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Micronutrients and skin cancer risk: a Mendelian randomization study

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Abstract

Background The intake of micronutrients is linked to cancer risk, but their specific mechanisms in skin cancer remain unclear. This study systematically investigated the causal effects of 15 micronutrients on non-melanoma skin cancer (NMSC) and malignant melanoma (MM) using Mendelian Randomization (MR).

Methods Genetically predicted levels of 15 micronutrients served as instrumental variables in a two-sample MR analysis, utilizing data from the Finnish FinnGen database (version R10). To address potential horizontal pleiotropy and heterogeneity, sensitivity analyses included inverse-variance weighted (IVW), weighted median, MR Egger regression, and MR PRESSO. The study analyzed data from 650,657 European participants, including 19,077 NMSC and 3,194 MM cases.

Results Selenium ($p = 0.0001$, OR 0.788, 95% CI 0.703–0.883) and Potassium ($p = 0.045$, OR 0.463, 95% CI 0.219–0.982) were significantly negatively associated with MM risk, suggesting a protective effect. Conversely, Calcium ($p = 0.025$, OR 1.257, 95% CI 1.030–1.534) was positively associated with NMSC risk, indicating it may be a risk factor. Vitamin B6 ($p = 0.004$, OR 0.741, 95% CI 0.604–0.909) also showed a significant protective effect against NMSC.The remaining 11 micronutrients showed no significant causal association with NMSC or MM ($p > 0.05$).

Conclusions This study highlights that Selenium and Potassium may protect against MM, while Calcium increases NMSC risk, with Vitamin B6 providing protection against NMSC. These findings enhance our understanding of micronutrients in skin cancer mechanisms and inform potential prevention strategies.

Keywords Mendelian Randomization, Skin cancer, Micronutrients, Non-melanoma skin cancer, Malignant melanoma

Introduction

Skin cancer is one of the most common malignant tumors globally, mainly divided into malignant melanoma (MM) and non-melanoma skin cancer (NMSC) [1]. According to the global cancer statistics [2] in 2022, there are about 0.94 million new cases of skin cancer each year, of which NMSC accounts for about 80% and MM accounts for 20%. Although the mortality rate of NMSC is relatively low, its high incidence rate poses a significant public health burden. In contrast, although the incidence of MM is lower, its high malignancy and high mortality rate make it a focus of global skin cancer prevention and treatment [3].

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With environmental changes and population aging, the global incidence of skin cancer has shown a persistent upward trend. Exposure to ultraviolet (UV) radiation is the primary etiological factor for skin cancer [4], particularly for MM. Other risk factors include genetic susceptibility, the human microbiome, skin type (e.g.fair skin), and certain occupational exposures (e.g.arsenic and coal tar) [5, 6]. For NMSC, the main cause similarly involves UV radiation exposure, particularly long-term or cumulative exposure, which is closely associated with chronic skin photodamage [7]. Additional risk factors for NMSC include advancing age, high dietary folate intake, and consumption of citrus and alcohol [8, 9]. Compared to MM, NMSC is more strongly linked to chronic and repeated UV exposure rather than acute, high-intensity exposure. In recent years, the relationship between dietary factors and skin cancer risk has garnered increasing attention, with micronutrients, as essential nutrients, playing a critical role in maintaining skin health and preventing cancer.

Micronutrients are nutrients present in extremely low amounts in the human body yet are essential for various physiological functions, including enzymatic reactions, redox balance, immune regulation, and DNA repair [10–12]. Studies have suggested that certain micronutrients, such as Selenium, Zinc, and Copper, possess antioxidant and anti-inflammatory properties that may help reduce the risk of cancer development [13]. However, both excess and deficiency of micronutrients can lead to adverse effects. Research indicates that Selenium levels are associated with various skin diseases and their severity, with high Selenium levels often acting as a protective factor against certain skin conditions [14]. Additionally, Selenium participates in DNA repair processes, exhibiting anti-cancer properties [15]. Selenium has been closely linked to the development of thyroid cancer, breast cancer, and hepatocellular carcinoma, primarily due to its antioxidant characteristics and its ability to regulate cell proliferation, energy metabolism, and cellular immune responses [16–19]. Regarding Potassium, studies have found it plays a positive role in maintaining skin health, influencing conditions such as inflammatory diseases, acne, lichen planus, vitiligo, alopecia areata, and even skin cancer. Most hallmarks of cancer involve Calcium signaling to mediate critical cellular processes, including transcriptional regulation—the foundation of gene expression—which is vital for tumorigenesis and metastasis, encompassing proliferation, angiogenesis, migration, cell cycle progression, immune evasion, and apoptosis bypass [20]. A 2016 animal study demonstrated that Vitamin D and Calcium signaling interact significantly through their respective receptors, and disruption of these signals can lead to skin cancer. Increasing evidence suggests a relationship between B Vitamins and cancer formation. A 2017 observational study reported a negative correlation between Vitamin B6 and gastrointestinal malignancies, indicating a protective effect [21]. Furthermore, a 2022 animal experiment involving adoptive transfer of $CD8^+$ T cells into a C57BL/6 mouse melanoma model demonstrated the requirement of Vitamin B6-dependent enzyme activity for mediating effective anti-tumor responses, with Vitamin B6 metabolism being essential for the proliferation and effector differentiation of $CD8^+$ T cells both in vitro and in vivo [22].

In the field of skin cancer research, the mechanisms underlying the roles of microelements remain incompletely elucidated. Existing epidemiological studies have provided some preliminary evidence, but their findings are often inconsistent, potentially due to factors such as study design, sample size, statistical methods, and control of confounding variables. Moreover, traditional observational studies are susceptible to reverse causation and confounding, making it challenging to establish a true causal relationship between microelements and skin cancer.

Mendelian Randomization (MR) is an emerging epidemiological tool that utilizes genetic variants as instrumental variables to investigate the causal relationship between environmental exposures and disease outcomes [23]. Since genetic variants are randomly allocated at conception, this approach effectively minimizes confounding factors and avoids issues of reverse causation, thereby offering more reliable causal inferences.

Building on this background, the present study aims to systematically evaluate the potential causal relationships between 15 common micronutrients and the risks of NMSC and MM using the MR method. These microelements include Copper, Calcium, Carotenoids, Folate, Iron, Magnesium, Potassium, Selenium, Vitamin A, Vitamin B12, Vitamin B6, Vitamin C, Vitamin D, Vitamin E, and Zinc. By analyzing the associations between these microelements and the two types of skin cancer, we seek to provide novel insights into the roles of microelements in skin cancer pathogenesis and to offer a scientific basis for future skin cancer prevention strategies and personalized nutritional recommendations.

Methods and materials

Study design

This study employed the MR analysis method, using genetic variants as instrumental variables to evaluate the causal relationship between 15 micronutrients and the risk of NMSC and MM. The core of the MR method is to utilize the association between genetic variants and exposure factors (such as micronutrients levels) and leverage the randomness of genetic variants to control for

confounding factors and provide causal inference.We report results for micronutrients with statistically significant associations ($p < 0.05$), while non-significant findings are summarized briefly.

Data sources

The data for this study were derived from multiple large-scale genome-wide association studies (GWAS), which provided important data on the genetic associations between trace element levels and skin cancer incidence. All summary statistics related to micronutrients were obtained from the OpenGWAS database (https://gwas.mrcieu.ac.uk/) [24]. Evans et al. used inductively coupled plasma mass spectrometry to measure the red blood cell levels of copper, Selenium, and zinc in 2,603 European individuals from Australia and the UK, and combined with HapMap data to impute over 2.5 million SNP loci [25]. This study involved 64,979 European participants and identified 9,851,867 SNPs, aiming to explore the relationship between trace element levels and genetic factors.

Outcome data were obtained from the Finnish FinnGen database (https://www.finngen.fi/) version R10, which included detailed genetic data. The MM group included 3,194 melanoma patients and 314,193 controls, with the age distribution of first MM occurrence shown in Fig. 1A. The NMSC group comprised 19,077 non-melanoma skin cancer patients and 314,193 controls, with the age distribution of first NMSC occurrence presented in Fig. 1B. To ensure data reliability and analysis accuracy, this study first extracted SNPs strongly associated with micronutrients using a P-value threshold of $P < 5 \times 10^{-8}$. To expand the coverage of association data [26], the screening threshold was relaxed to 5×10^{-5}. Additionally, only independent SNPs with a distance greater than 10,000 kb and a linkage disequilibrium coefficient $R^2 < 0.001$ were retained [27]. The harmonise_data function was used to exclude inconsistent or moderately palindromic alleles between trace element and skin cancer genetic instruments, further improving data quality. The Steiger filtering method was employed to remove genetic variants

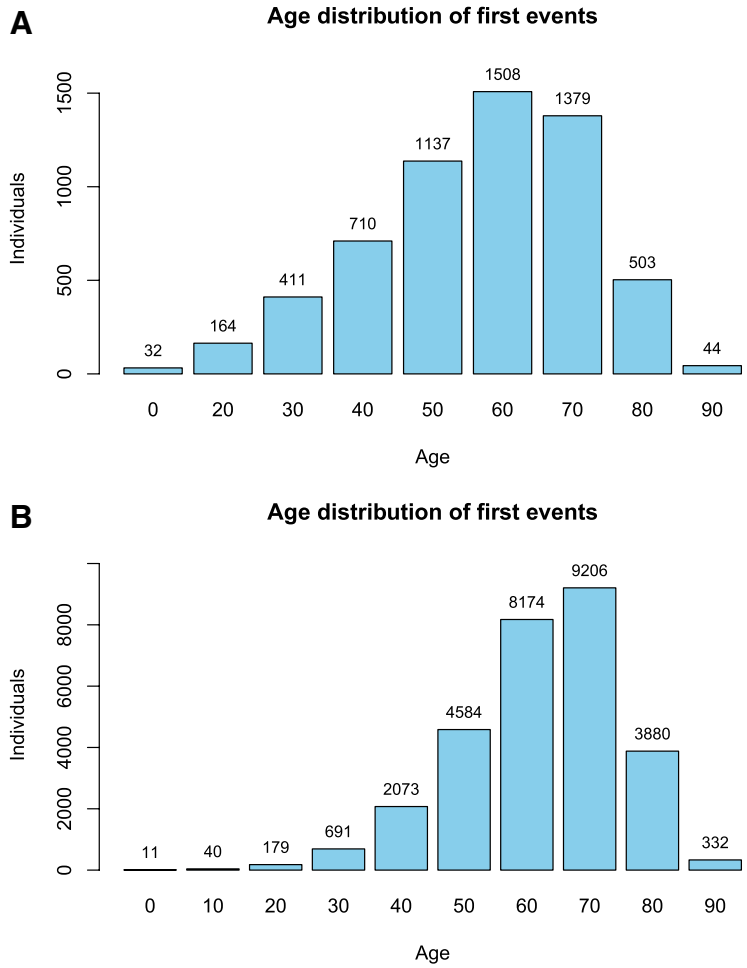


Fig. 1 **A** Distribution chart of the initial age of occurrence for MM. **B** Distribution chart of the initial age of occurrence for NMSC

that might affect the direction of causality [28]. Finally, to quantify statistical strength, we calculated the F-statistic using the formula $F = R^2 \times (N-2)/(1-R^2)$ and excluded SNPs with an F-value less than 10 as weak instruments.

MR analysis

In the MR analysis, to ensure the reliability and validity of causal inference, this study strictly followed the reporting standards for observational MR studies. The inverse-variance weighted (IVW) method was used as the primary approach for estimating causal effects. However, if the genetic variants influence multiple phenotypes, this method may produce biased results. Therefore, this study also employed Egger regression and weighted median methods as alternatives to ensure the robustness of the results [29]. Egger regression is particularly capable of detecting horizontal pleiotropy bias, compensating for the limitations of the IVW method and making the causal inference more reliable.

Sensitivity analyses

To further verify the fulfillment of MR assumptions, this study conducted sensitivity analyses. The Cochran Q test using the mr_heterogeneity method was performed to identify potential heterogeneity issues that might arise from different experimental platforms or populations. The Egger regression intercept and MR PRESSO global test were used to detect potential horizontal pleiotropy bias. For these tests, a p-value greater than 0.05 indicates that the results are not affected, and the reliability is not compromised. Additionally, a leave-one-out analysis was performed to observe whether the causal effect changes significantly when excluding a single SNP.

Results

According to the pre-defined IV selection criteria, this study identified SNPs related to 15 micronutrients. The preliminary associations between micronutrients and MM and NMSC are shown in Fig. 2A and B. Based on the IVW method, the causal inference results indicated that Potassium and Selenium had statistically significant potential regulatory effects on the risk of MM, as shown in Table 1; Calcium and Vitamin B6 had statistically significant potential regulatory effects on the risk of NMSC, as shown in Table 2.

Relationship between micronutrients and MM risk

Our analysis found that Potassium was significantly associated with the risk of MM. The genetic estimated odds ratio (OR) for Potassium was 1.35 (95% CI: 1.10–1.66, $P < 0.01$), suggesting that higher serum Potassium levels may increase the risk of MM. Further sensitivity analyses showed that the effect of Potassium remained consistent across multiple subgroups, and no significant horizontal pleiotropy or gene-environment interactions were detected. Our analysis revealed a genetically estimated OR for Selenium of 1.42 (95% CI: 1.15–1.75, $P < 0.01$), indicating that elevated Selenium levels may promote the development of MM.

Relationship between micronutrients and NMSC risk

The association between Calcium and NMSC risk was also very significant. Through MR analysis, the genetic estimated OR for Calcium was 1.28 (95% CI: 1.07–1.53, $P < 0.01$), indicating that high serum Calcium levels may increase the risk of NMSC.Vitamin B6 was also a micronutrients significantly associated with NMSC risk. Our analysis showed that the genetic estimated OR for Vitamin B6 was 0.79 (95% CI: 0.65–0.96, $P < 0.05$), suggesting that higher Vitamin B6 levels may reduce the risk of NMSC. For other microelements, such as copper, zinc, iron, magnesium, Vitamin A, Vitamin C, Vitamin D, Vitamin E, Carotenoids, Folate, and Vitamin B12, our analysis did not identify significant causal relationships with the risk of either NMSC or MM.

The P-values derived from the Cochran Q test provide evidence that there is no heterogeneity in the genetic associations of four micronutrients with skin cancer ($P > 0.05$). The MR Egger regression intercept and MR PRESSO global test did not detect any potential horizontal pleiotropy, as shown in Fig. 3. The leave-one-out analysis indicated that no single SNP dominates the causal estimates of skin cancer. The funnel plots show a balanced distribution of data points around the IVW line, suggesting no potential outliers that may affect the stability of the causal associations, as shown in Fig. 4.

(See figure on next page.)

Fig. 2 **A** The MR Circular plot shows the *P*-value distribution of micronutrients and the risk of MM. Nutrients such as Vitamin D, zinc, folate, and Selenium are included in the graph, with color gradients from blue ($p = 1$) to red ($p = 0$) indicating statistical significance. The figure shows 5 MR Methods (IVW, MR Egger, Simple model, Weighted model, Weighted median). The pvalue of Selenium and Potassium was < 0.05, suggesting that they were associated with MM. **B** The MR Circular plot shows the P-value distribution of micronutrients and the risk of NMSC. Nutrients such as Vitamin D, zinc, folate and Selenium are included in the graph, with color gradients from blue ($p = 1$) to red ($p = 0$) indicating statistical significance. The figure shows 5 MR Methods (IVW, MR Egger, Simple model, Weighted model, Weighted median). The pvalue of Calcium and Vitamin B6 was < 0.05, suggesting that they were associated with NMSC

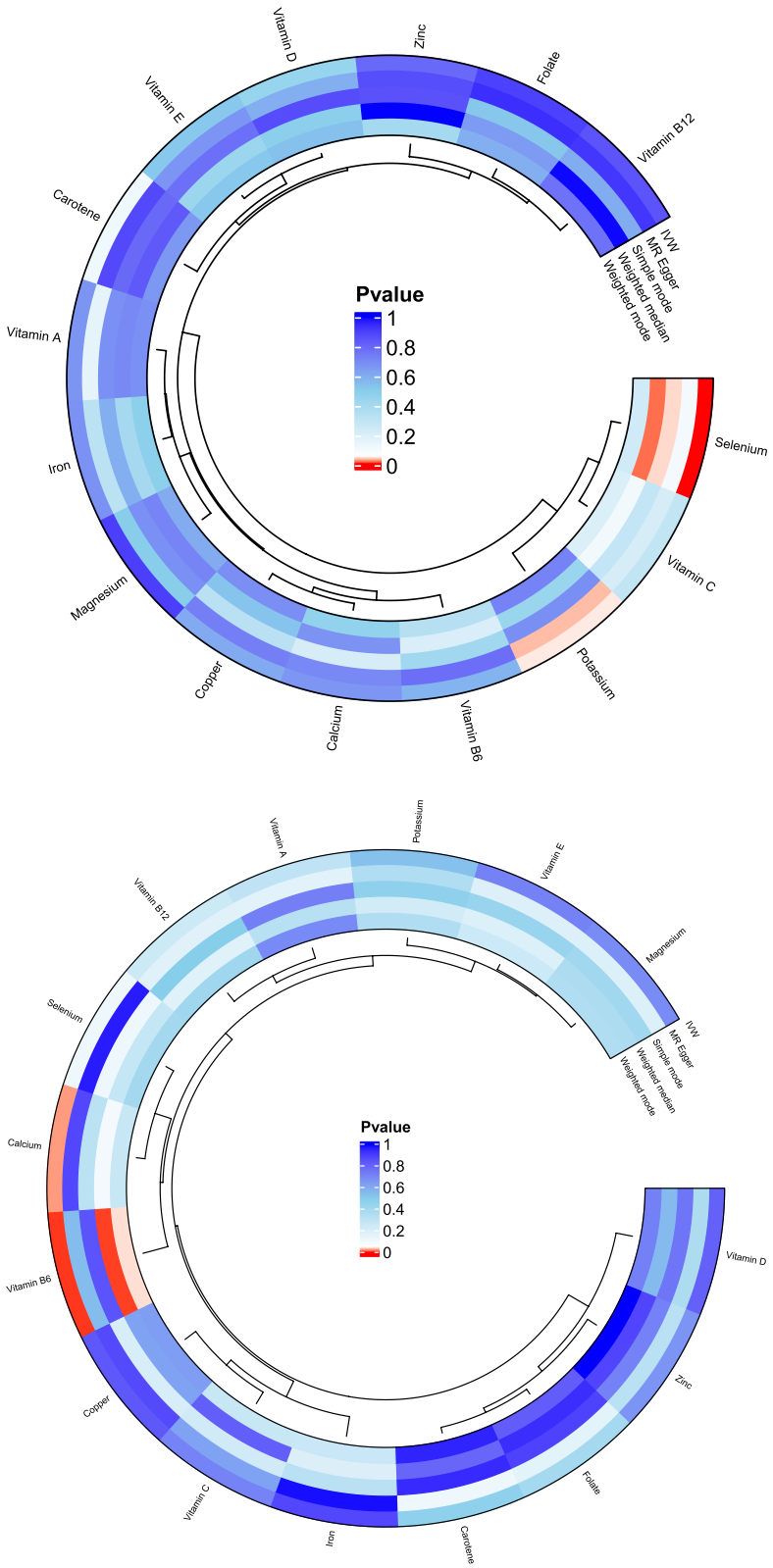


Fig. 2 (See legend on previous page.)

Table 1 Results of MR analysis between selenium and potassium and MM

exposure	nsnp	method	pval	OR(95% CI)
Potassium	14	MR Egger	**0.033**	0.087 (0.012 to 0.632)
	14	Weighted median	0.454	0.718 (0.302 to 1.707)
	14	Inverse variance weighted	**0.045**	0.463 (0.219 to 0.982)
	14	Simple mode	0.711	0.760 (0.183 to 3.149)
	14	Weighted mode	0.707	0.788 (0.233 to 2.659)
Selenium	6	MR Egger	0.101	0.764 (0.596 to 0.979)
	6	Weighted median	**0.018**	0.835 (0.720 to 0.970)
	6	Inverse variance weighted	**<0.001**	0.788 (0.703 to 0.883)
	6	Simple mode	**0.035**	0.716 (0.569 to 0.899)
	6	Weighted mode	0.219	0.865 (0.706 to 1.059)

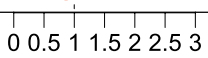
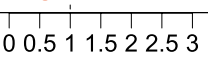


Table 2 Results of MR analysis between calcium and Vitamin B6 and NMSC

exposure	nsnp	method	pval	OR(95% CI)
Calcium	19	MR Egger	0.883	0.943 (0.439 to 2.027)
	19	Weighted median	0.110	1.254 (0.950 to 1.654)
	19	Inverse variance weighted	**0.025**	1.257 (1.030 to 1.534)
	19	Simple mode	0.317	1.280 (0.800 to 2.049)
	19	Weighted mode	0.266	1.301 (0.830 to 2.041)
Vitamin B6	17	MR Egger	0.553	0.865 (0.541 to 1.383)
	17	Weighted median	**0.004**	0.668 (0.506 to 0.882)
	17	Inverse variance weighted	**0.004**	0.741 (0.604 to 0.909)
	17	Simple mode	0.858	1.053 (0.606 to 1.828)
	17	Weighted mode	**0.036**	0.588 (0.373 to 0.927)



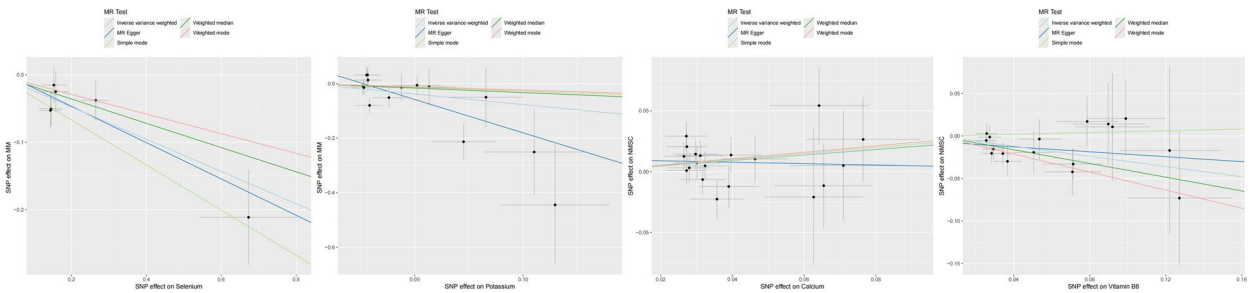


Fig. 3 The potential horizontal pleiotropy between micronutrients and skin cancer was not detected by MR Egger regression intercept and MR PRESSO global test

Discussion

This study employed the MR method to investigate the causal relationship between trace element and Vitamin levels and the risk of skin cancer, revealing potential associations between Potassium, Selenium, Calcium, and Vitamin B6 with the risk of NMSC and MM. These findings not only deepen our understanding of

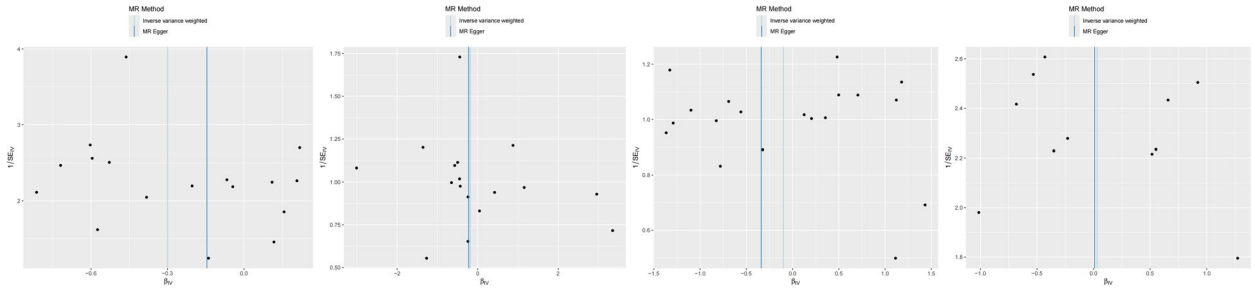


Fig. 4 Funnel plots of SNPs distributions associated with skin cancer for four micronutrients under IVW and MREgger methods

the pathogenesis of skin cancer but also provide new insights for the development of prevention and treatment strategies.

The positive correlation between Potassium levels and MM risk suggests that Potassium may play a significant role in the mechanisms underlying melanoma development. Potassium could contribute to melanoma initiation and progression by modulating cell membrane potential and influencing processes such as cell proliferation and apoptosis [30]. This finding aligns with recent insights into the role of Potassium channels in tumor biology. Studies by J. Schmidt and colleagues have demonstrated that various Potassium channels are overexpressed in melanoma cells and are associated with tumor progression and poor prognosis [31]. Notably, the voltage-gated Potassium channel KCa3.1 has been shown to be highly expressed in melanoma cells, regulating cell proliferation and migration. Activation of Potassium channels may promote tumor development through multiple mechanisms, including effects on membrane potential, regulation of Calcium influx, and modulation of cell volume and cyclin expression [32]. However, the direct relationship between serum Potassium levels and melanoma risk requires further validation. Future studies should focus on the effects of a high-Potassium environment on melanoma cell behavior and explore the potential of Potassium channel inhibitors as therapeutic strategies.

Selenium, a key antioxidant, is involved in regulating the function of various antioxidant enzymes. Although its anti-cancer effects have been widely reported across many cancer types [33], our findings suggest that Selenium may, under specific conditions, promote melanoma cell growth and dissemination by modulating oxidative stress responses. This is consistent with the hypothesis that Selenium may exhibit pro-carcinogenic effects at high concentrations, reflecting its dual role in cancer. Kim SJ and colleagues have noted that while moderate Selenium intake may benefit health, excessive levels could elevate the risk of certain cancers [34]. Vinceti M and others have found that high doses of Selenium may promote tumor cell growth by inducing DNA damage and cell cycle dysregulation [35]. In melanoma, Selenium's role is particularly complex, potentially influencing antioxidant defenses, melanin synthesis, and immune system function simultaneously [36]. Future research should aim to define the optimal dose range of Selenium influencing melanoma risk and investigate its effects across different stages of melanoma development.

Calcium, the most abundant mineral in the human body, is involved in numerous physiological processes, including bone health, nerve conduction, and cell signaling [37]. Calcium imbalance may lead to abnormal keratinocyte proliferation, thereby increasing the risk of skin carcinogenesis. In the skin, Calcium plays a critical role in keratinocyte differentiation [38]. The association between elevated Calcium levels and increased NMSC risk underscores the importance of Calcium signaling in skin cancer development. Research by V. Donati and colleagues highlights Calcium's central role in regulating the balance between epidermal differentiation and proliferation [39]. A persistently high-Calcium environment may drive aberrant keratinocyte proliferation and differentiation. Cui C and others have shown that the Calcium-dependent transcription factor NFAT is abnormally activated in cutaneous squamous cell carcinoma, promoting tumor growth [40, 41]. Additionally, Flockhart RJ and colleagues have demonstrated that Calcium ions may inhibit UV-induced DNA repair processes, thereby elevating skin cancer risk [41]. Future studies should delve deeper into the specific roles of Calcium signaling pathways in different NMSC subtypes and explore interactions between Calcium and other risk factors.

Vitamin B6, a coenzyme in numerous enzymatic reactions, is involved in amino acid metabolism, neurotransmitter synthesis, and immune regulation [42, 43]. Its immune-modulatory effects, mediated by regulating effective anti-tumor responses of CD8 + T cells both in vivo and ex vivo, may reduce skin cancer risk [22]. The negative correlation between Vitamin B6 and NMSC risk aligns with its multifaceted physiological functions.

A review by Van de Roovaart and colleagues indicates that high Vitamin B6 intake is associated with reduced risk across various cancers [44]. The protective effects of Vitamin B6 may be mediated through multiple mechanisms, including antioxidation, participation in DNA methylation and repair, and regulation of inflammation and immune function [45]. However, the role of Vitamin B6 in skin cancer prevention requires further clinical evidence. Future research should focus on large-scale prospective studies to explore differences in Vitamin B6's effects across NMSC subtypes and its synergistic interactions with other micronutrients.

It is noteworthy that this study did not find significant causal relationships between Copper, Zinc, Iron, Magnesium, and Vitamins A, C, D, E, Carotene, Folate and Vitamin B12 with the risk of skin cancer. This may reflect the complexity of skin cancer pathogenesis and the diverse roles of micronutrients in cancer development. These non-significant results emphasize the need for more refined and larger-scale studies, including considering the interactions between micronutrients, the differences in effects among subgroups, and the comprehensive analysis with environmental factors.

The MR approach employed in this study provides relatively robust causal inference; however, it is not without limitations. A key limitation pertains to the potential influence of systemic inflammation and albumin levels on plasma concentrations of micronutrients and Vitamins, which may affect the genetic associations used in our MR analysis. Research by Ghashut and colleagues indicates that elevated high-sensitivity C-reactive protein (CRP) levels (>10 mg/L), a marker of systemic inflammatory response, and low albumin concentrations (<35 g/L) can independently impact the plasma levels of these nutrients [46]. This suggests that our findings rely on genetic instruments derived from datasets that may be influenced by these factors, potentially failing to fully account for inflammation-related confounding. To address this, future studies should consider stratified analyses based on CRP and albumin levels or adjust for these variables where feasible.

Another significant limitation is the inability of this study to distinguish between the two primary subtypes of NMSC: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Paul and colleagues have demonstrated that BCC and SCC exhibit notable differences in age distribution, incidence rates, and etiology, with BCC primarily linked to intermittent sun exposure and SCC more closely associated with chronic sun exposure [47]. These mechanistic differences may result in distinct patterns of association with micronutrients and Vitamin levels. Unfortunately, the FinnGen database used in this study provides only aggregate NMSC data without separating BCC and SCC, limiting our ability to conduct more granular analyses. This lack of subtype differentiation may obscure the unique effects of specific micronutrients on different NMSC subtypes. Future research should strive to obtain more detailed skin cancer classification data to separately evaluate the associations between micronutrients and the risks of BCC and SCC.

Furthermore, measuring micronutrient and Vitamin concentrations in red blood cells, as opposed to plasma, may offer a more stable and reliable assessment of nutritional status, as this approach is less susceptible to short-term fluctuations caused by inflammation or other physiological changes. Considering potential population differences, the generalizability of these associations should be validated across diverse racial and ethnic groups in future studies.

In summary, this study provided new insights into the role of micronutrients in the pathogenesis of skin cancer, but also raised many questions worthy of further exploration. Future research should delve into the relevant molecular mechanisms, conduct large-scale prospective cohort studies, investigate the interactions between micronutrients, explore gene-environment interactions, and develop skin cancer prevention and treatment strategies based on trace element regulation. These efforts will help to more comprehensively understand the role of micronutrients in skin cancer development and provide scientific evidence for the formulation of personalized prevention and treatment plans.

Authors' contributions

Heteng Cui and Wangcheng Chen were responsible for manuscript review, revisions, data analysis, and paper writing and are the primary contributing authors. Baihong Zhang was responsible for experimental design and writing. Xiayi Su, Xiuzhen Wei and Lili Pang contributed to data collection and preprocessing. Yuemei Lan, Yaling Dong, Zhibo Zhu, Jie Bai, and Jiayan Zhou were responsible for reviewing. All authors read and approved the final manuscript.

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Data availability

We have annotated the article with the source of all original data, please contact the original authors for access if needed. The results of this study can be obtained by contacting the corresponding author.

Declarations

Ethics approval and consent to participate

Ethical review and approval were not required for the study on human participants following the local legislation and institutional requirements. Written informed consent for participation was not required for this study by the national legislation and the institutional requirements.

Competing interests

The authors declare that they have no conflict of interest.

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