Received: 11 March 2024 | Accepted: 20 May 2024

DOI: 10.1111/srt.13781

ORIGINAL ARTICLE

WILEY

Genetically predicted TWEAK mediates the association between lipidome and Keratinocyte Carcinomas

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Hao Lei and Xin Chen are co-first authors.

Funding information
National Natural Science Foundation of China, Grant/Award Number: 82273541

Abstract

Background: Reports suggest that lipid profiles may be linked to the likelihood of developing skin cancer, yet the exact causal relationship is still unknown.

Objective: This study aimed to examine the connection between lipidome and skin cancers, as well as investigate any possible mediators.

Methods: A two-sample Mendelian randomization (MR) analysis was conducted on 179 lipidomes and each skin cancer based on a genome-wide association study (GWAS), including melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC). Then, Bayesian weighted MR was performed to verify the analysis results of two-sample MR. Moreover, a two-step MR was employed to investigate the impact of TNF-like weak inducer of apoptosis (TWEAK)-mediated lipidome on skin cancer rates.

Results: MR analysis identified higher genetically predicted phosphatidylcholine (PC) (17:0_18:2) could reduce the risk of skin tumors, including BCC (OR = 0.9149, 95% CI: 0.8667–0.9658), SCC (OR = 0.9343, 95% CI: 0.9087–0.9606) and melanoma (OR = 0.9982, 95% CI: 0.9966–0.9997). The proportion of PC (17:0_18:2) predicted by TWEAK-mediated genetic prediction was 6.6 % in BCC and 7.6% in SCC. The causal relationship between PC (17:0_18:2) and melanoma was not mediated by TWEAK.

Conclusion: This study identified a negative causal relationship between PC (17:0_18:2) and keratinocyte carcinomas, a small part of which was mediated by TWEAK, and most of the remaining mediating factors are still unclear. Further research on other risk factors is needed in the future.

KEYWORDS
genome-wide association study, lipidome, Mendelian randomization, single nucleotide polymorphisms, skin cancer

1 | INTRODUCTION

Skin cancers, such as melanoma, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are seen as some of the most harmful cancers in recent years.[1] It was estimated that about one-fifth of Americans will develop skin cancer, which causes nearly 15 000 deaths per year and more than 3 billion dollars in medical costs.[2] More than 80 % of melanomas relapse within the first 3 years after the appearance of the primary tumor.[3] The frequency of keratinocyte carcinoma recurrence after surgery varies.[4]Therefore, recognizing risk factors for skin cancer would help in understanding the development of the disease and suggesting strategies for prevention and treatment.[5]

Recently, the role of lipid metabolism has gained extensive attention in skin cancer, in addition to external factors such as ultraviolet radiation, immunosuppression, old age, chronic scarring and so on.[6] A study revealed that individuals with disrupted cholesterol production pathways are at a higher risk for developing skin cancer.[7] Lipidomic analysis of melanoma-resistant cells revealed dysregulation of fatty acid and cholesterol metabolism, as well as changes in lipid composition.[8] Mass spectrometry analysis revealed elevated levels of 12-hydroxyeicosatetraenoic acid in actinic keratoses and SCC.[9] Abnormal membrane sterol metabolism increases the risk of BBC.[10] Lipid peroxidation marker malondialdehyde was significantly increased in melanoma tissues and cutaneous SCC.[11] Refined lipidomes show improved accuracy in predicting diseases compared to standard lipid components.[12] Research has shown that specific lipid species can better predict the risk of cardiovascular disease compared to traditional lipids.[13] Another study showed that long-term wearing of N95 respirators may impair facial skin function and alter lipid composition, which indicated that lipidomic analysis is starting to be appreciated in dermatology.[14] Yet, the connection between lipid species and skin cancer is still not fully understood.

Additionally, there has been no exploration of potential pathways between lipidome and skin cancers. Prior research has shown that the TNF-like weak inducer of apoptosis (TWEAK) was upregulated in SCC and contributed to tumor advancement.[15] Moreover, the TWEAK pathway was upregulated in thick non-metastasizing melanoma, which could be a discriminant between metastasizing and non-metastasizing thick melanoma.[16] It has been found that soluble TWEAK could significantly increase the expression of lipogenesis, lipolysis, and lipid transport.[17] Consequently, TWEAK might be a potential mediator between lipidome and skin cancers.

The use of Mendelian randomization (MR) analysis, a developing epidemiological method, involves utilizing genetic variations as instrumental variables (IVs) to investigate causal connections between exposure factors and outcomes.[18] The advantage of MR is to reduce the influence of non-measurement errors or confounding factors and to avoid reverse causality.[19] This strategy can be used to study the biological effect of liposomes on skin cancer.

Given the mechanism of liposome in skin cancer has not been fully explored, and the role of TWEAK in it is unclear. This study hypothesized that liposomes could affect the occurrence of skin cancers at the genetic level. A two-sample, two-step MR study was conducted to investigate the causal relationship between lipidome and skin cancers, as well as to evaluate the role of TWEAK in mediating the effects of lipidome on skin cancer.

2 | METHODS

2.1 | Study design

The study initially conducted a two-sample MR analysis to explore the potential causal link between individual lipidome components and different types of skin cancer. Then, the intersection of lipid species with significant differences in the three types was used to conduct further analysis (Figure 1A). The definitions of total, indirect, and direct effects are shown in (Figure 1B).

2.2 | Genome-wide Association Study (GWAS) summary data sources

All the data utilized in this research was accessible to the public, and the individuals involved in the GWAS belonged to the European population. The summary data of lipidome was derived from the GWAS catalog uploaded by Linda Ottensmann, which included 179 lipid species and 7174 Finnish individuals. The lipid species are identified using the notation class name (sum of carbon atoms):(sum of double bonds);(sum of hydroxyl groups).[12] Summary data for BCC and SCC were collected from a GWAS meta-analysis, which involved 272 754 BCC cases and 2 558 560 controls, and 142 102 SCC cases and 2 681 591 controls of European descent from Europe, the United States, and Australia.[20] The summary data of Melanoma was retrieved from the UK Biobank, consisting of 4602 cases and 356 592 controls. The summary data of TWEAK level in blood was detected by Jing Hua Zhao, with a sample size of 14 824.[21] More details of data sources are shown in (Table S1).

2.3 | Selection of IVs

The study used the following criteria to screen the IVs: (1) Single nucleotide polymorphisms (SNPs) were closely linked to exposure; (2) SNPs were not linked to confounders of exposure and outcome; (3) SNPs could only impact outcome through exposure, with no direct link between SNPs and exposure.[22] SNPs associated with exposure were extracted by $p < 1\times10^{-5}$. In order to maintain the independence of IVs, SNPs that were in linkage disequilibrium ($r^2 < 0.001$; clumping window = 10 000 kb) were removed. Next, we isolated the IVs mentioned above within the SNPs related to exposure and aligned the exposure data with the outcome data to confirm that the SNPs' impact on exposure and outcome matched the same alleles. Palindromic and incompatible allele SNPs were removed. The F-statistic was also computed to address any bias resulting from weak IVs in the findings. It was calculated as F = R2(n-k-1)/[k (1-R2)], and F-statistic of < 10 is removed.

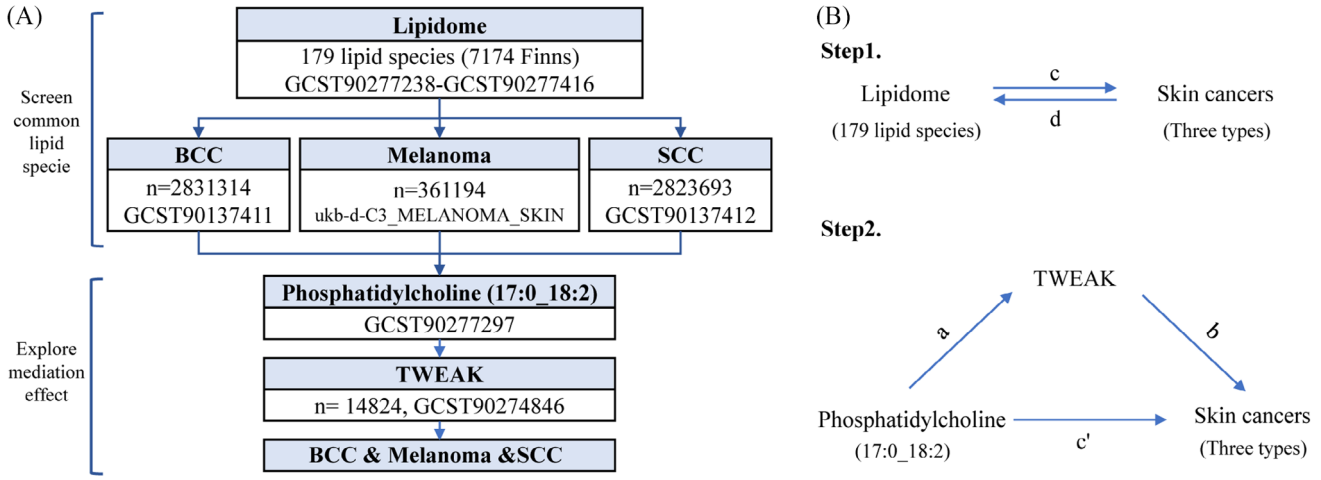

FIGURE 1 The design of this study. (A) The workflow of this study. (B) Step 1: The total effect between lipidome and skin cancers. c is the total effect using genetically predicted lipidome as exposure and each skin cancer as an outcome. d is the total effect using genetically predicted skin cancer as exposure and each lipidome as an outcome. Step 2: The total effect was decomposed into (1) indirect effect (a × b) using a two-step approach (where a is the total effect of each lipid on TWEAK, and b is the effect of TWEAK on each skin cancer (2) direct effect (c′ = c−a × b). TWEAK, TNF-like weak inducer of apoptosis.

2.4 | MR analysis

The causality of lipidome on three types of skin cancers was analyzed using the R package "TwoSampleMR".Five regression models were selected to determine the causation, such as Inverse variance weighted (IVW), MR-Egger, weighted median, simple mode, and weighted mode. The IVW test was the primary approach used due to its reliability among the methods employed, with significance defined as a p-value < 0.05. Then, Bayesian weighted MR (BWMR) was performed to verify the analysis results of the two-sample MR above.[23] Pleiotropic effects were tested using MR-Egger regression tests. If $p > 0.05$, even if the intercept term is not 0, the data does not exist pleiotropic. Next, Cochran's Q test was employed to examine the diversity between exposure and outcome. In order to further verify the results' stability, sensitivity analysis was conducted by the leave-one-out method. The calculation method of indirect effect is shown in (Figure 1B). In reverse MR analysis, each skin cancer was treated as exposure and the exact lipid species was the outcome, which is to determine the unidirectionality of causality.

3 | RESULTS

3.1 | Association of lipidome with skin cancers

It performed a two-sample MR analysis between each lipid species and each skin cancer. In 179 lipid species, 22 lipid species were significant between lipidome and BCC,38 lipid species in SCC, and 11 lipid species in melanoma by IVW test. When verified by BWMR, it changed into 14 lipid species in BCC, 24 lipid species in SCC, and 9 lipid species in melanoma (Table S2). As a result of taking the intersection, It determined that phosphatidylcholine (PC) (17:0_18:2) is the common lipidome (GCST90277297), which is the focus of subsequent analysis. In BCC and SCC, 16 SNPs were included as IVs, while in melanoma, 12 SNPs were included as IVs (Table S3). The IVW test indicated strong evidence for the negative association of PC (17:0_18:2) on skin cancers (BCC-OR = 0.9149, 95% CI: 0.8667–0.9658; SCC-OR = 0.9343, 95% CI: 0.9087–0.9606; melanoma -OR = 0.9982, 95% CI: 0.9966–0.9997) (Figure 2). Cochran's Q test did not reveal any heterogeneity, and the pleiotropy was not detected using the MR-Egger regression test (Table S4). The leave-one-out showed that the results were sensitive (Figures S1–S3). The inverse MR analysis confirmed that the causal relationship between PC (17:0_18:2) and skin cancers was unidirectional (Figure 2 and Table S5).

3.2 | Association of lipidome with TWEAK

25 genome-wide significant SNPs were extracted as IVs (Table S3). It is shown that there was a negative association of lipidome on TWEAK level in blood by IVW test (OR = 0.9427, 95% CI: 0.8976–0.9900; $p = 0.0181$) (Figure 2). Cochran's Q test indicated the absence of heterogeneity ($Q = 24.3910$, $p = 0.3824$), and no evidence of pleiotropy was observed with the MR-Egger regression test ($p = 0.5180$) (Table S6). The leave-one-out analysis demonstrated that the MR results remained consistent for the remaining SNPs after each SNP was removed, indicating the sensitivity of the findings (Figure S4).

3.3 | Association of TWEAK with skin cancers

A total of 28 genome-wide significant SNPs were extracted as IVs when examining the connection between TWAEK and BCC or SCC (Table S3). The results showed that TWEAK was positively correlated with the occurrence of BCC (OR = 1.1051, 95% CI: 1.0401–1.1742; $p = 0.0012$), as well as SCC (OR = 1.0917, 95% CI: 1.0431–1.1425; $p = 0.0002$)

Exposure and outcome	nSNP	beta	OR(95%CI)	P Value
Phosphatidylcholine (17:0_18:2) on BCC	16	−0.0889	0.9149(0.8667−0.9658)	0.0013
BCC on Phosphatidylcholine (17:0_18:2)	157	0.0084	1.0084(0.9289−1.0947)	0.8414
Phosphatidylcholine (17:0_18:2) on TWEAK	25	−0.0590	0.9427(0.8976−0.9900)	0.0181
TWEAK on BCC	28	0.1000	1.1051(1.0401−1.1742)	0.0012
Phosphatidylcholine (17:0_18:2) on SCC	16	−0.0679	0.9343(0.9087−0.9606)	<0.0001
SCC on Phosphatidylcholine (17:0_18:2)	157	−0.0037	0.9963(0.9224−1.0761)	0.9251
TWEAK on SCC	28	0.0877	1.0917(1.0431−1.1425)	0.0002
Phosphatidylcholine (17:0_18:2) on Melanoma	12	−0.0018	0.9982(0.9966−0.9997)	0.0168
Melanoma on Phosphatidylcholine (17:0_18:2)	36	1.9889	-	0.4818
TWEAK on Melanoma	18	0.0010	1.001(0.9992−1.0028)	0.2658

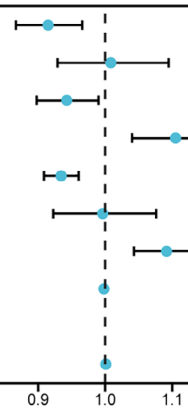

FIGURE 2 Association of TWEAK with lipidome and skin cancers. IVW test of melanoma on Phosphatidylcholine (17:0_18:2) is difficult to visualize (OR = 7.3078, 95% CI: 0.0286–1866.0478). IVW, Inverse variance weighted; TWEAK, TNF-like weak inducer of apoptosis.

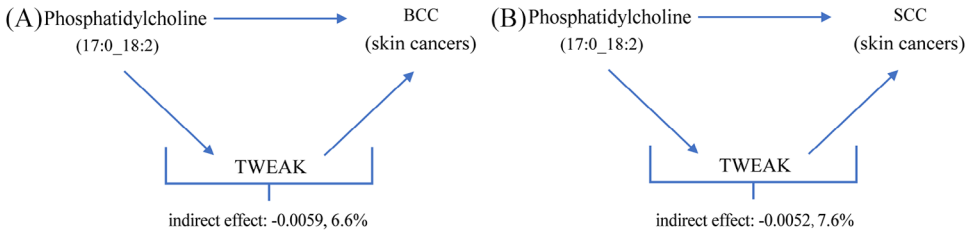

FIGURE 3 Schematic diagram of the TWEAK mediation effect. TWEAK, TNF-like weak inducer of apoptosis.

(Figure 2). Cochran's Q test did not detect any heterogeneity, and pleiotropy was not observed with the MR-Egger regression test (Table S6). The leave-one-out showed that the results were sensitive (Figures S5,S6). In contrast, it appears that TWEAK was not causally related to melanoma (OR = 1.0010, 95% CI: 0.9992–1.0028; $p = 0.2658$) (Table S6).

3.4 | Indirect effect of TWEAK between lipidome and skin cancers

TWEAK was analyzed as a mediator of the causality from PC (17:0_18:2) to each skin cancer. Elevated PC (17:0_18:2) levels were found to be linked to lower TWEAK levels in blood, which in turn were linked to a reduced likelihood of developing BCC or SCC. In total, the indirect effect of TWEAK between PC (17:0_18:2) and BCC was negative (−0.0059, proportion:6.6%), as well as SCC (−0.0052, proportion:7.6%) (Figure 3). The causal relationship between PC (17:0_18:2) and melanoma was not mediated by TWEAK.

4 | DISCUSSION

This study found that PC (17:0_18:2) was negatively associated with BCC, SCC, and melanoma. Furthermore, TWEAK can mediate the causal relationship between PC (17:0_18:2) and keratinocyte carcinomas, including BCC and SCC. This study is believed to be the first to explore the causal relationship between PC (17:0_18:2) and skin cancers by MR analysis, while also highlighting TWEAK as a mediator.

PC, a crucial component of the cell membrane, is produced from scratch through the Kennedy pathway, and disruptions in this process have been linked to numerous illnesses, such as cancer.[24] The findings are consistent with previous research. Maciel E et al. showed that long-term exposure to UVA can affect the phospholipid profile of melanoma cells and decrease PC levels.[25] In another study, systemic treatment with PC liposomes inhibited tumor growth in mice carrying skin tumors.[26] Deletion of p73 exon 12 leads to decreased PC levels and p73α1 isoform conversion, resulting in strong tumor suppressor activity.[27] It has also been observed that PC levels are negatively associated with tumorigenesis in many non-skin tumors. PC could trigger cell death in liver cancer cells in a way that depends on the dosage, and comparable outcomes have been seen in liver cancer animal models as well.[28] Patients with endometrial cancer had lower levels of three single PCs based on electrospray ionization-tandem mass spectrometry.[29] Compared with breast epithelial cells, PC levels in breast cancer cells were significantly decreased.[30] In a prospective cohort study, Yin MZ et al. identified low levels of PC and high levels of Lys PC as novel biomarkers for cervical SCC.[31] In recent years, lipidomic has gained popularity, which is helpful in understanding the relationship between PC and cancer. Research has demonstrated that there are nine types

of polyunsaturated PC that vary between patients with oral SCC and the control group. Among these, four decreases as cancer progresses, specifically PC (32:2), PC (34:4), and PC (36:7).[32] In some cases, this correlation is positive. Ishikawa S et.al. found that the levels of PC (16:0/18:1) and (16:0/18:2) were markedly elevated in thyroid papillary cancer than in normal thyroid tissue, as revealed by tandem mass spectrometry analysis.[33]

TWEAK was found to be a mediator between PC (17:0_18:2) and keratinocyte carcinomas. On the one hand, PC (17:0 _ 18:2) was negatively correlated with TWEAK. Few studies have examined their relationship before. Therefore, we will focus on the relationship between TWEAK and serum lipids. Results from a case–control study show that lower levels of soluble TWEAK concentrations are linked to NAFLD independently, aligning with the fact that TWEAK helps decrease lipid buildup in liver cells.[34] Findings from the population-based Study of Health in Pomerania indicated a negative correlation between TWEAK and HDL2 Apo-A1, HDL3 Apo-A1, or HDL2 Apo-A2.[35] TWEAK was found to prevent lipid accumulation in a dose-dependent manner without any harmful effects on cells.[36] TWEAK and Fn14 were expressed within atherosclerotic plaques in regions abundant with macrophages and foam cells, facilitating lipid uptake by macrophages.[37] It was found in animal models that TWEAK exacerbated the inflammatory response associated with a high-fat diet.[38] On the other hand, TWEAK was positively correlated with keratinocyte carcinomas. A lower level of TWEAK expression was found in normal tissues, while a high level was found in many tumors and metastases, such as colorectal, esophageal, and bladder cancers.[39–41] Studies have shown that TWEAK/Fn14 interaction promoted the proliferation of SCC cells by activating cIAP1 signaling.[42] Also, Animal and cell models have shown that TWEAK/Fn14 signaling contributed to the progression of SCC.[15] Of course, there are some discrepant findings. The down-regulation of TWEAK in the skin might be an early indicator of keratinocyte differentiation disorder associated with inflammatory and neoplastic skin diseases.[43] In their study, Zou H et.al. found that lowering TWEAK levels could enhance the advancement and infiltration of cervical cancer, potentially offering novel targets for treating the disease.[44]

This study has a significant benefit in providing ample evidence to establish the causal relationship between lipidomes and skin cancers. Simultaneously, based on the findings of the lipidomic analysis, a direct link has been established between refined lipids and keratinocyte carcinomas. This connection enhances our comprehension of the correlation between various lipid elements and illnesses, aiding in the identification of more precise treatment targets. In addition, this study found the mediator of PC (17:0_18:2) and keratinocyte cancers, which provides more options for us to intervene in carcinomas.

However, this study has several limitations. The study primarily was based on European populations, which restricted the generalization of the findings. People in other regions need corresponding GWAS datasets. Second, the GWAS data originated from the publicly available database. The details of the patient's age, gender, and severity of the disease remain unclear, and only a relatively macro analysis can be performed. Third, when choosing IVs, addressing linkage disequilibrium and identifying pleiotropy may decrease the impact of internal factors, but cannot completely eradicate them. Fourth, the causal relationship is based on a public database, and more prospective cohort studies are needed to verify the reliability of the causality. Finally, this study showed that the gene prediction rate of TWEAK-mediated PC (17:0 _ 18:2) is about 7 %, which is relatively low. More research is needed to quantify other mediating factors.

5 | CONCLUSION

In conclusion, this study identified a negative causal relationship between PC (17:0_18:2) and keratinocyte carcinomas, a small part of which was mediated by TWEAK, and most of the remaining mediating factors are still unclear. Further research on other risk factors is needed in the future.

ACKNOWLEDGMENTS

We are grateful to all the investigators who provided the publicly available data. This study was supported by the National Natural Science Foundation of China (82273541).

CONFLICT OF INTEREST STATEMENT

There are no competing interests.

DATA AVAILABILITY STATEMENT

The authors verify that the data supporting the findings of this study are available within the article and its supplementary materials.

ETHICS STATEMENT

There is no ethics involved.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lei H, Chen X, Bai R, et al. Genetically predicted TWEAK mediates the association between lipidome and Keratinocyte Carcinomas. *Skin Res Technol*. 2024;30:e13781. https://doi.org/10.1111/srt.13781