

运动通过降低慢性炎症降低癌症风险: 中国双队列研究

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四大慢病重大专项(2023ZD0500100)、上海市加强公共卫生体系建设三年行动计划(2023~2025年)(GWVI-11.1-10)和国家自然科学基金面上项目(82473715)资助

摘要 我国大陆地区2022年人口恶性肿瘤发生与死亡分别占全球的24.17%和26.44%, 癌症负担严重, 探索经济有效的癌症预防策略有重要意义. 运动有望降低癌症发生和死亡风险, 但在人群中效果及作用机制仍有待阐明. 本研究旨在揭示中国人群中运动与癌症发生和死亡风险之间的关系及其可能作用途径, 为此整合中国嘉道理生物样本库(China Kadoorie Biobank, CKB)和上海浦东前瞻性队列(简称“上海队列”)数据, 共纳入522165名研究对象. 研究采用外周血C反应蛋白(C-reactive protein, CRP)/高敏C反应蛋白(high-sensitivity CRP, hs-CRP)代表炎症水平; 并使用结构化问卷收集信息; 健康人群被定义为基线无慢性病者. 两队列全人群及健康人群基线数据中运动组的CRP/hs-CRP均低于非运动组($P < 0.05$). 高炎症水平与高癌症发病风险(上海队列: 风险比(hazard ratio, HR)=1.252, 95%置信区间(confidence interval, CI): 1.031~1.520; CKB队列: HR=1.351, 95% CI: 1.172~1.558)和死亡风险(上海队列: HR=1.491, 95% CI: 1.179~1.886; CKB队列: HR=1.428, 95% CI: 1.203~1.696)显著相关. 限制性立方样条曲线分析表明CKB队列中CRP/hs-CRP水平与癌症发生和死亡风险呈显著非线性正相关. 在上海队列中, 运动与较低的癌症死亡风险相关(log-rank $P=0.020$). 在CKB队列中, 慢跑人群的炎症水平($P < 0.001$)、癌症发生与死亡风险显著(log-rank $P < 0.0001$)低于其他运动类型. 综上, 运动可通过降低炎症水平降低癌症发生与死亡风险, 运动尤其是慢跑对我国人口癌症的预防具有重要意义.

关键词 运动, 炎症, C反应蛋白, 癌症, 队列研究, 癌症预防

癌症是全球面临的重大公共卫生问题. 2022年, 我国大陆地区人口占全球18.66%, 但新发癌症病例和癌症死亡病例分别占全球的24.17%(482.47万)和26.44%(257.42万)^[1~3], 癌症负担非常严重. 此外, 人口老龄化和不健康生活方式可能进一步加剧我国癌症负担^[2,4,5].

多数癌症患者确诊时已进展至晚期, 传统治疗(放射、化疗及手术)常难以获得理想疗效^[6,7], 新疗法如靶向和免疫治疗成本高昂^[8]. 因此, 癌症预防是控制癌症的关键, 当前亟需制定具有良好成本效益的癌症预防与控制策略.

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Feng Y, Yang Z, Ke J, et al. Physical activity reduces cancer risk by lowering chronic inflammation: a dual-cohort study in the Chinese population (in Chinese). Chin Sci Bull, 2026, 71: 266–277, doi: [10.1360/CSB-2025-5270](https://doi.org/10.1360/CSB-2025-5270)

研究表明,慢性炎症是癌症发生的重要病理基础^[9-11]。肥胖等代谢综合征、感染、自身免疫性疾病,环境刺激物暴露以及组织损伤均是引发全身慢性炎症的病理因素^[9]。降低炎症水平可能是预防癌症发生和死亡的关键。已有研究表明运动可以降低超过35种不同疾病的风险,即使是单次运动也可产生抗炎作用^[12],且运动对乳腺癌、结直肠癌和子宫内膜癌有一定的预防作用^[13-15]。但也有证据表明运动与某些癌症包括胆囊癌、肾癌和多发性骨髓瘤缺乏关联性^[16]。因此,目前针对运动控制癌症负担的影响仍需要有力的流行病学证据,尤其是基于我国本土人群的证据。同时,运动能降低体内炎症水平,预防心血管疾病和2型糖尿病^[17]。然而,运动是否能够通过降低炎症水平而降低癌症的发生与死亡仍缺乏证据支持,运动、炎症、癌症三者之间的关系尚不明确。

为揭示运动、炎症、癌症之间的关联,我们开展了基于本国人群的双队列研究。基于中国嘉道理生物样本库(China Kadoorie Biobank, CKB)和上海浦东自然人群(下文简称“上海队列”)两大队列,为将运动干预纳入癌症预防策略提供了相互验证的流行病学证据,并为阐明其潜在生物学机制提供了线索。

1 对象与方法

1.1 研究人群

CKB大型前瞻性队列的研究对象覆盖了中国大陆5个城市和5个农村地区30~80岁人群^[18-20]。在基线调查阶段(2004~2008年),CKB通过问卷访谈、生物样本采集和体格检查纳入512891名研究对象,排除2例体质指数(body mass index, BMI)缺失者。死亡率随访数据从关联中国疾病监测系统登记库中获取。本研究通过中国慢性病前瞻性研究数据共享平台(CKB Data Access System, <https://www.ckbiobank.org>, 申请编号DAR-2024-00174)获取公开数据,发表研究结果不需要获得CKB项目团队的审核及批准,所有参与者均签署知情同意书。上海队列于2013年在上海市浦东新区建立,采用多阶段分层随机整群抽样法招募常住居民^[21]。上海队列通过上海居民身份证号码与浦东新区肿瘤登记数据库和浦东新区生命统计数据库进行匹配,从而获取癌症发生和死亡数据。其中,非上海户籍人群因无法通过上海居民身份证号追踪疾病结局而未被纳入。在排除非上海户籍($n=233$)、无实验室检测结果($n=538$)、

未完成问卷调查($n=436$)及BMI缺失者($n=7$)后,上海队列最终纳入了9443名研究对象。研究方案经上海市浦东新区疾病预防控制中心伦理委员会批准(审批号:PDCDCLL-20250508-003)。

1.2 数据收集

采用结构化问卷收集两个队列人群的基线人口学特征、生活方式史、运动特征、慢性病史及癌症发生情况,根据问卷调查中参与者自述有无运动将参与者分为运动组(有体育运动)和非运动组(无体育运动)。本研究中的运动指代以日常锻炼为目的的非职业性体育活动。健康人群被定义为基线无慢性病者(基线时无糖尿病、心血管疾病(cardiovascular disease, CVD)、癌症、高血压或肥胖者)。C反应蛋白(C-reactive protein, CRP)是临床常用炎症生物标志物^[22,23],本研究中以CRP或高敏CRP(high-sensitivity CRP, hs-CRP)的中位数为界将参加者分为“高炎症组”和“低炎症组”(依据队列指标:CKB队列采用hs-CRP,上海队列采用标准CRP,均来自外周血)。

1.3 疾病结局

癌症事件按照国际疾病分类第10版(ICD-10)编码(C00-C97)定义进行统计:CKB队列通过户籍系统与死因登记系统追踪至2017年1月1日^[24],上海队列通过上海市肿瘤登记系统年度核查新发癌症和死亡至2023年9月30日^[21]。

1.4 统计学分析

使用Stata 18.0(Stata Corp, College Station, TX)和R 4.0.2(R Foundation for Statistical Computing, Vienna, Austria)软件进行数据分析。符合正态分布的连续变量以均值±标准差($mean \pm SD$)表示,非正态分布变量以中位数(四分位数)[$M(Q1, Q3)$]表示;运动组与非运动组的组间比较采用两独立样本 t 检验或Mann-Whitney U检验。采用Cox比例风险模型估计癌症发病与死亡的风险比(hazard ratio, HR)及其95%置信区间(95% CI),Kaplan-Meier法计算累积发病率。使用限制性立方样条(restricted cubic spline, RCS)曲线分析结合Cox比例风险模型检验CRP或hs-CRP与癌症风险的剂量-效应关系。校正变量包括年龄、性别、吸烟、饮酒、就业、教育水平、糖尿病、癌症病史、CVD、高血压及BMI。统计学显著性定义为双侧 $P < 0.05$ 。

2 结果

2.1 基线特征

本研究纳入CKB队列和上海队列共522165名研究对象。CKB队列总样本量512722人(健康人群385037人,占75.10%),上海队列总样本量9443人(健康人群4029人,占42.67%)。CKB总人群年龄 52.0 ± 10.7 岁(健康人群 50.6 ± 10.4 岁),上海队列总人群年龄 57.9 ± 12.9 岁(健康人群 53.4 ± 13.6 岁)。女性占比:CKB总人群59.0%(302518/512722),健康人群58.1%(223880/385037);上海队列总人群63.2%(5964/9443),健康人群64.1%(2581/4029)。缺乏运动者占比:CKB队列61.2%(313786/512722),上海队列74.3%(7012/9443)。基线癌症患病率:CKB总人群0.5%(2578/512722),上海队列11.1%(1045/9443)。中位

随访时间:上海队列128(127~129)个月,CKB队列123(112~135)个月。炎症水平:上海队列CRP 1.34 ± 4.72 mg/L,CKB队列hs-CRP 2.52 ± 7.06 mg/L(表1,表2)。

2.2 运动与低癌症相关死亡风险相关

如图1(a),Kaplan-Meier分析显示上海队列中运动与较低的癌症死亡风险相关(log-rank $P=0.020$)。而如图1(b),在CKB队列中,运动只在低炎症水平人群而非高炎症水平人群中与较低的癌症死亡风险相关(CKB:HR=0.73, $P<0.05$)。如图2所示,CKB队列中,慢跑人群较其他运动类型人群具有更低的hs-CRP水平($P<0.001$),慢跑人群较其他运动类型人群具有更低的癌症发生风险(log-rank $P<0.0001$)与死亡风险(log-rank $P<0.0001$)。

表 1 上海队列与CKB全部参与者的基线特征及随访情况^{a)}

Table 1 The baseline characteristics and follow-up summaries of all participants in the CKB and Shanghai cohorts

特征	上海队列	CKB队列
总人数	$n=9443$	$n=512722$
年龄(岁), 平均值 $\pm$ 标准差	57.9 ± 12.9	52.0 ± 10.7
女性, 人数(百分比)	5964(63.2%)	302518(59.0%)
在职/在校/退休, 人数(百分比)	8283(87.7%)	437391(85.3%)
教育水平, 人数(百分比)		
大学及以上	348(3.7%)	29976(5.8%)
高中或同等学历	3022(32.0%)	77509(15.1%)
高中以下	6073(64.3%)	405237(79.0%)
从不吸烟, 人数(百分比)	7271(77.0%)	348054(67.9%)
当前饮酒者, 人数(百分比)	1310(13.9%)	268355(52.3%)
BMI分类, 人数(百分比)		
体重过轻(<18.5 kg/m ²)	171(1.8%)	14067(2.7%)
正常体重($18.5\sim 23.9$ kg/m ²)	3664(38.8%)	274175(53.5%)
超重($24.0\sim 27.9$ kg/m ²)	3938(41.7%)	170139(33.2%)
肥胖(≥ 28.0 kg/m ²)	1670(17.7%)	54341(10.6%)
无日常锻炼, 人数(百分比)	7012(74.3%)	313786(61.2%)
基线自报及医生诊断疾病, 人数(百分比)		
癌症	1045(11.1%)	2578(0.5%)
心血管疾病(CVD)	622(6.6%)	15472(3.0%)
糖尿病	1045(11.1%)	30300(5.9%)
高血压	3701(39.2%)	59703(11.6%)
CRP/hs-CRP (mg/L), 平均值 $\pm$ 标准差	1.34 ± 4.72	2.52 ± 7.06
随访时间(月), 中位数(IQR)	128(127, 129)	123(112, 135)
新发癌症病例数(百分比)	610(6.5%)	22731(4.4%)
全因死亡数(百分比)	937(9.9%)	44065(8.6%)
癌症相关死亡数(百分比)	286(3.0%)	14317(2.8%)

表 2 上海队列与CKB健康人群的基线特征及随访情况总结^{a)}

Table 2 The baseline characteristics and follow-up summaries of healthy participants in the CKB and Shanghai cohorts

特征	上海队列	CKB队列
总人数	<i>n</i> =4029	<i>n</i> =385037
年龄(岁), 平均值±标准差	53.38±13.64	50.61±10.43
女性, 人数(百分比)	2581(64.1%)	223880(58.1%)
在职/在校/退休, 人数(百分比)	3493(86.7%)	333361(86.6%)
教育水平, 人数(百分比)		
大学及以上	199(5.0%)	21798(5.7%)
高中或同等学历	1427(35.4%)	58729(15.3%)
高中以下	2403(59.6%)	304510(79.1%)
从不吸烟, 人数(百分比)	3149(78.1%)	253952(66.0%)
当前饮酒者, 人数(百分比)	536(13.3%)	207818(54.0%)
BMI分类, 人数(百分比)		
体重过轻(<18.5 kg/m ²)	119(3.0%)	12551(3.3%)
正常体重(18.5~23.9 kg/m ²)	2214(55.0%)	240000(62.3%)
超重(24.0~27.9 kg/m ²)	1696(42.0%)	132486(34.4%)
CRP (mg/L)/hs-CRP (mg/L), 平均值±标准差	0.93±3.74	2.28±7.07
随访时间(月), 中位数(IQR)	128(127, 129)	121(112, 135)
全因死亡数(百分比)	221(5.5%)	—
癌症相关死亡数(百分比)	81(2.0%)	9699(2.5%)

a) 连续变量以平均值(标准差)或中位数(四分位距)表示, 分类变量以人数(百分比[%])表示; IQR: 四分位距(interquartile range)

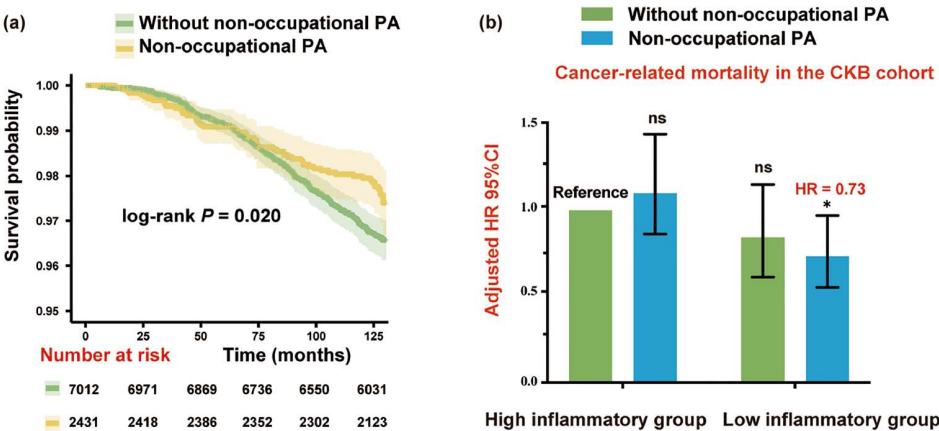


图 1 CKB与上海队列中运动对癌症相关死亡风险的影响。(a) 上海队列中运动对人群癌症相关死亡风险的影响; (b) CKB队列中运动对高炎症和低炎症人群癌症相关死亡风险的影响。上海队列中运动组相较于非运动组具有更低的癌症死亡率。CKB中低炎症运动人群相较于高炎症不运动人群具有更低的癌症死亡率。*, $P<0.05$; ***, $P<0.001$; ns: 无显著性差异。组间比较采用对数秩检验(log-rank test); PA: 运动(physical activity)

Figure 1 Effect of non-occupational PA on cancer-related mortality risk in the CKB and Shanghai cohorts. (a) Effect of non-occupational PA on cancer-related mortality risk for all participants in the Shanghai cohort. (b) Effect of non-occupational PA on cancer-related mortality risk by inflammation status in the CKB cohort. In the Shanghai cohort, the physically active group had a lower cancer mortality rate compared to the inactive group. In the CKB cohort, the physically active low-inflammatory group had a lower cancer mortality rate compared to the inactive high-inflammatory group. *, $P<0.05$; ***, $P<0.001$; ns, no significant difference. Inter-group comparisons were performed using the log-rank test; PA, physical activity

2.3 慢性炎症的影响因素与运动的抗炎作用

如图3所示, 在CKB队列与上海队列中, 全人群与健康人群的CRP/hs-CRP均随年龄的增加而上升(Bon-

ferroni校正 $P<0.05$), 患有慢性病人群的CRP/hs-CRP水平显著高于健康人群(Bonferroni校正 $P<0.05$)。由于CKB队列基线数据中有hs-CRP数据人群中未出现癌症

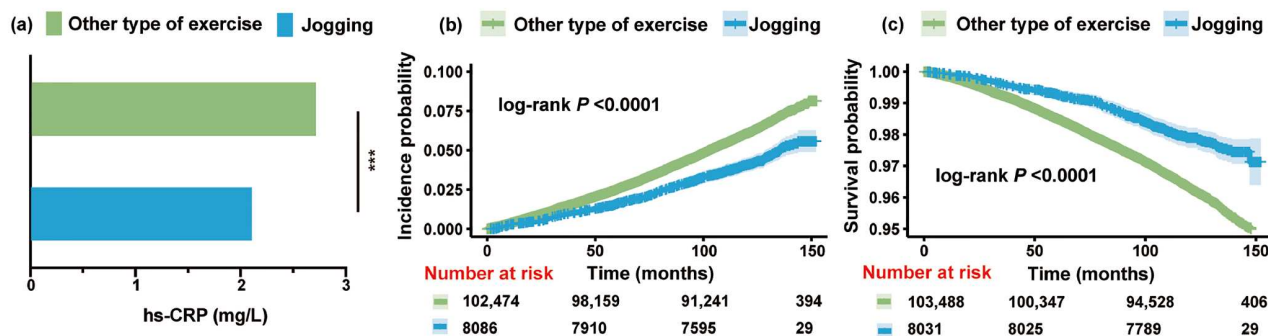


图 2 CKB队列中慢跑及其他运动类型对炎症水平与癌症发生和死亡风险的影响。(a) 慢跑与其他运动类型对炎症水平的影响；(b) Kaplan-Meier曲线分析慢跑及其他运动类型对癌症发病风险的影响；(c) Kaplan-Meier曲线分析慢跑及其他运动类型对癌症死亡风险的影响。慢跑较其他运动类型与较低的炎症水平及癌症发病与死亡风险显著相关。***, $P < 0.001$ 。组间比较采用对数秩检验(log-rank test)

Figure 2 Impact of jogging versus other exercise types on systemic inflammation levels and the risk of cancer occurrence and mortality in the CKB cohort. (a) Effect of jogging versus other exercise types on systemic inflammation levels. (b) Kaplan-Meier curve analysis of the impact of jogging versus other exercise types on the risk of cancer occurrence. (c) Kaplan-Meier curve analysis of the impact of jogging versus other exercise types on the risk of cancer mortality. Jogging was associated with a significantly greater reduction in systemic inflammation levels and lower risks of cancer occurrence and mortality compared to other exercise types. ***, $P < 0.001$. Inter-group comparisons were performed using the log-rank test

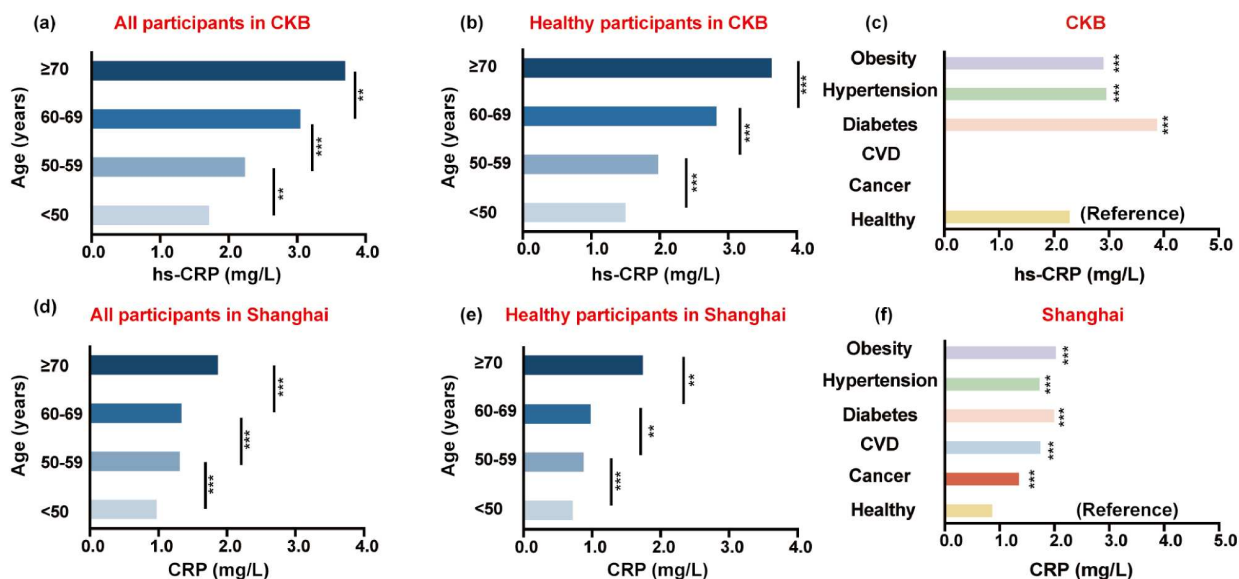


图 3 CKB队列与上海队列炎症水平与年龄和慢性病的相关性。(a) CKB队列中全人群各年龄组hs-CRP水平。(b) CKB队列中健康人群各年龄组hs-CRP水平。(c) CKB队列中慢性病人群hs-CRP水平。(d) 上海队列中全人群各年龄组CRP水平。(e) 上海队列中健康人群各年龄组CRP水平。(f) 上海队列中慢性病人群CRP水平。两大队列全部参与者及健康人群CRP/hs-CRP随着年龄的增长上升, 患有慢性病人群的CRP/hs-CRP显著高于健康人群。**, 经Bonferroni法校正后 $P < 0.01$; ***, 经Bonferroni法校正后 $P < 0.001$

Figure 3 Associations of inflammation levels with age and chronic diseases in the CKB and Shanghai cohorts. (a) The hs-CRP levels by age group in the all CKB cohort population. (b) The hs-CRP levels by age group in the healthy subgroup of the CKB cohort. (c) The hs-CRP levels in the chronic disease subgroup of the CKB cohort. (d) The CRP levels by age group in the all Shanghai cohort population. (e) The CRP levels by age group in the healthy subgroup of the Shanghai cohort. (f) The CRP levels in the chronic disease subgroup of the Shanghai cohort. CRP/hs-CRP levels increased with advancing age among all participants and healthy subgroups in both cohorts. Individuals with chronic diseases exhibited significantly higher CRP/hs-CRP levels compared to healthy individuals. **, with the Bonferroni correction, $P < 0.01$; ***, with the Bonferroni correction, $P < 0.001$

或CVD患者, 因此未对这两类慢性病患者进行CRP/hs-CRP分析。如图4, 在CKB与上海队列的全人群与健康人群中, 运动组CRP/hs-CRP中位数均低于非运动组

(CKB全人群: $P < 0.001$; CKB健康人群: $P < 0.001$; 上海队列全人群: $P < 0.01$; 上海队列健康人群: $P < 0.05$), 证明运动与低炎症水平显著相关。

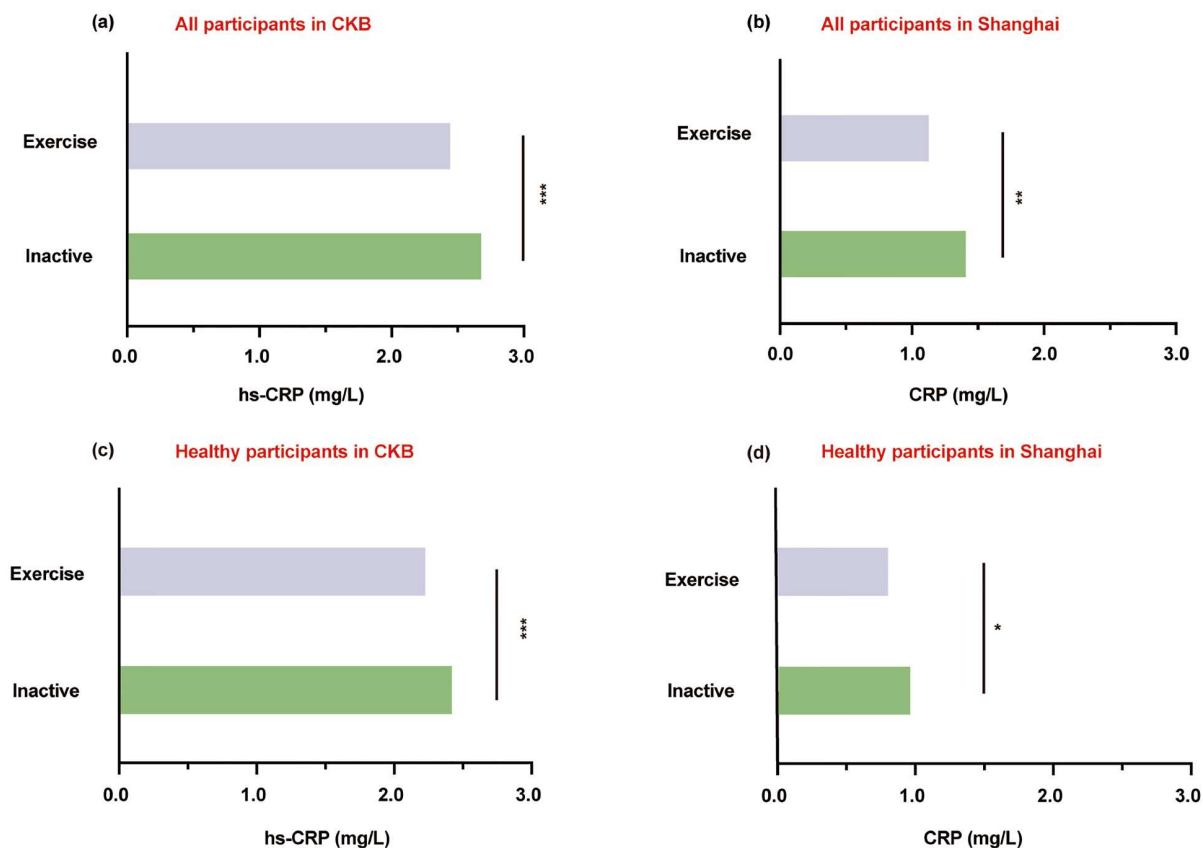


图4 CKB队列与上海队列全人群与健康人群中运动与炎症水平的相关性。(a) CKB队列全人群中运动与炎症水平的相关性。(b) 上海队列全人群中运动与炎症水平的相关性。(c) CKB队列健康人群中运动与炎症水平的相关性。(d) 上海队列健康人群中运动与炎症水平的相关性。两大队列全人群及健康人群中运动均与低炎症水平显著相关。*, $P<0.05$; **, $P<0.01$; ***, $P<0.001$

Figure 4 Association of PA with inflammation levels in all population and healthy subgroup of the CKB and Shanghai cohorts. (a) Association of PA with inflammation levels in the CKB cohort. (b) Association of PA with inflammation levels in the Shanghai cohort. (c) Association of PA with inflammation levels in the healthy subgroup of the CKB cohort. (d) Association of PA with inflammation levels in the healthy subgroup of the Shanghai cohort. PA was significantly associated with lower inflammation levels in both the overall study populations and the healthy subgroups across the two cohorts. *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$

2.4 高炎症水平与高癌症发病与死亡风险显著相关

在CKB队列与上海队列中, 如图5(a)和(b), 高炎症水平与较高的癌症发病风险显著相关(log-rank $P<0.05$): 上海队列HR=1.252(95% CI: 1.031~1.520); CKB队列HR=1.351(95% CI: 1.172~1.558)。如图5(c)和(d), 高炎症水平与较高的癌症死亡风险显著相关(log-rank $P<0.05$): 上海队列HR=1.491(95% CI: 1.179~1.886); CKB队列HR=1.428(95% CI: 1.203~1.696)。如图6, RCS分析进一步显示CRP/hs-CRP水平与癌症发病和死亡风险呈显著的正向剂量反应关系(Overall $P<0.05$)。CKB队列中CRP/hs-CRP水平与癌症发病和死亡风险呈显著非线性正相关。

3 讨论

本研究通过CKB队列与上海队列两大中国本土队列证明, 运动与较低的癌症死亡风险相关, 同时运动与全人群和健康人群中较低的CRP或hs-CRP水平相关, 高炎症水平与较高的癌症发病与死亡风险相关, 因此运动可能通过降低炎症水平降低癌症发生与死亡风险。此外, 我们还发现炎症水平随个体年龄增长而升高, 且与慢性疾病显著相关。因此我们认为运动能够抵抗衰老和慢性疾病等因素导致的高炎症水平, 从而降低癌症的发生与死亡风险。这项研究为运动在癌症预防方面的作用及其潜在机制提供了有力的流行病学证据。

本研究证明, 运动与较低的癌症死亡风险显著相

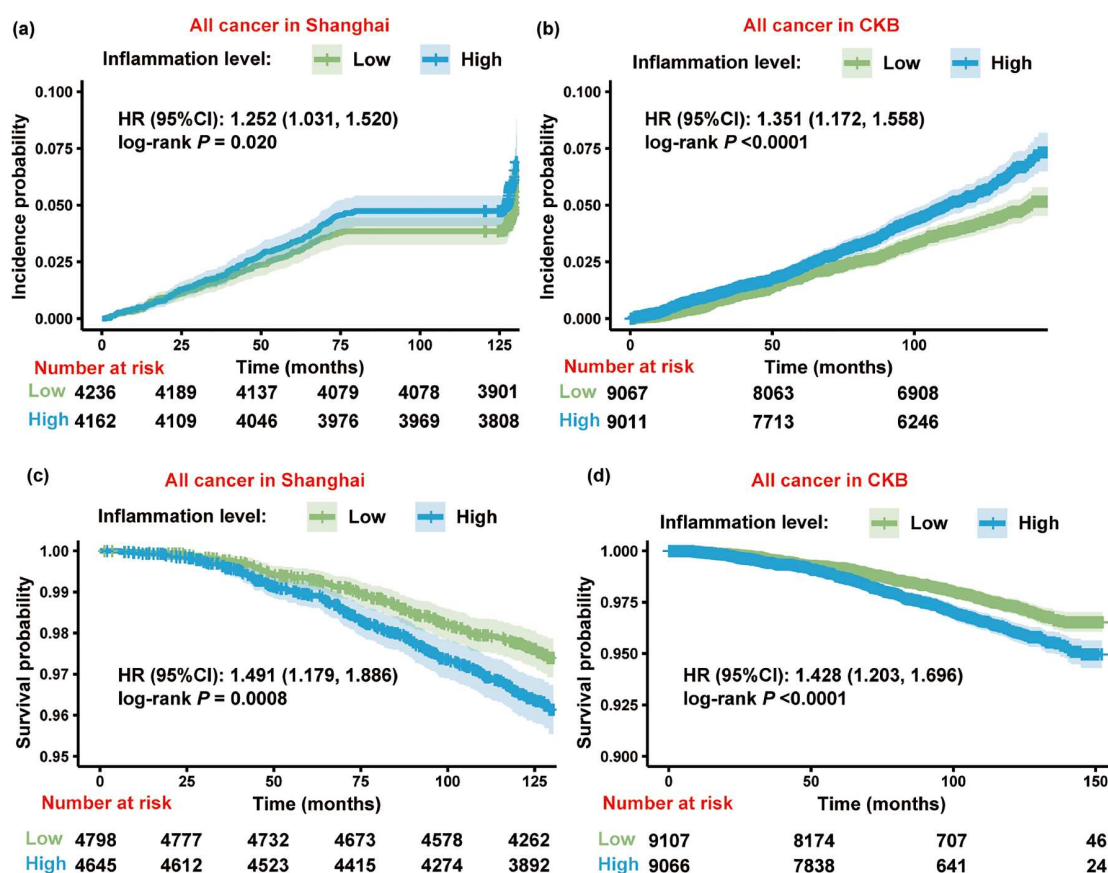


图 5 CKB队列及上海队列中炎症水平对癌症发病与死亡风险的Kaplan-Meier生存曲线分析。(a) 上海队列中全身性炎症水平对癌症发病风险的影响。(b) CKB队列中全身性炎症水平对癌症发病风险的影响。(c) 上海队列中全身性炎症水平对癌症死亡风险的影响。(d) CKB队列中全身性炎症水平对癌症死亡风险的影响。两大队列中低炎症水平人群具有更低的癌症发病与死亡风险。组间比较采用对数秩检验(log-rank test)

Figure 5 Kaplan-Meier survival curve analysis of the association between systemic inflammation and the risks of cancer occurrence and mortality in the CKB and Shanghai cohorts. (a) Effect of systemic inflammation status on cancer incidence risk in the Shanghai cohort. (b) Effect of systemic inflammation status on cancer incidence risk in the CKB cohort. (c) Effect of systemic inflammation status on cancer mortality risk in the Shanghai cohort. (d) Effect of systemic inflammation status on cancer mortality risk in the CKB cohort. Individuals with low systemic inflammation levels exhibited significantly lower cancer incidence and mortality risks in both cohorts. Inter-group comparisons were performed using the log-rank test

关, 且慢跑人群较其他运动类型人群具有更低的癌症发生与死亡风险。上海队列中运动与较低的癌症死亡风险显著相关; 而在CKB队列中, 运动只与低炎症水平人群中较低的癌症死亡风险相关, 而不对高炎症人群产生此效应, 主要原因可能是CKB队列使用问卷调查进行运动数据的采集, 其中存在大量体力劳动者因未进行非职业体育锻炼为被归类为“非运动人群”, 这与英国UK Biobank(UKB)队列使用加速度计客观衡量全部体力活动的研究不同。在使用UKB队列加速度计数据的相关研究中, 运动对癌症的保护效益是十分确切的^[25]。因此, CKB的运动量统计偏差可能导致了本研究中运动并未在CKB高炎组人群中表现出显著的癌症

死亡保护作用, 但这并不影响运动强大的抗癌作用。我们首次发现, 在CKB队列的运动人群中慢跑相比于其他运动类型能够显著降低癌症发病与死亡风险, 提示慢跑具有极强的预防癌症潜能。一项动物研究表明, 低强度跑步运动能够显著抑制小鼠体内胰腺癌细胞的生长, 不论是自发性肿瘤还是移植肿瘤模型中均是如此^[26]。此外, 老年人和具有慢性病基础的人群是癌症发生的高危人群, 而慢跑作为低中强度运动对这类人群而言具有较高的可行性。因此, 我们提倡将慢跑作为一项具有强大癌症预防措施, 列入公共卫生防癌指南。

个体炎症水平在癌症发生和发展阶段均起到重要作用。目前已有研究表明, 癌症的发生是由炎症与遗传

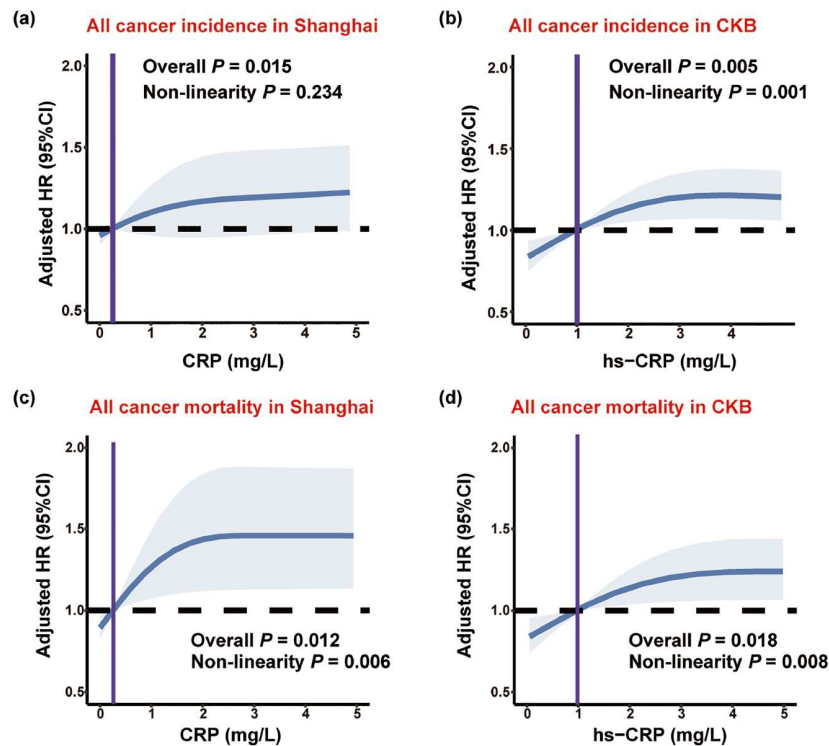


图 6 校正协变量后CKB队列和上海队列中炎症水平对癌症发病与死亡风险的RCS回归分析. (a) 上海队列中CRP与癌症发病风险的关联. (b) CKB队列中hs-CRP与癌症发病风险的关联. (c) 上海队列中CRP与癌症死亡风险的关联. (d) CKB队列中hs-CRP与癌症死亡风险的关联. CRP/hs-CRP水平升高均显著增加癌症发病和死亡率风险校正变量: 年龄、性别、糖尿病、癌症病史、CVD、BMI

Figure 6 RCS regression analysis of the association between inflammation levels and cancer incidence/mortality after adjustment for the covariates in the CKB and Shanghai cohorts. (a) Association between CRP and cancer incidence risk in the Shanghai cohort. (b) Association between hs-CRP and cancer incidence risk in the CKB cohort. (c) Association between CRP and cancer mortality risk in the Shanghai cohort. (d) Association between hs-CRP and cancer mortality risk in the CKB cohort. Elevated CRP/hs-CRP levels were significantly associated with increased risks of cancer incidence and mortality. Adjusted variables: age, sex, diabetes, cancer history, CVD, BMI

变异、代谢紊乱、微生物组失衡等多种中间因子协同作用共同驱动的过程^[27-29]。肿瘤微环境在癌症的发病、发展和进展中起关键作用^[30,31]。肿瘤微环境中癌症相关成纤维细胞和代谢重编程通过多种生物活动调节肿瘤进展, 包括肿瘤免疫抑制、慢性炎症和生态位重塑^[32]。慢性炎症过程中活化的成纤维细胞又可通过细胞外基质的调节促进肿瘤发生^[30]。在某些类型的癌症中, 炎症在恶性转化之前就已经存在; 相反, 在其他类型的癌症中, 致癌过程会诱导炎症微环境, 从而促进肿瘤的发展^[33]。因此, 慢性炎症是癌症发生的重要中间因子, 对癌症的发展起到促进作用, 同时癌症也会诱导慢性炎症, 两者之间存在相互促进作用。本研究选择CRP和hs-CRP作为炎症指标。CRP是炎症和组织损伤时血浆浓度急剧升高的急性期蛋白, 健康人群中hs-CRP水平可作为心血管事件的预测因子^[34,35]。生理状态下

CRP合成缓慢, 急性反应期由白细胞介素6(interleukin-6, IL-6)等细胞因子刺激大量合成并释放入血^[36]。CRP可识别病原体及损伤坏死细胞, 并通过补体系统和吞噬细胞介导其清除^[37]。与肿瘤坏死因子 α (tumor necrosis factor α , TNF α)、IL-6和白细胞介素10(interleukin-10, IL-10)等细胞因子一样, CRP被广泛用作炎症标志物, 体现体内炎症水平^[38-40]。两项队列研究均证实, 高炎症水平与高癌症发生与死亡风险显著相关。当CRP/hs-CRP超过特定阈值时, 癌症发病与死亡风险显著上升, 且癌症风险与CRP/hs-CRP水平显著相关。

运动尤其是慢跑能够显著降低全身慢性炎症水平。我们研究显示, 在两个队列的全人群和健康人群中高运动水平均与低炎症水平相关。缺乏身体活动可导致内脏脂肪堆积, 伴随促炎免疫细胞浸润脂肪组织、脂肪因子释放增加及低强度全身性炎症状态的发展^[41]。

这种慢性低强度炎症与胰岛素抵抗、动脉粥样硬化、神经退行性变及肿瘤生长等病理过程密切相关^[42~44]。与之前的研究一致^[45]，我们的研究还证明了衰老和慢性疾病均可导致炎症水平增高。此外，我们首次证实，慢跑人群较其他运动类型人群具有显著更低的hs-CRP水平，说明了慢跑强大的抗炎潜力与其作为一项抗炎防癌策略的价值。

综上所述，运动可通过降低个体炎症水平从而降低癌症发生和死亡风险。已有研究表明缺乏身体活动会增加患2型糖尿病、心血管疾病、慢性阻塞性肺病、结肠癌、乳腺癌、痴呆和抑郁症的风险^[46]。而炎症与上述疾病的发病机制存在病因学联系^[42,47~49]。我们的研究提示，运动可能通过抗炎机制来降低癌症负担。定期运动一方面减少脂肪积累^[46]，另一方面降低IL-6、TNF α 和CRP水平^[50~52]，增加IL-10水平^[52]，从而降低体内炎症水平。这些研究与本研究观察到的运动显著降低CRP/hs-CRP的结果一致。

值得注意的是，运动对全身性炎症的抑制作用可能存在年龄修饰效应。研究表明，衰老细胞的表现遗传改变显著增加促炎细胞因子和趋化因子的分泌^[53]，这与本研究中观察到的年龄与CRP/hs-CRP水平同步上升的现象一致。研究表明，即使是在小鼠生命早年进行定期锻炼也能在中年时期产生抗炎免疫作用^[54]。运动的抗炎作用可能受个体年龄的影响，因此对于个体而言尽早开展运动或许能产生更强的健康效益。

本研究中CKB队列与上海队列结果互相验证，为“运动-降炎-防癌”的潜在通路提供了重要的人群证据，揭示了运动可显著降低癌症死亡风险，并提示运动通

过降低炎症水平降低癌症发病与死亡风险的内在机制。上海队列的结果直接显示，运动人群癌症死亡风险显著低于不活动者。CKB队列进一步表明，慢跑在降低癌症发病与死亡风险中的效应强度高于其他类型运动，提示运动类型可能影响其保护效应强度。

本研究存在一定局限性。一方面，在CKB队列基线非运动人群中，低炎症组仍呈现出比高炎症组更低的癌症死亡风险趋势，但是未达到统计学显著程度，可能与终点事件数较少统计学把握度较低有关。另一方面，运动是通过二分类问卷记录的且可能存在健康人偏倚。尽管我们已通过多变量调整和分层分析尽力控制，但仍不能完全排除未测量混杂因素(如遗传因素、健康意识)的影响。因此，对效应量的解释应保持谨慎。未来研究需要采用更精确的运动测量设备(如加速度计)并收集更详细的运动参数，以证实我们的发现并深入探索其机制。抗炎或激素药物在两队列中原始数据缺失，因此没有被纳入模型，混杂因素控制不足。此外，两个队列均只在基线时测量了运动情况和炎症标志物水平，而在随访时未进行动态监测，未来还需要包含动态数据的大规模前瞻性队列进一步验证。

本研究基于大规模中国人群队列数据表明，运动与较低的全身炎症水平显著相关，且高炎症水平与高癌症发生和死亡风险显著相关。研究结果支持运动可能通过抑制炎症来降低癌症发生与死亡风险这一科学理论。在多种运动类型中，慢跑可能具有相对更优的癌症预防效果。因此，尽早推广和普及规律运动(尤其是慢跑)对于降低中国人群的癌症负担具有重要的公共卫生意义。

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Summary for “运动通过降低慢性炎症降低癌症风险: 中国双队列研究”

Physical activity reduces cancer risk by lowering chronic inflammation: a dual-cohort study in the Chinese population

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The mainland of China accounts for 18.66% of the world's population, 24.17% of global cancer new cases, and 26.44% cancer-related death worldwide in 2022, indicating cancer burden is extremely heavy in this region. It is of great significance to explore a cost-effective strategy for cancer prevention and control. Physical activity (PA) is expected to decrease the risks of cancer occurrence and cancer-related death. However, the effects of PA on cancer burden in China and the mechanisms by which PA prevents cancer remain to be elucidated because these data are current lacking. Here, a total of 522165 subjects from the China Kadoorie Biobank (CKB) and Shanghai cohort were invited to join in this study to reveal the associations of PA with the risks of cancer occurrence and cancer-related death and their underlying mechanisms by which PA decreases the burden of cancer. Circulating C-reactive protein (CRP) and high-sensitivity CRP (hs-CRP) were used to represent inflammation levels in the two cohorts, respectively. Demographic information was collected using a structured questionnaire. Healthy participants were defined as those without any chronic disease at baseline. Cox proportional hazard model was used to analyze factors that contribute to cancer occurrence and cancer-related mortality. It was found that the circulating levels of CRP and hs-CRP were significantly lower in the participants with PA than in those without PA in either entire study subjects or healthy participants at baselines. Compared to the participants with lower inflammation, those with higher inflammation had a higher risk of cancer occurrence, with a hazard ratio (HR) and 95% confidence interval (95% CI) of 1.252 and 1.031–1.520 in Shanghai cohort and 1.351 and 1.172–1.558 in CKB as well as a higher risk of cancer-related death, with a HR and 95% CI of 1.491 and 1.179–1.886 in Shanghai cohort and 1.428 and 1.203–1.696 in CKB. Restricted cubic spline (RCS) analysis demonstrated a significant non-linear positive correlation between the circulating levels of CRP/hs-CRP and the risks of cancer occurrence and cancer-related death. In Shanghai cohort, PA was significantly associated with a decreased risk of cancer mortality (log-rank $P=0.020$). In the CKB cohort, jogging was associated with a lower level of systemic inflammation, lower risk of cancer occurrence, and lower risk of cancer mortality than did other PA modalities. The study provides robust population-based evidence supporting the hypothesis that PA, particularly jogging, confers efficient protection against cancer occurrence and cancer-related mortality partly via lowering systemic low-grade inflammation, indicating that PA especially jogging is of public health significance for cancer prevention and control, which can be suggested as a useful public health strategy against cancer.

exercise, inflammation, C-reactive protein, cancer, cohort study, cancer prevention

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