communications medicine

A Nature Portfolio journal

Article

https://doi.org/10.1038/s43856-025-00805-x

Long-term risk of malignancies in persons with ischemic heart disease treated with trimetazidine dihydrochloride

Yuen-Ting Cheng[1], Chun-Fung Sin[2], Edmond S. K. Ma[3], Stephen T. S. Lam[4], Shiu-Lun Au Yeung[5], Bernard M. Y. Cheung[1], Hung-Fat Tse[1,6,7], Kai-Hang Yiu[1,6,8] & Yap-Hang Chan[1,7,8,9,10]

Abstract

Background Metabolic reprogramming of energy processes is a cellular hallmark of various cancers. Whether trimetazidine, an anti-ischemic agent that preferentially potentiates cellular glucose oxidation, alters the long-term risk of malignancies is unknown.

Methods In this multi-center, retrospective cohort study, we studied the effect of trimetazidine on new-onset malignancies in 200,563 ischemic heart disease patients (mean age 70.8 years, 46.6% female) using the Hong Kong Clinical Data Analysis and Reporting System (CDARS), comparing trimetazidine users (n = 16,873) to nitrate users (n = 183,690, as control) over at least 30 days. The primary endpoint was defined as the estimated effect of trimetazidine on the overall new-onset occurrence of any malignancies a priori specified, diagnosed 90 days or more after the cohort entry.

Results Over a mean follow-up duration of 8.36 (6.42) years, the incidence rate of new-onset malignancies amongst trimetazidine users is significantly lower compared to the non-users (8.76 vs 12.3 per 1000-person years, trimetazidine to control incidence ratio, 0.71). Trimetazidine use is associated with improved event-free survival from new-onset malignancies (Mean survival: 231 [0.53] versus 225 [0.21] months, Chi-square = 161, $P < 0.001$). Multivariable Cox regression demonstrates an independently lower risk of new-onset malignancies associated with trimetazidine use, with (adjusted HRs, 0.71, 95% CI, 0.66–0.77, $P < 0.001$) and without (adjusted HRs, 0.71, 95% CI, 0.68–0.75, $P < 0.001$) propensity score matching. Subgroup analyses of new-onset malignancies including lung, colorectal, hepatobiliary & pancreatic, breast, stomach & oesophageal, renal & genito-urinary, prostate, and hematological malignancies, show similar risk reductions.

Conclusions Modulation of metabolic reprogramming may represent a new therapeutic target for cancer prevention.

Plain language summary

Metabolic reprogramming describes how cancer cells exhibit altered behaviour in deriving energy for survival. Studies suggest that targeting metabolic reprogramming can help prevent cancer. Here, we looked at the effect of trimetazidine, an anti-anginal medication in ischemic heart disease that works by metabolic modulation, on the risk of developing malignancies. Our study shows that trimetazidine use is associated with a lower risk of various types of malignancies in persons with ischemic heart disease. These suggests that metabolic reprogramming may represent a new therapeutic avenue for prevention of cancer.

Ischemic heart disease (IHD) and cancers, as the two leading causes of deaths and morbidities worldwide[1], present ever-rising threats to our aging populations. The pressing need to conjunctively combat these two major pandemics cannot be overstated. Accumulating evidence supports some common pathophysiological origins between cardiovascular diseases and cancers, such as systemic inflammation[2]. Such perspectives in shared etiology may imply the potentials for some cardiovascular drugs to be re-purposed as anti-cancer agents[3,4]. In this regard, metabolic

[1]Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong SAR, China. [2]Department of Pathology, School of Clinical Medicine, The University of Hong Kong, Hong Kong SAR, China. [3]Department of Molecular Pathology, Hong Kong Sanatorium & Hospital, Hong Kong SAR, China. [4]Clinical Genetics Service, Hong Kong Sanatorium & Hospital, Hong Kong SAR, China. [5]School of Public Health, The University of Hong Kong, Hong Kong SAR, China. [6]Department of Medicine, Shenzhen Hong Kong University Hospital, Hong Kong SAR, China. [7]Genetics Research Program for Personalized Medicine in Cardiac Oncology, The University of Hong Kong, Hong Kong SAR, China. [8]Institute of Cardiovascular Science and Medicine, The University of Hong Kong, Hong Kong SAR, China. [9]Experimental Medicine and Immunotherapeutics, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK. [10]Department of Cardiology, Royal Papworth Hospital, Cambridge Biomedical Campus, Cambridge, UK. e-mail: chanwill@hku.hk

reprogramming represents one clinical arena that is relatively under-explored.

Metabolic reprogramming is a well-recognized cellular hallmark in various cancers. The Warburg effect described a preferential shift of cellular metabolism in cancer cells from fatty acid oxidation to aerobic glycolysis. This facilitates the derivation of anabolic substrates, and lactic acid formation and creates an acidic environment conducive to cancer cell survival[5,6]. On the other hand, recapitulation of the fatty acid oxidation pathways has been described in some cancers, particularly in the context of treatment resistance[7–9]. Here, trimetazidine dihydrochloride, a second-line anti-anginal drug in patients with IHD that specifically inhibits fatty acid oxidation, may impact cancer risk via modulating the metabolic reprogramming pathways[10]. Firstly, by potentiating glucose oxidation for energy derivation generally in cells, trimetazidine may obliterate the relative survival advantage of cancer cells obtained via the Warburg effect. Secondly, inhibition of fatty acid oxidation by trimetazidine may compromise cellular metabolism in cancer cells that rely predominantly on the beta-oxidation pathways, thus curtailing cancer cell survival. Indeed, these postulations are substantiated by some animal and human experimental studies[7,11,12]. Studies have shown that trimetazidine induced tumour apoptosis in pancreatic and breast cancer[11,12], and may have a protective effect in oxidative lung carcinomas[7]. Nevertheless, relevant clinical data is absent. We hypothesized that trimetazidine may clinically reduce the risk of new-onset malignancies in persons with IHD. These laid the foundations for this current study.

In this multi-center, territory-wide retrospective cohort study, we find that the use of trimetazidine in patients with IHD is independently associated with reduced risks of malignancy.

Methods

Data source

We conducted this multicenter, retrospective cohort study from the Hong Kong Clinical Data Analysis and Reporting System (CDARS) clinical database. A key strength of CDARS is its comprehensive inclusion of data, including demographic data, laboratory results, clinical diagnosis by ICD codes, drug dispensing records etc, from all 42 public hospitals with a coverage of more than 90% of the population[13]. The use of CDARS data for clinical research has been validated in our previous studies[4,13–15] and other studies[16–18]. The present study was approved by the Ethics Committee of The University of Hong Kong/ Hospital Authority (UW-23095). Patient data were all de-identified so no informed consent was required. Different from our earlier published study on the potential protective effects of trimetazidine in patients with established lung cancer[13], this current study has entirely different objectives in studying the putative protective effects of trimetazidine in the primary prevention of malignancies in patients with IHD but nil previous history of malignancy.

Study design, subjects, and exposure definitions

Subjects with IHD who were treated with long-acting nitrates or trimetazidine for at least 30 consecutive days (period: January 1, 1999, and December 31, 2020) were included for analyses (Supplementary Data 5 and Supplementary Table 1 in the Supplementary Information). Definitions of IHD and trimetazidine use have been described in our earlier study[13]. Subjects were further divided into trimetazidine users ($n = 16,873$), and non-users who received long-acting nitrate therapy only (control, $n = 183,690$). Cohort entry was defined as the first prescription date of trimetazidine or long-acting nitrate, and the earlier prescription date for subjects receiving both trimetazidine and nitrate treatments. To study the effect of trimetazidine on new-onset malignancies, subjects with any of the malignancies defined in our primary endpoint at baseline were excluded (Fig. 1). To take account of cancer latency, malignancies diagnosed immediately within 90 days of trimetazidine or nitrate use initiation were deemed biologically unlikely to be related to study exposure and were excluded from the final analyses to avoid overestimation and underestimation of new-onset malignancy. Furthermore, subjects younger than 18 years old, or with a drug prescription duration shorter than 30 days, and those with incomplete sociodemographic, clinical and drug data, were excluded.

Definition of study endpoints

We defined the primary endpoint as the estimated trimetazidine effect on the overall new-onset occurrence of any malignancies a priori specified, including lung, breast, colorectal, stomach & oesophageal, hepatobiliary &

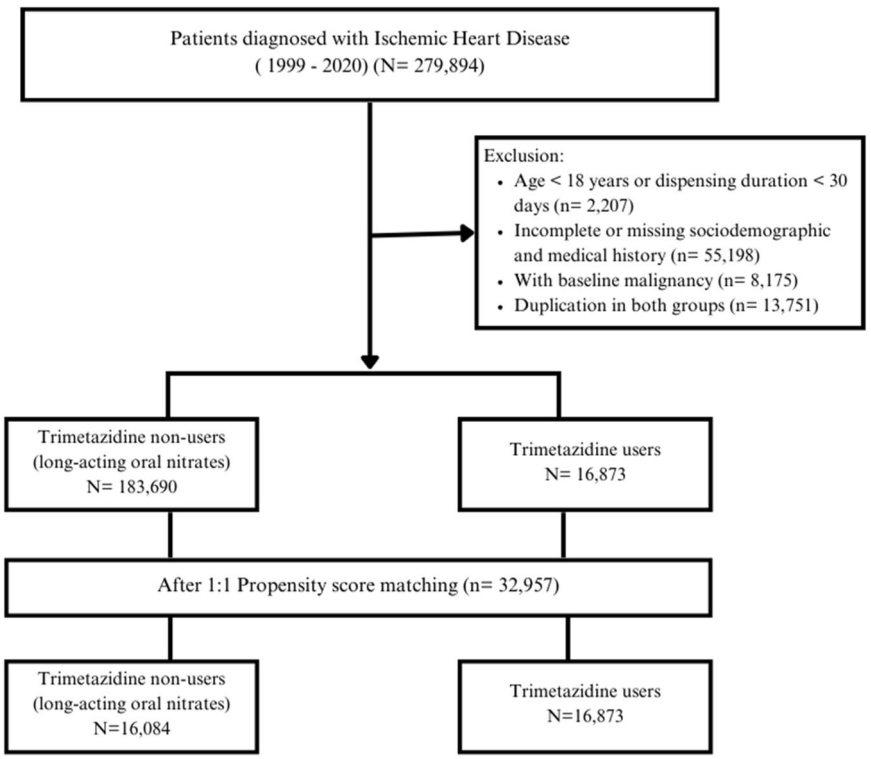

Fig. 1 | Study Flowchart

pancreatic, prostate, renal & genitourinary, hematological, and thyroid cancers, diagnosed 90 days or more after the cohort entry (Supplementary Data 6). The cancer categories were defined by referencing the common cancers listed under the Hong Kong Cancer Registry (https://www3.ha.org.hk/cancereg/topten.html). Secondary endpoints were defined as the estimated trimetazidine effect on new-onset occurrences of these pre-specified subgroup categories of malignancies, and all-cause mortality.

Statistical analysis

Propensity score-matched analyses were performed to assess statistical robustness in addition to the primary and secondary endpoints in the overall sample. Covariates with a propensity to affect the probability of receiving trimetazidine treatment were assessed by logistic regression and identified as sex, age, socioeconomic status, and drug history of aspirin/ antiplatelet and lipid-lowering therapy. Propensity matching was performed based on the inverse propensity of treatment weighting (IPTW) method to derive trimetazidine users versus non-users ratio of 1:1 with a matching tolerance of 0.1. Subjects were followed up until the earliest occurrence of a malignancy event, death, or the end of the study period, which was 31 December 2020. In subjects with multiple new-onset malignancies diagnosed within the study period, right censoring occurred at the time point when the earliest diagnosis of the first new-onset malignancy was made. Intention-to-treat principle was observed for all analyses.

Clinical characteristics were presented in frequencies (percentages) or mean (standard deviation [SD]). Hazard ratios (HRs) and 95% confidence intervals (CIs) for the primary and secondary endpoints were derived from the Cox proportional hazard regression models. We included (1) Crude model, (2) Multivariable model with co-variates with a P-value ≤ 0.10 in the univariable analysis, and (3) Multivariable with all potential confounders as a priori defined in the crude model. Potential confounders included sex, age, socioeconomic status (proxied by social security allowance dependency status), chronic kidney disease, chronic liver disease, chronic smoking (proxied by a history of chronic obstructive pulmonary diseases), hypertension, heart failure, ischemic stroke, myocardial infarction, type 2 diabetes, use of aspirin and lipid-lowering agents, at the baseline of cohort entry. Subgroup analyses included potential confounders based on specific clinical relevance: Colorectal malignancy: inflammatory bowel disease; Hepatobiliary and pancreatic malignancy: Hepatitis B, Hepatitis C; Stomach and oesophageal malignancy: baseline infection of Helicobacter pylori; Hematological malignancy: Hepatitis B, Hepatitis C, Human immunodeficiency virus. Bonferroni corrections with a P value cut-off <0.005 (0.05 divided by 10) were applied for all comparisons in the secondary endpoints of malignancy subgroups. Furthermore, an interaction analysis was performed by multivariable Cox regression to determine any effect modification of trimetazidine by nitrate use on the primary endpoint[19,20]. Similarly, interaction analyses were performed to study any potential effect modification of trimetazidine by aspirin use. Specifically, a categorical computation variable was constructed based on the presence or absence of nitrate/aspirin use versus the use of trimetazidine. Unbiased estimates of the relation between trimetazidine use and the primary endpoint were compared with or without the respective computation variable entered as a covariate in the regression model. A P-value for interaction was obtained. We used IBM SPSS Statistics (Version 29.0) for the data analysis. Results with a two-sided P value less than 0.05 were considered statistically significant.

Results

Baseline characteristics

A total of 200,563 eligible subjects were included in the final analyses. Mean (SD) age of the cohort was 70.8 (12.2) years. 46.6% were female. As shown in Supplementary Table 2 in the Supplementary information, demographic and clinical characteristics were largely similar in the trimetazidine group versus the control group at baseline.

Trimetazidine use and reduced risk of new-onset malignancies

Over a mean follow-up duration of 8.36 (6.42) years, 19,969 of 200,563 (10%) developed a primary endpoint of any new-onset malignancy. Trimetazidine users had a significantly lower incidence of developing a primary endpoint, compared with control (8.76 vs 12.3 per 1000-person years, trimetazidine to control incidence ratio [IR], 0.71, Table 1). Propensity score matched analyses yielded similar estimates (8.76 vs 11.6, per 1000-person years, IR, 0.76, Supplementary Table 3 in the Supplementary information). Kaplan-Meier analyses showed that trimetazidine use was associated with significantly longer incident malignancy event-free survival (Mean survival: 231 [0.53] versus 225 [0.21] months, Chi-square=161, $P < 0.001$, Fig. 2). Using Cox proportional hazard regression models, trimetazidine use was independently associated with a reduced risk of new-onset malignancies, before and after adjustments for potential confounders (crude HRs, 0.72, 95% CI, 0.68–0.75, $P < 0.001$; adjusted HRs, 0.71, 95% CI, 0.68–0.75, $P < 0.001$, Table 2). Repeated analyses after propensity score matching had

Table 1 | Incidence Rate of New-Onset Malignancies in Trimetazidine Users Versus Control in the Overall Sample (n = 198,703)

	Control (n = 181,885)			Trimetazidine (n = 16,818)			
	No. of cases/ Total population within the group	Mean follow-up years (SD) [a]	Incidence per 1000-person years [b]	No. of cases/ Total population within the group	Mean follow-up years (SD) [a]	Incidence per 1000-person years [b]	Trimetazidine to Control ratio [b]
Overall (Primary endpoint)	18,419/ 181,885	8.2 (6.4)	12.3	1550/ 16,818	10.5 (7.1)	8.76	0.71
Lung	4595/ 183,279	8.5 (6.4)	2.96	360/ 16,862	11.1 (7.1)	1.92	0.65
Breast	1288/ 183,600	8.4 (6.4)	0.83	74/ 16,872	11.1 (7.1)	0.39	0.47
Stomach & oesophageal	1448/ 183,537	8.5 (6.4)	0.93	129/ 16,872	11.1 (7.1)	0.69	0.74
Hepatobiliary & pancreatic	2668/ 183,478	8.5 (6.4)	1.72	207/ 16,868	11.1 (7.1)	1.11	0.65
Colorectal	3885/ 183,268	8.4 (6.4)	2.52	312/ 16,854	11.0 (7.1)	1.68	0.67
Renal & Genito-urinary	2399/ 183,454	8.4 (6.4)	1.55	217/ 16,869	11.1 (7.1)	1.16	0.75
Prostate	1638/ 96,939	8.5 (6.3)	1.99	183/ 10,098	11.1 (7.1)	1.64	0.82
Thyroid	154/ 183,680	8.5 (6.4)	0.10	14/ 16,872	11.1 (7.1)	0.07	0.75
Haematological	1408/ 183,518	8.5 (6.4)	0.91	130/ 16,867	11.1 (7.1)	0.69	0.77

[a]All numbers were corrected to the nearest one decimal place.
[b]All numbers were corrected to the nearest two decimal places or three significant figures.

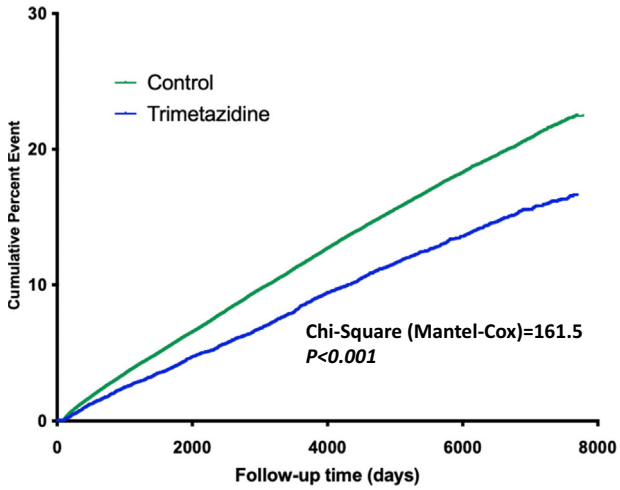

Fig. 2 | Kaplan-Meier curve analyses on the effect of trimetazidine on cumulative hazards of new-onset malignancies. Trimetazidine use was associated with reduced cumulative hazards of the primary endpoint of any new-onset malignancies (Chi-Square [Mantel-Cox]=161.5, $P < 0.001$).

yielded coherent results (adjusted HRs, 0.71, 95% CI, 0.66–0.77, $P < 0.001$, Supplementary Table 4 in the Supplementary information).

Prespecified malignancy subgroup analyses with Bonferroni correction

We found that trimetazidine use was associated with a similar risk reduction in various specific malignancy subgroups. As shown in Table 1, the incidence rates of lung, colorectal, hepatobiliary & pancreatic, breast, hematological, renal & genito-urinary, prostate, and stomach & oesophageal malignancy were all lower in the trimetazidine group compared to the control. Multivariable Cox proportional regression models showed that trimetazidine use was associated with reduced risks of these pre-specified new-onset malignancies, compared to control (Fig. 3). Trimetazidine use was associated with the greatest malignancy risk reduction in breast cancer (adjusted HRs, 0.54, 95% CI, 0.42–0.69, $P < 0.001$, Supplementary Table 5 in the Supplementary information), followed by lung cancer (adjusted HRs, 0.60, 95% CI, 0.54–0.67, $P < 0.001$, Supplementary Table 6 in the Supplementary information) and colorectal cancer (adjusted HRs, 0.65, 95% CI, 0.58–0.74, $P < 0.001$, Supplementary Table 7 in the Supplementary information). There were also other trimetazidine-associated malignancies risk reductions (Renal & Genito-urinary: adjusted HRs, 0.73, 95% CI, 0.63–0.85, $P < .001$, Supplementary Table 8 in the Supplementary information) (Hepatobiliary & Pancreatic: adjusted HRs, 0.70, 95% CI, 0.61–0.82, $P < 0.001$, Supplementary Table 9 in the Supplementary information) (Stomach & oesophageal: adjusted HRs, 0.78, 95% CI, 0.64–0.94, $P < 0.001$, Supplementary Table 10 in the Supplementary information) (Prostate: adjusted HRs, 0.70, 95% CI, 0.60–0.83, $P < 0.001$, Supplementary Table 11 in the Supplementary information) (Hematological: crude HRs, 0.77, 95% CI, 0.64–0.92, $P = 0.03$ [borderline statistical significance at Bonferroni correction], Supplementary Table 12 in the Supplementary information). Nevertheless, no significant association was observed for thyroid cancer (adjusted HRs, 0.86, 95% CI, 0.48–1.53, $P = 0.60$, Supplementary Table 13 in the Supplementary information).

Risk of All-cause mortality

A total of 115,466 (57.6%) subjects, including 6451 (38.2%) trimetazidine users and 109,015 (59.3%) control group, experienced death by the end of the study period (December 31, 2020). Kaplan-Meier analyses showed that trimetazidine use was associated with significantly longer overall survival (Mean survival: 182^{73} versus 133 [0.23] months, Chi-square = 3092, $P < 0.001$). Multivariable Cox proportional hazards regression showed that trimetazidine use was independently associated with reduced all-cause mortality compared to the control (crude HRs, 0.50, 95% CI, 0.49–0.51, $P < 0.001$).

Effect modification of trimetazidine by nitrate use

We further explored any potential effect of concurrent nitrate use on the putative protective effect of trimetazidine on the primary outcome. Interaction analyses showed that there was no significant effect modification of trimetazidine by nitrates use on the primary endpoint (P for interaction = 0.89).

Effect modification of trimetazidine by aspirin/ antiplatelet therapy use

Interaction analysis of aspirin and trimetazidine over the risk of new-onset malignancy has been performed, showing no significant effect modification of trimetazidine by aspirin on the primary endpoint (P for interaction = 0.29).

Discussion

To our knowledge, this is the largest clinical study on the association between trimetazidine use and the risk of new-onset malignancies. Our study indicates that trimetazidine may potentially harbor a protective effect against the development of malignancies in patients with IHD. These pioneering findings may potentially lead to a paradigm shift in cancer prevention through the modulation of metabolic reprogramming.

Albeit novel, our theoretical framework was well supported by several animal and experimental studies. It is well known that metabolic reprogramming occurs early in malignant cells. According to the Warburg effect, cancer cells exhibited altered bioenergetic profiles with a metabolic shifting towards aerobic glycolysis coupled with increased lactate formation, despite intact mitochondrial functions and favorable oxygen tensions. It has been postulated that such changes, possibly via enhanced provision of anabolic substrates or the creation of an acidic environment, are essential for cancer cell survival[5]. In this regard, trimetazidine, a drug that inhibits the fatty acids beta-oxidation via blocking mitochondrial long-chain 3-ketoacyl Coenzyme A Thiolase[3], may potentiate cellular glucose oxidation in the body. In other words, trimetazidine may obliterate any evolutionary selective advantage of malignant or pre-malignant cell lines acquired from their adaptive changes by the Warburg effect. Secondly, evidence purports that some malignancies reprogrammed their cellular metabolism to be more reliant on fatty acid oxidation. Inhibition of fatty acid oxidation may represent a novel treatment target for malignancies[11,21,22]. Correspondingly, trimetazidine may directly interfere with the interactions between the respiratory chain complex I and trifunctional mitochondrial proteins, leading to an imbalance of cellular redox states and metabolic dysfunction that hinder cancer cell survival. Such advantageous effects were supported by trimetazidine leading to oxidative lung carcinoma shrinkage and improved survival in an animal study[7]. The aforementioned mechanisms may prevent the occurrence and progression of malignancies by re-wiring cellular metabolism.

Furthermore, there was experimental evidence that substantiates a potentially protective role of trimetazidine in specific types of malignancies. For example, trimetazidine was also found to induce apoptosis and reduce migration by affecting the ATP level of human pancreatic cancer cells[11]. Furthermore, in-vivo studies showed that a combination of trimetazidine and doxorubicin activated AMPK, reduced tumor NAD + /NADH ratio and ATP levels, decreased nuclear levels of NF-κB and induced tumor apoptosis in breast cancer[12]. Other potential mechanisms through which trimetazidine may protect against the development of malignancies include its effects against systemic inflammation and oxidative stress[23,24], as well as activation of the AMP-activated protein kinase[25].

Our study possesses several strengths. Firstly, we adopted thorough methodologies including propensity-matched analyses and multivariable analyses for potential confounders, that yielded consistent and reliable results. We also adopted Bonferroni correction with a stringent p-value cut-

Table 2 | Crude and Multivariable Cox Proportional Hazards Regression Models on Risk of New-Onset Malignancies Predicted by Trimetazidine Use [a]

	Crude Model		Multivariable Model 1		Multivariable Model 2	
	HR [95%CI]	*P*-value	HR [95%CI]	*P*-value	HR [95%CI]	*P*-value
Age	1.03 [1.03–1.03]	<0.001*	1.03 [1.03–1.03]	<0.001*	1.03 [1.03–1.03]	<0.001*
Male	1.34 [1.30–1.38]	<0.001*	1.66 [1.61–1.71]	<0.001*	1.66 [1.61–1.71]	<0.001*
Socioeconomic indicator	0.97 [0.92–1.03]	0.31	N/A	N/A	0.90 [0.85–0.96]	0.001*
COPD	1.58 [1.48–1.69]	<0.001*	1.18 [1.09–1.27]	<0.001*	1.18 [1.10–1.27]	<0.001*
Recruitment period 1999-2000	Ref.	<0.001*	Ref.	<0.001*	Ref.	<0.001*
2001–2010	0.90 [0.88–0.93]	<0.001*	0.92 [0.89–0.95]	<0.001*	0.92 [0.89–0.95]	<0.001*
2011–2020	0.86 [0.82–0.90]	<0.001*	0.92 [0.88–0.97]	0.001*	0.92 [0.88–0.97]	0.001*
Hypertension	1.06 [1.02–1.10]	0.001*	1.03 [0.99–1.06]	0.19	1.03 [0.99–1.07]	0.20
Diabetes mellitus	0.99 [0.95–1.03]	0.66	N/A	N/A	1.04 [0.99–1.09]	0.13
Myocardial infarction	1.00 [0.94–1.06]	0.90	N/A	N/A	1.05 [0.99–1.12]	0.11
Heart failure	1.17 [1.11–1.23]	<0.001*	0.93 [0.88–0.99]	0.02*	0.93 [0.88–0.99]	0.02*
Ischemic stroke	0.95 [0.87–1.05]	0.31	N/A	N/A	0.86 [0.78–0.95]	0.004*
Chronic kidney disease	0.98 [0.89–1.08]	0.64	N/A	N/A	0.93 [0.84–1.03]	0.16
Chronic liver disease	1.95 [1.67–2.29]	<0.001*	2.00 [1.70–2.38]	<0.001*	2.02 [1.70–2.38]	<0.001*
Aspirin/ antiplatelet therapy [b]	0.59 [0.56–0.61]	<0.001*	0.70 [0.67–0.74]	<0.001*	0.70 [0.67–0.74]	<0.001*
Lipid-lowering therapy [c]	0.56 [0.55–0.58]	<0.001*	0.72 [0.69–0.74]	<0.001*	0.72 [0.69–0.74]	<0.001*
Trimetazidine Use	0.72 [0.68–0.75]	<0.001*	0.72 [0.68–0.76]	<0.001*	0.71 [0.68–0.75]	<0.001*
Trimetazidine Use						
Propensity score-adjusted [d]	N/A	N/A	N/A	N/A	0.76 [0.72–0.80]	<0.001*

*Statistically significant $p < 0.05$.

[a]Hazard ratio (HR) prediction estimates and 95% confidence interval explained by variable of interest as shown by univariable and multivariable Cox proportional hazards regression; Crude Model: unadjusted; Multivariable Model 1: adjusted for potential confounders with *P*-value ≤ 0.10 in Crude Model; Multivariable Model 2: adjusted for all potential confounders as defined a priori.

[b]Included aspirin/ acetylsalicylic acid, clopidogrel, ticagrelor, and prasugrel, from the cohort entry to the censored date.

[c] Included simvastatin, rosuvastatin, pravastatin, fluvastatin, atorvastatin, ezetimibe, fenofibrate, alirocumab, and evolocumab, from the cohort entry to the censored date.

[d]Trimetazidine use adjusted by propensity scores only (matched by sex, age, socioeconomic status, aspirin/ antiplatelet therapy, and lipid-lowering therapy).

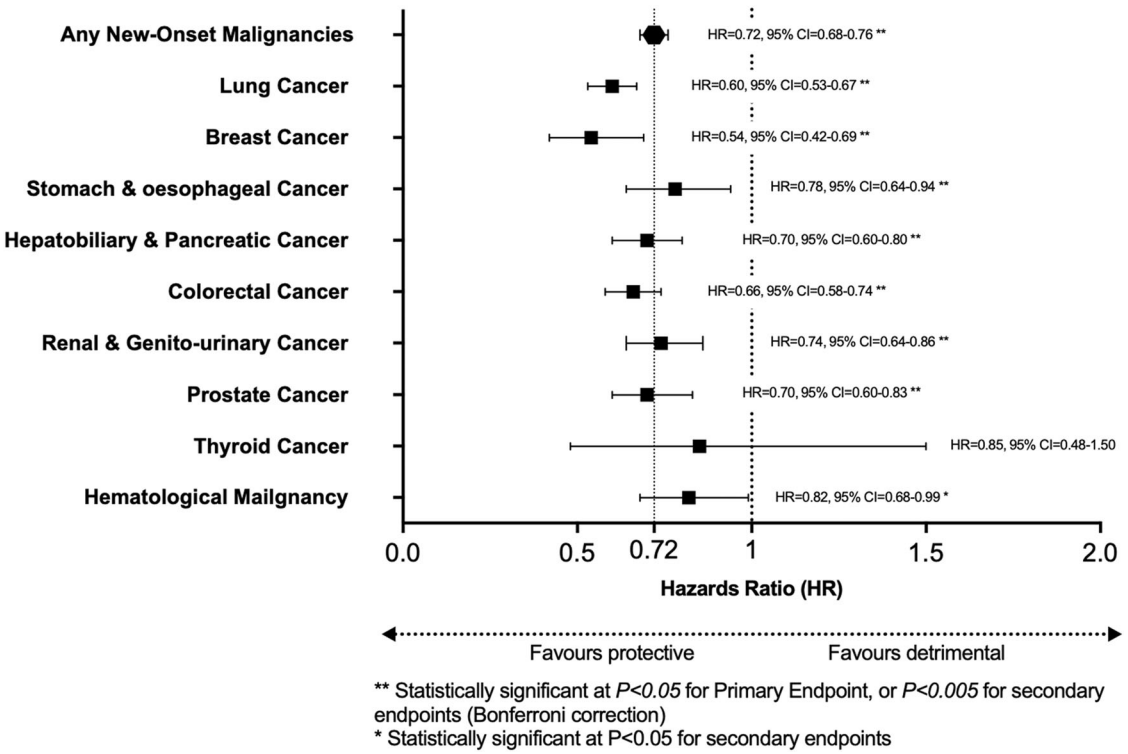

Fig. 3 | Effect of trimetazidine on new-onset malignancies endpoints. Trimetazidine use was independently predictive of reduced risks of any new-onset malignancies (primary endpoint) and several subgroups of malignancies (secondary endpoints with Bonferroni correction). Statistical estimates of effect sizes are appended.

off for statistical significance for all pre-specified exploratory secondary analyses. Secondly, our study is a multi-site, territory-wide longitudinal study encompassing a population of 7.5 million, incorporating hard clinical endpoints. Our study is one of the largest trimetazidine clinical datasets worldwide. Furthermore, we also considered the potential effects of competing risk of death. The finding of trimetazidine users having better overall clinical survival in all-cause mortality suggests that a competing risk of death is unlikely to bias and affect the associations between trimetazidine use and the primary endpoint.

However, there are several limitations in our study. Firstly, due to its observational nature, we cannot establish causality. Despite propensity matching and the inclusion of most potential confounders for multivariable adjustments, unmeasured confounding cannot be excluded. Secondly, mechanisms underlying the observed protective effects of trimetazidine against malignancies cannot be established due to the lack of experimental data. Further randomized controlled trials with mechanistic assessments are needed to confirm our findings. Thirdly, further studies are needed to determine whether our results can be generalized to healthy individuals without IHD and to other ethnicities.

Conclusions

We conclude that trimetazidine use is associated with a lower risk of new-onset malignancies in patients with IHD. Modulation of metabolic reprogramming may represent a new therapeutic target for cancer prevention. Further randomized controlled trials are needed to confirm these findings.

Data availability

The data used in this manuscript was from the Hong Kong Clinical Data Analysis and Reporting System (CDARS). Source data for all figures and tables is located in Supplementary Data 1–6. Supplementary Data 1 and 2 is the original source for Figs. 2 and 3, respectively. Supplementary Data 3 and 4 is the original source for Tables 1 and 2, respectively. Supplementary Data 5 is the drug item code and Supplementary Data 6 is the ICD-9 diagnostic codes of malignancy.

Received: 9 July 2024; Accepted: 12 March 2025;
Published online: 25 March 2025

References

1. Global burden of 369 diseases and injuries in 204 countries and territories. 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* **396**, 1204–1222 (2020).
2. Chan, A. O. et al. Prevalence of colorectal neoplasm among patients with newly diagnosed coronary artery disease. *JAMA* **298**, 1412–1419 (2007).
3. Chan, Y. H. & Schooling, C. M. Performance of immunochemical fecal occult blood tests among users of low-dose aspirin. *JAMA* **305**, 1093 (2011).
4. Ren, Q. W. et al. Statin associated lower cancer risk and related mortality in patients with heart failure. *Eur. Heart J.* **42**, 3049–3059 (2021).
5. Vander Heiden, M. G., Cantley, L. C. & Thompson, C. B. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* **324**, 1029–1033 (2009).
6. Liberti, M. V. & Locasale, J. W. The Warburg Effect: How Does it Benefit Cancer Cells? *Trends Biochem Sci.* **41**, 211–218 (2016).
7. Amoedo, N. D. et al. Targeting the mitochondrial trifunctional protein restrains tumor growth in oxidative lung carcinomas. *J. Clin. Invest*. **4**, 131 https://doi.org/10.1172/jci133081 (2021).
8. Chen, J. et al. PFKP alleviates glucose starvation-induced metabolic stress in lung cancer cells via AMPK-ACC2 dependent fatty acid oxidation. *Cell Discov.* **8**, 52 (2022).
9. Corbet, C. et al. Acidosis Drives the Reprogramming of Fatty Acid Metabolism in Cancer Cells through Changes in Mitochondrial and Histone Acetylation. *Cell Metab.* **24**, 311–323 (2016).
10. Guarini, G., Huqi, A., Morrone, D., Capozza, P. F. G. & Marzilli, M. Trimetazidine and Other Metabolic Modifiers. *Eur. Cardiol.* **13**, 104–111 (2018).
11. Atlı Şekeroğlu, Z., Şekeroğlu, V., Işık, S. & Aydın, B. Trimetazidine alone or in combination with gemcitabine and/or abraxane decreased cell viability, migration and ATP levels and induced apoptosis of human pancreatic cells. *Clin. Res. Hepatol. Gastroenterol.* **45**, 101632 (2021).
12. Abdeljalil, S. M., Wahdan, S. A., Elghazaly, H. & Tolba, M. F. Insights into the therapeutic outcomes of trimetazidine/doxorubicin combination in Ehrlich solid-phase carcinoma mouse tumor model. *Life Sci.* **328**, 121874 (2023).
13. Chan, Y. H. et al. Treatment with trimetazidine dihydrochloride and lung cancer survival: Implications on metabolic re-programming. *Lung Cancer* **197**, 107996 (2024).
14. Yu, S. Y. et al. Low-dose aspirin and incidence of lung carcinoma in patients with chronic obstructive pulmonary disease in Hong Kong: A cohort study. *PLoS Med* **19**, e1003880 (2022).
15. Wu, M. Z. et al. Risk of hyperkalemia in patients with type 2 diabetes mellitus prescribed with SGLT2 versus DPP-4 inhibitors. *Eur Heart J Cardiovasc Pharmacother*. **6**, https://doi.org/10.1093/ehjcvp/pvad081 (2023).
16. Wong, A. Y. et al. Cardiovascular outcomes associated with use of clarithromycin: population based study. *Bmj* **352**, h6926 (2016).
17. Chai, Y. et al. Risk of self-harm after the diagnosis of psychiatric disorders in Hong Kong, 2000-10: a nested case-control study. *Lancet Psychiatry* **7**, 135–147 (2020).
18. Man, K. K. C. et al. Association of Risk of Suicide Attempts With Methylphenidate Treatment. *JAMA Psychiatry* **74**, 1048–1055 (2017).
19. Corraini, P., Olsen, M., Pedersen, L., Dekkers, O. M. & Vandenbroucke, J. P. Effect modification, interaction and mediation: an overview of theoretical insights for clinical investigators. *Clin. Epidemiol.* **9**, 331–338 (2017).
20. Dézsi, C. A. Trimetazidine in Practice: Review of the Clinical and Experimental Evidence. *Am. J. Ther.* **23**, e871–e879 (2016).
21. Feng, Y. et al. PAX2 promotes epithelial ovarian cancer progression involving fatty acid metabolic reprogramming. *Int J. Oncol.* **56**, 697–708 (2020).
22. Wang, L. et al. GC-MSC-derived circ_0024107 promotes gastric cancer cell lymphatic metastasis via fatty acid oxidation metabolic reprogramming mediated by the miR-5572/6855-5p/CPT1A axis. *Oncol. Rep*. **50**, https://doi.org/10.3892/or.2023.8575 (2023).
23. El-Khodary, N. M., Ghoneim, A. I., El-Tayaar, A. A. & El-Touny E. M. The Impact of Trimetazidine on Cardiac Fibrosis, Inflammation, and Function in Ischemic Cardiomyopathy Patients. *Cardiovasc Drugs Ther*. **10**, https://doi.org/10.1007/s10557-022-07340-0 (2022).
24. Shu, H., Peng, Y., Hang, W., Zhou, N. & Wang, D. W. Trimetazidine in Heart Failure. *Front Pharm.* **11**, 569132 (2020).
25. Gatta, L. et al. Modulating the metabolism by trimetazidine enhances myoblast differentiation and promotes myogenesis in cachectic tumor-bearing c26 mice. *Oncotarget* **8**, 113938–113956 (2017).

Acknowledgements

This study received support from Li Shu Fan Fellowship for Internal Medicine 2021/22, Li Shu Pui Medical Foundation Fellowship 2022; and Seed Funding for Basic Research (104006735, 109001715) and Start-Up Funding, The University of Hong Kong, and Hong Kong Research Grants Council General Research Fund (GRF 17110122 and 17108523). YHC was supported by the Sir David Todd Memorial Scholarship 2022/23, Hong Kong College of Physicians, Doris Zimmern HKU-Cambridge Hughes Hall Fellowship 2024/25, and Hong Kong Research Grants Council Clinical Research Fellowship 2024/25.

Author contributions

Cheng YT contributed to the research methodology, collected the data, performed the analyses, and wrote the manuscript; Sin CF contributed to cancer pathology expertise, research methodology, and co-authored the

manuscript; Ma ESK and Lam STS contributed to the research methodology and obtained funding support, and co-authored the manuscript; Au Yeung SL contributed statistical analyses support and co-authored the manuscript; Cheung BMY, Tse HF and Yiu KH contributed to research methodology and advisory support, and writing and revision of manuscript; Chan YH originated the study hypothesis, obtained research funding, designed and implemented the study, performed and supervised the analyses, wrote and revised the manuscript, and was the overall guarantor of the study.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s43856-025-00805-x.

Correspondence and requests for materials should be addressed to Yap-Hang Chan.

Peer review information *Communications Medicine* thanks Mai Tolba and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.