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ORIGINAL RESEARCH

Genetic Causal Relationship Between Sex Hormones and Basal Cell Carcinoma: A Two-Sample Mendelian Randomization Study

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Background: The primary aim of this study was to explore whether sex hormones affect the occurrence of basal cell carcinoma (BCC) from a genetic perspective using a two-sample Mendelian randomization (MR) study.

Methods: Exposure and outcome data for this MR analysis were derived from previously published GWAS studies. In this study, estradiol, sex hormone-binding globulin (SHBG), bioavailable testosterone, and total testosterone were used as exposures, and BCC was used as the outcome for the two-sample MR analysis. The random effects inverse variance weighted (IVW) model was the primary analytical model, and the simple mode, weighted median, MR-Egger, and weighted mode methods were applied as complementary approaches. Furthermore, the "leave-one-out" sensitivity analysis was performed to assess stability, Cochran's Q test to evaluate heterogeneity, and the MR-Egger intercept test to analyze horizontal multiplicity.

Results: The two-sample MR analysis of the sex hormone and BCC showed that estradiol, sex hormone-binding globulin (SHBG), bioavailable testosterone, and total testosterone were not a causal factor in BCC ($P>0.05$). The results of the heterogeneity test and horizontal pleiotropic analysis showed that no heterogeneity or horizontal pleiotropic existed in all MR analyses (Cochran's Q-$P>0.05$, Egger intercept-$P>0.05$).

Conclusion: The two-sample MR analysis showed that estrogen and testosterone did not affect the occurrence and development of BCC at the genetic level.

Keywords: sex hormone, basal cell carcinoma, Mendelian randomization study, genetics, causal relationship

Introduction

Basal cell carcinoma (BCC) ranks as the most common form of skin cancer.[1] Studies have shown that men exhibit a higher occurrence rate of BCC than do women and have more than double the likelihood of developing over six non-melanin skin cancers.[2,3] Therefore, it has been proposed that being male inherently increases the risk of developing BCC.[4]

Steroid hormones that foster the growth of sexual organs, advance secondary sexual traits, and uphold sexual functions are produced by tissues such as the gonads, placenta, and the reticular zone of the adrenal cortex, and are known as sex hormones. Among them, testosterone, along with its more potent derivative 5-dihydrotestosterone, are naturally produced sex hormones that are crucial for both the establishment and preservation of fertility in males and females.[5–7] In humans, the main sources of testosterone are the testicles of males and the ovaries of females. Not only are androgens vital for men's sexual and reproductive well-being, but they are also crucial for the well-being of the female reproductive system.[5,8] The genetic determinants of testosterone levels vary widely between the sexes, and genetically higher testosterone levels are harmful for metabolic diseases in women but beneficial for men.[9] Ruth et al found that higher testosterone levels adversely affect breast and endometrial cancer in women and prostate cancer in men.[9] Characterized by their common capability to attach to and activate estrogen receptors (ERα and ERβ), estrogens and

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their artificial analogs are steroid hormones. In targeted organs, these receptors display diverse affinity levels and expression profiles. Consequently, they govern a wide range of functions beyond male and female reproduction, including bone mineralization, immune response, metabolic activity, and other vital biological processes.[10] The occurrence of skin cancer is closely related to skin pigmentation, which is regulated by sex and endocrine hormones. Some studies have shown that sex hormones may affect skin cancer, but the specific mechanism requires further research.[11]

Currently, some observational studies have found that sex hormones are related to BCC,[12] but observational studies cannot directly determine causality because the observed exposure-result correlation may not reflect causality, and the result may be caused by confusion or reverse causality.[13] Thus, Mendelian randomization (MR) can be used to infer the correlation between exposure and the resultant effects using genetic variation as a proxy variable. Variants of this genetic alteration are allocated randomly and are not affected by reverse causality; therefore, MR can avoid the bias caused by observational studies.[14] Numerous studies have examined the associations between various traits and BCC, such as body mass index and telomere length.[15,16] Thus, the main objective of this study was to examine the effect of sex hormones on the occurrence of BCC using a two-sample MR approach from a genetic perspective.

Methods and Materials

Study Design and Data Sources

Study Design

In this study, we used estradiol, sex hormone-binding globulin (SHBG), bioavailable testosterone, and total testosterone as the exposures and BCC as the outcome for the two-sample MR analysis (Figure 1). The following three suppositions were made by the MR analysis: (1) Single nucleotide polymorphisms (SNPs) were strongly related to the exposures, (2) SNPs showed no relationship with confounding factors, and (3) SNPs were not directly related to the outcome and could only be affected by the exposures. The data used in this study were obtained from publicly available databases. The proposed hypothesis was that there is no causal relationship between the exposures (estradiol, bioavailable testosterone, SHBG, and total testosterone) and the outcome (BCC).

Data Sources

Genetic variant data for testosterone and estradiol were obtained from a genome-wide association study (GWAS).[9] UK Biobank (https://www.ukbiobank.ac.uk/) is a significant prospective cohort study that includes approximately 500,000 individuals from different areas of the United Kingdom.[17] The genome-wide association analysis of

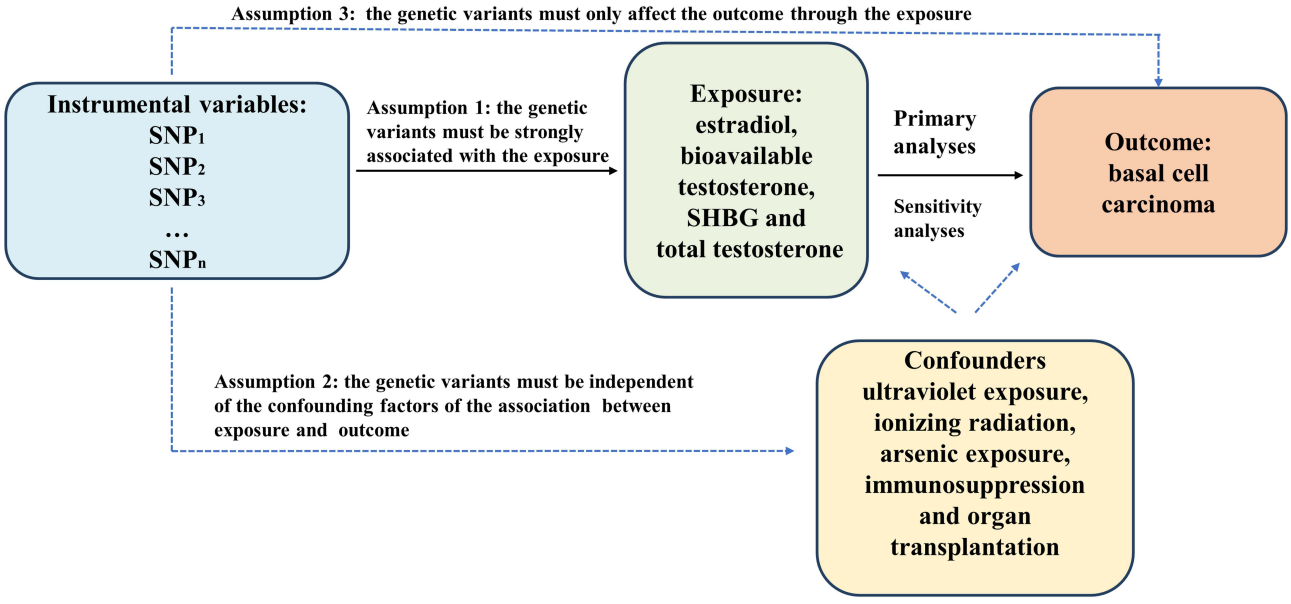

Figure 1 Flowchart of the study.

425,097 participants from the UK Biobank study showed genetic factors affecting serum levels of SHBG, estradiol, and other sex hormones. The GWAS estimated bioavailable testosterone in 384578 participants. Genetic association tests were performed on individuals of European descent, and four traits within each sex and a linear mixed model were used as controls for genetic relationships and population structures.[9] Quality control, phenotype preparation in the UK Biobank study, and signal selection for these data are described in previously published studies.[9]

Herein, we used BCC data extracted from a detailed GWAS,[18] in which an extensive GWAS analysis with a sample comprising 17,416 cases and 375,455 controls was performed. Adolphe et al incorporated multi-omics data from diverse population-based genetic studies, which encompassed various data elements, such as expression quantitative trait loci specific to both blood and skin and methylation quantitative trait loci. Through this rigorous process, they identified a set of functionally significant potential BCC susceptibility genes related to the GWAS loci.[18] All the included patients were of European descent. Table S1 summarizes the basic information on the data included in this study.

Genetic Variants

The selection of SNPs related to estradiol, bioavailable testosterone, SHBG, and total testosterone was based on the GWAS analysis.[19] SNPs were used as tool variables in this study. The data used in the analysis were obtained from a database provided by the GWAS. First, we selected exposure-related SNPs at genome-wide significance ($p<5\times10^{-8}$) as instrumental variables in secondary analysis to maximize specificity. Second, we ensured that none of the SNPs involved in coverage were in strong association with disequilibrium (LD), as LD can lead to skewed results. We used European samples from the 1000 Genome Project to perform an aggregation process (R2 < 0.001, window size = 10000 kb) to estimate the LD between SNPs in this study. SNPs not found in the LD reference panel were also eliminated. Third, SNPs with minor allele frequency (MAF) < 0.01 were removed. If the intended SNP was not discovered in the GWAS result, an SNP (proxy) in LD with the desired SNP (target) was sought instead. LD proxies were defined using 1000 alleles from European sources of data. Fifth, the effect of ambiguous SNPs with nonconcordant alleles (eg, A/G vs A/C) and palindromic SNPs with an ambiguous strand (ie, A/T or G/C) was corrected, or the ambiguous and palindromic SNPs were directly excluded from the above-selected instrument SNPs in the harmonizing process to ensure that the effect of a SNP on the exposure and the effect of that same SNP on the outcome corresponded to the same allele. These stringently selected SNPs were used as the instrumental variables for subsequent two-sample MR analysis. We then manually checked and eliminated all identified SNPs associated with confounders. We used the PhenoScanner GWAS database to rule out confounding factors associated with the outcome, such ultraviolet exposure, ionizing radiation, arsenic exposure, immunosuppression, and organ transplantation that can cause BCC. Additionally, it is necessary to ensure that a substantial number of bases exist between two SNPs.[20]

The selected SNPs were used as instrumental variables (IVs) in the associated two-sample MR study. Using the R2 value, we estimated how much of the variance in testosterone and estradiol was explained by each SNP,[21] with the instrument strength of each SNP being evaluated using F-statistic[22] (calculated as, $F=\frac{R^2}{1-R^2}\times\frac{N-K-1}{K}$,$R^2=2\times MAF\times(1-MAF)\times\left(\frac{\beta}{sd}\right)^2$). SNPs with palindromic characteristics and allele frequencies were excluded from the study.[23] If the SNP for a particular request did not exist in the generated GWAS, a search was conducted for an SNP (agent) in LD with the requested SNP (target). The comprehensive data are presented in Tables S2–S5.

Ethics

Our study was a secondary analysis of publicly available data. Informed consent was obtained from all participants as per the original GWAS protocols, and all ethical approvals for the GWAS were obtained by the original GWAS authors.

Assumptions

We assumed that there was no causal relationship between sex hormones and BCC.

MR Analysis

Herein, the random effects IVW model functioned as the main framework for the analysis, and the relevant weighted median,[24] simple mode,[25,26] weighted mode,[25,27] and MR–Egger methods served as auxiliary approaches.[28,29] The random effects inverse variance weighted (IVW) model was used to perform the primary analysis; this model is widely recognized for its robustness in providing causal estimates, particularly when there is no evidence of pleiotropy.[30,31] With no fewer than half of the instrumental variables proving to be effective, the weighted median method provided accurate estimation.[25] Under the condition that the maximum group IV with consistent MR estimation was valid, the causal relationship was estimated using a consistent method based on the weighted mode method.[27] The MR–Egger model method was used to identify pleiotropy ($p < 0.05$).[32] However, the estimation accuracy of this method was not high.[33]

Analysis for Pleiotropy and Sensitivity

The MR–Egger approach was used to evaluate the soundness of the IVs. The intercept term of this model reflected whether the findings of the multiple MR analysis were affected by multiple validity factors.[33] MR-PRESSO was primarily used to detect and correct the outliers. This method was mainly used to remove SNPs that induced unanticipated variability during the analytical procedure, enhance the precision of the assessment, and diminish the adverse effects caused by heterogeneity. When a regression analysis was performed using the MR–Egger model, heterogeneity was tested and its level was determined using the Cochran Q method. When the p-value was below 0.05, it indicated that heterogeneity in this study was significant. To analyze the potentially affecting SNPs, a leave-one-out test was conducted.

The beta value and odds ratio (OR) reflected the association between the type of exposure and the outcome variables. In the main analysis, the Bonferroni-adjusted p-values for the four exposures ($p < 0.0125$) were used to denote significance. In all sensitivity analyses, a $p < 0.05$ criterion was applied.

Software

All statistical analyses were performed using the R packages: two-sample MR and MR-PRESSO.[34]

Results

Tables S1–S4 lists the independent SNP data. In the study, the F-test value of the variables related to exposure was >10, suggesting that the factor deviation risk was extremely low.

Causal Association of Estradiol with BCC

As indicated by the data in Table 1, the analysis revealed no causal association between estradiol and BCC according to multiple MR analysis (IVW: OR = 1.073, 95% confidence interval (CI) = 0.412–2.794, p = 0.884). The p-values of the weighted median, MR–Egger, weighted mode, and simple mode were all more than 0.05 (Table 1 and Figure 2). In the forest plot shown in Supplementary Figure S1, which focuses on the inverse variance estimates of the relationship between estradiol and BCC. As shown in Supplementary Figure S2, the leave-one-out test confirmed the stability of the results. This was further corroborated by the funnel plot shown in Supplementary Figure S3.

As shown in Table 2, no indication of pleiotropic effects on the relationship between estradiol and BCC was observed (odds [intercept], 0.014; p = 0.296). The MR-PRESSO analysis revealed no outliers (MR-PRESSO global p-value = 0.054). The significance level of Cochran's Q test suggested no heterogeneity (Q = 17.97, p = 0.082).

Causal Association of Bioavailable Testosterone with BCC

The results of the IVW and weighted mode methods in Table 1 indicate no causal association between bioavailable testosterone and BCC, and bioavailable testosterone did not affect BCC (IVW: OR = 0.940, 95% CI = 0.838–1.056, p = 0.302). Moreover, the p-values of the MR–Egger, weighted median, simple mode, and weighted mode methods were all more than 0.05 (Table 1 and Figure 3). As indicated in Supplementary Figure S4, the forest plot featuring variant-specific inverse variance calculations revealed no robust causal association between bioavailable testosterone

Table 1 Mendelian Randomization Results of Different Sex Hormones and Basal Cell Carcinoma

Exposure	Outcome	Method	SNP(n)	Beta	SE	OR (95% CI)	P value
BDL	**BCC**						
		MR Egger	13	−1.199	1.255	0.301 (0.025–3.527)	0.359
		Weighted median	13	0.151	0.610	1.163 (0.351–3.846)	0.804
		Inverse variance weighted	13	0.070	0.488	1.073 (0.412–2.794)	0.884
		Simple mode	13	−0.119	1.153	0.887 (0.092–8.509)	0.919
		Weighted mode	13	0.130	0.988	1.139 (0.164–7.916)	0.897
BTL	**BCC**						
		MR Egger	125	−0.190	0.114	0.826 (0.660–1.035)	0.099
		Weighted median	125	−0.189	0.082	0.827 (0.703–0.972)	0.021
		Inverse variance weighted	125	−0.060	0.059	0.940 (0.838–1.056)	0.302
		Simple mode	125	−0.067	0.177	0.934 (0.659–1.324)	0.704
		Weighted mode	125	−0.161	0.085	0.850 (0.719–1.005)	0.061
SHBG	**BCC**						
		MR Egger	212	0.164	0.169	1.178 (0.846–1.642)	0.332
		Weighted median	212	0.107	0.099	1.112 (0.916–1.351)	0.280
		Inverse variance weighted	212	0.011	0.095	1.011 (0.838–1.221)	0.901
		Simple mode	212	0.095	0.201	1.099 (0.741–1.631)	0.636
		Weighted mode	212	0.131	0.103	1.139 (0.931–1.395)	0.205
TTL	**BCC**						
		MR Egger	154	−0.184	0.182	0.831 (0.581–1.189)	0.313
		Weighted median	154	−0.052	0.125	0.949 (0.742–1.213)	0.676
		Inverse variance weighted	154	−0.029	0.100	0.971 (0.798–1.181)	0.771
		Simple mode	154	0.310	0.278	1.364 (0.790–2.353)	0.266
		Weighted mode	154	−0.103	0.140	0.901 (0.684–1.188)	0.464

Abbreviations: BDL, Estradiol levels; BTL, Bioavailable testosterone levels; SHBG, Sex hormone-binding globulin levels; TTL, Total testosterone levels; BCC, Basal cell carcinoma.

and BCC. This robustness was further corroborated by the leave-one-out test, as shown in Supplementary Figure S5. Supplementary Figure S6 presents a funnel plot, further confirming the causal relationship between bioavailable testosterone and BCC.

As shown in Table 2, no signs of pleiotropy were observed for the relationship between bioavailable testosterone and BCC [odds (intercept), 0.004; p = 0.191]. The MR-PRESSO analysis revealed no outliers (MR-PRESSO global p-value =0.105). The significance level of Cochran's Q test suggested the absence of heterogeneity (Q = 212.808, P = 0.125).

Causal Association of SHBG with BCC

According to the results of MR–Egger, IVW, and simple mode methods, no causal association was observed between SHBG and BCC (IVW: OR = 1.011, 95% CI = 0.838–1.221, p = 0.901; MR–Egger: OR = 1.178, p = 0.332; weighted median: OR = 1.112, p = 0.280; simple mode: OR = 1.099, 95% CI = 0.741–1.631, p = 0.636; weighted mode: OR = 1.139, p = 0.205) (Table 1 and Figure 4). Based on this analysis, the forest plot in Supplementary Figure S7 shows the variant-specific inverse variance estimates. This robustness was confirmed by performing the leave-one-out test, as described in Supplementary Figure S8. Furthermore, the funnel plot in Supplementary Figure S9 confirms the causal association between SHBG and BCC.

As shown in Table 2, no signs of pleiotropy were observed for the relationship between SHBG and BCC [odds (intercept), −0.002; p = 0.274]. The MR-PRESSO analysis revealed no outliers (MR-PRESSO global p-value = 0.203). The significance level of Cochran's Q test suggested the absence of heterogeneity (Q = 588.382, p = 0.162).

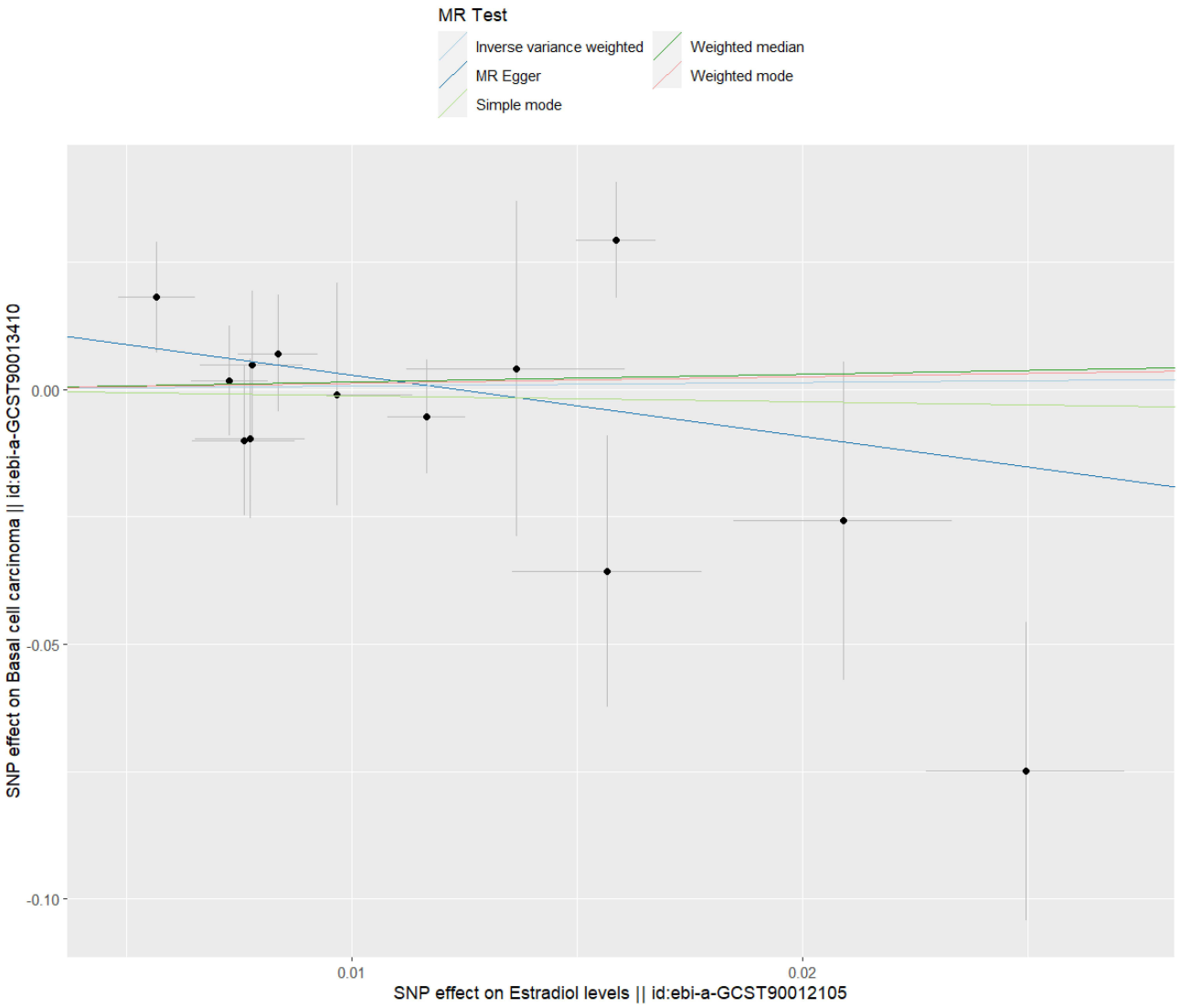

Figure 2 Scatter plot of the causal association between estradiol and basal cell carcinoma.
Notes: The x-axis represents the impact of SNP on exposure, and the y-axis represents the impact of SNP on outcome. The slope is less than 0, indicating that exposure factors are favorable factors for the outcome.

Causal Association of Total Testosterone with BCC

Table 1 presents MR estimations from different methodologies employed to assess the causal effects of total testosterone on BCC, indicating that total testosterone and BCC show no causal association at the degree of genetic prediction (IVW:

Table 2 Heterogeneity Tests and MR-Egger Intercept of Different Sex Hormones Causally Linked to Basal Cell Carcinoma

Exposure	Exposure	Egger Intercept	P-value[a]	Q-Statistic	Q-df	P-value[b]	MR-PRESSO	P-value[c]
BDL	**BCC**	0.014	0.296	17.97	11	0.082	27.97	0.054
BTL	**BCC**	0.004	0.191	212.808	123	0.125	229.843	0.105
SHBG	**BCC**	−0.002	0.274	588.382	210	0.162	605.51	0.203
TTL	**BCC**	0.002	0.309	281.727	152	0.102	288.99	0.112

Notes: P-value [a]MR-Egger P-value; P-value [b]Cochran's Q test P-value; P-value [c]MR-PRESSO global p-value.
Abbreviations: BDL, Estradiol levels; BTL, Bioavailable testosterone levels; SHBG, Sex hormone-binding globulin levels; TTL, Total testosterone levels; BCC, Basal cell carcinoma.

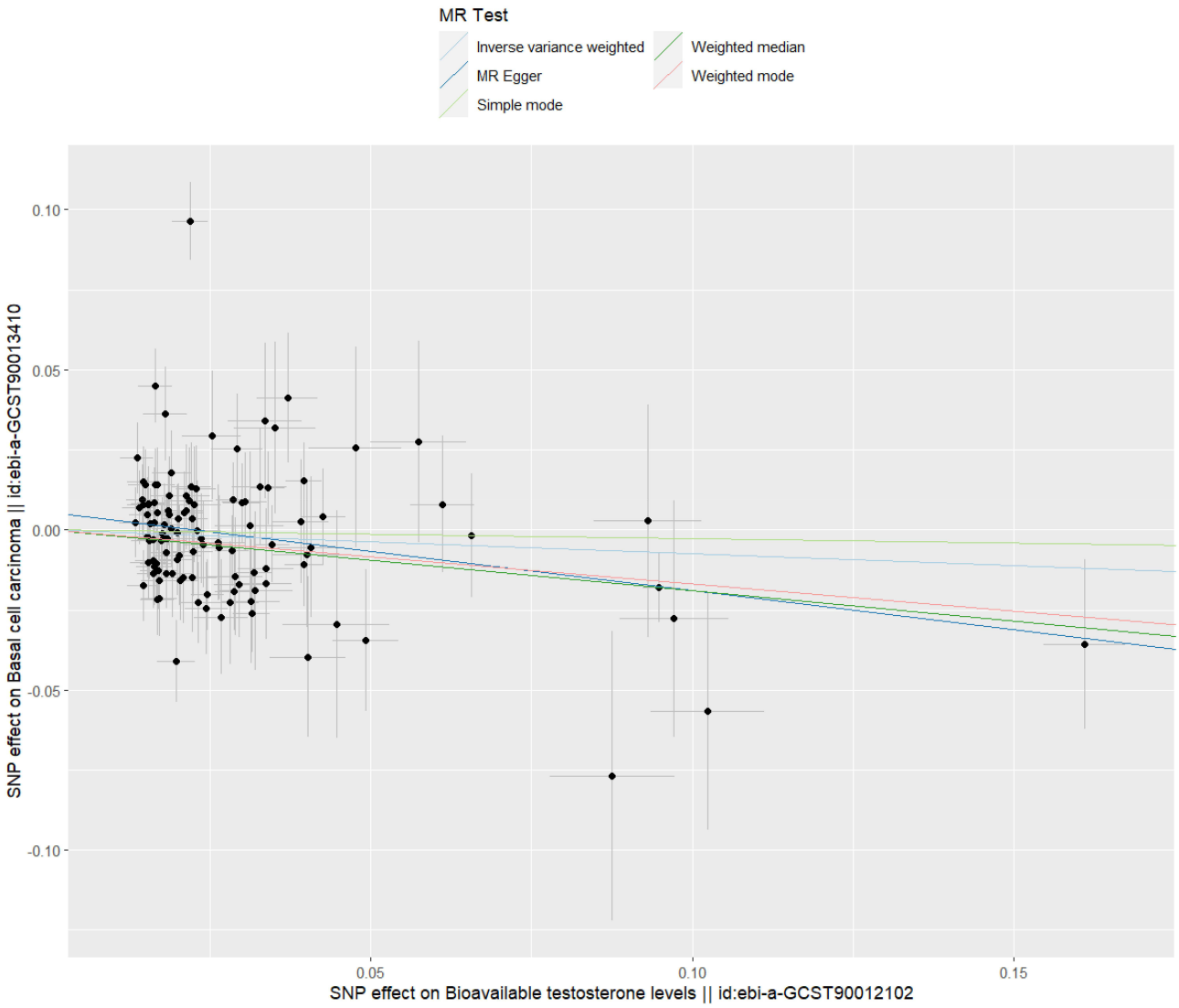

Figure 3 Scatter plot of the causal association between bioavailable testosterone and basal cell carcinoma.
Notes: The x-axis represents the impact of SNP on exposure, and the y-axis represents the impact of SNP on outcome. The slope is less than 0, indicating that exposure factors are favorable factors for the outcome.

OR = 0.971, 95% CI = 0.798–1.181, p = 0.771), and the p-values of the weighted median, MR–Egger, simple mode, and weighted mode methods were all more than 0.05 (Table 1 and Figure 5). As shown in Supplementary Figure S10, the forest plot indicating variant-specific inverse variance estimates revealed no robust causal association between total testosterone and BCC. This robustness was further supported by the leave-one-out test results. Supplementary Figures S11 and S12 show the funnel plot associated with the causal relationship between total testosterone and BCC, further validating the results.

As shown in Table 2, no evidence of pleiotropic effects was found for the relationship between total testosterone and BCC [odds (intercept), 0.002; p = 0.309]. The MR-PRESSO analysis revealed no outliers (MR-PRESSO global p-value =0.112). The significance level of Cochran's Q test suggested the absence of heterogeneity (Q = 281.727, p = 0.102).

Discussion

We performed an analysis to investigate the causal connection between sex hormones and BCC using a two-sample MR; however, our analysis showed that sex hormones did not increase the likelihood of developing BCC. A previous meta-analysis showed that hormonal factors did not play a role in the pathogenesis of female non-melanoma skin cancer

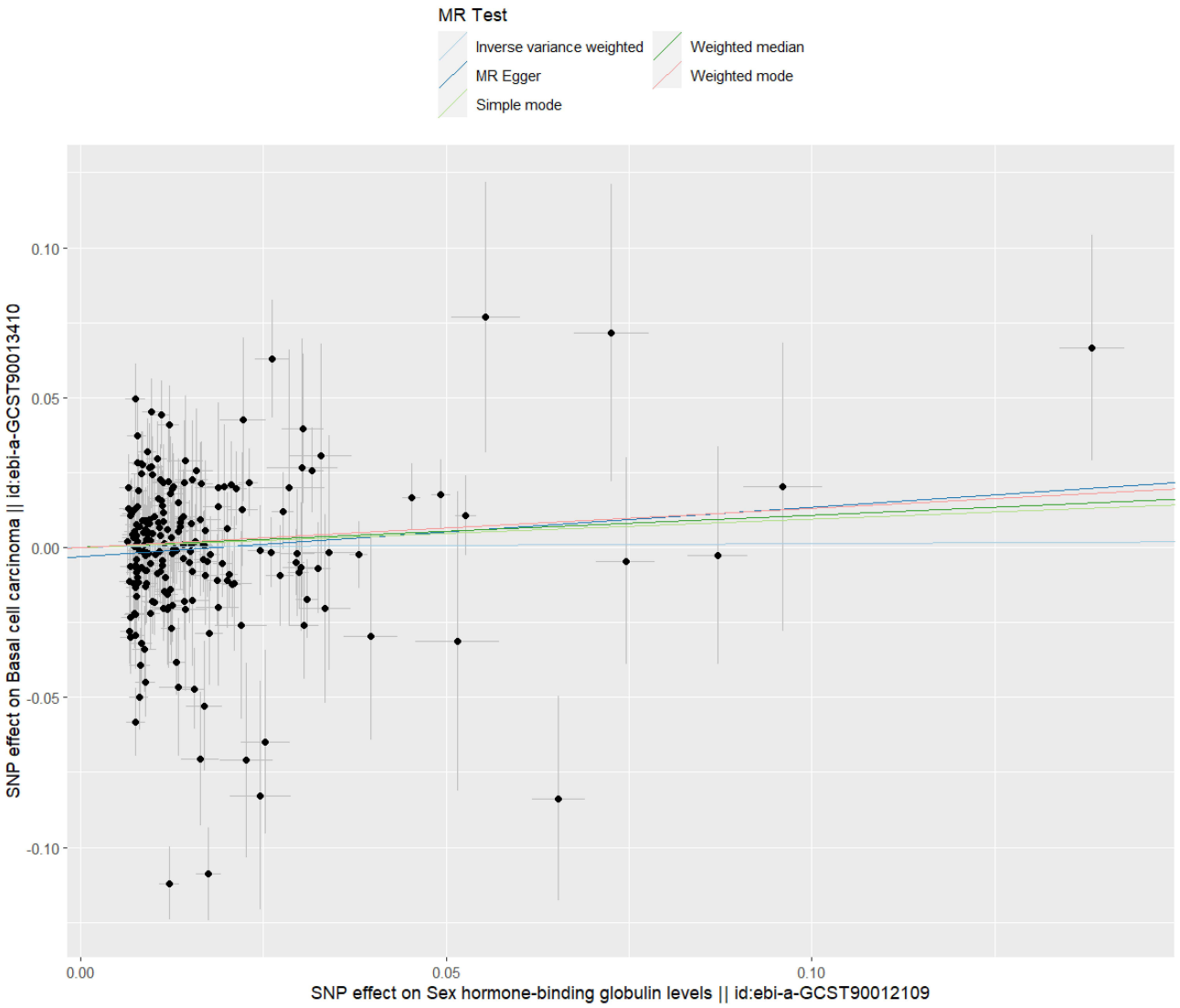

Figure 4 Scatter plot of the causal association between sex hormone-binding globulin and basal cell carcinoma.
Notes: The x-axis represents the impact of SNP on exposure, and the y-axis represents the impact of SNP on outcome. The slope is less than 0, indicating that exposure factors are favorable factors for the outcome.

(NMSC),[12] and our findings are consistent with this meta-analysis. However, we cannot rule out the possibility that sex hormones affect the occurrence of BCC in other ways. For example, From a pathophysiological perspective, exogenous estrogen is considered to be a proliferation factor in melanocytes and melanoma cells, exerting its biological role through nuclear estrogen receptor (ERS)-based genomic and non-genomic pathways.[35] Estrogen is considered a photosensitizer that can affect the sensitivity of the skin to UV exposure. The main risk factor for the initiation of BCC is UV-induced skin damage, resulting in accumulation of keratinocyte mutations, impaired ability of DNA repair mechanisms, and reduced immune responses in tumor areas.[36]

Estrogen, a key sex hormone, plays a crucial role in controlling the proliferation of both normal and tumor tissues, such as those found in ovarian, endometrial, and breast cancers.[37,38] Specifically, estrogen exerts its effects through interactions with specific receptors, namely, nuclear estrogen receptor α (ERα) and β (ERβ), situated on the cell membrane. In an observational study by Kuklins et al and a Danish study, an increased risk of NMSC was associated with the use of high doses of estrogen. ERs are present on the surface of keratinocytes, and ER activation induces keratinocyte proliferation.[39] Additionally, ER activation modifies the ability of keratinocytes to repair DNA, making them more vulnerable to ongoing environmental damage.[40] Similarly, ER activation compromises DNA repair in

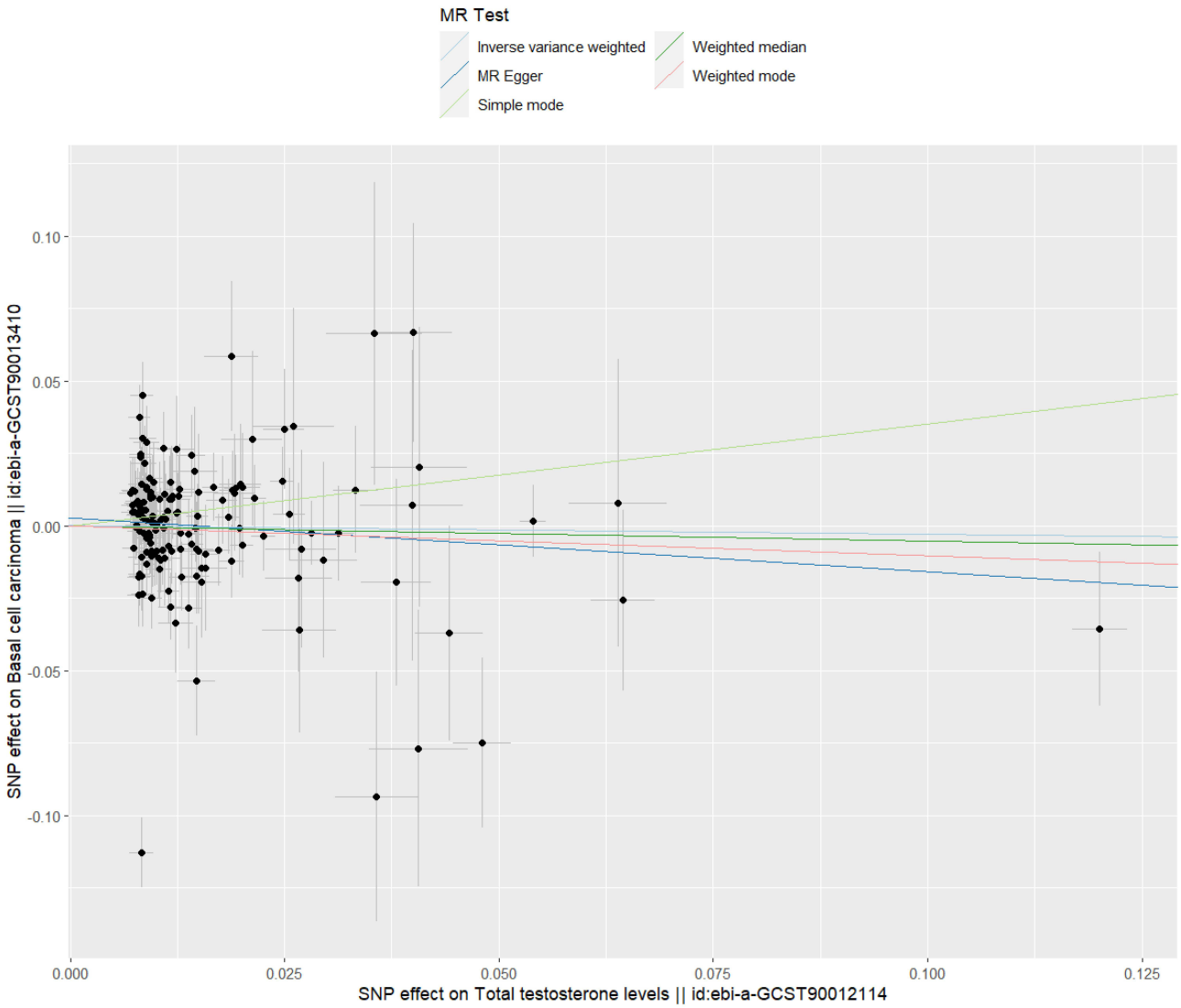

Figure 5 Scatter plot of the causal association between total testosterone and basal cell carcinoma.
Notes: The x-axis represents the impact of SNP on exposure, and the y-axis represents the impact of SNP on outcome. The slope is less than 0, indicating that exposure factors are favorable factors for the outcome.

keratinocytes, increasing their susceptibility to recurring environmental damages.[41] Although there is considerable evidence linking estrogen to the risk of BCC, we did not find that estrogen could affect the occurrence of BCC at the genetic level. However, the possibility that the effect of estrogen on BCC may be explained at other levels cannot be ruled out.

Testosterone exists in the human body in the form of free and bound testosterone, of which free testosterone accounts for only 1% of the total testosterone, whereas the rest is in the form of bound testosterone.[42] Approximately 1% of the bound testosterone binds to corticosteroid-binding globulin, 43% binds to albumin with a lower affinity, and the remaining 55% binds to SHBG with a high degree of specificity and strong affinity. Albumin-bound and free testosterone are also known as bioavailable testosterone.[43] Herein, we did not find that testosterone (bioavailable testosterone and total testosterone) was associated with the risk of BCC at the genetic level. The primary purpose of SHBG is to compete with carrier proteins for the same binding sites, especially sex hormones, such as testosterone and estrogens. Notably, testosterone has a stronger binding affinity than has estrogen.[42] SHBG binds to testosterone and estradiol in a high-affinity manner in 60% of the cycles, whereas 50% of SHBG binds to albumin and other proteins nonspecifically.[44] Some studies have shown that SHBG affects the occurrence and development of tumors mainly by regulating testosterone and

estradiol levels.[45,46] However, our results and those of a previous study by Ong et al uncovered no evidence of a cause-and-effect relationship between endogenous hormone levels (SHBG, bioavailable testosterone, and total testosterone) and skin cancer.[47] The combined results of our MR study of testosterone and the Ong et al study suggested that testosterone did not directly contribute to the development of BCC at the genetic level.

This is the first study to show that sex hormones do not affect BCC at the genetic level. Additionally, our MR study mitigated the effect of internal extraneous factors and avoided deviations caused by reverse causality. Moreover, our sensitivity analysis did not show any signs of diversity or heterogeneity, indicating the statistical robustness of the results. However, our study has certain limitations. The data used in this study were sourced from a European population, so we should be careful when applying our findings to other non-European populations. Further, the non-statistically significant outcomes did not entirely eliminate the possibility of an association between sex hormones and BCC, which might be attributed to the restricted sample size or insufficient statistical power of the MR analysis. Future MR studies on the causal relationship between sex hormones and BCC should be conducted in different European and non-European populations to achieve better results.

Conclusion and Prospection

Through the two-sample MR analysis, we found that estrogen and testosterone did not affect the occurrence and development of BCC at the genetic level; however, other related sex hormones could not be ruled out as factors affecting the occurrence of BCC in other ways. Future research should aim to narrow the gap between MR and real-world clinical trials by combining high-dose short-term exposure experiments with MR analysis. This approach will improve understanding of the relationship between biological effects observed in MR and clinical outcomes, and strengthen the translation of research results into practical medical applications. To address potential bias and increase the universality of results, future research should include diverse groups of people representing different ethnic backgrounds. Validation of study results in individuals with different genetic backgrounds can improve the applicability of the study results to a broader patient population.

Data Sharing Statement

The data will be available from the corresponding author.

Ethical Statement

Our study was a secondary analysis of publicly available data. Informed consent was obtained from all participants as per the original GWAS protocols, and all ethical approvals for the GWAS were obtained by the original GWAS authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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