Healthy Lifestyle and Cancer Survival

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Healthy lifestyle and cancer survival: A multinational cohort study

Zilong Bian[1,2] | Rongqi Zhang[1] | Shuai Yuan[3] | Rong Fan[1] | Lijuan Wang[4] | Susanna C. Larsson[3,5] | Evropi Theodoratou[4,6] | Yimin Zhu[7] | Shouling Wu[8] | Yuan Ding[9] | Xue Li[1,4]

[1]Department of Big Data in Health Science, School of Public Health and Center of Clinical Big Data and Analytics of The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

[2]Department of Biostatistics, Center for Global Health, School of Public Health, Nanjing Medical University, Nanjing, China

[3]Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[4]Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, UK

[5]Unit of Medical Epidemiology, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

[6]Cancer Research UK Edinburgh Centre, Medical Research Council Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK

[7]Department of Epidemiology and Biostatistics, School of Public Health, Zhejiang University School of Medicine, Hangzhou, China

[8]Department of Cardiology, Kailuan General Hospital, Tangshan, China

[9]Department of Hepatobiliary and Pancreatic Surgery, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Correspondence
Xue Li, Department of Big Data in Health Science, School of Public Health and Center of Clinical Big Data and Analytics of The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China.
Email: xueli157@zju.edu.cn

Shouling Wu, Department of Cardiology, Kailuan General Hospital, Tangshan, China.
Email: klyybgs@kailuan.com.cn

Yuan Ding, Department of Hepatobiliary and Pancreatic Surgery, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China.
Email: dingyuan@zju.edu.cn

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Abstract

Lifestyle factors after a cancer diagnosis could influence the survival of cancer 60 survivors. To examine the independent and joint associations of healthy lifestyle factors with mortality outcomes among cancer survivors, four prospective cohorts (National Health and Nutrition Examination Survey [NHANES], National Health Interview Survey [NHIS], UK Biobank [UKB] and Kailuan study) across three countries. A healthy lifestyle score (HLS) was defined based on five common lifestyle factors (smoking, alcohol drinking, diet, physical activity and body mass index) that related to cancer survival. We used Cox proportional hazards regression to estimate the hazard ratios (HRs) for the associations of individual lifestyle factors and HLS with all-cause and cancer mortality among cancer survivors. During the follow-up period of 37,095 cancer survivors, 8927 all-cause mortality events were accrued in four cohorts and 4449 cancer death events were documented in the UK and US cohorts. Never smoking (adjusted HR = 0.77, 95% CI: 0.69–0.86), light alcohol consumption (adjusted HR = 0.86, 95% CI: 0.82–0.90), adequate physical activity (adjusted HR = 0.90, 95% CI: 0.85–0.94), a healthy diet (adjusted HR = 0.69, 95% CI: 0.61–0.78) and optimal BMI (adjusted HR = 0.89, 95% CI: 0.85–0.93) were

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significantly associated with a lower risk of all-cause mortality. In the joint analyses of HLS, the HR of all-cause and cancer mortality for cancer survivors with a favorable HLS (4 and 5 healthy lifestyle factors) were 0.55 (95% CI 0.42–0.64) and 0.57 (95% CI 0.44–0.72), respectively. This multicohort study of cancer survivors from the United States, the United Kingdom and China found that greater adherence to a healthy lifestyle might be beneficial in improving cancer prognosis.

KEYWORDS
cancer survival, cancer survivors, healthy lifestyle, multinational cohort

What's new?

This study investigated the independent and joint associations of healthy lifestyle factors with mortality outcomes among cancer survivors by analyzing data from four prospective cohorts across three countries—the National Health and Nutrition Examination Survey and National Health Interview Survey in the United States, the UK Biobank and the Kailuan study in China. Adhering to a healthy lifestyle could reduce the risk of all-cause and cancer mortality by half among cancer survivors. Specifically, avoiding smoking and excessive alcohol consumption, maintaining a healthy diet, engaging in physical activity and maintaining a healthy body mass index were associated with improved prognosis.

1 | INTRODUCTION

Cancers have posed a substantial threat to public health, and the global cancer burden has been projected to increase continuously for at least two decades to come.[1] With the development of early detection strategies, clinical treatment and supportive care, the risk of cancer-cause death has decreased. The 5-year relative survival rate for all cancers combined is around 68% in the United States, which has resulted in over 16.9 million cancer survivors since January 2019.[2,3] However, cancer survivors still suffer from long-term health effects and disability, and have impaired life quality.[4] Therefore, it is necessary to develop cost-effective interventions to reduce the mortality of cancer survivors and thus address the evolving cancer burden.

Modifiable risk factors are associated with cancer survival, such as body mass index,[5] cigarette smoking,[6] alcohol drinking,[6] physical activity[7] and diet.[8] For example, prolonged sitting time and physical inactivity were associated with an elevated risk of mortality among cancer survivors.[7] Nevertheless, most studies examined the associations of a single or two lifestyle factors with cancer survival.[5,7,9] The joint association of multiple lifestyle factors with cancer survival is scarcely explored. In addition, a few studies have been conducted on overall cancer. A multicenter cohort study in China found a positive association between a healthy lifestyle and a longer life expectancy in cancer survivors.[10] In addition, many relevant studies took mortality statistics in the general population as an indicator, while survival statistics in cancer survivors could provide an accurate measure of cancer prognosis.[11,12] Hence, the extent to which the overall cancer survival could be improved by adherence to a healthy lifestyle remained elusive.

In this study, we aimed to evaluate the associations of a combination of healthy lifestyle factors with overall cancer survival, leveraging data from four prospective cohorts of cancer survivors in three countries.

2 | METHODS

2.1 | Study population

Cancer survivors (individuals with prevalent cancer) from four cohorts were included in this study. In US NHANES (1999–2018) and US NHIS (2000, 2005, 2010, 2015), cancer survivors were identified by the self-reported medical question, "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?"[13,14] In the UK Biobank, cancer survivors were ascertained by the International Classification of Diseases, Ninth or Tenth Revision (ICD-9 or ICD-10) from the national cancer registries and hospital in-patient records.[15] In the Kailuan study, cancer cases were defined by an annual linkage with the local vital statistics data (the Tangshan medical insurance system, or the Kailuan Social Security Information System) and self-reported information through questionnaires.[16] In total, after excluding skin cancer (non-melanoma) survivors, 45,267 cancer survivors were identified in four cohorts. We excluded 8172 individuals younger than 20 years old, missing data on healthy lifestyle factors and follow-up, leaving 37,095 cancer survivors in the analysis. Details of the study population selection are displayed in Figure S1.

2.2 | Assessment of lifestyle factors

We included five lifestyle factors, including BMI, cigarette smoking, alcohol drinking, diet and physical activity, possibly related to cancer survival[17] in our analysis. These factors were defined in accordance with previous studies (Table S1). Healthy levels of smoking and alcohol consumption were defined as never smokers and light drinkers (<28 g/day for men and <14 g/day for women[18–20]) calculated from self-reported frequency and current alcohol consumption, respectively. Regarding diet, dietary intake was obtained from 24-h dietary recalls, and the quality was assessed by Healthy Eating Index 2015 (HEI-2015) scores in US NHANES.[21] In the US NHIS, the diet score was calculated according to previous studies.[22,23] Individuals with the highest tertile of HEI were defined as those with a healthy diet in NHANES and NHIS.[24] In the UK Biobank, diet score was defined based on former studies[25] and the American Cancer Society nutrition and physical activity guideline for cancer survivors.[17] A healthy diet was defined as meeting five of eight items (Fruits: ≥3 servings/day; Vegetables: ≥3 servings/day; Fish: ≥2 times/week; Processed meats: ≤1 times/week; Unprocessed red meats: ≤2 times/week; Whole grains: ≥3 servings/day; Refined grains: ≤2 servings/day; sugar: no consumption). Given no dietary information collected in the Kailuan study, the Kailuan study used a three-category, self-perceived salt intake level (ie, low, medium or high) as a surrogate for dietary quality.[26] Low or medium salt intakes were defined as a healthy diet. The healthy level of physical activity was defined as moderate-to-vigorous leisure-time physical activity (≥150 min/week) (NHANES and NHIS).[24] In the UK Biobank, regular physical activity was referred to as ≥150 min of moderate activity per week, or ≥75 min of vigorous activity per week (or an equivalent combination), or engaging in moderate physical activity at least 5 days a week, or vigorous activity once a week, as recommended by the American Heart Association.[27] For the Kailuan study, more than 80 min of weekly time spent on exercise in the last 5 years was defined as a healthy level. The optimal body mass index was set between 25 and 30 kg/m^2.[28–30]

We constructed healthy lifestyle scores by summing the number of healthy lifestyle factors (ie, never smoking, light alcohol consumption, adequate physical activity, healthy diet and optimal BMI). A healthy lifestyle score was derived according to the number of low-risk lifestyle factors, ranging from 0 to 5, with higher scores indicating a healthier lifestyle. Since few participants had 0 or 5 healthy lifestyle factors, those with 0–1 and 4–5 healthy lifestyle factors were combined, respectively, to improve statistical power.

2.3 | Outcome ascertainment

In US NHANES and NHIS, death records were linked by the National Center for Health Statistics (NCHS) through the National Death Index up to December 2019.[31] Likewise, the UK Biobank includes death information from official national death registry data from the National Health Service digital for participants in England and Wales, and from the National Health Service central register for participants in Scotland. In our analysis, data for cancer survivors in UK Biobank were censored on December 31, 2021. Death events were ascertained using the ICD-10 coding system and obtained from data field 40,000 and 40,001. In the Kailuan study, all-cause mortality data were obtained from the Kailuan Social Security Information System up to December 31, 2019. The current analysis included all-cause and cancer (C00-97) mortality as endpoints.

2.4 | Covariates

The covariates included age, sex, race (white and non-white, except in the Kailuan study), education levels (college or above, high school or equivalent and less than high school), marital status (currently in or not in a relationship, except in UK Biobank), income levels, employment status (except in Kailuan study), comorbidity and family history of cancer (except in NHANES). These covariates slightly varied in the included cohorts due to data availability. In the US NHANES and NHIS, income levels were classified according to the federal poverty income ratio (PIR) as high (≥4), medium (<4 to >1) and low (≤1). In the UK Biobank, income levels were categorized into low, medium and high based on the Townsend deprivation index (TDI)[32] quintiles 1, 2 to 4 and 5. In the Kailuan study, income levels were evaluated based on monthly household income per capita <1000 RMB or ≥1000 RMB. We classified diabetes, hypertension and cardiovascular disease as comorbidities.

2.5 | Statistical analysis

Considering the multistage and complex probability design of US NHANES[33] and NHIS,[34] all analyses in these two cohorts were based on survey weight stratification and clustering. Missing data was coded as a missing indicator category for categorical variables.[35] Sex-specific means were used to impute the missing value for continuous variables due to the small proportion of missing data (Table S2). Baseline characteristics of cancer survivors were described as frequency (*n*) and proportion (%) for categorical variables and mean (SD) for normally distributed continuous variables. Person-years were calculated from the recruitment date to the date of death or the end of the study, whichever came first. Multivariable Cox proportional hazards regression models were adopted to examine the associations of all-cause and cancer mortality with each lifestyle factor and the healthy lifestyle score in each cohort. The proportional hazard assumption of Cox regression was assessed using the Schoenfeld residuals method and was found to be satisfied ($P > .5$, Figure S2). Hazard ratios (HRs) with 95% confidence intervals (CIs) of the associations from four cohorts were pooled using the random-effects model of meta-analysis. Several sensitivity analyses were performed. First, participants who died within the first year of follow-up after a cancer diagnosis were excluded. Second, participants whose follow-up time was <2 years before death were excluded to lessen the possibility of reverse causation. Third, cancer survivors with missing covariates were excluded.

Subgroup analyses were conducted by age, sex, education and duration after cancer diagnosis (more or less than 5 years). All *P* values were two-sided and considered statistically significant at <.05. All statistical analyses were performed under R version 4.2.1. Statistical analysis was performed between October and December 2022.

3 | RESULTS

3.1 | Baseline characteristics of participants

Of the 45,267 cancer survivors enrolled in the study, 67 were excluded since they were younger than 20 years old, and 7549 were excluded due to missing information on variables considered in the analyses. A further 556 participants with missing information on the outcome were also excluded. As a result, 37,095 cancer survivors were included in our analysis (Figure S1). The baseline characteristics of the included participants (10,733 from the United States, 24,142 from the United Kingdom and 2220 from China) are summarized in Table 1. The mean age of participants was 60.0 years for Kailuan study, 60.4 years for UKB, 61.5 years for NHANES and 64.6 years for NHIS. The proportion of women in Kailuan study was smaller than that in other cohorts (26.8% vs 38.2%–66.8%). A total of 18,990 reported never smoking, 14,768 reported light alcohol consumption, 17,260 reported a healthy diet, 18,141 reported adequate physical activity and 14,739 reported an optimal BMI. Adequate physical activity was more prevalent in the UK cohort (58.2%) compared to the other three cohorts. During the follow-up period, 8927 all-cause mortality events were accrued in four cohorts, and 4449 cancer death events were documented in UK Biobank and the other two US cohorts (Table 3). The details of missing data in four cohorts were shown in more detail in Table S2.

3.2 | Associations of individual healthy lifestyle factors with all-cause and cancer mortality

The five healthy lifestyle factors were dichotomized into low-risk and high-risk (the reference group). Table 2 exhibited the associations between each healthy lifestyle factor and the mortality outcome. Never smoking (adjusted HR = 0.77, 95% CI: 0.69–0.86), light alcohol consumption (adjusted HR = 0.86, 95% CI: 0.82–0.90), adequate physical activity (adjusted HR = 0.90, 95% CI: 0.85–0.94), a healthy diet (adjusted HR = 0.69, 95% CI: 0.61–0.78) and an optimal BMI (adjusted HR = 0.89, 95% CI: 0.85–0.93) were significantly associated with a lower risk of all-cause mortality in the analysis of pooling the results from the four cohorts among individuals with cancer. A similar pattern of associations could be observed in NHANES, NHIS and the UK Biobank. However, only a healthy diet (adjusted HR = 0.76; 95% CI: 0.64–0.90) and optimal BMI (adjusted HR = 0.83; 95% CI: 0.72–0.96) were associated with a lower risk of all-cause mortality in the Kailuan study.

3.3 | Associations of the healthy lifestyle score with all-cause and cancer mortality

In the analysis where five healthy lifestyle factors were considered jointly using a healthy lifestyle score, a higher healthy lifestyle score was associated with a lower risk of all-cause mortality and cancer mortality after adjusting for confounders. Compared to an unfavorable lifestyle (0–1 healthy lifestyle factor), adherence to a favorable lifestyle (4–5 healthy lifestyle factors) was associated with a 66% (adjusted HR = 0.34, 95% CI: 0.23–0.49), 49% (adjusted HR = 0.51, 95% CI: 0.42–0.62), 42% (adjusted HR = 0.58, 95% CI: 0.52–0.63) and 37% (adjusted HR = 0.63, 95% CI: 0.46–0.88) lower risk of all-cause mortality for participants in the NHANES, NHIS, UK Biobank and Kailuan study, respectively. In the analysis of pooling four cohorts, the fully adjusted HR for participants with 4–5 healthy lifestyle factors was 0.52 (95% CI 0.42–0.64). Furthermore, each point gained in the healthy lifestyle score was accompanied by an 18% reduction in mortality risk among cancer survivors (adjusted HR = 0.82, 95% CI: 0.77–0.88). As shown in Table 3, a higher healthy lifestyle score was inversely associated with cancer mortality. We observed that individuals with cancer whose healthy lifestyle score is 4–5 had lessened cancer mortality risk compared to those with a 0–1 healthy lifestyle score. The fully adjusted HRs were 0.34 (95% CI: 0.16–0.71) in NHANES, 0.52 (95% CI: 0.37–0.74) in NHIS, 0.63 (95% CI: 0.57–0.71) in UK Biobank and 0.57 (95% CI: 0.44–0.72) in the analysis of pooling these results. Also, we found an antagonism interaction between cancer history and HLS in the UK Biobank (HR = 1.05, 95% CI: 1.02–1.09, Table S3).

3.4 | Subgroup and sensitivity analyses

The associations of the healthy lifestyle score with mortality remained consistent in the subgroups by sociodemographic and cancer-related features in the pooled analysis of four cohorts (Figure 1) and in the analysis in NHANES, NHIS and UK Biobank (Tables S4–S6). In the Kailuan study, the association of a favorable lifestyle (4–5 healthy lifestyle factors) with all-cause mortality was stronger in the younger subgroup. We conducted the sensitivity analyses by excluding participants with <2 years of follow-up time, participants with <1 year of duration of cancer diagnosis and participants with missing covariates. Due to the limitation of data about the duration of cancer diagnosis in NHANES, the sensitivity analyses of NHANES were conducted only by excluding participants with <2 years of follow-up time and excluding participants with missing covariates. The pattern of associations between adhering to a healthy lifestyle and all-cause mortality and cancer death was consistent in the above sensitivity analyses (Tables S7–S10).

4 | DISCUSSION

We conducted a cohort study using data from four cohorts to investigate the associations of modifiable lifestyle factors with the risk

TABLE 1 Baseline characteristics of cancer survivors from four different cohorts.

Characteristic	No. (%)[a] US NHANES ($n = 3112$)	US NHIS ($n = 7621$)	UK biobank ($n = 24,142$)	Kailuan study ($n = 2220$)
Age [Mean (SD)]	61.5 (0.31)	64.6 (0.2)	60.4 (7.1)	60.0 (11.0)
Sex				
Male	1283 (35.2)	2920 (38.8)	14,920 (61.8)	1626 (73.2)
Female	1829 (64.8)	4701 (61.2)	9222 (38.2)	594 (26.8)
Race				
White	1947 (83.1)	6605 (90.0)	23,363 (96.8)	—
Non-white	1165 (16.9)	1016 (10.0)	717 (3.0)	—
Education				
College or above	1758 (65.4)	4055 (54.5)	9191 (38.1)	442 (19.9)
High school or equivalent	708 (22.0)	2761 (36.2)	10,135 (42.0)	
Less than high school	643 (12.6)	775 (9.0)	4531 (18.8)	1752 (78.9)
Marital status				
Not in relationship	1236 (34.5)	3834 (50.1)	—	50 (2.3)
In relationship	1858 (64.7)	3787 (49.9)	—	2163 (97.4)
PIR/TDI/Income level[b]				
High	889 (39.5)	2496 (34.6)	4394 (18.2)	769 (34.6)
Medium	1528 (43.6)	4109 (53.6)	14,758 (61.1)	
Low	448 (9.5)	1016 (11.8)	4990 (20.7)	1262 (56.8)
Employment status				
Employed	996 (41.1)	2899 (38.2)	10,018 (41.5)	—
Unemployed	2112 (58.7)	4722 (61.8)	13,934 (57.7)	—
Comorbidities				
Yes	2065 (58.9)	4985 (64.8)	6885 (28.5)	1146 (51.6)
No	1047 (41.1)	2636 (35.2)	17,257 (71.5)	528 (23.8)
Family history of cancer				
No	—	4579 (60.4)	15,821 (65.5)	1711 (77.1)
Yes	—	2788 (36.1)	7869 (32.6)	179 (8.1)
Healthy lifestyle factors				
Never smoking	1428 (46.3)	3552 (46.1)	12,385 (51.3)	1625 (73.2)
Light drinking	1302 (45.2)	2634 (36.2)	10,486 (43.4)	346 (15.6)
Healthy diet	1076 (33.4)	2811 (33.3)	11,366 (47.1)	2007 (90.4)
Adequate physical activity	1004 (37.0)	2610 (35.5)	14,047 (58.2)	480 (21.6)
Optimal BMI[c]	1088 (32.9)	2704 (35.7)	10,119 (41.9)	828 (37.3)

Note: —, data not available.

[a]Analyses of percentages and means were conducted using the survey weights in US NHANES and NHIS. Variable categories may not sum to 100% because of missing data or rounding. More details are available in Section 2.5.

[b]PIR, poverty income ratio (low income, PIR <1; middle income, PIR = 1.0–4; and high income, PIR ≥4); TDI, Townsend deprivation index (calculated based on participants' postal code and information from the national census output area as a proxy of socioeconomic status); Income level: monthly household income per capita <1000 RMB/≥1000 RMB in the Kailuan study.

[c]BMI, body mass index (calculated as weight in kilograms divided by height in meters squared) 25–30 were defined as optimal in this study.

of all-cause mortality and cancer mortality. We found that each healthy lifestyle factor, namely never smoking, light alcohol consumption, adequate physical activity, a healthy diet and optimal BMI, was independently associated with longer survival of cancer survivors. Adherence to a favorable healthy lifestyle (combined 4–5 healthy lifestyle factors) was significantly associated with a lower risk of all-cause

TABLE 2 Associations of individual healthy lifestyle factor with risks of all-cause mortality in cancer survivors.

Cohort	Never smoking		Light drinking		Adequate physical activity		Healthy diet		Optimal BMI	
	Deaths/PY	HR (95% CI)	Deaths/PY	HR (95% CI)	Deaths/PY	HR (95% CI)	Deaths/PY	HR (95% CI)	Deaths/PY	HR (95% CI)
US NHANES	538/12,380	1 [Reference]	498/13,400	1 [Reference]	550/15,059	1 [Reference]	617/14,410	1 [Reference]	545/15,238	1 [Reference]
	306/11,128	0.68 (0.58–0.80)	346/10,109	0.78 (0.66–0.93)	294/8450	0.86 (0.72–1.03)	227/9099	0.62 (0.51–0.76)	299/8271	0.82 (0.69–0.99)
US NHIS	1664/33,558	1 [Reference]	1976/41,632	1 [Reference]	1977/41,043	1 [Reference]	2185/40,122	1 [Reference]	1818/40,862	1 [Reference]
	1154/30,319	0.74 (0.68–0.80)	842/22,245	0.85 (0.78–0.93)	841/22,833	0.89 (0.82–0.98)	633/23,755	0.61 (0.56–0.68)	1000/23,014	0.89 (0.82–0.97)
UK Biobank	2576/135,852	1 [Reference]	2615/159,763	1 [Reference]	2562/148,736	1 [Reference]	2096/117,075	1 [Reference]	2582/164,451	1 [Reference]
	1839/148,099	0.77 (0.72–0.81)	1800/124,189	0.87 (0.82–0.92)	1853/135,216	0.89 (0.84–0.95)	2319/166,877	0.77 (0.73–0.82)	1833/119,500	0.91 (0.86–0.97)
Kailuan Study	258/4539	1 [Reference]	717/14,731	1 [Reference]	83/1746	1 [Reference]	682/13,188	1 [Reference]	571/10,559	1 [Reference]
	592/12,832	0.93 (0.80–1.09)	133/2640	0.88 (0.73–1.08)	767/15,625	1.00 (0.79–1.27)	168/4183	0.76 (0.64–0.90)	279/6812	0.83 (0.72–0.96)
Pooled	5036/186,329	1.00 (Reference)	5806/229,526	1.00 (Reference)	5172/206,584	1.00 (Reference)	5580/184,795	1.00 (Reference)	5516/231,110	1.00 (Reference)
	3891/202,378	0.77 (0.69–0.86)	3121/159,183	0.86 (0.82–0.90)	3755/182,124	0.90 (0.85–0.94)	3347/203,914	0.69 (0.61–0.78)	3411/157,597	0.89 (0.85–0.93)

Note: Data are presented as hazard ratio (HR) and 95% confidence interval (CI). In the NHANES, complex survey designs were accounted for to derive nationally representative estimates. Covariates included age, sex, education level, marital status (except for UK Biobank), race (except for Kailuan Study), income level, employment status (except for Kailuan Study), comorbidities, family history of cancer (except for US NHANES) and five lifestyle factors were mutually adjusted for each other.

Abbreviations: BMI, body mass index; NHANES, National Health and Nutrition Examination Survey; NHIS, National Health Interview Survey; PY, person-year.

and cancer mortality compared to their counterparts with an unfavorable lifestyle (0–1 healthy lifestyle factors). Among the healthy lifestyle factors, never smoking contributed the most to the reduction of mortality risk. Furthermore, the associations were consistent between sociodemographic and cancer-related subgroups and stable in sensitivity analyses. Our results suggested that modifiable lifestyle factors might play a vital role in the health management of cancer survivors.

The associations of healthy lifestyle factors with mortality in the general population have been well established,[36] while the associations among cancer survivors are still obscure. Several studies found that high adherence to a healthy lifestyle was associated with reduced mortality among cancer survivors in specific countries. A study from the Guangzhou Cancer Registry (GCR)[10] found the benefit of adopting a healthy lifestyle for the extension of life expectancy and the prevention of premature death among cancer survivors in China. A previous study in the United States also showed that cancer survivors with a higher healthy lifestyle score (3–5) had a substantially lower risk of all-cause and noncancer mortality.[37] Besides, a prospective study that enrolled 1425 newly diagnosed stages I–III colorectal cancer survivors found having a lifestyle highly in line with the WCRF/AICR recommendations was associated with a decreased all-cause mortality risk.[38] However, there were also limitations in these studies, which restricted the generalizability of their findings. First, insufficient sample size and short follow-up duration might lead to less robust conclusions for cancer survival. Second, these studies are conducted in a single country. Therefore, a multicountry cohort study with a considerable sample size is warranted to provide more compelling evidence. To our knowledge, this is the first multicountry cohort study to examine whether a combined healthy lifestyle among cancer survivors worldwide could confer benefits for overall and cancer survival.

A prospective cohort study exploring the effect of the combined healthy lifestyle factors (BMI, smoking, alcohol consumption, physical activity and diet) on mortality in healthy participants found that the combination of low-risk lifestyle factors was associated with a reduction of all-cause mortality risk by 61%.[39] Consistently, our study showed that the premature death risk was ∼50% lower in those with a healthy lifestyle compared to those without, which further illustrated that lifestyle modifications are instrumental in improving the prognosis of cancer survivors. Furthermore, our study indicated that each healthy lifestyle factor might reduce mortality risk independently in cancer survivors. A previous study showed that active smokers were more likely to die of cancer among breast cancer survivors.[40] Similarly, our study revealed an inverse association between never smoking and all-cause mortality in cancer survivors, and the association was the most robust compared to other lifestyle factors. This finding highlighted the significance of smoking cessation in prolonging survival and suggested a cost-effective strategy for health management for cancer survivors.

In addition, a healthy diet and an optimal BMI were associated with a lower risk of all-cause mortality across all cohorts in our study. Evidence from laboratory and observational studies also suggested that diet quality and obesity might affect the risk of recurrence and overall survival after cancer diagnosis.[17] Of note, studies found that obesity was related to a lower mortality risk in cancer survivors and the protective effect had been termed the "obesity paradox."[41]

TABLE 3 Associations of healthy lifestyle score with all cause and cancer mortality in cancer survivors.

Outcome	0–1 healthy lifestyle factor	2 healthy lifestyle factors	3 healthy lifestyle factors	4–5 healthy lifestyle factors	Each healthy lifestyle factor
All-cause mortality					
US NHANES					
Deaths/PY	357/8290	291/7694	138/4854	58/2671	844/23,508
HR (95% CI)	1 [Reference]	0.74 (0.61–0.89)	0.57 (0.43–0.74)	0.34 (0.23–0.49)	0.75 (0.69–0.82)
US NHIS					
Deaths/PY	1416/24,440	860/20,373	406/13,407	136/5657	2818/63,877
HR (95% CI)	1 [Reference]	0.74 (0.67–0.81)	0.57 (0.51–0.63)	0.51 (0.42–0.62)	0.79 (0.77–0.83)
UK Biobank					
Deaths/PY	1318/60,819	1350/85,913	1118/84,341	629/52,879	4415/283,951
HR (95% CI)	1 [Reference]	0.75 (0.69–0.80)	0.64 (0.59–0.69)	0.58 (0.52–0.63)	0.84 (0.82–0.86)
Kailuan Study					
Deaths/PY	125/2080	406/7314	267/6400	52/1576	850/17,371
HR (95% CI)	1 [Reference]	0.99 (0.82–1.17)	0.81 (0.54–0.85)	0.63 (0.46–0.88)	0.91 (0.85–0.97)
Pooled					
Deaths/PY	3216/93,549	2907/113,980	1929/102,602	875/61,207	8927/371,336
HR (95% CI)	1 [Reference]	0.78 (0.69–0.89)	0.63 (0.55–0.73)	0.52 (0.42–0.64)	0.82 (0.77–0.88)
Cancer mortality					
US NHANES					
Deaths/PY	139/8290	96/7694	46/4854	16/2671	297/23,508
HR (95% CI)	1 [Reference]	0.60 (0.42–0.85)	0.58 (0.34–1.00)	0.34 (0.16–0.71)	0.76 (0.65–0.90)
US NHIS					
Deaths/PY	466/24,440	296/20,373	133/13,407	48/5657	943/63,877
HR (95% CI)	1 [Reference]	0.73 (0.63–0.85)	0.49 (0.40–0.61)	0.52 (0.37–0.74)	0.78 (0.73–0.84)
UK Biobank					
Deaths/PY	924/60,819	965/85,913	825/84,341	495/52,879	3209/283,951
HR (95% CI)	1 [Reference]	0.76 (0.69–0.83)	0.66 (0.60–0.73)	0.63 (0.57–0.71)	0.86 (0.84–0.89)
Pooled					
Deaths/PY	1529/32,730	1357/28,067	1004/18,261	559/8328	4449/87,385
HR (95% CI)	1 [Reference]	0.74 (0.69–0.8)	0.58 (0.47–0.73)	0.57 (0.44–0.72)	0.82 (0.75–0.89)

Note: Data are presented as hazard ratio (HR) and 95% confidence interval (CI). In NHANES, complex survey designs were accounted for to derive nationally representative estimates. Definitions of healthy lifestyle factors are listed above. Models adjusted for age, sex, education level, marital status (except for UK Biobank), race (except for Kailuan Study), PIR/TDI/income level, employment status (except for Kailuan Study), comorbidities, family history of cancer (except for US NHANES).

Abbreviations: NHANES, National Health and Nutrition Examination Survey; NHIS, National Health Interview Survey; PY, person-year.

Consequently, we chose 25–30 kg/m^2 as the standard of optimal BMI in cancer survivors, which is higher than that in the general population. Further studies are still needed to investigate the effect of BMI on the prognosis of cancer survivors. In addition, moderate alcohol consumption has been considered a protective factor in the general population.[42] Light alcohol consumption was also associated with a lower risk of all-cause mortality in cancer survivors in this study. Nevertheless, current evidence is not enough to support patients without an alcohol-drinking habit to initiate light alcohol consumption for the benefit of survival improvement. The World Health Organization 2020 guidelines on physical activity and sedentary behavior stated that limiting sedentary time and substituting it with physical activity is conducive to improving health, especially for individuals with long-term diseases.[43] Our current study supported this and provided evidence that adequate physical activity was associated with better survival after cancer diagnosis. Still, more research is required to verify the causal relationship, and intervention studies could be conducted to explore the feasibility of the appropriate increase of physical activity in the care of cancer survivors.

5 | STRENGTHS AND LIMITATIONS

Our study has several strengths, including the prospective design, a comparatively long follow-up, a large sample size and data from

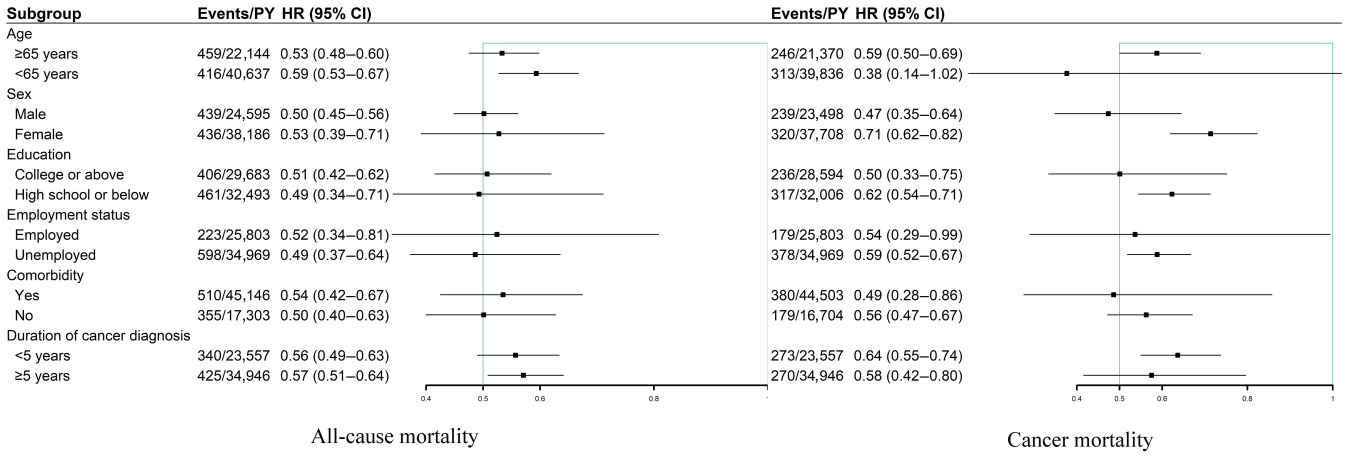

FIGURE 1 Associations of healthy lifestyle score with mortality in individuals with cancer stratified by demographic and duration of cancer diagnosis. The dots indicate the HRs comparing individuals with four or five healthy lifestyle scores vs 0 or 1 healthy lifestyle score, and the horizontal lines indicate the 95% CIs.

multicountry cohorts. However, there are limitations that should be taken into consideration when interpreting the results. First, although data from multiple cohorts improved the reliability of statistical analyses, different cohorts have varying definitions for each healthy lifestyle factor, which may cause bias. Pooling results from different cohort studies with varied exposure definitions can introduce biases, reduce comparability and challenge consistent conclusions, necessitating careful adjustments and interpretation. For example, this can lead to misclassification of the exposures. However, due to the prospective cohort nature, this non-differential bias would underestimate these associations conservatively. In addition, we used the random-effects meta-analysis to combine estimates, which provided a potentially accurate estimate after considering heterogeneity between studies. Second, information on lifestyle factors was collected at baseline, which might not reflect behavioral changes during the follow-up period. Third, information on the cancer stages and duration from disease onset to diagnosis was not considered due to data unavailability. The survival of cancer survivors is influenced by many factors, including tumor stages, cancer types, treatment methods, etc., which are difficult to account for with no relevant data available. Patients with a more advanced stage of cancer might not be able to maintain an optimal BMI or spend adequate time on physical activity and their healthy lifestyle score could be affected accordingly. The lack of this information might lead to a confounding bias. However, previous studies have implied that both early-stage cancer survivors and advanced cancer survivors could benefit from the maintenance of healthy lifestyles[44,45] and consistent results were observed after excluding deaths occurring during the first 2-year follow-up period, which may lessen the probability of reverse causation.

6 | CONCLUSIONS

In conclusion, our study provided compelling evidence that adopting a healthy lifestyle was associated with a lower risk of all-cause and cancer mortality among cancer survivors in the United States, the United Kingdom and China. Our findings suggest that a multicomponent healthy lifestyle consisting of no smoking, light alcohol consumption, adequate physical activity, a healthy diet and an optimal BMI may be an effective strategy that could be recommended and practiced in primary care and clinical interventions. Further studies are still in demand to explore the potential influence of other lifestyle factors on cancer survivors, such as sleep traits and sedentary behaviors, and also confirm the causality of these associations.

AUTHOR CONTRIBUTIONS

Zilong Bian: Conceptualization; methodology; software; investigation; formal analysis; writing – original draft. **Rongqi Zhang**: methodology; software; investigation; formal analysis; writing – original draft. **Shuai Yuan**: Methodology; Writing – review and editing. **Rong Fan**: Writing – review and editing; **Lijuan Wang**: Writing – review and editing. **Susanna C. Larsson**: Funding acquisition; writing – review and editing; **Evropi Theodoratou**: Funding acquisition; writing – review and editing. **Yimin Zhu**: Writing – review and editing. **Shouling Wu**: Conceptualization; data curation; writing – review and editing. **Yuan Ding**: conceptualization; funding acquisition; writing – review and editing. **Xue Li**: Conceptualization; funding acquisition; resources; supervision; writing – review and editing. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest for this article.

DATA AVAILABILITY STATEMENT

Only publicly available data were used in this study, and data sources and handling of these data are described in the Materials and Methods. UK Biobank study was under Application Number 66354. The UK Biobank is an open access resource and bona fide researchers can apply to use the UK Biobank dataset by registering and applying at http://ukbiobank.ac.uk/register-apply/. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

This prospective multicohort study was conducted based on US National Health and Nutrition Examination Survey (NHANES) (approved by the National Centre for Health Statistics Research Ethics Review Board), US National Health Interview Survey (NHIS) (approved by National Center for Health Statistics Disclosure Review Board), UK Biobank (approved by the North West Multicentre Research Ethics Committee) and Kailuan study (approved by the Ethics Committee of Kailuan General Hospital [approval number: 2006-05] and Beijing Tiantan Hospital [approval number: 2010-014-01]).

ORCID

Zilong Bian https://orcid.org/0000-0002-2628-7535
Rongqi Zhang https://orcid.org/0000-0001-8166-2660
Shuai Yuan https://orcid.org/0000-0001-5055-5627
Yimin Zhu https://orcid.org/0000-0001-8409-7636
Shouling Wu https://orcid.org/0000-0001-7095-6022
Xue Li https://orcid.org/0000-0001-6880-2577

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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