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Cancer risk according to lifestyle risk score trajectories: a population-based cohort study

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BACKGROUND: While individual lifestyle behaviors have been associated with cancer risk, combined impact of these factors remains understudied. This research explores relationships between lifestyle risk score trajectories and cancer risk within the Korean population.

METHODS: A cohort of 3,451,189 cancer-free men and women who participated in a health examination between 2002 and 2003, provided by the National Health Insurance, was studied. Lifestyle risk score trajectories were determined using group-based trajectory modeling based on total score of four modifiable unhealthy behaviors: current smoking, heavy alcohol drinking, excess body weight, and physical inactivity repeatedly observed three times between 2002 and 2007. Scores ranged between 0 (low risk) and 8 (high risk). The Cox proportional hazards model was applied to examine the association between these trajectories and cancer incidence.

RESULTS: During the follow-up time (2008-2019), 312,075 cancer cases were identified. Among men, seven trajectories were identified, and trajectories of high lifestyle risk scores increased cancer risk of all cancer combined, cancer subgroupings, upper aero-digestive, stomach, colorectal, liver, gallbladder, pancreatic, lung, and bladder cancer, but inverse relation was observed for prostate cancer. Among women, four trajectory groups showed similar trends.

CONCLUSIONS: Maintaining a healthy lifestyle and avoiding unhealthy behaviors are essential for cancer prevention.

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BACKGROUND

Cancer represents a major public health and economic challenge in the 21st century. According to the International Agency for Research on Cancer (IARC) in 2022, cancer accounts for nearly one in six deaths worldwide (16.8%) and one in four deaths from non-communicable diseases (22.8%) [1]. In South Korea, cancer is the leading cause of death, responsible for 27.0% of all fatalities [2]. With a population of 51.8 million, Korea faced a substantial cancer burden in 2020, with approximately 144,000 new cases in men and 134,000 in women [2] (https://kostat.go.kr/). Although advancements in screening and treatment have reduced mortality for certain cancers, limited access to clinical interventions and existing technologies still affect cancer mortality rates, even in developed countries [3].

Over the past two decades, more than half of cancer cases could have been prevented through well-known preventative measures [4]. Modifiable risk factors such as tobacco smoking, alcohol consumption, sedentary lifestyles, unhealthy diets, obesity, and infectious agents significantly influence cancer incidence [4]. According to a recent study, 40% of cancer is attributable to potentially modifiable factors [5]. Research has consistently highlighted the benefits of healthy lifestyles on cancer-related outcomes, underscoring the importance of lifestyle modifications in cancer prevention [6]. However, most previous studies have focused on common cancer types, including colorectal [7–9], pancreatic [8, 10], lung [8, 9], postmenopausal endometrial [8], postmenopausal ovarian [8], and kidney cancer [8]. In addition, the effectiveness of these health behaviors varies across cancer types, with favorable outcomes seen in some cancers but not all cancers [6]. Therefore, extra studies involving larger populations are needed to comprehensively investigate the effects of these behaviors on specific cancer types.

Furthermore, while individuals tend to change in their lifestyle behaviors over time, most studies have assessed these behaviors at a single baseline, which may not accurately reflect their long-term lifestyle status and could lead to inaccurate estimates [11]. In addition, epidemiological studies have recently adopted trajectory analysis to identify behavioral patterns over time [12, 13]. Limited research has explored the relationship between lifestyle risk score trajectories and cancer development [9]. This approach enables us to track changes in lifestyle behaviors over time and assess their influence on cancer incidence. To address these limitations, this study aims to explore the relationships between combinations of lifestyle risk score and cancer risk in the Korean population.

METHODS

Study population

This study used data from a population-based cohort created by the National Health Insurance Service (NHIS) in South Korea. The NHIS is a

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compulsory health insurance system that includes all Korean residents and provides coverage for a wide range of health services [14]. Participants were advised to undergo comprehensive medical examinations [14].

Our analysis included data from 4,157,101 participants who attended the national health screening at least three times from 2002 to 2007. We excluded 88,510 people younger than 30 years, 10,491 deaths, 74,688 cancer cases, and 532,223 individuals with missing information on lifestyle behaviors during the 2002–2007 period. After these exclusions, a total of 3,451,189 eligible participants remained for analysis (Supplement Fig. 1).

Exposure and covariates

Lifestyle risk score. Information was collected over three biennial visits regarding four unhealthy lifestyle behaviors: current smoking, heavy drinking, excess body weight, and physical inactivity. Each behavior was categorized into three groups: 0 (ideal level), 1 (intermediate level), and 2 (poor level) (Table 1). The lifestyle risk score, ranging from 0 to 8, represents the total of the four scores, with higher values indicating greater unhealthy lifestyles.

Body weight categories included: (0) normal weight (<23.0 kg/m^2), (1) overweight and obese (23.0–29.9 kg/m^2), and (2) severity obese (≥30.0 kg/m^2) [15]. Tobacco smoking status was classified: (0) non-smoker, (1) former smoker, and (2) current smoker. Alcohol consumption was determined based on daily intake and categorized: (0) non-drinker (0 g/day), (1) light drinker (≤50.0 g/day), and (2) heavy drinker (>50.0 g/day) [16]. Physical activity levels were categorized by exercise frequency per week as: (0) regular (5–7 times/week), (1): sometimes (1–4 times/week), and (2): rarely (<1 time/week).

Covariates. Demographic information, including age, income level using health insurance premiums, Charlson Comorbidity Index (CCI), family history of cancer, and the existence of chronic viral hepatitis B or C infection, was gathered from the baseline of 2002–2003. CCI was treated as a continuous variable, while other covariates were categorized as follows: age (30–39, 40–49, 50–59, ≥60 years), income (5 quintiles), family history of cancer (yes or no), and chronic viral hepatitis B or C infections (yes or no).

Case ascertainment

Our outcome of interest was primary cancer incidence which includes all cancer combinations, cancer subgroupings (alcohol-, tobacco-, and obesity-related cancers), and specific cancer types. These were identified using claim data linked to the Korea Central Cancer Registry database, based on the International Classification of Diseases 10th Revision (ICD-10: C00-C97).

Alcohol-related cancers included colorectal cancer [C18–C20], female breast cancer [C50], upper aero-digestive (UADT) cancers ([C01–C10 without C08 = salivary gland], larynx [C32], pharynx [C11–C14], esophagus [C15]), and liver cancer [C22–C24] [17, 18].

Table 1. Criteria for four lifestyle behaviors.

Healthy lifestyle factor	Score	Interpretation of the score
Smoking status	0	Nonsmoker
	1	Former smoker: used to smoke in the past but quit now
	2	Current smoker
Alcohol consumption	0	Nondrinker
	1	Light drinker: ≤50 g per day
	2	Heavy drinker: >50 g per day
Physical activity	0	Regular: ≥5 times per week
	1	Sometimes: rarely or less than 4 times per week
	2	No exercise: never taking exercise
Healthy weight	0	Normal weight: <23.0 kg/m^2
	1	Overweight or obese: 23.0–29.9 kg/m^2
	2	Severity obese: ≥ 30.0 kg/m^2

Tobacco-related cancers included upper aero-digestive cancers ([C01–C10 without C08 = salivary gland], larynx [C32], pharynx [C11–C14], esophagus [C15]), liver [C22–C24], pancreas [C25], bladder [C67], kidney [C64, C65], cervix [C53], stomach [C16], trachea [C33], lung [C34], acute myeloid leukemia [C92], and colorectal [C18–C20] [18].

Obesity-related cancers included esophagus [C15], pancreas [C25], colorectal [C18-C20], breast [C50], endometrium [C54], kidney [C64, C65], thyroid [C73], and gallbladder [C23] [17].

Statistical methods

Trajectory analysis. Trajectory analysis has become a valuable tool in epidemiological research for identifying longitudinal changes over time [13]. Group-based trajectory modeling (GBTM) is often chosen by investigators due to its effectiveness, and simplicity [12]. In our study, we independently calculated lifestyle risk scores for the periods 2002–2003, 2004–2005, and 2006–2007. Trajectory was then determined using GBTM with the PROC TRAJ package in SAS version 9.4. To determine the optimal number of groups, we initially evaluated one-to-eight quadratic models for men and one-to-six quadratic models for women. Further increases in group numbers were avoided to prevent excessively small group memberships. The Bayesian Information Criterion (BIC) was used to determine the most favorable number of groups, considering model parsimony, distinct features, and group membership percentages (≥1%). A model with seven groups for men and four groups for women was selected according to predefined criteria (Supplement Tables 1 and 2).

The next step was to identify the functional forms of each group based on the significance (p-value < 0.05) in models with different polynomial degrees, starting with the quadratic polynomial. The final model for men included seven quadratic trajectories, whereas the model (2221) was chosen for women.

Men were divided into seven groups: (1) very low-stable (N = 122,457, 5.32%, mean lifestyle risk score at each wave = 1.5); (2) low-stable (N = 634,559, 27.59%, mean = 3); (3) moderate-stable (N = 682,877, 29.69%, mean = 4); (4) low-increase (N = 73,209, 3.18%, mean score increase from 3 to 5); (5) high-stable (N = 544,015, 23.65%, mean = 5); (6) high-decrease (N = 102,193, 4.44%, mean score decrease from 5 to 3); and (7) very high-stable (N = 140,946, 6.13%, mean = 5.7) (Supplement Fig. 2).

Women were divided into four groups: (1) very low-stable (N = 76,606, 6.66%, mean = 1; (2) low-stable (N = 614,213, 53.37%, mean = 2); (3) moderate-stable (N = 426,982, 37.10%, mean = 3; and (4) high-stable (N = 33,132, 2.88%, mean = 4) (Supplement Fig. 3).

The selected models were then evaluated for their accuracy using the average posterior probability of assignment (AvePP), odds of correct classification (OCC), and estimated group probabilities compared to the percentage of the population assigned to the group. In our study, all groups in both genders had AvePP exceeding 0.7 and OCC exceeding 5.0, indicating accurate group membership classification (Supplement Tables 3 and 4).

Cox proportional hazards models. Cox proportional hazards models were employed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer development across different lifestyle risk score trajectories. In both genders, the "very low-stable" group was used as the reference group. Censored cases included participants who passed away or were not experienced in the event between 2008 and 2019. The time-to-event was measured from January 01, 2008, to the date of cancer diagnosis, censoring, or the end of the observation period on 31 December 2019.

Age, income level, CCI, and family history of cancer were adjusted to account for potential confounders. Additionally, chronic viral hepatitis B and C (ICD-10: B18.*) was used to evaluate liver cancer. The Log-rank test was used to assess linear trends, and all models satisfied the assumption of proportional hazards.

Cox models were stratified based on age groups at baseline, employing a cutoff of 50 years, and were subsequently adjusted for covariates. This adjustment was applied to all cancers combined and cancer subgroupings for both genders, including female breast and reproductive-related cancers in women (i.e., ovary, endometrium, and cervical cancers).

To measure the contribution of individual lifestyle factors to the overall observed associations, we divided the population into two subgroups based on trajectory groups: never and ever engaged in unhealthy individual behavior. The "very low-stable" in the second subgroup was chosen as the reference group. This analysis was conducted only among men, as the female population was not sufficiently large for detailed analysis. Analysis of the Cox proportional hazards model was conducted using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Population characteristics at baseline and cancer incidence

During an average follow-up period of 11.3 years, our cohort comprised 3,451,189 participants (2,300,256 men and 1,150,933 women). The average age at baseline was 45.70 years (Standard deviation (SD) = 10.88). The mean BMI (kg/m^2) was 23.94 (SD = 18.51), with approximately 61.97% of the population classified as having excess body weight (BMI ≥ 23 kg/m^2). Physical activity levels were low, with more than half the participants (52.21%) reporting no engagement in physical activity. Nearly half of the population (46.70%) reported having rarely consumed alcohol, and approximately 57.10% of the participants were non-smokers at baseline. Additionally, 12.43% of participants reported a family history of cancer (Table 2). The characteristic of lifestyle risk score at baseline was shown in the Supplement Table 5.

Table 2. General characteristics of study participants at baseline (2002–2003).

Characteristics	Total (n = 3,451,189)		Men (n = 2,300,256)		Women (n = 1,150,933)	
	N	%	*N*	%	*N*	%
Age (year)						
30–39	1,131,226	32.78	901,996	39.21	229,230	19.92
40–49	1,876,735	54.38	772,953	33.60	424,926	36.92
50–59	354,417	10.27	391,640	17.03	287,216	24.96
60+	88,811	2.57	233,667	10.16	209,561	18.21
Mean ± SD	45.70 ± 10.88		44.12 ± 10.56		48.84 ± 10.82	
Income						
Missing	86,615	2.51	69,028	3.00	17,587	1.53
1st quintile	370,306	10.73	159,516	6.93	210,790	18.31
2nd quintile	409,406	11.86	237,661	10.33	171,745	14.92
3rd quintile	759,676	22.01	540,836	23.51	218,840	19.01
4th quintile	852,349	24.70	606,128	26.35	246,221	21.39
5th quintile	972,837	28.19	687,087	29.87	285,750	24.83
CCI						
0	3,447,588	99.9	2,297,399	99.88	1,150,189	99.94
1	3444	0.1	2729	0.12	715	0.06
≥2	157	0	128	0.01	29	0
Family history of cancer						
Missing	379,245	10.99	262,271	11.40	116,974	10.16
No	2,643,074	76.58	1,762,726	76.63	880,348	76.49
Yes	428,870	12.43	275,259	11.97	153,611	13.35
Alcohol drinking frequency						
Rarely drinking	1,611,842	46.70	680,662	29.59	931,180	80.91
2–3 times/month	729,777	21.15	584,453	25.41	145,324	12.63
1–2 times/week	762,107	22.08	703,123	30.57	58,984	5.12
3–4 times/week	244,731	7.09	235,246	10.23	9485	0.82
Almost everyday	102,732	2.98	96,772	4.21	5960	0.52
Smoking status						
Never smoker	1,970,780	57.10	850,565	36.98	1,120,215	97.33
Former smoker	398,007	11.53	387,004	16.82	11,003	0.96
Current smoker	1,082,402	31.36	1,062,687	46.20	19,715	1.71
Physical exercise frequency (time/week)						
None	1,801,881	52.21	1,033,919	44.95	767,962	66.73
1–2 times/week	1,014,855	29.41	811,116	35.26	203,739	17.70
3–4 times/week	367,079	10.64	277,622	12.07	89,457	7.77
5–6 times/week	86,495	2.51	61,076	2.66	25,419	2.21
Almost everyday	180,879	5.24	116,523	5.07	64,356	5.59
BMI (kg/m^2)						
<18.5	80,912	2.34	43,633	1.90	37,279	3.24
18.5–24.9	1,231,545	35.68	751,563	32.67	479,982	41.70
25.0-29.9	1,156,880	33.52	821,158	35.70	335,722	29.17
≥ 30	981,852	28.45	683,902	29.73	297,950	25.89
Mean ± SD	23.94 ± 18.51		24.12 ± 19.17		23.59 ± 17.12	

By 31 December 2019, 312,075 cancer cases have been reported. The most common cancers were stomach (15.51%), colorectal (11.96%), lung (10.03%), and thyroid (11.98%) (Supplement Table 6).

Cancer risks according to lifestyle risk score trajectories

During the follow-up period, 206,743 incident cancers were recorded in men. Compared to the very low-stable group, groups with higher lifestyle risk scores exhibited a dose-dependent increase in the risk of all cancers combined (p_{trend} <0.0001). The hazards ratios (HRs) and 95% CI were as follows: 1.103 [1.08–1.126] for low-stable; 1.266 [1.24–1.293] for moderate-stable; 1.355 [1.312–1.399] for low-increase; 1.436 [1.405–1.468] for high-stable; 1.436 [1.396–1.477] for high-decrease; and 1.530 [1.488–1.572] for very high-stable. Elevated risks were also significantly observed across all trajectories for cancer subgroupings, with the highest risk noted in tobacco-related cancers (17.5–93.5% increase), followed by alcohol-related cancers (15.6–75.7% increase), and obesity-related cancers (20.5–60.3% increase) (Fig. 1a). Significant positive associations were observed for cancers of the larynx, esophagus, stomach, colorectal, lung, oral, pharynx, liver, gallbladder, pancreatic, testis, kidney, and bladder. An inverse association was observed for prostate cancer across all trajectories (Fig. 2a and Supplement Table 7).

Among women, 105,332 new cancer cases were recorded during the follow-up period. These findings mirrored those of men, groups with higher lifestyle risk scores associated with increased risks of all cancers combined in a dose-dependent manner (p_{trend} <0.0001). The HRs and 95% CIs were: 1.045 [1.017–1.073] for low-stable; 1.079 [1.050–1.109] for moderate-stable; and 1.185 [1.133–1.239] for high-stable. Elevated risks were observed across all trajectories for cancer subgroupings, with the highest risk in tobacco-related cancers (HR = 1.427) in the high-stable group, followed by alcohol-related cancers (5.5–26.5% increase), and obesity-related cancers (5.3–11.4% increase) (Fig. 1b). For specific cancers in women, trajectories with higher lifestyle risk scores were significantly associated with stomach, colorectal, liver, gallbladder, pancreatic, lung, cervical, and thyroid cancers, as well as leukemia. An inverse association was observed for ovarian cancer in the low-stable group and non-Hodgkin lymphoma in both the low- and high-stable groups (Fig. 2b and Supplement Table 8).

Figure 3 and Supplement Table 9a–d illustrate the impact of excluding individual lifestyle factors from the overall risk scores on cancer incidence estimates across various subgroups in men. Men who never smoked or drank between 2002 and 2007 exhibited lower risks than those who engaged in these unhealthy behaviors, even within the same trajectory groups. Conversely, the risk of alcohol- and tobacco-related cancers was higher among men of normal weight, and inactive individuals showed a lower risk of all cancer types. By age groups, groups with higher lifestyle risk scores were associated with risk of all cancers and cancer subgroupings in men in both age groups. Specifically, among men younger than 50, risks increased by 14.3–57% for all cancers and 18.2–200% for cancer subgroupings. In men aged 50 and older, risks increased by 11.1–64.7% for all cancers and 17.0–208% for cancer subgroupings. Women in both age groups showed higher risks of all cancers, tobacco-, and alcohol-related cancers with higher lifestyle risk scores. Trajectories with higher lifestyle risk scores were associated with higher risks of obesity-related cancers in women aged 50 or younger, mostly pre-menopausal women, and endometrial cancer in women aged 50 or older, mostly post-menopausal. Pre-menopausal women in the high-stable group also had an increased cervical cancer risk compared with those in the reference group (very low-stable) (Supplement Tables 10 and 11).

DISCUSSION

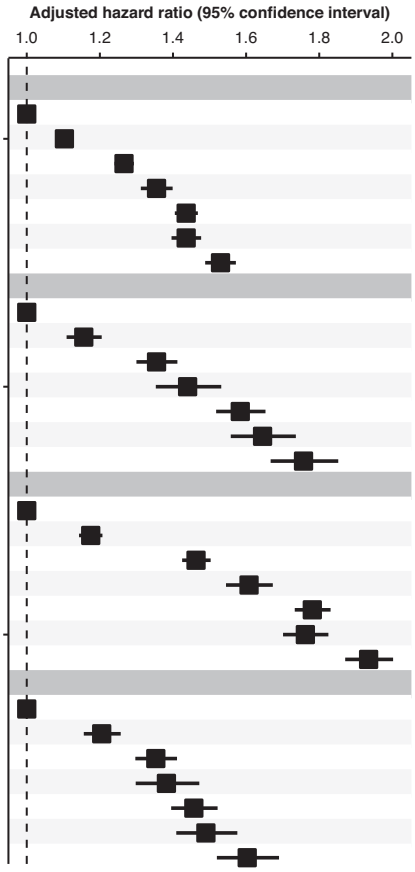
Our study employed trajectory analysis to explore changes in lifestyle risk scores across three time points from 2002 to 2007 in Korea. Although three waves of exposure measurement may not fully capture lifestyle behavior changes, the trajectory approach offers advantages over single-time measurements by reducing misclassification through repeated assessments (e.g., nonsmokers and former smokers). We identified distinct subgroups with varying lifestyle risk scores, such as the low-increase and high-decrease groups. Recognizing these changing trajectories is crucial for cancer prevention and highlights the health effects associated with lifestyle changes. In addition, compared to baseline classification, trajectory analysis more effectively demonstrates the association between lifestyle risk scores and cancer risk, specifically yielding higher magnitude estimates. This is because trajectory analysis captures the cumulative and evolving nature of lifestyle behaviors, offering a more comprehensive understanding of their impact on health outcomes (Supplement Figs. 5 and 6).

Our findings indicated an increased cancer risk associated with specific lifestyle risk score trajectories across various cancer types in both genders, consistent with previous research showing the protective effects of healthy lifestyles. One study found that adhering to the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) recommendations has been associated with reduced cancer risk, including components such as obesity, physical inactivity, an unhealthy diet, and alcohol consumption [19]. A meta-analysis examining the relationship between combined lifestyle factors and cancer incidence revealed that individuals with the healthiest lifestyles had a HR of 0.71 (95% CI: 0.66–0.76) for cancer incidence, compared to those with the least healthy lifestyles, based on 16 studies involving 1.9 million participants [20]. Furthermore, adopting the healthiest lifestyle was associated with a 17% to 58% reduction in the risk of various cancers, including bladder, breast, colon, endometrial, esophageal, kidney, liver, lung, rectal, and gastric cancers [20]. A Danish study reported an 11% reduction in colorectal cancer risk with each added healthy behavior, while a National Institutes of Health—the American Association of Retired Persons Diet and Health Study analysis showed a 58% decrease in pancreatic cancer risk with the highest healthy score [7, 10]. In Korea, a study using the same data source as ours (NHIS health examinee data from 2002 to 2018) found that men with steady light drinking, moderate smoking, low physical activity, and obesity had a 1.47 times higher cancer risk than healthy individual [9]. This study utilized GBTM to identify trajectories of each lifestyle behavior, and then used latent class analysis to combine these trajectories into subgroups [9]. Both methods help identify subgroups within the population that share similar features, rather than focusing on individual profiles. While trajectory analysis describes changes in exposure over time, latent class analysis identifies subgroups with shared characteristics at a given time. Compared to this two-step process, our approach is simpler in analysis and more straightforward in interpreting how lifestyle risks change over time. Additionally, the two-step method can pose challenges in accurately classifying individuals into subgroups in certain cases.

When dividing the population based on engagement in unhealthy lifestyle behaviors across the three waves, we gained insights into how these behaviors contribute to cancer risk. Compared to non-smokers, individuals with equivalent lifestyle risk scores but a history of smoking exhibited elevated cancer risks, highlighting the importance of tobacco cessation in mitigating cancer risk, even among those with high overall lifestyle risk scores. Similarly, non-drinkers showed notably lower cancer risks compared to those who had consumed alcohol at any point. Maintaining a normal BMI was associated with reduced risks of all cancers combined and obesity-related cancers. However, for alcohol- and tobacco-related cancers, risks were higher among participants with a normal BMI, implicating tobacco smoking, alcohol consumption, and physical inactivity as significant contributors to cancer risk. Likewise, physically active individuals had higher cancer risks compared to their inactive counterparts, suggesting that the influence of

a

Group	Case	aHR (95%CI)	*p*–trend
All cancers combined			
Very low–stable	12,442	Reference	<0.0001
Low–stable	59,171	1.103(1.080,1.126)	
Moderate–stable	60,937	1.266(1.240,1.293)	
Low–increase	6689	1.355(1.312,1.399)	
High–stable	45,651	1.436(1.405,1.468)	
High–decrease	10,084	1.436(1.396,1.477)	
Very high–stable	11,769	1.530(1.488,1.572)	
Alcohol–related cancers			
Very low–stable	3122	Reference	0.2433
Low–stable	15,692	1.156(1.109,1.205)	
Moderate–stable	16,692	1.355(1.300,1.412)	
Low–increase	1823	1.440(1.353,1.532)	
High–stable	12,900	1.584(1.518,1.653)	
High–decrease	2954	1.645(1.558,1.736)	
Very high–stable	3469	1.757(1.667,1.852)	
Tobacco–related cancers			
Very low–stable	7354	Reference	<0.0001
Low–stable	36,873	1.175(1.143,1.207)	
Moderate–stable	40,783	1.463(1.425,1.503)	
Low–increase	4598	1.608(1.545,1.673)	
High–stable	32,385	1.781(1.733,1.831)	
High–decrease	7183	1.762(1.701,1.825)	
Very high–stable	8512	1.935(1.871,2.002)	
Obesity–related cancers			
Very low–stable	2980	Reference	0.0017
Low–stable	16,073	1.205(1.156,1.257)	
Moderate–stable	17,181	1.353(1.297,1.411)	
Low–increase	1795	1.382(1.298,1.472)	
High–stable	12,975	1.457(1.395,1.522)	
High–decrease	2749	1.490(1.409,1.576)	
Very high–stable	3503	1.603(1.520,1.690)	



b

Group	Case	aHR (95%CI)	*p*–trend
All cancers combined			
Very low–stable	6730	Reference	<0.0001
Low–stable	54,908	1.045(1.017,1.073)	
Moderate–stable	40,345	1.079(1.050,1.109)	
High–stable	3349	1.185(1.133,1.239)	
Alcohol–related cancers			
Very low–stable	2038	Reference	<0.0001
Low–stable	17,053	1.055(1.005,1.108)	
Moderate–stable	12,683	1.106(1.052,1.163)	
High–stable	1102	1.265(1.169,1.368)	
Tobacco–related cancers			
Very low–stable	2416	Reference	<0.0001
Low–stable	20,245	1.066(1.019,1.115)	
Moderate–stable	16,646	1.128(1.078,1.181)	
High–stable	1580	1.427(1.333,1.527)	
Obesity–related cancers			
Very low–stable	3735	Reference	0.0032
Low–stable	30,504	1.053(1.015,1.092)	
Moderate–stable	21,469	1.093(1.053,1.134)	
High–stable	1679	1.114(1.048,1.185)	

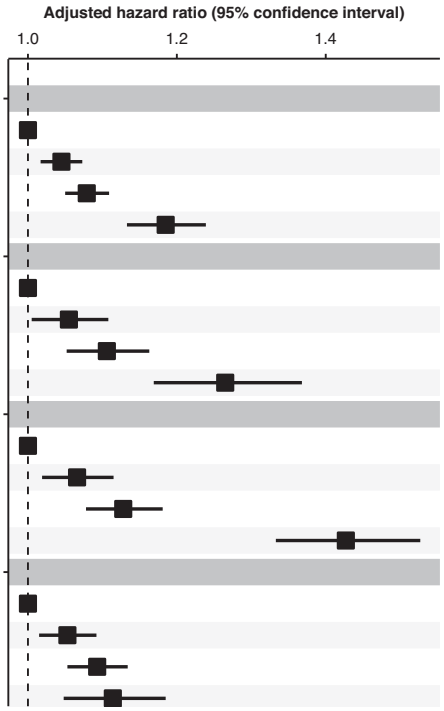


Fig. 1 **a** Adjusted HRs (95% CI) for the association between lifestyle risk score trajectories and the risk for all cancers combined and cancer subgroupings among men. **b** Adjusted HRs (95% CI) for the association between lifestyle risk score trajectories and the risk for all cancers combined and cancer subgroupings among women.

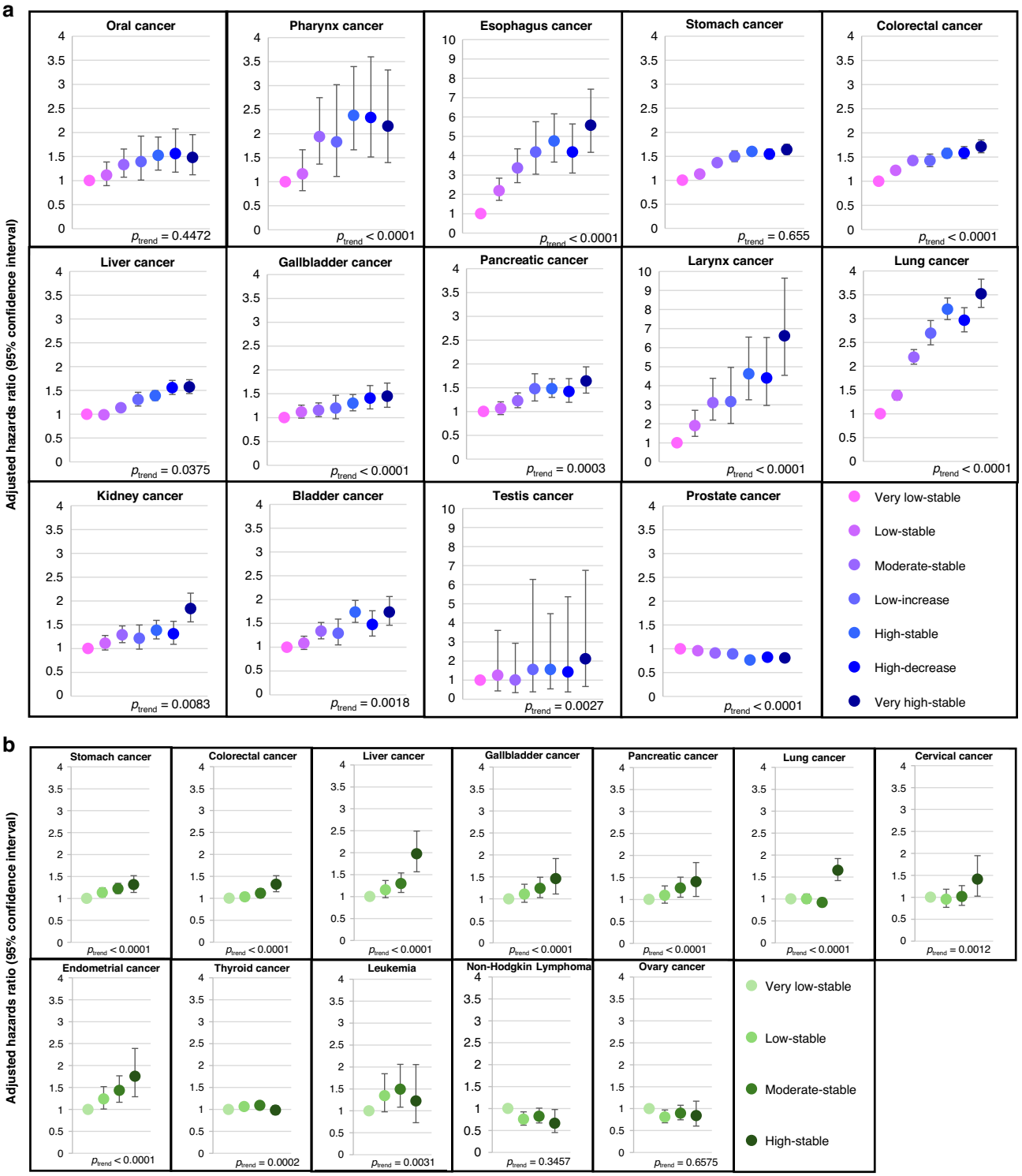


Fig. 2 **a** Adjusted HRs (95% CI) for the association between lifestyle risk score trajectories and the risk for specific cancer among men. **b** Adjusted HRs (95% CI) for the association between lifestyle risk score trajectories and the risk for specific cancer among women.

behaviors like smoking and drinking, maintaining a healthy weight may outweigh the protective effects of regular exercise. These findings underscore the importance of addressing multiple lifestyle factors in cancer prevention efforts, as evidenced by studies from the general population [21, 22].

Subgroup by age revealed different results in pre- and post-menopausal women. Our results showed an increased risk of obesity-related cancers in pre-menopausal women. A cross-sectional study in California showed a stronger association between obesity-related health conditions in younger individuals (20–39.9 years old), despite older individuals being more likely to be extremely obese [23]. Another study confirmed that obesity-related morbidities are more strongly associated with young and middle-aged populations than with older populations [24].

In women aged 50 or older, trajectories with higher lifestyle risk scores were associated with higher endometrial cancer risk.

	All cancer combined		Alcohol-related cancer		Tobacco-related cancer		Obesity-related cancer		
Very low-stable	**0.86**	1.00	**0.84**	1.00	**0.79**	1.00	0.96	1.00	Very low-stable
Low-stable	**0.92**	**1.06**	0.94	**1.09**	**0.87**	**1.13**	**1.15**	**1.18**	Low-stable
Moderate-stable	1.00	**1.15**	**1.10**	**1.20**	0.96	**1.28**	**1.39**	**1.29**	Moderate-stable
Low-increase	1.06	**1.21**	n/a	**1.24**	**1.17**	**1.35**	n/a	**1.33**	Low-increase
High-stable	1.11	**1.28**	**1.31**	**1.38**	1.14	**1.49**	**1.55**	**1.40**	High-stable
High-decrease	n/a	**1.28**	n/a	**1.43**	n/a	**1.48**	n/a	**1.44**	High-decrease
Very high-stable	n/a	**1.36**	n/a	**1.53**	n/a	**1.62**	n/a	**1.68**	Very high-stable
	Never smoker	Ever smoker	Never smoker	Ever smoker	Never smoker	Ever smoker	Never smoker	Ever smoker	

	All cancer combined		Alcohol-related cancer		Tobacco-related cancer		Obesity-related cancer		
Very low-stable	1.03	1.00	1.00	1.00	1.03	1.00	1.02	1.00	Very low-stable
Low-stable	**1.12**	**1.15**	**1.14**	**1.17**	**1.19**	**1.22**	**1.21**	**1.23**	Low-stable
Moderate-stable	**1.28**	**1.37**	**1.22**	**1.38**	**1.47**	**1.63**	**1.24**	**1.40**	Moderate-stable
Low-increase	**1.38**	**1.42**	**1.23**	**1.47**	**1.64**	**1.70**	1.16	**1.43**	Low-increase
High-stable	**1.46**	**1.55**	**1.36**	**1.60**	**1.81**	**1.90**	**1.45**	**1.48**	High-stable
High-decrease	**1.47**	**1.50**	**1.35**	**1.67**	**1.80**	**1.84**	**1.33**	**1.53**	High-decrease
Very high-stable	**1.44**	**1.57**	**1.62**	**1.76**	**1.98**	**1.94**	n/a	**1.63**	Very high-stable
	Never drinker	Ever drinker	Never drinker	Ever drinker	Never drinker	Ever drinker	Never drinker	Ever drinker	

	All cancer combined		Alcohol-related cancer		Tobacco-related cancer		Obesity-related cancer		
Very low-stable	**0.90**	1.00	**0.90**	1.00	**0.90**	1.00	**0.87**	1.00	Very low-stable
Low-stable	1.02	**1.04**	1.06	**1.10**	**1.15**	**1.08**	1.00	**1.15**	Low-stable
Moderate-stable	**1.17**	**1.25**	**1.33**	**1.25**	**1.59**	**1.31**	**1.09**	**1.29**	Moderate-stable
Low-increase	**1.24**	**1.35**	**1.50**	**1.30**	**1.69**	**1.45**	**1.22**	**1.28**	Low-increase
High-stable	**1.33**	**1.43**	**1.62**	**1.46**	**1.90**	**1.62**	**1.22**	**1.36**	High-stable
High-decrease	**1.33**	**1.42**	**1.72**	**1.50**	**1.84**	**1.61**	**1.31**	**1.38**	High-decrease
Very high-stable	**1.43**	**1.70**	n/a	**1.64**	**2.20**	**1.82**	n/a	**1.63**	Very high-stable
	Normal BMI	Ever abnormal BMI	Normal BMI	Ever abnormal BMI	Normal BMI	Ever abnormal BMI	Normal BMI	Ever abnormal BMI	

	All cancer combined		Alcohol-related cancer		Tobacco-related cancer		Obesity-related cancer		
Very low-stable	**1.11**	1.00	1.09	1.00	**1.11**	1.00	1.08	1.00	Very low-stable
Low-stable	**1.27**	**1.12**	**1.39**	**1.16**	**1.42**	**1.19**	**1.29**	**1.22**	Low-stable
Moderate-stable	**1.46**	**1.28**	**1.53**	**1.37**	**1.78**	**1.48**	**1.25**	**1.37**	Moderate-stable
Low-increase	n/a	**1.37**	n/a	**1.45**	n/a	**1.63**	n/a	**1.39**	Low-increase
High-stable	n/a	**1.46**	n/a	**1.60**	n/a	**1.81**	n/a	**1.47**	High-stable
High-decrease	n/a	**1.46**	n/a	**1.66**	n/a	**1.79**	n/a	**1.50**	High-decrease
Very high-stable	n/a	**1.55**	n/a	**1.78**	n/a	**1.96**	n/a	**1.62**	Very high-stable
	Active	Ever inactive	Active	Ever inactive	Active	Ever inactive	Active	Ever inactive	

Fig. 3 Relative risk of cancer incidence according to the lifestyle risk score trajectories in men after excluding, in turn, each lifestyle behavior: smoking, drinking, BMI and physical activity. n/a indicate cells with the number of cases smaller than 100. HR hazard ratio; BMI body mass index.

This finding suggests that the relationship between lifestyle behaviors and endometrial cancer risk may differ between older and younger women. Several studies have highlighted differences in endometrial cancer incidence between age groups. Several studies have shown that later age is predominantly associated with endometrial cancer [25–28]. A retrospective cohort study in China found that the percentage of endometrial cancer diagnosed was significantly higher in post- compared to pre-menopausal women [27]. In the United States, the decrease use of menopausal hormone therapy has been connected to a higher incidence of type 1 endometrial cancer in post-menopausal women [25]. Another study in the U.S. described that 75% of type 1 and 86% of type 2 endometrial cancers occurred in post-menopausal women, compared to only 18% of type 1 and 8.5% of type 2 endometrium cancer in pre-menopausal women [26]. This may be due to the cessation of estrogen and progesterone synthesis after

menopause, leading to hormonal imbalances that may result in the higher risk of endometrial cancer in post-menopausal women [29].

One intriguing result of our study was the inverse association between lifestyle risk score trajectories and prostate cancer risk, with a 20% decrease in risk (HR = 0.807) observed in the very-high stable group compared with the reference group. Several factors could explain this unexpected outcome. First, the higher risk group predominantly consisted of younger men (mean age 42.82 years at baseline), who generally have a lower incidence of prostate cancer, which typically manifests in older individuals, around 70 years of age according to our study (Supplement Fig. 4). Thus, younger men in the high-risk group might not have reached the age where prostate cancer is more common. In addition, maintaining a healthy lifestyle may be more common among health-conscious individuals, potentially leading to prolonged life expectancy and a higher likelihood of prostate cancer diagnosis later in life. Moreover, it is possible that due to more health-conscious behavior, including attending prostate cancer screening, men living a healthy lifestyle could be overrepresented among cases. Secondly, heavy drinkers often have moderate to severe health issues and exhibit lower levels of prostate-specific antigen (PSA) [30], reducing their chances of prostate cancer diagnosis, and severe health issues may cause death before the typical onset age for prostate cancer. Lastly, individuals diagnosed with chronic diseases often adopt healthier lifestyle practices, leading to misclassification where non-drinkers or non-smokers include former heavy drinkers or smokers, potentially skewing the results (i.e., sick quitter bias).

Our study has several strengths. This retrospective, population-based cohort study with an 11 follow-up year provided robust longitudinal data. We investigated various types of cancer using data from a national cohort of the Korean population. Additionally, linking the NHIS claims data with the National Cancer Registry data enhances the accuracy of cancer risk estimation. Furthermore, we utilized the GBTM technique to identify trajectories in lifestyle behaviors measured over six years, providing a deeper understanding of their changes over time.

Nevertheless, this study had some limitations. Firstly, apart from BMI index, smoking status, alcohol intake, and frequency of physical activity relied on self-reported data, which may have introduced misclassification. Secondly, the absence of information on dietary habits and adherence to healthy dietary guidelines restricted the ability to explore their influence on cancer risk. Given the recognized association between a healthy diet and reduced cancer risk from previous studies [31], further research should incorporate dietary and nutrition factors. Thirdly, our definition of exposure treated each lifestyle behavior equally, which may not be appropriate for assessing specific cancers (e.g., giving equal weight to smoking and physical activity in assessing lung cancer). Fourth, despite adjusting for key covariates, residual confounding factors could persist owing to data unavailability, such as infection-related variables like HPV for cervical cancer and *Helicobacter pylori* for stomach cancer. Fifthly, our study population included only participants who voluntarily attended the national health check-ups, potentially excluding those who did not participate. Sixthly, the 6-year period of measuring exposure was not long enough to capture significant lifestyle behavior changes. In addition, although trajectory analysis offers advantages, it may misclassify individuals since the model assigns group membership based on estimated probabilities.

In conclusion, our research examined the relationship between lifestyle risk score trajectories, which encompassed reductions in smoking and alcohol consumption, low BMI maintenance, moderate to high physical activity, and cancer risk in men and women. We found that a healthy lifestyle had a dose-dependent protective effect against all cancers combined, as well as tobacco-, alcohol-, and obesity-related cancers, in a dose-dependent manner for both genders. The risks of specific cancers such as upper aero-digestive, stomach, colorectal, gallbladder, pancreatic, lung, kidney, bladder, and testicular cancers were positively associated with trajectories that reflect unhealthy lifestyle behaviors, whereas an inverse relationship was observed for prostate cancer. In women, trajectories with lower lifestyle risk scores were associated with increased risks of stomach, colorectal, liver, gallbladder, pancreatic, lung, cervical, endometrial, thyroid, and leukemia cancers. Our findings underscore the importance of maintaining a healthy lifestyle over time in reducing cancer risk.

DATA AVAILABILITY

The data used in this study (NHIS-2022-1-785) were provided by the National Health Insurance Service. To protect personal information, data cannot be shared because the NHIS prohibits the transfer, rental, or sale of the database to third parties, except for researchers who have been approved for access. The NHIS data can be requested through the NHIS website (https://nhiss.nhis.or.kr).

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AUTHOR CONTRIBUTIONS

The contribution of the authors was as follows: Conceptualization: JKO, TMTK. Methodology: TMTK, TTB. Formal analysis: TMTK. Investigation: JKO, TMTK. Writing-original draft preparation: TMTK. Writing-review and editing: JKO, HYK, EP, MK, YJC, BK. All authors approved the final version of the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

CONSENT FOR PUBLICATION

Consent for publication is not applicable for this article.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study protocol was approved by the Institutional Review Board of the National Cancer Center, Korea (NCC2022-0180) and the Korea NHIS Medical Information Disclosure Committee (NHIS- 2022-2-185). As this study used anonymous secondary data, informed consent was waived. All methods were performed in accordance with the relevant guidelines and regulations.

ADDITIONAL INFORMATION

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