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ORIGINAL RESEARCH

Causal Effects of Smoking, Alcohol, Coffee, and Tea Intake on Gynecologic Cancers: A Mendelian Randomization Study

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Objective: The two-sample Mendelian randomization (MR) approach was used to evaluate the causal association between modifiable lifestyle and gynecological tumors.

Methods: Based on publicly accessible summary level genome-wide association study (GWAS), the exposures were age of smoking initiation, cigarettes per day, smoking cessation, smoking initiation, alcohol intake, tea intake, coffee intake, and the outcomes were cervical, ovarian and endometrial cancer. IVW, MR-Egger, WM, Weighted Mode and Simple Mode method were used to evaluate the causal relationship, and sensitivity analysis, heterogeneity analysis and heterogeneity analysis were performed.

Results: Smoking initiation (OR: 1.186, 95% CI: 1.009–1.394, P= 0.040) and alcohol intake (OR: 1.235, 95% CI: 1.063–1.436, P= 0.010) increased the risk of ovarian cancer, smoking cessation (OR: 0.636, 95% CI: 0.441–0.917, P= 0.020) was a protective factor for endometrial cancer, while alcohol intake (OR: 1.262, 95% CI: 1.051–1.517, P= 0.010) was a risk factor for endometrial cancer. Cigarettes per day (OR: 1.004, 95% CI: 1.001–1.007, P= 0.000) and smoking initiation (OR: 1.003, 95% CI: 1.001–1.005, P= 0.000) both increase the risk of cervical cancer. The sensitivity analysis of each group showed robust results, no pleiotropy was found, and there were no abnormal variables in the heterogeneity test.

Conclusion: Smoking and alcohol intake are causally linked to gynecological tumors, whereas the tea and coffee intake do not exhibit a causal association with gynecological tumors.

Keywords: lifestyle, cervical cancer, ovarian cancer, endometrial cancer, Mendelian randomization

Introduction

Gynecologic tumors, including cervical, ovarian, and endometrial cancers, represent a significant global health burden, accounting for over 1.2 million new cases annually and ranking among the leading causes of cancer-related mortality in women worldwide.[1,2] Gynecological tumors, including cervical cancer, ovarian cancer, and endometrial cancer, stand as the primary contributors to cancer-related fatalities among women worldwide.[3] While considerable advancements have been made in the early identification and management of gynecological tumors, preventing the occurrence and progression of these tumors remains a major challenge. The specific mechanisms underlying cervical cancer, ovarian cancer, and endometrial cancer are not yet fully understood, and they may be influenced by various factors such as genetics, environment, and lifestyle. Epidemiological studies suggest that tobacco consumption, alcohol intake, and certain lifestyle choices, such as coffee consumption, may be risk factors for these cancers.[4] There is also research indicating that these lifestyle factors are associated with poor cancer prognosis, possibly because these behaviors themselves have adverse effects on survival.[5] Tobacco smoking is strongly associated with cervical carcinogenesis, largely mediated by interactions with human papillomavirus (HPV) infection.[6] However, its relationship with ovarian and endometrial cancers is inconsistent across studies, likely due to residual confounding by hormonal therapies or socioeconomic factors.[7,8] Similarly, alcohol intake has been variably linked to ovarian cancer risk in cohort studies, while its association with endometrial cancer remains ambiguous, with some suggesting a protective effect via estrogen modulation.[9,10]

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Coffee and tea consumption, hypothesized to influence carcinogenesis through caffeine's dual roles in DNA repair inhibition and antioxidant activity, also lack consensus in observational data.[11,12]

Traditional epidemiological approaches are limited by confounding and reverse causality, particularly for lifestyle factors intertwined with complex behavioral and environmental variables.[13] Mendelian randomization (MR), which uses genetic variants as instrumental variables, circumvents these biases by leveraging the random allocation of alleles at conception, mimicking a randomized controlled trial design.[14] Recent MR studies have clarified causal relationships between smoking and lung cancer, alcohol and breast cancer,[5] and obesity and endometrial cancer,[15] underscoring its utility in disentangling etiology. However, no MR study has comprehensively assessed smoking, alcohol, coffee, and tea intake across all three major gynecologic tumors, leaving critical gaps in causal evidence.

This study employs a two-sample MR analysis to evaluate the causal effects of seven modifiable lifestyle factors—ever smoking, age of ever smoking, cigarettes per day, smoking cessation, alcohol intake, coffee intake, and tea intake—on cervical, ovarian, and endometrial cancers. Using large-scale genome-wide association study (GWAS) data from European populations, we aim to resolve inconsistencies in observational literature and provide robust evidence to inform prevention guidelines.

Materials and Methods

Study Design

We conducted a two-sample MR analysis to explore the potential causal relationships between modifiable lifestyle factors and gynecologic cancers (cervical, ovarian, and endometrial cancers). Genetic variants associated with lifestyle exposures were used as instrumental variables (IVs) to infer causality. This study adheres to the three core assumptions of MR:[16] The genetic instrumental variables must be closely associated with cervical cancer, ovarian cancer, and endometrial cancer; Genetic instrumental variables are independent of confounding factors influencing exposure and outcome; Genetic instrumental variables can only influence cervical cancer, ovarian cancer, and endometrial cancer through modifiable lifestyle factors. This study utilized summary-level GWAS data from publicly available databases. All original studies contributing to these databases obtained ethical approval and participant consent. As no individual-level data were accessed or analyzed, additional ethical approval was not required.

Exposure Data

The summary data on smoking is derived from the Alcohol and Nicotine use Genome-Wide Association Studies and Sequencing Consortium (GSCAN). The GSCAN study incorporated data from 2.6 million individuals of European ancestry across 59 cohorts. It encompassed four smoking-related phenotypes: ever smoking (n=2,669,029), age of ever smoking (n=618,541), cigarettes per day (n=618,489), and smoking cessation (n=1147). The smoking-related traits (ever smoking, smoking cessation, etc.) were obtained from independent GWAS datasets conducted within the GSCAN consortium. Each phenotype was analyzed separately, and care was taken to minimize sample overlap and confounding between traits. Summary data on alcohol intake, coffee intake, and tea intake were derived from aggregated data from the MRC-IEU UK Biobank.

Outcome Data

The summary data for gynecological tumors were obtained from the MRC IEU OpenGWAS database of the UK Biobank. The GWAS data from the Ovarian Cancer Association Consortium (OCAC) included a total of 66,450 individuals of European descent from 14 countries (comprising 25,509 cases and 40,941 controls).[11] The aggregated data for endometrial cancer were derived from the meta-GWAS dataset, comprising 12,906 endometrial cancer cases and 108,979 controls.[12] The summary data for cervical cancer comprised a total of 1889 cases and 461,044 controls.

Statistical Analysis

Mendelian Randomization Analysis

Genetic instrumental variables were selected by setting criteria, specifically choosing SNPs associated with the exposure variable that achieved genome-wide significance ($P < 5E-8$). To mitigate bias due to strong linkage disequilibrium (LD)

between SNPs, LD parameter $r^2 < 0.001$ was utilized to obtain independent SNPs linked with each trait. This study employed the inverse-variance weighted method (IVW), MR-Egger method, weighted median method (WM), Weighted Mode method, and Simple Mode method. The results of the IVW method served as the main information source, and individual SNP Wald estimates were meta-analyzed through a synthesis analysis.[17] To mitigate bias resulting from insufficient instrumental variables, the statistical strength F value for each SNP was computed. The calculation formula is given by R2(N-2)/(1-R2), where R2 represents the coefficient of determination and N is the sample size. F > 10 indicates the absence of weak instrument bias. Leave-one-out method for sensitivity was employed to explore the impact of individual SNPs on causal associations. MR-pleiotropy was used to examine pleiotropy, and P>0.05 indicated that there was no pleiotropy. These analyses were conducted using the "TwoSampleMR" and "MRPRESSO" packages in RStudio software (version 4.2.1). All data used in this study came from published GWAS databases, so ethical approval is not required.

Results

Causal Relationship between Modifiable Lifestyle and Ovarian Cancer

The relationship between modifiable lifestyle factors and ovarian cancer is illustrated in Figure 1. The IVW random-effects model results suggest that initiating smoking (OR: 1.186, 95% CI: 1.009–1.394, $P = 0.040$) and alcohol consumption (OR: 1.235, 95% CI: 1.063–1.436, $P = 0.010$) are linked to an increased risk of ovarian cancer. In contrast, other smoking-related traits (age of ever smoking, cigarettes per day, and smoking cessation), as well as tea and coffee consumption, showed no causal association with ovarian cancer risk. No significant impact on the estimated causal relationship was observed for SNPs

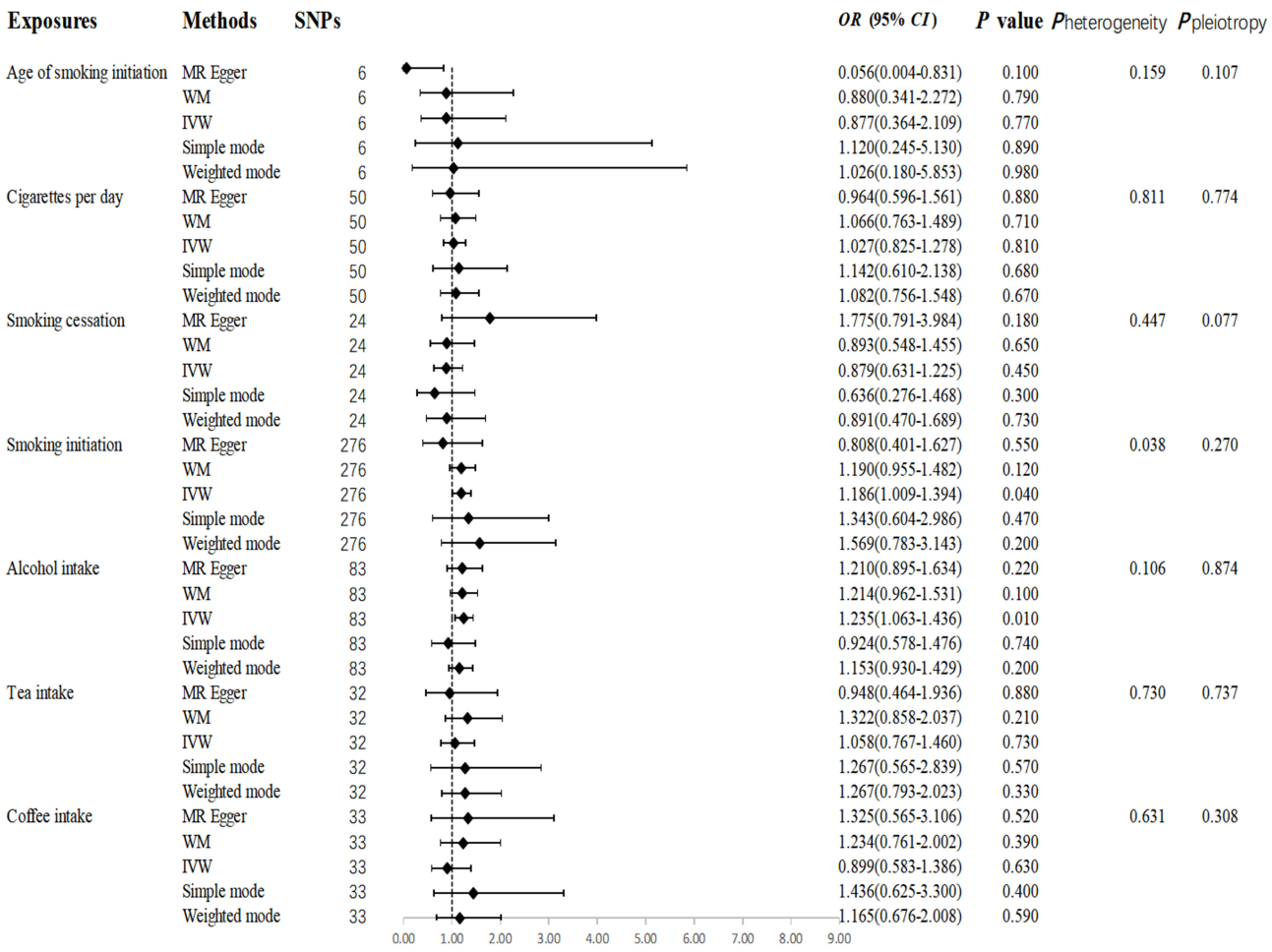

Figure 1 Mendelian randomization method for assessing the causal association between modifiable risk factors and ovarian cancer.
Abbreviations: IVW, inverse-variance weighted; WM, weighted median; SNPs, single nucleotide polymorphisms; OR, odd ratio.

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during the stepwise exclusion process (Figure 2). The results indicate that tea and coffee consumption is not linked to the risk of ovarian cancer. No significant impact on the estimated causal relationship was observed for SNPs during the stepwise exclusion process. The all P-values in the ME-Egger method were exceeded 0.05, indicating the absence of heterogeneity. The results of pleiotropy analysis showed that all P-values were greater than 0.05, so there was no pleiotropy (Figure 1).

Causal Relationship between Modifiable Lifestyle and Endometrial Cancer

The effect values and their 95% CIs for the MR results for the two samples are shown in Figure 3. IVW-MR results showed that smoking cessation (OR: 0.636, 95% CI: 0.441–0.917, $P = 0.020$) reduced the risk of endometrial cancer, while alcohol consumption (OR: 1.262, 95% CI: 1.051–1.517, $P = 0.010$) increased the risk of endometrial cancer. Age at ever smoking, daily smoking, ever smoking, and tea versus coffee consumption were not related to the endometrial cancer risk. Sensitivity analyses showed no SNPs were found that had a large impact on the estimates (Figure 2). The absence of horizontal pleiotropy biased the results (Figure 3).

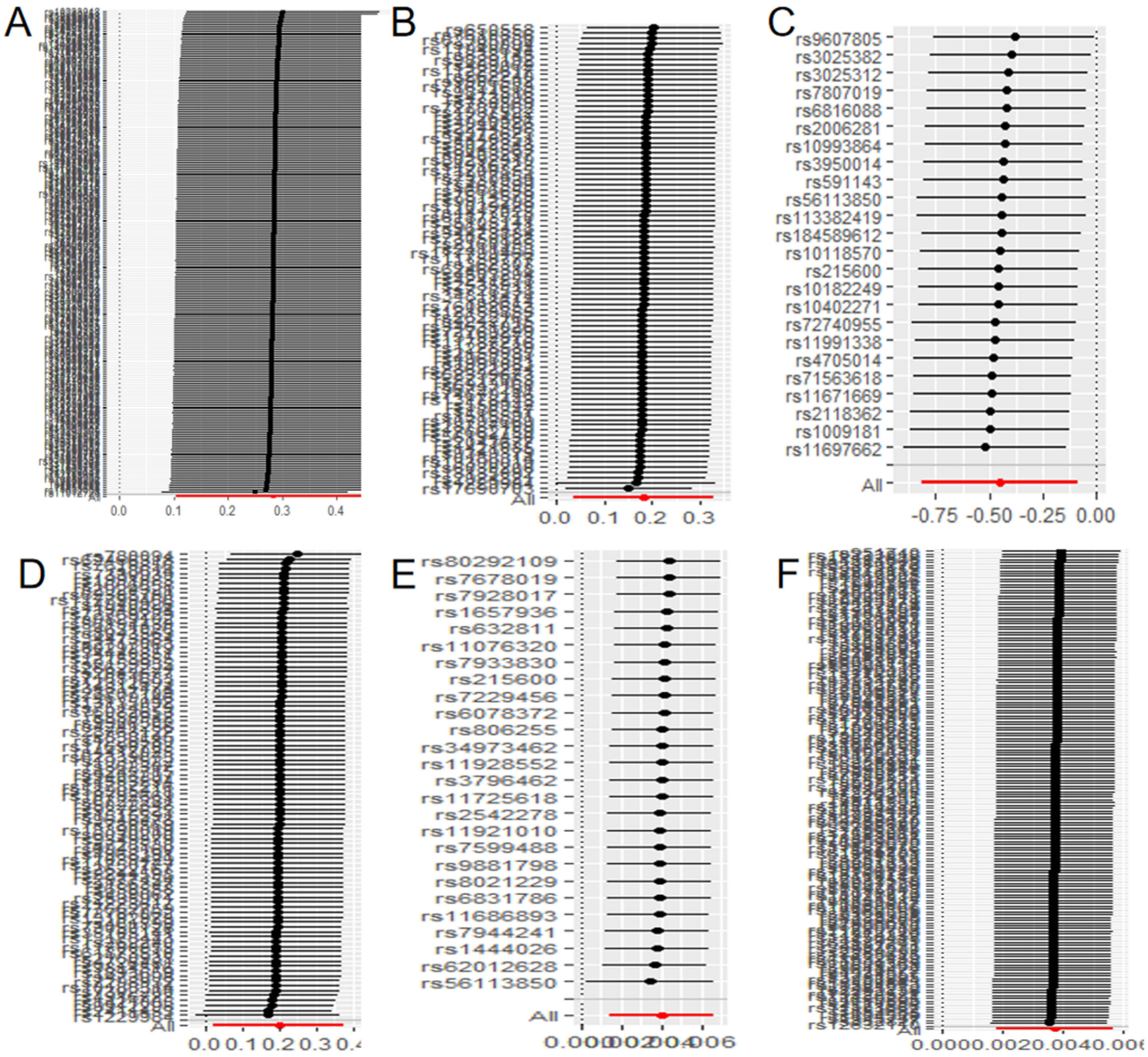

Figure 2 "Leave one out" sensitivity analysis results. (**A**) ever smoking and ovarian cancer; (**B**) Alcohol intake and ovarian cancer; (**C**) Smoking cessation and endometrial cancer; (**D**) Alcohol intake and endometrial cancer; (**E**) Cigarettes per day and cervical cancer; (**F**) ever smoking and cervical cancer.

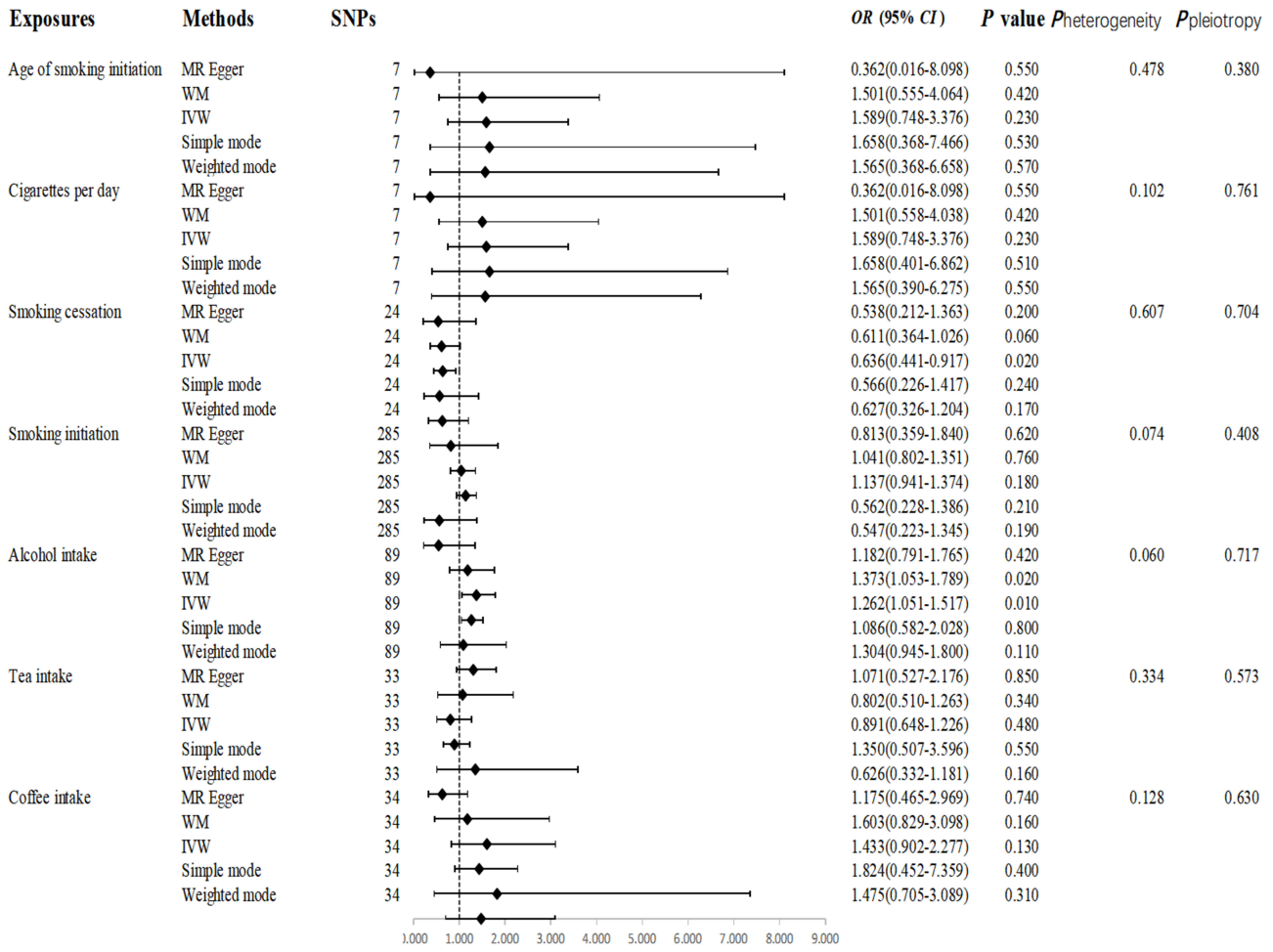

Figure 3 Mendelian randomization method for assessing the causal association between modifiable risk factors and endometrial cancer.
Abbreviations: IVW, inverse-variance weighted; WM, weighted median; SNPs, single nucleotide polymorphisms; OR, odd ratio.

Causal Relationship between Modifiable Lifestyle and Cervical Cancer

Mendelian randomization showed that both daily smoking (OR: 1.004, 95% CI: 1.001–1.007, $P = 0.000$) and initiation of smoking (OR: 1.003, 95% CI: 1.001–1.005, $P = 0.000$) increased the cervical cancer risk. Alcohol consumption, tea consumption, and coffee consumption are not associated with the risk of cervical cancer (Figure 4). In order to assess result reliability, the sensitivity analysis was conducted, and the leave-one-out method showed that individual SNPs had no impact on the overall MR estimate (Figure 2). Neither MR-Egger method nor MR_pleiotropy detected any potential horizontal pleiotropy ($P > 0.05$) and the results were robust.

Discussion

The prevention of cervical, ovarian and endometrial cancers remains a great challenge. However, the relationship between modifiable lifestyle and gynecologic cancers is currently inconclusive. This study reveals the relationship between modifiable lifestyle and cervical, ovarian and endometrial cancers by two-sample MR based on pooled data from GWAS. This is the first study to assess the association between modifiable lifestyle and gynecologic neoplasms using a Mendelian randomization approach that eliminates potential confounders through the use of genetic instrumental variables. Our findings suggest that initiation of smoking and alcohol consumption increase the ovarian cancer risk, smoking cessation is a protective factor for endometrial cancer, and alcohol consumption is a risk factor for endometrial cancer. Both daily smoking and ever smoking increased the risk of cervical cancer.

Exposures	Methods	SNPs	OR (95% CI)	P value	Pheterogeneity	Ppleiotropy
Age of smoking initiation	MR Egger	6	0.965(0.838-1.110)	0.640	0.193	0.678
	WM	6	0.998(0.988-1.008)	0.670		
	IVW	6	0.996(0.987-1.005)	0.360		
	Simple mode	6	1.001(0.984-1.018)	0.940		
	Weighted mode	6	1.001(0.986-1.016)	0.940		
Cigarettes per day	MR Egger	26	1.005(0.999-1.010)	0.130	0.060	0.839
	WM	26	1.005(1.001-1.009)	0.010		
	IVW	26	1.004(1.001-1.007)	0.000		
	Simple mode	26	1.008(1.001-1.016)	0.040		
	Weighted mode	26	1.005(1.001-1.009)	0.010		
Smoking cessation	MR Egger	14	0.987(0.976-0.999)	0.050	0.667	0.054
	WM	14	1.000(0.994-1.006)	0.960		
	IVW	14	0.999(0.995-1.003)	0.670		
	Simple mode	14	1.001(0.990-1.013)	0.810		
	Weighted mode	14	1.001(0.993-1.009)	0.810		
Smoking initiation	MR Egger	204	1.005(0.995-1.015)	0.330	0.101	0.689
	WM	204	1.003(1.001-1.006)	0.010		
	IVW	204	1.003(1.001-1.005)	0.000		
	Simple mode	204	0.999(0.991-1.007)	0.860		
	Weighted mode	204	1.004(0.996-1.012)	0.290		
Alcohol intake	MR Egger	66	1.000(0.994-1.006)	1.000	0.067	0.620
	WM	66	1.001(0.999-1.004)	0.240		
	IVW	66	1.002(1.000-1.003)	0.070		
	Simple mode	66	1.002(0.997-1.008)	0.360		
	Weighted mode	66	1.002(0.999-1.006)	0.220		
Tea intake	MR Egger	27	1.000(0.994-1.006)	0.910	0.682	0.737
	WM	27	1.000(0.996-1.004)	0.990		
	IVW	27	1.001(0.998-1.003)	0.690		
	Simple mode	27	1.003(0.996-1.010)	0.440		
	Weighted mode	27	1.000(0.996-1.005)	0.820		
Coffee intake	MR Egger	26	1.000(0.994-1.007)	0.950	0.921	0.891
	WM	26	1.000(0.995-1.005)	0.970		
	IVW	26	1.000(0.996-1.003)	0.920		
	Simple mode	26	0.999(0.990-1.008)	0.800		
	Weighted mode	26	1.000(0.995-1.005)	0.990		

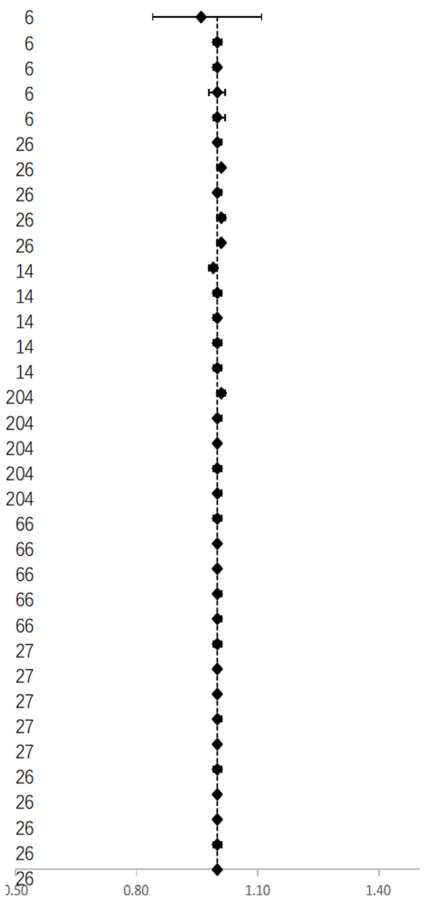

Figure 4 Mendelian randomization method for assessing the causal association between modifiable risk factors and cervical cancer.
Abbreviations: IVW, inverse-variance weighted; WM, weighted median; SNPs, single nucleotide polymorphisms; OR, odd ratio.

Smoking plays a role in the onset, progression and metastasis of cancer and is associated with poor prognosis. It has been shown that patients with ovarian cancer before and after diagnosis have a significantly higher specific mortality rate compared to non-smokers.[18] Smoking increases a woman's risk of progressing from HPV infection to cervical cancer. Munoz et. al[19] demonstrated a correlation that varies with the dosage level between tobacco smoke and the HPV-16 oncogene. Previous studies have shown that individuals who quit smoking experience a notably reduced likelihood of developing endometrial cancer.[20] This study suggests that smoking increases the risk of ovarian and cervical cancer. On the other hand, ceasing smoking is associated with a decreased risk of endometrial cancer. This aligns with findings reported in prior studies. Sensitivity analysis showed the results to be robust. The exact mechanism of how smoking contributes to cervical, ovarian and endometrial cancers is unknown. Nicotine found in tobacco exhibits a pro-cancer effect, and prolonged smoking is associated with the proliferation of cancer cells and the occurrence of epithelial-mesenchymal transition,[21] while smoke includes carcinogens such as aromatic amines and N-nitrosamines,[22] which increase pro-inflammatory factors and chemokines in the tumor microenvironment, and may lead to chemotherapy resistance. Although ever smoking and smoking cessation are genetically and behaviorally linked traits, the protective association observed for smoking cessation should be interpreted cautiously. This does not imply that smoking followed by quitting is more beneficial than never smoking. Instead, the result emphasizes the benefit of cessation among ever smokers. Future studies may consider multivariable MR approaches to disentangle overlapping behavioral traits.

The association between alcohol consumption and the risk of ovarian and endometrial cancer remains a topic of ongoing debate and disagreement. The mechanism by which alcohol consumption contributes to carcinogenesis may be through increased cumulative estrogen, epithelial cell genotoxicity, and mitogenesis leading to the development of

ovarian and endometrial cancers.[11] Meanwhile, acetaldehyde, the main metabolite of alcohol, has been classified as a carcinogen.[9] Reducing alcohol consumption is not linked to ovarian cancer development, and elevated alcohol intake is only associated with an increased risk of junctional ovarian cancer.[23] In another extensive prospective study involving 795,121 women, the findings indicated that the consumption of alcohol had no impact on the occurrence of endometrial cancer when compared to non-drinking women.[24] Therefore, the association between alcohol consumption and ovarian and endometrial cancers needs to be verified by more epidemiologic studies.

Whether tea and coffee consumption affects the development of gynecologic tumors remains unclear. Our MR study results indicated the absence of a causal link between the consumption of tea and coffee and the occurrence of cervical, ovarian, and endometrial cancers. Caffeine, present in both tea and coffee, might elevate the risk of cancer through its impact on the cell cycle and DNA repair processes,[25] in addition to caffeine's preventive role by interfering with pro-inflammatory processes through antioxidants.[26] Further large-scale studies are necessary to investigate the correlation between the consumption of tea and coffee and the occurrence of gynecologic neoplasms. Our study did not detect causal associations between tea or coffee consumption and the risk of cervical, ovarian, or endometrial cancers. While observational studies have reported both protective and adverse effects, these findings are often inconsistent and may be confounded by lifestyle, socioeconomic, or dietary patterns. The lack of association in our MR analysis suggests that if any effect exists, it may be weak or confounded in traditional studies. Further research with beverage subtype-specific exposures may clarify potential biological effects.

Our findings highlight smoking and alcohol consumption as modifiable risk factors for gynecologic tumors. While this study focused on causal lifestyle effects, emerging evidence suggests that tumor biomarkers such as CA125 and CA199 may mediate or reflect the biological pathways linking these exposures to cancer progression. For instance, elevated CA125 levels, a hallmark of ovarian cancer, are associated with chronic inflammation and oxidative stress—processes exacerbated by smoking and alcohol use.[27,28] Recent studies propose that smoking-induced systemic inflammation may upregulate CA125 expression, potentially accelerating malignant transformation in ovarian epithelial cells.[29] Clinically, CA125 remains pivotal for ovarian cancer diagnosis and monitoring, though its specificity is limited, as benign conditions may also elevate CA125 levels.[30] This underscores the importance of integrating imaging modalities with biomarker profiling to distinguish malignant from benign pelvic masses, particularly in symptomatic women.[31] Future studies should explore whether lifestyle interventions modulate tumor marker dynamics, offering dual benefits in prevention and early detection.

MR is an analytical approach that employs genetic variation as a mediating tool to effectively overcome potential confounders and reverse causality, and is widely used in studies of various disease exposures and outcomes to explore relationships between diseases. MR studies have explored the connection between smoking and endometrial cancer,[10] as well as the correlation between smoking, alcohol consumption, and coffee intake with ovarian cancer.[11,32] In comparison to these investigations, the current study stands out for its utilization of a substantial sample of GWAS data in the two-sample MR analysis. The ample sample size enhances the causal validity, providing a robust etiological explanation for the association between modifiable lifestyle and gynecological tumors. The selected exposures in this study were ever smoking, age of ever smoking, daily smoking, smoking cessation, alcohol consumption, coffee and tea consumption 7 modifiable lifestyle. For the Mendelian randomization study of smoking and endometrial cancer,[10] the selected exposures in this literature were lifetime smoking and regular smoking, and the MR analysis indicated the absence of a causal link between lifetime smoking, regular smoking, and the risk of endometrial cancer. In this study, MR findings indicated that smoking cessation (OR: 0.636, 95% CI: 0.441–0.917, P= 0.020) was associated with a reduced risk of endometrial cancer, whereas alcohol consumption (OR: 1.262, 95% CI: 1.051–1.517, P= 0.010) was linked to an increased risk of endometrial cancer.

In the MR investigation on the correlation of smoking, alcohol consumption, and coffee intake with ovarian cancer,[11] the literature indicates that initiating smoking and coffee consumption heightened the ovarian cancer risk. Contrarily, no causal link was observed between alcohol consumption and the risk of ovarian cancer. The MR analysis aligned with these results, showing that the initiation of smoking (OR: 1.186, 95% CI: 1.009–1.394, P= 0.040) corroborated the aforementioned findings, albeit using a distinct database for this study. However, the database selected for this study ultimately included 89 SNPs for alcohol consumption, and the results of MR analysis showed that alcohol consumption (OR: 1.235, 95% CI: 1.063–1.436, P= 0.010) increased the risk of ovarian cancer. For the MR Study of Alcohol Consumption and Ovarian Cancer,[32] the exposures selected for

this study were weekly drinking, drinking disorders and age-adjusted alcohol use disorder identification tests, which were inconsistent with the exposure database used in this study. This paper uses the latest large-scale GWAS genetic data to assess causal associations between seven modifiable lifestyle variables (ever smoking, age of ever smoking, daily smoking, smoking cessation, alcohol consumption, coffee and tea consumption) and gynecologic neoplasms (cervical, ovarian, and endometrial cancers) using a two-sample MR approach, which improves the statistical efficacy of the causal associations and efficiently overcomes potential confounders and reverse causality. The exposure and outcome databases included in this study for analysis were all European, effectively reducing demographic-induced bias and excluding spurious associations caused by population stratification. However, to ascertain the applicability of these findings to diverse populations, additional validation is essential. Samples from different ethnic groups should be considered to increase the generalizability of the results. This study utilized summary data from GWAS research, precluding the assessment of non-linear relationships between exposure factors and outcome variables. Additionally, due to data limitations, subgroup analyses by age of onset could not be conducted. Causal inference regarding the association between modifiable lifestyle factors and the occurrence of gynecologic tumors using MR can only be preliminary, as the underlying biological mechanisms remain incompletely understood. Therefore, future research endeavors necessitate the inclusion of diverse populations, larger case numbers, and sample sizes, as well as the utilization of more advanced experimental techniques and statistical methodologies to elucidate causal relationships.

In conclusion, this study explored the relationship between modifiable lifestyle and gynecologic neoplasms based on MR of a large sample of data. The findings indicated a causal link between smoking and alcohol consumption with gynecologic neoplasms. However, no causal association was observed between tea and coffee consumption and gynecologic neoplasms.

Abbreviations

GSCAN, Genome-Wide Association Studies and Sequencing Consortium; GWAS, genome-wide association study; IVW, inverse-variance weighted method; LD, linkage disequilibrium; MR, Mendelian randomization; OCAC, Ovarian Cancer Association Consortium; OR, odd ratio; SNPs, single nucleotide polymorphisms; WM, weighted median method.

Ethics and Consent Statements

All datasets utilized in this study are publicly available and de-identified, ensuring compliance with the General Data Protection Regulation (GDPR) of the European Union. No individual-level data were processed, eliminating privacy concerns. Original GWAS studies contributing to the GSCAN, UK Biobank, and OCAC databases obtained written informed consent from participants, explicitly permitting secondary analyses of aggregated genetic data.

Ethics Approval and Consent to Participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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 that they have no competing interests in this work.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Arbyn M, Weiderpass E, Bruni L, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health*. 2020;8(2):e191–e203. doi:10.1016/S2214-109X(19)30482-6
3. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: an overview. *Int J Cancer*. 2021;149(4):778–789. doi:10.1002/ijc.33588
4. Tanha K, Mottaghi A, Nojomi M, et al. Investigation on factors associated with ovarian cancer: an umbrella review of systematic review and meta-analyses. *J Ovarian Res*. 2021;14(1):153. doi:10.1186/s13048-021-00911-z
5. Wang T, Townsend MK, Vinci C, et al. Early life exposure to tobacco smoke and ovarian cancer risk in adulthood. *Int J Epidemiol*. 2021;50(3):965–974. doi:10.1093/ije/dyab018
6. Roura E, Castellsague X, Pawlita M, et al. Smoking as a major risk factor for cervical cancer and pre-cancer: results from the epic cohort. *Int J Cancer*. 2014;135(2):453–466. doi:10.1002/ijc.28666
7. Nkondjock A. Coffee consumption and the risk of cancer: an overview. *Cancer Lett*. 2009;277(2):121–125. doi:10.1016/j.canlet.2008.08.022
8. Tang N, Wu Y, Zhou B, et al. Green tea, black tea consumption and risk of lung cancer: a meta-analysis. *Lung Cancer*. 2009;65(3):274–283. doi:10.1016/j.lungcan.2008.12.002
9. Rumgay H, Murphy N, Ferrari P, et al. Alcohol and cancer: epidemiology and biological mechanisms. *Nutrients*. 2021;13(9):3173. doi:10.3390/nu13093173
10. Dimou N, Omiyale W, Biessy C, et al. Cigarette smoking and endometrial cancer risk: observational and Mendelian randomization analyses. *Cancer Epidemiol Biomarkers Prev*. 2022;31(9):1839–1848. doi:10.1158/1055-9965.EPI-21-1176
11. Liu S, Feng S, Du F, et al. Association of smoking, alcohol, and coffee consumption with the risk of ovarian cancer and prognosis: a Mendelian randomization study. *BMC Cancer*. 2023;23(1):256. doi:10.1186/s12885-023-10737-1
12. Bouras E, Karhunen V, Gill D, et al. Circulating inflammatory cytokines and risk of five cancers: a Mendelian randomization analysis. *BMC Med*. 2022;20(1):3. doi:10.1186/s12916-021-02193-0
13. Sanderson E, Glymour MM, Holmes MV, et al. Mendelian randomization. *Nat Rev Meth Primers*. 2022;2. doi:10.1038/s43586-021-00092-5
14. Burgess S, Swanson SA, Labrecque JA. Are Mendelian randomization investigations immune from bias due to reverse causation? *Eur J Epidemiol*. 2021;36(3):253–257. doi:10.1007/s10654-021-00726-8
15. Del Riccio M, Vettori V, Raimondi S, et al. The clinical impact of continued smoking in patients with breast and other hormone-dependent cancer: a systematic literature review. *Crit Rev Oncol Hematol*. 2023;184:103951. doi:10.1016/j.critrevonc.2023.103951
16. de Leeuw C, Savage J, Bucur IG, et al. Understanding the assumptions underlying Mendelian randomization. *Eur J Hum Genet*. 2022;30(6):653–660. doi:10.1038/s41431-022-01038-5
17. Wang Q, Shi Q, Lu J, et al. Causal relationships between inflammatory factors and multiple myeloma: a bidirectional Mendelian randomization study. *Int J Cancer*. 2022;151(10):1750–1759. doi:10.1002/ijc.34214
18. Wang T, Townsend MK, Simmons V, et al. Prediagnosis and postdiagnosis smoking and survival following diagnosis with ovarian cancer. *Int J Cancer*. 2020;147(3):736–746. doi:10.1002/ijc.32773
19. Munoz JP, Carrillo-Beltran D, Aedo-Aguilera V, et al. Tobacco exposure enhances human papillomavirus 16 oncogene expression via egfr/pi3k/akt/c-jun signaling pathway in cervical cancer cells. *Front Microbiol*. 2018;9:3022. doi:10.3389/fmicb.2018.03022
20. Felix AS, Yang HP, Gierach GL, et al. Cigarette smoking and endometrial carcinoma risk: the role of effect modification and tumor heterogeneity. *Cancer Causes Control*. 2014;25(4):479–489. doi:10.1007/s10552-014-0350-1
21. Liang Z, Fang S, Zhang Y, et al. Cigarette smoke-induced gastric cancer cell exosomes affected the fate of surrounding normal cells via the circ0000670/wnt/beta-catenin axis. *Toxics*. 2023;11(5):465. doi:10.3390/toxics11050465
22. Ji H, Jin Z. Analysis of six aromatic amines in the mainstream smoke of tobacco products. *Anal Bioanal Chem*. 2022;414(14):4227–4234. doi:10.1007/s00216-022-04075-7
23. Rota M, Pasquali E, Scotti L, et al. Alcohol drinking and epithelial ovarian cancer risk. A systematic review and meta-analysis. *Gynecol Oncol*. 2012;125(3):758–763. doi:10.1016/j.ygyno.2012.03.031
24. Je Y, De Vivo I, Giovannucci E. Long-term alcohol intake and risk of endometrial cancer in the nurses' health study, 1980-2010. *Br J Cancer*. 2014;111(1):186–194. doi:10.1038/bjc.2014.257
25. Meisaprow P, Aksorn N, Vinayanuwattikun C, et al. Caffeine induces g0/g1 cell cycle arrest and inhibits migration through integrin alphav, beta3, and fak/akt/c-myc signaling pathway. *Molecules*. 2021;26(24):7659. doi:10.3390/molecules26247659
26. Rodak K, Kokot I, Kratz EM. Caffeine as a factor influencing the functioning of the human body-friend or foe? *Nutrients*. 2021;13(9):3088.
27. Trabert B, Pinto L, Hartge P, et al. Pre-diagnostic serum levels of inflammation markers and risk of ovarian cancer in the prostate, lung, colorectal and ovarian cancer (plco) screening trial. *Gynecol Oncol*. 2014;135(2):297–304. doi:10.1016/j.ygyno.2014.08.025
28. Watts EL, Perez-Cornago A, Appleby PN, et al. The associations of anthropometric, behavioural and sociodemographic factors with circulating concentrations of igf-i, igf-ii, igfbp-1, igfbp-2 and igfbp-3 in a pooled analysis of 16,024 men from 22 studies. *Int J Cancer*. 2019;145(12):3244–3256. doi:10.1002/ijc.32276
29. Zhang M, Cheng S, Jin Y, et al. Roles of ca125 in diagnosis, prediction, and oncogenesis of ovarian cancer. *Biochim Biophys Acta Rev Cancer*. 2021;1875(2):188503. doi:10.1016/j.bbcan.2021.188503
30. Henderson JT, Webber EM, Sawaya GF. Screening for ovarian cancer: updated evidence report and systematic review for the us preventive services task force. *JAMA*. 2018;319(6):595–606. doi:10.1001/jama.2017.21421
31. Radosa MP, Camara O, Vorwergk J, et al. Preoperative multimodal strategies for risk assessment of adnexal masses: analysis of 1362 cases in a gynecologic cancer center. *Int J Gynecol Cancer*. 2011;21(6):1056–1062. doi:10.1097/IGC.0b013e3182187eb0
32. Zhu J, Jiang X, Niu Z. Alcohol consumption and risk of breast and ovarian cancer: a Mendelian randomization study. *Cancer Genet*. 2020;245:35–41. doi:10.1016/j.cancergen.2020.06.001