A E A D E D

C- t t n t t n t n t :
A t h t t

n [1,2,3] n n h n [4] [5] h n n [6]
h h [7] h n [1,2,3] n m n n [1,2,3] n C [8]
n n h [1,2,3]

[1]Department of Gastrointestinal Surgery/

SCW2018-06; National Key Research and Development Program, Grant/Award Number: 2017YFC1309200

based cohort study with a two-year follow-up frequency provides a novel perception of the potential association between longitudinal CRP trajectory patterns and cancer risk. The results show that CRP trajectories play an important role in the occurrence of cancers, especially in the lung, breast, bladder, stomach, colorectal, liver, gallbladder or extrahepatic bile duct cancer and leukemia. The decreasing CRP trajectory pattern is associated with decreased esophageal and colorectal cancer risk.

1 | DUC

Cancer is the first or second leading cause of premature death in 134 of 183 countries, and it ranks third or fourth in 45 of the remaining countries.[1] About one-third of deaths from non-communicable diseases are due to cancer.[1] The morbidity and mortality rates vary across countries due to different prevalence of key risk factors, as well as the impact of preventive methods, screening and therapeutic interventions.[2,3] Robust scientific evidence is essential for understanding its cause and prevention. In addition to some recognized factors like smoking,[4] drinking,[5] obesity,[6] nutrition,[7] family history of cancer, infectious disease[8] and environmental factors,[9] chronic inflammation has been demonstrated to be closely associated with cancers.[10,11] Cancer-associated inflammation is known as the seventh hallmark of cancer, associated with the six generally recognized hallmarks of cancer: self-sufficient growth signals, evasion of apoptosis, insensitivity to antigrowth signals, unlimited replicative potential, sustained angiogenesis and metastasis.[10]

C-reactive protein (CRP) is a classic acute-phase protein that responds to inflammation, infection and tissue damage, and is the most widely used biomarker of inflammation.[12,13] Recently, epidemiologic studies have demonstrated an association of elevated levels of circulating high sensitivity CRP (hs-CRP), CRP measured by a high-sensitivity assay which can accurately detect low-grade inflammatory state, with an increased risk of incident cancers.[14-16] However, results from previous studies were based on a single measurement of CRP level at baseline which may yield a certain degree of variability during the follow-up period and lead to misclassification of the participants.

No prospective study has used multiple CRP measurements to examine the association of long-term patterns of CRP concentration with subsequent cancer risk. Kailuan study is an ongoing, prospective, population-based cohort study with follow-up conducted every 2 years. Repeated CRP measurements can offer us a great opportunity to ascertain the association between CRP trajectory patterns and the risk of incident cancers.

2 | E D

2.1 | t

Data was taken from the Kailuan cohort study, which was designed to explore the risk factors for common chronic diseases. The detailed study design and procedures were described previously.[17] All 155 418 Kailuan Corporation employees (including retirees) were invited to participate in baseline physical examinations at Kailuan General Hospital and its 10 affiliated institutions between July 2006 and October 2007. A total of 101 510 individuals (65.3%) ranging in age from 18 to 98 years, with 81 110 males and 20 400 females, accepted and were enrolled after receiving written informed consent. All participants underwent health examinations including questionnaire assessments, clinical examinations and laboratory tests at baseline examination (2006-2007), and underwent follow-up examinations with the same examinations conducted every 2 years.

In the current study, CRP trajectories were developed from 2006 to 2010 to predict cancer risk from 2010 to 2019. In other words, the study was restricted to the population who participated in the examinations in 2006, 2008 and 2010 and had their plasma CRP measurements taken biennially. Participants were excluded if they: (1) failed to take 2008 and/or 2010 examinations; (2) had missing information of plasma CRP during 2006-2010; (3) lacked measurements of relevant confounders including age, sex, total cholesterol (TC, in mmol/L), triglyceride (TG, in mmol/L), body mass index (BMI, in kg/m^2), alanine aminotransferase (ALT, in u/L), total bilirubin (TBil, in umol/L), fasting blood glucose (FBG, in mmol/L), hepatitis B surface antigen (HBsAg), dietary salt intake, marital status, sedentary lifestyle, educational background, tobacco consumption, alcohol drinking, physical exercise, family history of cancer, liver cirrhosis, fatty liver, gallstone disease, gallbladder polyp, diabetes mellitus and hypertension; and (4) had a history of cancer at baseline or were diagnosed with cancer during 2006 to 2010 (trajectory patterns). A total of 52 276 individuals were left in the final analyses and scheduled a follow-up (Figure 1).

2.2 | A mnt m C

After an overnight fasting period (at least 8 hours), blood samples were obtained from the antecubital vein in EDTA tubes for each individual. The blood was further centrifuged for 10 minutes at 3000 rotations per minute at 25°C. Plasma was separated and stored at −80°C until laboratory determinations were performed. CRP was measured using a high-sensitivity nephelometry assay (Cias Latex CRP-H, Kanto Chemical Co. Inc., Tokyo, Japan) and the lower limit of detection is 0.1 mg/L. The intra- and interassay coefficient of variation for CRP measurement were 6.53% and 4.78%, respectively. Plasma CRP and other blood variables were all analyzed at the central laboratory of the Kailuan Hospital using an autoanalyzer (Hitachi 747; Hitachi).

2.3 | Outcome ascertainment

Incident cancer cases were identified via (1) checking clinical examinations or questionnaires in the routine follow-up until 31 December 2019; (2) checking medical linkage with the provincial vital statistics data, the Tangshan medical insurance system and the Kailuan Social Security Information System annually; and (3) reviewing death certificates from the Provincial Vital Statistics Offices (PVSO) to prevent missed diagnosis. Trained medical staff further reviewed the hospitalization records including pathology and imaging results to identified the incident cancer cases and coded cases according to the International Classification of Diseases, Tenth Revision (ICD-10) as the following: head and neck cancer (00-14, 30-32, 71, 73), esophageal cancer (15), stomach cancer (16), small intestine cancer (17), colorectal cancer (18-21), liver cancer (22), gallbladder or extrahepatic bile duct cancer (23-24), pancreatic cancer (25), lung cancer (34), bone and soft tissue cancer (40-41, 49), skin cancer (43-44), breast cancer (50), cervix cancer (53), uterus cancer (54-55), ovarian cancer (56), prostate cancer (61), kidney cancer (64-65), bladder cancer (67), lymphoma (81-89), leukemia and multiple myeloma (90-96).

2.4 | Assessment of covariates

Information on age, sex, socioeconomic status, educational background, lifestyle behaviors, medical histories of personal and family members were collected through a questionnaire which was done via trained medical staff. Drinking and smoking status was classified into three categories: never, past or current. Physical exercise was evaluated from responses regarding the frequency of physical activity and classified as: never, occasionally or regularly (≥3 times/week, ≥30 minutes/time). Information on perceived salt intake was determined via a questionnaire survey about regular salt consumption and classified into three categories: low (<6 g/day), intermediate (6-9 g/day) or high (≥10 g/day). In 2012, a validation study was conducted by collecting random spot urine samples from 231 hypertensive participants who did not use any antihypertensive drugs from the Kailuan Study.[18] A sedentary lifestyle was categorized into three groups according to the responses about daily sedentary time.

Trained medical staff performed physical examinations for each participant. BMI was classified into normal (<24 kg/m^2), overweight (24.00-27.99 kg/m^2) or obese (≥28 kg/m^2). Hypertension was defined as having a SBP ≥140 mm Hg, and/or a DPB ≥90 mm Hg, and/or a previous diagnosis of hypertension. The abdominal region, including liver, gallbladder, pancreas and spleen of each participant was examined by specialists after fasting for at least 8 hours using the real-time ultrasound sonography (PHILIPS HD-15). The diagnoses of liver cirrhosis, fatty liver, gallstone disease and gallbladder polyp were based on the results of abdominal ultrasonography or through medical records from the Tangshan medical insurance system. Diabetes mellitus was defined as having a FBG level ≥7.0 mmol/L, taking oral hypoglycemic agents or insulin or having a self-reported history. TG, TC, ALT and TBil were grouped into three categories based on the tertiles of each variable.

2.5 | Statistical analysis

The changes in CRP from 2006 to 2010 were set up as the primary exposure. B

ABLE 1 (Continued)

	-C t t tt n				
	w- t	t -n n	n n - n	E t - n	P-
Drinking status (%)					<.0001
Never	24 149 (55.83)	1479 (57.08)	1259 (60.88)	2558 (58.68)	
Past	1377 (3.18)	88 (3.40)	63 (3.05)	119 (2.73)	
Moderate	9606 (22.21)	458 (17.68)	321 (15.52)	598 (13.72)	
Severe	8126 (18.78)	566 (21.84)	425 (20.55)	1084 (24.87)	
Salt intake (%)					<.0001
Low (<6 g/day)	4198 (9.70)	202 (7.80)	156 (7.54)	269 (6.17)	
Intermediate (6-10 g/day)	33 879 (78.32)	1985 (76.61)	1589 (76.84)	2949 (67.65)	
High (>10 g/day)	5181 (11.98)	404 (15.59)	323 (15.62)	1141 (26.18)	
Sedentary lifestyle (%)					<.0001
<4 hours/day	31 346 (72.46)	1904 (73.49)	1490 (72.05)	2838 (65.11)	
4-8 hours/day	9981 (23.08)	443 (17.10)	393 (19.00)	574 (13.17)	
>8 hours/day	1931 (4.46)	244 (9.42)	185 (8.95)	947 (21.72)	
Hypertension (%)	15 917 (36.80)	1179 (45.50)	997 (48.21)	2124 (48.73)	<.0001
Diabetes mellitus (%)	2918 (6.75)	216 (8.34)	206 (9.96)	441 (10.12)	<.0001
Gallbladder polyp (%)	365 (0.84)	15 (0.58)	18 (0.87)	19 (0.44)	.1428
Gallstone disease (%)	851 (1.97)	73 (2.82)	59 (2.85)	100 (2.29)	<.0001
Fatty liver (%)	12 843 (29.69ing	multivar69ing012.6(18)-9B	170.9(.49)t1141)-267((53.61))-6635.8(212401)]TJTf(Diabe)-10.1L(%))-9addercirr		

increasing-decreasing trajectory pattern were associated with an elevated risk of pooled caners with the corresponding multivariate HR (95%) CI of 1.44 (1.19-1.69), 1.22 (1.04-1.41), respectively. However, no significant association between elevated-decreasing pattern and overall cancer risk after adjusting for potential confounders.

3.4 | A t n C t t tt n wth th - t n

Table 3 demonstrates the effect of CRP trajectories from 2006 to 2010 on the risk of specific-site cancer. In the site-specific analyses, compared to the low-stable pattern of CRP, individuals in moderate-increasing trajectory pattern exhibited an increased risk of lung cancer (HR = 1.21, 95% CI: 1.04-1.42), breast cancer (HR = 1.30, 95% CI: 1.09-1.59), leukemia (HR = 9.54, 95% CI: 6.35-14.34), bladder cancer (HR = 1.31, 95% CI: 1.11-1.54), stomach cancer (HR = 1.22, 95% CI: 1.03-1.49), colorectal cancer (HR = 1.13, 95% CI: 1.01-1.23), liver cancer (HR = 1.07, 95% CI: 1.02-1.11) and gallbladder or extrahepatic bile duct cancer (HR = 1.33, 95% CI: 1.12-1.53) in the fully-adjusted analyses.

After adjusting for the aforementioned confounders, participants in the increasing-decreasing trajectory pattern were associated with an elevated risk of lung cancer (HR = 1.09, 95% CI: 1.02-1.15), breast

driver of lowering CRP concentration, regardless of diet composition.[35] In this current study, the reversed association between the decreased trajectory of CRP and cancer risk is independent of BMI. Taken together, the antiinflammatory effect produced by changing a healthy lifestyle and weight loss may partially clarify the anticancer effect of the decreasing trajectory of CRP in our study. Future studies should be conducted to better assess the potential mechanism of decline in serum CRP levels for the anticarcinogenesis effect.

Although the exact mechanisms surrounding the association of elevated CRP levels with increased risk of cancer remain unsolved, several possible mechanisms may help to elucidate this matter. Long-term low degree inflammation can promote tumor development and progression by leading to oxidation of protein and DNA.[36] Crucial pathways that maintain normal cellular homeostasis can be altered by genetic and epigenetic variations, due to mediators of the inflammatory response such as cytokines, free radicals, prostaglandins and growth factors. These variations include point mutations in tumor suppressor genes, DNA methylation and posttranslational variations, all of which can lead to the eventual presence and growth of cancer.[36] The association between inflammation and cancer has also been further fortified after observing the interaction of microRNAs and innate immunity during inflammation.[37] Previous research suggested that CRP was not just a marker of inflammation but has numerous critical proinflammatory properties.[38,39] Specifically, CRP can cause the initiation of endothelial cells, monocytes and smooth muscle cells, prompt expression of adhesion molecules, chemoattractant, tissue factors and activation of the NF-κB pathway.[40] Adhesion molecule expression is essential for the invasion of cancer, whereas NF-κB pathway activation has been linked to crucial oncogenic effects.

The major strength of this current study is that it provides a novel perception of the potential association between longitudinal CRP trajectory patterns and cancer risk. Furthermore, the broad evaluation of potential confounders has been well addressed in our

C D

Mengmeng Song https://orcid.org/0000-0003-0258-3935

Hanping Shi https://orcid.org/0000-0003-4514-8693

EFE E CE

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30.
2. Arnold M, Karim-Kos HE, Coebergh JW, et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: analysis of the European cancer observatory. *Eur J Cancer*. 2015; 51(9):1164-1187.
3. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the global burden of disease study 2015. *Lancet*. 2016;388(10053):1659-1724.
4. Alberg AJ, Shopland DR, Cummings KM. The 2014 surgeon general's report: commemorating the 50th anniversary of the 1964 report of the advisory committee to the US surgeon general and updating the evidence on the health consequences of cigarette smoking. *Am J Epidemiol*. 2014;179(4):403-412.
5. Pflaum T, Hausler T, Baumung C, et al. Carcinogenic compounds in alcoholic beverages: an update. *Arch Toxicol*. 2016;90(10): 2349-2367.
6. Whiteman DC, Wilson LF. The fractions of cancer attributable to modifiable factors: a global review. *Cancer Epidemiol*. 2016;44: 203-221.
7. Fitzmaurice C, Akinyemiju TF, Al Lami FH, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the global burden of disease study. *JAMA Oncol*. 2018;4(11):1553-1568.
8. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. *Lancet Glob Health*. 2020;8(2):e180-e190.
9. Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev*. 2005;14(8): 1847-1850.
10. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis*. 2009;30(7):1073-1081.
11. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436-444.
12. Black S, Kushner I, Samols D. C-reactive protein. *J Biol Chem*. 2004; 279(47):48487-48490.
13. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest*. 2003;111(12):1805-1812.
14. Heikkilä K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. *J Epidemiol Community Health*. 2007;61(9):824-833.
15. Allin KH, Bojesen SE, Nordestgaard BG. Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. *J Clin Oncol*. 2009;27(13):2217-2224.
16. Chaturvedi AK, Caporaso NE, Katki HA, et al. C-reactive protein and risk of lung cancer. *J Clin Oncol*. 2010;28(16):2719-2726.
17. Liu T, Song C, Zhang Y, et al. Hepatitis B virus infection and the risk of gastrointestinal cancers among Chinese population: a prospective cohort study. *Int J Cancer*. 2021;150:1018-1028.
18. Tanaka T, Okamura T, Miura K, et al. A simple method to estimate populational 24-h urinary sodium and potassium excretion using a casual urine specimen. *J Hum Hypertens*. 2002;16(2):97-103.
19. He MM, Fang Z, Hang D, et al. Circulating liver function markers and colorectal cancer risk: a prospective cohort study in the UK biobank. *Int J Cancer*. 2021;148(8):1867-1878.
20. Larsen IK, Myklebust T, Babigumira R, Vinberg E, Møller B, Ursin G. Education, income and risk of cancer: results from a Norwegian registry-based study. *Acta Oncol*. 2020;59(11):1300-1307.
21. Sun D, Li H, Cao M, et al. Cancer burden in China: trends, risk factors and prevention. *Cancer Biol Med*. 2020;17(4):879-895.
22. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66(2):115-132.
23. Wang G, Li N, Chang S, et al. A prospective follow-up study of the relationship between C-reactive protein and human cancer risk in the Chinese Kailuan female cohort. *Cancer Epidemiol Biomarkers Prev*. 2015;24(2):459-465.
24. Otani T, Iwasaki M, Sasazuki S, Inoue M, Tsugane S. Plasma C-reactive protein and risk of colorectal cancer in a nested case-control study: Japan Public Health Center-based prospective study. *Cancer Epidemiol Biomarkers Prev*. 2006;15(4):690-695.
25. Allin KH, Bojesen SE, Nordestgaard BG. Inflammatory biomarkers and risk of cancer in 84,000 individuals from the general population. *Int J Cancer*. 2016;139(7):1493-1500.
26. Siyin ST, Liu T, Li W, et al. A prospective follow-up study of the relationship between high-sensitivity C-reactive protein and primary liver cancer. *BMC Cancer*. 2020;20(1):1168.
27. Sjövall D, Staffas A. The origin of leukemia: genetic alterations and inflammatory factors in the development of premalignant clonal hematopoiesis. *Semin Hematol*. 2020;57(1):7-12.
28. Köhler A, Eggers H, Kuczyk MA, Schrader AJ, Steffens S. Utility of the serum CRP value for assessing the prognosis and therapeutic response of urological malignancies. *Aktuelle Urol*. 2013;44(6): 452-455.
29. Zhang SM, Lin J, Cook NR, et al. C-reactive protein and risk of breast cancer. *J Natl Cancer Inst*. 2007;99(11):890-894.
30. Siemes C, Visser LE, Coebergh JW, et al. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam study. *J Clin Oncol*. 2006;24(33):5216-5222.
31. Platz EA, De Marzo AM, Erlinger TP, et al. No association between pre-diagnostic plasma C-reactive protein concentration and subsequent prostate cancer. *Prostate*. 2004;59(4): 393-400.
32. De Marzo AM, Platz EA, Sutcliffe S, et al. Inflammation in prostate carcinogenesis. *Nat Rev Cancer*. 2007;7(4):256-269.
33. Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017; 390(10105):1833-1842.
34. van't Klooster CC, van der Graaf Y, Ridker PM, et al. The relation between healthy lifestyle changes and decrease in systemic inflammation in patients with stable cardiovascular disease. *Atherosclerosis*. 2020;301:37-43.
35. Nicklas JM, Sacks FM, Smith SR, et al. Effect of dietary composition of weight loss diets on high-sensitivity c-reactive protein: the randomized POUNDS LOST trial. *Obesity (Silver Spring)*. 2013;21(4): 681-689.
36. Hussain SP, Harris CC. Inflammation and cancer: an ancient link with novel potentials. *Int J Cancer*. 2007;121(11):2373-2380.
37. Esquela-Kerscher A, Slack FJ. Oncomirs - microRNAs with a role in cancer. *Nat Rev Cancer*. 2006;6(4):259-269.
38. Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation*. 2000; 102(18):2165-2168.

39. Pasceri V, Cheng JS, Willerson JT, Yeh ET. Modulation of C-reactive protein-mediated monocyte chemoattractant protein-1 induction in