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Original Article

Adherence to Cancer Prevention Guidelines and Cancer Incidence and Mortality: A Population-Based Cohort Study

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Purpose This study aimed to estimate the risk of cancer incidence and mortality according to adherence to lifestyle-related cancer prevention guidelines.

Materials and Methods Men and women who participated in the general health screening program in 2002 and 2003 provided by the National Health Insurance Service were included (n=8,325,492). Self-reported smoking, alcohol consumption, and physical activity habits and directly measured body mass index were collected. The participants were followed up until the date of cancer onset or death or 31 December 2018. The Cox proportional hazard model was used to evaluate the hazard ratio (HR) for cancer incidence and mortality according to different combinations of lifestyle behaviors.

Results Only 6% of men and 15% of women engaged in healthy behavior at baseline, such as not smoking, not drinking alcohol, being moderately or highly physically active, and within a normal body mass index range. Compared to the best combination of healthy lifestyle behaviors, the weak and moderate associations with increased all cancer incidence (HR < 1.7) and mortality (HR < 2.5) were observed in those with heavy alcohol consumption and in former or current smokers. HRs of cancer mortality were significantly increased among current smokers in most combinations.

Conclusion Compared to full adherence to cancer prevention recommendations, unhealthy behaviors increase cancer risk. As few people meet these recommendations, there is a great opportunity for cancer prevention.

Key words Neoplasms, Prevention, Smoking, Alcohol, Body mass index, Physical activity, Republic of Korea

Introduction

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020. Tobacco use, alcohol consumption, unhealthy dietary patterns, physical inactivity, infectious agents, and air pollution are well-known risk factors of cancer. Approximately 40% of cancers are preventable by avoiding risk factors and implementing existing evidence-based prevention strategies [1]. Primary prevention has the greatest public health potential and is the most cost-effective long-term way to reduce the growing burden of cancer. Successful cancer prevention requires a combination of individual action (avoiding or reducing harmful exposures) and group action (eliminating or reducing exposures by population-level measures) [2]. Individuals need to understand the relevant evidence to successfully reduce their cancer risk. Several health agencies provide cancer prevention guidelines to encourage people to avoid or reduce harmful exposures, including the Cancer Prevention Recommendations by the World Cancer Research Fund in collaboration with the American Institute for Cancer Research (WCRF/AICR) [3], American Cancer Society (ACS) Guidelines for Cancer Prevention [4], and the European Code against Cancer [2].

Several studies have examined the relationship between adherence to cancer prevention guidelines and cancer incidence and mortality. Adherence to the WCRF/AICR recommendations was associated with reduced risk of total cancer and some specific cancers [5]. Compliance with the ACS guidelines was associated with a reduction in overall and some specific cancer incidence and mortality rates [6,7]. However, most of the studies involved individuals from the U.S. or Europe, but not an Asian population.

Cancer is the leading cause of death in the Republic of Korea (Korea), accounting for 26.5% of all deaths, followed by heart disease, cerebrovascular disease, and pneumonia. In 2018, age-standardized cancer incidence and mortality rates were 270.4 and 73.3 per 100,000, respectively [8]. The Korean Cancer Society first published recommendations on cancer prevention in Korea in 1991 [9]. It recommends 15 ways to prevent cancer, including: maintaining a healthy diet, limit-

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ing alcohol consumption, do not smoke, avoiding too much sun, engaging in physical activity, maintaining a healthy body weight, avoiding psychological stress and maintaining personal hygiene. In addition, the National Codes against Cancer is a set of recommendations providing advice on cancer prevention to public. In collaboration with academic societies, its first edition was developed by the National Cancer Center and published by the Korea Ministry of Health and Welfare in 2006 [10]. It lists 10 recommendations on the adoption of healthier lifestyles to improve general health and prevent cancer: do not smoke, maintaining a healthy diet, limiting alcohol consumption, engaging in physical activity, maintaining a healthy body weight, receiving the hepatitis B virus vaccine, following safety measures to avoid cancer-causing agents in the workplace, and engaging in regular cancer screening. Its second edition, published in 2016 [11], strongly recommends avoiding alcohol consumption and recommends the human papillomavirus (HPV) vaccination (S1 Fig.). Several studies have examined the relationship between combined unhealthy lifestyle behaviors and cancer mortality in Korea [12,13]. However, this research only examined overall cancer mortality, not cancer-specific mortality or cancer incidence.

In this study, we examined type-specific cancer incidence and mortality according to adherence to cancer prevention guidelines focusing on smoking, alcohol consumption, physical activity, and body weight.

Materials and Methods

1. Data sources and study population

Data collected by the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) between 2002 and 2018 were used for this study. NHIS is a mandatory single-payer insurance that provides benefits for medical services. This service provides free general health screening programs to all insured adults biennially. The NHIS-HEALS database contains demographic information, diagnoses, date of death, and information from health examinations, such as health questionnaire surveys, physical examinations, and biochemical test results [14].

Men and women who participated in the NHIS general health screening program in 2002 and 2003 were included in this study (n=8,968,212). To construct a cancer-free cohort, anyone ever diagnosed with cancer (i.e., ICD-10, an International Classification of Diseases-10th revision, code corresponding to cancer [C00-C99], n=208,912) or who died from cancer (n=1,021) between 2002 and 2004 were removed. After excluding those with missing age and sex data (n=42,638), those under 20 years of age (n=28,838), cases in which there was an error in the death date (n=573), and cases missing smoking, alcohol consumption, body weight, or physical activity information (n=360,738), a total of 8,325,492 cohort members were included in the final analysis (Fig. 1).

As this study used anonymous secondary data, it was exempt from review by the Institutional Review Board of the National Cancer Center, Korea (NCC2018-0279). This study generally follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for data organization, procedures, and interpretation in cohort studies.

2. Information on lifestyle behaviors

Adherence to cancer prevention guidelines was measured based on lifestyle information obtained from the national health screening program. During the health examination, data regarding self-reported smoking habits, alcohol consumption, and physical activity levels were collected through a structured questionnaire. Body mass index (BMI) was calculated using body weight and height, which are directly measured in health examinations using standardized techniques and equipment. Each behavior was categorized into three groups. Smoking was categorized as never (0), former (1), and current smoker (2). Pure alcohol grams per day were calculated using self-reported average drinking frequency and alcohol consumed per occasion in relation to Korea's most popular alcohol beverage "soju," which has an alcohol content of 20% [15]. Alcohol consumption was categorized into three groups using grams of alcohol per day [16]: 0, no drinking (0 g/day); 1, moderate drinking (≤ 50.0 g/day); 2, heavy drinking (> 50.0 g/day). Physical activity was categorized according to exercise frequency: 0, very active (five or more times a week); 1, moderate exercise (one to four times per week); 2, inactive (less than once a week). Bodyweight was categorized using BMI: 0, normal weight (< 23.0 kg/m^2); 1, overweight (23.0-24.9 kg/m^2); 2, obese (≥ 25.0 kg/m^2) according to the World Health Organization obesity standards for an Asian population. We had 81 combinations (three groups in the four behaviors categories) in a cancer risk matrix (Table 1).

3. Follow-up and cancer diagnosis

The participants were followed up from 1 January 2002 until the date of cancer onset, death, or 31 December 2018, whichever came first. The ICD-10 codes corresponding to cancer (C00-C99) combined with a special code for cancer claims (V193, V194, and V027) were used to identify cancer occurrence during the follow-up period. In the claims data, these special codes indicated a confirmed cancer diagnosis for expanded benefit coverage. Cancer death was ascertained using the cause of death (ICD-10: C00-C99) data provided by

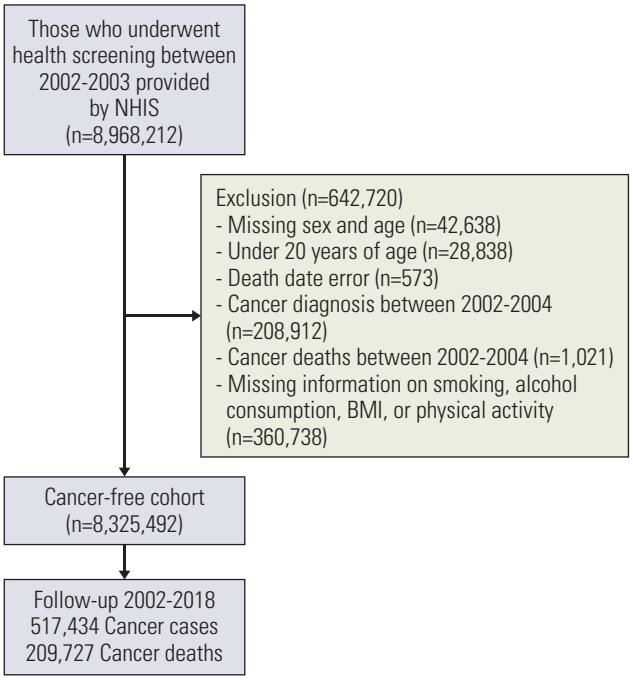


Fig. 1. Study flow diagram: selection of the study population and cancer outcomes. BMI, body mass index; NHIS, National Health Insurance System.

Statistics Korea.

4. Statistical analysis

We used Cox proportional hazard models to evaluate the hazard ratio (HR) for cancer incidence and mortality according to different combinations of four lifestyle behaviors. HRs of all and site-specific cancer incidence and mortality were adjusted for age and sex. The HR of liver cancer was adjusted for chronic viral hepatitis (ICD-10: B18). HRs were considered statistically significant when the associated 95% confidence intervals (CIs) did not include unity, corresponding to a statistical test on the two-sided 5% significance level. Full adherence to cancer prevention guidelines was indicated by healthy lifestyle combinations (i.e., never smoker, nondrinking, physically very active, and normal weight). This combination was used as a reference group for estimating relative risks. Eighty hypothesized predictors were tested against one reference combination, a Bonferroni-adjusted significance level of 0.000625 was calculated to account for the increased possibility of type-I error [17]. The statistical package SAS enterprise guide ver. 7.1 (SAS Institute Inc., Cary, NC) was used to perform the analyses. For reporting effect size, we used five categories of HRs adapted from the published literature [18]: none HR, 0.9 to 1.19; weak HR, 0.7 to 0.9 or 1.2 to < 1.5; moderate HR, 0.4 to < 0.7 or 1.5 to < 3.0; strong HR, 0.2 to < 0.4 or 3.0 to < 7.0; very strong HR, ≤ 0.2 or ≥ 7. The color of each cell in tables indicates the effect size (darker red indicates stronger HR).

Table 1. Matrix components and criteria for four lifestyle behaviors

Criteria	Group
Do not smoke	
Never	0
Former	1
Current	2
Limit alcohol consumption (g/day)	
0	0
≤ 50	1
> 50	2
Be physically active (frequency per week)	
≥ 5	0
1-4	1
< 1	2
Maintain healthy weight (body mass index, kg/m²)	
< 23.0	0
23.0-24.9	1
≥ 25.0	2

Results

Table 2 shows the general characteristics of the study subjects at baseline measured between 2002 and 2003. The participants were largely male (60.1%) with a mean age of 44.0 (standard deviation, ±13.6) years old. Among men, the proportions of never smoking, nondrinking, physically very active (≥ 5 times a week), normal body weight (BMI < 23) subjects were 35.7%, 30.0%, 7.7%, and 39.0%, respectively. More than one-third (38.5%) of men were current smokers with moderate alcohol drinking levels (S2A Fig.). Women had healthier profiles compared to men. The proportions of never smoking, nondrinking, physically very active, and normal body weight females were 95.6%, 74.6%, 7.0%, and 52.5%, respectively. Most women (72.7%) were nonsmokers and nondrinkers (S2B Fig.). Only 0.5% of men and 2.0% of women had a healthy lifestyle (nonsmoking or quit smoking, nondrinking, physically very active, and normal weight).

During 16 years of follow-up, 517,434 incident cancer cases and 209,727 cancer deaths were observed (Fig. 1). The most common cancer types were stomach, colorectum, lung, and liver (S3 Table). Fig. 2 shows the age and sex-adjusted HRs of cancer incidence according to 81 combinations of adherence to cancer prevention guidelines. Compared to the healthiest lifestyle (the combination of never smoking, no consumption

Table 2. General characteristics of the study population at baseline in 2002-2003

	Men (n=5,007,393)	Women (n=3,318,099)
Age (yr)		
20-39	2,262,087 (45.2)	1,047,836 (31.6)
40-64	2,415,269 (48.2)	1,895,236 (57.1)
≥ 65	330,037 (6.6)	375,027 (11.3)
Income level		
High (Q4)	1,632,288 (32.6)	883,234 (26.6)
Middle high (Q3)	1,440,544 (28.8)	765,250 (23.1)
Middle low (Q2)	1,162,550 (23.2)	809,340 (24.4)
Low (Q1)	772,011 (15.4)	860,275 (26.0)
Tobacco smoking		
Never	1,787,052 (35.7)	3,170,854 (95.6)
Former smoker	737,427 (14.7)	48,344 (1.5)
Current smoker	2,482,914 (49.6)	98,901 (3.0)
Alcohol consumption (ethanol gram/day)		
0	1,500,807 (30.0)	2,473,794 (74.6)
≤ 50	3,373,001 (67.4)	840,530 (25.3)
> 50	133,585 (2.7)	3,775 (0.1)
Frequency of physical activity		
None	2,403,537 (48.0)	2,287,969 (69.0)
1-4 times per week	2,220,982 (44.4)	799,241 (24.1)
≥ 5 times per week	382,874 (7.7)	230,889 (7.0)
Body mass index (kg/m^2)		
< 23.0	1,950,293 (39.0)	1,742,768 (52.6)
23.0-24.9	1,345,694 (26.9)	717,850 (21.6)
≥ 25.0	1,711,406 (34.2)	857,481 (25.8)
Fasting blood sugar (mg/dL)		
< 100	3,586,268 (71.6)	2,587,464 (78.0)
100-126	1,107,700 (22.1)	578,294 (17.4)
≥ 126	309,278 (6.2)	148,061 (4.5)
Total cholesterol (mg/dL)		
< 200	2,928,819 (58.5)	1,971,217 (59.4)
200-240	1,519,677 (30.4)	944,052 (28.5)
≥ 240	552,339 (11.0)	396,452 (12.0)
Charlson's comorbidity index		
≥ 1	63,208 (1.3)	40,228 (1.2)

Values are presented as number (%). The number of subgroups varies due to missing values for each variable.

of alcohol, normal BMI and physically very active), HRs for all cancer were significantly elevated among heavy alcohol drinkers regardless of smoking status. Among heavy drinkers, increased risks were observed in both physically very active and active groups, regardless of BMI. Former and current smokers had higher risk of all cancer even without alcohol consumption. The combination of current smoking and heavy alcohol drinking further increased cancer risk. For example, the highest HRs (1.69 and 1.62) were observed in subjects who were former or current smokers, heavy alcohol drinkers, a normal body weight, and physically very active or inactive. The combination of quitting smoking, drinking alcohol moderately, being moderately active, and having a normal weight had a lower risk of all cancer incidence (HR, 0.88). For cancer-specific, esophageal and liver cancer risk significantly increased with alcohol consumption. Smoking significantly increased lung cancer risk regardless of alcohol drinking and physical activity patterns and body weight.

In an age- and sex-specific subgroup analysis, an increased risk of cancer was observed in former or current smokers who were obese among young men (aged < 40 years). Among middle-aged men (aged 40-64), never or quitting smoking in combination with not drinking alcohol heavily and moderate or less physically active revealed a reduction

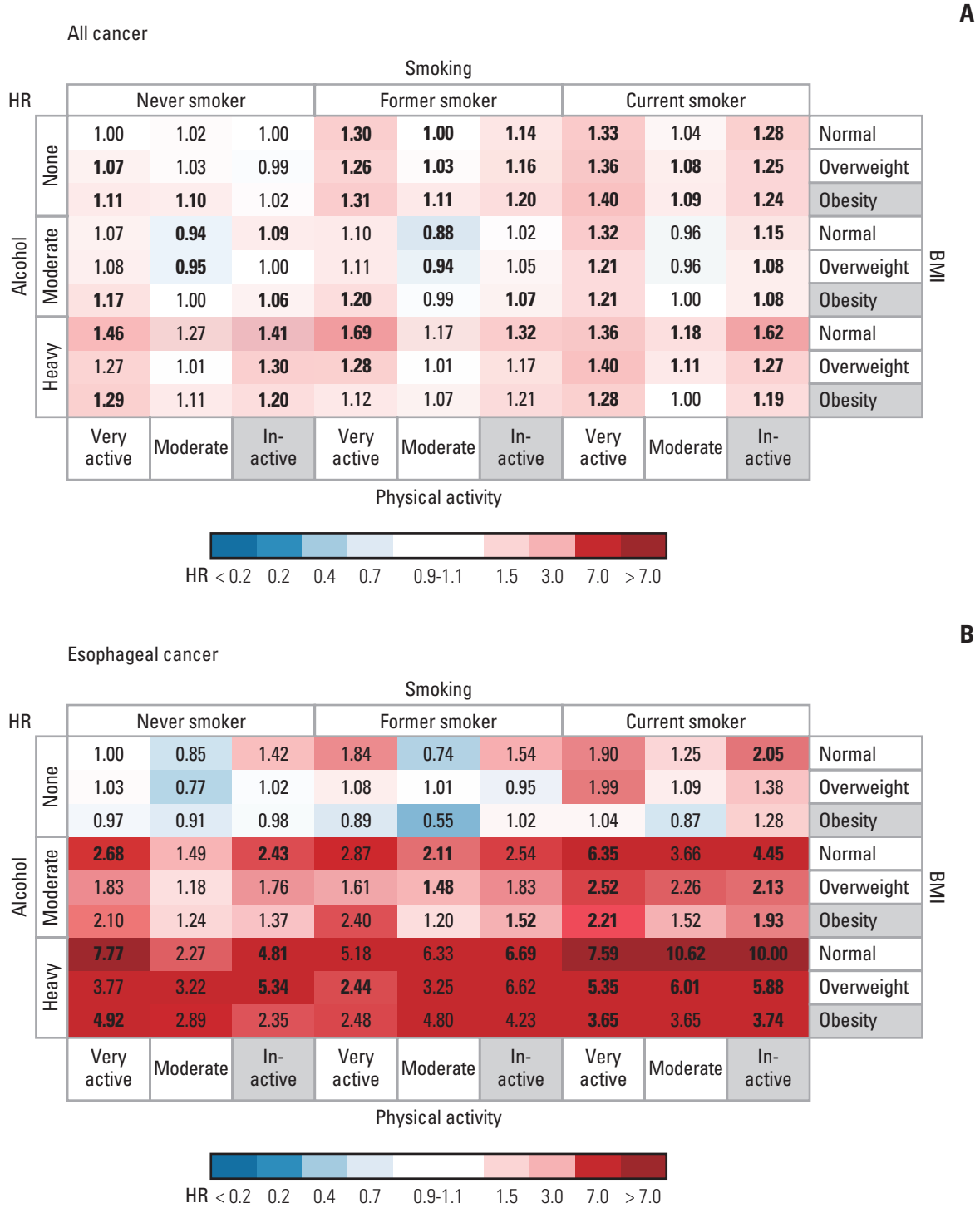
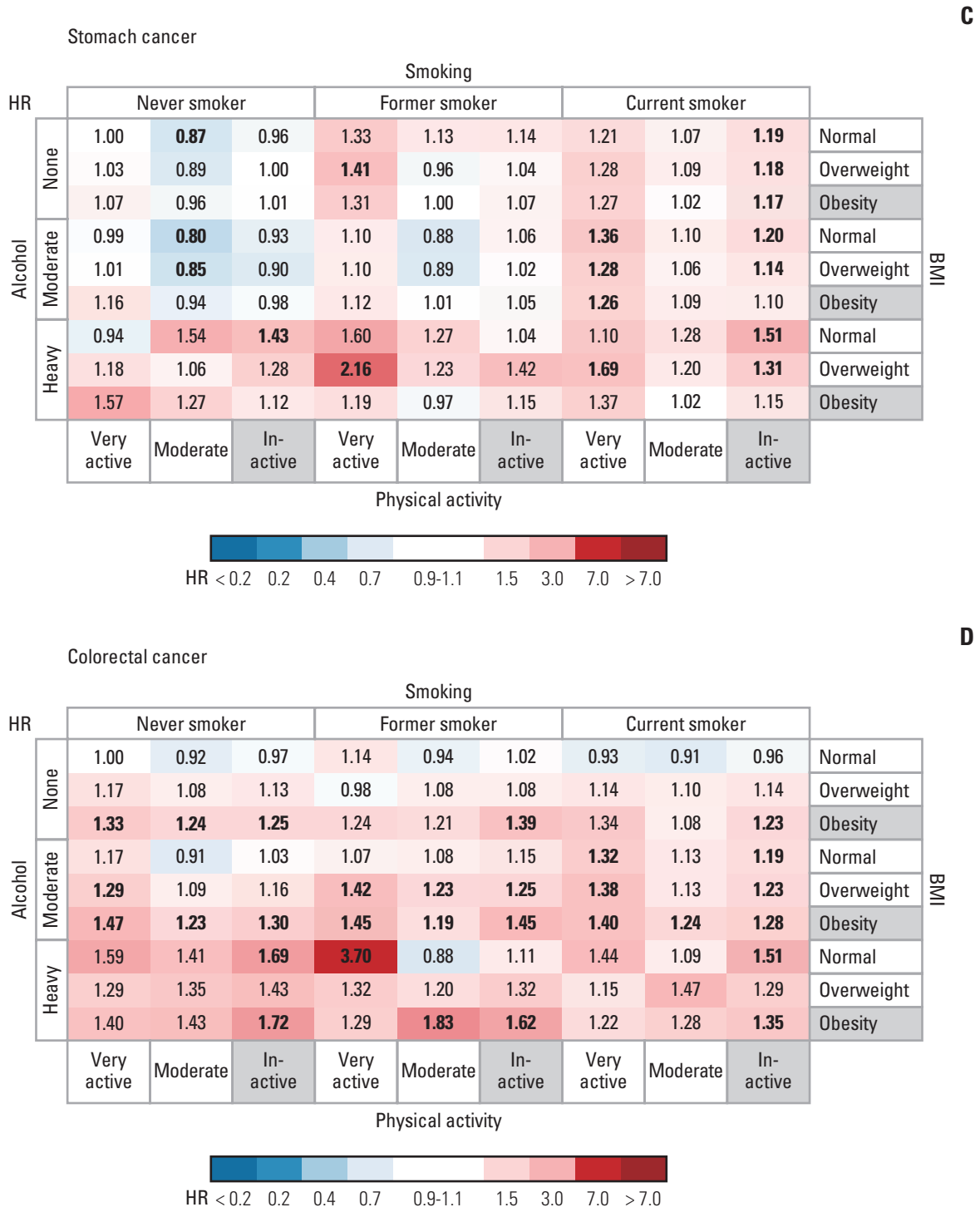


Fig. 2. (A-G) Relative risks of cancer incidence according to 81 combinations of adherence to cancer prevention guidelines. Smoking: 0, never; 1, former; 2, current smoker. Alcohol consumption: 0, nondrinking (0 g/day); 1, moderate drinking (≤ 50 g/day); 2, heavy drinking (> 50 g/day). Physical activity: 0, very active (5 or more times per week); 1, moderate (1-4 times per week); 2, inactive (< 1 time per week). Body mass index (BMI): 0, normal weight (< 23.0 kg/m^2); 1, overweight (23.0-24.9 kg/m^2); 2, obese (≥ 25.0 kg/m^2). Reference group: full adherence to a healthy lifestyle (combination of never smoking, no consumption of alcohol, normal BMI and physically very active). Adjusted for age, sex, and (for liver cancer) chronic hepatitis. Bold fonts indicate statistically significant according to a Bonferroni-adjusted significance level of 0.000625. Gray and italic fonts indicate cells with an insufficient number of cases. HR, hazard ratio. *(Continued to the next page)*



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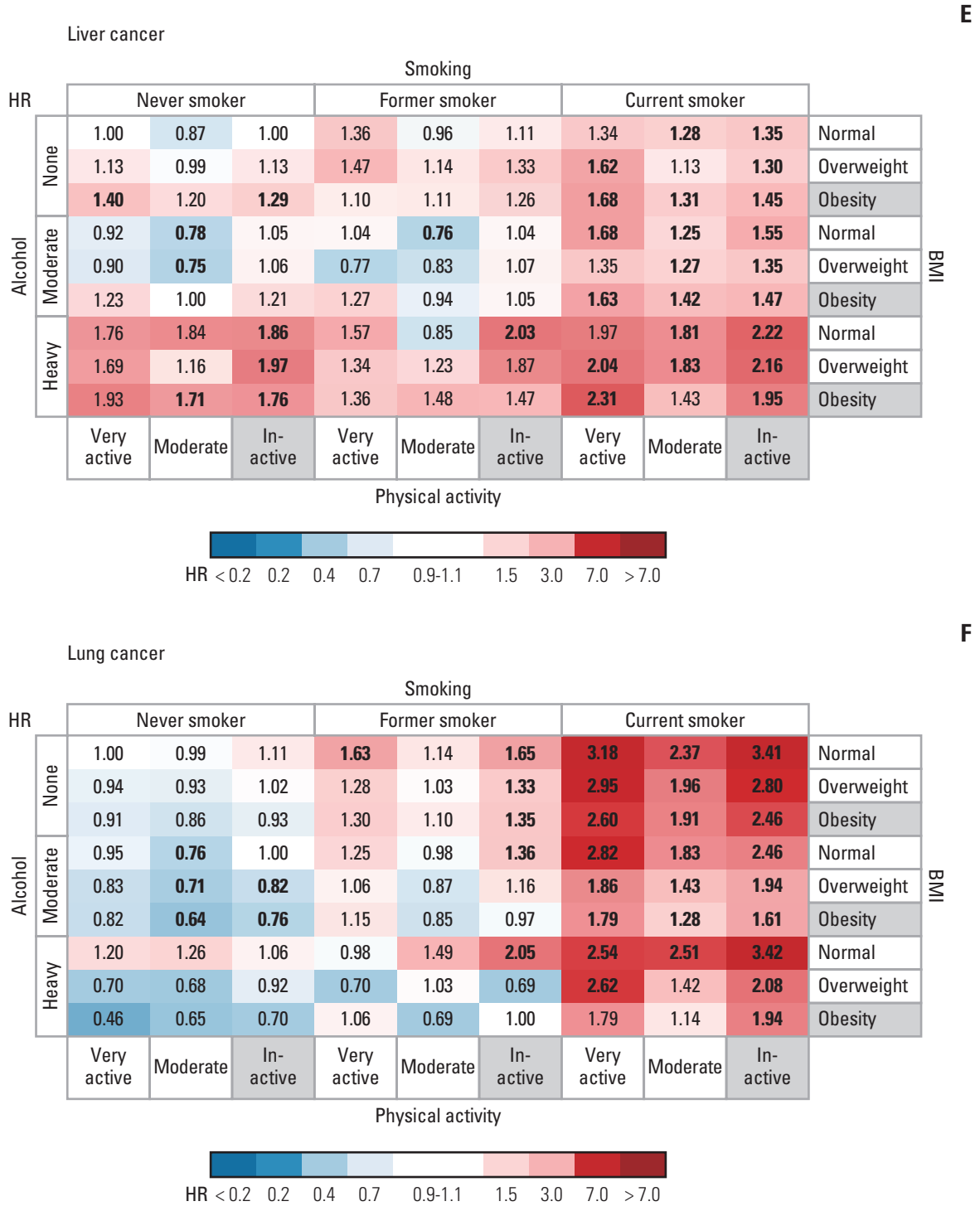
in cancer risk while an increased risk was observed among current smokers who were physically very active. An increased risk was observed in men aged over 65 who were current smokers and heavy drinkers. Among women, an increased risk was observed in current smokers who did not drink alcohol in middle- or old aged groups but not in the young group (S4 Fig.).

A similar pattern was observed for cancer mortality. Fig.



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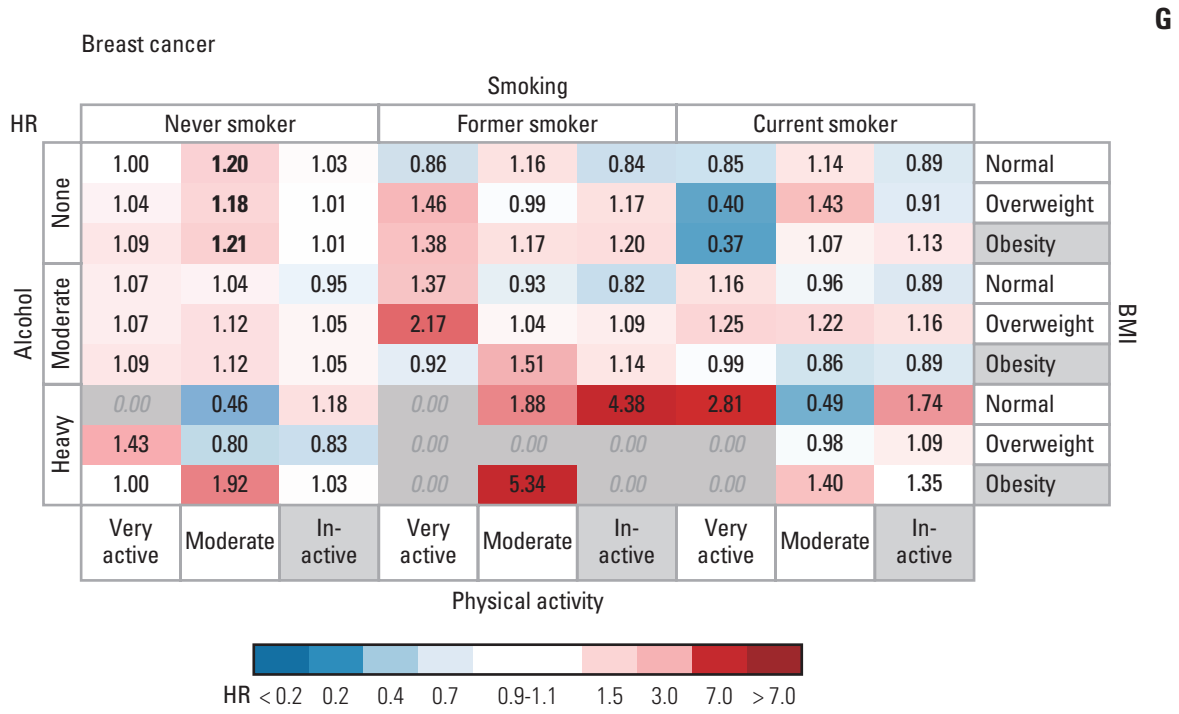
3 shows the HRs of all cancer mortality according to 81 lifestyle behavior combinations. Compared to the healthiest combination, HRs of cancer mortality were significantly increased among current smokers in every combination except current smokers who consumed alcohol moderately, were moderately physically active and overweighted. The highest HRs (2.29-2.48) were observed in current smokers who were heavy drinkers. Moderately physically active



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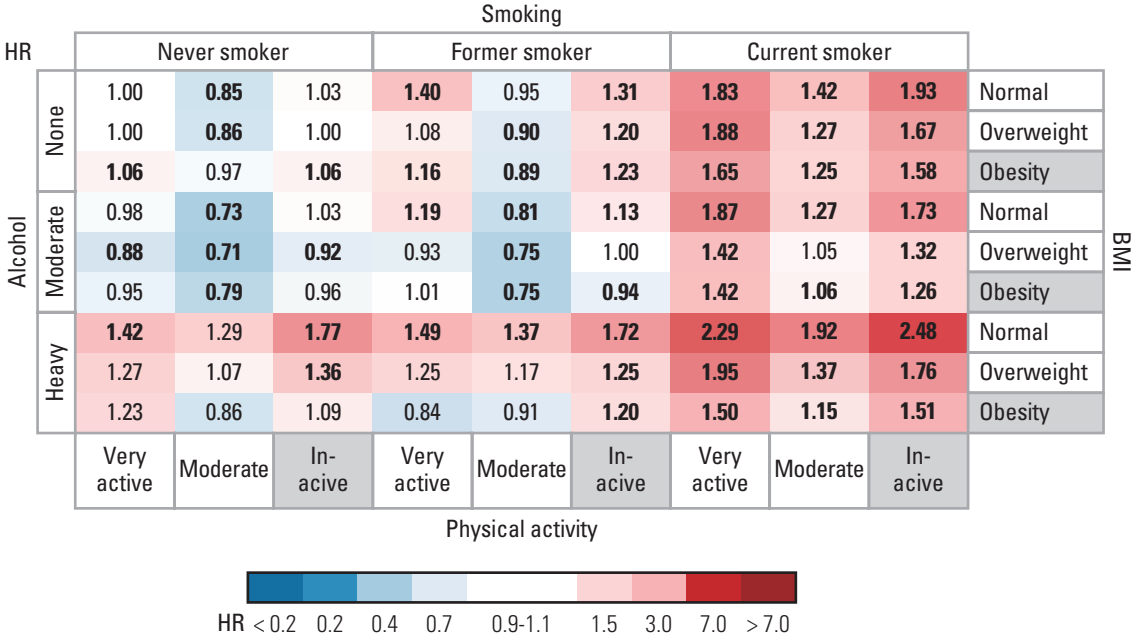

Fig. 3. Relative risks of all cancer mortality according to 81 combinations of adherence to cancer prevention guidelines. Smoking: never, former, current smoker. Alcohol consumption: 0 g/day, nondrinking; ≤ 50 g/day, moderate drinking; > 50 g/day, heavy drinking. Physical activity: very active, 5 or more time a week; moderate, 1-4 times per week; inactive, < 1 time per week. Body mass index (BMI): normal weight, < 23.0 kg/m^2; overweight, 23.0-24.9 kg/m^2; obesity, ≥ 25.0 kg/m^2. Reference group: full adherence to a healthy lifestyle (combination of never smoking, no consumption of alcohol, normal BMI and physically very active). Adjusted for age and sex. Bold fonts indicate statistically significant according to a Bonferroni-adjusted significance level of 0.000625. HR, hazard ratio.

nonsmokers and former smokers who did not drink alcohol heavily had a lower risk of cancer death (HRs < 0.9) compared to the reference group.

Discussion

Cancer prevention recommendations in Korea were first published in 1991 by the Korean Cancer Society [9]. National recommendations on cancer prevention was published in 2006 by the Ministry of Health and Welfare (S5 Table) [10]. Cancer prevention campaigns led by the government, community, and academic societies have been conducted. For example, through an annual event commemorating Cancer Prevention Day (March 21, enacted in 2006), awareness of cancer prevention has been promoted to the public. Celebrities appointed as cancer prevention ambassadors also participated in the media campaigns. Detailed information and guidelines on cancer prevention are provided throughout the year through the National Cancer Information Center (http://www.cancer.go.kr) and various media channels. Through those efforts, the awareness of 'cancer is preventable' among the general population improved from 50.3% in 2007 to 66.8% in 2016 [19].

In our study, we found a weakly increased cancer incidence (HR < 1.7) and a moderately increased mortality (HR < 2.5) in individuals who heavily consumed alcohol and were former or current smokers compared to those who had healthy lifestyle behaviors. Lifestyle behaviors are closely related to an increase or decrease in cancer risk. Several health authorities provide cancer prevention guidelines, including no smoking, no drinking alcohol, being physically active, and maintaining a normal body weight (WCRF/AICR) [2-4]. Some research has found that adherence to these recommendations was associated with a reduced risk of cancer [5-7].

For example, a prospective cohort study in the United States which constructed a five-level scoring system to measure adherence to ACS guidelines, including BMI, physical activity, alcohol intake, and diet, found that increased adherence was associated with a reduced risk of all cancers, 14 specific cancer sites, and cancer mortality [6]. A Swedish cohort study also found that adherence to WCRF/AICR recommendations substantially reduced cancer risk. However, this study found that many people do not meet the recommendations [5]. A meta-analysis found that high adherence to diet and physical activity guidelines is consistently associated with reduced risk of all cancer incidence and mortality and for some site-specific cancers [7].

In Korea, a hospital-based cohort study found that combined unhealthy lifestyle factors, including smoking, heavy alcohol consumption, obesity, and a lack of physical activity, increased risk of all-cause and cancer mortality to twice that of a healthy lifestyle [13]. A more recent study found that unhealthy behaviors were associated with an increased risk of total and cardiovascular mortality, but not cancer mortality [12]. Those studies used a binary score for each lifestyle factor. For example, participants received one point each for current smoking, heavy alcohol consumption, obesity, and being physically inactive. Otherwise, they received zero points for each factor. Those studies included former smokers, light or moderate alcohol drinkers, overweight individuals (i.e., BMI between 20-23 kg/m^2), and those who engage in physical activity less than three times per week as a reference group [12,13].

In our study, we examined the relative cancer risk according to adherence to guidelines regarding four lifestyle factors (i.e., smoking, alcohol consumption, physical activity, and body weight). We used three levels for each factor, but no scoring system. A standardized scoring system was developed to examine the adherence to the WCRF/AICR recommendations concerning cancer risk [20]. The standardized WCRF/AICR 2018 score ranges from 0 (no adherence) to 7 (full adherence) for seven components: healthy weight, physical activity levels, fruit and vegetable/fiber intake, fat/starches/sugar and fast-food consumption, red and processed meat consumption, sugary drink consumption, and alcohol consumption. A simplified version was developed ranging from 0 to 8 for the seven components and dietary supplement use [5]. One of the limitations of the scoring system is that it weighs each recommendation equally [20]. It is unclear whether the weighting should be equal within the components (for example, giving equal weight to smoking and physical activity.) Future studies are needed to develop a valid scoring system to examine the impact of adherence to cancer prevention guidelines in Korea.

Tobacco smoking is one of the most well-known risk factors for cancer. Smoking is responsible for 11.8% of cancer incidence and 22.7% of cancer deaths in Korea [21]. The smoking rate for Korean males is relatively high compared to that of other developed countries, despite a decline from 66.3% in 1998 to 36.7% in 2018 [22]. We observed that current and former smokers have a higher risk of cancer compared to nonsmokers, which is consistently observed regardless of alcohol consumption, physical activity levels, and BMI, especially among men aged 65 or older. Quitting smoking at a young age reduces cancer risk (S4B Fig.).

Alcohol consumption increases the risk of cancer of the oral cavity, pharynx, esophagus, colorectum, liver, larynx, and female breast [3]. In our study, strong and very strong associations were observed, especially in esophageal cancer. Alcoholic beverages are widely consumed in Korea. Annual alcohol consumption in Korea was 8.7 liters of pure alcohol

per capita in 2018 [23]. Among adults, 70.5% of men and 51.2% of women drink alcohol at least once a month [22]. It has been estimated that 3.0% and 0.5% of cancer incident cases among Korean men and women, respectively, are attributable to alcohol consumption [24].

A meta-analysis including 222 articles comprising more than 92,000 light drinkers (up to one drink per day) and 60,000 nondrinkers with cancer shows that even light consumption increases the risk of cancer of the oral cavity and pharynx, esophagus, and female breast [16]. According to a Global Burden of Disease Study, the risk of cancer rises with increasing levels of alcohol consumption, and the level of consumption that minimizes health loss is zero [25]. However, in our study, moderate alcohol drinking shows a lower risk of cancer incidence and mortality compared to nondrinkers among never or former smokers who are moderately physically active. Due to a lack of data regarding former drinkers in our study, never drinkers and former drinkers were classified in a single category (i.e., reference group). However, this may lead to sick quitter bias, as those who stop drinking tend to have poor health [26].

Some studies suggest that the classic J-shaped curve disappears when the sick quitter bias is controlled. For example, a meta-analysis replicated the J-shaped curve with low-volume drinkers (1.3-24.9 g of ethanol per day) having a reduced mortality risk. However, after adjusting for abstainer biases, the J-shaped curve disappeared and no significant reduction in mortality risk was observed for low-volume drinkers [27]. A recent observational study in Korea found that light drinkers had the lowest risk of cancer mortality compared with nondrinkers and current drinkers (J-shaped). However, when former drinkers were excluded from the reference group to mitigate sick quitter bias, the risk of cancer mortality increased monotonically with alcohol consumption, showing a clear dose-response relationship [28].

In our study, a combination of alcohol consumption and smoking weakly or moderately increased the risk of all cancers, and very strongly increased the risk of esophageal cancer. In other study, a multiplicative interaction was observed for breast cancer when alcohol and tobacco were used in combination [29].

Physical activity is recommended for preventing cancer. According to the WCRF/AICR grading system, there is strong evidence that physical activity decreases the risk of colorectal, breast, and endometrial cancer [3]. Physical activity levels have declined in Korea. According to a national survey, the rate of physical activity has decreased from 72.5% in 2007 to 47.6% in 2018 in both sexes [22]. In our study, we observed a weakly decreased risk of all cancers in men and women who are moderately physically active, who quit smoking, drink alcohol moderately and are within a normal body weight range (i.e., BMI < 25). However, heavy alcohol drinkers who are physically very active are weakly associated with a higher risk of all cancers. Physical activity is positively associated with alcohol intake. Moderate and heavy drinkers are more like to be physically active compared to abstainers [30]. In an observational study in Korea, those who started drinking alcohol were more likely to be physically active and to have fewer comorbidities compared to abstainers [31]. This positive association could be explained by an extroverted personality, decreased social anxiety, exercising to relieve guilt after drinking, and drinking to reward hard work [32]. Alcohol consumption and physical activity are likely to co-occur. In our study, physically active men were more likely to drink alcohol (odds ratio [OR], 1.487; 95% CI, 1.481 to 1.492) but less likely to smoke (OR, 0.89; 95% CI, 0.886 to 0.892). These relationships were also noted for women (S5 Table).

Being overweight and obese increases the risk of cancer of the head and neck, stomach, pancreas, gallbladder, liver, colorectum, breast, ovaries, endometrium, prostate, and kidney [3]. Excess body weight was responsible for 1.5% and 2.2% of cancer cases among men and women, respectively, in 2009 in Korea [33]. According to a 2018 national examination, more than one-third of Korean men (44.7%) and women (28.3%) are obese (BMI ≥ 25 kg/m^2), a trend that is increasing, especially in men [34]. In our study, increased risk of cancer was observed in former or current smokers who are obese among young men (aged < 40 years). However, obesity was minimally associated with all cancer risk while smoking and alcohol consumption increased all cancer risk.

According to a national survey, only 10.7% of men and 18.3% of women practice healthy behaviors, including not smoking or drinking alcohol and being physically active, and the proportion of individuals practicing these healthy behaviors is decreasing [22]. In our study, only 6% of men and 15% of women engaged in healthy behavior at baseline, such as not smoking, not drinking alcohol, being moderately or highly physically active, and not being obese. However, the proportion increased to 10% in men and 36% in women 10 years later (in 2012-2013, data shown in S2C and S2D Fig.), which was contributed mainly by the decreased number of smokers, but a large proportion remains to change their lifestyles to prevent cancer. The increased proportion of people engaging in healthy behavior reflects the achievement of health policies and campaigns, particularly in tobacco control. In addition to continuous tobacco control, it is needed to strengthen various health policies and campaigns such as alcohol control and promotion of physical activity.

There are several potential limitations to this study. First, information on lifestyle behaviors was based on self-reports,

which may be subjective and unreliable. For example, self-reported physical activity levels tend to be overestimated [35] and self-reported alcohol consumption tends to be underreported [36]. Selection bias (i.e., sick quitter phenomenon) may lead to a systematic overestimation of the protective effects of moderate alcohol consumption. Furthermore, we used information on lifestyle behaviors measured once at baseline. However, lifestyle behaviors can change over time. As shown in S2 Fig., the proportion of smokers decreased among men, and proportion of physically inactivity decreased among women in 2012-2013. This may be due to the strong policy implementation on tobacco control and changes in the social norm. In consideration of the improved adherence to recommendations, the cancer risks shown in this study may be underestimated.

Second, cancer incidence was defined with ICD-10 code as a primary diagnosis combined with a special code for verifying cancer in the claims data. Cancer in secondary locations or sub-diagnoses might not be captured in this study, which may underestimate cancer risk. We suggest that a cancer diagnosis be verified by the national cancer registry in future analysis.

Third, in this study, adherence to healthy dietary guidelines was not examined due to a lack of information regarding diet and nutrition in our study population. Several studies suggest that adherence to a healthy diet may reduce the risk of cancer [7]. Further studies in a Korean population on adherence to cancer prevention guidelines that include diet are needed. Fourth, the cancer risk among women in 81 matrices should be interpreted with caution because there was a very small number of smokers (former smokers, 1.46%; current smokers, 2.98%) and heavy drinkers (0.26%). In a sub-analysis by sex and age, many HR cells in the female matrices are blank or insignificant due to an insufficient number of cases.

Fifth, we did not fully adjust for potential confounding factors. For example, we adjusted the risk of liver cancer for chronic viral hepatitis, but other infection-related cancers, such as cervical cancer and stomach cancer, were not adjusted for infection status with HPV and *helicobacter pylori* due to a lack of information. Lastly, caution should be taken when generalizing the results as subjects who did not take a health examination were excluded.

Compared to full adherence to cancer prevention recommendations, unhealthy behaviors increase the risk of cancer incidence and mortality. There is a great opportunity for cancer prevention as not many people meet these recommendations.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

As this study used anonymous, secondary data, it was exempt from review by the Institutional Review Board of the National Cancer Center, Korea (NCC2018-0279). Consent was waived for the same reason.

Author Contributions

Conceived and designed the analysis: Oh JK, Han M.
Collected the data: Oh JK, Han M.
Contributed data or analysis tools: Han M.
Performed the analysis: Han M.
Wrote the paper: Oh JK.
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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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