Discover Oncology

ANALYSIS Open Access

# Pan-cancer analysis of the impact of fatty acids: a two-sample and multivariable Mendelian randomization study

Xiaogen Kuang[1,2,3†], Bingquan Wu[1,2†], Dan Hu[4], Juliet Matsika[1,2], Chunliang Cheng[1,2], Jiatong Xiao[1,2], Zhiyong Cai[1,2], Mingyong Li[3], Jinbo Chen[1,2], Weimin Zhou[1,2*] and Bolong Liu[5*]

†Xiaogen Kuang and Bingquan Wu contributed equally to this work.

*Correspondence:
Weimin Zhou
zhouwm0223@163.com
Bolong Liu
zndxlbl@csu.edu.cn
[1]Departments of Urology, Xiangya Hospital, Central South University, Changsha, Hunan, China
[2]National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Changsha, Hunan, China
[3]Department of Urology, The First Affiliated Hospital, Hengyang Medical School, University of South China, Hengyang, Hunan, China
[4]Department of Urology, Liuyang Jili Hospital, Liuyang City, Hunan, China
[5]Department of Andrology, The First Affiliated Hospital, Hengyang Medical School, University of South China, Hengyang, Hunan, China

## Abstract

**Background** This study used Mendelian randomization (MR) to investigate the causal association between circulating fatty acids (FAs) and the incidence of 10 human cancer types.

**Methods** Single nucleotide polymorphisms (SNPs) significantly associated with circulating FAs were selected from 500,000 UK Biobank blood samples and 114,999 plasma samples from a large GWAS. Summary-level data on 174,006 cancer patients were obtained from the FinnGen biobank. The inverse variance weighted method was used for causal estimation, with additional analyses including MR-Egger regression, weighted median, weighted mode, Cochrane Q test, MR-PRESSO global test, and leave-one-out analyses. Multivariable Mendelian randomization (MVMR) was applied to adjust for potential confounders.

**Result** This study found a genetically causal effect of polyunsaturated FAs on kidney cancer incidence (OR: 1.528; 95% CI 1.164–2.266; $P=0.001$), which remained significant after Bonferroni adjustment. The causal impact of omega-6, omega-3, and linoleic acid on kidney cancer risk was also observed (omega-6: OR = 1.586, $P=0.002$; omega-3: OR = 1.311, $P=0.014$; linoleic acid: OR = 1.527, $P=0.007$). MVMR confirmed the consistent causal relationship (OR = 1.553, $P=0.0047$) after adjusting for multiple variables. Results were validated in a larger cohort.

**Conclusions** Higher circulating polyunsaturated FAs, especially omega-6, were associated with an increased risk of kidney cancer. Suggestive associations were found in small cell lung, rectal, bladder, pancreatic, and esophageal cancer.

**Keywords** Kidney cancer, Mendelian randomization, Pan cancer analysis, Saturated fatty acid, Unsaturated fatty acid

## 1 Background

An estimated 19.3 million new cases of cancer occurred globally in 2020 and about 10 million people die from cancer each year [1]. While several factors, including obesity, smoking, drinking, and infection, are associated with the occurrence of cancer [2–5],

most have not been studied in detail.

The relationship between fatty acids (FAs) and cancer risk remains unclear. FAs are a vital source of nutrition for humans, requiring daily intake. They can be divided into three categories based on the number of double bonds in the side chain: saturated FAs (SFAs), monounsaturated FAs (MUFAs), and polyunsaturated FAs (PUFAs). PUFAs are further classified into omega-6 PUFAs (e.g. linoleic acid, LA) and omega-3 PUFAs (e.g. DHA) based on the position of the first double bond in the methyl terminal. Human desaturase deficiency resulting in PUFA has an important influence on human health [6].

Some studies have shown an association between FAs and cancer. Diets enriched in omega-6 FAs contribute to inflammation, constricted blood vessels, and platelet aggregates [7]. An increase in inflammatory stimuli can provide an ideal microenvironment for the development of cancers. At the same time, omega-3 FAs can help to resolve inflammation and alter the function of vascular and carcinogen biomarkers, thus reducing the risk of cancer and CVD [8, 9]. Cancer cells use MUFAs to synthesize cell membranes [10], and SFAs correlate with drug resistance. This may explain why tumors have a relatively higher proportion of MUFA and SFA than corresponding normal tissues [11]. Cancer cells often maintain their ability to take up lipids from the circulation and adjacent adipose tissue [12]. These findings suggest that FAs may play a pivotal role in carcinogenesis and could be used to aid the development of novel therapeutic targets.

Cohort studies have shown that FAs have a potential effect on multiple cancer types, however, no consensus about their role has been reached. While previous case-control studies failed to identify a significant association between total fish intake (an important source of omega-3 FAs) and breast cancer [13–15], a meta-analysis of 16 prospective cohort studies suggested that breast cancer risk in premenopausal women is negatively correlated with the intake of omega-3 FAs from a marine diet and supplements [16–18]. Meanwhile, Stearoyl-CoA desaturase 1 (SCD1) is expressed in samples from all clear cell renal cell carcinoma (ccRCC) tumor stages but not in matched benign tissue samples [19]. However, kidney cancer tissue has a lower unsaturation level than normal kidney tissue [20]. These findings indicate that the relationship between fatty acids and cancer incidence requires further exploration. While randomized controlled trials (RCTs) are the gold standard for inferring causality, they may be too expensive or complex to perform over an extended period, making it difficult to assess the potential long-term effects of FAs.

Mendelian randomization (MR) is a novel method for making causal inferences between lifelong exposures and outcomes [21] and can be used to identify the potential role of FAs in the development of different types of cancer. MR studies share some similarities with RCTs. For example, the random allocation of single nucleotide polymorphisms (SNPs) that occur at conception is equivalent to interventions that are randomly allocated at the start of a trial [22]. MR studies are performed to predict and evaluate the effect of an exposure on a particular outcome using genetic variants, thus alleviating concerns of reverse causation [23]. MR is also less susceptible to environmental confounders [24, 25]. To measure the association between FAs and cancer risk, two-sample MR and MVMR were performed using large-scale data from genome-wide association studies maintained in the UK and FinnGen Biobanks.

## 2 Methods

### 2.1 Study design

A pan-cancer analysis was conducted involving 10 human cancer types to evaluate the causal effect of multiple FAs on cancer incidence. MVMR was then used to test for potential confounding. The results were validated using a large-scale genome-wide association study (GWAS) cohort. To reduce bias in the results, three important assumptions had to be met by the SNPs: (1) they were strongly associated with the exposure, (2) they were not affected by any confounding factors, and (3) they did not affect the outcome through any variable other than the exposure. A detailed flowchart is shown in Fig. 1.

### 2.2 Exposure data

Instrument variants of circulating monounsaturated FAs, polyunsaturated FAs, and saturated FAs were selected from the program conducted by Nightingale Health in 2018, which analyzed over 200 metabolic biomarkers in 500,000 blood samples from the UK Biobank (https://gwas.mrcieu.ac.uk/). Genetic instrument variants of circulating DHA, linoleic acid, total omega 3 FAs, and total omega 6 FAs were obtained in a large published GWAS analysis of plasma samples from 114,999 individuals in the UK Biobank [26]. Detailed information about the exposure data source is included in Supplementary Table 1.

### 2.3 Outcome data

Cancer outcomes were defined as incident or prevalent cases of site-specific malignancies. Summary level GWAS data on 10 cancer types, which was summarized by the IEU OpenGWAS project, was selected from the FinnGen Biobank. The FinnGen study was launched in 2017 to analyze genome and health data from Finnish biobanks and digital health record data. The current study collected FinnGen data from round 5, which included 217,677 participants of European genetic ancestry (https://gwas.mrcieu.ac.uk/). GWAS round 8 data, a more scaled population from the FinnGen biobank (https://r8.finngen.fi/), was used to validate the findings. Detailed information about the outcome data source is included in Supplementary Table 1.

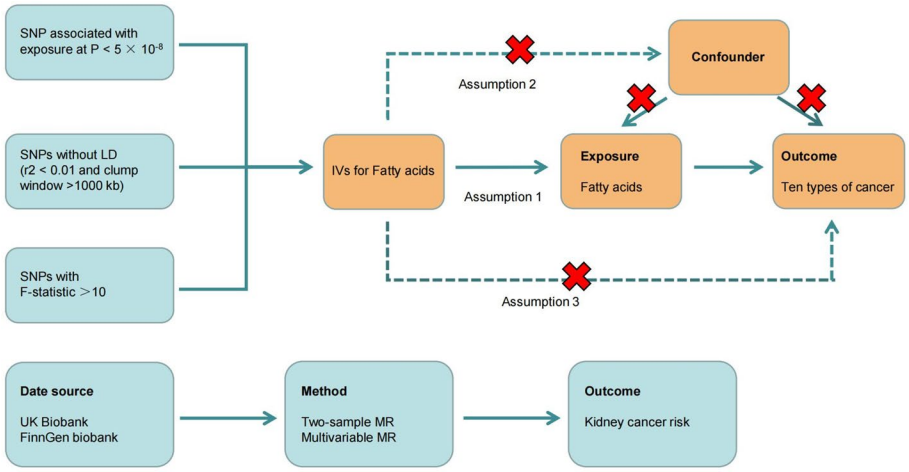


**Fig. 1** Overall study design of the MR analysis used to explore the relationship between fatty acids and the risk of cancer

### 2.4 Selection of instrumental variables

Strict selection criteria were used to determine the availability of instrumental variables associated with circulating FAs. The MR Steiger filtering method was used to examine the causality between FA and cancer. The 'TwoSampleMR' R package was used to filter out SNPs that were significantly linked to circulating monounsaturated FAs, polyunsaturated FAs, and saturated FAs at a threshold of $P < 5 \times 10^{-8}$. Eligible SNPs for circulating DHA, linoleic acid, total omega 3 FAs, and total omega 6 FAs were selected by Borges et al., who demonstrated the significance of each instrumental variable ($P < 5 \times 10^{-8}$). SNPs with a threshold of $r^2 \leq 0.01$ were also eliminated to avoid linkage disequilibrium. SNPs that were not found in the GWAS outcome data for the 10 cancer types were eliminated during the harmonization stage. Proxy SNPs were not used to replace the eliminated SNPs in subsequent analyses. F-statistics of the remaining SNPs were calculated to avoid the possibility of weak instrument bias and quantify the strength of the instrumental variables using the following formula: $F = R^2 \times (N\text{-}1\text{-}k)/(1\text{-}R^2)$ [27]. $R^2$ was calculated using the following formula: $R^2 = 2 \times beta^2 \times (1\text{-}eaf)/[2 \times beta^2 \times (1\text{-}EAF) + 2 \times se^2 \times N \times EAF \times (1\text{-}EAF)]$. SNPs with F-statistics values > 10 were considered eligible instrumental variables [28]. After strict selection using these criteria, the instrumental variables were found to fulfill the first MR assumptions. After strict selections, the identified IVs and corresponding F statistic were presented in Supplementary Table 2.

### 2.5 Mendelian randomization

MR analysis was used to explore the causal effect of circulating FAs on pan-cancer risk. The inverse variance weighted (IVW) method is primarily adopted to generate the combined effect (beta value) by meta-analyzing the Wald ratio of each SNP [29], and the results are usually considered final. MR Egger, weighted median, weighted mode, simple mode methods and MR-robust adjusted profile score (MR-RAPS) were also performed. Associations were considered to have Bonferroni correction significance if P values were $< 1.66 \times 10^{-3}$ ($P = 0.05/10$ types of human cancer/3 fatty acids). Those with P values < 0.05 but $> 1.67 \times 10^{-3}$ were considered suggestive causal associations.

### 2.6 Multivariable Mendelian randomization

Pan-cancer identified that kidney cancer was at the highest risk of being influenced by FAs. Individuals' genotypes no more change after conception, making MR less sensitive to confounding factors. Multivariable MR was conducted to further identify potential confounders. MVMR incorporates potential confounding factors into the model to eliminate their influence. If the relationship between exposure and outcome remains robust, it can be inferred that the effect independent of confounding factors. Meanwhile, the instrumental variables meet the second assumption. Previous MR analyses have shown that increased BMI, HDL cholesterol, body size at age 10, diastolic blood pressure, and systolic blood pressure were associated with an increased risk of kidney cancer [30–32]. Thus, it is possible that metabolic factors were confounding the relationship between FAs and kidney cancer. Considering the influence of traditional risk factors, smoking was also defined as a potential confounder. Instrumental variables for these factors were selected from the UK Biobank using the accordant selection criteria described above.

### 2.7 Sensitivity analysis

To test the robustness of our two sample MR results, several sensitivity analyses were performed. The MR Egger method can be used to detect directional horizontal pleiotropy [33], the weighted median method can provide a consistent estimate even if half of the SNPs are pleiotropic [34], and the weighted mode method can provide consistent results even if most SNPs are pleiotropic [35]. Scatter plots were generated to display the results of the six MR methods. The MR-PRESSO global test was also used to detect horizontal pleiotropy [36]. Heterogeneity in the IVW estimates was examined using the Cochran Q test. Leave-one-out sensitivity analysis was also performed to assess genetically causal estimates determined after excluding each SNP one by one. The absence of horizontal pleiotropy indicates that the instrumental variables have fulfilled the third MR assumption. For MVMR analyses, we used the multivariable MR-Egger method for pleiotropy testing, Cochran's Q statistic for heterogeneity testing and tests for weak instrument bias.

### 2.8 Negative control

To the best of the author's knowledge, there was no evidence of a link between myopia and 10 cancers. Myopia was analyzed as a negative control outcome. Summary-level data for myopia were obtained from the FinnGen biobank (https://www.finngen.fi/), including 460,536 individuals of European ancestry.

All analyses were conducted in R 4.4.1 using "TwoSampleMR", "MendelianRandomization", "MVMR" and "coloc" R package.

## 3 Results

### 3.1 Description of the selected IVs

A total of 62, 60, and 52 genome-wide significant SNPs were selected as IVs associated with monounsaturated FAs, polyunsaturated FAs, and circulating saturated FAs, respectively, at a cutoff of $P < 5 \times 10^{-8}$ and $r^2 \leq 0.01$. A total of 215 significant SNPs were also obtained and used for the IVs of DHA, linoleic acid, total omega 3 FAs, and circulating total omega 6 FAs. Detailed information about the genetic instruments is shown in Supplementary Table 2. The F-statistics of these SNPs were much larger than 10, suggesting that the probability of weak instrument bias was low. Before analyzing, it should be clear that the ORs mentioned in the results section are derived from the IVW method.

### 3.2 Pan-cancer analysis to screen the types of cancer associated with FAs

Pan-cancer analysis of 10 human cancer types using the IVW method found that circulating FAs had a genetically causal effect on the incidence of different types of cancer (Fig. 2, Supplementary Fig. 1 and Supplementary Table 3). Several FA types were strongly associated with kidney, pancreatic, and cervical or uterine cancer. Polyunsaturated FAs (OR: 1.528; 95% CI, 1.176–1.987; $P = 0.001$), monounsaturated FAs (OR: 1.319; 95% CI, 1.004–1.738; $P = 0.049$) and circulating saturated FAs (OR: 1.397; 95% CI, 1.021–1.912; $P = 0.036$) had a genetically causal effect on the incidence of kidney cancer. Remarkably, the association between polyunsaturated FAs and kidney cancer risk was significant after Bonferroni adjustment ($P < 0.0017$). A borderline association between polyunsaturated FAs and pancreatic cancer (OR: 0.685; 95% CI, 0.476–0.984; $P = 0.040$) and cervical or uterine cancer risk (OR: 1.345; 95% CI, 1.100–1.644; $P = 0.038$) was also observed.

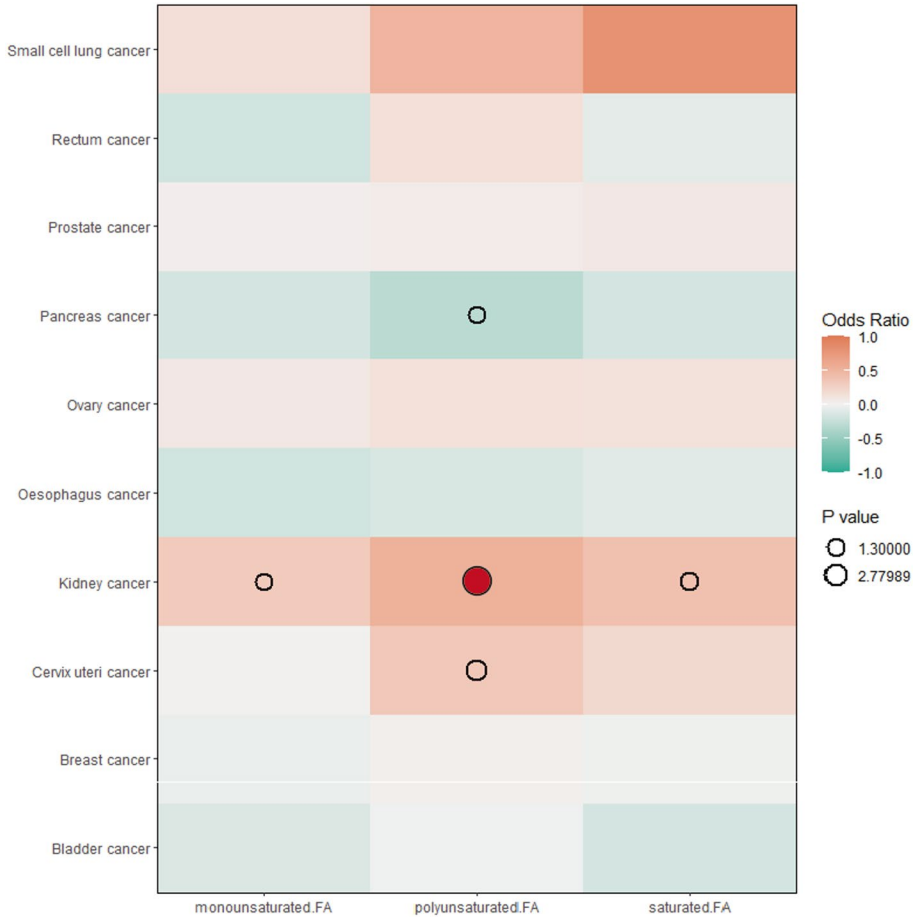


**Fig. 2** Heatmap of the association between the incidence of 10 cancer types and three kinds of fatty acids using the IVW method. The circle sizes represent the p values of each association. The red circles indicate the significance after Bonferroni adjustment ($1.66 \times 10^{-3}$). The other four are suggestive associations

MR Egger, weighted median, simple mode, and weighted mode methods were also used to verify the causal effect between kidney cancer and these FAs (Supplementary Tables 4 and Supplementary Fig. 2). The MR-Egger intercept and MR-PRESSO global test did not identify directional pleiotropy and the Cochrane Q test did not identify heterogeneity (Supplementary Table 4). Leave-one-out sensitivity analysis revealed that genetically causal estimates were still stable after excluding single SNPs one by one (Supplementary Fig. 3).

### 3.3 Evaluating the causal effect of four polyunsaturated FA components

Since polyunsaturated FAs were significantly associated with the risk of kidney (using the Bonferroni adjustment), pancreatic, and cervical or uterine cancer in the pan-cancer analysis, the genetically causal effect of four polyunsaturated FA components on the incidence of these cancers was also explored (Supplementary Table 5). Remarkably, a Bonferroni-adjusted causal effect was found between circulating total omega 6 FAs and the risk of kidney cancer (OR: 1.586; 95% CI, 1.184–2.125; $P = 0.002$). A suggestive causal effect was also found between linoleic acid (OR: 1.527; 95% CI, 1.124–2.074; $P = 0.007$) and total omega 3 FAs (OR: 1.311; 95% CI, 1.056–1.627; $P = 0.014$) on the occurrence of kidney cancer, and no relationship was observed between circulating DHA (OR: 1.271;

95% CI, 0.942–1.716; $P = 0.1170$) and kidney cancer incidence. Meanwhile, a protective causal effect was found between circulating total omega 6 FAs and the incidence of pancreatic cancer (OR: 0.582; 95% CI, 0.385–0.880; $P = 0.01$) (Fig. 3). Conversely, no causal effects were observed between the four polyunsaturated FAs components and cervical or uterine cancer. Results using the different methods of validation are shown in Supplementary Tables 6 and Supplementary Fig. 4. No directional pleiotropy and causal relationship geneity were identified, and leave-one-out sensitivity analysis revealed stable causal estimates (Supplementary Fig. 5).

A less significant association was found between three additional types of human cancer and the three circulating polyunsaturated FAs components. Rectal cancer was genetically associated with circulating DHA (OR 1.354; 95% CI, 1.061–1.729; $P = 0.015$). Oesophageal cancer (OR: 0.651; 95% CI, 0.427–0.993; $P = 0.046$) were genetically associated with circulating total omega 3 FAs.Small cell lung cancer incidence was genetically influenced by circulating linoleic acid (OR: 2.010; 95% CI, 1.004–4.027; $P = 0.049$) (Supplementary Tables 7 and Supplementary Fig. 6).

### 3.4 Measuring confounding using multivariable MR

Among the 10 cancer types, kidney cancer was most highly associated with circulating FA levels, especially polyunsaturated and total omega 6 FAs. The causal effect between kidney cancer incidence and monounsaturated and saturated FAs was suggestive. To identify potential confounding, multivariable MR was used to validate the kidney cancer results. Previously published MR studies were assessed to identify the risk of kidney cancer associated with BMI, HDL cholesterol, body size at age 10, diastolic blood pressure, and systolic blood pressure and to determine the likelihood that these variables could act as confounders between circulating FAs and kidney cancer. Smoking was also considered a confounding factor. Additional information about the potential confounders is shown in Supplementary Table 1, which includes demographic details. After adjusting for BMI, ever smoked, LDL cholesterol, body size at age 10, diastolic blood pressure, and systolic blood pressure, polyunsaturated and saturated FAs remained associated with the risk of kidney cancer (OR 1.553; 95% CI, 1.140–2.061; $P = 0.0047$) (Fig. 4). However, the model has problems of weak tool offset and horizontal pleiotropy.

| Exposure | SNP number | OR (95%CI) | p value | MR Egger | Cochrane Q | MR-PRESSO global |
|---|---|---|---|---|---|---|
| **DHA** | | | | | | |
| Pancreas cancer | 40 | 0.775 (0.570, 1.056) | 0.106 | 0.203 | 0.92 | 0.918 |
| Kidney cancer | 40 | 1.271 (0.942, 1.716) | 0.117 | 0.953 | 0.026 | 0.044 |
| Cervix uteri cancer | 40 | 1.232 (0.991, 1.532) | 0.06 | 0.502 | 0.075 | 0.122 |
| **Total omega 3 FAs** | | | | | | |
| Pancreas cancer | 45 | 0.829 (0.637, 1.077) | 0.16 | 0.363 | 0.699 | 0.766 |
| Kidney cancer | 45 | 1.311 (1.056, 1.627) | 0.014 * | 0.545 | 0.349 | 0.409 |
| Cervix uteri cancer | 45 | 1.119 (0.902, 1.389) | 0.306 | 0.633 | 0.001 | 0.001 |
| **Linoleic acid** | | | | | | |
| Pancreas cancer | 44 | 0.684 (0.462, 1.014) | 0.059 | 0.329 | 0.359 | 0.433 |
| Kidney cancer | 44 | 1.527 (1.124, 2.074) | 0.007 * | 0.204 | 0.437 | 0.306 |
| Cervix uteri cancer | 44 | 1.153 (0.848, 1.568) | 0.362 | 0.771 | 0.002 | 0.002 |
| **Total omega 6 FAs** | | | | | | |
| Pancreas cancer | 54 | 0.582 (0.385, 0.880) | 0.01 * | 0.691 | 0.078 | 0.08 |
| Kidney cancer | 54 | 1.586 (1.184, 2.125) | 0.002 ** | 0.762 | 0.438 | 0.512 |
| Cervix uteri cancer | 54 | 1.279 (0.976, 1.676) | 0.074 | 0.593 | 0.012 | 0.026 |

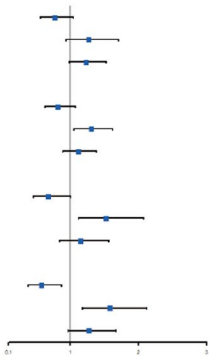

**Fig. 3** Causal association between four polyunsaturated FAs components and kidney, pancreatic, and cervical uterine cancer risk. One asterisk indicates suggestive evidence while two asterisks indicate statistical significance after a multiple comparison correction ($P = 0.05/3$ types of human cancer/4 fatty acids)

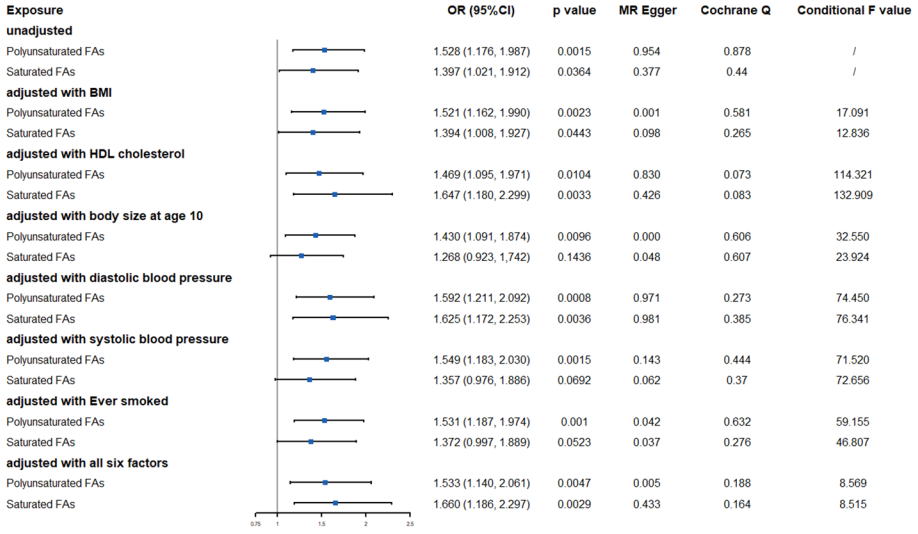


**Fig. 4** Causal association between circulating polyunsaturated and saturated FAs for kidney cancer risk by multivariable mendelian randomization after adjusting for BMI, HDL cholesterol, body size at age 10, diastolic blood pressure, and systolic blood pressure

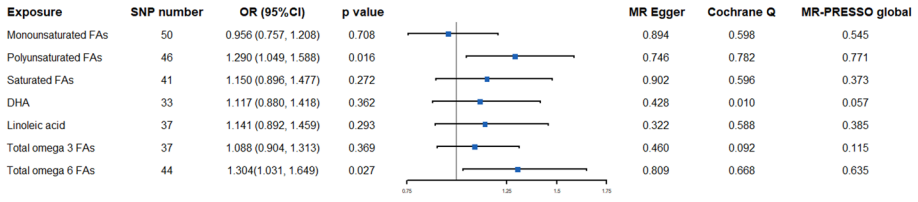


**Fig. 5** Causal relationship between kidney cancer risk and circulating FAs validated in a more scaled cohort

### 3.5 Validation in a scaled cohort

The most recent GWAS data (R8), including 1,830 kidney cancer patients in the FinnGen Biobank, was used to further validate the genetic effect of FAs in a more scaled population (Supplementary Table 8). While circulating polyunsaturated FAs (OR 1.290; 95% CI, 1.049–1.588; $P = 0.016$) and total omega 6 FAs (OR 1.304; 95% CI, 1.031–1.649; $P = 0.027$) were consistently associated with the risk of kidney cancer, circulating monounsaturated FAs (OR 0.956; 95% CI, 0.757–1.208; $P = 0.706$), saturated FAs (OR 1.505; 95% CI, 0.896–1.477; $P = 0.272$), total omega 3 FAs (OR 1.089; 95% CI, 0.904–1.313; $P = 0.369$), LA (OR 1.141; 95% CI, 0.892–1.459; $P = 0.293$), and DHA (OR 1.117; 95% CI, 1.880–1.417; $P = 0.362$) had no genetic effect (Fig. 5 and Supplementary Table 9). MR Egger, weighted median, simple mode, and weighted mode methods were also used to evaluate these cancers (Supplementary Fig. 7 and Supplementary Table 9). The stable causal estimates of leave-one-out sensitivity analysis are shown in Supplementary Fig. 8.

### 3.6 Negative control outcome analysis

To further verify the specificity of the results, we used Myopia for the analysis of negative control results. The results showed that FA was not related to renal cell carcinoma, so the IV we chose was appropriate (Supplementary Tables 10, 11).

## 4 Discussion

The current study explored the causal relationship between circulating FAs and the risk of 10 types of human cancer in European individuals using two-sample MR. A robust relationship between FA components and kidney cancer risk was identified. After adjusting for BMI, HDL cholesterol, body size at age 10, diastolic blood pressure, and systolic blood pressure, PUFAs were still associated with the risk of kidney cancer. This association was also evaluated in a more scaled population obtained from the FinnGen Biobank. Overall, these findings revealed that circulating polyunsaturated FAs and total omega 6 FAs have a causal effect on kidney cancer incidence.

Kidney cancer is one of the most studied malignancies characterized by metabolic reprogramming [37, 38]. Several studies have shown that SFAs, MUFAs, and PUFAs play a potential role in the development of kidney cancer. A recent metabolomics study identified an increased number of long-chain fatty acids in clear cell renal cell carcinoma (ccRCC) tissues [37], along with higher cholesterol ester storage levels [39]. The expression of Stearoyl-CoA desaturases 1 (SCD1), a final enzyme involved in the FA synthetic pathway [40, 41], is associated with the growth and survival of ccRCC [19]. Knocking down or reducing the expression of SCD1 has shown promising efficacy by decreasing MUFA synthesis to promote cancer cell ferroptosis and inhibit tumor cell migration and regrowth [41]. PUFAs are also highly oxidizable, making cancer cells more susceptible to ferroptosis [12]. However, FABP4, a known PUFA shuttle [42], can protect cancer cells from ROS-induced lipotoxicity and contribute to tumor recurrence [41]. Higher SFA levels in cancers can reduce the fluidity of the cell membrane, promoting drug resistance [11] by interrupting the passive diffusion or endocytosis of large molecules [43–45]. Together, these findings suggest that dietary interventions to regulate circulating FAs could serve as promising cancer treatment or prevention strategies.

To our knowledge, no large-scale epidemiological study has been conducted to confirm the relationship between kidney cancer and FAs. Our study used MR to study the genetic causality between FAs and 10 common human cancers and identified a robust association between FAs and kidney cancer risk. PUFAs, especially omega-6 FAs, had a significant effect on the incidence of kidney cancer even after adjusting for potential confounding variables. This exploratory MR analysis could provide a novel direction for future epidemiological surveys. The findings can be used to encourage patients to reduce their risk of kidney cancer by regulating their lifestyle and diet.

Inducing FA biosynthesis by reducing citrate is shown to prevent cervical and uterine cancer cell proliferation and accelerate cell death [46]. A controlled cross-sectional study found that plasma concentrations of SFA/MUFA were higher and SFAs and LA concentrations were lower in cervical and uterine cancer patients than in healthy controls [47]. In the current study, plasma FA levels represent transient blood samples and cannot be used to assess the long-term effect of FAs on the human body. The MR analysis identified a genetically suggestive relationship between circulating polyunsaturated FAs and cervical or uterine cancer risk, but not between four polyunsaturated FA components and these cancer types. Further study is needed to verify these associations.

A recent cohort study observed a significant association between higher plasma Omega-6 FA levels and the risk of pancreatic cancer [48]. Another Iranian cohort including 75 pancreatic cancer cases identified a protective, albeit borderline significant, relationship between dietary total PUFA levels and the incidence of pancreatic cancer

[49]. A European cohort study of 375 incident PC cases showed that conjugated LAs (LA isomers) were negatively associated with pancreatic cancer in women [50]. The current MR study also indicated that circulating polyunsaturated FAs and their components had a protective effect on pancreatic cancer risk.

This study suggests that the effect of some types of PUFA differs depending on the type of cancer. For example, total omega-6 has a distinct effect on pancreatic and renal cancer and omega-6 tends to promote cancer development. Notably, enzyme expression patterns differ by tissue type, impacting downstream metabolite production and lipid composition [51]. PLA2 is a key enzyme that catalyzes membrane phospholipid hydrolysis, reduces the membrane phospholipid oxidation rate, and generates fatty acids such as arachidonic acid (omega 6), as well as hemolytic phospholipids. Inhibiting $Ca^{2+}$-independent PLA21β (iPLA21β) expression is shown to significantly enhance iron-regulated cell death by increasing lipid peroxidation [52]. While PLA2G1B is highly expressed in pancreatic acinar cells, this gene is not typically expressed in the kidneys [51]. Hemolytic phospholipids generated by PLA2G1B can inhibit fatty acid oxidation [53]. Thus, it is probable that PLA2G1B is abnormally activated in pancreatic cancer [54, 55]. High levels of the metabolite, omega 6, suppress enzyme activity and reduce phospholipid levels, increasing the peroxidation rate of fatty acids and making tumor cells more susceptible to iron toxicity. Some studies have shown that PLA2 inhibitors have anti-cancer activity against various cancers [56–58].

While our study found no significant associations between the remaining cancer types and FAs, it remains possible that FAs can influence the risk of other cancers. Exploratory analysis identified multiple suggestive associations between FAs and small cell lung, rectal, pancreatic, and esophageal cancer. Prostate cancer cells usually express more saturated and mono-unsaturated acyl chains [11]. Low lipid saturation mediated by drugs can reduce the drug resistance of prostate cancer cells, and palmitic acid (a type of SFA) can reverse this effect. Some studies have shown that FAs from adipocytes accumulate in cancer cells [59–61], further illustrating the relationship between FAs and cancers. Overall, FAs and FA saturation play an important role in tumor progression, proliferation, and drug resistance.

The current study has several limitations. First, we assumed a linear association between the risk factors and outcomes. While the causal estimate may be inaccurate if the true association is nonlinear, it still reflects the presence and direction of the average causal effect of each group [62]. Second, genetic instruments used in MR studies typically represent a small amount of variation in the exposure [63]. Third, due to the biological plausibility and multi-stage nature of the statistical process, it would have been overly conservative to apply a rigorous multiple-testing correction (Bonferroni correction). Finally, while the result was validated in a more scaled population (1, 830 kidney cancer cases) of European ancestry from the FinnGen Biobank, validation in other GWAS cohorts is also required to verify the results. In addition, the effect of total PUFAs on different pathological types of kidney cancer is warranted.

## 5 Conclusions

This study used two sample MR and MVMR analysis to show that higher levels of circulating unsaturated FAs, especially total omega 6 FAs, increased the risk of kidney cancer. A suggestive association was also found between FAs and small cell lung, rectal,

pancreatic, and esophageal cancer. Large-scale prospective studies are needed to validate the study findings.

**Abbreviations**

| | |
|---|---|
| FAs | Fatty acids |
| MR | Mendelian randomization |
| MVMR | Multivariable Mendelian randomization |
| SFAs | Saturated FAs |
| MUFAs | Monounsaturated FAs |
| PUFAs | Polyunsaturated FAs |
| SCD1 | Stearoyl-CoA desaturase 1 |
| ccRCC | Clear cell renal cell carcinoma |
| RCTs | Randomized controlled trials |
| SNPs | Single nucleotide polymorphisms |
| GWAS | Genome-wide association study |
| IVW | Inverse variance weighted |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s12672-025-03010-3.

Supplementary Material 1

Supplementary Material 2

**Acknowledgements**
This study recognizes the work of numerous researchers whose important datasets were crucial for this analysis.

**Author contributions**
B.L. and W.Z. designed the study managed the project. D.H. and C.C. conducted the formal analysis and interpreted the results. X.K. and B.W. wrote the first draft of the manuscript with critical feedback from J.M., Z.C., J.X., M.L. and J.C. J.M., Z.C., J.X., M.L. and J.C. were responsible for validation and visualization. All authors have read and approved the final manuscript.

**Funding**
This work was supported by the National Natural Science Foundation of China (82373337), Natural Science Foundation of Hunan Province (2023JJ30870).

**Data availability**
The summary-level data used in this study can be obtained from two publicly available datasets, the UK Biobank (https://gwas.mrcieu.ac.uk/) and the FinnGen Biobank (https://www.finngen.fi/). One can find these summary-level data according to the navigation on the corresponding official websites. The details of all data used in this study and their download links are included in Supplementary Table 1.

## Declarations

**Ethics approval and consent to participate**
This study only used publicly available data. No original data were collected. Ethical approval for each of the studies included in the investigation can be found in the original publications.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

Received: 5 February 2025 / Accepted: 17 June 2025
Published online: 01 July 2025

**References**

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Iyengar NM, Gucalp A, Dannenberg AJ, Hudis CA. Obesity and cancer mechanisms: tumor microenvironment and inflammation. J Clin Oncol. 2016;34(35):4270–6.
3. Parkin DM, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer. 2011;105(Suppl 2):S77–81.
4. Rumgay H, Shield K, Charvat H, Ferrari P, Sornpaisarn B, Obot I, et al. Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study. Lancet Oncol. 2021;22(8):1071–80.
5. Mantovani A. Cancer: inflammation by remote control. Nature. 2005;435(7043):752–3.

6. Dyall SC, Balas L, Bazan NG, Brenna JT, Chiang N, da Costa Souza F, et al. Polyunsaturated fatty acids and fatty acid-derived lipid mediators: recent advances in the Understanding of their biosynthesis, structures, and functions. Prog Lipid Res. 2022;86:101165.
7. Dennis EA, Norris PC. Eicosanoid storm in infection and inflammation. Nat Rev Immunol. 2015;15(8):511–23.
8. Del Gobbo LC, Imamura F, Aslibekyan S, Marklund M, Virtanen JK, Wennberg M, et al. ω-3 polyunsaturated fatty acid biomarkers and coronary heart disease: pooling project of 19 cohort studies. JAMA Intern Med. 2016;176(8):1155–66.
9. Shahidi F, Ambigaipalan P. Omega-3 polyunsaturated fatty acids and their health benefits. Annu Rev Food Sci Technol. 2018;9:345–81.
10. Magtanong L, Ko P-J, To M, Cao JY, Forcina GC, Tarangelo A, et al. Exogenous monounsaturated fatty acids promote a ferroptosis-resistant cell state. Cell Chem Biol. 2019;26(3):420–32.
11. Rysman E, Brusselmans K, Scheys K, Timmermans L, Derua R, Munck S, et al. De novo lipogenesis protects cancer cells from free radicals and chemotherapeutics by promoting membrane lipid saturation. Cancer Res. 2010;70(20):8117–26.
12. Butler LM, Perone Y, Dehairs J, Lupien LE, de Laat V, Talebi A, et al. Lipids and cancer: emerging roles in pathogenesis, diagnosis and therapeutic intervention. Adv Drug Deliv Rev. 2020;159:245–93.
13. Ambrosone CB, Freudenheim JL, Sinha R, Graham S, Marshall JR, Vena JE, et al. Breast cancer risk, meat consumption and N-acetyltransferase (NAT2) genetic polymorphisms. Int J Cancer. 1998;75(6):825–30.
14. Fernandez E, Chatenoud L, La Vecchia C, Negri E, Franceschi S. Fish consumption and cancer risk. Am J Clin Nutr. 1999;70(1):85–90.
15. Toniolo P, Riboli E, Protta F, Charrel M, Cappa AP. Calorie-providing nutrients and risk of breast cancer. J Natl Cancer Inst. 1989;81(4):278–86.
16. Zheng J-S, Hu X-J, Zhao Y-M, Yang J, Li D. Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. BMJ. 2013;346:f3706.
17. Chajès V, Torres-Mejía G, Biessy C, Ortega-Olvera C, Angeles-Llerenas A, Ferrari P, et al. ω-3 and ω-6 polyunsaturated fatty acid intakes and the risk of breast cancer in Mexican women: impact of obesity status. Cancer Epidemiol Biomarkers Prev. 2012;21(2):319–26.
18. Goodstine SL, Zheng T, Holford TR, Ward BA, Carter D, Owens PH, et al. Dietary (n-3)/(n-6) fatty acid ratio: possible relationship to premenopausal but not postmenopausal breast cancer risk in U.S. Women. J Nutr. 2003;133(5):1409–14.
19. von Roemeling CA, Marlow LA, Wei JJ, Cooper SJ, Caulfield TR, Wu K, et al. Stearoyl-CoA desaturase 1 is a novel molecular therapeutic target for clear cell renal cell carcinoma. Clin Cancer Res. 2013;19(9):2368–80.
20. Katz-Brull R, Rofsky NM, Morrin MM, Pedrosa I, George DJ, Michaelson MD, et al. Decreases in free cholesterol and fatty acid unsaturation in renal cell carcinoma demonstrated by breath-hold magnetic resonance spectroscopy. Am J Physiol Ren Physiol. 2005;288(4):F637–41.
21. Lawlor DA, Harbord RM, Sterne JAC, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. Stat Med. 2008;27(8):1133–63.
22. Nitsch D, Molokhia M, Smeeth L, DeStavola BL, Whittaker JC, Leon DA. Limits to causal inference based on Mendelian randomization: a comparison with randomized controlled trials. Am J Epidemiol. 2006;163(5):397–403.
23. Sekula P, Del Greco MF, Pattaro C, Köttgen A. Mendelian randomization as an approach to assess causality using observational data. J Am Soc Nephrol. 2016;27(11):3253–65.
24. Burgess S, Labrecque JA. Mendelian randomization with a binary exposure variable: interpretation and presentation of causal estimates. Eur J Epidemiol. 2018;33(10):947–52.
25. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-base platform supports systematic causal inference across the human phenome. Elife. 2018;7:e34408.
26. Borges MC, Haycock PC, Zheng J, Hemani G, Holmes MV, Davey Smith G, et al. Role of circulating polyunsaturated fatty acids on cardiovascular diseases risk: analysis using Mendelian randomization and fatty acid genetic association data from over 114,000 UK biobank participants. BMC Med. 2022;20(1):210.
27. Palmer TM, Lawlor DA, Harbord RM, Sheehan NA, Tobias JH, Timpson NJ, et al. Using multiple genetic variants as instrumental variables for modifiable risk factors. Stat Methods Med Res. 2012;21(3):223–42.
28. Papadimitriou N, Dimou N, Tsilidis KK, Banbury B, Martin RM, Lewis SJ, et al. Physical activity and risks of breast and colorectal cancer: a Mendelian randomisation analysis. Nat Commun. 2020;11(1):597.
29. Bowden J, Del Greco MF, Minelli C, Davey Smith G, Sheehan N, Thompson J. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. Stat Med. 2017;36(11):1783–802.
30. Mariosa D, Smith-Byrne K, Richardson TG, Ferrari P, Gunter MJ, Papadimitriou N, et al. Body size at different ages and risk of 6 cancers: a Mendelian randomization and prospective cohort study. J Natl Cancer Inst. 2022;114(9):1296–300.
31. Alcala K, Mariosa D, Smith-Byrne K, Nasrollahzadeh Nesheli D, Carreras-Torres R, Ardanaz Aicua E, et al. The relationship between blood pressure and risk of renal cell carcinoma. Int J Epidemiol. 2022;51(4):1317–27.
32. Riscal R, Bull CJ, Mesaros C, Finan JM, Carens M, Ho ES, et al. Cholesterol auxotrophy as a targetable vulnerability in clear cell renal cell carcinoma. Cancer Discov. 2021;11(12):3106–25.
33. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol. 2017;32(5):377–89.
34. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol. 2016;40(4):304–14.
35. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. Int J Epidemiol. 2017;46(6):1985–98.
36. Verbanck M, Chen C-Y, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet. 2018;50(5):693–8.
37. Hakimi AA, Reznik E, Lee C-H, Creighton CJ, Brannon AR, Luna A, et al. An integrated metabolic atlas of clear cell renal cell carcinoma. Cancer Cell. 2016;29(1):104–16.
38. Wettersten HI, Hakimi AA, Morin D, Bianchi C, Johnstone ME, Donohoe DR, et al. Grade-Dependent metabolic reprogramming in kidney cancer revealed by combined proteomics and metabolomics analysis. Cancer Res. 2015;75(12):2541–52.
39. Gebhard RL, Clayman RV, Prigge WF, Figenshau R, Staley NA, Reesey C, et al. Abnormal cholesterol metabolism in renal clear cell carcinoma. J Lipid Res. 1987;28(10):1177–84.

40. Holder AM, Gonzalez-Angulo AM, Chen H, Akcakanat A, Do K-A, Fraser Symmans W, et al. High stearoyl-CoA desaturase 1 expression is associated with shorter survival in breast cancer patients. Breast Cancer Res Treat. 2013;137(1):319–27.
41. Luis G, Godfroid A, Nishiumi S, Cimino J, Blacher S, Maquoi E, et al. Tumor resistance to ferroptosis driven by Stearoyl-CoA Desaturase-1 (SCD1) in cancer cells and fatty acid biding Protein-4 (FABP4) in tumor microenvironment promote tumor recurrence. Redox Biol. 2021;43:102006.
42. Hotamisligil GS, Bernlohr DA. Metabolic functions of FABPs–mechanisms and therapeutic implications. Nat Rev Endocrinol. 2015;11(10):592–605.
43. Peetla C, Bhave R, Vijayaraghavalu S, Stine A, Kooijman E, Labhasetwar V. Drug resistance in breast cancer cells: biophysical characterization of and doxorubicin interactions with membrane lipids. Mol Pharm. 2010;7(6):2334–48.
44. Callaghan R, van Gorkom LC, Epand RM. A comparison of membrane properties and composition between cell lines selected and transfected for multi-drug resistance. Br J Cancer. 1992;66(5):781–6.
45. Zong L, Pi Z, Liu S, Xing J, Liu Z, Song F. Liquid extraction surface analysis nanospray electrospray ionization based lipidomics for in situ analysis of tumor cells with multidrug resistance. Rapid Commun Mass Spectrom. 2018;32(19):1683–92.
46. Tyszka-Czochara M, Konieczny P, Majka M. Caffeic acid expands anti-tumor effect of metformin in human metastatic cervical carcinoma HTB-34 cells: implications of AMPK activation and impairment of fatty acids De novo biosynthesis. Int J Mol Sci. 2017;18(2):462.
47. Lisboa AQ, Rezende M, Muniz-Junqueira MI, Ito MK. Altered plasma phospholipid fatty acids and nutritional status in patients with uterine cervical cancer. Clin Nutr. 2008;27(3):371–7.
48. Ghamarzad Shishavan N, Mohamadkhani A, Ghajarieh Sepanlou S, Masoudi S, Sharafkhah M, Poustchi H, et al. Circulating plasma fatty acids and risk of pancreatic cancer: results from the Golestan cohort study. Clin Nutr. 2021;40(4):1897–904.
49. Ghamarzad Shishavan N, Masoudi S, Mohamadkhani A, Sepanlou SG, Sharafkhah M, Poustchi H, et al. Dietary intake of fatty acids and risk of pancreatic cancer: Golestan cohort study. Nutr J. 2021;20(1):69.
50. Matejcic M, Lesueur F, Biessy C, Renault AL, Mebirouk N, Yammine S, et al. Circulating plasma phospholipid fatty acids and risk of pancreatic cancer in a large European cohort. Int J Cancer. 2018;143(10):2437–48.
51. Harayama T, Riezman H. Understanding the diversity of membrane lipid composition. Nat Rev Mol Cell Biol. 2018;19(5):281–96.
52. Chen D, Chu B, Yang X, Liu Z, Jin Y, Kon N, et al. iPLA2β-mediated lipid detoxification controls p53-driven ferroptosis independent of GPX4. Nat Commun. 2021;12(1):3644.
53. Labonté ED, Pfluger PT, Cash JG, Kuhel DG, Roja JC, Magness DP, et al. Postprandial lysophospholipid suppresses hepatic fatty acid oxidation: the molecular link between group 1B phospholipase A2 and diet-induced obesity. FASEB J. 2010;24(7):2516–24.
54. Peng Z, Chang Y, Fan J, Ji W, Su C. Phospholipase A2 superfamily in cancer. Cancer Lett. 2021;497:165–77.
55. Feng Y, Wang B, Cao Y, He R. Two novel approaches targeting cancer cell membrane for tumor therapy. Med Hypotheses. 2013;80(4):380–2.
56. Baskar AA, Ignacimuthu S, Paulraj GM, Al Numair KS. Chemopreventive potential of beta-sitosterol in experimental colon cancer model–an in vitro and in vivo study. BMC Complement Altern Med. 2010;10:24.
57. Al-Ashaal HA, El-Sheltawy ST. Antioxidant capacity of hesperidin from citrus peel using electron spin resonance and cytotoxic activity against human carcinoma cell lines. Pharm Biol. 2011;49(3):276–82.
58. Yarla NS, Bishayee A, Sethi G, Reddanna P, Kalle AM, Dhananjaya BL, et al. Targeting arachidonic acid pathway by natural products for cancer prevention and therapy. Semin Cancer Biol. 2016;40–41:48–81.
59. Balaban S, Shearer RF, Lee LS, van Geldermalsen M, Schreuder M, Shtein HC, et al. Adipocyte lipolysis links obesity to breast cancer growth: adipocyte-derived fatty acids drive breast cancer cell proliferation and migration. Cancer Metab. 2017;5:1.
60. Laurent V, Toulet A, Attané C, Milhas D, Dauvillier S, Zaidi F, et al. Periprostatic adipose tissue favors prostate cancer cell invasion in an obesity-dependent manner: role of oxidative stress. Mol Cancer Res. 2019;17(3):821–35.
61. Yang D, Li Y, Xing L, Tan Y, Sun J, Zeng B, et al. Utilization of adipocyte-derived lipids and enhanced intracellular trafficking of fatty acids contribute to breast cancer progression. Cell Commun Signal. 2018;16(1):32.
62. Burgess S, Thompson SG. Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. Am J Epidemiol. 2015;181(4):251–60.
63. Smith GD, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. Int J Epidemiol. 2004;33(1):30–42.


## Publisher's note