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# Use of metformin and aspirin is associated with delayed cancer incidence

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ABSTRACT

*Background:* While the chemoprevention effect of aspirin is well-established, the effects of metformin in cancer prevention is still controversial. This study is to investigate the use of aspirin, metformin, or the combination of both is associated with delayed cancer incidence.

*Method:* This dataset is based on the electronic medical record of public hospitals in Hong Kong. Patients were classified into 1. aspirin user, 2. metformin user, 3. both aspirin and metformin user and 4. control group with neither aspirin nor metformin used. Aspirin and/or metformin must have been taken for over 6 months in the treatment group and cancer incidences was counted at least 6 months after exposure to such medications. The primary outcome of this study was overall incidence of cancer during the follow-up period. The secondary outcomes were cancer incidences of specific sites, including colon/rectum, liver, oesophagus, pancreas, stomach, lung, breast, kidney, bladder and prostate. Cox proportional hazards regression models were fitted to estimate hazard ratios of cancer risks. Inverse probability of treatment weighting was used to control for the medication effects.

*Results:* A total of 120,971 aspirin users, 11,365 metformin users, and 6630 aspirin plus metformin users, were identified. Compare to the control groups, those who used aspirin alone demonstrated a significant reduction in overall cancer risk (HR 0.80, 95% CI 0.73-0.87). Similarly, those who used metformin alone also showed an overall reduction in cancer risk (HR 0.79, 95% CI 0.71-0.88). Patients who received both aspirin and metformin showed the most significant reduction in overall cancer risk (HR 0.53, 95% CI 0.45-0.63). Metformin showed a significant reduction in cancer risk of lung, oesophagus and bladder.

*Conclusion:* There is a similar decrease in overall cancer rate with the use of aspirin or metformin alone. A more significant reduction in overall cancer risk was found with the use of both agents.

## 1. Introduction

The chemoprevention effect of aspirin against various types of cancer have been well documented. From the initial data on aspirin preventing the progression of adenoma to carcinoma in the colon and rectum [1–3] to the reduced risk of other cancers, liver, stomach, pancreas, oesophagus and leukemia [4,5], the cancer prevention effects of aspirin have been rather consistent, and is related to the dose and duration of medication prescribed to the patients.

On the other hand, the cancer preventive effect of metformin has been a subject of controversy for almost two decades. Early observational studies suggested that metformin use can significantly reduce risk of cancer, especially colorectal, liver and pancreatic cancers [6,7]. Initial enthusiasm came from two large nation-wide dataset with respectable number of subjects in these retrospective cohorts. Using the UK general practice dataset, Currie et al reported that type 2 diabetes (T2D) patients receiving metformin alone has lower cancer risk than those who received sulfonylurea (alone or in combination with metformin) or insulin-based therapy [8]. There was even suggestion that mortality after incident cancer diagnosis was lower in those who were treated with metformin [8]. This study, however, suffered from a short follow up time and did not address the time-lag bias of different T2D patients. In Taiwan, using the national Health Insurance data, it was reported that diabetics without using anti-hyperglycemic treatment have at least 2-fold increase for total colorectal cancer and hepatocellular cancer. T2D patients who were put on metformin has colorectal cancer and hepatocellular cancer almost reduced to non-diabetic levels [9]. Yet, this study also suffered from immortal time bias, which occurs

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when exposure groups have to survive event-free until the first exposure to the study drug. In addition, the number of cancer events were small.

As pointed out by Suissa et al, immortal time bias, time-window bias and time-lag bias tend to exaggerate the benefit of metformin [10,11]. Time-window bias may occur in case-control studies when cases have shorter person-time to be possibly exposed to the study drug, resulting in overrepresentation of unexposed cases and artificial benefits of the drug.11] Time-lag bias may occur in cohort study when comparison is made between patients receiving different pharmaceutical agents to treat the same disease, as patients receiving different drugs may not be at the same disease stage and different agents may represent different lines of treatment [10].

With more carefully designed observation studies, the benefit of metformin has been questions. Several major nested case-controlled study from the UK using the UK General Practice Research Database have failed to report cancer protective effect in using metformin against the development of colorectal [12], prostate [13], bladder [14], lung [15] and so-called viral associated cancers (hepatitis B virus, hepatitis C virus, human papillomavirus, human T-cell lymphotropic virus type 1, and Epstein-Barr virus) [16]. The lack of benefit for protection against prostate cancer is also reported from a study in Canada [17]. However, two studies from Taiwan showed beneficial effects against onset of lung and ovarian cancers [18,19].

More recently, metformin has also been reported to be associated with a 3-fold-increases risk of pancreatic cancer [20] while recent reviews demonstrated decreased risk of lung and colorectal cancers [21–23]. Putting all these together, it is possible that metformin may exercise different effects, from protection to aggravation, on specific site of cancer development.

The global epidemic of metabolic syndrome and the ageing of the world's population is leading to the increased rates of coronary heart diseases and diabetes mellitus, and many people are now receiving both drugs which are fundamentally the core therapy of these two conditions. However, there is little information on the use of aspirin and metformin and their effects on cancer development risk. This study is set to investigate whether the use of aspirin, metformin, or the combination of both is associated with delayed cancer incidence.

## 2. Material and methods

### 2.1. Study design

This is a retrospective cohort study followed the standard guidelines of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [24] and focused clinic attendee electronic medical records of the public hospitals in Hong Kong. The Hospital Authority (HA) is composed of 43 government-funded hospitals in Hong Kong and takes care of over 90% of in-patients service of the general public. Under the HA, the Clinical Data Repository, also known as the Clinical Management System, is Hong Kong's central electronic medical record system that captures patients' demographics, prescription details and clinical diagnosis in the format of the International Classification of Diseases (ICD-9 or ICD-10) or the International Classification of Primary Care for every clinical consultation. This database forms a good representative of health conditions and medical history of the Hong Kong population. Patients' data in this study were extracted anonymously and assigned with a unique identifier. Ethical approval of the study was obtained from the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee.

### 2.2. Study participants

A total of 254,489 patients who had prescribed Aspirin from 4,564,100 patients at any public hospitals between 2000 and 2004 were identified from the electronic database records. After some exclusion criteria, 138,966 aspirin and/or metformin users were included in this study (Fig. 1). Patients were classified into 1. aspirin users, 2. metformin users, 3. both aspirin and metformin users and 4. control group with neither aspirin nor metformin used between 2000 and 2013. Aspirin use was defined as at least 6-month prescription records of aspirin no less than 80 mg daily while metformin use was defined as at least 6-month prescription records of metformin no less than 500 mg daily. Patients must be aged 18 or above at cohort entry and have no previous cancer diagnosis. Index time was defined as first prescription record of aspirin or metformin. To avoid immortal time bias, patients with cancer diagnosis or early deaths within six months were excluded [10,11]. Patients who ever used insulin or sulfonylurea were further excluded as these drugs indicate higher severity of diabetes mellitus which increase the risk of cancers. All subjects were followed until the diagnosis of first cancer, death from any cause, and were followed up until the end of 2013, whichever came first. Duration of aspirin or metformin were calculated as the time difference between the first and last prescription records of the relevant drug.

### 2.3. Outcome variables

The primary outcome of this study was overall incidence of cancer at any site during the follow-up period. The secondary outcomes were cancer incidences of specific sites, including colon/rectum, liver, oesophagus, pancreas, stomach, lung, breast, kidney, bladder and prostate. A patient with newly diagnosed cancer at two different sites during follow-up were counted separately. This applied to patients with cancer diagnoses at more than two sites. The cancer diagnoses were based on ICD-9 in the Clinical Management System.

### 2.4. Statistical analysis

Baseline characteristics are described in frequency with percentage for categorical variables and mean with standard deviation (SD) for continuous variables. Cox proportional hazards models were fitted to estimate the effects of aspirin use, metformin use, and aspirin plus metformin use on cancer incidences controlling for age, sex and comorbidities. As the main purpose of aspirin prescription in Hong Kong is primarily to prevent cardiovascular and cerebrovascular diseases, patients with a diagnosis of coronary heart disease (ICD-9: 410-414) and stroke (ICD-9: 430, 431, 433, 434, 436) were identified. Inverse probability weighting is to create a pseudo-population by assigning a weight to individuals so that treatment assignment is independent of measured covariates. The assigned weight is called inverse probability treatment weight, which is the inverse of the probability of a subject to be assigned into a treatment group given a number of covariates. All models were adjusted for age, gender, comorbidities, and with inverse probability treatment weights [25] on baseline medications including histamine-2 receptor antagonists (H2 antagonists), statins, non-steroidal anti-inflammatory drugs (NSAIDs) and anti-coagulants. To avoid multiple comparison, control subjects were randomly split when comparison is made between one of the treatment groups and control groups. To achieve comparison with a more balanced sample size for any one treatment subject, two control subjects were randomly assigned to each subject on treatment groups. Cancer risks were estimated in hazard ratio (HR) with 95% confidence intervals (CI). Analyses of cancer risks of different treatment groups at various follow-up time points were also

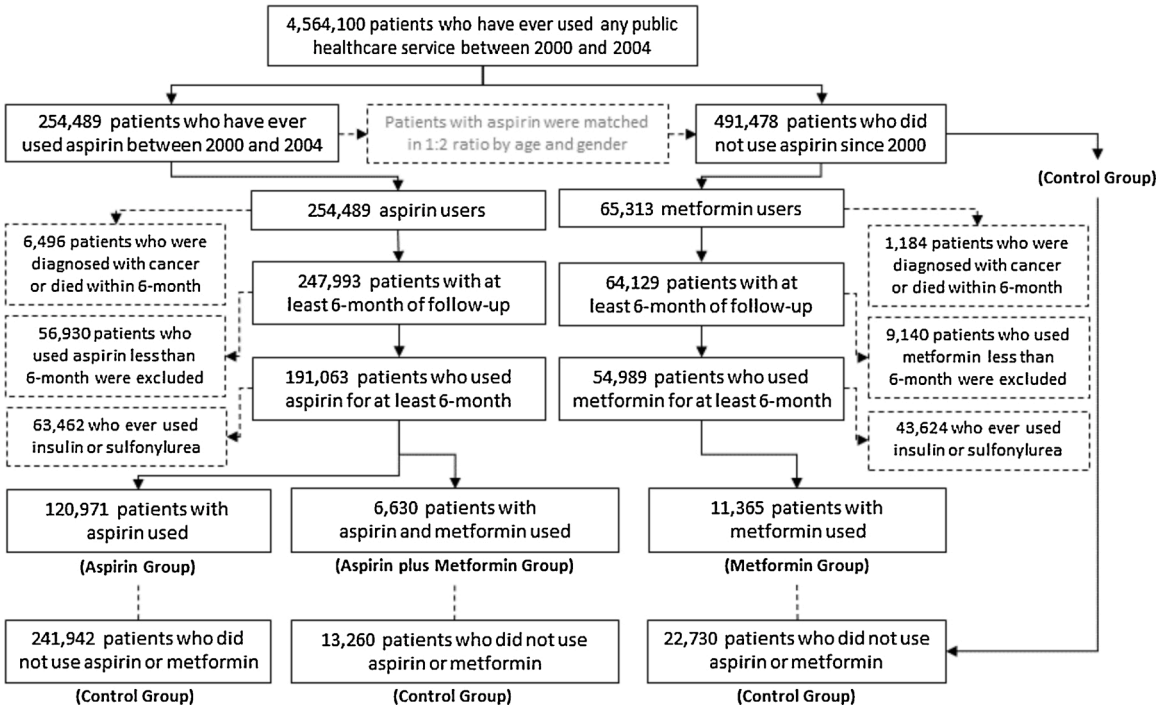


**Fig. 1.** Inclusion criteria for the patients with aspirin and/metformin used.

conducted and statistical significance is set at 0.05.

## 3. Results

There were 120,971 patients who received aspirin alone, 11,365 patients took metformin alone, 6630 patients received both aspirin and metformin, and 277,932 patients received neither aspirin nor metformin during the study period. Among those who took aspirin alone and those who took aspirin with metformin, mean duration of aspirin use were 7.5 years and 9.8 years respectively. Among those who took metformin alone and those who took aspirin with metformin, mean duration of metformin use were 4.4 years and 4.7 years respectively. Baseline demographics, prescription of drugs and history of coronary heart disease and stroke of the subjects are displayed in Table 1.

Cancer incidence of subjects in all four groups during the follow-up period are shown in Table 2. The unadjusted overall cancer incidence (including all cancers) of the metformin receivers, aspirin receivers, aspirin plus metformin receivers and control (who received neither metformin nor aspirin) were 6.1%, 11.4%, 6.3% and 15.5% respectively. Cancer incidence of individual cancers, including 5 gastrointestinal cancers (colon/rectum, liver, oesophagus, pancreas and stomach) and 5 non-gastrointestinal cancers (lung, female breast, kidney, bladder and

**Table 1**
Baseline characteristics of the study population.

| | Intervention group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Metformin | | Aspirin | | Aspirin plus Metformin | | Control group | |
| | ($n$ = 11,365) | | ($n$ = 120,971) | | ($n$ = 6630) | | ($n$ = 277,932) | |
| Age group (years) | | | | | | | | |
| <50 | 173 | (1.5%) | 8484 | (7.0%) | 586 | (8.8%) | 37,369 | (13.4%) |
| 50-64 | 2173 | (19.1%) | 25,891 | (21.4%) | 2604 | (39.3%) | 72,678 | (26.1%) |
| 65-79 | 6469 | (56.9%) | 58,611 | (48.5%) | 3071 | (46.3%) | 126,630 | (45.6%) |
| ≥80 | 2550 | (22.4%) | 27,985 | (23.1%) | 369 | (5.6%) | 41,255 | (14.8%) |
| Sex, male | 5285 | (46.5%) | 66,847 | (55.3%) | 3502 | (52.8%) | 148,276 | (53.3%) |
| Other medication used | | | | | | | | |
| - Histamine-2 antagonist | 6225 | (54.8%) | 94,370 | (78.0%) | 4986 | (75.2%) | 139,061 | (50.0%) |
| - Statin | 6047 | (53.2%) | 55,187 | (45.6%) | 5021 | (75.7%) | 19,381 | (7.0%) |
| - Non-steroidal anti-inflammatory drugs | 7107 | (62.5%) | 61,673 | (51.0%) | 3802 | (57.3%) | 134,234 | (48.3%) |
| - Anti-coagulant | 309 | (2.7%) | 33,808 | (27.9%) | 1610 | (24.3%) | 10,203 | (3.7%) |
| - Disease diagnosis | | | | | | | | |
| - Coronary heart disease/Stroke | 314 | (2.8%) | 74,892 | (61.9%) | 3811 | (57.5%) | 12,470 | (4.5%) |
| - Coronary heart disease | 152 | (1.3%) | 52,468 | (43.4%) | 2738 | (41.3%) | 6733 | (2.4%) |
| - Stroke | 174 | (1.5%) | 32,758 | (27.1%) | 1464 | (22.1%) | 6247 | (2.2%) |
| Mean duration of aspirin use | NA | | 7.5 years | | 9.8 years | | NA | |
| Mean duration of metformin use | 4.4 years | | NA | | 4.7 years | | NA | |

NA, not applicable.

**Table 2**
Cancer Incidence across intervention and control groups.

| | Intervention group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Metformin ($n$ = 11,365) | | Aspirin ($n$ = 120,971) | | Aspirin plus Metformin ($n$ = 6,630) | | Control group ($n$ = 277,932) | |
| Gastrointestinal cancers | | | | | | | | |
| Colon/rectum | 145 | (1.3%) | 2557 | (2.1%) | 78 | (1.2%) | 8208 | (3.0%) |
| Liver | 48 | (0.4%) | 679 | (0.6%) | 24 | (0.4%) | 3414 | (1.2%) |
| Oesophagus | 9 | (0.1%) | 322 | (0.3%) | 7 | (0.1%) | 1342 | (0.5%) |
| Pancreas | 26 | (0.2%) | 276 | (0.2%) | 7 | (0.1%) | 995 | (0.4%) |
| Stomach | 57 | (0.5%) | 747 | (0.6%) | 25 | (0.4%) | 2732 | (1.0%) |
| Non-gastrointestinal cancers | | | | | | | | |
| Lung | 141 | (1.2%) | 3432 | (2.8%) | 71 | (1.1%) | 11,443 | (4.1%) |
| Breast (female) | 60 | (0.5%) | 663 | (0.5%) | 32 | (0.5%) | 1993 | (0.7%) |
| Kidney | 10 | (0.1%) | 355 | (0.3%) | 18 | (0.3%) | 848 | (0.3%) |
| Bladder | 25 | (0.2%) | 803 | (0.7%) | 20 | (0.3%) | 2114 | (0.8%) |
| Prostate | 46 | (0.4%) | 1129 | (0.9%) | 36 | (0.5%) | 2912 | (1.0%) |
| All cancers | 688 | (6.1%) | 13,805 | (11.4%) | 419 | (6.3%) | 43,005 | (15.5%) |

**Table 3**
Cancer risks of metformin, aspirin, and aspirin plus metformin users as compared with controls adjusted for age, sex, comorbidities, and other medications.

| | Metformin ($n$ = 11,365) | vs Control ($n$ = 22,730)Aspirin ($n$ = 120,971) | | | vs Control ($n$ = 241,942) | | Aspirin plus Metformin ($n$ = 6630)vs Control ($n$ = 13,260) | | |
|---|---|---|---|---|---|---|---|---|---|
| | **HR** | **(95% CI)** | **p** | **HR** | **(95% CI)** | **p** | **HR** | **(95% CI)** | **p** |
| Gastrointestinal cancers | | | | | | | | | |
| Colon/rectum | 0.92 | (0.72-1.17) | 0.495 | **0.83** | **(0.76-0.90)** | **<0.001** | **0.54** | **(0.39-0.74)** | **<0.001** |
| Liver | 0.81 | (0.57-1.15) | 0.233 | **0.66** | **(0.59-0.74)** | **<0.001** | **0.39** | **(0.23-0.67)** | **0.001** |
| Oesophagus | **0.27** | **(0.12-0.59)** | **0.001** | **0.71** | **(0.61-0.84)** | **<0.001** | 0.26 | (0.05-1.28) | 0.098 |
| Pancreas | 1.45 | (0.83-2.53) | 0.187 | 0.93 | (0.77-1.11) | 0.416 | 0.58 | (0.20-1.65) | 0.305 |
| Stomach | 0.78 | (0.51-1.19) | 0.245 | 0.43 | (0.18-1.04) | 0.061 | **0.51** | **(0.28-0.92)** | **0.025** |
| Non-gastrointestinal cancers | | | | | | | | | |
| Lung | **0.63** | **(0.51-0.78)** | **<0.001** | **0.78** | **(0.72-0.85)** | **<0.001** | **0.29** | **(0.19-0.44)** | **<0.001** |
| Breast (female) | 1.32 | (0.88-1.97) | 0.175 | 0.97 | (0.82-1.16) | 0.767 | 1.03 | (0.58-1.80) | 0.930 |
| Kidney | 0.56 | (0.25-1.26) | 0.163 | 0.76 | (0.45-1.30) | 0.318 | 1.38 | (0.69-2.78) | 0.365 |
| Bladder | **0.54** | **(0.31-0.91)** | **0.022** | 0.93 | (0.83-1.05) | 0.267 | 0.82 | (0.47-1.46) | 0.506 |
| Prostate | 0.80 | (0.53-1.22) | 0.302 | **0.87** | **(0.76-0.99)** | **0.042** | 0.77 | (0.39-1.55) | 0.471 |
| All cancers | **0.79** | **(0.71-0.88)** | **<0.001** | **0.80** | **(0.73-0.87)** | **<0.001** | **0.53** | **(0.45-0.63)** | **<0.001** |

Abbreviations: HRhazard ratio; CIconfidence interval.

prostate), are displayed in Table 2.

Using the Cox model with inverse probability treatment weights to compare those who did not take either metformin or aspirin against those who used aspirin alone, it demonstrated a significant reduction in overall cancer risk (HR 0.80, 95% CI 0.73-0.87). Those who used metformin alone also showed an overall reduction in cancer risk (HR 0.79, 95% CI 0.71-0.88). Patients who received both aspirin and metformin showed the most significant reduction in overall cancer risk (HR 0.53, 95% CI 0.45-0.63). (Table 3). Analysis of cancer risk of individual malignancy showed that, while aspirin alone reduced cancer risk of colon/rectum, liver, oesophagus, lung and prostate, the effects of metformin alone resulted in a reduction in cancer risk of fewer cancers (oesophagus, lung and bladder). For those who were prescribed aspirin and metformin, the combined effects of cancer reduction were shown in cancers of the colon/rectum, liver, stomach and lung. (Table 3).

Metformin alone users demonstrated a reduction in overall cancer risk after mean metformin use for more than 4 years (Table 4). For mean metformin use of less than 4 years, there was an increased risk of female breast cancer among metformin alone users (Appendix 1). However, the risk of breast cancer was decreased after more than 4 years of mean

**Table 4**
Cancer risks of metformin, aspirin, and aspirin plus metformin users as compared with controls adjusted for age, sex, comorbidities, and other medications at different follow-up time.

| | End of 2006 | | | | End of 2009 | | | | End of 2013 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean duration of medication use | Overall cancer risk | | | Mean duration of medication use | Overall cancer risk | | | Mean duration of medication use | Overall cancer risk | | |
| | | HR | (95% CI) | p | | HR | (95% CI) | p | | HR | (95% CI) | p |
| **Metformin($n$ = 11,365)** | 2.7 years | 1.13 | (0.96-1.34) | 0.151 | 3.3 years | 0.93 | (0.82-1.06) | 0.287 | 4.4 years | **0.79** | **(0.71-0.88)** | **<0.001** |
| **Aspirin($n$ = 120,971)** | 4.1 years | **0.71** | **(0.62-0.80)** | **<0.001** | 5.9 years | **0.75** | **(0.68-0.84)** | **<0.001** | 7.5 years | **0.80** | **(0.73-0.87)** | **<0.001** |
| **Aspirin & Metformin ($n$ = 6630)** | 4.6 years & 3.1 years | **0.34** | **(0.26-0.45)** | **<0.001** | 7.0 years &3.6 years | **0.39** | **(0.31-0.49)** | **<0.001** | 9.8 years &4.7 years | **0.53** | **(0.45-0.63)** | **<0.001** |

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

follow up with metformin alone. The long-term use of metformin showed that metformin reduced risk of certain cancers, including oesophagus, lung and bladder (Appendix 1). The use of aspirin was associated with decreased cancer risk for colon/rectum, liver, oesophagus, lung and prostate over 4 years of use on average (Appendix 2). The use of aspirin and metformin was associated with decreased cancer risk for colon/rectum, liver, stomach and lung after mean duration of aspirin and metformin for 9.8 years and 4.7 years, respectively (Appendix 3).

## 4. Discussion

Our study shows that there was a similar decrease on overall cancer rate with the use of aspirin or metformin alone. The combined use of both aspirin metformin showed a further reduction in overall cancer risk. Metformin demonstrates modest association with cancer risk reduction. Its potential cancer preventive effect is weaker than that of low-dose aspirin and when combined with aspirin. Still, metformin use shows protective effects on certain cancer sites, including colon/rectum, liver, stomach and lung.

Aspirin exercise a strong and consistent cancer preventive effect in this study, as shown in many other studies [1–5]. Its effect is not confined to colorectal cancer or liver cancer, but to many other gastrointestinal and non-gastrointestinal cancers. On the other hand, metformin also demonstrated an overall reduction in cancer risk. When individual cancers were analyzed separately, only risk of oesophageal cancer, lung cancer and bladder cancer were reduced with the use of metformin. This is quite distinct from the over-arching effects of low-dose aspirin in cancer prevention. However, the effect of metformin is compounded by the fact that this drug is used primarily for the treatment of diabetes mellitus.

As early as 1959, Joslin et al have proposed a positive correlation between diabetes and cancer [26]. It has subsequently been shown by epidemiological studies that diabetes itself increases the risk of several types of cancers including pancreas, liver, breast, colorectal, urinary tract and female reproductive systems [27]. Hyperglycemia, hyperinsulinemia, steatosis, and increased oxidative stress may contribute to the increased cancer risk in diabetes. Several meta-analyses indicate that the strongest association between T2D and cancer is found in pancreatic and liver cancers, two key organs involved in the metabolic derangement of T2D [28,29]. In our study, the metformin group actually showed an increased female breast cancer risk in the short term to the control group who did not receive metformin. But no effect of metformin on breast cancer was observed in the long run. As limitations from cohort study, we cannot determine whether the modest link with reduced cancer risk in metformin users is related to the weak cancer suppressive effect or the cancer promotion effect of diabetes. This question can only be addressed by a randomized control trial applying metformin in non-diabetic patients.

Combined use of aspirin and metformin may enhance the effect of aspirin alone on certain cancer sites, including colon/rectum, liver and lung. This combined therapy also demonstrated protective effect against gastric cancer but no individual effect on gastric cancer was observed when two drugs were used separately. In this study, aspirin and metformin alone were associated with lower cancer risk on oesophagus when used alone. However, when these drugs were used together, the decreased risk on oesophagus was lost. We don't understand the rationale behind this interaction. A larger number of oesophageal cancer cases is needed to verify this finding.

In this study, we have tried to avoid repeating pitfalls in cohort design as in previous studies, namely neglecting the effect of immortal bias, time-window bias and time-lag bias. Patients entered into this study must have no diagnosis of any type of cancer prior to recruitment. The medications that they received, metformin alone, aspirin alone or metformin in combination with aspirin must be used at least 6 months and all subjects must survive without cancer diagnosis in the first 6 months to avoid immortal time bias. A window of 6 months was imposed on the first outcome of cancer development to avoid inclusion of an early cancer cases which were unlikely related to the medication used. This design should be able to address the issues raised by Suissa et al in introducing various bias in cohort study of metformin and cancer risk [10,11].

There are several limitations of this study. First, as mentioned above, in this study we cannot separate the potential anti-cancer effects of metformin from the pro-cancer effects of diabetes and/or hyperglycemia and/or hyperinsulinemia. All metformin users were diagnosed as diabetics and hence the use of this oral hypoglycemic. The control of blood glucose with metformin are not regularly monitored in all patients and hence the effects of hyperglycemia on cancer risk cannot be evaluated. However, we tried to minimize this confounding factor by excluding patients with more severe form of diabetes who required sulfonylurea and/or insulin. Second, aspirin users in this cohort are not routine checked for fasting blood glucose or HbA1c. Therefore, undiagnosed diabetes cannot be excluded. However, since most of these patients, over 90%, suffered from coronary heart disease and/or cerebrovascular disease, routine checking of blood glucose should be done in most of the cases. Therefore, missing undiagnosed diabetes in this group is unlikely. Third, the rate of cancer in patients with the use of a particular agent can not only be attributed to the pharmacological properties of the drug, other demographic and environmental factors which are common to cancer and diabetes such as age, obesity, physical activity, diet, alcohol and smoking, metabolic control, toxic exposure, psychological status, social network, and genomics may impact on the cancer risk of these patients. Since this dataset comes from in-patient cohorts and such lifestyle parameters were not routinely included in the hospital electronic medical record, we cannot correct for those factors. However, we did include important drug items, including H2 antagonist, statins, non-steroidal anti-inflammatory drugs and anti-coagulants in the inverse probability of treatment weighting which should counterbalance some of these comorbidities. We have also adjusted for two important comorbid illness, namely cardiovascular and cerebrovascular diseases in our analysis. Fourth, the number of cases in certain cancer groups are small, especially for patients receiving metformin only, or a combination of aspirin and metformin. We need to exercise caution when interpreting results in specific cancers. Future studies in certain cancer groups will be helpful. Fifth, as cohort studies are prone to selection bias, we used inverse probability weighting so that group assignment of study subjects is unrelated to observed confounders. Finally, as a limitation of observational studies, we cannot fully establish causal relationship between the use of metformin and cancer onset from the results of a single study alone. Further study is needed to verify the potential chemoprevention effects of metformin and its combined use with aspirin.

In conclusion, there is a similar decrease on overall cancer rate with the use of aspirin or metformin alone. A more significant reduction in overall cancer risk was found with the use of both agents.

## CRediT authorship contribution statement

**Joseph JY Sung:** Conceptualization, Methodology, Writing - original draft. **Jason MW Ho:** Methodology, Formal analysis, Data curation. **Amy SM Lam:** Methodology. **Sarah TY Yau:** Methodology, Formal analysis, Data curation. **Kelvin KF Tsoi:** Conceptualization, Methodology, Writing - review & editing.

## Declaration of Competing Interest

None.

**Appendix 1 Cancer risks of metformin users as compared with controls adjusted for age, sex, comorbidities, and other medications at different follow-up time**

| Mean duration of metformin use | End of 2006 | | | End of 2009 | | | End of 2013 | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2.7 years | | | 3.3 years | | | 4.4 years | | |
| | HR | (95% CI) | p | HR | (95% CI) | p | HR | (95% CI) | p |
| Gastrointestinal cancers | | | | | | | | | |
| Colon/rectum | 0.83 | (0.54-1.28) | 0.394 | 1.01 | (0.74-1.39) | 0.941 | 0.92 | (0.72-1.17) | 0.495 |
| Liver | 1.51 | (0.86-2.65) | 0.155 | 1.08 | (0.70-1.67) | 0.719 | 0.81 | (0.57-1.15) | 0.233 |
| Oesophagus | 0.71 | (0.21-2.44) | 0.584 | 0.46 | (0.18-1.14) | 0.093 | **0.27** | **(0.12-0.59)** | **0.001** |
| Pancreas | 2.23 | (0.96-5.21) | 0.063 | 1.88 | (0.92-3.84) | 0.085 | 1.45 | (0.83-2.53) | 0.187 |
| Stomach | 1.40 | (0.77-2.54) | 0.274 | 0.98 | (0.59-1.63) | 0.947 | 0.78 | (0.51-1.19) | 0.245 |
| Non-gastrointestinal cancers | | | | | | | | | |
| Lung | 1.26 | (0.93-1.72) | 0.140 | 0.83 | (0.64-1.08) | 0.171 | **0.63** | **(0.51-0.78)** | **<0.001** |
| Breast (female) | **2.26** | **(1.23-4.15)** | **0.008** | **1.63** | **(1.03-2.58)** | **0.039** | 1.32 | (0.88-1.97) | 0.175 |
| Kidney | 1.53 | (0.47-4.99) | 0.485 | 0.62 | (0.21-1.86) | 0.397 | 0.56 | (0.25-1.26) | 0.163 |
| Bladder | 0.77 | (0.31-1.92) | 0.578 | 0.57 | (0.29-1.11) | 0.096 | **0.54** | **(0.31-0.91)** | **0.022** |
| Prostate | 0.38 | (0.12-1.17) | 0.092 | 0.62 | (0.32-1.20) | 0.158 | 0.80 | (0.53-1.22) | 0.302 |
| All cancers | 1.13 | (0.96-1.34) | 0.151 | 0.93 | (0.82-1.06) | 0.287 | **0.79** | **(0.71-0.88)** | **<0.001** |

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

**Appendix 2 Cancer risks of aspirin users as compared with controls adjusted for age, sex, comorbidities, and other medications at different follow-up time**

| Mean duration of aspirin use | End of 2006 | | | End of 2009 | | | End of 2013 | | |
|---|---|---|---|---|---|---|---|---|---|
| | 4.1 years | | | 5.9 years | | | 7.5 years | | |
| | HR | (95% CI) | p | HR | (95% CI) | p | HR | (95% CI) | p |
| Gastrointestinal cancers | | | | | | | | | |
| Colon/rectum | **0.76** | **(0.68-0.85)** | **<0.001** | **0.79** | **(0.72-0.87)** | **<0.001** | **0.83** | **(0.76-0.90)** | **<0.001** |
| Liver | **0.59** | **(0.50-0.68)** | **<0.001** | **0.62** | **(0.54-0.70)** | **<0.001** | **0.66** | **(0.59-0.74)** | **<0.001** |
| Oesophagus | **0.73** | **(0.59-0.90)** | **0.004** | **0.70** | **(0.59-0.84)** | **<0.001** | **0.71** | **(0.61-0.84)** | **<0.001** |
| Pancreas | 0.93 | (0.72-1.19) | 0.544 | 0.89 | (0.72-1.09) | 0.257 | 0.93 | (0.77-1.11) | 0.416 |
| Stomach | 0.34 | (0.10-1.18) | 0.089 | 0.39 | (0.14-1.11) | 0.077 | 0.43 | (0.18-1.04) | 0.061 |
| Non-gastrointestinal cancers | | | | | | | | | |
| Lung | **0.72** | **(0.65-0.80)** | **<0.001** | **0.74** | **(0.68-0.82)** | **<0.001** | **0.78** | **(0.72-0.85)** | **<0.001** |
| Breast (female) | 0.92 | (0.74-1.15) | 0.485 | 0.93 | (0.76-1.13) | 0.459 | 0.97 | (0.82-1.16) | 0.767 |
| Kidney | 0.54 | (0.22-1.31) | 0.175 | 0.69 | (0.35-1.35) | 0.281 | 0.76 | (0.45-1.30) | 0.318 |
| Bladder | 0.87 | (0.75-1.02) | 0.082 | 0.89 | (0.78-1.02) | 0.100 | 0.93 | (0.83-1.05) | 0.267 |
| Prostate | **0.75** | **(0.64-0.88)** | **<0.001** | 0.88 | (0.76-1.02) | 0.079 | **0.87** | **(0.76-0.99)** | **0.042** |
| All cancers | **0.71** | **(0.62-0.80)** | **<0.001** | **0.75** | **(0.68-0.84)** | **<0.001** | **0.80** | **(0.73-0.87)** | **<0.001** |

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

**Appendix 3 Cancer risks of aspirin and metformin users as compared with controls adjusted for age, sex, comorbidities, and other medications at different follow-up time**

| Mean duration of aspirin & metformin use | End of 2006 | | | End of 2009 | | | End of 2013 | | |
|---|---|---|---|---|---|---|---|---|---|
| | 4.6 years & 3.1 years | | | 7.0 years & 3.6 years | | | 9.8 years & 4.7 years | | |
| | HR | (95% CI) | p | HR | (95% CI) | p | HR | (95% CI) | p |
| Gastrointestinal cancers | | | | | | | | | |
| Colon/rectum | **0.26** | **(0.15-0.46)** | **<0.001** | **0.38** | **(0.24-0.58)** | **<0.001** | **0.54** | **(0.39-0.74)** | **<0.001** |
| Liver | 0.49 | (0.22-1.12) | 0.092 | **0.40** | **(0.20-0.81)** | **0.011** | **0.39** | **(0.23-0.67)** | **0.001** |
| Oesophagus | **0.10** | **(0.01-0.77)** | **0.027** | **0.08** | **(0.01-0.58)** | **0.012** | 0.26 | (0.05-1.28) | 0.098 |
| Pancreas | 0.39 | (0.07-2.00) | 0.257 | 0.46 | (0.11-1.92) | 0.287 | 0.58 | (0.20-1.65) | 0.305 |
| Stomach | 0.72 | (0.33-1.58) | 0.418 | 0.52 | (0.24-1.10) | 0.088 | **0.51** | **(0.28-0.92)** | **0.025** |
| Non-gastrointestinal cancers | | | | | | | | | |
| Lung | **0.09** | **(0.04-0.22)** | **<0.001** | **0.24** | **(0.13-0.42)** | **<0.001** | **0.29** | **(0.19-0.44)** | **<0.001** |
| Breast (female) | **0.32** | **(0.13-0.78)** | **0.013** | **0.43** | **(0.19-0.97)** | **0.042** | 1.03 | (0.58-1.80) | 0.930 |
| Kidney | 1.35 | (0.42-4.29) | 0.611 | 1.61 | (0.69-3.74) | 0.273 | 1.38 | (0.69-2.78) | 0.365 |
| Bladder | 0.69 | (0.28-1.66) | 0.403 | 0.57 | (0.27-1.22) | 0.150 | 0.82 | (0.47-1.46) | 0.506 |
| Prostate | **0.35** | **(0.13-0.96)** | **0.042** | 0.47 | (0.23-1.00) | 0.050 | 0.77 | (0.39-1.55) | 0.471 |
| All cancers | **0.34** | **(0.26-0.45)** | **<0.001** | **0.39** | **(0.31-0.49)** | **<0.001** | **0.53** | **(0.45-0.63)** | **<0.001** |

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

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