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 i

TABLE 1 Baseline characteristics of the participants according to hs-CRP trajectory patterns

	Hs-CRP trajectory patterns				
Variables	**Low-stable**	**Moderate-increasing**	**Increasing-decreasing**	**Elevated-decreasing**	***P*-value**
n (%)	43 258	2591	2068	4359	
Age (year)	48.40 ± 11.62	49.99 ± 11.97	52.70 ± 12.15	55.17 ± 11.07	<.0001
Male (%)	32 915 (76.09)	2072 (79.97)	1509 (72.97)	3195 (73.30)	<.0001
Marital status (%)					<.0001
Never	734 (1.70)	36 (1.39)	24 (1.16)	28 (0.64)	
Married	40 637 (93.94)	2337 (90.20)	1871 (90.48)	3397 (77.95)	
Divorced	382 (0.88)	18 (0.69)	17 (0.82)	32 (0.73)	
Widowed	580 (1.34)	45 (1.74)	34 (1.64)	103 (2.36)	
Remarried	925 (2.14)	155 (5.98)	122 (5.90)	799 (18.32)	
Educational background (%)					<.0001
Never	276 (0.64)	19 (0.73)	19 (0.92)	40 (0.91)	
Primary school	2954 (6.83)	174 (6.72)	176 (8.51)	406 (9.30)	
Middle school	29 542 (68.29)	1823 (70.36)	1436 (69.43)	2781 (63.80)	
High school	6801 (15.72)	313 (12.08)	270 (13.06)	470 (10.80)	
College graduate or above	3685 (8.52)	262 (10.11)	167 (8.08)	662 (15.19)	
TC (%)					<.0001
<4.50 mmol/L	14 712 (34.01)	741 (28.60)	564 (27.28)	1473 (33.80)	
4.50-5.32 mmol/L	14 197 (32.82)	862 (33.27)	700 (33.85)	1451 (33.29)	
>5.32 mmol/L	14 349 (33.17)	988 (38.13)	804 (37.83)	1435 (32.91)	
TG (%)					<.0001
<1.02 mmol/L	14 970 (34.61)	703 (27.14)	546 (26.41)	1409 (32.33)	
1.02-1.65 mmol/L	14 302 (33.06)	773 (29.84)	640 (30.95)	1375 (31.55)	
>1.65 mmol/L	13 986 (33.58)	1115 (43.02)	882 (42.64)	1575 (36.12)	
ALT (%)					.0095
<15.00 u/L	15 538 (35.92)	908 (35.05)	729 (35.26)	1649 (37.83)	
15.00-22.00 u/L	13 193 (30.50)	735 (28.37)	627 (30.32)	1328 (30.47)	
>22.00 u/L	14 527 (33.07)	948 (36.58)	712 (34.42)	1382 (31.70)	
TBil (%)					<.0001
<10.70 umol/L	13 079 (30.23)	986 (38.06)	705 (34.09)	2320 (53.23)	
10.70-14.00 umol/L	14 757 (34.12)	756 (29.18)	647 (31.29)	1085 (24.90)	
>14.00 umol/L	15 422 (35.65)	849 (32.76)	716 (34.62)	954 (21.87)	
BMI (%)					<.0001
<24 kg/m^2	17 638 (40.77)	780 (30.10)	622 (30.08)	1509 (34.62)	
24-28 kg/m^2	17 902 (41.38)	1108 (42.76)	842 (41.72)	1930 (44.28)	
>28 kg/m^2	7718 (17.85)	703 (27.13)	604 (29.20)	920 (21.10)	
Physical exercise (%)					<.0001
Never	3924 (9.07)	181 (6.99)	143 (6.92)	224 (5.14)	
Occasionally	32 406 (74.91)	1945 (75.07)	1518 (73.40)	2834 (65.01)	
Regularly	6928 (16.00)	465 (17.94)	407 (19.68)	1301 (29.85)	
Smoking status (%)					<.0001
Never	25 299 (58.49)	1404 (54.19)	1243 (60.11)	2446 (56.11)	
Past	2314 (5.35)	102 (3.94)	109 (5.27)	207 (4.75)	
Moderate	1676 (3.87)	92 (3.55)	57 (2.76)	119 (2.73)	
Severe	13 969 (32.29)	993 (38.32)	659 (31.86)	1587 (36.41)	

(Continues)

				-decreasing
				61-1.02)
				.51-1.56)
				3.27-7.26)
				(0.15-1.77)
				(0.33-1.59)
				0 (0.30-1.45)
				43 (0.10-1.80)
				.04 (0.44-2.45)
				0.23 (0.05-0.95)
				0.82 (0.46-1.47)
				0.54 (0.35-0.85)
				0.88 (0.48-1.61)
				0.29 (0.07-1.2

arital status, salt

		Adjusted models	
	-years	HR (95% CI)	*P*-value
	5 006	Ref.	
	14 999	1.86 (1.54-2.24)	<.0001
	1/11 627	1.84 (1.53-2.22)	<.0001
	156/27 284	1.02 (0.87-1.20)	.0532
	1927/363 222	Ref.	
	210/21 423	1.44 (1.21-1.70)	<.0001
	154/17 310	1.42 (1.19-1.68)	.0001
	195/35 668	1.03 (0.70-1.42)	.2129
statins			
	1929/361 654	Ref.	
g pattern	207/21 367	1.40 (1.17-1.65)	.0001
reasing pattern	151/17 214	1.38 (1.16-1.65)	.0003
decreasing pattern	178/35 350	0.90 (0.77-1.04)	.1555
participants with follow-up <1 year			
Low-stable pattern	1773/363 832	Ref.	
Moderate-increasing pattern	179/21 345	1.41 (1.16-1.64)	<.0001
Increasing-decreasing pattern	129/17 271	1.34 (1.11-1.58)	.0001
Elevated-decreasing pattern	150/35 662	0.94 (0.80-1.10)	.2331

dels were adjusted for age (every 10 years), gender, BMI, TG, TC, TBiL, ALT, diabetes, family
ational background, marital status, salt consumption, current smoker, drinking status,
dentary lifestyle and family history of cancer.

cancer (HR = 2.47, 95% CI: 1.16-2.51), bladder cancer (HR = 6.71, 95% CI: 4.30-10.48), pancreatic cancer (HR = 1.92, 95% CI: 1.10-2.88) and liver cancer (HR = 1.29, 95% CI: 1.15-1.44). Remarkably, the increasing-decreasing trajectory pattern was also associated with the decreased risk of colorectal cancer in the multivariate analyses (HR = 0.33, 95% CI: 0.15-0.73).

Compared to the low-stable pattern of CRP, individuals in the elevated-decreasing trajectory pattern had a 4.8-fold increased risk of leukemia in the adjusted models (HR = 4.87, 95% CI: 3.27 to 7.26). However, the elevated-decreasing trajectory pattern is also associated with decreased risk of esophageal cancer (HR = 0.23, 95% CI: 0.05 to 0.95) and colorectal cancer (HR = 0.54, 95% CI: 0.35 to 0.85).

3.5 | Sensitivity analysis

In the sensitivity analysis, after excluding individuals with CRP levels greater than 10 mg/L during 2006 to 2010 (n = 2601), or who had received oral aspirin therapy (n = 282), or who took statins (n = 535) at baseline examination, or with follow-up less than 1 year (n = 879), the association between CRP trajectory patterns and the risk of pooled cancers remained significant in the multivariate analysis (Table 4).

4 | DISCUSSION

In this large, prospective cohort study, compared to the low-stable CRP trajectory pattern within 4 years, we found (i) a positive association of the moderate-increasing CRP and increasing-decreasing CRP trajectory pattern with overall cancer risk; (ii) participants in the moderate-increasing CRP trajectory pattern exhibited elevated risk of lung, breast, bladder, stomach, colorectal, liver, gallbladder or extrahepatic bile duct cancer and leukemia; (iii) the increasing-decreasing CRP trajectory pattern was associated with increased risk of lung, breast, bladder, pancreatic, liver cancer and decreased risk of colorectal cancer. (iv) elevated-decreasing CRP trajectory pattern was associated with increased leukemia risk and decreased esophageal and colorectal cancer risk. As far as we are aware, this is the first study to comprehensively evaluate the impact of heterogeneous CRP trajectories on the risk of overall and specific-site cancers worldwide.

Participants in the moderate-increasing and increasing-decreasing CRP trajectory patterns were at a higher risk of developing cancer in

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 study, including lifestyle behaviors and history of cancer-associated diseases. Finally, cancer cases were obtained through inspection of the Tangshan medical insurance system and the Kailuan social security system which record all the health information of participants. Using this method, the follow-up rate was almost 100% in the current study.

Limitations should also be noticed in our study when interpreting the results. First, the Kailuan study does not contain detailed information on other cancer-associated causal factors including hepatitis C virus

39. Pasceri V, Cheng JS, Willerson JT, Yeh ET. Modulation of C-reactive protein-mediated monocyte chemoattractant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs. Circulation. 2001;103(21):2531-2534.
40. Hattori Y, Matsumura M, Kasai K. Vascular smooth muscle cell activation by C-reactive protein. Cardiovasc Res. 2003;58(1):186-195.
41. Cui Y, Jia J. Update on epidemiology of hepatitis B and C in China. J Gastroenterol Hepatol. 2013;28:7-10.
42. da Silva AP, Valente A, Chaves C, et al. Characterization of Portuguese centenarian eating habits, nutritional biomarkers, and cardiovascular risk: a case control study. Oxid Med Cell Longev. 2018;2018:5296168.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Liu T, Zhang Q, Song C, et al. C-reactive protein trajectories and the risk of all cancer types: A prospective cohort study. Int J Cancer. 2022;1-11. doi:10.1002/ijc.34012