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ORIGINAL RESEARCH

The Role of Healthy Lifestyle in Cancer Incidence and Temporal Transitions to Cardiometabolic Disease

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ABSTRACT

BACKGROUND Cardiometabolic disease, including cardiovascular disease (CVD) and type 2 diabetes (T2D), can result in serious late effects in patients with cancer. Preventing long-term complications in this population is an increasingly important priority in public health and clinical practice.

OBJECTIVES The aim of this study was to investigate the role of a healthy lifestyle in the transition from a healthy status to the development of cancer and subsequent CVD and T2D.

METHODS The analysis was based on data from the UK Biobank and included 2 subsamples: a cancer-free cohort of 397,136 individuals in the general population and a cancer-prevalent cohort of 35,564 patients with cancer. All participants were 40 to 70 years of age and were free of CVD and T2D at recruitment. A healthy lifestyle that included no current smoking, regular physical activity, a healthy diet, and moderate alcohol consumption and sleep duration were included in a healthy lifestyle index (HLI).

RESULTS In the cancer-free cohort, during a maximum follow-up period of 15 years, 6.38% and 4.18% of patients with cancer developed CVD and T2D, respectively. A healthy lifestyle significantly mitigated the risk for transition from cancer to subsequent CVD and T2D, with HRs per 1-point increment in HLI of 0.90 (95% CI: 0.86-0.94) and 0.84 (95% CI: 0.79-0.89), respectively. In the cancer-prevalent cohort, each 1-point increment in HLI was similarly associated with lower risk for CVD (HR: 0.90; 95% CI: 0.87-0.93) and T2D (HR: 0.87; 95% CI: 0.83-0.91) in cancer survivors.

CONCLUSIONS A healthy lifestyle is associated with a slower transition from cancer development to the subsequent development of CVD and T2D. Moreover, among patients with cancer, a healthy lifestyle is associated with lower risk for CVD and T2D. This study highlights the practical benefits of adherence to a healthy lifestyle.
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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CVD = cardiovascular disease

HLI = healthy lifestyle index

ICD-10 = International Classification of Diseases-Tenth Revision

NHS = National Health Service

T2D = type 2 diabetes

Cancer, cardiovascular disease (CVD), and type 2 diabetes (T2D) are 3 leading causes of death worldwide (1). Two thirds of patients diagnosed with cancer will survive more than 5 years beyond their cancer diagnoses (2). Furthermore, there were more than 16.9 million cancer survivors in the United States in 2019 alone, and this number is projected to reach more than 22.1 million by 2030 (3). It is estimated that cardiometabolic disease, defined as either CVD or T2D, is the number 1 comorbidity in patients with cancer (4). The Childhood Cancer Survivor Study suggested that cancer survivors are 7 times more likely than the general population to die as a result of CVD, making CVD the leading cause of noncancer deaths in this population (5). Therefore, directing the focus toward secondary prevention strategies in patients with cancer has become a priority for both public health and clinical practice.

Underlying risk factors for both CVD and T2D include unhealthy behaviors, such as smoking, insufficient physical activity, and unhealthy dietary patterns, suggesting that the risk for these diseases might be interrelated. Numerous studies have shown that a healthy lifestyle is associated with lower risk for CVD and T2D (6,7). However, the associations between healthy lifestyle factors in combination and CVD and T2D in cancer survivors remain unclear. We hypothesized that adherence to a healthy lifestyle is particularly important in patients with cancer for preventing or delaying the development of CVD and T2D complications. Although some studies have suggested that lifestyle factors are associated with an increased risk for CVD in survivors of childhood cancers (8,9), there is limited evidence regarding the effect of a healthy lifestyle on the risk for transitioning from healthy status to incident cancer and the subsequent onset of CVD and T2D.

Therefore, the purpose of the present study was to use a large-scale UK Biobank cohort study with 14-year follow-up to examine whether the beneficial effect of a healthy lifestyle on the risk for CVD and T2D is generated before or after the onset of cancer. We used multistate models that allowed estimation of the role of a healthy lifestyle in the transition from the healthy state to incident cancer and the subsequent transition to CVD or T2D. Moreover, a cancer-prevalent cohort was separately studied to confirm the effect of a healthy lifestyle on the risk for CVD or T2D among long-term cancer survivors.

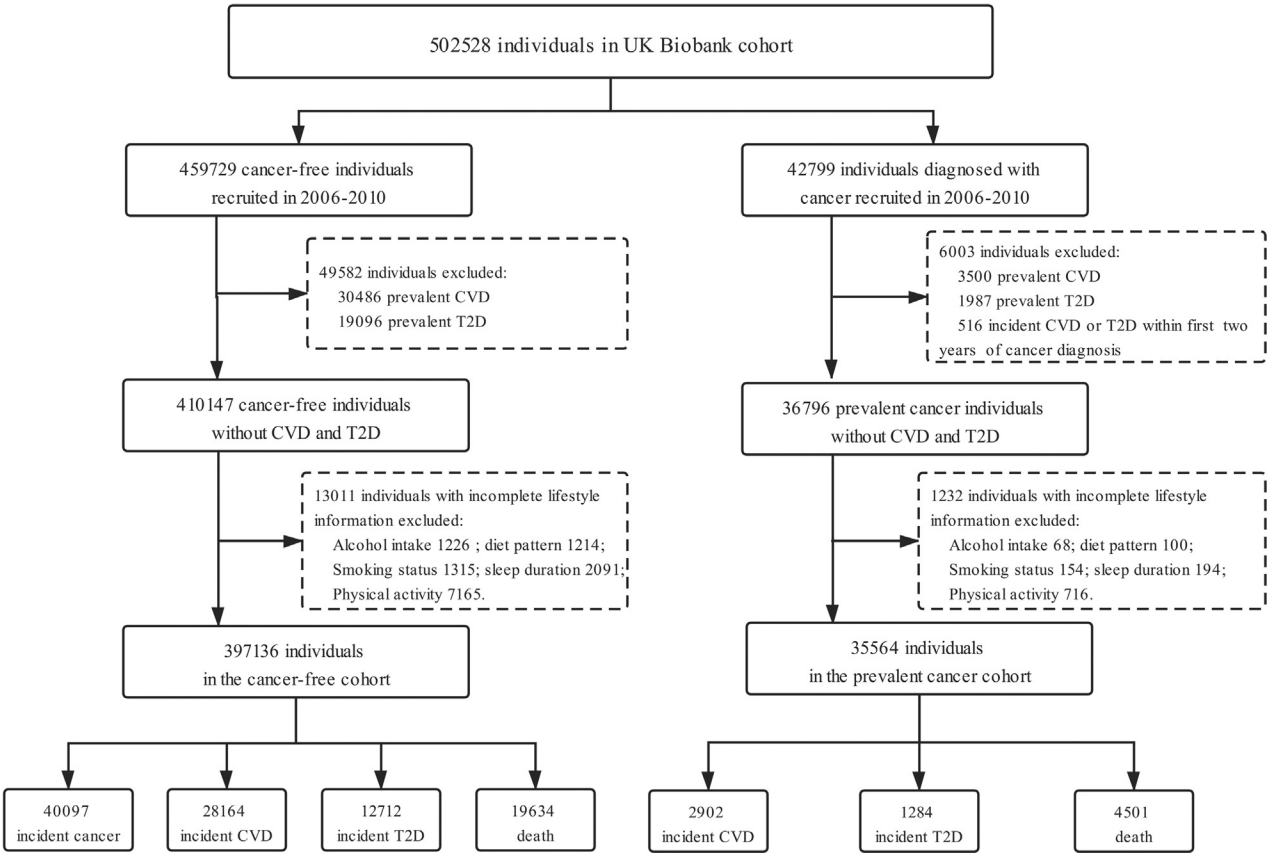
METHODS

STUDY DESIGN AND POPULATION. This was a prospective, population-based cohort study of participants enrolled in UK Biobank. Between April 2006 and December 2010, UK Biobank recruited 502,528 adults (40-70 years of age) from the general population. Participants attended 1 of 22 assessment centers across England, Scotland, and Wales, where they completed touchscreen and nurse-led questionnaires, had physical measurements taken, and provided biological samples (10).

Our study consisted of 2 cohorts based on cancer prevalence at baseline (**Figure 1**). The cancer-free cohort included participants without cancer at baseline (other than nonmelanoma skin cancer) and excluded participants with CVD and/or T2D, as well as those with incomplete lifestyle information (n = 397,136). The cancer-prevalent cohort was restricted to patients diagnosed with cancer (other than nonmelanoma skin cancer) at baseline and excluded participants diagnosed with CVD or T2D at baseline, those with incident CVD or T2D within 2 years of cancer diagnosis, and those with incomplete lifestyle information (n = 35,564). Participants provided written informed consent to participate in research, as previously described (10). The UK Biobank has full ethical approval from the National Health Service (NHS) National Research Ethics Service.

HEALTHY LIFESTYLE INDEX. In the present study, a healthy lifestyle index (HLI) was constructed on the basis of 5 cardiometabolic disease–related healthy behaviors (smoking status, physical activity, diet, alcohol consumption, and sleep duration) assessed at baseline using a touchscreen questionnaire. Smoking status was categorized as current or no current smoking. Regular physical activity was defined as meeting the American Heart Association recommendation of at least 150 minutes of moderate activity per week or 75 minutes of vigorous activity per week (or an equivalent combination) (11). A healthy diet was defined in UK Biobank as an adequate intake of at least 4 of 7 dietary components (fruits, vegetables, whole grains, refined grains, fish, unprocessed meat, and processed meat), following the recommendations on dietary components for cardiovascular health (12). Moderate consumption of alcohol was defined as 0 to 14 g/d for women and 0 to 28 g/d for men, with the maximum limit reflecting U.S. dietary guidelines (13). Moderate sleep duration was defined as 6 to 8 hours every day (14). For each healthy lifestyle factor, participants received a score of 1 if they met the

FIGURE 1 Flowchart of the Study Population



Process for selection of the study population. CVD = cardiovascular disease; T2D = type 2 diabetes.

criterion and 0 if they did not. The sum of these 5 components yielded a final score ranging from 0 to 5, with higher scores indicating a healthier lifestyle. Details on the assessment of individual lifestyle factors can be found in Supplemental Table 1.

ASCERTAINMENT OF OUTCOMES. Information on incident cancers at any site (excluding non-melanoma skin cancer), CVD, T2D, and death were obtained through hospital admissions and death registries linked to UK Biobank (10). Dates and causes of hospital admissions were identified using record linkage to health episode statistics records for participants from England and Wales and from Scottish morbidity records for participants from Scotland. Dates and causes of death were obtained from death certificates held by the NHS Information Centre for participants from England and Wales and from the NHS Central Register Scotland for participants from Scotland. At the time of analysis, the data detailing the incidence of cancer, CVD, and T2D, and death were available up to March 20, 2021. Therefore, for the analyses of these outcomes, we censored follow-up at this date or at the disease date, if it occurred earlier.

Data on cancer incidence were coded according to the International Classification of Diseases-Tenth Revision (ICD-10) (Supplemental Table 2). Several common, site-specific cancers (prostate, breast, colorectal, lung, malignant melanoma, and bladder cancer) were selected as secondary outcomes because of their higher incidence. In the cancer-prevalent cohort, targeted study populations included patients who had been diagnosed with any site-specific cancer at baseline. CVD and T2D (ICD-10 code E11) were ascertained in both the cancer-free and cancer-prevalent cohorts. CVD endpoints were defined as any coronary heart disease (ICD-10 codes I20-I25) and stroke (ICD-10 codes I60, I61, I63, and I64).

COVARIATE ASSESSMENT. All analyses in our study were adjusted for age, sex, ethnicity, educational

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level, employment status, Townsend deprivation index, hypertension, and body mass index (BMI). We additionally adjusted for time since cancer diagnosis in the cancer-prevalent cohort. Models for breast cancer were additionally adjusted for menopause status, hormone replacement therapy, and oral contraceptive use in the cancer-free cohort. Information on participants' age, sex, ethnicity, education, employment, menopause, hormone replacement therapy, and oral contraceptive use was collected using a self-reported questionnaire at baseline. The Townsend deprivation index was assigned as a continuous measure on the basis of postal codes, which were derived from census data on housing, employment, social class, and car availability; a higher index indicated more deprivation (15). Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or use of antihypertensive medication. We calculated BMI as weight (in kilograms) divided by height (in meters) squared. In the cancer-prevalent cohort, time since cancer diagnosis was calculated according to the date on the linked record. On the whole, <2% of the data for the study covariates were missing; missing information on covariates was coded as a missing indicator category for categorical variables. Adjustment variables were selected a priori on the basis of a search of the published research (16,17).

STATISTICAL ANALYSES. We summarized baseline characteristics using descriptive statistics, reporting the mean ± SD for normal distributions and the median and interquartile range for non-normal distributions for continuous variables and proportions for categorical variables.

The cancer-free cohort. Multistate Markov models were constructed to estimate the role of the HLI in transitions from the healthy state to incident cancer (transition A), the healthy state to incident CVD or T2D in those without incident cancer (transition B), and diagnosed cancer status to incident CVD or T2D (transition C) (**Central Illustration**). Additionally, the potential risk for death in each state was considered as a competing event. We considered only the first entry into a state, and no reversal of state was allowed. The multistate model allowed simultaneous and transition-specific estimation of the risks per 1-point increment in HLI. We also report the roles of the individual healthy lifestyle factors, including no current smoking, a healthy dietary pattern, regular physical activity, and moderate alcohol consumption and sleep duration in multistate models. Moreover, several site-specific cancers were explored simultaneously as secondary outcomes in multistate models. Each transition was modeled using flexible parametric survival analysis, with 3 degrees of freedom for the baseline hazard function, as the model was fitted to have the best Akaike information criterion (18). The 3 transitions could occur at any point over the entire follow-up period, but once a person transitioned into the diagnosed cancer state, he or she was considered to stay there until the transition to CVD or T2D, death, or the end of follow-up. Moreover, because CVD and T2D are commonly comorbid, we ran additional transition models. These first showed the transition from healthy status to incident cancer, then to the first CVD or T2D event, followed by the transition to the subsequent progression to both CVD and T2D, termed cardiometabolic disease multimorbidity.

The cancer-prevalent cohort. In the cancer-prevalent cohort, flexible parametric competing risk models (19) were used to estimate standardized HRs and 95% CIs for the associations of HLI with CVD and T2D in cancer survivors. As mentioned previously, we used 3 degrees of freedom for the baseline hazard because of its optimal Akaike information criterion. Furthermore, we calculated and plotted the cumulative incidence of CVD and T2D according to HLI category with time since baseline examination as the underlying time scale. In addition, we evaluated effect modification of sex and age (40-49, 50-59 or ≥60 years) on the associations between HLI and risk for CVD and T2D in the cancer-prevalent cohort. The test for interaction was performed by using likelihood ratio tests comparing models with and without the cross-product term.

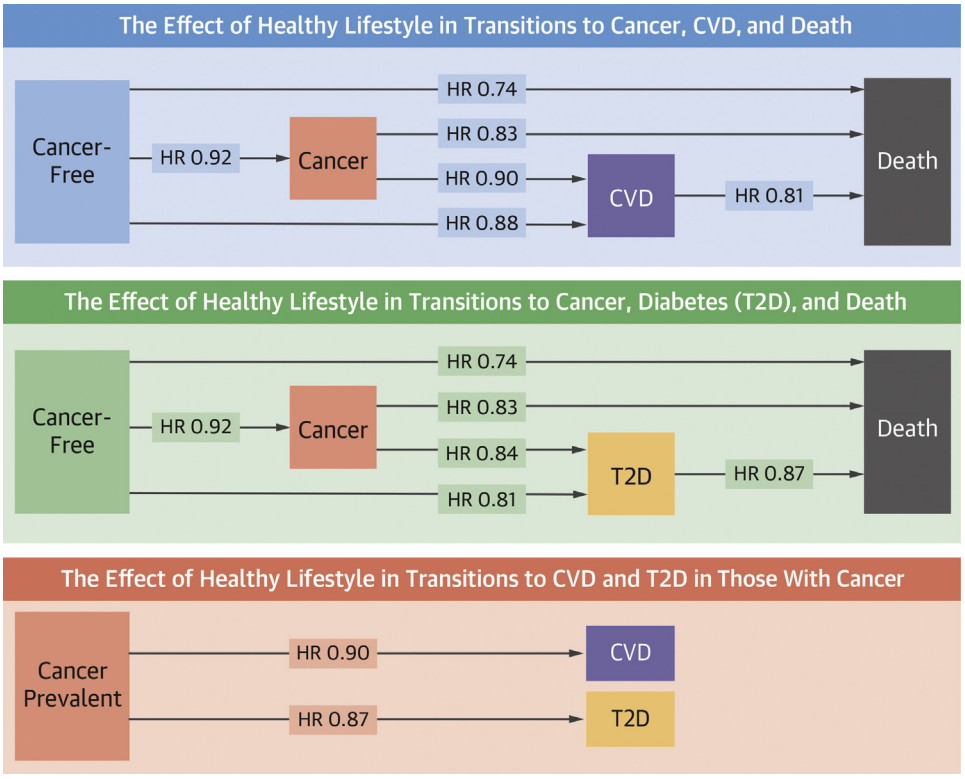
Sensitivity analyses. To examine the robustness of our findings, we also conducted several sensitivity analyses. First, in line with the definition of a healthy lifestyle profile in previous studies, we excluded sleep duration from the HLI and reanalyzed the multistate models. Second, to minimize the potential contribution of reverse causality to these findings, we repeated the analysis by excluding those who developed cancer within 2 years after baseline and CVD or T2D within 1 year after being diagnosed with cancer.

All analyses were performed using Stata version 15 (StataCorp) and R i386 version 3.4.3 (R mstate package for multistate Markov models; R Foundation for Statistical Computing). All P values were 2 sided, and P values < 0.05 were considered to indicate statistical significance.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION. **Table 1** shows the characteristics of the participants in the cancer-free and cancer-prevalent cohorts. Among

CENTRAL ILLUSTRATION **The Effect of a Healthy Lifestyle on the Transition From Cancer to Cardiovascular Disease or Type 2 Diabetes**



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In the cancer-free cohort, multistate Markov models examining the role of the healthy lifestyle index on the risk for transition from the healthy state to cancer and subsequent cardiovascular disease and type 2 diabetes. The HRs derived from multistate models are displayed for each transition. All multistate models were adjusted for age, sex, Townsend deprivation index, ethnicity, education, employment, hypertension, and body mass index. In the cancer-prevalent cohort, standardized HRs were derived from flexible parametric competing risk models adjusting for age, sex, Townsend deprivation index, ethnicity, education, employment, hypertension, body mass index, and time since cancer diagnosis.

397,136 cancer-free participants (mean age 55.7 ± 8.1 years, 44.6% men), a total of 40,097 individuals (10.1%) developed cancer, 28,164 (7.1%) developed CVD, 12,712 (3.2%) developed T2D, and 19,634 deaths (4.9%) occurred during a maximum follow-up of 15 years. Among 35,564 individuals in the cancer-prevalent cohort (mean age 59.3 ±7.3 years, 33.0% men), a total of 2,902 cases of CVD (8.2%), 1,284 cases of T2D (3.6%), and 4,501 deaths (12.7%) were documented during a maximum follow-up period of 15 years (Supplemental Table 3).

HLI, CANCER, AND CVD IN THE CANCER-FREE COHORT. The number of events, absolute risk, and effect of HLI on the transition from healthy status to incident total cancer and subsequent CVD are displayed in **Figure 2** and the **Central Illustration**. In the multistate model, a 1-point increment in HLI was associated with an 8% lower risk for cancer (HR: 0.92; 95% CI: 0.91-0.93). A 1-point increment in HLI was also significantly associated with a lower risk for incident CVD in patients diagnosed with cancer (HR: 0.90; 95% CI: 0.86-0.94) and in those free of cancer (HR: 0.88; 95% CI: 0.87-0.89). The risk for mortality at each transition was reduced by 17% to 26% per 1-point increment in HLI. The numbers of events and the HRs for each transition are shown in Supplemental Table 4. We further examined the associations of individual healthy lifestyle factors with the transitions and found smoking to be the strongest risk factor for all 6 transitions (**Table 2**). Subsequent analyses focused on cancer at specific sites. Supplemental Table 5 shows the results of these analyses. We

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TABLE 1 Baseline Characteristics of the Cancer-Free and Cancer-Prevalent Cohorts

	Cancer-Free Cohort (n = 397,136)	Cancer-Prevalent Cohort (n = 35,564)
Sex		
Male	177,253 (44.6)	11,730 (33.0)
Female	219,883 (55.4)	23,834 (67.0)
Age, y	55.7 ± 8.1	59.3 ± 7.3
Townsend deprivation index		
1 (least deprived)	81,574 (20.5)	7,529 (21.2)
2	79,985 (20.1)	7,365 (20.7)
3	78,418 (19.7)	7,027 (19.8)
4	84,083 (21.2)	7,399 (20.8)
5 (most deprived)	72,604 (18.3)	6,197 (17.4)
Missing	472 (0.1)	47 (0.1)
Ethnicity		
White	376,395 (94.8)	34,634 (97.4)
Black	5,943 (1.5)	251 (0.7)
South Asian	7,809 (2.0)	254 (0.7)
Mixed background	5,748 (1.5)	327 (0.9)
Missing	1,241 (0.3)	98 (0.3)
Employment status		
Worked	246,027 (61.9)	16,126 (45.3)
Retired	117,916 (29.7)	16,360 (46.0)
Unemployed	26,826 (6.7)	2,544 (7.2)
Other	6,367 (1.6)	534 (1.5)
Education level		
College or university degree	135,684 (34.2)	11,556 (32.5)
Professional qualifications	198,016 (49.9)	17,240 (48.5)
Other	57,281 (14.4)	6,227 (17.5)
Missing	6,155 (1.5)	541 (1.5)
Hypertension	167,002 (42.1)	16,197 (45.5)
BMI, kg/m^2	27.1 ± 4.6	26.9 ± 4.6
Menopause (female)	129,061 (58.7)	16,786 (70.4)
HRT history (female)	16,308 (7.4)	1,641 (6.9)
Oral contraceptive use (female)	6,367 (2.9)	278 (1.2)

Values are n (%) or mean ± SD.
BMI = body mass index; HRT = hormone replacement therapy.

found a consistent effect of HLI on all of the transitions, except for the transition from site-specific cancer to CVD. A 1-point increment in HLI was significantly associated with a lower risk for incident CVD in patients with breast cancer (HR: 0.80; 95% CI: 0.70-0.91); however, this association was not statistically significant for other site-specific cancers.

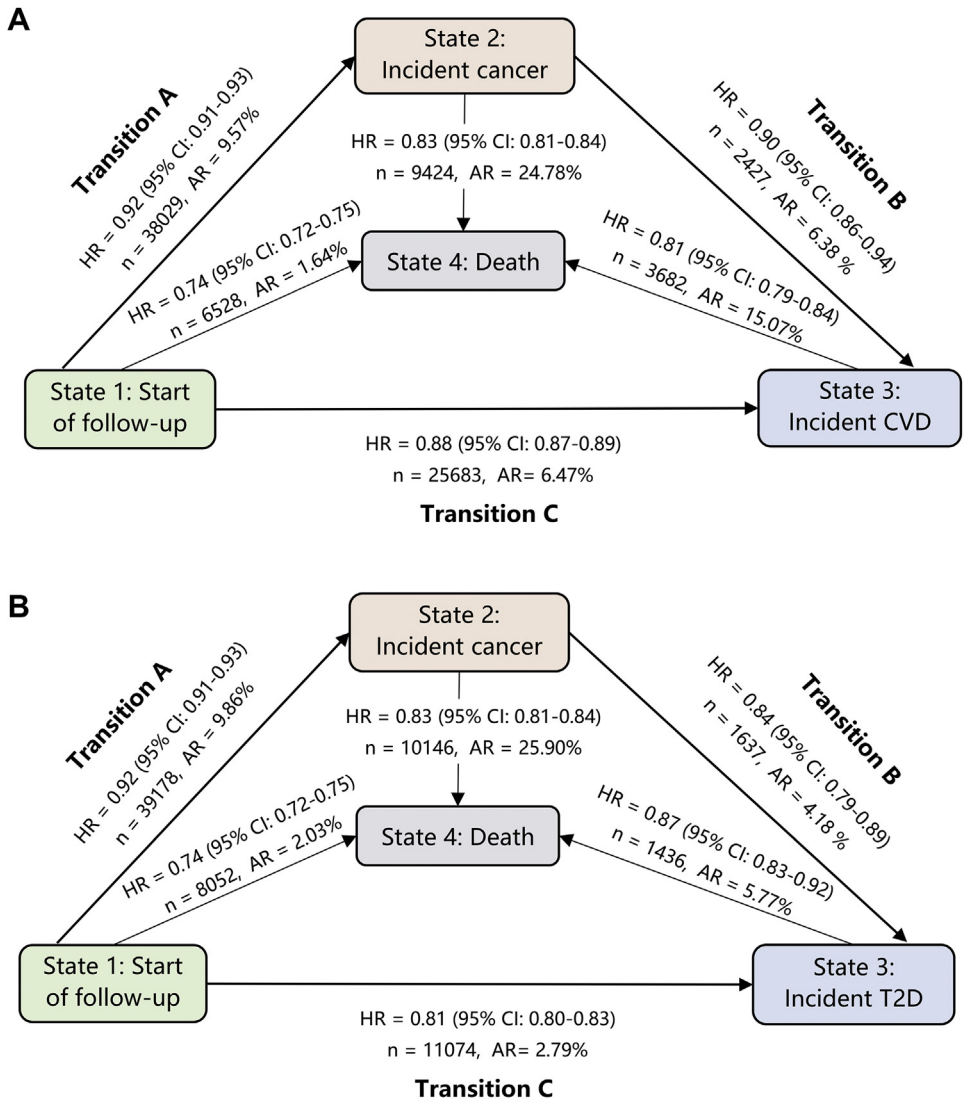
HLI, CANCER, AND T2D IN THE CANCER-FREE COHORT. The results from multistate models in participants free of cardiometabolic disease are displayed in **Figure 2** and the **Central Illustration**. A 1-point increment in HLI was associated with a lower risk for incident cancer over follow-up (transition A: HR: 0.92; 95% CI: 0.91-0.93). Among patients free of cancer and T2D, a 1-point increment in HLI was associated with a lower risk for T2D (transition C: HR: 0.81; 95% CI: 0.80-0.83). In those diagnosed with cancer over the follow-up period, a 1-point increment in HLI was also associated with a lower risk for T2D following the cancer diagnosis (transition B: HR: 0.84; 95% CI: 0.79-0.89). The numbers of events and the HRs for each transition are shown in Supplemental Table 6. Individual lifestyle factors, including no current smoking, regular physical activity, and a healthy diet, can substantially mitigate the risk for transition from cancer to T2D (**Table 3**). Subsequent analyses focused on site-specific cancers suggested that the risk for incident T2D was also significantly attenuated in patients with breast, prostate, and colorectal cancer (Supplemental Table 7).

We further explored the transition from cancer to cardiometabolic multimorbidity, as defined by the development of both CVD and T2D, in the cancer-free cohort (Supplemental Figure 1). Each 1-point increment in HLI was significantly associated with a lower risk for transitioning from cancer to the first occurrence of cardiometabolic disease (HR: 0.88; 95% CI: 0.85-0.91) and from the first cardiometabolic disease occurrence to a subsequent cardiometabolic disease event (HR: 0.86; 95% CI: 0.83-0.90).

HLI AND CARDIOMETABOLIC DISEASE IN THE CANCER-PREVALENT COHORT. In the cancer-prevalent cohort, among 35,564 cancer survivors, breast cancer was the most common (9,675 [27.2%]), followed by cervical cancer, malignant melanoma, and prostate cancer (Supplemental Table 2). We found that the cumulative incidence of CVD and T2D in participants with 5 healthy lifestyle factors was lower than in those with lower HLI categories over the follow-up period (**Figure 3**). Compared with cancer survivors with HLIs of 0 or 1, cancer survivors with 5 healthy lifestyle factors had standardized HRs of 0.56 (95% CI: 0.46-0.67) for the risk for incident CVD and 0.62 (95% CI: 0.47-0.83) for the risk for incident T2D (**Figure 4, Central Illustration**). Moreover, a 1-point increment in HLI was associated with risk reductions of 10% and 13% in incident CVD and T2D, respectively. We also found that the beneficial effect of HLI on CVD was stronger in female cancer survivors than in male survivors (P for interaction < 0.05) (Supplemental Table 8). Higher HLI was associated with lower risk for CVD and T2D, regardless of age group, and there were no significant interactions between HLI and CVD or T2D (P for interaction > 0.05) (Supplemental Table 9).

SENSITIVITY ANALYSES. Similar results were obtained when we conducted the following analyses in the cancer-free cohort. After excluding sleep duration from the HLI, the association between

FIGURE 2 Healthy Lifestyle Index and Incident Cancer and Subsequent CVD and T2D in the Cancer-Free Cohort



In the cancer-free cohort, multistate Markov models examining the role of the healthy lifestyle index on the risk for transition from the healthy state to cancer and subsequent CVD **(A)** and T2D **(B)** in the cancer-free cohort. The start of follow-up is a state in which participants were free of cardiometabolic disease for both **(A)** and **(B)**. All multistate models were adjusted for age, sex, Townsend deprivation index, ethnicity, education, employment, hypertension, and body mass index. AR = absolute risk; n = number of events transited to reach a specific state; other abbreviations as in Figure 1.

1-point increments in HLI and postcancer CVD or T2D remained significant (HR: 0.89; 95% CI: 0.85-0.93 for CVD; HR: 0.82; 95% CI: 0.80-0.83 for T2D) (Supplemental Table 10). When we excluded those who developed cancer within 2 years after baseline and CVD or T2D within 1 year after being diagnosed with cancer, the beneficial effects of HLI on the risk for transition from healthy status to incident cancer and subsequent CVD and T2D was consistent and remained statistically significant (Supplemental Table 11).

DISCUSSION

In a large cohort of nearly 400,000 participants from UK Biobank, we assessed the effect of a healthy lifestyle on the risk for incident cancer and the transition to subsequent CVD and T2D. We found that favorable

TABLE 2 HRs (95% CIs) of Incident Cancer and the Transition to CVD by Individual Healthy Lifestyle in the Cancer-Free Cohort

Transition	No Current Smoking	Moderate Alcohol Consumption	Regular Physical Activity	Healthy Diet	Moderate Sleep Duration
Transition 1: free to cancer	0.70 (0.68-0.72)	0.94 (0.93-0.96)	0.92 (0.90-0.94)	0.92 (0.90-0.94)	0.98 (0.95-1.01)
Transition 2: free to CVD	0.63 (0.60-0.65)	0.94 (0.91-0.96)	0.90 (0.88-0.93)	0.89 (0.86-0.91)	0.84 (0.82-0.87)
Transition 3: free to death	0.43 (0.41-0.46)	0.79 (0.75-0.83)	0.71 (0.67-0.74)	0.78 (0.75-0.83)	0.67 (0.63-0.71)
Transition 4: cancer to CVD	0.59 (0.52-0.66)	0.97 (0.89-1.06)	0.91 (0.83-1.01)	0.91 (0.83-0.99)	0.94 (0.83-1.07)
Transition 5: cancer to death	0.51 (0.48-0.53)	0.82 (0.79-0.86)	0.89 (0.85-0.94)	0.84 (0.81-0.88)	0.87 (0.82-0.92)
Transition 6: CVD to death	(0.45-0.54)	0.85 (0.79-0.91)	0.83 (0.77-0.90)	0.79 (0.74-0.85)	0.90 (0.82-0.99)

The multistate models were adjusted for age, sex, Townsend deprivation index, ethnicity, education level, employment status, hypertension, and body mass index.
CVD = cardiovascular disease.

lifestyle habits, summarized by higher HLI, were associated with a reduced risk of transitioning from healthy status to incident cancer and from cancer to CVD or T2D (**Central Illustration**). In both the cancer-prevalent and the incidental cancer cohorts, a healthy lifestyle was notably associated with lower risk for CVD and T2D. These findings highlight the benefits of adopting a combination of healthy behavioral practices in reducing the risk for CVD and T2D complications among patients with and without prevalent cancer.

In a community-based study of 165,000 patients with cancer, the most frequent adverse outcomes were the development of heart failure, acute coronary syndrome, and diabetes (20). Several previous studies showed an increased risk for CVD among childhood cancer survivors, which was attributable largely to treatment exposures at a young age (8,21,22). Survivors of adolescent and young adult cancer were also at increased risk for developing CVD (23). A retrospective cohort study including 36,232 adult-onset cancers (age ≥40 years) similarly revealed a higher risk for CVD compared with matched control subjects without cancer (24). Several pathophysiological mechanisms, such as oxidative stress as a result of anthracycline-generated free radicals and increased inflammation, have been suggested to be involved in the pathogenesis of CVD in cancer survivors (25). Moreover, CVD among patients with cancer is more likely to be multifactorial, involving not only therapeutic exposures that may compromise the cardiovascular system but also comorbidities and lifestyle factors that may increase the risk for long-term CVD (24). It is well established that a healthy lifestyle is associated with lower risk for CVD in the general population (26). The Childhood Cancer Survivor Study of 22,643 cancer survivors showed that traditional cardiovascular risk factors remain important for predicting the risk for CVD among adult survivors of childhood cancer (8). Our study found beneficial effects of a healthy lifestyle (such as no current smoking and a healthy diet) on the risk for CVD among survivors of adult-onset cancer. Additionally, our study provided evidence that the risk for CVD can be attenuated by adherence to a healthy lifestyle.

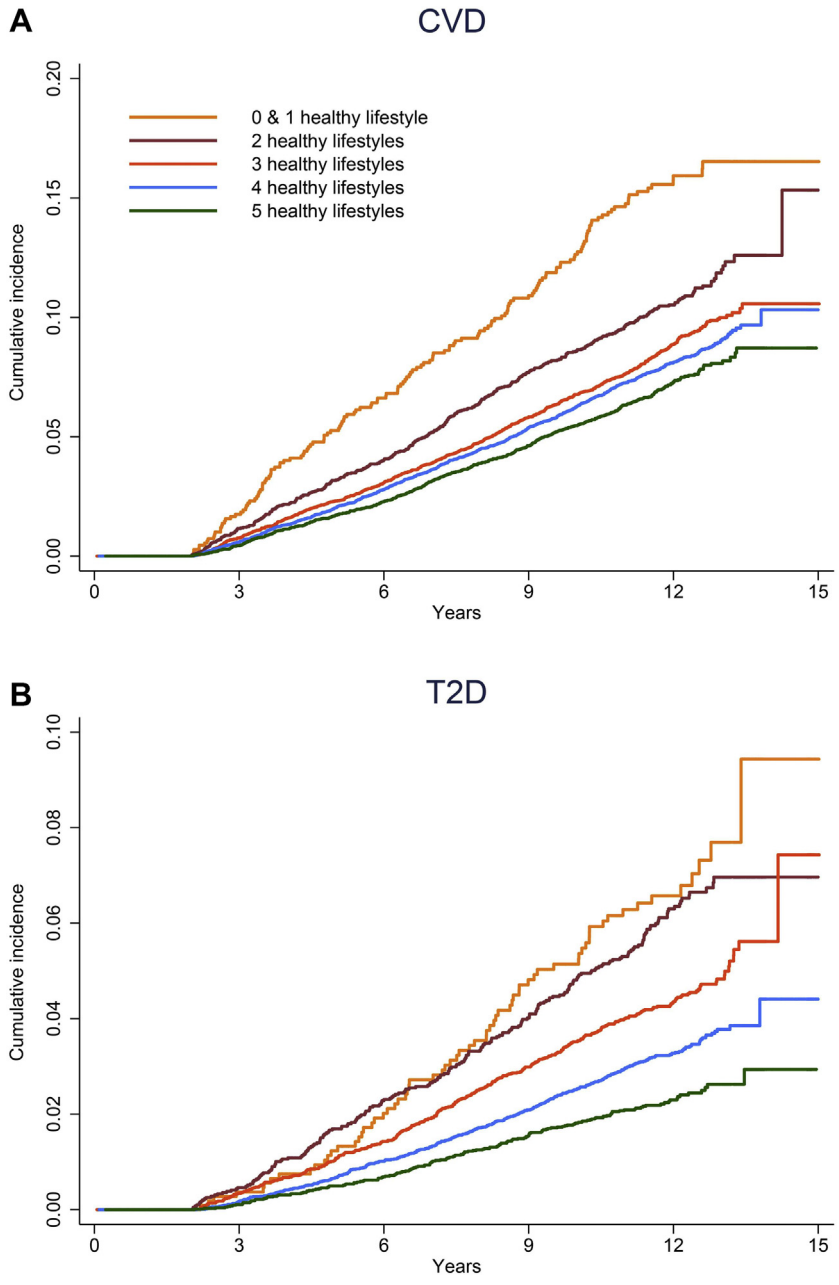
The increased risk for T2D among cancer survivors is consistent with findings from previous studies. The Childhood Cancer Survivor Study, including 8,599 cancer survivors, also found that cancer survivors were 1.6 times more likely to develop diabetes than sibling control subjects (27). Consistent with these findings, a recent study of 10,438 cancer survivors showed an earlier onset of diabetes in childhood cancer survivors compared with the general population (28). Of note, a recent meta-analysis of 13 population-based cohort studies including 1,686,595 participants

TABLE 3 HRs (95% CIs) of Incident Cancer and Transition to T2D by Individual Healthy Lifestyle in the Cancer-Free Cohort

Transition	No Current Smoking	Moderate Alcohol Consumption	Regular Physical Activity	Healthy Diet	Moderate Sleep Duration
Transition 1: free to cancer	0.69 (0.67-0.71)	0.94 (0.92-0.96)	0.93 (0.91-0.95)	0.92 (0.90-0.94)	0.98 (0.95-1.01)
Transition 2: free to T2D	0.60 (0.57-0.63)	0.88 (0.84-0.91)	0.81 (0.78-0.84)	0.79 (0.76-0.82)	0.76 (0.73-0.80)
Transition 3: free to death	0.43 (0.41-0.45)	0.80 (0.76-0.84)	0.71 (0.68-0.75)	0.76 (0.73-0.80)	0.69 (0.65-0.73)
Transition 4: cancer to T2D	0.69 (0.58-0.83)	0.92 (0.81-1.05)	0.76 (0.67-0.86)	0.76 (0.66-0.86)	0.96 (0.80-1.14)
Transition 5: cancer to death	0.49 (0.46-0.52)	0.83 (0.79-0.86)	0.90 (0.86-0.94)	0.84 (0.81-0.88)	0.87 (0.82-0.92)
Transition 6: T2D to death	0.64 (0.55-0.74)	0.80 (0.71-0.91)	0.91 (0.81-1.02)	0.99 (0.88-1.11)	0.88 (0.76-1.01)

The multistate models were adjusted for age, sex, Townsend deprivation index, ethnicity, education level, employment status, hypertension, and body mass index.
T2D = type 2 diabetes.

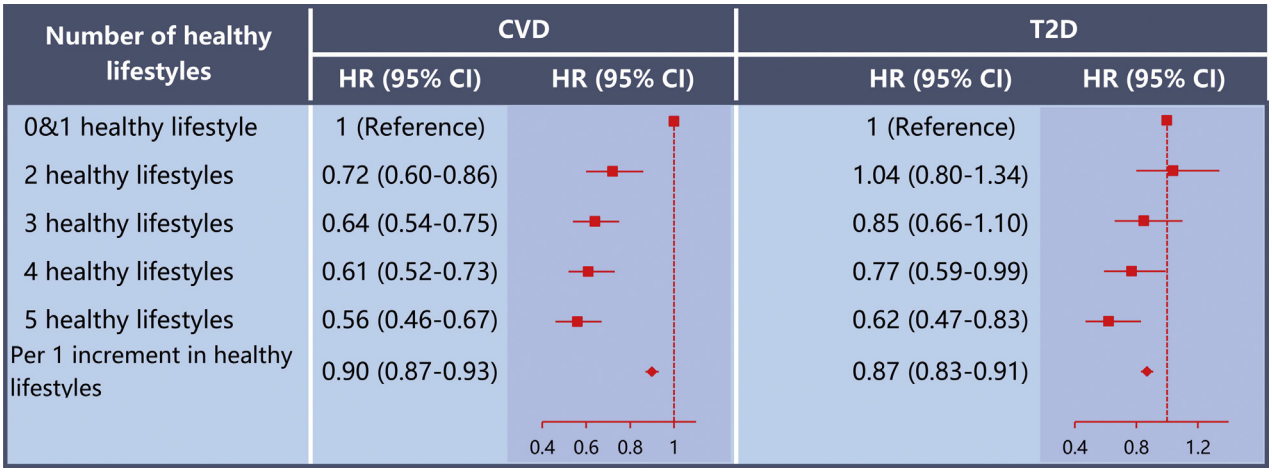
FIGURE 3 Time to Incident CVD and T2D in the Cancer-Prevalent Cohort



Healthy lifestyle index included no current smoking, regular physical activity, healthy diet, and moderate alcohol consumption, and sleep duration. Abbreviations as in Figure 1.

summarized the increased risk for diabetes in cancer survivors (HR: 1.39; 95% CI: 1.29-1.50; $I^2 = 82.3\%$; $P < 0.001$) compared with control subjects without cancer, with similar findings in survivors of gynecologic, breast, and colorectal cancer (29). Several meta-analyses have also revealed the importance of healthy behaviors for incident T2D prevention in the general population (30,31). Lifestyle intervention trials among people at elevated risk for developing T2D demonstrated the beneficial effects of lifestyle modification on reducing the risk for T2D (32). Lifestyle factors are increasingly being recognized as important contributing factors in the management of cancer. Behavioral interventions addressing modifiable

FIGURE 4 Healthy Lifestyle Index and Incident CVD and T2D in the Cancer-Prevalent Cohort



Standardized HRs were derived from flexible parametric competing risk models adjusting for age, sex, Townsend deprivation index, ethnicity, education, employment, hypertension, body mass index, and time since cancer diagnosis. Abbreviations as in Figures 1.

lifestyle risk factors (such as alcohol intake, smoking, physical activity, sleep duration, and dietary pattern) may result in improved outcomes in patients with cancer. The results of the present study provide strong evidence for the importance of a healthy lifestyle for lowering the risk for T2D in patients with cancer.

By restricting the multistate model to specific types of cancer, we found that a healthy lifestyle was significantly associated with a lower risk for incident CVD only in patients with breast cancer and was not observed in other site-specific cancers. The risk for incident T2D was also significantly attenuated in patients with breast, prostate, or colorectal cancer. Multiple prior studies have reported an increased risk for CVD among breast cancer survivors (33,34). Similarly, survivors of breast, prostate, and colorectal cancer are also confirmed to be at increased risk for incident T2D (35-37). The exact reasons for these differences among cancer types is not clear, but we might conclude that the multistate models are underpowered because of the relatively small number of site-specific incident cancers and the limited number of events that occurred between transition routes. Another important reason is that because breast cancer survival time is longer than that of other cancer types (3), adherence to a healthy lifestyle might generate a greater beneficial effect on risk for incident CVD and T2D in patients with breast cancer.

The results in the cancer-free cohort and cancer-prevalent cohort were largely similar. Nearly 50% of cancers in the cancer-prevalent cohort (27% breast, 7.3% prostate, 8.6% cervical, and 4.0% colorectal) have high 5-year survival rates. Compared with the distribution of incident cancers in the cancer-free cohort, the cancer-prevalent cohort had a higher percentage of breast, prostate, and cervical cancers, suggesting that the cancer-prevalent group comprises longer term survivors. Multistate models in our study showed the beneficial effect of a healthy lifestyle on CVD or T2D after the onset of cancer. In comparison, those with prevalent cancer may have a greater effect of a healthy lifestyle on CVD or T2D among long-term cancer survivors.

Our study revealed the beneficial effect of a combination of healthy lifestyle practices on the risk for incident cancer and transition to CVD and T2D. In our study, BMI was not included as a lifestyle factor, as has been done previously (38,39); instead, findings were adjusted or stratified by BMI. The rationale is that obesity is a known precursor to T2D, and weight loss has been proved to reduce the risk for T2D. We included sleep duration as a component of the HLI and found that moderate sleep duration was associated with a lower risk for CVD and T2D but was not significantly associated with CVD or T2D after the transition to cancer. A previous study showed that only moderate sleep duration could increase the risk for mortality in patients with cancer (40), but no studies have revealed an association between sleep duration and cardiometabolic disease in cancer patients.

STUDY LIMITATIONS. Strengths of the present study include the large general population, the study of both incident and prevalent cancer patients, as well as the longer-term follow-up and larger number of events.

Despite these strengths, several limitations of our study need to be considered. First, given the observational study design, conclusions regarding causality cannot be made. Second, HLI increased according to the number of healthy lifestyle factors, which might not fully consider that individual lifestyle components may have different effects on the risks of CVD and T2D. The role of each lifestyle factor, however, in the transition from healthy status to incident cancer and subsequent CVD and T2D was examined.

Third, healthy lifestyle factors were obtained only at baseline, and changes over time were not accounted for in this study. Future studies to examine the effect of the lifestyle trajectory on CVD and T2D in patients with cancer are warranted.

Finally, this sample was largely restricted to volunteers of European ancestry 40 to 70 years of age at baseline; therefore, further research is warranted to investigate the extent to which these findings can be generalized to other populations.

CONCLUSIONS

Our study provides evidence to support the hypothesis that a healthy lifestyle may mitigate the risk of transition from diagnosed cancer to subsequent CVD and T2D. These findings further support the current recommendation that cancer survivors should engage in healthy lifestyle practices to maintain a lower risk for CVD and T2D complications.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A healthy lifestyle was significantly associated with a decreased risk of transitioning from healthy status to cancer and from incident cancer to the subsequent development of CVD or T2D. Similarly, a healthy lifestyle was associated with lower risk for incident CVD and T2D in cancer survivors.

TRANSLATIONAL OUTLOOK: Prevention is an important element in tackling the challenge posed by the increase in cardiometabolic disease in cancer survivors. These findings further support the current recommendation that patients with cancer should engage in healthy lifestyle practices to maintain a lower risk for developing CVD and T2D.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.