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ORIGINAL RESEARCH

Causal Relationship Between Matrix Metalloproteinase and Cervical Lesions: A Two-Sample Mendelian Randomization Analysis

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Purpose: This study aimed to investigate the causal relationship between matrix metalloproteinases (MMPs) and cervical lesions, as their correlation remains unclear despite reports of their involvement in the pathogenesis of these lesions.

Patients and Methods: A two-sample Mendelian randomization (MR) analysis was performed using genome-wide association studies (GWAS) summary data to assess the causal associations of MMPs (MMP-1, 2, 3, 7, 9, 10, 12, 14, 16, and 17) with cervical lesions. The primary analysis utilized the inverse-variance weighted (IVW) method, supplemented by weighted median, mode, and MR-Egger regression. Heterogeneity was evaluated using Cochran's Q test and Leave-one-out analysis, while MR-Egger regression and MR pleiotropy residual sum and outlier (MR-PRESSO) methods addressed horizontal pleiotropy.

Results: IVW analysis revealed causal effects of MMP-3 on cervical precancerous lesions (OR = 0.9993, P=0.0248), MMP-7 on cervical cancer (OR=0.6131, P = 0.0303), MMP-9 on cervical inflammation (OR = 1.1081, P = 0.0446), and MMP-12 on cervical erosion (OR = 0.8354, P = 0.0444), and cervical cancer (OR = 0.6836, P = 0.006). Sensitivity analyses confirmed these findings.

Conclusion: The study highlights causal associations between MMPs and cervical lesions, suggesting their potential as therapeutic targets and biomarkers for early detection. Future research should further explore the mechanisms involved.

Keywords: matrix metalloproteinase, cervical lesions, Mendelian randomization, causal relationship, genetic association, SNPs

Introduction

Cervical lesions encompass a spectrum of conditions ranging from benign to malignant, including cervical inflammation, cervical erosion and ectropion, cervical precancerous lesions, and cervical cancer. Cervical cancer is a significant global public health issue and one of the common malignant tumors that pose a severe threat to women's health worldwide.[1] In 2020, there were estimated to be 604,000 new cases of cervical cancer globally, with 342,000 deaths.[2] Clinically, cervical lesions often present with symptoms such as abnormal vaginal bleeding, discharge, and pain.[3] The risk factors for cervical lesions include smoking, multiple sexual partners, early sexual debut, and chronic infections, particularly with human papillomavirus (HPV)[3] Despite the potential of the latest nine-valent HPV vaccine to prevent up to 90% of cervical lesion cases,[4] the vaccination coverage remains suboptimal, especially in developing countries that account for approximately 85% of cervical cancer occurrences.[5] In a subset of women infected by HPV, the virus can persist, leading to cervical lesions and ultimately to the development of cervical cancer, which is a complex process involving multiple genetic and environmental factors.[6] Thus, it is particularly important to explore the influencing factors in the development process of cervical lesions and cervical cancer.

Matrix metalloproteinases (MMPs), a family of enzymes that regulate the degradation and remodeling of the extracellular matrix,[7] are involved in various cellular processes, including tissue remodeling, inflammation, and cancer

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progression.[8] In recent years, the association between cervical lesions and MMPs has attracted much attention.[9] A previous study indicated that MMP overexpression might be a poor prognostic marker in cervical cancer.[10] The elevated expression of MMP-1 in tumor tissue can be considered a predictive factor for the development of metastases.[11] MMP-7 was considered a potential oncogene in cervical cancer cells and was involved in cell proliferation, migration, and invasion.[12] MMP-9 was also demonstrated to promote cell invasion.[13] However, Wang et al demonstrated that there was no relation between MMP-2 overexpression and overall survival.[14] Davidson et al indicated that the presence of MMP-9 mRNA or protein did not predict the prognosis.[15] Thus, there are many contradictions in the research on the relationship between MMPs and cervical lesions. Further studies are warranted to demonstrate the causal association between them, thereby conferring a theoretical basis for follow-up research and clinical treatment.

To disentangle the complex relationship between cervical lesions and MMPs, we employed a two-sample Mendelian randomization (MR) analysis. MR leverages the correlation between disease genotype to mimic the influence of exposure factors on disease pathogenesis, achieved by employing genetic variations linked to exposure factors as instrumental variables (IVs).[16] MR is regarded as a complementary approach to randomized controlled trials as it minimizes the impact of confounding factors.[17]

Herein, a two-sample MR study was conducted, leveraging the publicly available genome-wide association studies (GWAS) databases, to delve into the potential causal relationships between cervical lesions and MMPs. The results of this study have the potential to provide new insights into the pathogenesis of cervical lesions.

Materials and Methods

Study Design

In this study, single-nucleotide polymorphisms (SNPs) derived from GWAS were selected as genetic IVs. The two-sample MR study was founded upon three fundamental assumptions:[18]

(1) Relevance assumption: The IVs had a strong connection to the exposure.
(2) Independence assumption: There was no correlation between the IVs and any variables that affected both exposure and outcome.
(3) Exclusion restriction assumption: The IVs did not alter the outcome through any other causal pathways other than their effects on the exposure.

In this MR analysis, MMPs (MMP-1, −2, −3, −7, −9, −10, −12, −14, −16, and −17) were considered as the exposure factors, with cervical lesions including cervical inflammation, cervical erosion and ectropion, cervical precancerous lesions, and cervical cancer serving as the outcome (Figure 1). The study was submitted to the ethics committee of Hongqi Hospital Affiliated to Mudanjiang Medical University. The need for ethical approval was waived by the committee because the study used publicly available aggregated data that did not allow the re-identification of the original participants, as supported by Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China, as well as various legislations around the globe.[19]

Data Source

The summary data on cervical inflammation, cervical erosion and ectropion, as well as cervical cancer, were derived from the FInGen consortium, which has aggregated GWAS results for various diseases, encompassing the genomic and electronic health record data of over 100,000 Finnish participants[20] The summary data on cervical precancerous lesions were sourced from UK Biobank (UKB), a large-scale biomedical database and research resource containing genetic, lifestyle, and health information from half a million UK participants.[21] SNPs related to the 10 kinds of MMPs (MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-10, MMP-12, MMP-14, MMP-16, and MMP-17) were obtained from the GWAS Catalog, which boasts an extensive collection of 589,865 genetic associations from 6,799 publications.[22] The specific information is shown in Table S1.

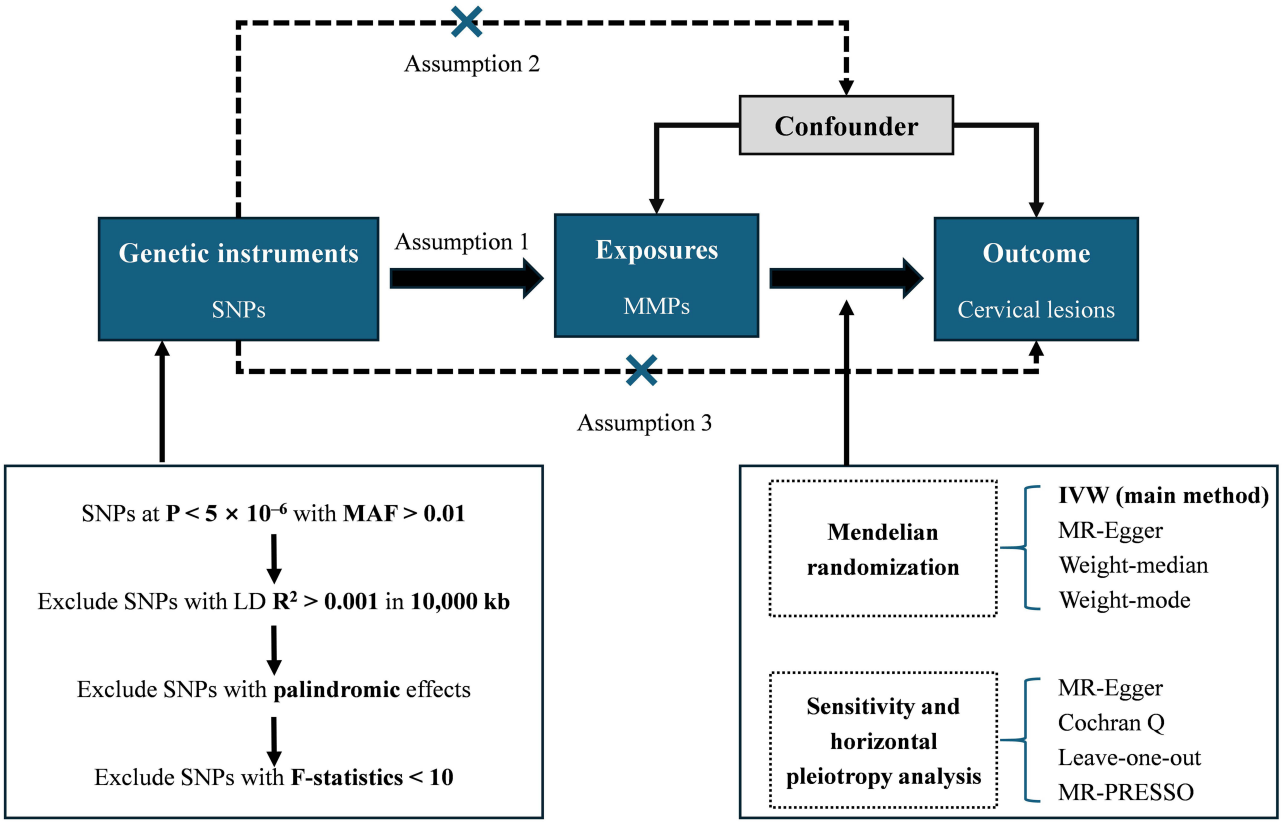

Figure 1 Diagram of three stringent assumptions and core design of the present MR study. Bold text was used to emphasize the important information.
Abbreviations: MR, Mendelian randomization; SNPs, single nucleotide polymorphisms. MMPs, matrix metalloproteinases; MAF, minor allele frequency. LD, linkage disequilibrium; IVW, inverse-variance weighted; MR-PRESSO, mendelian randomization pleiotropy residual sum and outlier.

Instrument Selection

Initially, SNPs significantly associated with the genome-wide MMPs were screened based on a loose cutoff at $P < 5 \times 10^{-6}$, among which, the SNPs with a minor allele frequency (MAF) > 0.01 were selected.[23] A more stringent cutoff (eg, $P < 5\times10^{-8}$) may improve instrument strength and reduce potential bias, but too few SNPs were initially identified to be able to conduct the MR analysis. Therefore, it had to be relaxed to $P < 5\times10^{-6}$. The linkage disequilibrium (LD) among SNPs was eliminated based on the criteria of $R^2 < 0.001$ and a window size of 10,000 kb.[23] If the selected IV was absent in the summary data of the outcome, a proxy SNP with a high LD ($R^2 > 0.8$) with that particular IV was identified and chosen for substitution.[24] The F-statistic of each SNP in the IVs was calculated to assess the IVs' strength, excluding potential weak instrument bias between the IVs and the exposure factors.[25] The formula for the F-statistic is as follows:

$F = R^2* (N-2) / (1-R^2)$, where R^2 represents the proportion of exposure variation explained by the SNP in the IV, and the F-value is required to be > 10.[26]

Statistical Analysis

This analysis prominently employed the inverse variance weighted (IVW) method as the primary analytical technique, assessing the causal association between exposure and outcome risk by computing the odds ratio (OR) alongside a 95% confidence interval (95% CI).[27] IVW stands as the pivotal method for interpreting MR results, determining the weighted average of effect sizes by leveraging the inverse variance of each SNP as the weighting factor.[28] Furthermore, the study's findings were rigorously tested for robustness using methods including MR-Egger, weighted median, and weighted mode. The MR-Egger method accounts for the potential presence of an intercept term, enabling it to provide precise causal effect estimates even in scenarios of pleiotropy bias.[26] Meanwhile, the weighted median method postulates that

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half of the instrumental variables remain valid, thereby facilitating the analysis of the causal relationship between exposure and outcome.[29] All analyses in this study were conducted using R version 4.0.5 along with the "TwoSampleMR" package. Visual representations were achieved through the use of scatter plots and sensitivity analysis graphs.[23] A scatter plot is used to demonstrate the effect relationship of IVs on exposure and outcome, a funnel plot is used to detect whether there is any bias, and a forest plot is used to display the effect estimates of SNPs and their consistency.

Sensitivity Analysis

Sensitivity analysis plays a crucial role in detecting potential pleiotropy that may arise in MR studies.[28] In this study, Cochran's Q test was employed to assess the heterogeneity among IVs.[23] When $P > 0.05$, it is considered that the heterogeneity is low, indicating that the estimates among instrumental variables are randomly varied and have minimal impact on the IVW results.[30] Simultaneously, considering the impact of genetic variation's pleiotropy on the estimation of association effects, this study employed the MR-Egger regression method to explore the existence of horizontal pleiotropy. When the intercept term of MR-Egger regression approaches zero or is not statistically significant, it suggests that there is no pleiotropy.[31] Additionally, this study employed the MR pleiotropy residual sum and outlier (MR-PRESSO) method to identify potential outliers (ie, SNPs with $P < 0.05$) and re-estimated the causal association after excluding them, thereby correcting for horizontal pleiotropy.[30] The Leave-one-out analysis was used to assess the robustness and consistency of the results.[28]

Results

Selection of Instrumental Variables

We respectively incorporated 20, 7, 16, 16, 10, 23, 23, 19, 14, 14 independent SNPs as IVs for MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-10, MMP-12, MMP-14, MMP-16, MMP-17. The minimum F-statistics of these SNPs were 86.92, 22.54, 160.51, 60.01, 24.87, 73.24, 110.09, 22.35, 22.75, and 26.00, respectively, all of which exceeded the threshold of 10, indicating enough strength of IVs (Table S2). Additionally, the information on SNPs that were unmatched in the summary data of outcomes and excluded due to palindrome structure is exhibited in Table S3. Notably, due to data quality issues related to cervical precancerous lesions, the number of MMPs-associated SNPs ultimately used for this outcome analysis was affected (see details in Table S3).

Causal Effects of MMPs on Cervical Lesions

The results of IVW (Table 1) found causal effects of MMP-3 on a lower risk of cervical precancerous lesions (OR (95% CI) = 0.9993 (0.9987–0.9999), P = 0.0248), MMP-7 on a lower risk of cervical cancer (OR (95% CI) = 0.6131

Table 1 MR Results of Causal Effects of MMPs on Cervical Lesions

Exposure	Outcome	Methods	N. SNPs	OR (95% CI)	P
MMP-1	Cervical inflammation	IVW	19	0.9888 (0.8651–1.1302)	0.8691
		MR Egger	19	0.9302 (0.7453–1.1608)	0.5303
		Weighted median	19	0.8792 (0.7370–1.0489)	0.1527
		Weighted mode	19	0.8872 (0.7408–1.0626)	0.2100
	Cervical erosion and ectropion	IVW	19	0.9956 (0.8137–1.2181)	0.9656
		MR Egger	19	0.9505 (0.6805–1.3275)	0.7694
		Weighted median	19	0.9912 (0.7670–1.2809)	0.9459
		Weighted mode	19	1.0092 (0.7911–1.2873)	0.9423
	Cervical precancerous lesions	IVW	10	1.0002 (0.9996–1.0008)	0.4662
		MR Egger	10	1.0010 (1.0001–1.0019)	0.0693
		Weighted median	10	1.0004 (0.9998–1.0011)	0.1871
		Weighted mode	10	1.0005 (0.9999–1.0012)	0.1406

(*Continued*)

Table 1 (Continued).

Exposure	Outcome	Methods	N. SNPs	OR (95% CI)	P
	Cervical cancer	IVW	19	0.8883 (0.6555–1.2037)	0.4448
		MR Egger	19	0.8248 (0.4922–1.3822)	0.4747
		Weighted median	19	0.8124 (0.5567–1.1857)	0.2815
		Weighted mode	19	0.7706 (0.5168–1.1491)	0.2174
MMP-2	Cervical inflammation	IVW	7	1.0107 (0.8776–1.1638)	0.8830
		MR Egger	7	0.8676 (0.5830–1.2912)	0.5151
		Weighted median	7	1.0170 (0.8605–1.2019)	0.8433
		Weighted mode	7	0.8627 (0.6361–1.1699)	0.3787
	Cervical erosion and ectropion	IVW	7	0.9897 (0.828 0–1.1829)	0.9091
		MR Egger	7	0.9790 (0.5970–1.6057)	0.9364
		Weighted median	7	1.0186 (0.8212–1.2635)	0.8668
		Weighted mode	7	1.0192 (0.7659–1.3563)	0.9004
	Cervical precancerous lesions	IVW	4	0.9998 (0.9990–1.0005)	0.5695
		MR Egger	4	0.9957 (0.9868–1.0046)	0.4442
		Weighted median	4	0.9999 (0.9991–1.0007)	0.8123
		Weighted mode	4	1.0000 (0.9989–1.0011)	0.9702
	Cervical cancer	IVW	7	0.9019 (0.6721–1.2104)	0.4916
		MR Egger	7	1.6548 (0.7891–3.4704)	0.24
		Weighted median	7	0.8828 (0.6102–1.2770)	0.508
		Weighted mode	7	0.8293 (0.4611–1.4916)	0.5551
MMP-3	Cervical inflammation	IVW	13	1.1335 (0.9828–1.3074)	0.0852
		MR Egger	13	1.0907 (0.8688–1.3692)	0.47
		Weighted median	13	1.1031 (0.9383–1.2968)	0.2346
		Weighted mode	13	1.1136 (0.9551–1.2984)	0.1947
	Cervical erosion and ectropion	IVW	13	1.1931 (0.9494–1.4994)	0.1299
		MR Egger	13	1.2338 (0.8545–1.7813)	0.2862
		Weighted median	13	1.1365 (0.8665–1.4906)	0.3553
		Weighted mode	13	1.1355 (0.8831–1.4602)	0.3414
	Cervical precancerous lesions	IVW	8	0.9993 (0.9987–0.9999)	0.0248
		MR Egger	8	0.9993 (0.9984–1.0002)	0.1557
		Weighted median	8	0.9994 (0.9987–1.0000)	0.0529
		Weighted mode	8	0.9994 (0.9987–1.0000)	0.0912
	Cervical cancer	IVW	13	1.0559 (0.7512–1.4842)	0.7543
		MR Egger	13	1.2763 (0.7539–2.1607)	0.3832
		Weighted median	13	1.2639 (0.8746–1.8264)	0.2125
		Weighted mode	13	1.3033 (0.9217–1.8430)	0.1598
MMP-7	Cervical inflammation	IVW	15	1.0257 (0.8351–1.2599)	0.8086
		MR Egger	15	0.8206 (0.6332–1.0635)	0.1589
		Weighted median	15	0.9019 (0.7255–1.1211)	0.3522
		Weighted mode	15	0.8466 (0.6715–1.0674)	0.1808
	Cervical erosion and ectropion	IVW	15	1.0172 (0.7934–1.3041)	0.8932
		MR Egger	15	0.9432 (0.6582–1.3515)	0.755
		Weighted median	15	1.0251 (0.7533–1.3950)	0.8747
		Weighted mode	15	1.0368 (0.7507–1.4319)	0.8297
	Cervical precancerous lesions	IVW	7	0.9985 (0.9965–1.0006)	0.1675
		MR Egger	7	0.9970 (0.9893–1.0047)	0.4798
		Weighted median	7	0.9988 (0.9969–1.0006)	0.1936
		Weighted mode	7	0.9989 (0.9964–1.0014)	0.4265

(*Continued*)

Table 1 (Continued).

Exposure	Outcome	Methods	N. SNPs	OR (95% CI)	P
	Cervical cancer	IVW	15	0.6131 (0.3939–0.9545)	0.0303
		MR Egger	15	0.6445 (0.3317–1.2525)	0.2176
		Weighted median	15	0.6464 (0.4026–1.0376)	0.0708
		Weighted mode	15	0.6579 (0.4105–1.0545)	0.1039
MMP-9	Cervical inflammation	IVW	10	1.1081 (1.0025–1.2248)	0.0446
		MR Egger	10	1.1720 (0.9333–1.4719)	0.2092
		Weighted median	10	1.1155 (0.9795–1.2703)	0.0994
		Weighted mode	10	1.1877 (0.9883–1.4273)	0.0998
	Cervical erosion and ectropion	IVW	10	0.9786 (0.8541–1.1214)	0.7557
		MR Egger	10	1.1287 (0.8389–1.5187)	0.447
		Weighted median	10	0.9971 (0.8281–1.2005)	0.9754
		Weighted mode	10	1.0384 (0.8218–1.3120)	0.7595
	Cervical cancer	IVW	10	1.1912 (0.9712–1.4611)	0.0931
		MR Egger	10	1.1636 (0.7451–1.8171)	0.5241
		Weighted median	10	1.2150 (0.9216–1.6018)	0.1673
		Weighted mode	10	1.2150 (0.8922–1.6546)	0.2478
MMP-10	Cervical inflammation	IVW	19	1.0353 (0.8820–1.2153)	0.6715
		MR Egger	19	0.9294 (0.7170–1.2048)	0.5876
		Weighted median	19	1.0807 (0.8603–1.3576)	0.5047
		Weighted mode	19	1.0782 (0.8115–1.4325)	0.6099
	Cervical erosion and ectropion	IVW	19	0.9346 (0.6844–1.2761)	0.6702
		MR Egger	19	0.9093 (0.5429–1.5228)	0.7222
		Weighted median	19	0.9134 (0.6419–1.2998)	0.6149
		Weighted mode	19	0.8090 (0.5624–1.1636)	0.2681
	Cervical precancerous lesions	IVW	6	1.0005 (0.9988–1.0023)	0.5743
		MR Egger	6	1.0017 (0.9952–1.0082)	0.6425
		Weighted median	6	1.0009 (0.9992–1.0026)	0.3137
		Weighted mode	6	1.0014 (0.9995–1.0033)	0.2153
	Cervical cancer	IVW	19	1.0157 (0.6507–1.5856)	0.9453
		MR Egger	19	1.6499 (0.8299–3.2801)	0.1714
		Weighted median	19	0.9271 (0.5062–1.6981)	0.8063
		Weighted mode	19	1.0162 (0.5252–1.9659)	0.9626
MMP-12	Cervical inflammation	IVW	19	0.9943 (0.8852–1.1169)	0.9236
		MR Egger	19	0.9365 (0.7854–1.1167)	0.4751
		Weighted median	19	0.9820 (0.8502–1.1343)	0.8053
		Weighted mode	19	0.9758 (0.8474–1.1236)	0.7375
	Cervical erosion and ectropion	IVW	19	0.8354 (0.7010–0.9955)	0.0444
		MR Egger	19	0.7988 (0.6126–1.0417)	0.1156
		Weighted median	19	0.8330 (0.6664–1.0414)	0.1087
		Weighted mode	19	0.8245 (0.6683–1.0173)	0.0886
	Cervical precancerous lesions	IVW	7	0.9993 (0.9979–1.0006)	0.2952
		MR Egger	7	0.9982 (0.9949–1.0015)	0.323
		Weighted median	7	0.9987 (0.9971–1.0002)	0.0889
		Weighted mode	7	0.9988 (0.9971–1.0005)	0.2118
	Cervical cancer	IVW	19	0.6836 (0.5211–0.8968)	0.0060
		MR Egger	19	0.6207 (0.4085–0.9429)	0.0391
		Weighted median	19	0.7023 (0.5110–0.9651)	0.0293
		Weighted mode	19	0.6935 (0.5050–0.9525)	0.0364

(*Continued*)

Table 1 (Continued).

Exposure	Outcome	Methods	N. SNPs	OR (95% CI)	P
MMP-14	Cervical inflammation	IVW	18	1.0730 (0.9277–1.2410)	0.3427
		MR Egger	18	0.9862 (0.7533–1.2913)	0.9210
		Weighted median	18	1.0515 (0.8599–1.2858)	0.6245
		Weighted mode	18	1.0075 (0.7789–1.3032)	0.9555
	Cervical erosion and ectropion	IVW	18	1.0678 (0.8568–1.3307)	0.5594
		MR Egger	18	1.2239 (0.8134–1.8416)	0.3469
		Weighted median	18	1.0726 (0.8049–1.4293)	0.6323
		Weighted mode	18	1.0943 (0.7439–1.6096)	0.653
	Cervical precancerous lesions	IVW	4	0.9997 (0.9982–1.0012)	0.6823
		MR Egger	4	0.9866 (0.9747–0.9986)	0.1601
		Weighted median	4	1.0001 (0.9988–1.0014)	0.9103
		Weighted mode	4	1.0004 (0.9986–1.0022)	0.7242
	Cervical cancer	IVW	18	0.8323 (0.5976–1.1592)	0.2775
		MR Egger	18	0.7916 (0.4256–1.4721)	0.4709
		Weighted median	18	0.8061 (0.5162–1.2588)	0.3432
		Weighted mode	18	0.7504 (0.4004–1.4061)	0.3826
MMP-16	Cervical inflammation	IVW	14	1.1068 (0.9561–1.2812)	0.1743
		MR Egger	14	0.9309 (0.6669–1.2995)	0.6814
		Weighted median	14	1.0037 (0.8228–1.2243)	0.9710
		Weighted mode	14	0.8981 (0.6560–1.2295)	0.5141
	Cervical erosion and ectropion	IVW	14	0.9499 (0.7753–1.1639)	0.6201
		MR Egger	14	0.9313 (0.5839–1.4852)	0.7700
		Weighted median	14	0.9960 (0.7461–1.3296)	0.9783
		Weighted mode	14	1.0803 (0.6899–1.6917)	0.7411
	Cervical precancerous lesions	IVW	3	1.0000 (0.9988–1.0012)	0.9834
		MR Egger	3	1.0004 (0.9756–1.0260)	0.9779
		Weighted median	3	1.0001 (0.9987–1.0014)	0.9304
		Weighted mode	3	1.0001 (0.9986–1.0016)	0.9170
	Cervical cancer	IVW	14	1.0473 (0.7571–1.4488)	0.7802
		MR Egger	14	0.8538 (0.4006–1.8197)	0.6896
		Weighted median	14	1.1485 (0.7578–1.7407)	0.5139
		Weighted mode	14	1.1801 (0.6905–2.0169)	0.5551
MMP-17	Cervical inflammation	IVW	12	0.9881 (0.8708–1.1212)	0.8525
		MR Egger	12	1.0808 (0.8164–1.4309)	0.5990
		Weighted median	12	0.9848 (0.8265–1.1734)	0.8638
		Weighted mode	12	0.9953 (0.7963–1.2439)	0.9676
	Cervical erosion and ectropion	IVW	12	0.9997 (0.8262–1.2096)	0.9977
		MR Egger	12	1.0178 (0.6620–1.5650)	0.9374
		Weighted median	12	0.9521 (0.7337–1.2354)	0.7117
		Weighted mode	12	0.9418 (0.7156–1.2396)	0.6773
	Cervical precancerous lesions	IVW	4	1.0000 (0.9991–1.0010)	0.9348
		MR Egger	4	1.0050 (0.9060–1.1147)	0.9341
		Weighted median	4	0.9999 (0.9988–1.0010)	0.8971
		Weighted mode	4	0.9998 (0.9984–1.0012)	0.8121
	Cervical cancer	IVW	12	0.7651 (0.5268–1.1114)	0.1598
		MR Egger	12	0.8360 (0.3488–2.0036)	0.6964
		Weighted median	12	0.8463 (0.5477–1.3077)	0.4523
		Weighted mode	12	0.8734 (0.4668–1.6342)	0.6801

Abbreviations: MR, mendelian randomization; SNP, single nucleotide polymorphisms; N. SNPs, number of SNPs used in MR; IVW, inverse variance weighted; CI, confidence interval; OR, odds ratio; MMPs, matrix metalloproteinases.

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(0.3939–0.9545), P = 0.0303), MMP-9 on a higher risk of cervical inflammation (OR (95% CI) = 1.1081 (1.0025–-1.2248), P = 0.0446), MMP-12 on lower risks of cervical erosion and ectropion (OR (95% CI) = 0.8354 (0.701–0.9955), P = 0.0444), and cervical cancer (OR (95% CI) = 0.6836 (0.5211–0.8968), P = 0.006). No genetic effects were observed from the remaining MMPs on cervical lesions. In addition, scatter plots provide intuitive visualizations of the SNP-specific effect sizes on MMPs and cervical lesions (Figures S1A–S5A). Forest plots illustrate the individual SNP effect estimates and coherence (Figures S1B–S5B).

Cochran's Q test found no heterogeneity in the MR analysis of MMP-3 on cervical precancerous lesions, MMP-7 on cervical cancer, MMP-9 on cervical inflammation, MMP-12 on cervical erosion and ectropion, or MMP-12 on cervical cancer (Table 2). The results of the MR-Egger regression suggested that the significant causal associations found above were not biased by horizontal pleiotropy (Table 2). The results of the MR-PRESSO global test indicated no outliers in the

Table 2 The Heterogeneity Analysis by Cochran's Q Test and Horizontal Pleiotropy Analysis by MR-Egger Regression

Exposure	Outcome	Heterogeneity (IVW)		Pleiotropy	
		Q	Q_pval	MR-Egger Intercept	*P* value
MMP-1	Cervical inflammation	11.54385664	0.8699	0.010672828	0.5065
	Cervical erosion and ectropion	17.04964012	0.5197	0.008100384	0.7372
	Cervical precancerous lesions	6.872571049	0.6504	−0.00013604	0.0676
	Cervical cancer	18.16377703	0.4449	0.012916751	0.7286
MMP-2	Cervical inflammation	8.674496536	0.1927	0.043429392	0.4557
	Cervical erosion and ectropion	1.967373902	0.9227	0.003052046	0.9652
	Cervical precancerous lesions	4.368203483	0.2244	0.000859073	0.4626
	Cervical cancer	7.310855111	0.2931	−0.171667846	0.1458
MMP-3	Cervical inflammation	13.72040685	0.3189	0.007889988	0.6708
	Cervical erosion and ectropion	15.59543371	0.2105	−0.006865174	0.8186
	Cervical precancerous lesions	3.562765608	0.8285	3.25E-06	0.9619
	Cervical cancer	15.68607003	0.2060	−0.039238964	0.3727
MMP-7	Cervical inflammation	21.8838659	0.0810	0.041908155	0.0363
	Cervical erosion and ectropion	9.837951366	0.7739	0.014164738	0.5791
	Cervical precancerous lesions	15.01978545	0.0201	0.000121736	0.6985
	Cervical cancer	19.78681891	0.1370	−0.0093613	0.8418
MMP-9	Cervical inflammation	11.14953924	0.2656	−0.031635152	0.6019
	Cervical erosion and ectropion	6.312354475	0.7083	−0.080257752	0.3198
	Cervical cancer	3.622749598	0.9344	0.013201736	0.9104
MMP-10	Cervical inflammation	14.0299963	0.7271	0.019186042	0.3148
	Cervical erosion and ectropion	30.16174663	0.0359	0.004918027	0.8957
	Cervical precancerous lesions	8.787489391	0.1178	−9.76E-05	0.7322
	Cervical cancer	26.82326619	0.0824	−0.085507713	0.0977
MMP-12	Cervical inflammation	15.50768072	0.6269	0.014988449	0.3866
	Cervical erosion and ectropion	8.934676969	0.9612	0.011224403	0.6651
	Cervical precancerous lesions	7.318900311	0.2924	9.96E-05	0.4939
	Cervical cancer	19.25081925	0.3765	0.024222196	0.5542
MMP-14	Cervical inflammation	14.18441323	0.6540	0.019703632	0.4770
	Cervical erosion and ectropion	7.927169619	0.9681	−0.031836449	0.4485
	Cervical precancerous lesions	6.212336537	0.1017	0.001713331	0.1649
	Cervical cancer	11.46746111	0.8313	0.011589428	0.8536
MMP-16	Cervical inflammation	15.5178792	0.2761	0.037565928	0.2811
	Cervical erosion and ectropion	11.84409996	0.5405	0.004300279	0.9278
	Cervical precancerous lesions	0.036921232	0.9817	−5.51E-05	0.9785
	Cervical cancer	15.0487773	0.3043	0.044784431	0.5667

(*Continued*)

Table 2 (Continued).

Exposure	Outcome	Heterogeneity (IVW)		Pleiotropy	
		Q	Q_pval	MR-Egger Intercept	*P* value
MMP-17	Cervical inflammation	8.431857439	0.6742	−0.022977993	0.4987
	Cervical erosion and ectropion	10.31075783	0.5027	−0.004594356	0.9289
	Cervical precancerous lesions	0.377353938	0.9449	−0.000672527	0.9346
	Cervical cancer	19.50327072	0.0526	−0.022838353	0.8287

Abbreviations: IVW, inverse variance weighted; MMPs, matrix metalloproteinases.

significant causal relationship between MMPs and cervical lesions (Table 3). Additionally, the leave-one-out analysis (Figure S1C–S5C), which evaluates the influence of each SNP individually, indicated that the causal estimates of MMPs were not unduly influenced by any single SNP. The funnel plots confirmed the unbiased nature of the results (Figures S1D–S5D).

Table 3 The Pleiotropy Analysis by MR-PRESSO Global Test

Exposure	Outcome	Raw		Outlier Corrected		Global P	Outliers	Distortion P
		OR (CI%)	*P*	OR (CI%)	*P*			
MMP-1	Cervical inflammation	0.9888 (0.8885–1.1005)	0.8393	NA (NA - NA)	NA	0.7137	0	0
	Cervical erosion and ectropion	0.9956 (0.8181–1.2115)	0.9652	NA (NA - NA)	NA	0.6190	0	0
	Cervical precancerous lesions	1.0002 (0.9997–1.0007)	0.4259	NA (NA - NA)	NA	0.4500	0	0
	Cervical cancer	0.8883 (0.6555–1.2037)	0.4547	NA (NA - NA)	NA	0.5017	0	0
MMP-2	Cervical inflammation	1.0107 (0.8776–1.1638)	0.8878	NA (NA - NA)	NA	0.2123	0	0
	Cervical erosion and ectropion	0.9897 (0.8936–1.0961)	0.8485	NA (NA - NA)	NA	0.9317	0	0
	Cervical precancerous lesions	0.9998 (0.9990–1.0005)	0.6093	NA (NA - NA)	NA	0.2927	0	0
	Cervical cancer	0.9019 (0.6721–1.2104)	0.5173	NA (NA - NA)	NA	0.2723	0	0
MMP-3	Cervical inflammation	1.1335 (0.9828–1.3074)	0.1109	NA (NA - NA)	NA	0.4330	0	0
	Cervical erosion and ectropion	1.1931 (0.9494–1.4994)	0.1558	NA (NA - NA)	NA	0.2673	0	0
	Cervical precancerous lesions	0.9993 (0.9988–0.9997)	0.0162	NA (NA - NA)	NA	0.8133	0	0
	Cervical cancer	1.0559 (0.7512–1.4842)	0.7597	NA (NA - NA)	NA	0.2130	0	0
MMP-7	Cervical inflammation	1.0257 (0.8351–1.2599)	0.8121	NA (NA - NA)	NA	0.1183	0	0
	Cervical erosion and ectropion	1.0172 (0.8259–1.2527)	0.8751	NA (NA - NA)	NA	0.8063	0	0
	Cervical precancerous lesions	0.9985 (0.9965–1.0006)	0.2168	NA (NA - NA)	NA	0.0450	0	0
	Cervical cancer	0.6131 (0.3939–0.9545)	0.0480	NA (NA - NA)	NA	0.2263	0	0
MMP-9	Cervical inflammation	1.1081 (1.0025–1.2248)	0.0755	NA (NA - NA)	NA	0.2653	0	0
	Cervical erosion and ectropion	0.9786 (0.8732–1.0968)	0.7189	NA (NA - NA)	NA	0.6650	0	0
	Cervical cancer	1.1912 (1.0464–1.3560)	0.0266	NA (NA - NA)	NA	0.9447	0	0
MMP-10	Cervical inflammation	1.0287 (0.8957–1.1814)	0.6936	NA (NA - NA)	NA	0.7490	0	0
	Cervical erosion and ectropion	0.9441 (0.6974–1.2780)	0.7138	NA (NA - NA)	NA	0.0450	0	0
	Cervical precancerous lesions	1.0003 (0.9986–1.0019)	0.7644	NA (NA - NA)	NA	0.1590	0	0
	Cervical cancer	1.0025 (0.6507–1.5446)	0.9911	NA (NA - NA)	NA	0.1050	0	0
MMP-12	Cervical inflammation	0.9943 (0.8926–1.1076)	0.9189	NA (NA - NA)	NA	0.6653	0	0
	Cervical erosion and ectropion	0.8354 (0.7383–0.9453)	0.0106	NA (NA - NA)	NA	0.9717	0	0
	Cervical precancerous lesions	0.9993 (0.9979–1.0006)	0.3355	NA (NA - NA)	NA	0.3550	0	0
	Cervical cancer	0.6836 (0.5211–0.8968)	0.0133	NA (NA - NA)	NA	0.4950	0	0
MMP-14	Cervical inflammation	1.0724 (0.9400–1.2235)	0.3120	NA (NA - NA)	NA	0.7073	0	0
	Cervical erosion and ectropion	1.0687 (0.9187–1.2432)	0.4005	NA (NA - NA)	NA	0.9637	0	0
	Cervical precancerous lesions	0.9997 (0.9982–1.0012)	0.7098	NA (NA - NA)	NA	0.1567	0	0
	Cervical cancer	0.8329 (0.6377–1.0877)	0.1961	NA (NA - NA)	NA	0.8563	0	0
MMP-16	Cervical inflammation	1.1068 (0.9561–1.2812)	0.1974	NA (NA - NA)	NA	0.2920	0	0
	Cervical erosion and ectropion	0.9499 (0.7825–1.1532)	0.6122	NA (NA - NA)	NA	0.5480	0	0
	Cervical precancerous lesions	0.8329 (0.6377–1.0877)	0.1961	NA (NA - NA)	NA	0.8563	0	0
	Cervical cancer	1.0473 (0.7571–1.4488)	0.7845	NA (NA - NA)	NA	0.3247	0	0

(*Continued*)

Table 3 (Continued).

Exposure	Outcome	Raw		Outlier Corrected		Global P	Outliers	Distortion P
		OR (CI%)	*P*	OR (CI%)	*P*			
MMP-17	Cervical inflammation	0.9881 (0.8846–1.1037)	0.8357	NA (NA - NA)	NA	0.7057	0	0
	Cervical erosion and ectropion	0.9997 (0.8313–1.2023)	0.9977	NA (NA - NA)	NA	0.5553	0	0
	Cervical precancerous lesions	1.0000 (0.9997–1.0004)	0.8324	NA (NA - NA)	NA	0.9453	0	0
	Cervical cancer	0.7651 (0.5268–1.1114)	0.1874	NA (NA - NA)	NA	0.0497	0	0

Abbreviations: MR, mendelian randomization; MR-PRESSO, MR pleiotropy residual sum and outlier; CI, confidence interval; OR, odds ratio; MMPs, matrix metalloproteinases.

Discussion

This study employed a two-sample MR analysis to investigate the potential causal associations between various MMPs and cervical lesions. Our results provide intriguing insights into the role of specific MMPs in the pathogenesis of cervical inflammation, cervical erosion and ectropion, cervical precancerous lesions, and cervical cancer.

Our analysis found a causal effect of MMP-3 on a lower risk of cervical precancerous lesions. MMP-3, also known as stromelysin-1, is a member of the MMP family that plays a crucial role in the degradation of extracellular matrix components, such as collagen, elastin, and proteoglycans.[8] Within the MMP family, MMP-3 is unique in its ability to activate other MMPs, thereby amplifying their proteolytic activities.[32] The results of this study, which found that MMP-3 may be interpreted as protective, contrast with previous research. Indeed, Shao et al found MMP-3 upregulation in cervical cancer patients' serum, which was associated with increased cell viability and proliferation, indicating its role as a risk factor in cervical cancer.[33] Possible reasons for this discrepancy could involve the complex interplay between MMP-3 and other factors in different stages of cervical lesion development, or variations in the study populations and methodologies employed. It is plausible that MMP-3 may exhibit protective effects in the early stages of cervical dysplasia by modulating inflammatory responses or facilitating tissue repair, whereas its overexpression in later stages may contribute to disease progression by promoting cell proliferation and invasion.[9] Furthermore, the dataset used in the present study was on blood MMP-3 levels, which may not necessarily represent the local MMP-3 levels in cervical tissues. Despite being statistically significant, the OR of MMP-3 was close to 1, raising doubts regarding the clinical significance of such results. Nevertheless, the OR of 0.9993 indicates that the risk of cervical precancerous lesions would decrease by 0.07% for each 1-unit increase of MMP-3 levels. Considering that the normal blood MMP-3 levels are in the range of 18–120 ng/mL and can increase in the range of 486±35 in inflammatory conditions like rheumatoid arthritis,[34] a change in risk based on 1-ng/mL changes can become clinically significant. Nevertheless, further research is needed to elucidate the precise role of MMP-3 in cervical carcinogenesis.

Importantly, the findings suggest a causal relationship between MMP-7 and a lower risk of cervical cancer. MMP-7, also known as matrilysin, is known for its ability to degrade extracellular matrix components and activate other MMPs.[35] MMP-7 appears to play a role in promoting tumorigenesis and progression.[36] Zhu et al revealed that MMP-7 functions as an oncogene in cervical cancer, exhibiting elevated expression in both tissues and serum of patients, and correlates with advanced pathological features.[12] Guo et al indicated that MMP-7 expression was associated with lymph node metastasis and indicated an invasive potential in early cervical cancers.[37] However, the functional properties of MMP-7 may change in specific contexts or under certain regulatory mechanisms. As for MMP-3 discussed above, the dataset was on blood MMP-7 levels, which may be different from local cervical levels. Alternatively, MMP-7 could be part of a complex regulatory network where its activity is tightly controlled and balanced with other factors, resulting in a net inhibitory effect on cancer progression in some cases.[10] The mechanisms of MMP-7 in cervical lesions remain to be investigated.

Our results indicated a causal effect of MMP-9 on increasing the risk of cervical inflammation. MMP-9, also known as gelatinase B, is involved in the degradation of gelatin and other extracellular matrix components.[38] In the context of cervical inflammation, MMP-9 may contribute to tissue damage and the promotion of inflammatory responses. Short et al demonstrated that MMP-9 plays a crucial role in cervical inflammation in pregnant women living with HIV infection, correlating with genital tract inflammation and adverse vaginal microbiota.[39] Matheus et al found that MMP-9 expression

increases with the severity of cervical lesions and is particularly elevated in the presence of infectious agents in low-grade squamous intraepithelial lesions.[40] The observed association between MMP-9 and cervical inflammation suggests that it may play a role in the pathogenesis of cervical lesions by facilitating the infiltration of inflammatory cells and the release of inflammatory mediators.[13] Therefore, targeting MMP-9 may be a promising strategy for reducing cervical inflammation and preventing disease progression.

Additionally, we found causal effects of MMP-12 on reducing the risks of cervical erosion and ectropion, as well as cervical cancer. MMP-12, also known as macrophage elastase, is primarily expressed by macrophages and plays a role in tissue repair and inflammation.[38] Makise et al indicated that MMP-12 expression, upregulated by the overexpression of Nup88, stimulates malignant phenotypes, including the invasive ability of cervical cancer cells.[41] Chen et al found that MMP-12 plays a crucial role in perineural invasion in cervical cancer by degrading the extracellular matrix.[42] However, it is plausible that the role of MMP-12 may be context-dependent, with protective effects in early stages of cervical lesions through tissue repair and inflammation, while its overexpression or deregulation in more advanced or malignant stages may contribute to disease progression. Therefore, the balance and regulation of MMP-12 activity within the cervical tissue microenvironment are likely crucial in determining its overall impact on cervical health and disease.

The clinical implications of our findings are significant. The identification of specific MMPs as causal factors in cervical diseases provides potential targets for therapeutic interventions. For example, inhibiting the activity or expression of MMPs implicated in disease progression may reduce the risk of cervical cancer development. Additionally, MMPs may serve as biomarkers for disease prediction, diagnosis, and prognosis. However, further studies are needed to confirm these associations and elucidate the underlying biological mechanisms.

A central feature of many cervical lesions is HPV infection, and HPV infection is a well-known cause of cervical cancer.[43] Although MR analyses examine associations between genetically predicted exposures and genetically predicted outcomes, hence excluding the impact of confounders, future MR studies should examine whether there are causal associations between HPV infection and MMP expression, and how it modulates the risk of cervical lesions. At the molecular level, it is known that HPV early genes encode oncoproteins (notably E5, E6, E7, and E2) that can modulate MMP expression. Indeed, these oncoproteins influence signaling pathways such as AKT, MEK/ERK, and AP-1, which in turn regulate MMP expression and activation. For example, the HPV E2 and E7 oncoproteins have been shown to increase MMP levels, facilitating carcinogenesis by promoting extracellular matrix degradation, tumor invasion, and metastasis.[44–46] HPV-positive cervical cancer cell lines show higher invasiveness and elevated MMP transcripts compared to HPV-negative lines.[47] HPV16 and HPV18 infections correlate with increased MMP-2 expression in papillomas, precancerous lesions, and squamous cell carcinomas, suggesting that HPV infection contributes to early malignant transformation via MMP upregulation.[48] HPV prophylactic vaccination is recognized as an appropriate method to decrease the risk of cervical cancer,[49] and its effect on MMP should be evaluated in future studies.

However, several limitations should be acknowledged. Firstly, the number of MMP-associated SNPs ultimately used for the outcome analysis was affected by data quality issues related to cervical precancerous lesions. This could have potentially limited the power to detect significant associations, especially for those MMPs with fewer high-quality SNPs available. Efforts should be made to improve the quality and quantity of genetic data available for cervical lesions. This could include collecting larger and more diverse sample sets, ensuring robust genotyping and phenotyping protocols, and harmonizing data across studies. Secondly, the genetic variants and their effects may differ across populations. The current study may not fully capture genetic diversity across different ethnicities, which could limit the generalizability of the findings. Conducting multi-ethnic studies will help to identify potential population-specific genetic associations and enhance the generalizability of findings. Such studies can provide insights into the genetic architecture of cervical lesions across diverse populations. Above all, while the current study provides valuable insights into the potential causal role of MMPs in cervical lesions, further research is needed to overcome existing limitations and fully elucidate the complex genetic underpinnings of these conditions.

Conclusion

In conclusion, our study provides evidence for the potential causal associations between specific MMPs and cervical lesions. These findings contribute to a better understanding of the pathogenesis of these conditions and may have

important implications for the development of new therapeutic strategies and diagnostic tools. However, further research is needed to validate these associations and explore the underlying biological mechanisms.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

The study was submitted to the ethics committee of Hongqi Hospital Affiliated to Mudanjiang Medical University. The need for ethical approval was waived by the committee because the study used publicly available aggregated data that did not allow the re-identification of the original participants, as supported by Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China, as well as various legislations around the globe.[19]

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 report no conflicts of interest in this work.

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