Original Article

Exploring the causal relationship between omega-3 and omega-6 fatty acids and kidney cancer: a Mendelian randomization study

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Background: The causal link between kidney cancer and omega-3/6 (ω-3/6) fatty acids is yet to be clearly established. Therefore, the objective of our study was to investigate these potential causal relationships.

Methods: We conducted a two-sample Mendelian randomization (MR) analysis to investigate the possible causal association between ω-3/6 fatty acids and kidney cancer. We utilized the random effect inverse variance weighted (IVW) method as our primary analytical approach for the two-sample MR analysis. In addition, sensitivity analyses such as heterogeneity tests, pleiotropy analyses, and leave-one-out analyses were performed to assess the robustness of the MR analysis results.

Results: The IVW method showed statistically significant associations between ω-3 and ω-6 fatty acids and increased risk of kidney cancer. The result for ω-3 and ω-6 were [odds ratio (OR) =1.27; 95% confidence interval (CI): 1.04–1.55; P=0.02] and (OR =1.56; 95% CI: 1.17–2.09; P=0.003), respectively. Moreover, in the results of sensitivity analyses, no apparent horizontal gene pleiotropy nor heterogeneity was observed. After performing "the leave-one-out" sensitivity analysis of the data one by one, no single nucleotide polymorphisms (SNPs) sites in each instrumental variable (IV) were found to have greatly affected the disease outcome.

Conclusions: Elevated serum ω-3/6 fatty acids levels are causally associated with an increased risk of kidney cancer. Therefore, it is crucial to monitor dietary intake and properly intervene to lower these levels in those at risk of kidney cancer.

Keywords: Kidney cancer; omega-3 fatty acids (ω-3 fatty acids); omega-6 fatty acids (ω-6 fatty acids); causal relationship; Mendelian randomization (MR)

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Introduction

The polyunsaturated fatty acids (PUFAs), as part of the human diet, are seen as modifiable factors in lifestyle and may have an impact on cancer risk (1). Omega-3 (ω-3) and omega-6 (ω-6) are essential PUFA that play important roles in various physiological functions and have been linked to human health (2,3). The majority of studies indicate that ω-3 fatty acid have a protective effect against cancer risk, such as colorectal cancer, breast cancer and prostate cancer (4-12), while the consumption of ω-6 fatty acid may exacerbate this risk (13-16). However, there were few studies on the relationship between ω-3 and ω-6 fatty acids and kidney cancer.

Kidney cancer is a significant health concern worldwide, with it being one of the top ten most common cancers.

More than 300,000 new cases were diagnosed every year globally, and in 2020 alone, there were 431,288 new cases reported worldwide, of which 90% of kidney cancer were renal cell carcinoma (RCC) (17). Among them, clear cell renal cell carcinoma (ccRCC) is the predominant subtype of RCC, occupying 80% of RCC (18). Studies have shown that RCC, especially ccRCC, is generally considered as a metabolic disease. Among them, abnormal alterations in lipid metabolism have important effects in the occurrence and development of ccRCC (19-22). At present, a study found that ccRCC samples demonstrate increased levels of fatty acid desaturase 1 (FADS1), which is an essential enzyme involved in the metabolism of PUFAs (23). Moreover, another study has revealed that levels of PUFAs are elevated in ccRCC tumors compared to normal kidney tissues. And high-grade tumor specimens exhibit higher levels of PUFA-phospholipids than low-grade ones (24). Therefore, based on existing evidence, it can be inferred that the occurrence and progression of kidney cancer require a higher level of PUFAs. However, there is currently no specific research to definitively establish a causal relationship between PUFAs and kidney cancer.

To further explore the causality and strength of association between PUFAs and kidney cancer, we used Mendelian randomization (MR). The MR method was first introduced by Katan (25) in 1986, where genetic variation is utilized as an instrumental variable (IV) to evaluate the causal association between exposure and outcome. The underlying principal stemmed from Mendel's second law of inheritance, where alleles were randomly assigned and remained fixed at conception. This concept is similar to traditional randomized controlled trials (RCTs), where patients were randomized to either a treatment or control group. This method eliminates confounding factors and reverse causality by leveraging the random distribution of genetic variation. It mimics the randomization process of RCTs and avoids potential confounders that may disrupt traditional RCTs (26). Therefore, it is extensively employed for exploring causal relationships. We present this article in accordance with the STROBE-MR reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2058/rc).

Highlight box

Key findings

- Elevated serum omega-3/6 (ω-3/6) fatty acids levels are causally associated with an increased risk of kidney cancer.

What is known and what is new?

- Previous studies have indicated the relationship between ω-3/6 fatty acid and certain cancer.
- And this study further explores the relationship between ω-3/6 fatty acids and kidney cancer.

What is the implication, and what should change now?

- This finding emphasizes the significance of closely monitoring the dietary intake of ω-3/6 fatty acids and implementing appropriate interventions to lower their levels in individuals at high risk, with the aim of reducing the occurrence of kidney cancer.

Methods

Research design

The MR method was utilized in this research to acquire the association data with ω-3/6 fatty acids levels (exposure factors) through the genome-wide association studies (GWAS) database, and to select the single nucleotide polymorphisms (SNPs) closely related to ω-3/6. Then, the association data with kidney cancer (disease outcome) were obtained. Finally, five complementary MR methods were employed to analyze the potential causality between ω-3/6 fatty acid levels and kidney cancer using SNPs that are closely associated with both variables as IVs. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data sources

The GWAS data for ω-3/6 fatty acids were derived from a meta-analysis of 114,999 participants in 2020 with a vast set of 12,321,875 SNPs; GWAS data for kidney cancer patients were derived from the FinnGen Consortium. A total of 971 cases of kidney cancer and 174,006 controls were included in this study. All summary data for association analyses can be accessed by the public on the database website (https://gwas.mrcieu.ac.uk) for further details.

IVs selection

(I) R software was used to incorporate the screened SNPs sites with genome-wide significance based on the GWAS database; (II) the threshold for the LD parameter r^2 was set at 0.001, with a genetic distance of 10,000 kb, SNPs were selected with $P<5\times10^{-8}$ to guarantee between IVs to exclude the influence of LD on the results; (III) to ensure that the SNPs used in the study were not associated with kidney cancer, the researchers

retrieved the secondary phenotype of each SNP. We calculated the F value for each individual SNP and used the weak IVs bias test $F = \beta^2 exposure/SE^2 exposure$ (27), where β is the effect size of the exposure allele, and SE is the standard error of the exposure; (IV) the data were preprocessed to keep their effect alleles and effect quantities unified.

Statistical analysis

MR analysis

The research employed five different methods to estimate the causal effect between ω-3/6 fatty acids and kidney cancer, which included the inverse-variance weighted (IVW) method (28), MR-Egger regression method (29), weighted median method (30), simple mode method (31), and weighted mode method. The principle of the IVW method is based on the assumption that all IVs are effective, and weights are assigned to each IV based on the inverse of its variance. This method is considered one of the most classical methods in MR analysis and has been widely used in research. The MR-Egger and IVW methods take into account the presence of pleiotropy in IVs by incorporating an intercept term in weighted regression analysis. The intercept term is used to evaluate the magnitude of pleiotropy among IVs, while the slope provides an estimate of causal effect. The simple mode method can be understood as a weighted median estimator with identical weights, but it is not very efficient when there are significant differences in estimation accuracy for different genetic variations. The weighted median approach addresses the issue of notable disparities in estimation precision, similar to the IVW method, which typically employs the inverse weight of variance for each genetic variation. In contrast, the simple mode method necessitates that a minimum of 50% of the genetic variations are effective IVs, whereas the weighted median approach only requires a minimum of 50% of the weights attributed to genetic variations to be effective. By using the weighted median approach and ensuring that at least half of the SNPs were valid, we achieved estimates that were consistent with the final effect through a weighted mode approach. The above methods used R software version 4.3.0, "TwoSampleMR" package version 0.5.6, and test level $\alpha = 0.05$.

Sensitivity analysis

Heterogeneity test is used mainly to test the difference between each IV. If there are significant differences between different IVs, then, heterogeneity would be larger. When significant heterogeneity ($P<0.05$) was present, the random-effects IVW model was utilized to estimate MR; otherwise, the fixed-effects IVW model was applied. Horizontal pleiotropic test is used to mainly test whether there is horizontal pleiotropy between each IV. Horizontal pleiotropy is often indicated by the intercept term of the MR-Egger method. A small or near-zero intercept suggests the absence of horizontal pleiotropy. The leave-one-out sensitivity test involves calculating the combined effect of the remaining SNPs after removing one SNP at a time to assess their impact on the overall result. If there is little difference between the MR results obtained from the remaining SNPs analysis and those obtained from analyzing all SNPs, it indicates that the MR analysis is robust and not overly influenced by any single SNP.

Results

IV

There were 49 SNPs associated with ω-3 PUFA and kidney cancer (Table S1), and 53 SNPs were associated with ω-6 PUFA and kidney cancer (Table S2). In the tables, CHR represents the chromosomal information of genes; EAF represents the effect allele frequency; EA/OA represents the allele; β is the effect size of ω-3 or ω-6 associated SNPs; SE is the standard error of β value; P value indicates the degree of association of SNP with ω-3 or ω-6. For a single SNP in this study, the corresponding F-statistic distribution ranged from 26.163 to 6,315.263 and 26.909 to 545.974, respectively, and all F-statistic were >10, which indicated that there were no weak IVs bias, indicating that the results were reliable.

MR analysis between ω-3/6 PUFAs and kidney cancer

After eliminating linkage disequilibrium, a total of 49 SNPs that demonstrated a strong association with both ω-3 fatty acid and renal cancer were identified through screening, and the results of five MR analysis methods (IVW, MR-Egger, weighted median, simple mode, and weighted mode) were [odds ratio (OR) =1.27; 95% confidence interval (CI): 1.04–1.55; P=0.02], (OR =1.30; 95% CI: 0.98–1.72; P=0.08), (OR =1.21, 95% CI: 0.93–1.57; P=0.15), (OR =1.44; 95% CI: 0.70–3.01; P=0.33), (OR =1.30, 95% CI: 1.00–1.70; P=0.054), respectively (*Figure 1A*). Using the same method as above, the results of five MR analysis methods including IVW, MR-Egger, weighted median, simple mode and weighted mode were (OR =1.56; 95% CI: 1.17–2.09; P=0.003), (OR =1.72; 95% CI: 0.95–3.08; P=0.08), (OR =1.47; 95% CI: 0.92–2.33; P=0.10), (OR

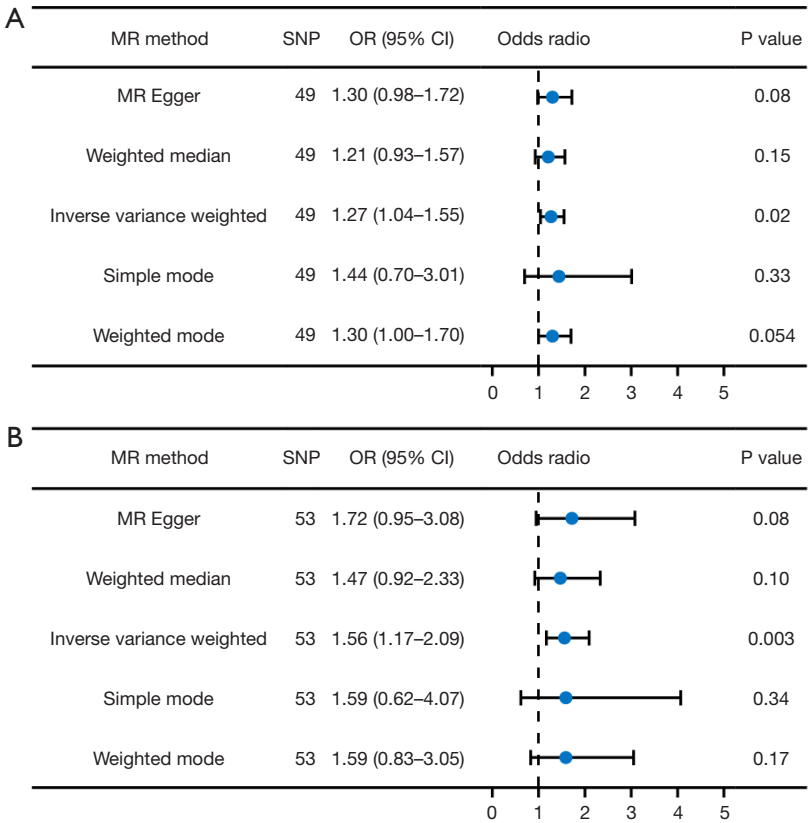

Figure 1 Forest plots of MR analysis. (A) Forest plot of MR analysis between omega-3 and kidney cancer. (B) Forest plot of MR analysis between omega-6 and kidney cancer. MR, Mendelian randomization; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

=1.59; 95% CI: 0.62–4.07; P=0.34), (OR =1.59; 95% CI: 0.83–3.05; P=0.17), respectively (*Figure 1B*). Among them, the IVW method was the primary analysis method for MR, and its results indicated a positive correlation between ω-3/6 fatty acids and kidney cancer, suggesting a causal relationship. According to the results of the IVW method, an increase of one standard deviation in ω-3 fatty acids level was associated with a 27% increase in the prevalence of kidney cancer (*Figure 2A*), while an increase of one standard deviation in ω-6 fatty acids level was associated with a 56% increase (*Figure 2B*).

Sensitivity analyses

Heterogeneity test

The results of heterogeneity test of 49 SNP IVs, MR-Egger regression, IVW method indicated no heterogeneity in each IV [P>0.05 (P=0.43, P=0.46)], thus we used the fixed-effect model to estimate the MR effect quantity. The results of the fixed-effect model showed that the OR values and 95% CI were both >1, and P<0.05 (OR =1.27; 95% CI: 1.04–1.55; P=0.02), demonstrating significant statistical significance, indicating a positive causal relationship between higher ω-3 fatty acids and the incidence of kidney cancer in the general population. By applying the same method mentioned above, the results indicated that there was no heterogeneity in MR SNPs between ω-6 fatty acids and kidney cancer [P>0.05 (P=0.47, P=0.50)]. The results obtained from the fixed-effect model further confirm a causal link between ω-6 fatty acids and kidney cancer (OR =1.56; 95% CI: 1.17–2.09; P=0.003).

Horizontal pleiotropy

The MR-Egger intercept between ω-3 PUFA and kidney cancer indicated that the intercept term was approximately 0, P>0.05 (intercept term =–0.003, P=0.82). The MR-Egger intercept between ω-6 PUFA and kidney cancer had the same result, with an intercept term also close to 0, P>0.05 (intercept term =–0.006, P=0.72). These findings imply

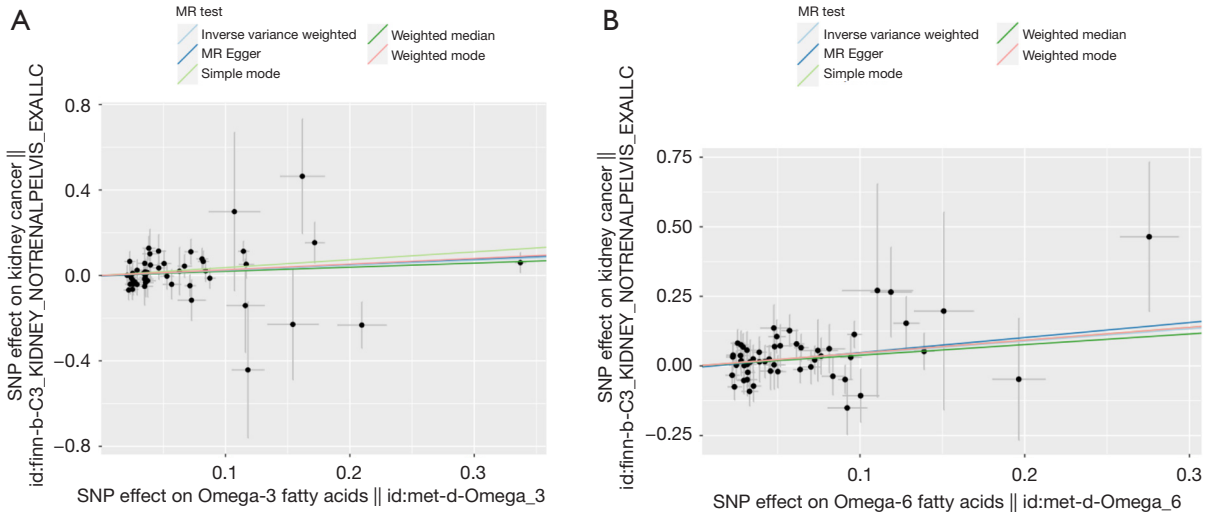

Figure 2 Scatter plots of MR analysis. (A) Scatter plot of MR analysis between omega-3 fatty acids and kidney cancer. (B) Scatter plot of MR analysis between omega-6 fatty acids and kidney cancer. MR, Mendelian randomization; SNP, single nucleotide polymorphism.

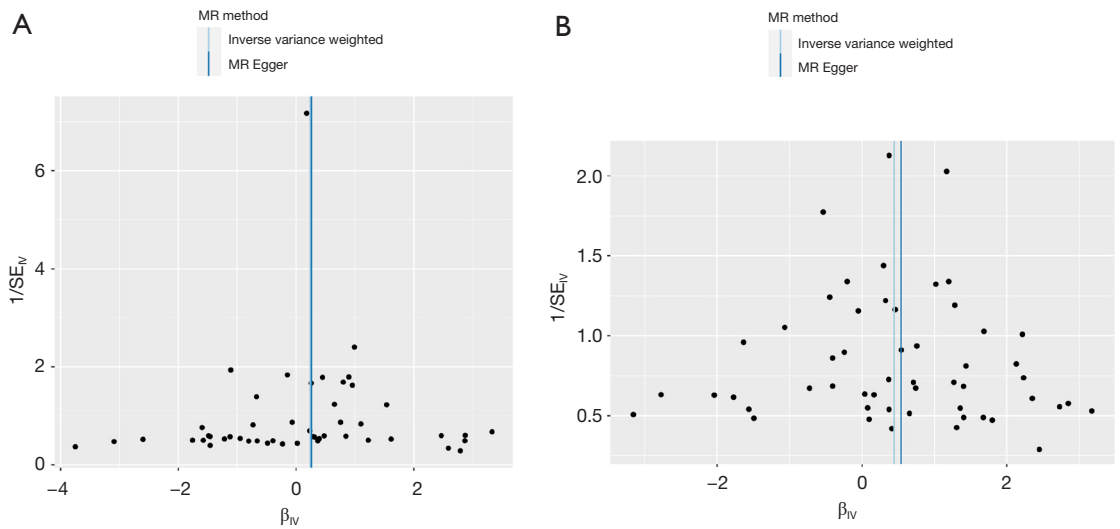

Figure 3 Funnel plots for MR analysis. (A) Funnel plot of MR analysis of omega-3 with kidney cancer. (B) Funnel plot of MR analysis of omega-6 with kidney cancer. MR, Mendelian randomization; SE, standard error.

that the results of this study are not affected by horizontal pleiotropy, which is a reassuring indication of the reliability of the data. Furthermore, the analysis of the funnel plot demonstrates that when using SNPs as IVs individually, the scatter of causal association effects appears to be distributed symmetrically, indicating the absence of potential bias in the results (*Figure 3*).

Leave-one-out analysis

After performing "the leave-one-out" sensitivity analysis of the data one by one, no SNPs sites in each IV were found to have greatly affected the disease outcome, and the analysis showed the robustness of MR results (*Figure 4*).

Discussion

In this research, a comprehensive GWAS database was utilized to discover 49 SNPs that have a strong association with both ω-3 PUFA and kidney cancer, along with 53 SNPs that have a significant correlation with both ω-6 PUFA and kidney cancer. To explore the cause-and-effect

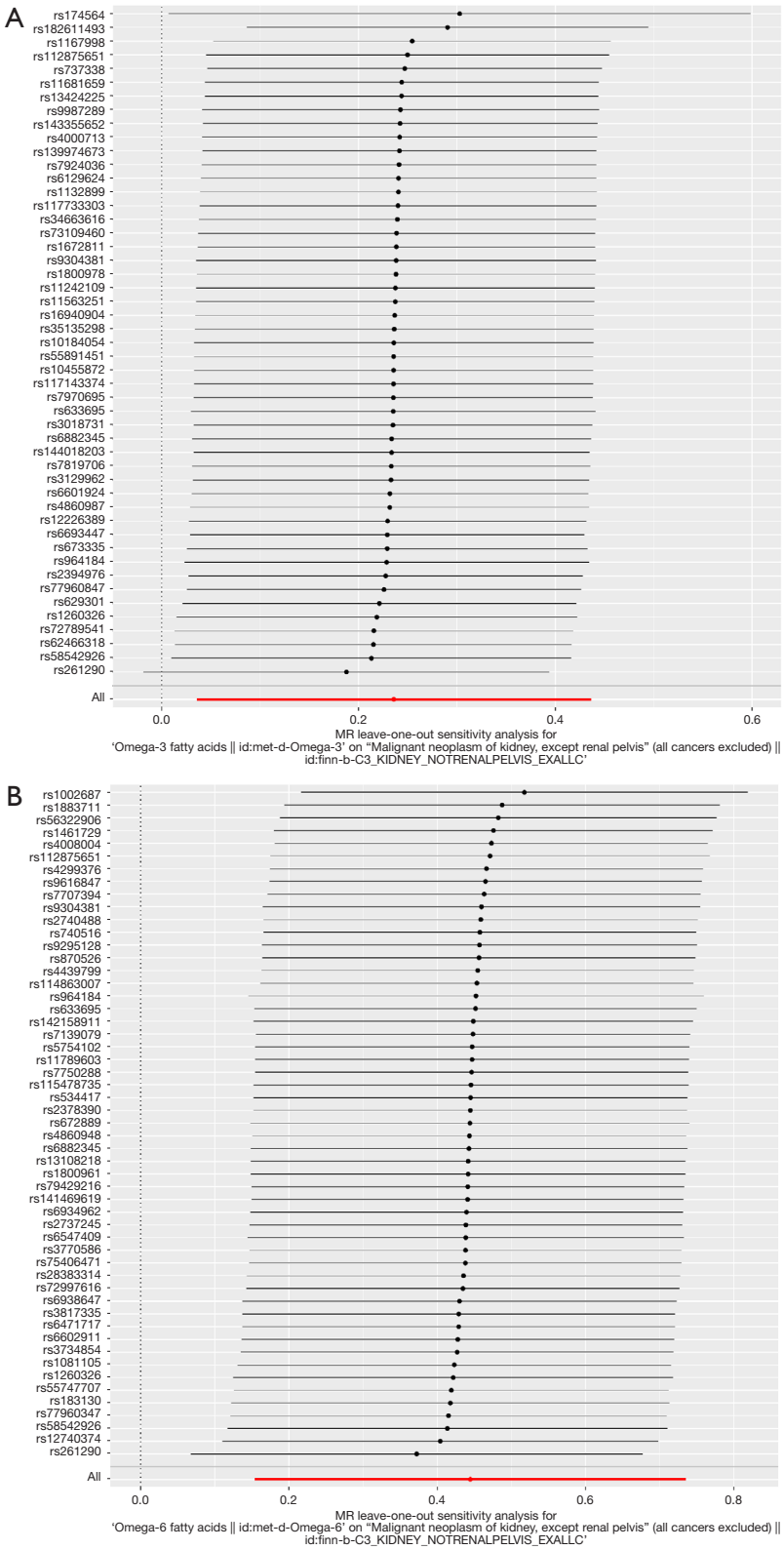

Figure 4 Result of leave-one-out sensitivity analysis. (A) Result of leave-one-out sensitivity analysis of omega-3. (B) Result of leave-one-out sensitivity analysis of omega-6. MR, Mendelian randomization.

connection between these factors, five complementary MR methods were employed. The results implied that there is a potential association between ω-3/6 fatty acids levels and kidney cancer, indicating that higher levels of ω-3/6 fatty acids could increase the chances of developing kidney cancer. This highlights the importance of monitoring dietary intake of ω-3/6 fatty acids to reduce the risk of kidney cancer.

There are several existing findings that could explain our results. Firstly, RCC possesses certain characteristics that set it apart from other types of cancer, with metabolism being the most prominent (32). One prominent character of RCC is the mutation of key genes involved in metabolic pathways. These mutations involve regulatory genes that were associated with aerobic glycolysis, lipid metabolism, and tryptophan metabolism (19,33-36). The mutations of these genes directly affect the metabolic processes of RCC cells, and changes in oxygen, energy, and nutrient metabolism pathways play a crucial role in the occurrence and development of RCC (33,37,38). Secondly, the key enzyme FADS1, involved in the metabolism of PUFAs, was found to be upregulated in ccRCC tissues (23). In addition, another study demonstrated that the levels of PUFAs were elevated in ccRCC compared to normal kidney tissue. Furthermore, the levels of PUFA-phospholipids were higher in high-grade tumor specimens than in low-grade tumor specimens (24). Thirdly, PUFAs play a critical role in various cell functions, including serving as essential components of cell membranes and impacting membrane fluidity. They also function as active molecules in cell signaling, inflammation, and cell death processes (39). PUFAs have been found to be associated with various and metabolic diseases, such as coronary heart disease, obesity, and malignant tumors, etc. (1,4,40). We know that kidney cancer, especially ccRCC, has been widely recognized as a metabolic disease. Therefore, based on the above studies, we believe that high levels of PUFAs are closely related to the occurrence and development of kidney cancer.

In addition, we believed that PUFAs were not only associated with the risk of kidney cancer, but also possibly related to its treatment and prognosis. Several recent studies collectively suggested that metabolic factors such as abnormal body fat, abnormal blood lipids, and abnormal local lipid metabolism in tumors were closely related to the occurrence and development of kidney cancer. The high or low levels of these factors were not only associated with the risk of kidney cancer, but can also be used to judge the prognosis of patients with kidney cancer (41-43). For example, it was known that there was a correlation between high body mass index (BMI) levels and an increased risk of kidney cancer (43). A meta-analysis showed that in RCC patients after undergoing nephrectomy, for every 5 kg/m^2 increase in BMI, their specific risk of RCC mortality decreased by 34% (44). Furthermore, in metastatic RCC (mRCC) patients treated with immunoncological (IO) drugs, another meta-analysis also showed that a higher BMI was associated with better survival (45). In addition, research by Van Hemelrijck *et al.* showed that the serum total cholesterol (TC) level was negatively associated with the incidence of RCC, and a lower level indicated a worse prognosis for RCC patients (46). At the same time, significant progress has been made in targeting lipid metabolism for kidney cancer treatment. Hypoxia-induced factor (HIF) played a crucial role in the pathophysiology of ccRCC, and they could influence tumorigenesis of ccRCC by controlling fatty acid metabolism (47). Multiple clinical trial studies have shown that the HIF-2α inhibitor MK-6482 and another HIF-2α antagonist PT2399 demonstrated significant therapeutic effects and good safety profiles in patients with ccRCC, making them potential treatment options for this type of cancer (48,49). In a population-based cohort study, the use of statin medications was found to lower the risk of RCC, with a risk ratio of 0.64 (95% CI: 0.38–0.87) (50). Further research has indicated that statin drugs can inhibit the growth of RCC cells by inducing cell cycle arrest and apoptosis in a dose and time-dependent manner (51). Therefore, based on the above studies, we believe that ω-3/6 fatty acids are not only associated with the risk of kidney cancer occurrence, but also related to its prognosis. However, more research is needed to confirm this, which will be the direction of our future studies.

This study had several notable strengths. Firstly, we provided novel insights into the causal relationship between ω-3/6 fatty acids and kidney cancer by utilizing MR analysis for the first time. Secondly, we implemented rigorous quality control measures and analysis methods, utilizing five complementary MR analytical techniques to explore the causal effect while also employing three different sensitivity analyses to ensure that our results were robust. Thirdly, by using MR methods, we were able to minimize the impact of confounding factors or reverse causality on our findings.

There are several limitations to consider regarding this study. Firstly, the sample population used in the research consisted solely of individuals of European ancestry. To expand upon our findings, it will be essential to include samples from Asia and Africa in future studies. Additionally,

the exact mechanism through which ω-3/6 fatty acids increases kidney cancer incidence remains unclear, and further research is necessary to verify our hypothesis.

Conclusions

In conclusion, the results of our study suggest that there is a causal relationship between elevated serum levels of ω-3 and ω-6 fatty acids and an increased risk of kidney cancer. Specifically, individuals with higher serum levels of these fatty acids are at an increased risk for developing kidney cancer. This finding highlights the importance of monitoring dietary intake these fatty acids, as well as considering proper interventions to reduce their levels in high-risk individuals to reduce the incidence of kidney cancer.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2058/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2058/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2058/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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