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Influence of healthy lifestyle on the incidence and survival of cancer and its comorbidities: evidence from a longitudinal cohort study

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Abstract

Objectives To examine whether adherence to a healthy lifestyle affects cancer incidence, cancer-related comorbidities, and survival among cancer patients.

Methods We analyzed 400,714 participants in the UK Biobank who were free of cancer and major noncommunicable diseases (NCDs)—including atherosclerotic cardiovascular disease (ASCVD), type 2 diabetes (T2D), chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD)—at baseline and remained cancer-free for at least 180 days post-enrollment. A Healthy Lifestyle Index (HLI) was constructed based on six lifestyle factors and categorized into low, intermediate, and high levels. Multivariable Cox regression was used to estimate associations between HLI levels and the risks of cancer and cancer-related comorbidities, defined as the co-occurrence of cancer and at least one NCD. Kaplan–Meier methods were used to assess survival outcomes among cancer patients, stratified by comorbidity status and HLI.

Results Over a median follow-up of 13.8 years, 53,380 (13.3%) participants developed cancer, with 16,188 (4.0%) having cancer-related comorbidities. Compared to the low HLI group, participants with a high HLI had a significantly lower risk of cancer (HR = 0.92, 95% CI 0.90–0.94) and cancer-related comorbidities (HR = 0.51, 95% CI 0.49–0.53). Subgroup analyses showed marked reductions in comorbidity risk for multiple cancer types. Higher HLI was also associated with better survival, regardless of comorbidity status.

Conclusions Adherence to a healthy lifestyle is associated with reduced cancer risk, fewer comorbidities, and improved survival outcomes, underscoring the value of lifestyle interventions in cancer prevention and survivorship care.

Keywords Cancer, Comorbidity, Non-communicable disease, Lifestyle, Cohort study

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Introduction

Cancer persists as a leading contributor to global disease burden, with GLOBOCAN 2022 reporting 19.96 million new cases and 9.74 million deaths globally [1]. Despite notable advances in screening and treatment, the global cancer burden continues to grow, particularly in aging populations. Given that a substantial proportion of cancers are attributable to modifiable behavioral factors, primary prevention through lifestyle interventions has become a pressing public health priority [2].

A substantial body of evidence supports the protective role of healthy lifestyle behaviors—including smoking cessation [3], balanced dietary intake [4], favorable body weight [5], regular physical activity [6], and low-risk alcohol consumption [7]—in reducing the incidence of several common cancers. Simultaneously, these interdependent lifestyle dimensions collectively regulate systemic inflammation, insulin signaling, and immune surveillance pathways, thereby exerting pleiotropic effects on cancer-related noncommunicable diseases (NCDs) such as atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes (T2D) [8]. These NCDs frequently share biological pathways with cancer and are increasingly prevalent in cancer-prone populations.

The co-occurrence of cancer and NCDs—termed cancer-related comorbidity—is particularly common in middle-aged and older adults [9]. Predominant among these are ASCVD, T2D [10], chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD), collectively creating complex clinical scenarios which not only exacerbates therapeutic complexity [11] but also amplifies mortality risks [12]. From a prevention perspective, understanding how lifestyle behaviors influence the dual burden of cancer and comorbidity is crucial for early intervention and health system planning.

Existing studies have made substantial progress in understanding specific cancer-NCD dyads. Evidence from the United States population has established ASCVD as a significant prognostic factor in cancer [13], and previous studies have characterized diabetes-associated hyperinsulinemia as a driver of hepatic carcinogenesis [14–16]. However, this prevailing "single comorbidity" paradigm fails to address the clinical reality where 27.2% of patients exhibit more than two chronic conditions [17]. Current evidence remains fragmented across three critical dimensions: first, most prior studies focus on individual cancers or single comorbidities, failing to capture the complex interplay between cancer and clustered comorbidity; second, the clustering patterns of comorbidities remain poorly characterized across heterogeneous cancer populations; third, while healthy lifestyle indices have been linked to favorable outcomes in general and cardiometabolic populations, their impact on the incidence of cancer and cancer-related comorbidities in large-scale, population-based cohorts is poorly understood. Critically, the role of cumulative lifestyle patterns in preventing both cancer and its associated comorbidities—particularly in middle-aged and older adults—has yet to be systematically evaluated.

To address these evidence gaps, this study leverages the UK Biobank cohort with longitudinal follow-up. Our objectives are to: (1) assess the associations between Healthy Lifestyle Index (HLI) categories and the incidence of cancer and cancer-related comorbidities; (2) characterize specific patterns of cancer-related comorbidities across HLI categories; and (3) describe survival outcomes among cancer patients according to comorbidity status and lifestyle categories. These findings may inform targeted strategies for cancer prevention and healthy aging in the context of increasing comorbidity.

Methods

Study design and participants

Data for this study were sourced from the UK Biobank, a population-based prospective cohort encompassing over 500,000 participants recruited between 2006 and 2010 across 22 assessment centers in England, Scotland, and Wales. The UK Biobank cohort provides comprehensive health-related data including but not limited to genetic, lifestyle, and clinical parameters. Full methodological details are available through peer-reviewed publications [18] and the official portal [19].

Eligible participants aged 37–73 years at enrollment provided written informed consent. We implemented rigorous exclusion criteria: (1) participants withdrawing consent; (2) those with incomplete baseline data; (3) pre-existing diagnoses of ASCVD, COPD, CKD, T2D at or before baseline; (4) cancer diagnoses at or before baseline, or within 180 days following the baseline assessment.

Epidemiological data collection and process

Data on demographic information and lifestyle factors were collected at baseline through a combination of touchscreen questionnaires, in-person interviews, and linkage to national census records. Key covariates included age, sex, and socioeconomic status (SES). Age groups are defined based on quartiles of the age distribution within the study population. SES was assessed using the Townsend Deprivation Index, a composite measure of area-level socioeconomic deprivation calculated for each participant at baseline. This index was derived from the national census data at the output-area level, whereby participants' residential postcodes were mapped to corresponding output areas to assign deprivation scores. The Townsend Deprivation Index quantifies relative deprivation based on four census-derived variables: unemployment, non-car ownership, household overcrowding,

and non-homeownership, with higher scores indicating greater socioeconomic disadvantage (Supplementary Table 1).

HLI derivation

The primary exposure was HLI categories assessed at baseline. The HLI integrated five modifiable lifestyle factors into a composite score (range: 0–6), reflecting adherence to cancer prevention guidelines from the World Cancer Research Fund (WCRF) and World Health Organization (WHO) [20, 21]. Dietary intake was assessed through four components: fruit and vegetable consumption (< 3 servings/day: 0; 3–5: 0.25; ≥ 5: 0.5), whole grains (≤ 2 servings/week: 0; 2–5.5: 0.25; ≥ 5.5: 0.5), red meat (> 4 servings/week: 0; 2–4: 0.25; < 2: 0.5), and processed meat (> 4 servings/week: 0; 2–4: 0.25; < 2: 0.5). Metabolic factors included Body Mass Index (BMI, 18.5–24.9 kg/m^2: 0.5; 25–29.9: 0.25; > 29.9: 0) and sex-specific waist circumference (females: < 80 cm: 0.5; 80–88 cm: 0.25; ≥ 88 cm: 0; males: < 94 cm: 0.5; 94–102 cm: 0.25; ≥ 102 cm: 0). Additional components comprised physical activity (< 75 min/week: 0; 75–150: 0.5; ≥ 150: 1), smoking status (never: 1; former: 0.5; current: 0), and alcohol intake (abstinence: 1; moderate [≤ 14 g/day females/ ≤ 28 g males]: 0.5; excessive: 0). The HLI total score was calculated by summing all component scores, with higher values indicating greater adherence to preventive lifestyles, and missing data were excluded from aggregation (Supplementary Table 2).

Outcomes

The primary outcomes were the incidence of cancer and cancer-related comorbidities. Cancer was defined as the first diagnosis of any malignant tumor during follow-up. Cancer-related comorbidity was defined as the co-occurrence of cancer and at least one major NCD, including ASCVD, T2D, COPD, or CKD, irrespective of the temporal sequence of diagnoses.

Among participants who developed cancer, further classification was performed based on comorbidity status throughout the follow-up period. Individuals who were never diagnosed with any of the specified NCDs during follow-up were categorized as the cancer without comorbidity group, whereas those who were diagnosed with at least one NCD at any time before or after the cancer diagnosis were categorized as the cancer-related comorbidity group. The cancer-related comorbidity group is a subset of all cancer cases and was used to characterize the burden of comorbidity among cancer patients. For participants with cancer-related comorbidities, the event date was defined as the later of the cancer or NCD diagnosis dates. Person-time for incidence rate calculations was accrued from baseline to the earliest occurrence of outcome of interest, death, or the end of follow-up (March 1, 2023), whichever came first.

Secondary outcomes included the specific types of cancer and their comorbidity with other NCDs, as well as the survival outcomes among cancer patients. Survival analyses were limited to participants diagnosed with cancer during follow-up. Follow-up for survival was measured from the date of cancer diagnosis for individuals in the cancer without comorbidity group, and from the latest of the cancer or NCD diagnosis dates for individuals in the cancer-related comorbidity group, until death or censoring at the study endpoint.

Cancer diagnoses were identified using ICD-9 and ICD-10 codes obtained from national cancer registries and hospital inpatient records. NCD diagnoses were ascertained based on ICD codes and validated using self-reported questionnaires and clinical records (Supplementary Tables 3 and 4). Deaths were identified through linkage to national death registries.

Statistical analysis

Baseline characteristics of the study population were evaluated using descriptive statistics. Age was presented as medians with interquartile ranges (IQRs), and categorical variables were reported as counts and percentages.

To characterize comorbidity patterns among cancer patients across HLI categories, cancer comorbidity networks were constructed. Degree centrality between specific cancer types and major NCDs (including ASCVD, T2D, COPD, and CKD) was calculated for each HLI group.

To estimate the incidence of cancer and cancer-related comorbidities, incidence rates were calculated per 100,000 person-years based on accumulated person-time during follow-up. Multivariable Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between HLI categories and the risks of incident cancer, overall cancer-related comorbidities, and specific comorbidity patterns, adjusting for potential confounders including age, sex, and socioeconomic status. To evaluate survival outcomes among cancer patients, Kaplan–Meier survival curves were plotted by comorbidity status and HLI categories.

Cancer comorbidity networks were visualized using Cytoscape software (version 3.10.3). All other statistical analyses were performed using R software (version 4.4.1, R foundation, www.r-project.org, Vienna, Austria).

Power analysis

Based on preliminary analyses and descriptive data from the UK Biobank, the distribution of the study population across HLI categories was approximately 35% for low HLI, 35% for intermediate HLI, and 30% for high HLI.

We estimated that more than 12,000, 18,000, and 20,000 primary outcome events—defined as incident cancer or cancer-related comorbidities—could be observed in the low, intermediate, and high HLI groups, respectively. Assuming a two-sided alpha level of 0.05 and using the low HLI group as the reference, the number of events provides 80.4% power to detect an HR smaller than 0.968 (or greater than 1.033) for the intermediate versus low HLI comparison, and 80.2% power to detect an HR smaller than 0.969 (or greater than 1.032) for the high versus low HLI comparison. These detectable hazard ratios are conservative and fall below thresholds typically considered clinically meaningful in observational studies, ensuring adequate power to detect relevant effects.

Results

The UK Biobank initially enrolled a total of 502,369 participants. After the exclusion of 158 individuals who withdrew informed consent, additional exclusions were made for participants with pre-existing NCDs at baseline, including 8,805 with COPD, 6,359 with CKD, 32,905 with ASCVD, and 16,953 with T2D. Furthermore, 36,475 participants diagnosed with cancer within 180 days post-baseline were excluded. Consequently, the analysis included 400,714 participants (Supplementary Fig. 1).

Table 1 Characteristics of the study population

Characteristics	All participants	Low HLI (*n* = 149,360)	Intermediate HLI (*n* = 142,392)	High HLI (*n* = 108,962)
Age at enrollment, median (IQR), y	56.0 (49.0–62.0)	56.0 (49.0–62.0)	56.0 (49.0–62.0)	56.0 (49.0–62.0)
Sex, %				
Female	225,105 (56.2)	80,281 (53.8)	79,350 (55.7)	65,474 (60.1)
Male	175,609 (43.8)	69,079 (46.2)	63,042 (44.3)	43,488 (39.9)
Socioeconomic status, %				
Lowest quintile (Q1)	80,133 (20.0)	25,043 (16.8)	29,550 (20.8)	25,540 (23.5)
Middle quintiles (Q2 ~ Q4)	240,034 (60.0)	85,981 (57.7)	86,638 (60.9)	67,415 (61.9)
Highest quintiles (Q5)	80,039 (20.0)	38,110 (25.6)	26,037 (18.3)	15,892 (14.6)
Outcome, %				
Cancer patients	53,380 (13.3)	20,821 (5.2)	18,813 (4.7)	13,746 (3.4)
Cancer without comorbidity	37,192 (9.3)	12,765 (3.2)	13,574 (3.4)	10,853 (2.7)
Cancer with comorbidity	16,188 (4.0)	8056 (2.0)	5239 (1.3)	2893 (0.7)
Non-cancer controls	347,334 (86.7)	128,539 (32.1)	123,579 (30.8)	95,216 (23.8)

BMI Body-mass index; *HLI* Healthy lifestyle index

In the study population, the median age (IQR) was 56 (49–62) years, and 225,105 (56.2%) were female. Eligible participants were categorized into low (37.3%, n = 149,360), intermediate (35.5%, n = 142,392), and high (27.2%, n = 108,962) HLI groups. Compared with the intermediate and high HLI groups, the low HLI group had a higher proportion of male participants (46.2%, n = 69,079) and individuals in the highest socioeconomic category (25.6%, n = 38,110). Additionally, the proportions of participants who developed cancer (5.2%, n = 20,821) and cancer-related comorbidities (2.0%, n = 8,056) were highest in the low HLI group (Table 1). After a median follow-up of 13.80 years, a total of 53,380 (13.3%) participants were diagnosed with cancer, including 37,192 cases (9.3%) without comorbidities and 16,188 cases (4.0%) with cancer-related comorbidities (Table 1). Among patients aged < 50 years, the majority of incident cancer cases were without any NCD comorbidity (85.9%, n = 5,487). However, with increasing age, the proportion of cancer patients who had one or more major NCDs rose steadily, reaching 40.5% in those aged > 62 years. In addition, male patients exhibited a higher cancer-comorbidity burden (35.5%, n = 9,551) than female patients (25.1%, n = 6,637). Notably, within each age and sex subgroup, the proportion of cancer-related comorbidity was highest among individuals with low HLI (Fig. 1A; Supplementary Tables 5 and 6).

To further explore the composition of cancer-related comorbidities, we analyzed specific NCD comorbidity patterns. Among all patients with cancer-related comorbidities, coexistence with a single NCD was most common, accounting for 75.7% of all cancer-related comorbidity cases. The most frequent pattern was cancer co-occurring with ASCVD alone (43.7%, n = 7,071). The proportion of cancer-related comorbidities declined sharply as the number of coexisting NCDs increased, with the proportion decreasing by 55.6% and 71.5% for two and three or more NCDs, respectively, compared to those with a single NCD. In patients with multiple comorbidities, the leading comorbidity patterns included Cancer + ASCVD + CKD (6.7%, n = 1,078) and Cancer + ASCVD + CKD + T2D (1.4%, n = 221). Across all HLI categories, older age and male sex were consistently associated with a higher burden of cancer-related comorbidities. The highest proportion of multiple NCD comorbidities was observed among male patients aged over 62 years. Within each age and sex category, the low HLI group demonstrated a higher proportion of cancer-related comorbidities compared to the intermediate and high HLI groups (Fig. 1B; Supplementary Tables 7 and 8).

Co-occurrence patterns between specific cancer types and NCDs across HLI categories were further examined. Network analyses revealed that lung and colorectal cancers emerged as the most frequently observed

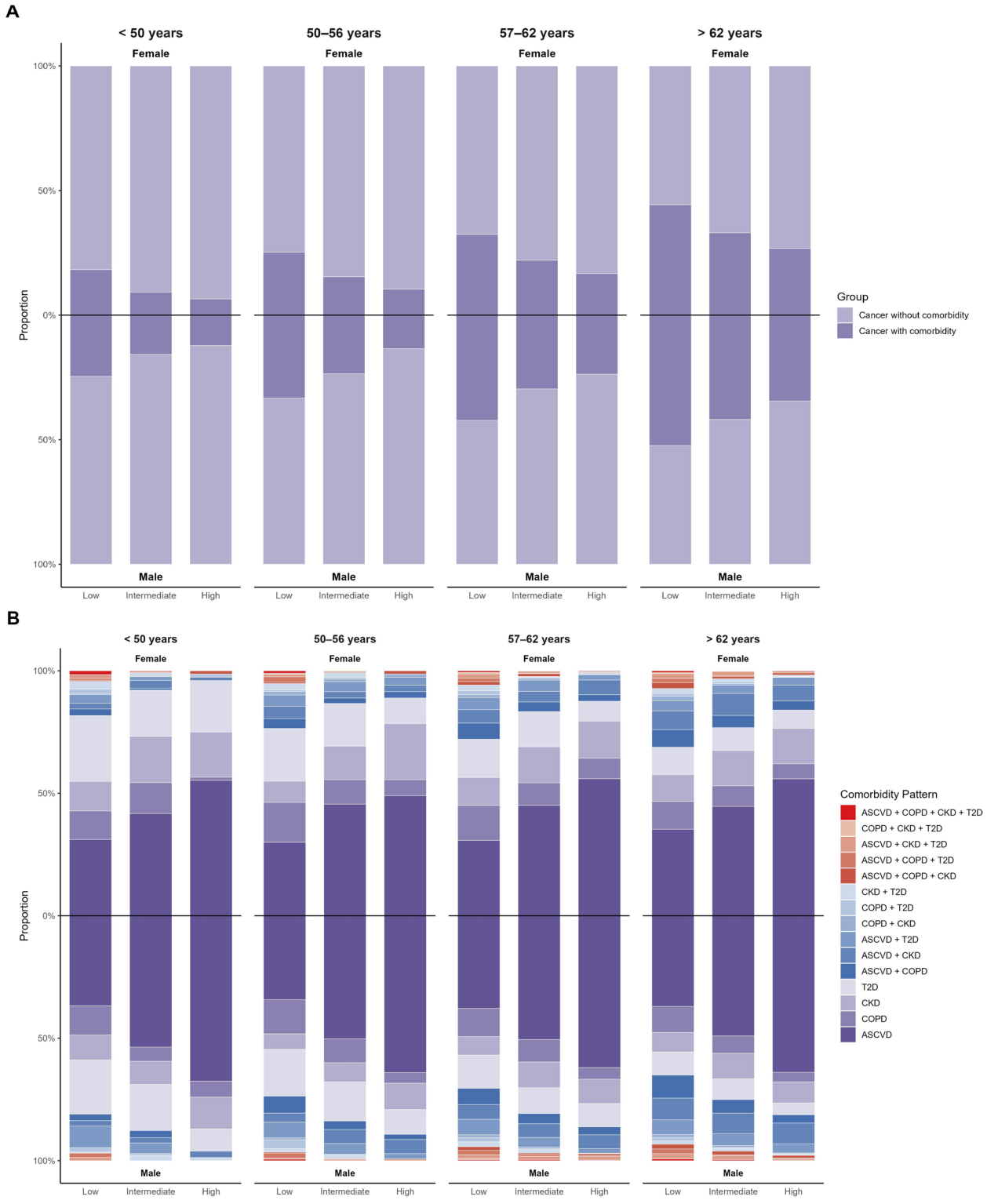

Fig. 1 Patterns of cancer (**A**) and cancer-related comorbidity (**B**) across sex groups, age groups and Healthy Lifestyle Index (HLI) categories

malignancies involved in comorbidity, while ASCVD remained the predominant comorbid condition across all HLI categories. Low HLI groups exhibited dense cancer-NCD interconnectivity, particularly in lung cancer-ASCVD clusters (degree centrality = 430, Fig. 2A). As lifestyle adherence improved in the intermediate HLI group, the comorbidity network began to disperse, though a notable link persisted between colorectal cancer

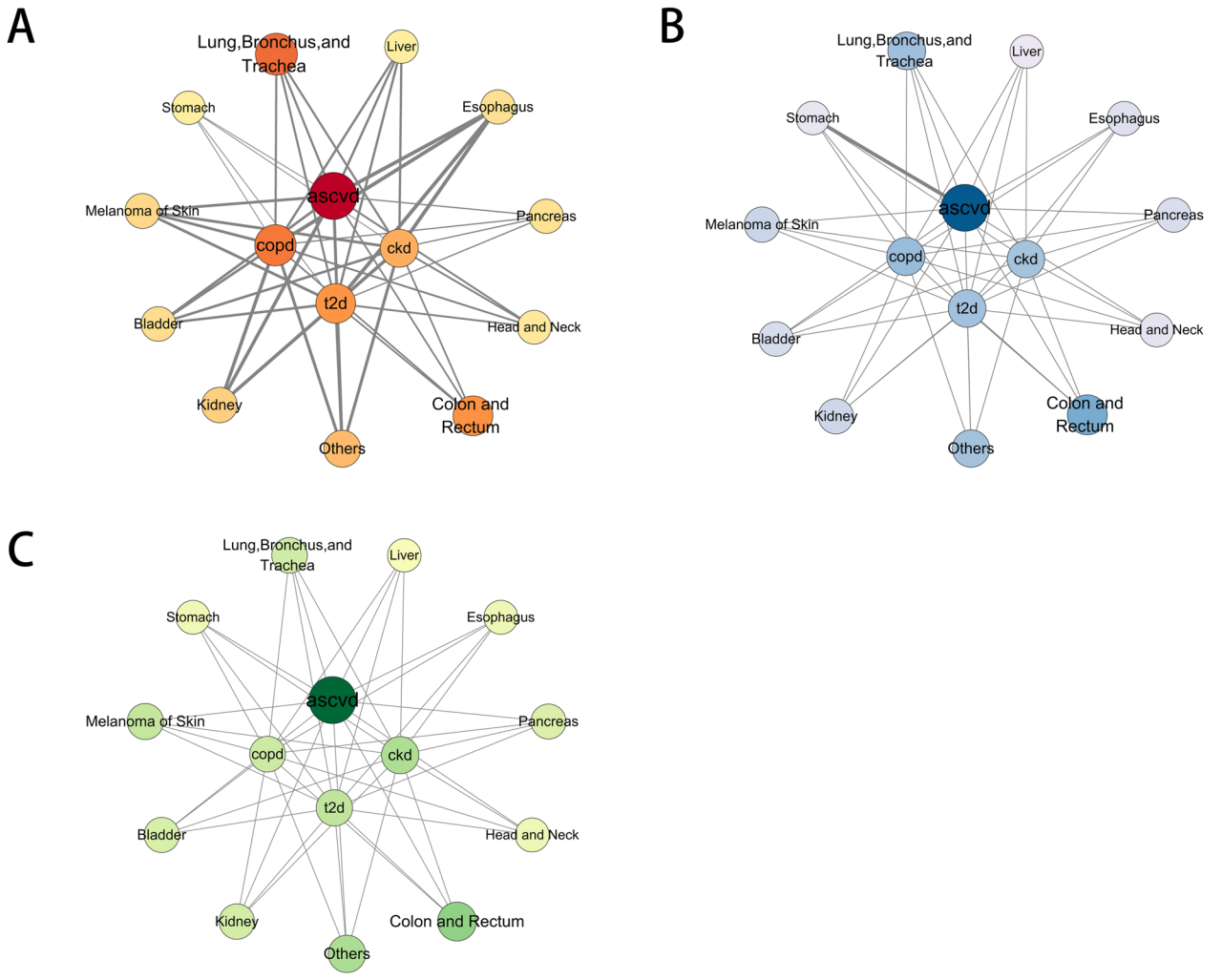

Fig. 2 Comparison of comorbidity patterns between specific cancer types and other NCDs by high (**A**), intermediate (**B**), and low (**C**) Healthy Lifestyle Index (HLI) categories

and ASCVD (degree centrality = 276, Fig. 2B). In the high HLI group (Fig. 2C), the network was further fragmented, reflecting attenuated co-occurrence patterns between cancers and NCDs. Nevertheless, lung cancer, colorectal cancer, and ASCVD consistently remained central nodes in the network structure. Degree centrality values of comorbidity patterns between cancer and other NCDs across various HLI categories are detailed in Supplementary Table 9.

The pathways of cancer with comorbidity revealed that ASCVD plays a significant role in the early stages of disease progression as cancer develops into a comorbid state. The most common pathways of cancer with a single NCD are Cancer → ASCVD and ASCVD → Cancer. The pathways involving cancer with two NCDs include Cancer → ASCVD → CKD and Cancer → ASCVD → COPD. Specifically, the time from the first disease to the emergence of cancer with comorbidity ranged from 2.49 to 5.65 years, while the time from cancer with comorbidity to death varied between 0.57 and 1.81 years (Supplementary Table 10).

A clear inverse gradient was observed across HLI categories in relation to the risk of developing cancer and cancer-related comorbidities. After adjusting for age, sex, and socioeconomic status, participants in the high HLI group had a significantly lower risk of incident cancer compared to those in the low HLI group (HR = 0.92, 95% CI: 0.90–0.94), while the intermediate HLI group also showed a modest reduction in risk (HR = 0.94, 95% CI: 0.92–0.96). When examining cancer-related comorbidities, a stronger protective association with healthy lifestyle emerged. Compared to the low HLI group, the risk of developing any cancer-related comorbidity was reduced by nearly half in the high HLI group (HR = 0.51, 95% CI: 0.49–0.53). Notably, the protective effect of lifestyle adherence strengthened as the number of coexisting NCDs increased. Among cancer patients with one NCD, the HR for the high HLI group was 0.62 (95% CI:

0.59–0.65), and this declined progressively to 0.29 (95% CI: 0.26–0.32) for two NCDs, 0.17 (95% CI: 0.12–0.22) for three, and 0.11 (95% CI: 0.04–0.30) for four NCDs. The intermediate HLI group also demonstrated reduced risks across all strata, although to a lesser extent than the high HLI group (Fig. 3).

Subgroup analyses for the incidence of cancer-related comorbidity focused on several common cancer types (Supplementary Fig. 2). Consistent inverse associations were observed in the high HLI group for the incidence of cancer with comorbidities. Significant reductions in risk were noted for head and neck cancer (HR = 0.60, 95% CI: 0.39–0.92), esophageal cancer (HR = 0.42, 95% CI: 0.28–0.63), gastric cancer (HR = 0.60, 95% CI: 0.36–0.98), colorectal cancer (HR = 0.70, 95% CI: 0.59–0.82), and renal cancer (HR = 0.68, 95% CI: 0.52–0.90), when compared to the low HLI group. The most pronounced associations were observed for liver cancer with comorbidity (HR = 0.25, 95% CI: 0.12–0.51) and lung cancer with comorbidity (HR = 0.26, 95% CI: 0.20–0.33).

We further investigated survival outcomes among cancer patients using Kaplan–Meier methods. Survival curves revealed marked differences in the rate of survival decline across both comorbidity status and HLI categories. Specifically, patients with cancer-related comorbidities exhibited the most pronounced decline in survival over time, whereas those with cancer alone maintained comparatively higher survival probabilities. Among cancer patients, survival declined progressively with an increasing number of coexisting NCDs. Notably, regardless of comorbidity status, cancer patients in the high HLI group had higher survival probabilities than those in the low HLI group within each corresponding subgroup (Fig. 4; Supplementary Fig. 3–13).

Discussion

In this longitudinal cohort study utilizing UK Biobank data, over 400,000 participants were followed to explore whether adherence to a healthy lifestyle influences the incidence of cancer, the presence of cancer-related comorbidities, and survival outcomes among

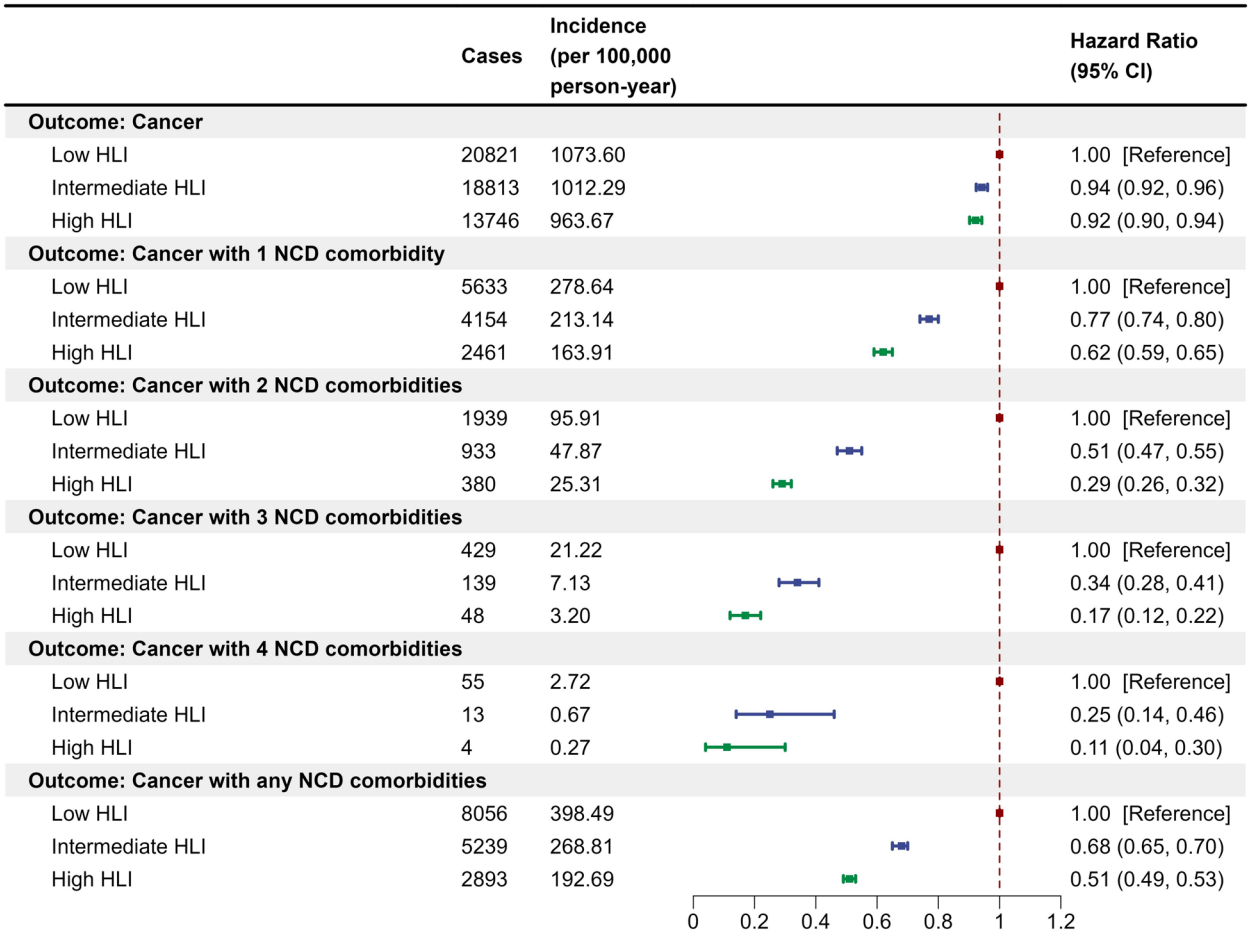

Fig. 3 Adjusted associations between Healthy Lifestyle Index (HLI) categories and the incidence of cancer and cancer-related comorbidities. Derived from Cox regression model with the adjustment of age, sex and socioeconomic status; the incidence rate represents the number of new cases occurring per 100,000 person-years

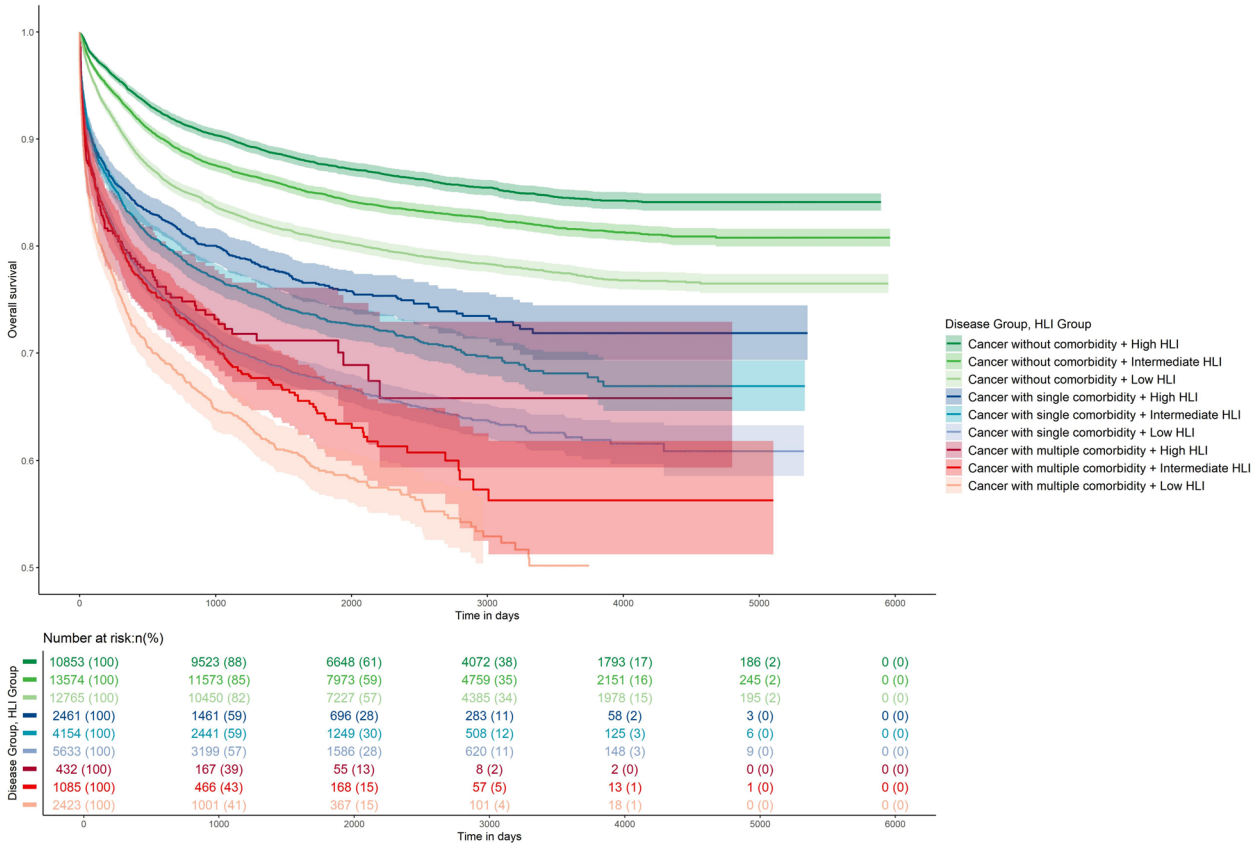

Fig. 4 Overall survival of cancer patients according to comorbidity status and Healthy Lifestyle Index (HLI) categories

cancer patients. Our findings indicate that adherence to a healthy lifestyle significantly reduces the incidence of cancer, particularly for those with comorbidities, and notably improves survival among cancer patients. Our study underscores the critical role of promoting healthy lifestyles in preventing cancer and its related comorbidities, providing a robust scientific foundation for clinical practice and public health strategies.

Assessment of healthy lifestyles typically involves a combination of factors such as diet, alcohol intake, physical activity, BMI, waist circumference, and smoking status. In this study, we introduced the HLI to integrate these multiple behavioral factors, and to more accurately differentiate lifestyle levels across different populations. Rather than examining individual components separately, the HLI enabled a holistic evaluation of lifestyle patterns. Our findings demonstrate that individuals in the low HLI group accounted for a greater proportion of incident cancer cases, particularly those with cancer-related comorbidities, suggesting that comprehensive lifestyle adherence may help mitigate the cumulative pathophysiological burden associated with multimorbidity. This is consistent with mechanistic evidence linking chronic hyperinsulinemia from obesity and tobacco-induced DNA damage to both cancer development and cardiometabolic dysfunction [22, 23]. The predictive value of HLI highlights the importance of comprehensive lifestyle interventions, especially in populations at elevated risk for comorbid disease [24].

While numerous studies have extensively observed the pattern of comorbidity among various NCDs [25–27], the specific comorbidity profiles in cancer patients remain underexplored. Network analysis unveiled ASCVD as the central comorbidity across all HLI categories, highlighting a profound interplay between ASCVD and cancer progression. These findings align with the recent observations reported by Luka et al. in 2024 and therefore further underscore the critical role of ASCVD in the context of cancer-related comorbidities [28]. However, HLI stratification exposed divergent topological patterns: low HLI groups exhibited dense lung cancer-ASCVD clusters, whereas high HLI networks fragmented into weaker colorectal cancer-ASCVD linkages, indicating a potential mitigating role of healthy lifestyle adherence in the interplay of high-prevalence diseases [29]. Beneficial lifestyle factors, such as a balanced diet and regular physical activity, may attenuate disease synergies by reducing systemic inflammation and improving metabolic function, thereby lowering comorbidity risks [30]. Age-stratified analyses further revealed that comorbidity multiplicity

increased disproportionately among low HLI patients aged > 62 years, highlighting lifestyle's role in mitigating age-related pathophysiological accumulation [31].

Furthermore, although some studies have reported the role of healthy lifestyle in patients with specific types of cancer, the impact of lifestyle adherence on the risk of incident cancer and cancer-related comorbidities in the broader population has not been widely explored. In this study, we observed a clear inverse association between HLI levels and the incidence of both cancer and cancer-related comorbidities. Notably, the risk reduction was particularly pronounced among individuals with multiple coexisting NCDs, suggesting a threshold effect in which lifestyle optimization disproportionately benefits high-comorbidity subgroups. This observation aligns with the "multiple-hit" hypothesis, wherein smoking and alcohol intake contribute directly to oncogenesis via genetic mutations, while physical inactivity and poor diet promote tumorigenesis through metabolic dysregulation and inflammatory signaling pathways (e.g., PI3K/AKT/mTOR), as well as through remodeling of the tumor microenvironment via cumulative metabolic stress [32]. Subgroup analyses further revealed that high HLI were strongly associated with reduced risk of lung and liver cancers with comorbidities. These effects may be mediated by mechanisms such as reduced exposure to tobacco-derived carcinogens through smoking cessation, and improved oxidative stress defenses via dietary and metabolic regulation [33].

During the study follow-up, an absolute survival difference of approximately 10%-20% was observed between high- and low-HLI groups in cancer patients, highlighting the underutilized therapeutic potential of lifestyle interventions. Notably, comorbidity burden amplified lifestyle-related survival disparities: cancer patients with multiple comorbidities in the low HLI group exhibited significantly higher mortality rates than matched high HLI counterparts. These findings underscore synergistic exacerbation effect in cancer patients with multiple NCDs—wherein metabolic dysregulation (e.g., obesity-associated insulin resistance [16, 34]) and chronic inflammation (e.g., smoking-induced pulmonary microenvironment imbalance [35]) may synergistically accelerate tumor progression, while integrated lifestyle interventions (smoking cessation, weight management, and dietary optimization) could concurrently improve comorbidity control and enhance antitumor immune responses [21, 36, 37].

To further reduce the incidence of cancer, the presence of cancer-related comorbidities, and improve survival outcomes among cancer patients, it is imperative to integrate healthy lifestyle management into cancer survivorship care, particularly for cancer patients with ASCVD, to disrupt shared pathological pathways through targeted lifestyle optimization [38]. Concurrently, multimodal interventions combining metabolic regulators (e.g., exercise-metformin synergy) and policy-driven reductions in obesogenic environmental exposures could amplify therapeutic efficacy [39, 40]. By aligning clinical protocols with community-level prevention, healthcare systems may mitigate comorbidity-related mortality through population-level lifestyle modification strategies.

Strengths of this study include the use of large-scale, long-term prospective cohort data, which provide robust evidence regarding the relationship between healthy lifestyles and the risk of cancer and cancer-related comorbidities. However, several limitations should be noted. Firstly, the lifestyle data in this study were based on self-reports from participants, which may introduce recall bias. Secondly, although adjustments were made for potential confounders using multiple statistical methods, residual confounding from unmeasured factors (e.g., medication adherence, environmental exposures and genetic predisposition) and potential survival bias in long-term follow-up warrant consideration. Thirdly, the lifestyle factors were assessed only at baseline, and changes in lifestyle behaviors during the follow-up period were not captured, which may lead to an underestimation of the effects of lifestyle on cancer and comorbidity outcomes. Fourthly, the generalizability of the results may be constrained by the geographic and cultural context of the sample.

Future research should consider employing more robust study designs, such as intervention trials or randomized controlled trials, and replicating the study across diverse countries and cultural contexts to mitigate the effects of confounding factors and strengthen causal inference. Additionally, it would be valuable for future studies to incorporate repeated assessments of lifestyle factors throughout the follow-up period and explore the interactions between these factors in greater depth, to better understand how they may synergistically influence health outcomes.

Maintaining a healthy lifestyle was associated with a lower risk of developing cancer and cancer-related comorbidities, as well as improved overall survival. These findings underscore the critical role of lifestyle interventions in preventing the onset of cancer and reducing its associated comorbidity burden, and in enhancing life expectancy, particularly in the elderly population.

Conclusions

Adherence to a healthy lifestyle significantly reduces the risk of cancer and cancer-related comorbidities, and improves overall survival. These findings highlight both the preventive and prognostic value of lifestyle modification, reinforcing its importance in early intervention strategies to support healthy aging.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-025-07141-7.

Supplementary material 1.

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Author contributions

HC and MD conceived and designed the study and hold responsibility for the integrity of the data and the accuracy of the data analysis. XC did the statistical analysis and data interpretation and drafted the manuscript. YZ, CL, BL, NL, YZ and YC helped with data processing and verified the data. All authors critically revised the manuscript, had full access to all data in the study, and had final responsibility for the decision to submit for publication.

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Data availability

Researchers registered with the UK Biobank can apply for access to the database by completing an application. The application must include a summary of the research plan, data fields required, any new data or variables that will be generated, and payment to cover the incremental costs of servicing an application (https://www.ukbiobank.ac.uk/enableyour-research/apply-for-access).

Declarations

Ethics approval and consent to participate

All participants provided electronically signed consent for their data to be used in health-related research. UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 21/NW/0157).

Consent for publication

This study used data from the UK Biobank under research ethics approval, with all participants providing informed consent. The manuscript contains no identifiable personal details and reports only aggregate, non-identifiable results.

Competing interests

The authors declare that they have no competing interests.

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References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229–63.
2. Spring B, King AC, Pagoto SL, Van Horn L, Fisher JD. Fostering multiple healthy lifestyle behaviors for primary prevention of cancer. Am Psychol. 2015;70:75–90.
3. Castillo JJ, Dalia S, Shum H. Meta-analysis of the association between cigarette smoking and incidence of Hodgkin's lymphoma. J Clin Oncol. 2011;29:3900–6.
4. Jayedi A, Emadi A, Shab-Bidar S. Dietary inflammatory index and site-specific cancer risk: a systematic review and dose-response meta-analysis. Adv Nutr Bethesda Md. 2018;9:388–403.
5. Wang F, Liu L, Cui S, et al. Distinct effects of body mass index and waist/hip ratio on risk of breast cancer by joint estrogen and progestogen receptor status: results from a case-control study in northern and eastern China and implications for chemoprevention. Oncologist. 2017;22:1431–43.
6. Stamatakis E, Ahmadi MN, Friedenreich CM, et al. Vigorous intermittent lifestyle physical activity and cancer incidence among nonexercising adults: the UK biobank accelerometry study. JAMA Oncol. 2023;9:1255.
7. Druesne-Pecollo N, Tehard B, Mallet Y, et al. Alcohol and genetic polymorphisms: effect on risk of alcohol-related cancer. Lancet Oncol. 2009;10:173–80.
8. Taranto D, Kloosterman DJ, Akkari L. Macrophages and T cells in metabolic disorder-associated cancers. Nat Rev Cancer. 2024;24:744–67.
9. Islam MT, Saif MSI, Alam N et al. Evaluating the risk of comorbidity onset in elderly patients after a cancer diagnosis. BMC Public Health. 2025;25(1):640.
10. World Health Organization. Non communicable diseases fact sheet. 2024; published online Dec 23. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases (accessed March 6, 2025).
11. Sarfati D, Koczwara B, Jackson C. The impact of comorbidity on cancer and its treatment. CA Cancer J Clin. 2016;66:337–50.
12. Søgaard M, Thomsen RW, Bossen KS, Sørensen HT, Nørgaard M. The impact of comorbidity on cancer survival: a review. Clin Epidemiol. 2013;5:3–29.
13. Sturgeon KM, Deng L, Bluethmann SM, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J. 2019;40:3889–97.
14. Yin J, Freedman ND, Liu Y, et al. Associations between serum glucose, insulin, insulin resistance and the risk of incident primary liver cancer or chronic liver disease mortality: a nested case–control study. Br J Cancer. 2023;128:275–84.
15. Loftfield E, Freedman ND, Lai GY, et al. Higher glucose and insulin levels are associated with risk of liver cancer and chronic liver disease mortality among men without a history of diabetes. Cancer Prev Res. 2016;9:866–74.
16. Zhang AMY, Wellberg EA, Kopp JL, Johnson JD. Hyperinsulinemia in obesity, inflammation, and cancer. Diabetes Metab J. 2021;45:285–311.
17. Boersma P, Black LI, Ward BW. Prevalence of multiple chronic conditions among US adults, 2018. Prev Chronic Dis. 2020;17:E106.
18. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12:e1001779.
19. UK biobank - UK biobank. 2025; published online Jan 10. https://www.ukbiobank.ac.uk (accessed March 6, 2025).
20. World Cancer Research Fund/American Institute of Cancer Research. Cancer prevention. Am. Inst. Cancer Res. https://www.aicr.org/cancer-prevention/how-to-prevent-cancer/ (accessed March 6, 2025).
21. Malcomson FC, Parra-Soto S, Ho FK, et al. Adherence to the 2018 world cancer research fund (WCRF)/American institute for cancer research (AICR) cancer prevention recommendations and risk of 14 lifestyle-related cancers in the UK biobank prospective cohort study. BMC Med. 2023;21:407.
22. Usman M, Volpi EV. DNA damage in obesity: initiator, promoter and predictor of cancer. Mutat Res Rev Mutat Res. 2018;778:23–37.
23. Tang M-S, Lee H-W, Weng M-W, et al. DNA damage, DNA repair and carcinogenicity: tobacco smoke versus electronic cigarette aerosol. Mutat Res Rev Mutat Res. 2022;789:108409.
24. Byrne S, Boyle T, Ahmed M, Lee SH, Benyamin B, Hyppönen E. Lifestyle, genetic risk and incidence of cancer: a prospective cohort study of 13 cancer types. Int J Epidemiol. 2023;52:817–26.
25. Yao K, Wang S, Xu Z et al. Mechanisms of comorbidity between alzheimer's disease and pain. Alzheimers Dement. 2025;21(2):e14605.
26. Salter A, Lancia S, Kowalec K, Fitzgerald KC, Marrie RA. Comorbidity and disease activity in multiple sclerosis. JAMA Neurol. 2024;81:1170–7.
27. Shantsila E, Choi E-K, Lane DA, Joung B, Lip GYH. Atrial fibrillation: comorbidities, lifestyle, and patient factors. The Lancet Regional Health. 2024;37:100784.
28. Katic L, Choi J, Diaz Saravia S, et al. The interplay between cardiovascular disease and lung cancer. Cureus. 2024;16:e62953.
29. Katzke VA, Kaaks R, Kühn T. Lifestyle and cancer risk. Cancer J. 2015;21:104–10.
30. Divella R, Marino G, Infusino S, Lanotte L, Gadaleta-Caldarola G, Gadaleta-Caldarola G. The Mediterranean lifestyle to contrast low-grade inflammation behavior in cancer. Nutrients. 2023;15:1667.
31. Li Y, Pan A, Wang DD, et al. Impact of healthy lifestyle factors on life expectancies in the US population. Circulation. 2018;138:345–55.

32. Altea-Manzano P, Decker-Farrell A, Janowitz T, Erez A. Metabolic interplays between the tumour and the host shape the tumour macroenvironment. Nat Rev Cancer. 2025. https://doi.org/10.1038/s41568-024-00786-4.
33. Box HC, O'Connor RJ, Patrzyc HB, et al. Reduction in oxidatively generated DNA damage following smoking cessation. Tob Induc Dis. 2011;9:5.
34. Chawla S, Pund A, B V, Kulkarni S, Diwekar-Joshi M, Watve M. Inferring causal pathways among three or more variables from steady-state correlations in a homeostatic system. PLoS ONE. 2018;13:e0204755.
35. Liu X, Sun W, Ma W, et al. Smoking related environmental microbes affecting the pulmonary microbiome in Chinese population. Sci Total Environ. 2022;829:154652.
36. Ra C, Km A, Ew D, et al. Adherence to cancer prevention lifestyle recommendations before, during, and 2 years after treatment for high-risk breast cancer. JAMA Netw Open. 2023. https://doi.org/10.1001/jamanetworkopen.2023.11673.
37. Zhu C, Ma H, He A, Li Y, He C, Xia Y. Exercise in cancer prevention and anticancer therapy: efficacy, molecular mechanisms and clinical information. Cancer Lett. 2022;544:215814.
38. Hill-Kayser CE, Vachani CC, Hampshire MK, Di Lullo G, Jacobs LA, Metz JM. Impact of internet-based cancer survivorship care plans on health care and lifestyle behaviors. Cancer. 2013;119:3854–60.
39. Martín-Rodríguez S, de Pablos-Velasco P, Calbet JaL. Mitochondrial complex I inhibition by metformin: drug-exercise interactions. Trends Endocrinol Metab. 2020;31:269–71.
40. Wickramasinghe K, Chatterjee S, Williams J, et al. Childhood overweight and obesity abatement policies in europe. Obes Rev. 2021;22(Suppl 6):e13300.

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