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The causal relationships between mitochondria and six types of cancer: a Mendelian randomization study

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Abstract

Background Mitochondria play a multifaceted role in tumorigenesis, influencing energy metabolism, redox balance, and apoptosis. However, whether mitochondrial traits causally affect cancer risk remains unclear. This study aimed to evaluate the potential causal effects of 82 mitochondrial-related exposures on six major cancers—hepatic, colorectal, lung, esophageal, thyroid, and breast—using Mendelian randomization (MR).

Methods Two-sample MR analysis was performed using the inverse variance weighted (IVW) method, with MR-Egger regression and weighted median as complementary approaches. Sensitivity analyses (Cochran's Q test, MR-Egger intercept, leave-one-out) and the Steiger test were applied to assess heterogeneity, pleiotropy, and causal directionality.

Results We observed a negative correlation between "39S ribosomal protein L34, mitochondrial", and others, with hepatic cancer, while "[Pyruvate dehydrogenase (acetyl-transferring)] kinase isozyme 2, mitochondrial", and others exhibited a positive correlation with hepatic cancer. "Phenylalanine-tRNA ligase, mitochondrial", and others demonstrated a negative association with colorectal cancer, whereas "Methylmalonyl-CoA epimerase, mitochondrial", and others exhibited a positive correlation with colorectal cancer. "Succinate dehydrogenase assembly factor 2, mitochondrial" exhibited a negative correlation with lung cancer, while "Superoxide dismutase [Mn], mitochondrial levels" showed a positive correlation with lung cancer. "Lon protease homolog, mitochondrial" demonstrated a positive correlation with esophageal cancer. "Iron-sulfur cluster assembly enzyme ISCU, mitochondrial", and others exhibited a negative correlation with thyroid cancer, while "Diablo homolog, mitochondrial", and others showed a positive correlation with thyroid cancer. "ADP-ribose pyrophosphatase, mitochondrial", and others exhibited a negative correlation with breast cancer, while "39S ribosomal protein L34, mitochondrial", and others showed a positive correlation with breast cancer.

Conclusions This study provides MR-based evidence that specific mitochondrial-related traits have causal effects on the risk of several common cancers. Notably, certain single-nucleotide polymorphisms (SNPs) acted as instrumental

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variables across multiple cancer types through shared mitochondrial mechanisms, such as oxidative stress regulation and metabolic reprogramming. These findings highlight mitochondria as cross-cutting contributors to cancer susceptibility and suggest potential avenues for mitochondrial-targeted prevention and therapy. The identification of pleiotropic genetic variants also offers insights for developing shared biomarkers and therapeutic targets across malignancies.

Keywords Mendelian randomization, Mitochondria, Cancers, Causal inference

Introduction

Cancer has consistently been a pivotal subject in the field of medicine. Recent studies show a global rise in early-onset cancer (diagnosed before age 50) since 1990, particularly in gastrointestinal, breast, and endocrine-related cancers, driven by lifestyle, diet, environment, and genetics [1]. A multi-country cancer registry analysis confirms a significant increase in early-onset colorectal, breast, and thyroid cancers over the past three decades [2]. Various therapeutic approaches for cancer, including surgical resection, radiation therapy, chemotherapy, immunotherapy, and others, are continuously being explored [3–6].

Mitochondria are dynamic cellular organelles that regulate cellular energy metabolism, apoptosis, proliferation, and differentiation. Their core function is energy production, and they maintain their dynamic equilibrium through processes such as fission and fusion to ensure the normal physiological functioning of cells. Mitochondria play a multifaceted and crucial role in the initiation, growth, recurrence, and metastasis of cancer. Various mitochondrial-related factors, including mitochondrial autophagy, abnormal mitochondrial copy numbers, distorted mitochondrial morphology, accumulation of reactive oxygen species (ROS), disrupted energy metabolism, and others, have been observed in a wide range of human cancers [7–11]. Research has indicated that targeting mitochondrial iron metabolism can in-duce mitochondrial autophagy and dysfunction, inhibit cancer cell proliferation and metastasis, and induce cancer cell death [12]. Multiple clinical trials have also demonstrated that inhibiting mitochondrial metabolism can serve as a novel approach to cancer treatment [13]. Inhibitors of several key enzymes are currently under clinical investigation [14]. Therefore, targeting mitochondria has become one of the new directions in cancer therapy.

To explore the causal link between mitochondria and cancer, we selected mitochondrial-related factors based on their known roles in cancer biology. Identified through genome-wide association studies (GWAS), these factors are involved in mitochondrial metabolism, oxidative stress, apoptosis, and DNA stability. Selection criteria included (1) genes associated with metabolism, oxidative phosphorylation, or apoptosis, (2) genes linked to oncogenesis via mitochondrial dysfunction, and (3) mitochondrial proteins regulating cell proliferation, differentiation, or stress responses [15]. Given mitochondria's key role in tumor progression, these factors are relevant to the six cancer types studied.

These six cancer types—hepatic, colorectal, lung, esophageal, thyroid, and breast cancer—were selected based on their high global disease burden, distinct pathophysiological links to mitochondrial dysfunction, and data availability in GWAS. According to GLOBOCAN 2022 [16], colorectal, breast, lung, and liver cancers are among the leading causes of cancer-related morbidity and mortality worldwide, while thyroid and esophageal cancers also exhibit increasing incidence in specific populations. Mitochondrial dysfunction—including alterations in oxidative phosphorylation, metabolic reprogramming, and accumulation of ROS—has been implicated in the pathogenesis of all six cancers [17]. These malignancies span major organ systems, representing a broad spectrum of tumor types across digestive, respiratory, endocrine, and reproductive systems, thereby providing a comprehensive framework for exploring mitochondrial involvement in oncogenesis.

In addition to these epidemiological and mechanistic considerations, the selection of these six cancers also reflects our research group's longstanding focus and accumulated expertise in these tumor types. This prior work provided us with valuable biological insights and analytical resources [18, 19], strengthening the feasibility and translational relevance of this Mendelian randomization (MR) study.

MR is a method that utilizes single-nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to investigate the potential causal relationship between exposure and outcomes. Currently, only MR has been utilized to explore the research on the causal relationship between mitochondrial dysfunction characterized by genetic susceptibility and cancer [20], along with related studies through meta-analysis investigating the relationship between telomere length and mitochondrial copy number with cancer [21]. The application of MR to investigate the causal relationships between mitochondrial-related exposures and various cancers is not yet comprehensive. Therefore, this study aimed to systematically evaluate whether genetically predicted mitochondrial-related traits have causal effects on the risk of six major cancers—including hepatic, colorectal, lung, esophageal, thyroid, and breast cancer—using a two-sample Mendelian randomization approach. By integrating

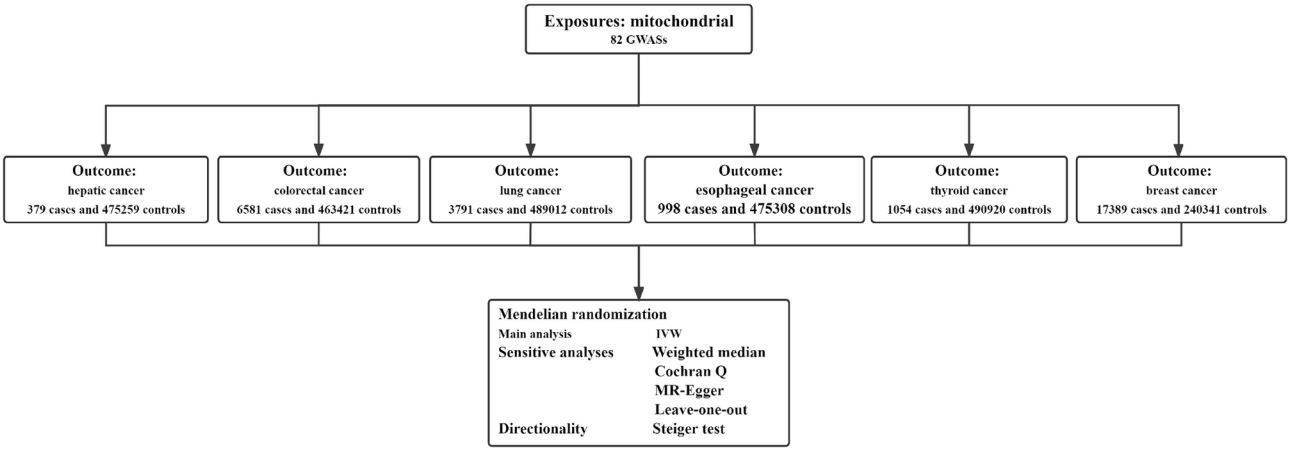

Fig. 1 The design of the entire study. IVW, inverse variance weighted. GWAS, genome-wide association study

Table 1 The GWAS datasets for six types of cancer

GWAS ID	Traits	Consortium	Number of cases	Number of controls	Sample size	Sex	Population
ebi-a-GCST90018858	Hepatic cancer	NA	379	475,259	475,638	NA	European
ebi-a-GCST90018808	Colorectal cancer	NA	6581	463,421	470,002	NA	European
ebi-a-GCST90018875	Lung cancer	NA	3791	489,012	492,803	NA	European
ebi-a-GCST90018841	Esophageal cancer	NA	998	475,308	476,306	NA	European
ebi-a-GCST90018929	Thyroid cancer	NA	1054	490,920	491,974	NA	European
ebi-a-GCST90018799	Breast cancer	NA	17,389	240,341	257,730	NA	European

GWAS summary statistics, we sought to clarify whether mitochondrial dysfunction contributes causally to cancer development, and to identify specific mitochondrial pathways or biomarkers with translational relevance for cancer prevention and therapy.

Materials and methods

Study design

In this study, we employed MR (Fig. 1). Exposure-related data and outcome-related data were obtained from GWAS databases, and SNPs meeting the criteria were selected. Potential causal relationships between exposure and outcomes were analyzed using various statistical methods, and the reliability and stability of the results were assessed through sensitivity analysis. The aim was to investigate the causal relationships between mitochondria and hepatic cancer, colorectal cancer, lung cancer, esophageal cancer, thyroid cancer, and breast cancer.

GWAS data sources

We procured SNPs associated with mitochondria as IVs from the IEU GWAS database (https://gwas.mrcieu.ac.uk/), encompassing 82 GWASs conducted on populations of European descent. These include factors such as mitochondrial fission regulatory factor 1, apoptosis-inducing factor 1, GrpE protein homolog 1, mitochondrial glutamine carrier 2, and others. Additionally, we obtained data related to hepatic cancer, colorectal cancer, lung cancer, esophageal cancer, thyroid cancer, and breast cancer from the IEU GWAS database (https://gwas.mrcieu.ac.uk/). This dataset comprises information from 6 GWASs, involving a total of 30,192 cancer cases originating from European populations. Due to the exclusive reliance on public databases for our data, considerations regarding patient informed consent and other ethical requirements were waived. The GWAS datasets for six types of cancer are provided in Table 1. The GWAS datasets for mitochondrial factors are outlined in the Table S1.

Selection of IVs

In this MR study, we will screen SNPs serving as IVs from various perspectives. Firstly, we will establish a genome-wide significance (GWS) threshold with a P value $< 5 \times 10^{-8}$ to identify SNPs closely associated with the exposure factor. However, only a limited number of SNPs meet this criterion. To explore a more comprehensive causal relationship between mitochondria and six types of cancer, we choose a threshold P value $< 5 \times 10^{6}$ as the screening criterion. This choice aimed to maximize the number of SNPs strongly associated with mitochondrial-related exposures. A stricter threshold would have reduced IVs but might exclude biologically significant variants with weaker associations.

We acknowledge the potential risk of weak instrument bias with a less stringent P-value threshold. However, we mitigated this by selecting IVs with an F-value > 10 to ensure instrument strength. Additionally, sensitivity analyses, including tests for heterogeneity, horizontal

pleiotropy, and leave-one-out analysis, were conducted to assess result robustness. With these safeguards, we believe the selected IVs remain reliable for investigating the causal relationship between mitochondrial dysfunction and cancer.

Secondly, we will mandate that the distance between adjacent SNPs is less than 10,000 kb, and the linkage disequilibrium R^2 value is < 0.001 to further exclude SNPs in linkage disequilibrium. Finally, we will apply a threshold F-value > 10 to exclude SNPs that do not have a strong correlation with the exposure factor. Through these criteria, suitable SNPs that can be used as IVs will be identified. The IVs in the causal relationships between mitochondria and six types of cancer through MR are presented in the Table S2.

Statistical analysis

To minimize confounding biases in our MR analysis, we applied strict criteria to ensure SNPs used as IVs were independent of confounders. MR-Egger regression was employed to detect pleiotropy and assess potential bias from unmeasured confounders. Sensitivity analyses, including the Cochran Q test, MR-Egger intercept test, and leave-one-out analysis, were conducted to evaluate horizontal pleiotropy and instrument validity. Finally, the Steiger test was used to confirm that mitochondrial-related exposures were upstream factors influencing cancer outcomes, reducing the risk of reverse causality. Scatter plots (Figure S1–S6) were used for visual representation of effect estimates, and all results are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

MR analyses were primarily conducted using the inverse variance weighted (IVW) method, with MR-Egger regression and weighted median (WM) methods serving as complementary approaches. In the IVW method, a P value < 0.05 indicates statistical significance in the relationship between the exposure variable and the outcome variable, while a P value > 0.05 suggests no statistical significance. An OR > 1 signifies the exposure factor as a risk factor, indicating an increase in outcome risk with an increase in the exposure factor. Conversely, an OR < 1 denotes the exposure factor as a protective factor. We conduct sensitivity analyses through tests for heterogeneity, horizontal pleiotropy, and leave-one-out analysis. If the P value < 0.05 in the Cochran Q test, indicating the presence of heterogeneity, this is likely due to potential differences in populations or sequencing methods between the two sample groups, leading to heterogeneity. When the P value < 0.05 in the MR-Egger intercept test, it indicates the presence of horizontal pleiotropy. This is typically due to the influence of other confounding factors in the study. The leave-one-out analysis does not directly provide a P value; by observing its effect forest plot, if the range of All values consistently remains greater than 0 or consistently less than 0, it indicates stable results with no significant impact from individual SNPs. Ideally, we aim for the P value > 0.05 in the Cochran Q test and the P value > 0.05 in the MR-Egger intercept test, and no individual SNPs significantly affect the results, indicating the reliability and stability of the results. Additionally, in the Steiger test, if the P value > 0.05, it cannot be proven that the exposure is an upstream factor causing the outcome.

Sex-stratified MR analyses were not performed in this study because the cancer-related summary statistics provided by the IEU GWAS database do not include sex-specific stratifications. As such, we were unable to explore potential sex differences in the causal effects of mitochondrial traits on cancer risk. Future research using sex-disaggregated GWAS data would be warranted to further examine this aspect.

All statistical analyses were performed using R 4.2.3 (https://www.r-project.org/), R studio software, and the "TwoSampleMR" R package.

Results

Causal effects of mitochondria on hepatic cancer

As shown in Fig. 2A, in the MR study investigating the causal relationship between mitochondria and hepatic cancer, we observed a negative correlation with hepatic cancer for "39S ribosomal protein L34, mitochondrial" (OR = 0.796, 95% CI = 0.642–0.987, P = 0.037), "Mitochondrial fission regulator 1" (OR = 0.824, 95% CI = 0.685–0.991, P = 0.039), and "Mitochondrial import inner membrane translocase subunit TIM14" (OR = 0.778, 95% CI = 0.621–0.974, P = 0.028), indicating them as protective factors. Conversely, "[Pyruvate dehydrogenase (acetyl-transferring)] kinase isozyme 2, mitochondrial" (OR = 1.545, 95% CI = 1.040–2.294, P = 0.031), "Steroidogenic acute regulatory protein, mitochondrial" (OR = 1.173, 95% CI = 1.033–1.331, P = 0.014), and "Coiled-coil-helix-coiled-coil-helix domain-containing protein 10, mitochondrial" (OR = 1.171, 95% CI = 1.045–1.311, P = 0.007) exhibited a positive correlation with hepatic cancer, indicating them as risk factors. The Steiger test confirms that "Coiled-coil-helix-coiled-coil-helix domain-containing protein 10, mitochondrial" (Steiger P value < 0.001) is an upstream factor for hepatic cancer. Apart from these 6 exposure factors with a causal relationship with hepatic cancer, no significant associations were found with the other 76 mitochondrial-related exposures.

Causal effects of mitochondria on colorectal cancer

As illustrated in Fig. 3A, in the MR study investigating the causal relationship between mitochondria and colorectal cancer, we observed a negative correlation with colorectal cancer for "Phenylalanine-tRNA ligase, mitochondrial" (OR = 0.946, 95% CI = 0.901–0.994,

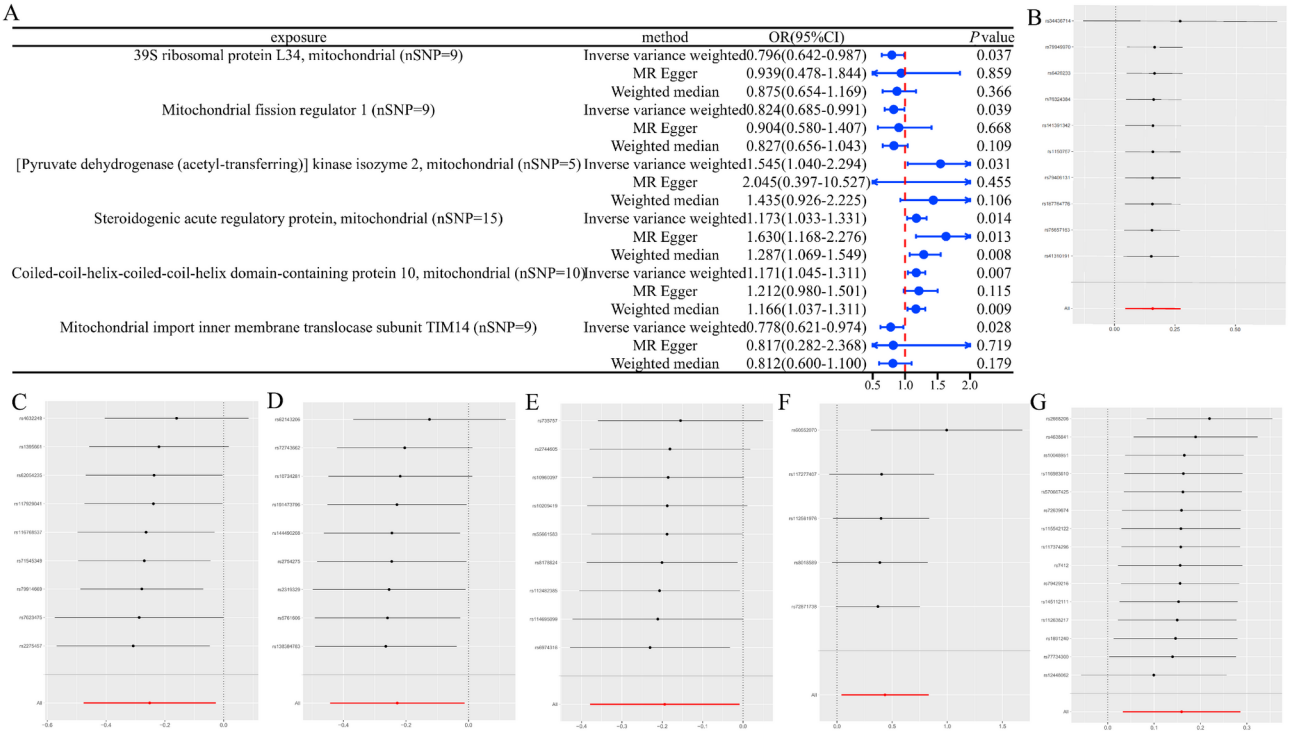

Fig. 2 MR Forest plot and leave-one-out analyses of the causal relationship between mitochondria and hepatic cancer. **A**. The results from Mendelian randomization analysis using the IVW method, MR-Egger regression and Weighted median method. **B**. Coiled-coil-helix-coiled-coil-helix domain-containing protein 10, mitochondrial. **C**. Mitochondrial import inner membrane translocase subunit TIM14. **D**. 39 S ribosomal protein L34, mitochondrial. **E**. Mitochondrial fission regulator 1. **F**. [Pyruvate dehydrogenase (acetyl-transferring)] kinase isozyme 2, mitochondrial. **G**. Steroidogenic acute regulatory protein, mitochondrial. OR, odds ratio. CI, confidence interval

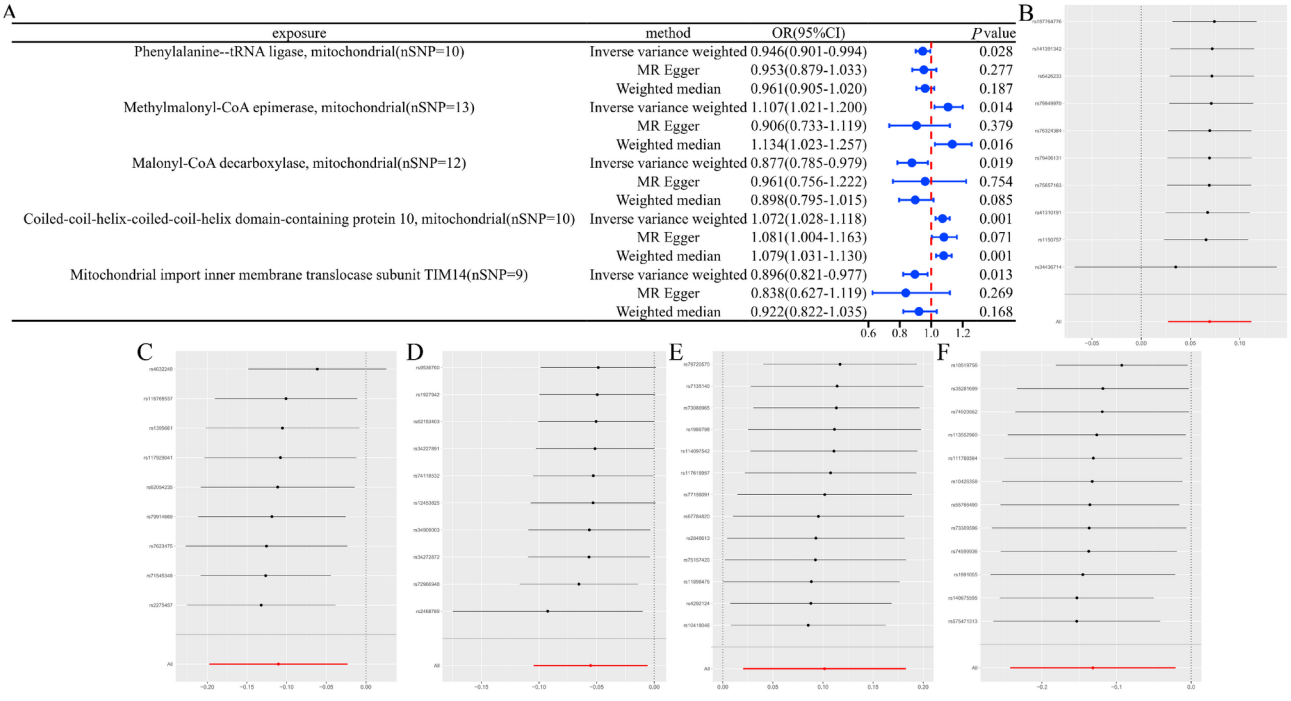

Fig. 3 MR Forest plot and leave-one-out analyses of the causal relationship between mitochondria and colorectal cancer. **A**. The results from Mendelian randomization analysis using the IVW method, MR-Egger regression and Weighted median method. **B**. Coiled-coil-helix-coiled-coil-helix domain-containing protein 10, mitochondrial. **C**. Mitochondrial import inner membrane translocase subunit TIM14. **D**. Phenylalanine-tRNA ligase, mitochondrial. E. Methylmalonyl-CoA epimerase, mitochondrial. **F**. Malonyl-CoA decarboxylase, mitochondrial. OR, odds ratio. CI, confidence interval

P = 0.028), "Malonyl-CoA decarboxylase, mitochondrial" (OR = 0.877, 95% CI = 0.785–0.979, *P* = 0.019), and "Mitochondrial import inner membrane translocase subunit TIM14" (OR = 0.896, 95% CI = 0.821–0.977, *P* = 0.013), indicating them as protective factors. Conversely, "Methylmalonyl-CoA epimerase, mitochondrial" (OR = 1.107, 95% CI = 1.021-1.200, *P* = 0.014) and "Coiled-coil-helix-coiled-coil-helix domain-containing protein 10, mitochondrial" (OR = 1.072, 95% CI = 1.028–1.118, *P* = 0.001) exhibited a positive correlation with colorectal cancer, indicating them as risk factors. Through Cochran Q test, heterogeneity was detected in the causal relationship between "Malonyl-CoA decarboxylase, mitochondrial" (*P* value = 0.041) and colorectal cancer. The Steiger test confirms that "Phenylalanine-tRNA ligase, mitochondrial" (Steiger *P* value = 0.029) and "Coiled-coil-helix-coiled-coil-helix domain-containing protein 10, mitochondrial" (Steiger *P* value < 0.001) are upstream factors for colorectal cancer. Apart from these identified 5 exposure factors with a causal relationship with colorectal cancer, no significant associations were found with the other 77 mitochondrial-related exposures.

Causal effects of mitochondria on lung cancer

As shown in Fig. 4A, in the MR study investigating the causal relationship between mitochondria and lung cancer, we observed a negative correlation with lung cancer for "Succinate dehydrogenase assembly factor 2, mitochondrial" (OR = 0.942, 95% CI = 0.894–0.992, *P* = 0.024), indicating it as a protective factor. Conversely, "Superoxide dismutase [Mn], mitochondrial levels" (OR = 1.054, 95% CI = 1.011–1.099, *P* = 0.013) exhibited a positive correlation with lung cancer, indicating it as a risk factor. The Steiger test confirms that "Superoxide dismutase [Mn], mitochondrial levels" (Steiger *P* value = 0.014) is an upstream factor for lung cancer. Apart from these 2 identified exposure factors with a causal relationship with lung cancer, no significant associations were found with the other 80 mitochondrial-related exposures.

Causal effects of mitochondria on esophageal cancer

As depicted in Fig. 5A, in our MR study, we observed a positive correlation between "Lon protease homolog, mitochondrial" (OR = 1.152, 95% CI = 1.006–1.320, *P* = 0.039) and esophageal cancer, indicating it as a risk factor. The Steiger test confirms that "Lon protease

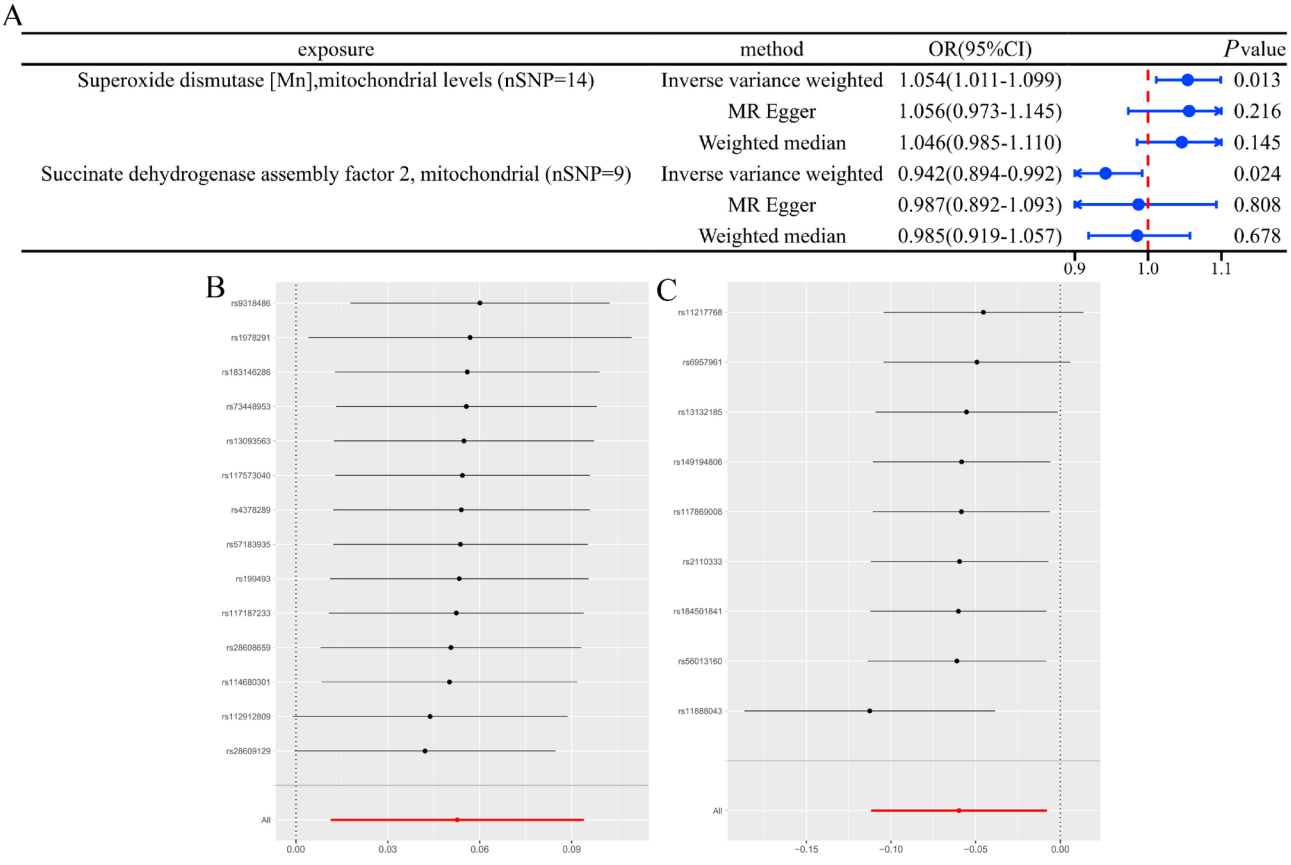

Fig. 4 MR Forest plot and leave-one-out analyses of the causal relationship between mitochondria and lung cancer. **A**. The results from Mendelian randomization analysis using the IVW method, MR-Egger regression and Weighted median method. **B**. Superoxide dismutase [Mn], mitochondrial levels. **C**. Succinate dehydrogenase assembly factor 2, mitochondrial. OR, odds ratio. CI, confidence interval

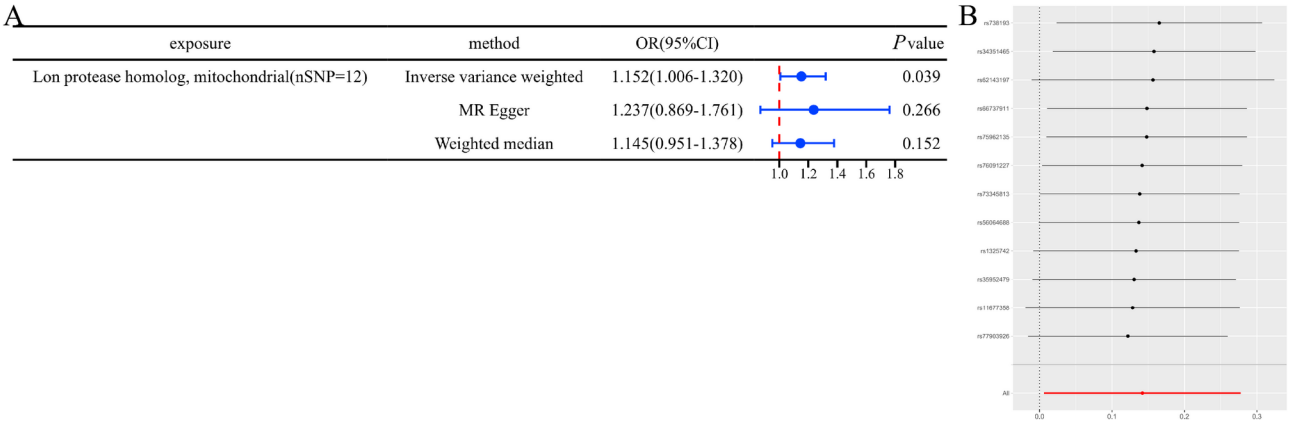

Fig. 5 MR Forest plot and leave-one-out analyses of the causal relationship between mitochondria and esophageal cancer. **A**. The results from Mendelian randomization analysis using the IVW method, MR-Egger regression and Weighted median method. **B**. Lon protease homolog, mitochondrial. OR, odds ratio. CI, confidence interval

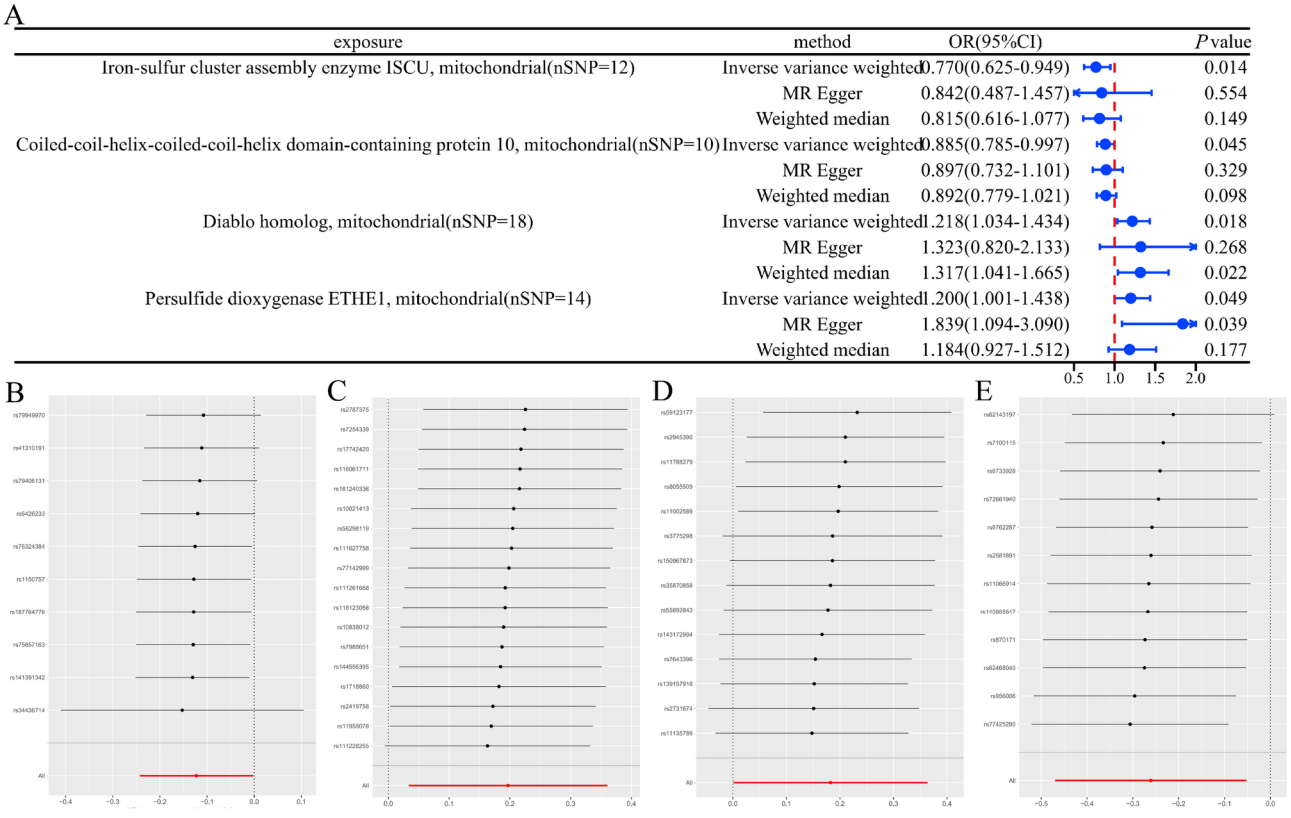

Fig. 6 MR Forest plot and leave-one-out analyses of the causal relationship between mitochondria and thyroid cancer. **A**. The results from Mendelian randomization analysis using the IVW method, MR-Egger regression and Weighted median method. **B**. Coiled-coil-helix-coiled-coil-helix domain-containing protein 10, mitochondrial. **C**. Diablo homolog, mitochondrial. **D**. Persulfide dioxygenase ETHE1, mitochondrial. **E**. Iron-sulfur cluster assembly enzyme ISCU, mitochondrial. OR, odds ratio. CI, confidence interval

homolog, mitochondrial" (Steiger P value = 0.007) is an upstream factor for esophageal cancer. Besides this exposure factor with a causal relationship with esophageal cancer, no significant associations were found with the other 81 mitochondrial-related exposures.

Causal effects of mitochondria on thyroid cancer

As depicted in Fig. 6A, in the MR analysis of mitochondria and thyroid cancer, we found a negative correlation with thyroid cancer for "Iron-sulfur cluster assembly enzyme ISCU, mitochondrial" (OR = 0.770, 95% CI = 0.625–0.949, P = 0.014) and "Coiled-coil-helix-coiled-coil-helix domain-containing protein 10,

mitochondrial" (OR = 0.885, 95% CI = 0.785–0.997, *P* = 0.045), indicating them as protective factors. Conversely, "Diablo homolog, mitochondrial" (OR = 1.218, 95% CI = 1.034–1.434, *P* = 0.018) and "Persulfide dioxygenase ETHE1, mitochondrial" (OR = 1.200, 95% CI = 1.001–1.438, *P* = 0.049) exhibited a positive correlation with thyroid cancer, signifying them as risk factors. The Steiger test confirms that "Coiled-coil-helix-coiled-coil-helix domain-containing protein 10, mitochondrial" (Steiger *P* value < 0.001) is an upstream factor for thyroid cancer. Apart from these identified 4 exposure factors with a causal relationship with thyroid cancer, no significant associations were found with the other 78 mitochondrial-related exposures.

Causal effects of mitochondria on breast cancer

As shown in Fig. 7A, in the MR study investigating the causal relationship between mitochondria and breast cancer, we identified "ADP-ribose pyrophosphatase, mitochondrial" (OR = 0.963, 95% CI = 0.930–0.997, *P* = 0.033), and "Cytochrome c oxidase subunit 8A, mitochondrial" (OR = 0.959, 95% CI = 0.928–0.990, *P* = 0.011) as protective factors, showing a negative correlation with breast cancer. Conversely, "39S ribosomal protein L34, mitochondrial" (OR = 1.069, 95% CI = 1.010–1.132, *P* = 0.021), "Pyruvate carboxylase, mitochondrial" (OR = 1.071, 95% CI = 1.019–1.127, *P* = 0.007), "rRNA methyltransferase 3, mitochondrial" (OR = 1.031, 95% CI = 1.006–1.057, *P* = 0.015), and "Cytochrome c oxidase assembly factor 3 homolog, mitochondrial" (OR = 1.067, 95% CI = 1.016–1.121, *P* = 0.009) were identified as risk factors, showing a positive correlation with breast cancer. The Steiger test confirms that "ADP-ribose pyrophosphatase, mitochondrial" (Steiger *P* value < 0.001), "rRNA methyltransferase 3, mitochondrial" (Steiger *P* value < 0.001), and "Cytochrome c oxidase subunit 8A, mitochondrial" (Steiger *P* value < 0.001) serve as upstream factors for breast cancer. Besides these identified 6 exposure factors with a causal relationship with breast cancer, no significant associations were found with the other 76 mitochondrial-related exposures.

Sensitivity analysis

As shown in Table 2, there is heterogeneity in the causal relationship between "Malonyl-CoA decarboxylase, mitochondrial" and colorectal cancer. In the remaining IVW calculations, a *P* value < 0.05 was obtained, with Cochran Q test *P* value > 0.05, MR-Egger intercept test *P* value > 0.05, and no significant impact from individual SNPs. Therefore, the other causal relationships are

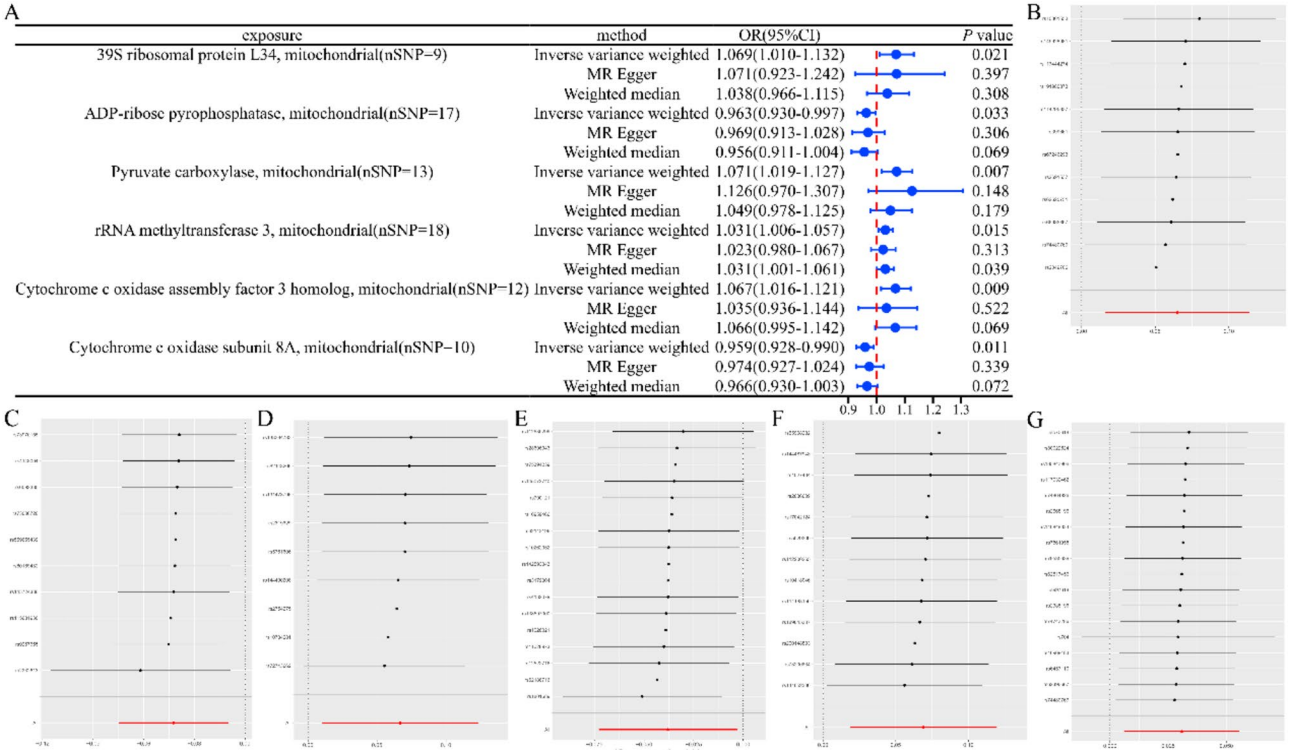

Fig. 7 MR Forest plot and leave-one-out analyses of the causal relationship between mitochondria and breast cancer. **A**. The results from Mendelian randomization analysis using the IVW method, MR-Egger regression and Weighted median method. **B**. Cytochrome c oxidase assembly factor 3 homolog, mitochondrial. **C**. Cytochrome c oxidase subunit 8 A, mitochondrial. **D**. 39 S ribosomal protein L34, mitochondrial. **E**. ADP-ribose pyrophosphatase, mitochondrial. **F**. Pyruvate carboxylase, mitochondrial. **G**. rRNA methyltransferase 3, mitochondrial. OR, odds ratio. CI, confidence interval

Table 2 The results of the Cochran Q test, Egger intercept test, and Steiger test were used to assess the causal relationship between mitochondria and six types of cancer

Outcome	Exposure	Cochran Q test *P* value	MR-Egger intercept test *P* value	Steiger test *P* value
Hepatic cancer	39 S ribosomal protein L34, mitochondrial	0.497	0.629	0.187
	Mitochondrial fission regulator 1	0.957	0.665	0.224
	[Pyruvate dehydrogenase (acetyl-transferring)] kinase isozyme 2, mitochondrial	0.338	0.751	0.349
	Steroidogenic acute regulatory protein, mitochondrial	0.515	0.056	0.064
	Coiled-coil-helix-coiled-coil-helix domain-containing protein 10, mitochondrial	0.934	0.713	< 0.001
	Mitochondrial import inner membrane translocase subunit TIM14	0.302	0.929	0.154
Colorectal cancer	Phenylalanine-tRNA ligase, mitochondrial	0.440	0.824	0.029
	Methylmalonyl-CoA epimerase, mitochondrial	0.209	0.073	0.163
	Malonyl-CoA decarboxylase, mitochondrial	0.041	0.414	0.186
	Coiled-coil-helix-coiled-coil-helix domain-containing protein 10, mitochondrial	0.747	0.796	< 0.001
	Mitochondrial import inner membrane translocase subunit TIM14	0.235	0.648	0.154
Lung cancer	Superoxide dismutase [Mn], mitochondrial levels	0.683	0.967	0.014
	Succinate dehydrogenase assembly factor 2, mitochondrial	0.800	0.329	0.247
Esophageal cancer	Lon protease homolog, mitochondrial	0.886	0.681	0.007
Thyroid cancer	Iron-sulfur cluster assembly enzyme ISCU, mitochondrial	0.787	0.737	0.168
	Coiled-coil-helix-coiled-coil-helix domain-containing protein 10, mitochondrial	0.671	0.871	< 0.001
	Diablo homolog, mitochondrial	0.657	0.723	0.076
	Persulfide dioxygenase ETHE1, mitochondrial	0.299	0.114	0.072
Breast cancer	39 S ribosomal protein L34, mitochondrial	0.869	0.984	0.188
	ADP-ribose pyrophosphatase, mitochondrial	0.609	0.810	< 0.001
	Pyruvate carboxylase, mitochondrial	0.888	0.505	0.144
	rRNA methyltransferase 3, mitochondrial	0.640	0.641	< 0.001
	Cytochrome c oxidase assembly factor 3 homolog, mitochondrial	0.638	0.505	0.097
	Cytochrome c oxidase subunit 8 A, mitochondrial	0.940	0.428	< 0.001

statistically significant, demonstrating no heterogeneity or horizontal pleiotropy, and the assessment results are reliable. Detailed sensitivity analysis and directionality test results are provided in Table 2. The leave-one-out analyses results illustrating the causal relationships between mitochondria and six types of cancer through MR are presented in Figs. 2, 3, 4, 5, 6 and 7.

Discussions

Mitochondria, crucial cellular organelles involved in substance and energy production, serve as metabolic sensors intricately linked to processes such as cancer cell death, migration, invasion, and metastasis. A growing body of research indicates the potential of targeted mitochondrial therapy for cancer [22]. In light of the causal relationships identified in this study between mitochondria-related exposures and six types of cancer, existing studies suggest that the artificial downregulation of "ribosomal protein L34" can inhibit the JAK2/STAT3 signaling pathway, thereby suppressing cancer metastasis and proliferation [23]. Mitochondrial fission-induced mtDNA stress promotes the development of hepatocellular carcinoma [24]. Suppression of the War-burg effect, achieved by down-regulating "pyruvate dehydrogenase kinase isozyme 1", contributes to inhibiting hepatic cancer metastasis [25]. "Steroidogenic acute regulatory protein" serves as a prognostic marker for breast cancer [26]. "Coiled-coil-helix-coiled-coil-helix domain-containing protein 2" mediates the proliferative response in glioblastoma [27]. Upregulation of "phenylalanyl-tRNA synthetase" in gastric cancer tissues is associated with poor prognosis and tumor metastasis [28]. The progression of renal cell carcinoma can be inhibited through fatty acid oxidation mediated by "malonyl-CoA decarboxylase" [29]. A mutation in the "succinate dehydrogenase assembly factor 2" gene is one of the causes of paraganglioma syndrome [30]. Elevated expression of "superoxide dismutase 2" is associated with the dysregulation of cancer cell proliferation and apoptosis [31]. "Diablo" plays a crucial role in nonsteroidal anti-inflammatory drug-induced apoptosis in colon cancer cells [32]. NUDIX hydrolase type 5, as one of the "ADP-ribose pyrophosphatase", exhibits a correlation between its high expression and adverse prognosis in breast cancer [33]. "Cytochrome c oxidase subunit 8A" is closely linked to forkhead box protein P3 (FOXP3) expression, and FOXP3 holds value in the prognosis of small cell lung cancer [34]. In breast cancer, the activity of "pyruvate carboxylase" is associated with cancer cell metastasis,

playing a role in protecting cancer cells from oxidative stress [35].

In this study, we found that 39 S ribosomal protein L34, mitochondrial (MRPL34) is negatively correlated with liver cancer. MRPL34, a mitochondrial ribosome component involved in oxidative phosphorylation and protein translation, may help maintain mitochondrial function. Its depletion could lead to metabolic reprogramming in hepatocellular carcinoma, activating stress pathways like the mitochondrial unfolded protein response, which induces apoptosis [36]. Additionally, impaired mitochondrial translation may shift metabolism toward glycolysis, a hallmark of tumors [37]. These findings suggest that preserving MRPL34 function could suppress hepatocellular carcinoma progression, making it a potential biomarker and therapeutic target.

Our study found a positive correlation between pyruvate dehydrogenase kinase isozyme 2, mitochondrial (PDK2) and hepatic cancer, consistent with PDK2's role in promoting metabolic reprogramming in cancer. PDK2 inhibits pyruvate dehydrogenase, shifting metabolism from oxidative phosphorylation to glycolysis, a hallmark of many aggressive tumors [38]. Increased PDK2 may enhance tumor growth by boosting glycolytic flux and supplying biosynthetic precursors for rapid cell proliferation. This finding suggests that targeting PDK2 with metabolic inhibitors, like dichloroacetate, could help restore mitochondrial function and limit tumor progression [39]. Future research should explore PDK inhibitors in hepatocellular carcinoma and their combination with other metabolic therapies.

We also identified coiled-coil-helix-coiled-coil-helix domain-containing protein 10, mitochondrial (CHCHD10) as an upstream factor influencing multiple cancer types. CHCHD10 is involved in mitochondrial integrity, oxidative stress response, and apoptosis regulation [40]. Its role in tumorigenesis seems context-dependent. In some cancers, CHCHD10 mutations are linked to increased ROS production, mitochondrial dysfunction, and apoptotic resistance [41], promoting tumor progression. In other cancers, CHCHD10 loss leads to mitochondrial fragmentation and increased oxidative stress, potentially creating metabolic vulnerabilities. This suggests that CHCHD10 acts as either an oncogene or tumor suppressor, depending on the cancer type, highlighting its potential as a therapeutic target.

In this study, we explored the potential causal relationships between mitochondrial-related exposures and hepatic cancer, colorectal cancer, lung cancer, esophageal cancer, thyroid cancer, and breast cancer, identifying corresponding protective and risk factors. Heterogeneity was observed in the causal relationship between "Malonyl-CoA decarboxylase, mitochondrial" and colorectal cancer, possibly due to population-level differences in sequencing methodology. The study also confirmed upstream mitochondrial-related factors for each cancer type, providing a basis for exploring unidirectional effects in future mechanistic research.

Importantly, our findings are derived from MR analysis using summary-level GWAS data. While MR is a robust tool for inferring potential causal relationships, it does not confirm biological mechanisms or therapeutic efficacy. Therefore, these results should be interpreted as exploratory and hypothesis-generating. Functional and mechanistic validation is essential to determine the actual role of these mitochondrial factors in tumorigenesis.

Targeting mitochondria in cancer therapy has gained attention due to their role in tumor metabolic reprogramming. Key strategies under investigation include targeting mitochondrial metabolism. For instance, oxidative phosphorylation inhibitors like IACS-010759 and CPI-613 have shown promise in cancers with high mitochondrial reliance, such as leukemia and pancreatic cancer [42, 43]. Similarly, PDK inhibitors like dichloroacetate aim to shift metabolism from glycolysis back to oxidative phosphorylation, reducing tumor cell proliferation [44]. Targeting these mitochondrial regulators may alter cancer cell metabolism, disrupt growth, and enhance treatment efficacy. Another promising approach is inducing mitochondrial dysfunction and apoptosis in cancer cells. Pro-oxidant therapies like elesclomol, which increase mitochondrial ROS production, selectively trigger apoptosis in cancer cells with weak antioxidant defenses [45]. Bcl-2 inhibitors, such as venetoclax, also target mitochondrial apoptosis regulators and have shown efficacy in hematological cancers [46]. However, these approaches remain experimental and context-dependent. Based on our results, future research may explore the integration of mitochondrial-targeted strategies with chemotherapy or immunotherapy, especially for tumors that exhibit mitochondrial dependence. Nonetheless, such applications must await rigorous biological and clinical validation.

Despite advances, several challenges remain in mitochondrial-targeted therapy. Tumor heterogeneity, with distinct mitochondrial metabolic profiles across cancer types, complicates the development of universal strategies. Cancer cells can also develop resistance by rewiring metabolic pathways, requiring combination therapies to overcome resistance [47]. Additionally, poor bioavailability and limited tumor penetration of many mitochondrial-targeting drugs remain a concern. Novel drug delivery methods, such as mitochondrial-targeted nanoparticles, are being developed to improve efficacy [48]. Future research should focus on optimizing combination therapies, enhancing drug delivery, and identifying patients who would benefit most from mitochondrial interventions.

Our study has several strengths. Firstly, we conducted a comprehensive MR study on the causal relationships between mitochondrial-related exposures and six different types of cancer. Secondly, we obtained a substantial sample size and diverse cancer outcomes from the IEU GWAS database (https://gwas.mrcieu.ac.uk/), all based on European population demographics. This broad dataset minimizes errors stemming from different genetic backgrounds. Thirdly, we employed various algorithms in our study, applying stringent thresholds for *P*-values and F-values to select appropriate SNPs, ensuring a close correlation between IVs and exposure factors. Additionally, we utilized multiple testing methods for sensitivity analysis, providing evidence for the reliability and stability of our results.

However, this study has several limitations. Firstly, we used cancer-related summary data derived from the IEU GWAS database, which predominantly comprises cohorts of European ancestry. Currently, the database includes limited high-quality GWAS data for non-European populations in cancer phenotypes. As a result, our analyses were restricted to European individuals, and the findings may not be directly generalizable to other populations. Future MR studies incorporating diverse ancestral groups, such as East Asian or African cohorts, are needed to validate and extend these conclusions. Future studies should validate these results in diverse populations to account for potential ethnic differences. Secondly, despite using sensitivity analyses, confounding bias cannot be entirely ruled out. While Mendelian randomization reduces confounding, horizontal pleiotropy may still exist. Further validation with independent datasets and functional studies is needed to confirm causality. Thirdly, the number of hepatic cancer cases ($n = 379$) is relatively small compared to other cancer types. This may affect statistical power, and future studies should use larger datasets to improve result robustness. Finally, to select sufficient IVs, we used a threshold of $P < 5 \times 10^{-6}$ instead of $P < 5 \times 10^{8}$, which may increase false positives. Although we minimized weak instrument bias by ensuring F-statistics > 10, larger GWAS datasets with stricter thresholds and multi-omics validation should be explored in future research.

Conclusions

This MR study provides genetic evidence for potential causal relationships between mitochondrial-related traits and the risk of six major cancers, including hepatic, colorectal, lung, esophageal, thyroid, and breast cancer. Notably, several mitochondrial exposures appeared to influence more than one cancer type, with some genetic variants (SNPs) acting as instrumental variables across different outcomes, suggesting shared mitochondrial mechanisms may underlie multiple malignancies.

While these findings improve our understanding of mitochondrial involvement in cancer susceptibility, they are based on genetically predicted associations rather than direct functional evidence. As such, the results should be interpreted as hypothesis-generating and exploratory. MR analysis infers potential causality at the population genetic level, but does not establish biological mechanisms or clinical relevance.

Further experimental studies are needed to validate these associations, clarify the roles of specific mitochondrial pathways, and determine whether the implicated traits or SNPs may serve as reliable biomarkers or therapeutic targets. Future work should also explore sex- and ancestry-specific effects and integrate multi-omics approaches to support mechanistic insights. This study lays a foundation for prioritizing mitochondrial traits in cancer research and for guiding future translational investigations.

Abbreviations

MR	mendelian randomization
SNP	single nucleotide polymorphism
ROS	reactive oxygen species
IV	instrumental variable
GWAS	genome-wide association study
IVW	inverse variance weighting
WGS	whole-genome significance
WM	weighted median
OR	odds ratio
CI	confidence intervals
FOXP3	forkhead box protein P3
MRPL34	39 S ribosomal protein L34
PDK2	pyruvate dehydrogenase kinase isozyme 2
CHCHD10	coiled-coil-helix-coiled-coil-helix domain-containing protein 10

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14201-0.

Supplementary Material 1: The scatter plot depicting the causal relationship between mitochondria and hepatic cancer through mendelian randomization.

Supplementary Material 2: The scatter plot depicting the causal relationship between mitochondria and colorectal cancer through mendelian randomization.

Supplementary Material 3: The scatter plot depicting the causal relationship between mitochondria and lung cancer through mendelian randomization.

Supplementary Material 4: The scatter plot depicting the causal relationship between mitochondria and esophageal cancer through mendelian randomization.

Supplementary Material 5: The scatter plot depicting the causal relationship between mitochondria and thyroid cancer through mendelian randomization.

Supplementary Material 6: The scatter plot depicting the causal relationship between mitochondria and breast cancer through mendelian randomization.

Supplementary Material 7: The GWAS datasets for mitochondrial factors.

Supplementary Material 8: All instrumental variables used in Mendelian randomization analysis.

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Author contributions
JT and JZ conceived the study, and wrote, revised and edited the manuscript. RY and HC conducted data analysis and management. XY analyzed the data and conducted data visualization. PZ and WP analyzed the data and revised the manuscript. JT and JZ confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

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Data availability
The datasets generated and/or analyzed during the current study are available in the IEU open GWAS project (https://gwas.mrcieu.ac.uk/). The GWAS datasets for mitochondrial factors is provided within the Table S1.

Declarations

Ethics approval and consent to participate
Not applicable as all analyses in this study were performed using published genome-wide association study summary statistics. Ethical approval and informed consent have been obtained.

Consent for publication
Not applicable as all analyses in this study were performed using published genome-wide association study summary statistics.

Competing interests
The authors declare no competing interests.

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