Genetically Predicted Circulating Levels of Cytokines and the Risk of Cancer

Jie Song†, Aole Li†, Yu Qian, Bin Liu, Linshuoshuo Lv, Ding Ye, Xiaohui Sun† and Yingying Mao†

1 School of Public Health, Zhejiang Chinese Medical University, Hangzhou, China, 2 The Fourth College of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou, China, 3 School of Life Sciences, Westlake University, Hangzhou, China

Background: Inflammation plays a pivotal role in the pathogenesis of cancer. Though previous studies have reported a link between several inflammatory biomarkers and risk of certain types of cancer, there is a lack of systematic investigation. Therefore, we aimed to assess the role of circulating cytokines on the risk of cancer using a two-sample Mendelian randomization (MR) approach.

Method: We used genetic variants associated with circulating levels of cytokines from a meta-analysis of genome-wide association studies (GWASs) of 8,293 Finns as instrumental variables. Summary level data of 20 site-specific cancer were obtained from the UK BioBank including up to 456,348 participants of European ancestry. We performed two-sample MR analyses using inverse-variance weighted (IVW) method as the main method, followed by weighted-median and likelihood-based methods as sensitivity analysis. Pleiotropic and outlier variants were assessed by MR-Egger regression and MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test.

Results: 224 genetic variants associated with 27 circulating cytokines achieving genome-wide significance (P<5×10^{-8}) were used as IVs. After Bonferroni correction, genetically predicted high levels of interleukin-18 (IL-18) were associated with a decreased risk of acute myeloid leukemia (odds ratio (OR) per 1 standard deviation (SD) increase = 0.55, 95% confidence interval (CI):0.43-0.69, P=5.39×10^{-7}), and circulating levels of IL-17 were associated with altered stomach cancer risk (OR per 1 SD increase = 0.15, 95% CI: 0.07-0.36, P=1.25×10^{-5}) by IVW. Results were stable across sensitivity analyses, and MR-Egger regression did not suggest the presence of directional pleiotropy. Additionally, we found suggestive evidence for 48 cytokine-cancer associations including tumor necrosis factor related apoptosis-inducing ligand (TRAIL) and cutaneous T-cell attracting chemokine (CTACK) with the risk of several types of cancer (9.26×10^{-5}≤P<0.05).

Conclusions: By using a genetic epidemiological approach, our study systematically evaluated the role of circulating cytokines on the risk of cancer, and provided clues for potential therapeutic targets. However, the exact underlying biological mechanism warrants further investigation.

Keywords: mendelian randomization, inflammation, cytokines, cancer, single nucleotide polymorphism
INTRODUCTION

Cancer is a leading cause of death before the age of 70 years in 183 countries in 2019 (1). Globally, an estimated 19.3 million new cancer cases and approximately 10.0 million cancer deaths occurred in 2020 (2). Established risk factors for cancer include obesity, smoking, alcohol consumption, and infection (3–7). Inflammation has been demonstrated to play a pivotal role in carcinogenesis, since the reactive oxygen/nitrogen species from inflammation damage not only DNA but also other biomacromolecules, such as proteins and lipids, may result in their dysfunction, thus exerting cancer promoting effects (8). Previous studies have shown that NLRP3 inflammasome and cytosolic multi-protein complexes involved in innate immune response (9), can promote the development of several malignancies, including head and neck squamous cell carcinoma, fibrosarcoma, melanoma, stomach cancer and lung cancer (10–15). Observational data also indicated that chronic inflammation can increase the risk of certain types of cancer. For example, chronic prostatitis can increase the risk of prostate cancer by 2-3 times, and ulcerative colitis can increase the risk of colon cancer by 6-19 times (16). In addition, several inflammatory markers have been tested in relation to cancer incidence. For instance, a meta-analysis showed that higher concentrations of circulating C-reactive protein (CRP), a non-specific marker of systemic inflammation, were associated with a higher risk of breast cancer (hazard ratio (HR)=1.14, 95% confidence interval (CI) 1.01-1.28), lung cancer (HR=2.03, 95% CI 1.59-2.60), colorectal cancer (OR=1.34, 95% CI 1.11-1.60) and prostate cancer (HR=1.09, 95% CI 1.03-1.15) (17). These findings suggested that cytokines may play pivotal roles in carcinogenesis, and intervening on these inflammatory biomarkers in cancer may help prevent its incidence and aid in the development of novel therapeutic targets (17).

Mendelian Randomization (MR) utilizes genetic variants as instrumental variables (IVs) to estimate the potential causal relationship between the exposure (i.e., circulating cytokines) and the outcome (i.e., cancer risk) (18). Since genotypes are randomly distributed in the process of gamete formation, the causal inference from MR analyses are less susceptible to common confounding factors in conventional observational studies, such as postnatal environment, socio-economic status, and behavioral factors (19). Moreover, since genotypes preceded the onset of diseases, MR analyses are less prone to reverse causation in traditional observational studies. Therefore, it becomes widely used to assess the potential causal associations between exposures and diseases.

In the present study, by leveraging large-scale data of genome-wide association studies (GWAS) from the UK BioBank, we implemented a two-sample MR design to systematically investigate the role of circulating cytokines on the risk of different cancer types.

METHOD

Study Design and Data Source

The overall design of the present study is shown in Figure 1. The detailed information on the summary-level data of GWASs on cytokines and 20 site-specific cancer from the UK BioBank are summarized in Table S1. Briefly, all data in our study were based on participants of European ancestry. The GWAS meta-analysis of cytokines included 8,293 Finnish individuals from three independent population cohorts: the Cardiovascular Risk in Young Finns Study, FINRISK1997, and FINRISK2002 Study (20). The effect estimates of each genetic variants retrieved were calculated using an additive genetic model and adjusted for the first ten genetic principal components, age, sex, and body mass index.

Summary-level data for the association between genetic variants and 20 site-specific cancer were obtained from the UK BioBank (UKBB), which is a large-scale cohort study of around 500,000 adults aged 40 to 69 years across the UK from 2006 to 2010 (21). In the present analyses, we included genetic data of up to 456,348 participants from UKBB (Table S1).

Selection of Genetic Variants

Single nucleotide polymorphisms (SNPs) associated with circulating levels of cytokines were selected at the genome-wide significance level ($P<5\times10^{-8}$). We then pruned these SNPs in linkage disequilibrium (LD) using an $r^2$ threshold < 0.1, and
selected the SNPs with the lowest P-value. A total of 958 independent SNPs were selected as IVs. Among them, 129 SNPs were associated with more than one cytokine and were thus excluded. Among the remaining 829 SNPs, 605 were not available in the outcome datasets. Finally, 224 SNPs associated with circulating levels of 27 cytokines were included in the subsequent MR analyses. Detailed information of the 27 cytokines and the SNPs used as IVs are displayed in Table S2.

**Statistical Analysis**

First, we calculated F-statistics to quantify the strength of the IVs, with the equation of $F=R^2/(N-1-k)/(1-R^2)$, in which $R^2$ represents the variance explained by the IVs, N indicates the sample size, and k is the number of SNPs included in the instrument (22).

We then used inverse-variance-weighted (IVW) method as the main MR analysis to evaluate the potential causal effects of the 27 cytokines on the risk of 20 site-specific cancer (19, 23). Cochran’s Q test was applied to assess the heterogeneity between the SNPs, and a fixed-effects model was used when there was no evidence of heterogeneity; otherwise, a random-effects model was used. In addition, to assess the robustness of our main findings, we used a series of sensitivity analyses, including the weighted-median and likelihood-based methods. Specifically, the weighted-median method combines the unweighted or weighted estimation with the median. As long as the weight of the causal effect calculated by the effective instrumental variable reaches 50%, a consistent estimation of the causal effect can be obtained (22). Meanwhile, the likelihood-based method evaluates the potential causal relationship under the assumption of a linear association between the risk factor and the outcome variables (24).

Moreover, MR-Egger regression was performed to assess the potential directional pleiotropy. The slope of MR-Egger regression can suggest pleiotropy corrected causal estimates, and the value of the intercept can provide an estimate of the degree of bias (25). The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test was also used to detect and correct for horizontal pleiotropic outliers. It conducts a global test of heterogeneity by regressing the SNP-outcome associations on the SNP-exposure associations and comparing the observed distance of each SNP from the regression with the distance expected under the null hypothesis of no pleiotropy (26).

Furthermore, to minimize the influence of pleiotropic instruments on MR estimates, we manually scanned the SNPs used as IVs in the GWAS Catalog, and excluded those associated with secondary phenotypes at genome-wide significance. We then reran the MR analyses using the updated IVs. Additionally, to test for the stability of our findings, we performed “leave-one-out” analyses, which excluded one single SNP at a time, and re-run the MR analysis using IVW method with the remaining IVs.

All analyses were performed using R (version 3.6.0) and related R packages (MendelianRandomization and MR-PRESSO). Associations with P values $<9.26\times10^{-5}$ ($P = 0.05/27$ cytokines/20 site-specific cancers) were considered statistically significant after Bonferroni correction for 27 cytokines and 20 site-specific cancer. A P-value $< 0.05$, but above the Bonferroni correction threshold, was considered suggestive evidence for a potential causal association.

**RESULTS**

Table S3 presents the detailed information of the IVs used for circulating levels of the 27 cytokines and growth factors. The median of F-statistics ranged from 30 to 788.96, satisfying the threshold of >10, suggesting that the IVs used in our study were unlikely to suffer from weak instrument bias (27).

The MR association estimates of the 27 cytokines with the risk of 20-site specific cancer are shown in Figure 2. Specifically, genetically predicted higher levels of circulating IL-18 was associated with a decreased risk of acute myeloid leukemia (OR=0.55, 95% CI: 0.43-0.69, $P=5.39\times10^{-7}$, per 1 standard deviation (SD) increase). Detailed information of the IVs used for circulating IL-18 levels and their associations with the risk of acute myeloid leukemia (AML) are presented in Table 1. In sensitivity analysis using different MR methods, the association remained statistically significant and the effect estimates were similar (OR=0.44, 95% CI: 0.32-0.60, $P=1.23\times10^{-7}$ for the weighted-median method; OR=0.55, 95% CI: 0.44-0.70, $P=1.06\times10^{-6}$ for the maximum-likelihood method). Moreover, there was no evidence for the presence of directional pleiotropy (P for MR-Egger intercept =0.095; P for MR-PRESSO global test=0.381; and number of outlier SNPs=0), and the results from MR-PRESSO test was similar (OR=0.55, 95% CI: 0.43-0.69, $P=1.55\times10^{-7}$). None of the SNPs used as IVs had documented pleiotropy as we searched the GWAS Catalog (last accessed on January 31, 2022). In the leave-one-out sensitivity analysis, the association estimates of genetically predicted IL-18 levels with the risk of AML did not change substantially after excluding one single SNP at a time (Figure S1).

Meanwhile, we found an inverse association between circulating levels of IL-17 and the risk of stomach cancer using the IVW method (per 1 SD increase OR=0.15, 95% CI: 0.07-0.36, $P=1.25\times10^{-5}$, Table 1, Figure 2). One SNP, rs1530455, was found to be associated with other phenotypes at genome-wide significance level (Table S4). After excluding this SNP, the effect estimate did not change essentially (OR=0.14, 95% CI: 0.04-0.49, $P=0.002$).

In addition, we found 48 suggestive associations of a specific cytokine with the risk of site-specific cancer ($9.26\times10^{-5} \leq P < 0.05$). The detailed results are shown in Figure 2 and Table S5. Among them, IL-18 was nominally associated with the risk of six types of cancer, including bladder cancer (OR=0.86, 95% CI: 0.79-0.93, $P=3.30\times10^{-4}$), breast cancer (OR=1.05, 95% CI: 1.01-1.09, $P=0.027$), chronic lymphoid leukemia (CLL) (OR=1.39, 95% CI: 1.29-1.71, $P=0.002$), kidney cancer (OR=0.87, 95% CI: 0.77-0.99, $P=0.028$), multiple myeloma (OR=0.76, 95% CI: 0.63-0.90, $P=0.002$), non-Hodgkin lymphoma (OR=0.84, 95% CI: 0.74-0.96, $P=0.008$). Similarly, genetically determined circulating levels of tumor necrosis factor related apoptosis-inducing ligand (TRAIL) were nominally associated with the risk AML (OR=1.27, 95% CI: 1.06-1.52, $P=0.011$), colon cancer (OR=1.07, 95% CI: 1.01-1.13, $P=0.021$), CLL (OR=1.27, 95% CI: 1.06-1.52, $P=0.011$), lung cancer (OR=0.93, 95% CI: 0.87-0.99, $P=0.034$), non-Hodgkin lymphoma (OR=0.91, 95% CI: 0.84-0.99, $P=0.034$), and rectal cancer (OR=1.08, 95% CI: 1.01-1.15, $P=0.032$). Moreover, circulating cutaneous T-cell attracting chemokine (CTACK) levels were nominally associated...
with the risk of kidney cancer (OR=0.72, 95% CI: 0.64-0.85, \( P=1.64\times10^{-4} \)), melanoma (OR=0.87, 95% CI: 0.79-0.95, \( P=0.002 \)), non-Hodgkin lymphoma (OR=1.29, 95% CI: 1.11-1.49, \( P=6.90\times10^{-4} \)), pancreatic cancer (OR=1.50, 95% CI: 1.20-1.87, \( P=4.17\times10^{-4} \)), and prostate cancer (OR=0.85, 95% CI: 0.79-0.92, \( P=1.58\times10^{-4} \)). We also identified nominal associations of genetically predicted circulating levels of macrophage inflammatory protein-1β (MIP1β) with the risk of AML (OR=0.86, 95% CI: 0.75-0.99, \( P=0.048 \)), colon cancer (OR=0.95, 95% CI: 0.90-0.99, \( P=0.015 \)) and rectal cancer (OR=0.89, 95% CI: 0.84-0.94, \( P=2.75\times10^{-5} \)), as well as eotaxin with the risk of colon cancer (OR=1.28, 95% CI: 1.09-1.49, \( P=0.003 \)), multiple myeloma (OR=1.58, 95% CI: 1.08-2.29, \( P=0.017 \)), and stomach cancer (OR=1.68, 95% CI: 1.16-2.44, \( P=0.006 \)).

FIGURE 2 | Heatmap of the associations of the 27 cytokines with the risk of 20 site-specific cancer from the inverse variance weighted (IVW) method. One asterisk indicates the suggestive evidence for a potential causal association (9.26×10^{-5} \( P<0.05 \)), while two asterisks denote that the associations were statistically significant after multiple comparison correction (\( P<9.26\times10^{-5} \)). Colour is scaled based on the odd ratio (OR) of the MR association estimate.

DISCUSSION

In this study, we adopted a two-sample MR approach and systematically evaluated the potential causal effect of 27 circulating cytokines and growth factors on the risk of 20 site-specific cancer. We found that genetically predicted higher levels of IL-18 were associated with an increased risk of AML, and IL-17 was associated with the risk of stomach cancer. Results were stable in sensitivity analyses using different MR methods and different IV sets. Additionally, we found nominal associations of some cytokine-cancer pairs, suggesting the potential role of these inflammatory biomarkers in the development of certain types of cancer.

IL-18 is a proinflammatory cytokine of the IL-1 family, which can stimulate interferon gamma production and regulate both T helper (Tb) 1 and Th2 responses, thus having multiple biological functions (28). IL-18 can promote the proliferation of activated T cells, activation of natural killer cells and cytokine production (29). Protective effects of IL-18 in cancer have been reported in different murine models. For instance, mice receiving IL-18 before or after challenge with CL8-1, both regimens significantly suppressed tumor growth and reduced the number of mice with growth of tumor from 60% (3/5) to 20% (1/5) (30). Hitzler et al. (31) found that IL-18 counteracts IL-1-driven inflammation and limits Helicobacter pathogenic effect. However, observational studies on the association between circulating IL-18 levels and AML are limited to date. A case-control study involving 70 patients and 50 controls reported that there were no differences in the expression level of IL-18 in patients with AML compared to healthy controls (\( P=0.100 \)), while another study of 47 patients with AML found that IL-18 was associated with unfavorable prognostic factors of AML (33). The potential mechanism may be that IL-18 plays an important role in anti-tumor immunity through enhancing interferon-γ production and Fas ligand dependent cytotoxicity of immune cells, and the dose of IL-18 was correlated with the level of serum IFN-γ. Additionally, IL-18 can induce tumor Hapten by activating natural killer (NK) cells, and NK-mediated cytotoxicity of tumor cells, which exert an important role in immune response (30, 34).

As for IL-17, previous observational studies have reported a positive association of circulating IL-17 levels with the risk of stomach cancer. For example, a case-control study including 76 patients and 30 healthy age- and sex-matched controls reported that the median serum levels of IL-17 in patients with stomach cancer were higher than those of controls (9.04 vs. 8.07 pg/ml, \( P=0.010 \)), but serum IL-17 levels were not associated with tumor stage (small (1-2 stage) vs. large (3-4 stage): 9.20 vs. 8.27 pg/ml, \( P=0.410 \)) (35). Another case-control study involving 50 patients and 50 controls reported similar results (36). However, Carneiro et al. reported that IL-17 levels in stomach patients were lower than that in the control group (median: 404.2 vs. 573.9 pg/ml, \( P=0.004 \)) (37). Our MR analysis found an inverse association of circulating IL-17 levels and the risk of stomach cancer. The conflicting results from observational studies may be related to the study design, study population, the stage and type of stomach cancer investigated. For example, a case-control study found that patients with early gastric carcinoma had higher levels of IL-17, whereas individuals with advanced gastric carcinoma had mean IL-17 concentrations comparable to those observed in healthy individuals (38). Another case-only study including 70 patients reported that the expression of IL-17 was lower in patients with diffuse type of stomach cancer compared with those with intestinal type (\( P=0.001 \)) (39). Moreover, Chen et al. found that intratumoral IL-17 expression was an independent factor...
affecting the five-year overall survival probability in patients with gastric adenocarcinoma (HR: 0.52; 95% CI: 0.33-0.82; *P*=0.005) (40). The potential biological mechanism of IL-17 mediated tumor immunity may be that IL-17 can absorb Th1-related chemokines, such as CXC19 and CXC110, which can promote tumor immunity (41). The potential biological mechanism of IL-17 mediated tumor immunity may be that IL-17 can absorb Th1-related chemokines, such as CXC19 and CXC110, which can promote tumor immunity (41). In conclusion, our findings provide evidence to support potential causal associations of IL-18 with AML and IL-17 with stomach cancer. Further studies are warranted to elucidate underlying biological mechanism and to explore the potential therapeutic targets.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.
AUTHOR CONTRIBUTIONS
JS and AL performed the literature review, conducted data analysis, interpreted findings, and drafted the manuscript. LL and BL carried out data analysis and interpreted findings. YQ and DY conducted data analysis, interpreted findings and revised the manuscript. JS, AL and BL took responsibility for the statistical reports, tables and figures of the data analysis. YM and XS directed analytic strategy, supervised the study from conception to completion and revised drafts of the manuscript. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2022.886144/ full#supplementary-material
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## GLOSSARY

| Acronym  | Definition                                                                 |
|----------|---------------------------------------------------------------------------|
| AML      | acute myeloid leukemia                                                     |
| CI       | confidence interval                                                      |
| CLL      | chronic lymphoid leukemia                                                 |
| CRP      | C-reactive protein                                                        |
| CTACK    | cutaneous T-cell attracting chemokine                                      |
| GWAS     | genome-wide association study                                             |
| HR       | hazard ratio                                                              |
| IV       | instrumental variable                                                     |
| IVW      | inverse-variance weighted                                                 |
| IL-17    | interleukin-17                                                            |
| IL-18    | interleukin-18                                                            |
| MAF      | minor allele frequency                                                    |
| MIP1β    | macrophage inflammatory protein-1β                                         |
| MR       | Mendelian randomization                                                   |
| OR       | odds ratio                                                                |
| PRESSO   | Pleiotropy RESidual Sum and Outlier                                       |
| SD       | standard deviation                                                        |
| SNP      | single nucleotide polymorphism                                            |
| TNF-α    | tumor necrosis factor α                                                   |
| TNF-γ    | tumor necrosis factor γ                                                   |
| TRAIL    | tumor necrosis factor related apoptosis-inducing ligand                   |