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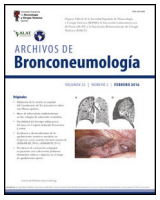

Scientific Letter

Unveiling the Link between Asthma and Cancer Risk: Shedding New Light through Mendelian Randomization

To the Director,

Asthma is the most common chronic respiratory disease, affecting an estimated 262 million people worldwide and associated with several comorbidities whose prevalence have increased in recent years.[1] Although the broader implications of asthma in the development of cancer have been of interest for many years, evidence regarding the risk of cancer development after asthma diagnosis is controversial and inconclusive. For instance, a Korean population-based cohort showed that asthma increased the risk of several cancer,[2] but other epidemiological studies suggested that asthma decreased the overall risk of cancer.[3] Conflicting observations may be from small sample sizes, inadequate adjustment for confounding factors that could affect cancer development, use of cross-sectional or case–control designs, or focus on specific cancer types. For example, traffic-related air pollution has been related to the development of a wide variety of cancers in adults and also has been found to be a risk factor for the development of adult-onset asthma. Pollutants vary by geographic location, and individuals living closer to major roadways may be at a higher risk for both asthma and cancer. Due to the limitation of observational design, it remains unclear if there is a true causal relationship between asthma itself and cancer risks. Mendelian randomization (MR) has emerged as a powerful tool to evaluate causal relationships between exposures and outcomes using genetic variants as instrumental variables. MR leverages the principle of genetic inheritance and random assortment of alleles during gamete formation to help identify causal effects. This method can provide valuable insights into the potential causal relationship between asthma and cancer risk, minimizing biases commonly encountered in observational studies. Thus, the present study aimed to explore the relationship between asthma and cancer risk using the MR method, identifying potential areas of future research.

To meticulously adhere to these principles, we employed four criteria for instrumental variables (IVs) selection. Firstly, we obtained SNPs from existing genome-wide association studies (GWASs) that demonstrated a substantial and consistent correlation with asthma and cancers ($p < 5 \times 10^{-8}$). Subsequently, we performed linkage disequilibrium (LD) clumping analysis at an $R^2 < 0.001$ and 10,000 kb window to preserve the SNPs that were most robustly related to asthma. Thirdly, to address potential pleiotropic effects, we performed a comprehensive analysis utilizing the PhenoScanner database (http://www.phenoscanner.medschl.cam.ac.uk/). Lastly, we eliminated palindromic SNPs to mitigate potential pleiotropic effects. We extracted genetic variants regarding childhood-onset and adult-onset asthma from a study enrolling 314,633 and 327,253 participants of European descent from the UK Biobank, respectively (Table 1). Other large-scale GWASs were used to obtain 18 specific-site cancer-related SNPs (Table 1). The main MR results were obtained through the utilization of the inverse variance weighted (IVW) method. To ensure the reliability of the findings, the weighted median and MR-Egger approaches were employed, each offering distinct advantages and assumptions. The results of the MR analysis were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). To assess potential pleiotropic effects, we conducted the MR-PRESSO test. Considering the extensive scope of our MR analyses, which encompassed 22 unique cancer subtypes, we deemed the statistical significance of potential associations to be contingent upon the *p*-value adjustment through the Bonferroni correction, falling within the range of 0.05–0.0022 (calculated as 0.05 divided by 22). Therefore, a *p*-value below 0.05 was considered indicative of a significant causal association, while results within the range of *p*-values from 0.05 to 0.0022 suggested a suggestive causality. All statistical analyses were performed using R (Version 4.2.0) with the TwosampleMR package.

Table 2 illustrates the results of our IV estimation in the present study. The results of our MR analyses revealed a positive association between asthma (childhood onset) and pancreatic cancer (OR_{IVW}: 1.0242, 95% CI: 1.0067–1.0421, $p = 0.0064$) (Table 2). Besides, the MR-PRESSO Global tests ($p = 0.455$) further validated the IVW results and revealed no obvious heterogeneity. However, no causality between asthma (childhood onset) and other cancers was observed (Table 2). Besides, the risks of lymphomas were higher in asthma (adult onset) patients when compared to the general population (OR_{IVW}: 1.0001, 95% CI: 1.00001–1.0002, $p = 0.033$) (Table 2). The MR-PRESSO Global tests ($p = 0.715$) further validated the IVW results and revealed no obvious heterogeneity. However, no causality between asthma (adult onset) and other cancers was observed (Table 2).

Asthma, being a chronic inflammatory ailment, is integral in the process of cancer development as inflammation takes precedence. Previous MR studies have endeavored to explore the underlying biological mechanisms linking intrinsic immunity and cancer, but have yielded no evidence suggesting a causal relationship between asthma and the risk of breast,[4] prostate,[4] or lung cancer.[5] It has been observed that airway inflammation in asthmatic individuals may exert an influence on the overall inflammatory response in other bodily regions, thereby being potentially linked to pancreatic cancer development. Consequently, the prevalence of pancreatic cancer is expected to be higher in asthma cases that manifest during childhood due to the prolonged impact of inflammation. Our

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Table 1
Details of GWASs Analyzed in the Present MR Analyses.

Phenotype	Sample Size	Number of Patients	Number of Controls	Number of Variants	Ethnicity	Trait ID in MR Base	PubMed ID	Year
Exposure								
Adult-onset asthma	327253	26582	300671	8949308	European	ebi-a-GCST00779	30929738	2019
Childhood-onset asthma	314633	13962	300671	8984776	European	ebi-a-GCST007800	30929738	2019
Outcome								
Basal cell carcinoma	392871	17416	375455	7244167	European	ebi-a-GCST90013410	33549134	2021
Bladder cancer	373295	1279	372016	9904926	European	ieu-b-4874	NA	2021
Breast cancer	228951	122977	105974	10680257	European	ieu-a-1126	29059683	2017
Breast cancer (ER+)	175475	69501	105974	10680257	European	ieu-a-1127	29059683	2017
Breast cancer (ER−)	127442	21468	105974	10680257	European	ieu-a-1135	29059683	2017
Cervical cancer	462933	1889	461044	9851867	European	ukb-b-8777	NA	2018
Colorectal cancer	32072	19948	12124	38356021	European	ebi-a-GCST012879	30510241	2018
Endometrial cancer	12906	108979	121885	9470555	European	ebi-a-GCST006464	30093612	2018
Gastric cancer	476116	1029	475087	24188662	European	ebi-a-GCST90018849	34594039	2021
Kidney cancer	463010	1114	461896	9851867	European	ukb-b-1316	NA	2018
Liver cancer	463010	304	218488	16380466	European	finn-b-C3_LIVER_INTRAHEPATIC_BILE_DUCTS	NA	2021
Lung adenocarcinoma	66756	11273	55483	8881354	European	ieu-a-965	24880342	2014
Lung cancer	85716	29266	56450	8945893	European	ieu-a-966	24880342	2014
Lymphoma	361194	1752	359442	361194	European	ukb-d-C_LYMPHOMA	NA	2018
Melanoma	337159	2677	334482	10855955	European	ukb-d-C3_MELANOMA_SKIN	NA	2018
Mesothelioma	174139	133	174006	16380303	European	finn-b-C3_MESOTHELIOMA_EXALLC	NA	2021
Oesophageal cancer	372756	740	372016	8970465	European	ieu-b-4960	NA	2021
Ovarian cancer	25509	40941	66450	NA	European	ieu-a-1120	28346442	2017
Pancreatic cancer	463010	233	462777	521863	European	ieu-a-822	19648918	2009
Prostate cancer	140254	79148	61106	19733911	European	ebi-a-GCST006085	29892016	2018
Squamous cell lung cancer	63053	7426	55627	8893750	European	ieu-a-967	24880342	2014
Thyroid cancer	174995	989	174006	16380316	European	finn-b-C3_THYROID_GLAND_EXALLC	NA	2021

MR: Mendelian randomization; GWAS: genome-wide association studies; NA: not available.

Table 2
Causality of the Risk for Asthma and Cancers.

Exposures	Outcomes	IVW		Weighted Median		MR-Egger	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Childhood-onset asthma	Basal cell carcinoma	1.0001 (0.9965–1.0037)	0.9652	0.9917 (0.9611–1.0232)	0.6025	0.9971 (0.9929–1.0014)	0.1905
	Bladder cancer	1 (1–1)	0.3249	0.9999 (0.9997–1.0002)	0.6454	1 (0.9999–1)	0.5038
	Breast cancer	1.0004 (0.9988–1.002)	0.6181	1.0245 (1.0096–1.0397)	0.0018	1.0013 (0.999–1.0037)	0.2628
	Breast cancer (ER−)	1.0019 (0.998–1.0058)	0.3379	1.0177 (0.9843–1.0523)	0.3053	1.003 (0.9972–1.0089)	0.3072
	Breast cancer (ER+)	1.0002 (0.9983–1.002)	0.8686	1.0141 (0.9967–1.0317)	0.1170	1.0005 (0.9976–1.0034)	0.7271
	Cervical cancer	1 (1–1)	0.5453	0.9998 (0.9995–1.0001)	0.2344	1 (0.9999–1)	0.4331
	Colorectal cancer	1 (0.9999–1.0000)	0.2084	0.9997 (0.9991–1.0003)	0.2989	0.9999 (0.9998–1)	0.0706
	Endometrial cancer	1.0012 (0.997–1.0054)	0.5845	1.0295 (0.9936–1.0667)	0.1113	1.0017 (0.9962–1.0073)	0.5490
	Glioma	1.0035 (0.9857–1.0217)	0.7024	1.0645 (0.9285–1.2204)	0.3783	1.0094 (0.9838–1.0357)	0.4758
	Lung adenocarcinoma	1.0054 (0.9986–1.0122)	0.1180	1.0057 (0.9453–1.0698)	0.8587	1.0071 (0.9972–1.0171)	0.1589
	Lung cancer	1.0031 (0.9986–1.0075)	0.1748	0.992 (0.9507–1.0351)	0.7130	1.0034 (0.9972–1.0096)	0.2853
	Lymphomas	1 (1–1)	0.8903	0.9998 (0.9995–1.0002)	0.3386	1 (0.9999–1.0001)	0.7623
	Malignant melanoma of skin	1 (1–1)	0.9258	0.9997 (0.9993–1.0002)	0.2193	1 (1–1.0001)	0.4152
	Malignant neoplasm of kidney	1 (1–1)	0.5524	1.0001 (0.9998–1.0004)	0.6399	1 (1–1.0001)	0.3518
	Malignant neoplasm of liver and intrahepatic bile ducts	1.0004 (0.9815–1.0197)	0.9647	1.0734 (0.9104–1.2657)	0.4015	1.0042 (0.9772–1.0319)	0.7633
	Malignant neoplasm of stomach	0.9892 (0.9761–1.0024)	0.1078	1.0624 (0.9407–1.1999)	0.3320	0.9921 (0.9727–1.012)	0.4345
	Malignant neoplasm of thyroid gland	0.9917 (0.981–1.0024)	0.1291	0.924 (0.8402–1.0161)	0.1063	0.9908 (0.9753–1.0064)	0.2458
	Oesophageal cancer	1 (1–1)	0.3301	1.0002 (1.0000–1.0004)	0.0954	1 (1–1)	0.3717
	Ovarian cancer	1.0021 (0.9988–1.0053)	0.2113	0.9985 (0.9699–1.0279)	0.9178	1.0016 (0.9968–1.0064)	0.5190
	Pancreatic cancer	**1.0242 (1.0067–1.0421)**	**0.0065***	1.073 (0.9253–1.2443)	0.3577	1.0185 (0.9943–1.0434)	0.1357
	Prostate cancer	0.9994 (0.9975–1.0014)	0.5828	1.0136 (0.9957–1.032)	0.1416	0.9985 (0.9954–1.0015)	0.3192
	Squamous cell lung cancer	1.0002 (0.9934–1.007)	0.9615	0.9987 (0.941–1.0599)	0.9651	0.9965 (0.987–1.0061)	0.4767
Adult-onset asthma	Basal cell carcinoma	1.0006 (0.9949–1.0062)	0.8433	0.9226 (0.8573–0.9929)	0.0397	1.0005 (0.9937–1.0074)	0.8780
	Bladder cancer	1.0000 (1.0000–1.0000)	0.8873	0.9999 (0.9992–1.0005)	0.7374	1 (0.9999–1.0000)	0.3075
	Breast cancer	1.0013 (0.9983–1.0042)	0.4041	1.0294 (0.9877–1.0729)	0.1782	1.0025 (0.999–1.0059)	0.1596
	Breast cancer (ER−)	0.9986 (0.993–1.0042)	0.6182	1.0132 (0.9337–1.0993)	0.7554	0.9991 (0.9908–1.0076)	0.8378
	Breast cancer (ER+)	0.9997 (0.9958–1.0035)	0.8596	1.0067 (0.954–1.0624)	0.8090	1.0009 (0.9969–1.0049)	0.6598
	Cervical cancer	1.0000 (0.9999–1.0000)	0.6402	0.9997 (0.9989–1.0005)	0.5293	1 (0.9999–1.0001)	0.5522
	Colorectal cancer	1.0000 (0.9999–1.0001)	0.9097	0.9993 (0.9977–1.0009)	0.4096	1 (0.9998–1.0001)	0.5865

Table 2 (*Continued*)

Exposures	Outcomes	IVW		Weighted Median		MR-Egger	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
	Endometrial cancer	1.0021 (0.9961–1.0082)	0.4877	1.0413 (0.9566–1.1335)	0.3555	1.0026 (0.995–1.0103)	0.4980
	Glioma	0.9817 (0.9473–1.0173)	0.3094	1.6059 (0.9772–2.639)	0.0862	1.0062 (0.9707–1.043)	0.7359
	Lung adenocarcinoma	1.005 (0.9952–1.015)	0.3179	1.0588 (0.9057–1.2378)	0.4782	0.9947 (0.9809–1.0087)	0.4549
	Lung cancer	0.9994 (0.9927–1.0061)	0.8504	0.9566 (0.8665–1.0561)	0.3860	0.9961 (0.9867–1.0055)	0.4161
	Lymphomas	**1.0001 (1.00001–1.0002)**	**0.0328***	1.0000 (0.9993–1.0007)	0.9739	1.0001 (1.0000–1.0001)	0.1876
	Malignant melanoma of skin	1.0000 (0.9999–1.0001)	0.9491	0.9986 (0.9977–0.9995)	0.0053	1 (0.9999–1.0001)	0.5266
	Malignant neoplasm of kidney	1.0000 (1.0000–1.0001)	0.1138	1.0002 (0.9995–1.0009)	0.5714	1.0001 (1–1.0001)	0.1058
	Malignant neoplasm of liver and intrahepatic bile ducts	0.9918 (0.9642–1.0203)	0.5708	1.0492 (0.6827–1.6126)	0.8277	0.985 (0.9461–1.0254)	0.4614
	Malignant neoplasm of stomach	0.9996 (0.9801–1.0194)	0.9664	0.9419 (0.7045–1.2592)	0.6882	1.0135 (0.9856–1.0422)	0.3462
	Malignant neoplasm of thyroid gland	0.9958 (0.9799–1.0121)	0.6134	0.8632 (0.6864–1.0855)	0.2159	1.0014 (0.9793–1.024)	0.9016
	Oesophageal cancer	1.0000 (0.9999–1.0000)	0.2308	1.0002 (0.9997–1.0007)	0.4477	1 (0.9999–1.0000)	0.8095
	Ovarian cancer	0.9988 (0.9943–1.0034	0.6177	0.9632 (0.8963–1.035)	0.3128	0.9973 (0.9904–1.0042)	0.4468
	Pancreatic cancer	0.9829 (0.9594–1.007)	0.1629	0.9375 (0.6562–1.3394)	0.7279	0.9795 (0.9485–1.0114)	0.2054
	Prostate cancer	0.9984 (0.9956–1.0013)	0.2801	0.9752 (0.9339–1.0184)	0.2627	0.9957 (0.9916–0.9997)	0.0375
	Squamous cell lung cancer	1.0035 (0.9936–1.0135)	0.4941	0.9474 (0.8219–1.0921)	0.4613	0.9992 (0.9856–1.013)	0.9089

* and bold values mean statistical significance.

research findings further corroborate this notion. Regarding the cellular mechanisms involved, STAT6, a constituent of a protein family encompassing seven analogous proteins, assumes a principal role.[6] Activation of STAT6 is primarily prompted by interleukins IL-4 and IL-13, thereby playing a vital role in the initiation of T helper type 2 immune response. The involvement of STAT6 has been established in various allergic conditions, including asthma, while also playing a part in regulating the tumor microenvironment. Perturbations in the STAT6 pathway have been associated with the progress and onset of lymphomas. In parallel, our results indicate that asthmatic individuals are more prone to developing lymphomas when compared to the general population lacking asthma, thereby aligning with our preceding findings. In summary, our investigation demonstrates a positive association between childhood-onset asthma and the incidence of pancreatic cancer, along with a heightened risk of lymphomas among asthma patients, particularly those with adult-onset asthma, when compared to the broader population. However, it is crucial to highlight the limitations of the present study. Despite both the current investigation and previous MR research[5] indicating no causal link between asthma and the risk of lung cancer, further studies are warranted due to the significant implications for public health.[7] Moreover, several pertinent confounding factors related to asthma were not accounted for in the current MR study. Specifically, the treatment of asthma, such as corticosteroids, may confer an impact on the onset of lung cancer.[8] Additionally, chronic activation pathways in the lung microenvironment induced by house dust mites, an etiological factor of asthma, may exert a tumorigenic effect.[9] Therefore, additional research is necessary to establish causality and elucidate potential underlying mechanisms.

Ethical Approval

No ethical approval and written consent were needed for the secondary analysis of public data.

Authors' Contributions

Wenjie Li and Peixin Dong: conceptualization, methodology, data curation, software and writing – review & editing. Wei Wang: funding acquisition, project administration, supervision and validation. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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Conflicts of Interest

None declared.

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Wenjie Li[a,1], Peixin Dong[b,1], Wei Wang[a,*]

[a] *Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515, China*
[b] *Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, China*

Corresponding author.
E-mail address: wwei9500@smu.edu.cn (W. Wang).
[1] These authors contributed equally.