# Effect of Aspirin on Cancer Chemoprevention in Japanese Patients With Type 2 Diabetes: 10-Year Observational Follow-up of a Randomized Controlled Trial

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## OBJECTIVE

**This study analyzed the efficacy of low-dose aspirin in cancer chemoprevention in patients with diabetes.**

## RESEARCH DESIGN AND METHODS

**This study was a posttrial follow-up of the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial. Participants in the JPAD trial (2,536 Japanese patients with type 2 diabetes and without preexisting cardiovascular disease) were randomly allocated to receive aspirin (81 or 100 mg daily) or no aspirin. After that trial ended in 2008, we followed up with the participants until 2015, with no attempt to change the previously assigned therapy. The primary end point was total cancer incidence. We investigated the effect of low-dose aspirin on cancer incidence.**

## RESULTS

**During the median follow-up period of 10.7 years, a total of 318 cancers occurred. The cancer incidence was not significantly different between the aspirin and no-aspirin groups (log-rank, *P* = 0.4; hazard ratio [HR], 0.92; 95% CI, 0.73–1.14; *P* = 0.4). In subgroup analyses, aspirin did not affect cancer incidence in men, women, or participants aged ≥65 years. However, it decreased cancer incidence in participants aged <65 years (log-rank, *P* = 0.05; HR, 0.67; 95% CI, 0.44–0.99; *P* = 0.048). After adjusting for sex, hemoglobin $A_{1c}$, smoking status, and administration of metformin and statins, aspirin significantly reduced cancer incidence in participants aged <65 years (adjusted HR, 0.66; 95% CI, 0.43–0.99; *P* = 0.04).**

## CONCLUSIONS

**Low-dose aspirin did not reduce cancer incidence in Japanese patients with type 2 diabetes.**


Malignant neoplasms have been the leading cause of death in Japan since 1981 (1). Mortality due to malignant neoplasms has been ~30% in the Japanese general population since the 2000s but has gradually increased up to 38% in patients with diabetes (2). Cumulative evidence supports the fact that diabetes is associated with a high incidence of cancer (3–7). A meta-analysis in a Japanese population showed that patients with diabetes had a 1.7-fold higher risk of cancer than those without diabetes

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(8). This risk varied among cancers, however, with hepatic, pancreatic, endometrial, and colorectal cancers demonstrating a higher incidence in patients with diabetes (8–10). This evidence shows that patients with diabetes are at high risk not only for cardiovascular diseases but also for cancer.

A chemopreventive effect of aspirin against cancer has been suggested by a series of studies during the past few decades (11–13). Several meta-analyses of randomized controlled trials (RCTs) recently reported reductions in cancer incidence and mortality with long-term use of aspirin (14–16). In particular, aspirin's chemopreventive efficacy against colorectal cancer was well investigated by RCTs (17,18). In 2016, the U.S. Preventive Services Task Force recommended the use of low-dose aspirin for prevention of colorectal cancer in selected patients, taking into consideration age, cardiovascular risk, bleeding risk, and life expectancy (19). Most evidence, however, has been derived from studies of people without diabetes; therefore, whether low-dose aspirin can prevent cancer in patients with diabetes remains uncertain.

We previously conducted an RCT, the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial, to evaluate the efficacy of low-dose aspirin in the primary prevention of cardiovascular events in Japanese patients with type 2 diabetes (20). The JPAD trial began in 2002. We reported the original results in 2008 (20) and the follow-up results in 2017 after a median follow-up period of more than 10 years (JPAD2 cohort study) (21). The current study used the JPAD2 cohort study data to analyze the effect of low-dose aspirin on cancer incidence and mortality in Japanese patients with type 2 diabetes.

## RESEARCH DESIGN AND METHODS

### Study Design

The detailed designs of the JPAD trial and JPAD2 cohort study have been previously described (20,21). In brief, the JPAD trial was a multicenter, randomized, standard care–controlled, open-label, blinded end point assessment trial conducted at 163 institutions throughout Japan to evaluate the effect of low-dose aspirin on the primary prevention of cardiovascular events in patients with type 2 diabetes (ClinicalTrials.gov, NCT00110448). Participant enrollment in the JPAD trial started in December 2002 and was completed in May 2005. After the JPAD trial was completed in April 2008, all participants were monitored until the day of any fatal event or July 2015, even if cardiovascular events occurred. The JPAD trial and its follow-up observational period together constitute the JPAD2 cohort study (Supplementary Fig. 1). Participants who were not monitored until July 2015 were censored on the day of their last visit.

The JPAD trial and JPAD2 cohort study were performed according to the Declaration of Helsinki and were approved by the ethics committee of each participating hospital (Nara Medical University Ethics Committee and Graduate School of Medical Science, and Kumamoto University Ethics Committee). Written informed consent was obtained from each participant.

### Study Participants

In the JPAD trial we recruited 2,539 Japanese patients with type 2 diabetes, age 30–85 years, and no history of cardiovascular disease. The detailed inclusion and exclusion criteria in the JPAD trial were described previously (20). After the JPAD trial was completed, three participants were excluded because they were found to have a history of cardiovascular disease before enrollment in the JPAD trial. A final total of 2,536 participants were enrolled in the JPAD2 cohort study.

### Intervention

The JPAD trial randomly allocated participants (1:1) to receive aspirin (81 mg or 100 mg daily; aspirin group) or no aspirin (no-aspirin group). All participants were allowed to undergo any concurrent treatments. At the end of the JPAD trial, participants were administered low-dose aspirin according to the decision of each physician during the follow-up period. We checked whether participants were administered low-dose aspirin during follow-up. On July 2015, 2,160 participants (85%) had retained their original allocation (21).

### Primary and Secondary End Points

In these post hoc analyses, we defined the primary end point as the time to first occurrence of any malignant neoplasm after the JPAD trial enrollment (total cancer incidence). The secondary end points were colorectal cancer incidence and total cancer mortality. Total cancer incidence and mortality were composite end points of all types of cancer, in accordance with previous studies to evaluate aspirin's cancer chemoprevention (16,22). Because aspirin's chemopreventive effect on colorectal cancer was previously reported in people without diabetes (17,18), we analyzed colorectal cancer incidence as a secondary end point. These end points were defined after the start of the JPAD trial. We collected data on cancer occurrence by contacting each treating physician. When these physicians reported the cancer occurrence, the study secretariat asked them about the detailed information of the cancers (i.e., onset date, site, and tissue type). We excluded cancer events that occurred before the enrollment. Hemorrhagic events, consisting of gastrointestinal bleeding, hemorrhagic stroke, and bleeding from any other sites, were reported previously (21). All potential end points were adjudicated by a central independent committee that was blinded to the group assignments.

### Statistical Analysis

Categorical variables are expressed as numbers and percentages. Continuous variables are expressed as means (SD) or medians (interquartile range). Based on their distribution, continuous variables were compared using the Student *t* test or the Wilcoxon rank sum test as appropriate. Comparisons between the aspirin and no-aspirin groups were made on the basis of time to the first event, according to the intention-to-treat principle, because 85% of participants retained their original allocation at the time of analysis and previous studies indicated that the long-term effect of aspirin on cancer chemoprevention persisted despite discontinuing aspirin (15,22). Because the mortality from cardiovascular events was low in the JPAD2 cohort study and we monitored all participants after these events, the cause-specific cumulative incidence of each end point was estimated using the Kaplan-Meier method in each group, and differences between groups were assessed with the log-rank test. We constructed Cox proportional hazards models to estimate the hazard ratio (HR) and 95% CI of the efficacy of low-dose aspirin in terms of the end point incidence. As a sensitivity analysis, we

analyzed the effect of low-dose aspirin on total cancer incidence in the period after 5 years from the randomization because previous studies reported that aspirin treatment for at least 5 years was shown to be effective for cancer chemoprevention (15).

In subgroup analyses, we stratified the participants by sex and age (≥65 or <65 years at randomization) and analyzed the effect of low-dose aspirin on cancer incidence. In each age subgroup, we developed multivariable Cox proportional hazards models to estimate the HR adjusted for sex, baseline hemoglobin $A_{1c}$ ($HbA_{1c}$), history of smoking (current or past smoking), and administration of metformin and any statin. These factors were considered to affect the incidence of cancer events in previous studies (23,24). In these models, $HbA_{1c}$ was dichotomized by a median value of 7.2% (55 mmol/mol). We also constructed multivariable Cox proportional hazards models to evaluate the interaction between age subgroup and low-dose aspirin.

Statistical analyses were conducted by an independent statistician (T.M.) with the use of JMP 12.2 (SAS Institute, Cary, NC) and SAS 9.4 (SAS Institute) software. Two-tailed *P* values of <0.05 were considered statistically significant.

## RESULTS

### Baseline Characteristics

The median follow-up period was 10.7 years (95% CI, 10.5–10.8). During the follow-up period, 267 participants in the aspirin group stopped taking low-dose aspirin, and 109 participants in the no-aspirin group started taking aspirin. Baseline characteristics of participants are presented in Table 1. The mean age of the entire population at baseline was 65 ± 10 years, and 55% of the participants were men. The median duration of diabetes was 7.0 years. There was a 21% prevalence of current and past smokers. Dyslipidemia was present in 53% of the participants, and 26% were administered a statin. The medical history of malignant neoplasms was not investigated at the JPAD trial enrollment.

### The Effect of Low-Dose Aspirin on Total Cancer Incidence

During the follow-up period, 318 cancer events occurred: 149 (14.4 per 1,000 person-years) in the aspirin group and 169 (15.9 per 1,000 person-years) in the no-aspirin group. The details regarding cancer incidence are presented in Table 2. The total cancer incidence was not significantly different between the aspirin and no-aspirin groups (log-rank, *P* = 0.4) (Fig. 1*A*), and the HR of aspirin was 0.92 (95% CI, 0.73–1.14; *P* = 0.4). The sensitivity analysis in cancer events after 5 years from the randomization showed similar results (log-rank, *P* = 0.2; HR, 0.81; 95% CI, 0.61–1.09; *P* = 0.2) (Supplementary Fig. 2).

We analyzed the effect of low-dose aspirin on total cancer incidence in subgroups stratified by sex and age. The cancer events occurred in 201 male participants and in 117 female participants (Supplementary Table 1). Low-dose aspirin did not affect total cancer incidence in men (log-rank, *P* = 0.5; HR, 0.92; 95% CI, 0.69–1.21; *P* = 0.5) or women (log-rank, *P* = 0.5; HR, 0.89; 95% CI, 0.61–1.28; *P* = 0.5) (Fig. 2*A*).

In the age subgroups, cancer events occurred in 217 participants aged ≥65 years and in 101 participants aged <65 years. In the subgroup of age ≥65 years, the total cancer incidence was 113 (19.9 per 1,000 person-years) in the aspirin group and 104 (20.2 per 1,000 person-years) in the no-aspirin group (Supplementary Table 1). Total cancer incidence did not differ significantly between the aspirin and no-aspirin groups in this subgroup (log-rank, *P* = 0.9; HR, 0.98; 95% CI, 0.75–1.28; *P* = 0.9) (Fig. 2*B*).

In the subgroup of age <65 years, the total cancer incidence was 36 (7.73 per

**Table 1—Participants' baseline characteristics in the JPAD2 cohort study**

| | Total (*n* = 2,536) | Aspirin group (*n* = 1,259) | No-aspirin group (*n* = 1,277) |
|---|---|---|---|
| Age, mean (SD), years | 65 (10) | 65 (10) | 64 (10) |
| Men, *n* (%) | 1,386 (55) | 705 (56) | 681 (53) |
| BMI, mean (SD), kg/m$^2$ | 24.4 (3.6) | 24.4 (3.6) | 24.3 (3.7) |
| Duration of diabetes, median (IQR), years | 7.0 (2.9–12.3) | 7.3 (2.8–12.3) | 6.7 (3.0–12.5) |
| $HbA_{1c}$, mean (SD), % | 7.5 (1.4) | 7.5 (1.5) | 7.4 (1.2) |
| $HbA_{1c}$, mean (SD), mmol/mol | 58 (15) | 58 (16) | 57 (13) |
| Fasting plasma glucose, mean (SD), mmol/L | 8.2 (2.7) | 8.2 (2.8) | 8.1 (2.7) |
| Diabetic microvascular complications, *n* (%) | | | |
| Retinopathy | 365 (14) | 187 (15) | 178 (14) |
| Nephropathy | 322 (13) | 169 (13) | 153 (12) |
| Neuropathy | 300 (12) | 163 (13) | 137 (11) |
| Smoking status, *n* (%) | | | |
| Current | 537 (21) | 289 (23) | 248 (19) |
| Past | 520 (21) | 274 (22) | 246 (19) |
| Presence of hypertension, *n* (%) | 1,470 (58) | 739 (59) | 731 (57) |
| Presence of dyslipidemia, *n* (%) | 1,344 (53) | 679 (54) | 665 (52) |
| Antihyperglycemic medications, *n* (%) | | | |
| Sulfonylurea | 1,445 (57) | 735 (58) | 710 (56) |
| Metformin | 353 (14) | 167 (13) | 186 (15) |
| Thiazolidinedione | 127 (5) | 62 (5) | 65 (5) |
| Insulin | 326 (13) | 166 (13) | 160 (13) |
| Statins, *n* (%) | 650 (26) | 322 (26) | 328 (26) |

IQR, interquartile range.

**Table 2—Details of cancer incidence**

| | Cancer incidence | | | | | |
|---|---|---|---|---|---|---|
| | Total (*n*) | *n*/1,000 person-years | Aspirin group (*n*) | *n*/1,000 person-years | No-aspirin group (*n*) | *n*/1,000 person-years |
| Total cancer | 318 | 15.1 | 149 | 14.4 | 169 | 15.9 |
| Colorectum | 58 | 2.76 | 27 | 2.61 | 31 | 2.91 |
| Stomach | 46 | 2.19 | 18 | 1.74 | 28 | 2.63 |
| Lung | 33 | 1.57 | 22 | 2.13 | 11 | 1.03 |
| Liver | 24 | 1.14 | 10 | 0.97 | 14 | 1.31 |
| Pancreas | 22 | 1.05 | 12 | 1.16 | 10 | 0.94 |
| Prostate | 20 | 0.95 | 9 | 0.87 | 11 | 1.03 |
| Breast | 17 | 0.81 | 4 | 0.39 | 13 | 1.22 |
| Bile duct and gall bladder | 12 | 0.57 | 9 | 0.87 | 3 | 0.28 |
| Lymphoma | 12 | 0.57 | 2 | 0.19 | 10 | 0.94 |
| Kidney | 11 | 0.52 | 4 | 0.39 | 7 | 0.66 |
| Bladder | 11 | 0.52 | 4 | 0.39 | 7 | 0.66 |
| Leukemia | 10 | 0.48 | 5 | 0.48 | 5 | 0.47 |
| Esophagus | 8 | 0.38 | 3 | 0.29 | 5 | 0.47 |
| Thyroid | 5 | 0.24 | 4 | 0.39 | 1 | 0.09 |
| Skin | 5 | 0.24 | 2 | 0.19 | 3 | 0.28 |
| Uterine | 4 | 0.19 | 4 | 0.39 | 0 | 0 |
| Brain | 4 | 0.19 | 3 | 0.29 | 1 | 0.09 |
| Others | 16 | 0.76 | 7 | 0.68 | 9 | 0.84 |

The incidence of prostate cancer calculated only in male participants was 1.75 cases per 1,000 person-years in total, 1.56 in the aspirin group, and 1.95 in the no-aspirin group. The incidence of breast and uterine cancer calculated only in female participants was 1.77 and 0.42 cases per 1,000 person-years in total, 0.88 and 0.88 in the aspirin group, and 2.59 and 0 in the no-aspirin group, respectively.

1,000 person-years) in the aspirin group and 65 (11.8 per 1,000 person-years) in the no-aspirin group (Supplementary Table 1). The cancer incidence was decreased in the aspirin group, but statistical significance was not reached by the log-rank test ($P = 0.05$) (Fig. 2*B*). Univariable Cox proportional hazards models demonstrated that low-dose aspirin significantly reduced total cancer incidence in the subgroup of age <65 years (HR, 0.67; 95% CI, 0.44–0.99; $P = 0.048$). The HR was still statistically significant after adjusting for sex, $HbA_{1c}$, smoking status, and administration of metformin and statins (adjusted HR, 0.66; 95% CI, 0.43–0.99; $P = 0.04$) (Supplementary Table 2). The interaction *P* value between age subgroup and low-dose aspirin was not significant ($P = 0.1$).

### The Effect of Low-Dose Aspirin on Colorectal Cancer Incidence

The most frequent cancer in the JPAD2 cohort study was colorectal cancer, with 27 events in the aspirin group and 31 events in the no-aspirin group (Table 2). We examined the effect of low-dose aspirin on colorectal cancer incidence and found no significant difference between the aspirin and no-aspirin groups (log-rank, $P = 0.8$; HR, 0.92; 95% CI, 0.55–1.55; $P = 0.8$). On one hand, the subgroup analysis according to age (Supplementary Table 3) found no significant difference in participants aged ≥65 years (log-rank, $P = 0.2$; HR, 1.50; 95% CI, 0.76–3.08; $P = 0.2$). On the other hand, the incidence of colorectal cancer was significantly lower in the aspirin group in participants aged <65 years (log-rank, $P = 0.048$; HR, 0.41; 95% CI, 0.15–0.97; $P = 0.04$).

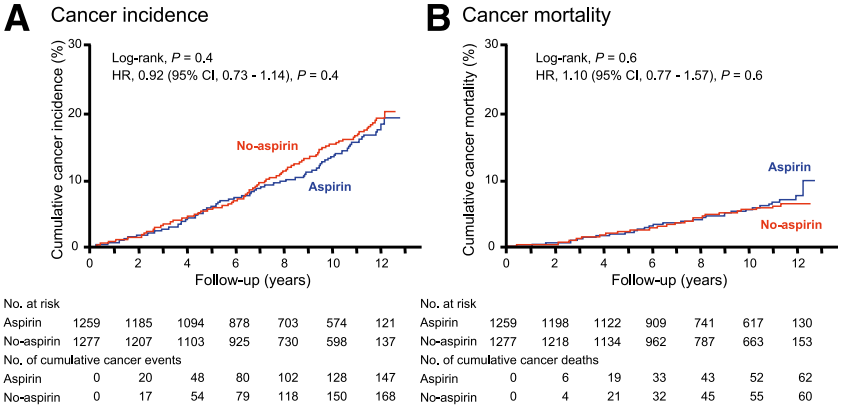


**Figure 1**—Kaplan-Meier estimates are shown of the effect of low-dose aspirin on total cancer incidence (*A*) and mortality (*B*) in the aspirin and no-aspirin groups. During the follow-up period, 318 cancer events and 123 cancer deaths occurred.

### The Effect of Low-Dose Aspirin on Total Cancer Mortality

In the JPAD2 cohort study, 331 participants died before July 2015. Of these, 123 died of cancer, which was the leading cause of death. The other causes of death were infectious diseases in 44 participants, cardiovascular disease in 42, and sudden death in 20. Cancer death occurred in 63 participants (5.90 per 1,000 person-years) in the aspirin group and in 60 participants (5.40 per 1,000 person-years) in the no-aspirin group. The total cancer mortality was similar in the aspirin and no-aspirin groups (log-rank, $P = 0.6$; HR, 1.10; 95% CI, 0.77–1.57; $P = 0.6$) (Fig. 1*B*).

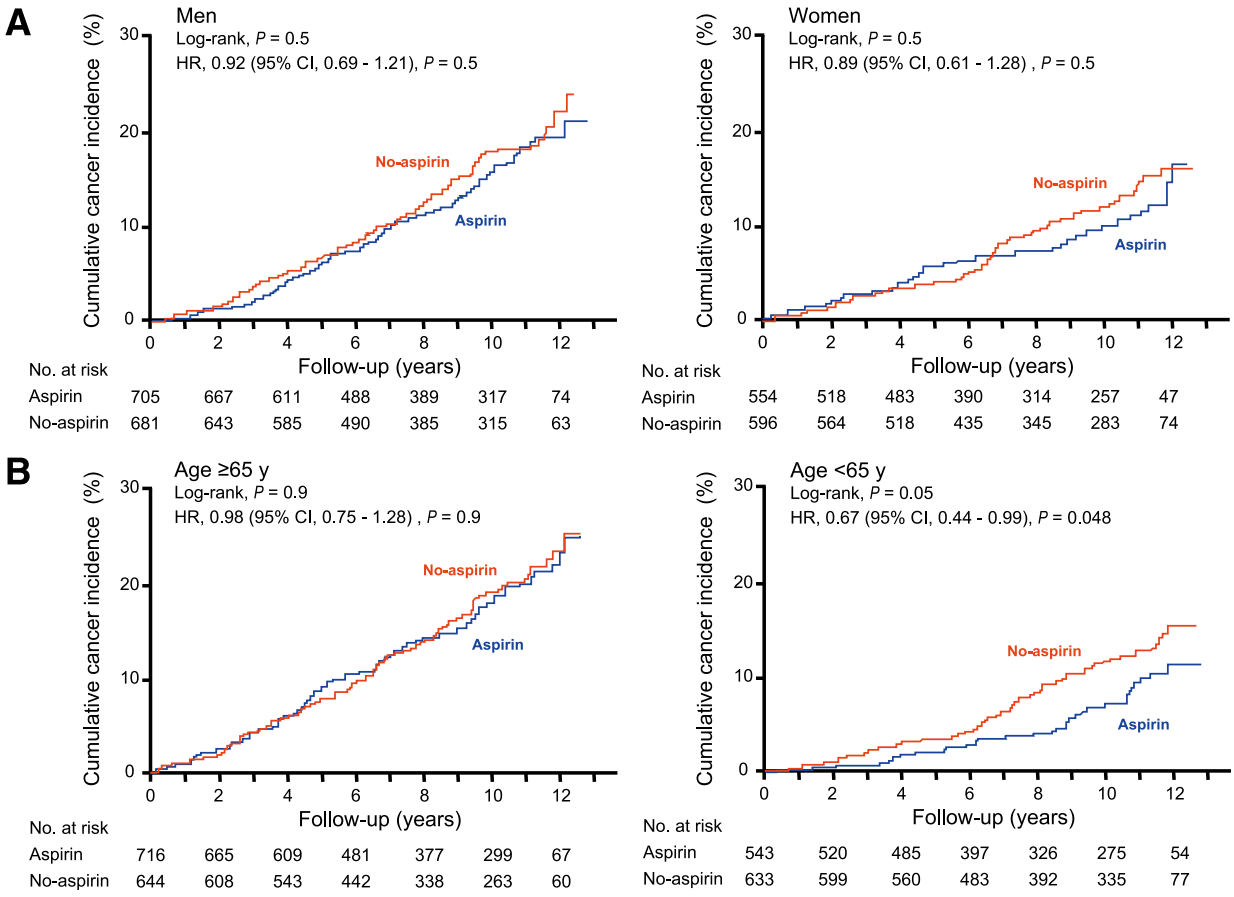


**Figure 2**—Kaplan-Meier estimates are shown for subgroup analyses of total cancer incidence stratified by sex (*A*) and age (≥65 or <65 years) (*B*) in the aspirin and no-aspirin groups. y, years.

## CONCLUSIONS

Our 10-year follow-up cohort study of the JPAD trial showed that long-term use of low-dose aspirin did not reduce cancer incidence or mortality in Japanese patients with type 2 diabetes. The effect of low-dose aspirin on total cancer incidence did not differ according to sex; however, in participants aged <65 years at randomization, total and colorectal cancer incidence was significantly lower in the aspirin group. These results suggest that low-dose aspirin has a beneficial effect on cancer chemoprevention in younger patients with type 2 diabetes. However, the findings should interpreted carefully because they were the results of the secondary analysis.

Low-dose aspirin is recommended for cardiovascular prevention in patients after myocardial infarction (25) and in patients at high cardiovascular risk (19,26). In terms of cancer chemoprevention, aspirin treatment for at least 5 years was shown to be effective (15). In our study, the HR of aspirin in the analysis in the period after 5 years from the randomization became smaller than that in all periods (HR of 0.81 in the period after 5 years from the randomization and 0.92 in all periods). The findings suggested that long-term treatment of low-dose aspirin was beneficial. Therefore, the U.S. Preventive Services Task Force does not recommend low-dose aspirin for people with short life expectancy or elderly people (19). Because the incidence of most types of cancer is higher in elderly people (27), the potential benefit of low-dose aspirin for cancer chemoprevention could be expected in this population. A previous meta-analysis showed that the absolute risk reduction of cancer death by aspirin was larger with age (15). However, a recent study indicated that the benefit of low-dose aspirin for colorectal cancer prevention was smaller when aspirin was initiated at the age of ≥70 years (28). Although the participants of the JPAD2 cohort study were restricted to patients with diabetes, our study supported that low-dose aspirin is beneficial for cancer chemoprevention in younger patients but not the elderly.

Several lines of evidence have demonstrated that low-dose aspirin has chemopreventive effects against colorectal cancer (14,17,18,22). Our findings showed that low-dose aspirin reduced the incidence of colorectal cancer only in participants aged <65 years. Colorectal cancer developed in 34 participants aged ≥65 and in 24 aged <65 years (Supplementary Table 3). There was a high incidence of colorectal cancer in the elderly participants, but no benefit of low-dose aspirin was detected. The gold standard for the diagnosis of colorectal cancer remains colonoscopy (29), but elderly people often have difficulty undergoing this procedure. The effect of low-dose aspirin on colorectal cancer chemoprevention might therefore be underestimated in the elderly.

Currently, half of Japanese people develop cancer in their lifetimes, and one-third of them die as a result (1). Diabetes

has been shown to confer a higher risk of cancer in Japan (8) and in other countries (30). In this study, the colorectum was the most common cancer site, followed by the stomach, lung, liver, pancreas, prostate, and breast. By contrast, the most frequent sites in the Japanese general population are, in descending order, the stomach, colorectum, lung, breast, prostate, liver, and pancreas (31). According to a pooled analysis of Japanese cancer registries (330,000 people aged >35 years), the cancer incidence in Japanese people without diabetes was calculated as 7.73 cases per 1,000 person-years in total, 1.66 in the stomach, 1.39 in the colorectum, 0.94 in the lung, 0.45 in the liver, and 0.29 in the pancreas (32). The incidence of these cancers in the JPAD2 cohort study was higher than that in Japanese people without diabetes. Previous reports showed that the incidence of hepatic, pancreatic, endometrial, and colorectal cancer was higher in patients with diabetes than in those without diabetes (8,10), whereas the incidence of prostate cancer was lower (33). Diabetic status might have contributed to the difference in cancer incidence between our results and the Japanese general population.

The multivariable Cox proportional hazards models in this study were adjusted for the administration of metformin and any statin. Metformin was reported to exert a cancer chemoprevention effect through the inhibition of the mammalian target of rapamycin pathway (34). However, our analysis did not show a relationship between metformin and cancer incidence (Supplementary Table 2). The low rate of metformin administration (14%) in the JPAD2 cohort study might have affected the results. Evidence regarding the cancer chemoprevention effect of statins is conflicting (35,36), but recent reports have indicated their benefit in this regard (24,37,38). Our results suggested that administration of any statin reduced the incidence of cancer regardless of whether participants were aged ≥65 or <65 years (Supplementary Table 2). Although the design of the JPAD2 cohort study did not aim to evaluate the effectiveness of statins, a possible benefit of statins on cancer chemoprevention should be expected in patients with diabetes.

This study had several limitations. First, the JPAD trial was designed as an RCT to evaluate the efficacy of low-dose aspirin in cardiovascular prevention, not in cancer chemoprevention, and the sample size was insufficient to evaluate the latter.

Second, because cancers are a heterogeneous group, there was a limit to analyze all types of cancer as one group. However, we used the composite end points of all types of cancer in accordance with previous studies (16,22), because we hypothesized that low-dose aspirin therapy reduced any cancer incidence, not a specific cancer. Thus, we did not analyze the effect of low-dose aspirin on the incidence of each cancer, excluding colorectal cancer. Our study did not determine whether low-dose aspirin affected the incidence of each cancer. However, the relationship between low-dose aspirin use and the incidence of other types of cancer should be investigated, when the follow-up period becomes longer.

Third, the past history of cancer in each participant was unknown. The potential cancer risk might have differed among participants. However, when cancer events were reported in the follow-up period, we obtained the detailed information about the cancer events and distinguished new-onset cancer from existing cancer.

Fourth, although we checked whether low-dose aspirin was prescribed for each patient during follow-up, we had no data on compliance of low-dose aspirin.

Fifth, we did not evaluate the daily intake of nonsteroidal anti-inflammatory drugs (NSAIDs) other than low-dose aspirin. Because a recent meta-analysis reported a positive effect of nonaspirin NSAIDs on cancer chemoprevention (39), the lack of data on nonaspirin NSAID administration might have affected our results.

Finally, whether these findings are broadly applicable to other populations remains uncertain because differences in race and regional lifestyle affect cancer incidence (27). International studies are needed to evaluate the efficacy of low-dose aspirin in cancer chemoprevention in patients with diabetes.

In conclusion, this study showed that low-dose aspirin did not reduce cancer incidence or mortality in the overall sample of Japanese patients with type 2 diabetes but suggested that low-dose aspirin was beneficial for cancer chemoprevention in those aged <65 years. Although recent guidelines were revised to deemphasize the use of low-dose aspirin for primary prevention of cardiovascular disease in patients with diabetes (26,40), cumulative evidence suggests the benefit of administering low-dose aspirin for cancer chemoprevention in this population.

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## References

1. Ministry of Health, Labour and Welfare. Outline of vital statics in 2015 [Internet]. Available from http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/geppo/nengai15/index.html. Accessed 1 September 2017

2. Nakamura J, Kamiya H, Haneda M, et al. Causes of death in Japanese patients with diabetes based on the results of a survey of 45,708 cases during 2001-2010: report of the Committee on Causes of Death in Diabetes Mellitus. J Diabetes Investig 2017;8:397–410

3. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA 1995;273:1605–1609

4. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 2005;97:1679–1687

5. Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. Diabetologia 2006;49:2819–2823

6. Mitri J, Castillo J, Pittas AG. Diabetes and risk of Non-Hodgkin's lymphoma: a meta-analysis of observational studies. Diabetes Care 2008;31:2391–2397

7. Noto H, Tsujimoto T, Sasazuki T, Noda M. Significantly increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis. Endocr Pract 2011;17:616–628

8. Noto H, Osame K, Sasazuki T, Noda M. Substantially increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis of epidemiologic evidence in Japan. J Diabetes Complications 2010;24:345–353

9. Kasuga M, Ueki K, Tajima N, et al. Report of the JDS/JCA Joint Committee on Diabetes and Cancer. Diabetol Int 2013;4:81–96

10. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829–841

11. Thun MJ, Namboodiri MM, Heath CW Jr. Aspirin use and reduced risk of fatal colon cancer. N Engl J Med 1991;325:1593–1596

12. Farrow DC, Vaughan TL, Hansten PD, et al. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. Cancer Epidemiol Biomarkers Prev 1998;7:97–102

13. Jacobs EJ, Rodriguez C, Mondul AM, et al. A large cohort study of aspirin and other nonsteroidal anti-inflammatory drugs and prostate cancer incidence. J Natl Cancer Inst 2005;97:975–980

14. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 2010;376:1741–1750

15. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011;377:31–41

16. Rothwell PM, Price JF, Fowkes FG, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 2012;379:1602–1612

17. Burn J, Gerdes AM, Macrae F, et al.; CAPP2 Investigators. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 2011;378:2081–2087

18. Cole BF, Logan RF, Halabi S, et al. Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. J Natl Cancer Inst 2009;101:256–266

19. Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2016;164:836–845

20. Ogawa H, Nakayama M, Morimoto T, et al.; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008;300:2134–2141

21. Saito Y, Okada S, Ogawa H, et al.; JPAD Trial Investigators. Low-dose aspirin for primary prevention of cardiovascular events in patients with type 2 diabetes mellitus: 10-year follow-up of a randomized controlled trial. Circulation 2017;135:659–670

22. Cook NR, Lee IM, Zhang SM, Moorthy MV, Buring JE. Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. Ann Intern Med 2013;159:77–85

23. Coyle C, Cafferty FH, Vale C, Langley RE. Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis. Ann Oncol 2016;27:2184–2195

24. Wang A, Aragaki AK, Tang JY, et al. Statin use and all-cancer survival: prospective results from the Women's Health Initiative. Br J Cancer 2016;115:129–135

25. Baigent C, Blackwell L, Collins R, et al.; Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849–1860

26. Pignone M, Alberts MJ, Colwell JA, et al.; American Diabetes Association; American Heart Association; American College of Cardiology Foundation. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. Diabetes Care 2010;33:1395–1402

27. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1674–1685

28. Dehmer SP, Maciosek MV, Flottemesch TJ, LaFrance AB, Whitlock EP. Aspirin for the primary prevention of cardiovascular disease and colorectal cancer: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2016;164:777–786

29. Bray C, Bell LN, Liang H, Collins D, Yale SH. Colorectal cancer screening. WMJ 2017;116:27–33

30. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009;16:1103–1123

31. National Cancer Center, Center for Cancer Control and Information Services. Monitoring of Cancer Incidence in Japan (MCIJ) [Internet], 2013. Available from http://ganjoho.jp/data/reg_stat/statistics/brochure/mcij2013_report.pdf. Accessed 10 November 2017

32. Sasazuki S, Charvat H, Hara A, et al.; Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Diabetes mellitus and cancer risk: pooled analysis of eight cohort studies in Japan. Cancer Sci 2013;104:1499–1507

33. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2006;15:2056–2062

34. Dowling RJ, Zakikhani M, Fantus IG, Pollak M, Sonenberg N. Metformin inhibits mammalian

target of rapamycin-dependent translation initiation in breast cancer cells. Cancer Res 2007; 67:10804–10812
35. Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. JAMA 2006;295:74–80
36. Kuoppala J, Lamminpää A, Pukkala E. Statins and cancer: a systematic review and meta-analysis. Eur J Cancer 2008;44:2122–2132
37. McGlynn KA, Hagberg K, Chen J, et al. Statin use and risk of primary liver cancer in the Clinical Practice Research Datalink. J Natl Cancer Inst 2015;107:djv009
38. Chen MJ, Tsan YT, Liou JM, et al. Statins and the risk of pancreatic cancer in type 2 diabetic patients–a population-based cohort study. Int J Cancer 2016;138:594–603
39. Dulai PS, Singh S, Marquez E, et al. Chemoprevention of colorectal cancer in individuals with previous colorectal neoplasia: systematic review and network meta-analysis. BMJ 2016; 355:i6188
40. Rydén L, Grant PJ, Anker SD, et al.; Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); Document Reviewers. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 2013; 34:3035–3087