancer was significantly higher than that in the no-aspirin group (P = .008) (Figure 2). CRC (66 [aspirin] and 50 [no-aspirin]) was most often diagnosed in the study population, followed by gastric (55 [aspirin] and 49 [no-aspirin]) and lung (56 [aspirin] and 37 [no-aspirin]) cancer (Table 2). The number of individual cancers was small, therefore we combined some cancers and divided into two categories: gastrointestinal (GI) cancer and non-GI cancer. GI cancer was newly diagnosed in 176 (aspirin group) and 151 (no-aspirin group) patients, and the cumulative incidence of GI
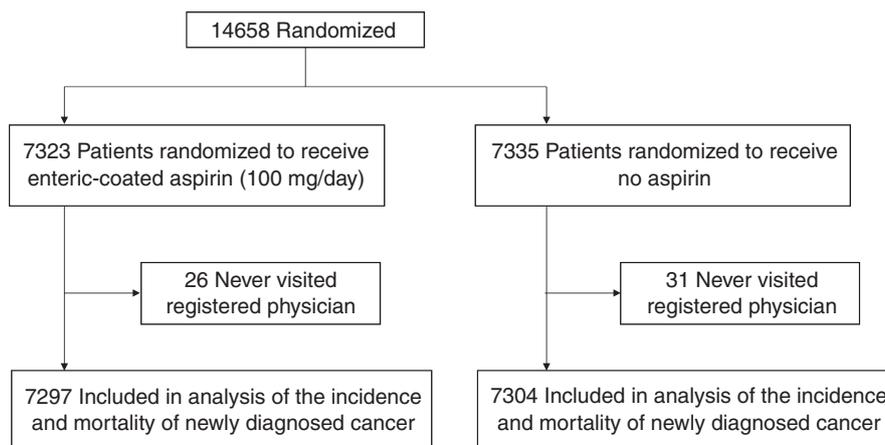
FIGURE 1 Flow of patients through the Japanese Primary Prevention Project (JPPP) subanalysis of the incidence and mortality of newly diagnosed cancer. 7323 patients and 7335 patients were randomized to the aspirin group and no-aspirin group, respectively. Of the 7323 patients in the aspirin group, 26 were excluded from the analysis because they never visited the registered physician after randomization, and 7297 were included in analysis. Of the 7335 patients in the no-aspirin group, 31 were excluded from the analysis because they never visited the registered physician after randomization, and 7304 were included in analysis

TABLE 1 Patient characteristics

Factor	Statistics	Aspirin group	No-aspirin group	Total
Total	N (%)	7297 (100)	7304 (100)	14 601 (100)
Sex				
Men	N (%)	3083 (42.3)	3096 (42.4)	6179 (42.3)
Women	N (%)	4214 (57.7)	4208 (57.6)	8422 (57.7)
Age	Mean (SD)	70.6 (6.2)	70.5 (6.2)	70.6 (6.2)
	<70, N (%)	3263 (44.7)	3274 (44.8)	6537 (44.8)
	≥70, N (%)	4034 (55.3)	4030 (55.2)	8064 (55.2)
HT	N (%)	6197 (84.9)	6195 (84.8)	12 392 (84.9)
DL	N (%)	5249 (71.9)	5245 (71.8)	10 494 (71.9)
DM	N (%)	2469 (33.8)	2477 (33.9)	4946 (33.9)
HT & DL	N (%)	4316 (59.1)	4302 (58.9)	8618 (59.0)
DL & DM	N (%)	1808 (24.8)	1809 (24.8)	3617 (24.8)
HT & DM	N (%)	1950 (26.7)	1953 (26.7)	3903 (26.7)
HT & DL & DM	N (%)	1456 (20.0)	1451 (19.9)	2907 (19.9)
BMI	Mean (SD)	24.2 (3.5)	24.2 (3.4)	24.2 (3.4)
	≥25, N (%)	2670 (36.6)	2628 (36.0)	5298 (36.3)
Current smoking	N (%)	967 (13.3)	948 (13.0)	1915 (13.1)

BMI, body mass index; DL, dyslipidemia; DM, diabetes; HT, hypertension.

FIGURE 2 Cumulative incidence of cancer in the aspirin and the no-aspirin group. The P value was determined using the log-rank test. CI, confidence interval; HR, hazard ratio. CI indicates confidence interval

cancer was 2.62% (2.25-3.03%) in the aspirin group and 2.31% (1.96-2.70%) in the no-aspirin group, respectively (Figure 3A). Non-GI cancer was newly diagnosed in 163 (aspirin group) and 123 (no-aspirin group), and the cumulative incidence of non-GI cancer was 3.12% (2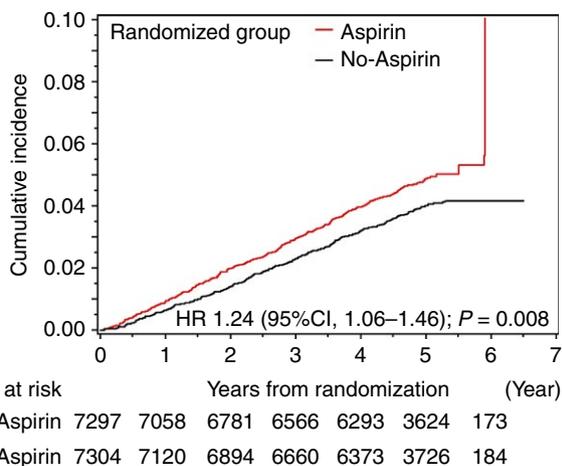.28-4.15%) in the aspirin and 1.92% (1.59-2.29%) in the no-aspirin group, respectively (Figure 3B). The HRs for GI cancer and non-GI cancer in the aspirin group compared to the no-aspirin group were 1.18 (0.95-1.46), and 1.34 (1.06-1.69), respectively. No statistically significant difference in the HR for GI cancer was detected between the aspirin group and no-aspirin group (P = .138), while the incidence

of non-GI cancer in the aspirin group was significantly higher than that in the no-aspirin group (P = .014).

Total death and death related to newly diagnosed cancer occurred in 303 and 134 (aspirin group), and 308 and 125 (no-aspirin group), and the cumulative mortality related to newly diagnosed cancer was 1.96% (1.65-2.31%) in the aspirin group and 1.87% (1.56-2.22%) in the no-aspirin group, respectively. In the aspirin group, the HR for cancer related death was 1.08 (0.85-1.38) compared to the no-aspirin group, and the risk of cancer-related death did not differ significantly between the two groups (P = .527) (Figure 4). Furthermore, the Fine and Gray model suggested that the difference in the incidence of newly diagnosed cancer between the two groups decreased year by year (Figure 5). The number of deaths due to cancer after 5 years of follow-up was relatively small, but there was a trend toward fewer deaths in the aspirin group (5 [aspirin] vs 16 [no-aspirin]; data not shown).

4 | DISCUSSION

In this subanalysis of the JPPP, the cumulative incidence of newly diagnosed cancer was significantly higher in the aspirin group (Figure 2). In contrast to other recent reports demonstrating inhibitory effects of aspirin on cancer incidence and cancer-related mortality, especially CRC,[8–18] we unexpectedly found that the cancer incidence was significantly higher in the aspirin group than in the no-aspirin group and failed to show preventive effects of aspirin on cancer incidence or mortality during the average study period of 5 years.

If aspirin had direct or indirect carcinogenic effects that caused an increased incidence of newly diagnosed cancer in the aspirin group in our study, the difference in the incidence of newly diagnosed cancer between the aspirin and no-aspirin groups would increase year by year and should also be accompanied by an increase in cancer deaths. The Fine and Gray model in our study, however, suggested that the difference in the incidence of newly diagnosed cancer between the two groups decreased year by year, and the cancer incidence in the aspirin group might decrease to less than that in the no-aspirin group after the study period (Figure 5). The cumulative incidence of cancer-related death did not differ significantly between the aspirin and no-aspirin groups during the study period (Figure 4). These findings suggest that cancer might not occur more frequently in the aspirin group, but rather that cancers were diagnosed earlier in the aspirin group. Indeed, there was a trend toward fewer cancer deaths after the 5-year follow-up, which is consistent with previous observations,[9,11] although these observations are based on a small number of cases.

It is not clear why our subanalysis failed to show the preventive effects of aspirin on cancer incidence or mortality. Hemorrhagic complications are common adverse events of patients taking aspirin. As previously reported, serious extracranial hemorrhage requiring transfusion or hospitalization occurred in 62 (aspirin) and 34 (no-aspirin) patients, and gastrointestinal hemorrhage occurred in 103 (aspirin) and 31 (no-aspirin) patients in our study population.[23] Although the definition of hemorrhagic complications varies among studies and available data are limited, the difference in the incidence of serious hemorrhagic complications between the aspirin group and no-aspirin group might be larger than that of other studies.[10] The mean age of participants in the JPPP was 70.6 years, whereas the mean age of participants in other trials was slightly >60 years.[10] A recent report indicated that major bleeding increases steeply with age in patients receiving antiplatelet drugs (mainly aspirin-based),[25] and the difference in the mean age of participants might be related to the increased incidence of hemorrhagic complications in the aspirin group in our study. The increased incidence of hemorrhagic complications in the aspirin group might have encouraged physicians to perform thorough examinations to identify the causes, which could have resulted in an earlier diagnosis of cancer and an increased incidence of newly-diagnosed cancer. As shown in Figure 3A, the difference of the cumulative incidence rate of GI cancer between the aspirin and no-aspirin groups became larger in the first 3 years, then became smaller (Figure 3A). Such a trend was not found in non-GI cancer (Figure 3B). These findings might suggest that GI cancers were diagnosed earlier in the aspirin group. Although there was no evidence of earlier diagnosis of cancers in the aspirin group in analyses of previous trials,[8,9,11] such a trend might be more apparent

TABLE 2 Organ site of newly diagnosed any cancer

	Aspirin	No-Aspirin
Head and Neck	7	6
Lung	56	37
Breast	12	9
Esophageal	9	6
Gastric	55	49
Colon	66	50
Hepato, Biliary, Pancreatic	54	50
Urinary	16	13
Prostate	22	21
Uterus	8	5
Hematologic	26	23
Others	23	14

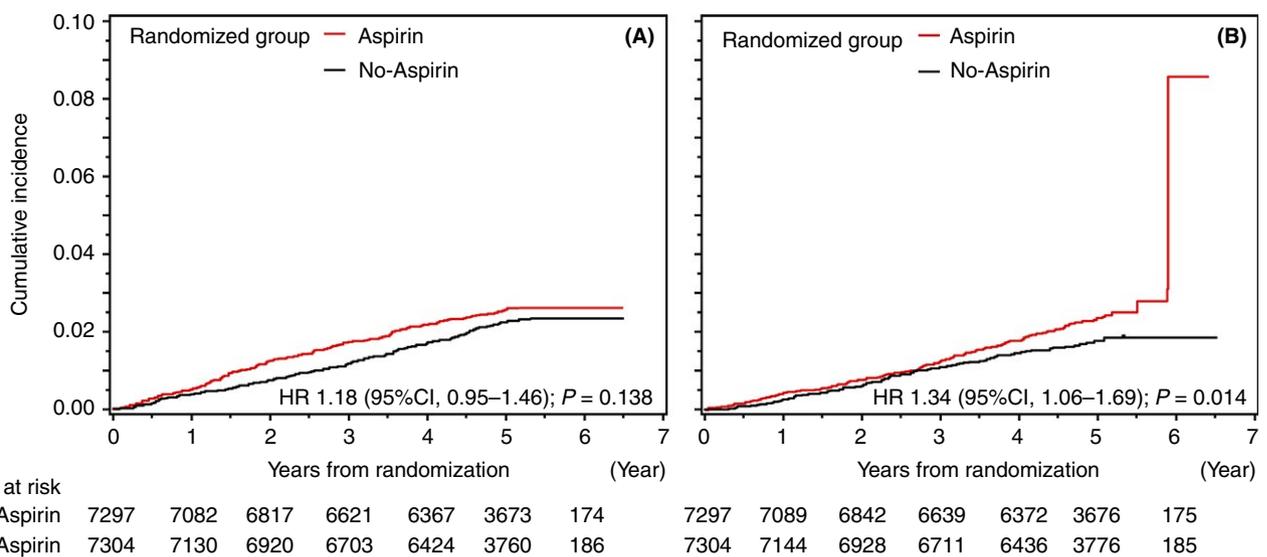| Number at risk	0	1	2	3	4	5	6
Aspirin	7297	7082	6817	6621	6367	3673	174
No-Aspirin	7304	7130	6920	6703	6424	3760	186
Aspirin	7297	7089	6842	6639	6372	3676	175
No-Aspirin	7304	7144	6928	6711	6436	3776	185

FIGURE 3 Cumulative incidence of gastrointestinal (GI) cancer (A) and non-GI cancer (B) in the aspirin and the no-aspirin group. The P value was determined using the log-rank test. CI, confidence interval; GI, gastrointestinal; HR, hazard ratio
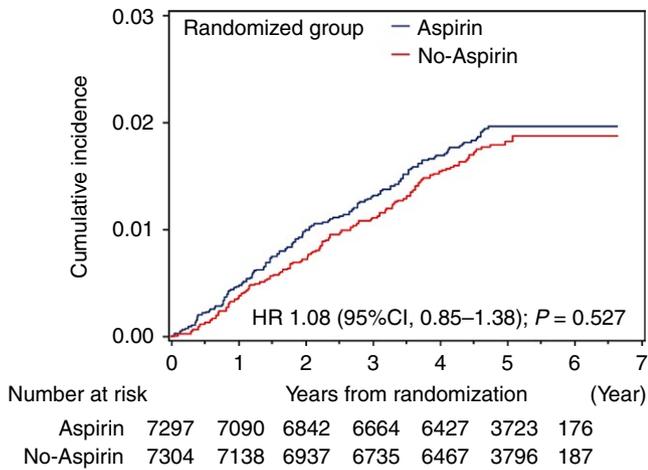
FIGURE 4 Cumulative incidence of cancer related death in the aspirin and the no-aspirin group. The *P* value was determined using the log-rank test. CI, confidence interval; HR, hazard ratio
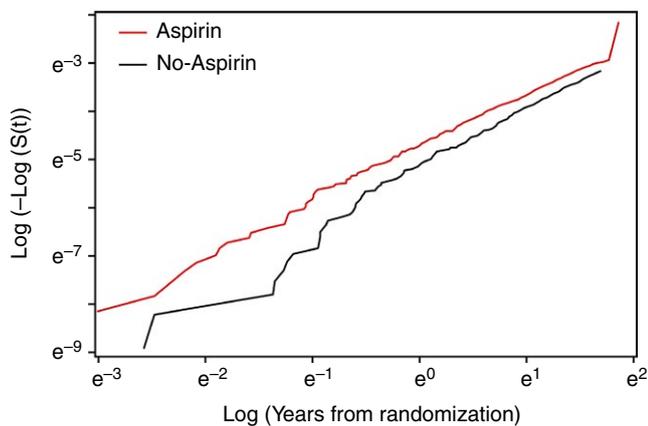

FIGURE 5 Log-log plot of newly diagnosed cancer in the aspirin group vs the no-aspirin group

with more recent advances in diagnosis and screening. The sensitivity analysis which censors the participants after a report of hemorrhagic complications or gastrointestinal adverse events could exclude cancers that were found due to diagnostic procedures to identify causes of these events. However, we did not have detail information about the day when the hemorrhagic complications or gastrointestinal adverse events occurred, and what diagnostic procedures were performed to detect the causes of these events, therefore we could not perform this analysis.

This study is a subanalysis of the JPPP, and the JPPP was terminated prematurely because it was judged that the statistical power to detect a between-group difference in the primary endpoint would not be sufficient and continuing the study could put participants at risk for aspirin-related adverse events.[23] Therefore, the median follow-up period of our study was 5.02 years, shorter than those of most previous studies, and might not be long enough to evaluate the inhibitory effects of aspirin on cancer. The effects of regular aspirin use for 5 years or less on cancer incidence or mortality have been evaluated in several studies with inconsistent results. Rothwell

et al. reported a meta-analysis of individual patient data from randomized trials of daily aspirin vs no aspirin in the prevention of vascular events, and revealed that aspirin reduced cancer incidence and deaths particularly after 5 years, with a weak effect on cancer incidence after 3 years,[11] but they found no benefit of aspirin on cancer death before 5 years, and aspirin use for 5 years or longer reduced the risk of proximal colon cancer and rectal cancer in other studies.[9,10] The Physicians' Health Study[3] and The Women's Health Study[26] were randomized trials that included cancer outcomes as predefined endpoints to evaluate the effects of aspirin on cancer incidence and mortality. The Physicians' Health Study reported no association between aspirin use and CRC incidence over a 12-year follow-up period.[27] The findings of the Women's Health Study also did not support inhibitory effects of aspirin on CRC incidence over the originally planned 10-year follow-up period,[26] but a reduced CRC incidence in the aspirin group was demonstrated over extended follow-up periods.[28] These studies also did not show significant effects of aspirin use of 5 years or less on cancer. The dose of aspirin differed among these studies. The dose of daily aspirin ranged from 81 to 500 mg in the studies analyzed by Rothwell.[11] Every other day, 325 mg and 100 mg of aspirin was administered in The Physicians' Health Study[3] and The Women's Health Study,[26] respectively. In our study, 100 mg of aspirin was administered daily. The difference of dose and schedule of aspirin might affect the short-term effects of aspirin on cancer in these trials, but further studies are needed to reach a conclusion.

Our study has some limitations. The JPPP was planned to evaluate the primary preventive effects of aspirin on the occurrence of cardiovascular diseases and death related to cardiovascular diseases. Although this was a relatively large-scale study and the aspirin and no-aspirin groups were well balanced, the study population, sample size, and study period were determined to evaluate the inhibitory effects of aspirin on cardiovascular diseases, and therefore these factors were not necessarily adequate to evaluate the effects of aspirin on cancer incidence and cancer mortality. The sample size in particular might not have been large enough to examine the effect of aspirin on specific types of cancer, and the study period might not have been long enough to confirm the effects of aspirin on cancer. As previously reported, a total of 89% of patients in the aspirin group continued taking the aspirin at year 1 and 76% at year 5. In the no-aspirin group, the proportion of patients who began to take daily low-dose aspirin was 1.5% at year 1 and 9.8% at year 5.[23] The number of patients who did not adhere to the aspirin treatment regimen could affect the results of our study, but adherence rates were nevertheless still higher than those reported in similar trials of daily aspirin that did not employ run-in periods.[8–11] The number of patients lost to follow-up could also affect the results: 791 in the aspirin group and 753 in the no-aspirin group were lost to follow-up during the study period.[23] In addition, most registered physicians of the JPPP were primary care physicians who worked at their own clinics, and therefore cancers were often diagnosed at other hospitals. These factors could lead to an underestimation of the frequency of cancer. A study with predefined regular examinations to detect cancer, for example, annual radiologic studies and endoscopic studies,

might be needed to confirm the effects of aspirin on cancer incidence and mortality in an elderly population. Nevertheless, the JPPP trial is the largest completed randomized trial of daily aspirin vs control with follow-up to an average of 5 years in an elderly population, and therefore adds substantially to the previously reported data on cancer outcomes from similar trials.

5 | CONCLUSION

Low-dose aspirin for 5 years did not reduce the cancer incidence or cancer mortality in the elderly Japanese patients during a 5-year-average study period, but the Fine and Gray model suggested that the cancer incidence in the aspirin group might decrease to less than that in the no-aspirin group after the study period. Cancers might have been diagnosed earlier in the aspirin group in our study.

RELATIONSHIP DISCLOSURES

Kenji Yokoyama has received honoraria from Nippon Shinyaku, Celgene Japan, Bayer, Bristol-Myers Squibb, Novartis, Takeda, Pfizer, Kyowa Hakko Kirin, and Otsuka; and research funding from Nippon Shinyaku, Bristol-Myers Squibb, Chugai, Takeda, Pfizer, Kyowa Hakko Kirin, and Eisai. Naoki Ishizuka is a former employee of Sanofi-Aventis (until May 2014). Mitsuru Murata has received honoraria from Pfizer and research funding from Daiichi Sankyo and Sanofi-Aventis. Shinichiro Uchiyama has received honoraria from Bayer, Boehringer Ingelheim, Daiichi Sankyo, and Otsuka; consulting fees from Sanofi-Aventis; and research funding from Bayer, Boehringer Ingelheim, Daiichi Sankyo, and Otsuka. Tamio Teramoto has received honoraria from Bayer, Astellas Pharma, Daiichi Sankyo, Pfizer, Kissei Pharmaceutical, Amgen, Takeda, Sanofi-Aventis, Eli Lilly, Shionogi, Astra-Zeneka, and MSD; consulting fees from MSD; and research funding from Bayer, Astellas Pharma, Aska, Daiichi Sankyo, Kissei Pharmaceutical, Takeda, Shionogi, and MSD. Kazuyuki Shimada has received honoraria from Bayer, Daiichi Sankyo, Dainippon Sumitomo Pharma, MSD, Novartis, Omron, and Takeda. Tsutomu Yamazaki has received honoraria from AstraZeneca, Daiichi Sankyo, Dainippon Sumitomo Pharma, Kowa, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Mochida, Novartis, and Sanofi-Aventis, Shionogi, Pfizer, Takeda, and Novaritis; and research funding from AstraZeneca, Daiichi Sankyo, Dainippon Sumitomo Pharma, Kowa, Kyowa Hakko Kirin, MSD, Mitsubishi Tanabe Pharma, Pfizer, and Takeda. Katsuyuki Ando has received honoraria from Daiichi Sankyo and Torii Pharmaceutical. Yasuo Ikeda has received consulting fees from AstraZeneca, Bayer, Daiichi Sankyo, GlaxoSmithKline, and Sanofi-Aventis. All other authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

K. Yokoyama and N. Ishizuka contributed to the study concept and design, analysis, and interpretation of data, wrote the manuscript, and provided critical intellectual content. N. Uemura, Y. Mizokami, H. Hiraishi, M. Murata, S. Uchiyama, T. Teramoto, K. Shimada, T. Yamazaki, S. Oikawa, M. Sugawara, K. Ando, and Y. Ikeda contributed to the study concept and design, interpretation of the data, and provided critical intellectual content during the revision process. All authors provided final approval of the manuscript to be published.

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