Original Article

Effect of smoking reduction, cessation, and resumption on cancer risk: A nationwide cohort study

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BACKGROUND: The objective of this study was to investigate the effects of reduction, cessation, and resumption of smoking on cancer development. **METHODS:** The authors identified 893,582 participants who currently smoked, had undergone a health screening in 2009, and had a follow-up screening in 2011. Among them, 682,996 participated in a third screening in 2013. Participants were categorized as quitters, reducers I (≥50% reduction), reducers II (<50% reduction), sustainers (referent), or increasers (≥20% increase). Outcome data were obtained through December 31, 2018. **RESULTS:** Reducers I exhibited a decreased risk of all cancers (adjusted hazard ratio [aHR], 0.96; 95% confidence interval [CI], 0.93-0.99), smoking-related cancers (aHR, 0.95; 95% CI, 0.92-0.99), and lung cancer (aHR, 0.83; 95% CI, 0.77-0.88). Quitters had the lowest risk of all cancers (aHR, 0.94; 95% CI, 0.92-0.96), smoking-related cancers (aHR, 0.91; 95% CI, 0.89-0.93), and lung cancer (aHR, 0.79; 95% CI, 0.76-0.83). In further analysis with 3 consecutive screenings, additional smoking reduction (from reducers II to reducers I) lowered the risk of lung cancer (aHR, 0.74; 95% CI, 0.58-0.94) in comparison with sustainers. Quitting among reducers I further decreased the risk of all cancers (aHR, 0.90; 95% CI, 0.80-1.00), smoking-related cancers (aHR, 0.81; 95% CI, 0.81-0.92), and lung cancer (aHR, 0.66; 95% CI, 0.52-0.84) in comparison with sustainers. Smoking resumption after quitting, even at a lower level, increased the risk of smoking-related cancers (aHR, 1.19; 95% CI, 1.06-1.33) and lung cancer (aHR, 1.48; 95% CI, 1.21-1.80) in comparison with sustained quitting. **CONCLUSIONS:** Smoking cessation and, to a lesser extent, smoking reduction decreased the risks of cancer. Smoking resumption increased cancer risks in comparison with sustained quitting. ***Cancer* 2022;128:2126-2137**. © *2022 American Cancer Society*.

LAY SUMMARY:

- Worldwide, tobacco use is the single leading preventable risk factor for cancer and cancer death.
- This study examined the effects of reduction, cessation, and resumption of smoking on cancer development by measuring smoking behavior repetitively.
- Although smoking reduction has a substantial cancer prevention benefit for those who cannot quit, cessation should be encouraged whenever possible. Quitters should be monitored to ensure that they do not resume smoking.

KEYWORDS: cancer, cessation, reduction, resumption, smoking.

INTRODUCTION

Worldwide, tobacco use is the single leading preventable risk factor for cancer and cancer death. In fact, the proportion of cancers attributable to cigarette smoking is approximately 35%, with cancers of the lungs and larynx exhibiting the highest attributable fraction.[1] Despite well-known health risks associated with smoking and a decreasing prevalence of smoking in Western countries over the past few decades, a comparable decline has not been observed in South Korea.[2] In South Korea, approximately 40% to 50% of men and 4% to 8% of women smoke, and this pattern of prevalence is similar to that observed in other non-Western countries.[2]

The most effective method for reducing the risk of cancer among those who smoke is smoking cessation. It is well established that smoking cessation substantially reduces the risk of all cancers[3] and smoking-related cancers,[3-5] such as lung

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The second and third authors contributed equally to this article.

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cancer,[3,5-7] laryngeal cancer,[8,9] esophageal cancer,[10,11] and pancreatic cancer.[5,12] For example, a recent study from the Framingham cohort found that the risk of lung cancer dropped by 39% within 5 years of quitting.[7] Furthermore, the risk continued to fall as the number of years after quitting increased.[7] Unfortunately, despite many attempts to quit smoking, relapse to smoking after cessation is common. Studies have reported relapse rates after smoking cessation in a 1-year period ranging from 51%[13] to 67%,[14] and the risk of relapse never disappears completely; it remains at 10% yearly even after 30 years of abstinence.[14] However, at present, there is a lack of data on the risk of cancer development for those who resume smoking.

Harm reduction strategies aim to reduce the adverse health effects of tobacco use in individuals who are unable or unwilling to quit. One element in harm reduction that is gaining increased attention concerns reducing the number of cigarettes smoked per day.[15] Recently, some researchers showed that smoking reduction could reduce risks for all cancers,[16] smoking-related cancers,[16] and lung cancer.[3,6,16] They defined smoking reduction in 2 different ways: 1) smokers who reduced the number of cigarettes smoked (eg, those who decreased from heavy to moderate smoking)[3,16] and 2) smokers who achieved a 50% reduction or more in the amount smoked.[6] As the former may capture trivial reductions such as a decrease of 1 or 2 cigarettes per day, the latter is more suitable for measuring substantial smoking reduction. A study defined smoking reduction as a set point of 50% reduction or more, but it considered only heavy smokers and lung cancer.[6] The study population was also limited to men[3,16] or a specific population of civil servants[3] who tended to be younger (aged 30-58 years) and have better overall health than the general population. Additional limitations of the previous studies included relatively small sample sizes and outcomes (eg, the largest included 18,196 cancer events among 479,156 men[3]).

In this context, we conducted a nationwide cohort study to investigate whether changes in smoking behavior would result in a subsequently altered risk of all cancers, smoking-related cancers, and lung cancers. By measuring smoking behavior repetitively, we were able to consider the effects of smoking reduction, cessation, and increases as well as resumption.

MATERIALS AND METHODS

Study Setting

The National Health Insurance Service (NHIS) is a single insurer in Korea and provides mandatory universal comprehensive medical care to 97% of the Korean population; the remaining 3% of the population in the lowest income bracket is covered by the Medical Aid Program. The NHIS collects information on demographic factors (eg, age, sex, place of residence, and income level), utilization of medical facilities, and records of prescriptions with *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis codes. In addition, the NHIS provides free biennial cardiovascular health screening for all beneficiaries older than 40 years and all employees, regardless of age, as well as annual screening for workers in jobs requiring physical labor; this enables the NHIS to collect data from health check-ups (self-questionnaires on health behavior, anthropometric measurements, and laboratory test results).[17] The NHIS database has been used to establish cohort data for various epidemiologic studies.[18]

Study Population

We initially included 1,006,803 individuals who currently smoked (aged ≥40 years) and had available data regarding their smoking behaviors from 2 consecutive biennial health screenings (2009 and 2011). We excluded participants who previously had been diagnosed with a history of any cancer (n = 15,552) or cardiovascular disease (n = 12,940) before the second health screening date (2011). To minimize reverse causality, those who were diagnosed with any cancer (n = 9579) or died (n = 2539) within 1 year after the second screening date were also excluded along with those who had missing information (n = 72,611). Finally, a total of 893,582 participants were included in the primary analysis. They were followed from 1 year after the second screening date (2011) to the date of incident cancer, death, or the end of the study period (December 31, 2018), whichever came first (Fig. 1).

In addition, to examine probable bias caused by changes in smoking behavior later in the follow-up, we traced participants who underwent another consecutive health examination in 2013 (the third screening). In this further analysis, those with any of the following conditions were excluded: 1) any cancers (n = 197,548) or cardiovascular diseases (n = 4293) before the third screening date or 2) any cancers (n = 7014) or deaths (n = 1761) that occurred within the year after the third screening date. Subsequently, 682,966 participants were included in the secondary analysis.

This study was approved by the institutional review board of Samsung Medical Center (institutional review board file SMC 2019-01-024). The review board waived the requirement for written informed consent from patients because the data were public and anonymized under confidentiality guidelines.

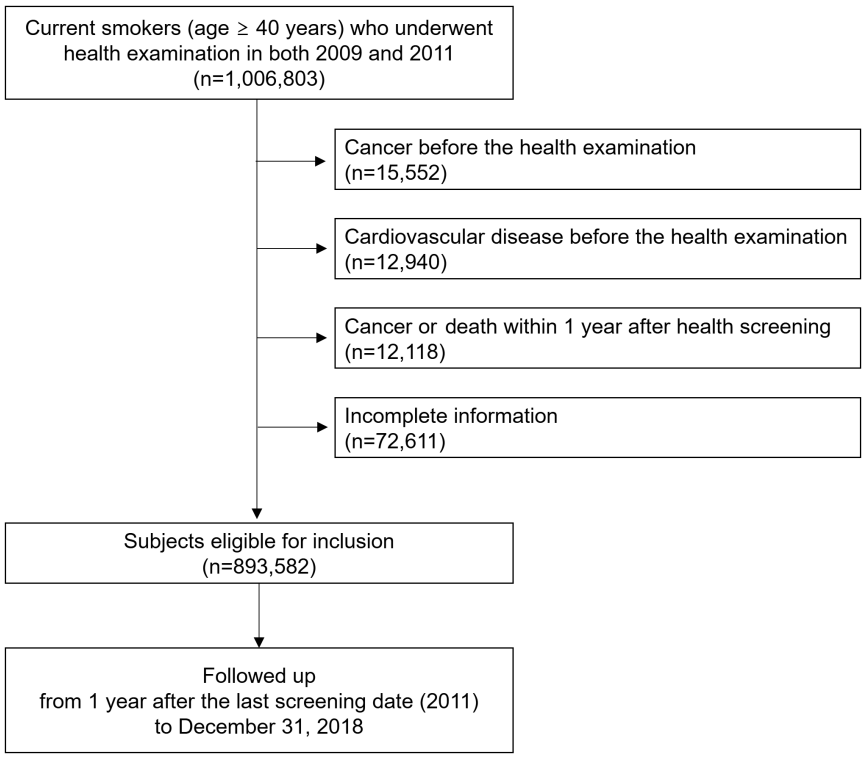

FIGURE 1. Flow chart of the study population.

Exposure: Smoking Behavior

In the current study of changes in smoking habits, we required complete information on smoking behavior from 2 consecutive examinations, one at the baseline (2009) and another at the second screening (2011). Smoking behavior and changes in smoking habits in this study were based on a self-administered questionnaire. At each examination, participants were asked whether they smoked or not and, if they smoked, about the amount and duration. At the baseline (2009), participants who currently smoked were stratified into 3 groups based on the amount of their daily cigarette smoking: light smokers (<10 cigarettes per day), moderate smokers (10-19 cigarettes per day), and heavy smokers (≥20 cigarettes per day). On the basis of the questionnaire from the second screening (2011), participants were divided into the following categories: 1) quitters (those who stopped between the first and second examinations), 2) reducers (those who reported a decrease in daily cigarette smoking by 20% or more without quitting), 3) sustainers (those who reported anywhere between a decrease and an increase of less than 20%), and 4) increasers (those who reported an increase in daily cigarette smoking of 20% or more). To measure a substantial reduction in tobacco consumption, we further categorized reducers in accordance with previous clinical studies[6,19,20] into 1) those who reported a decrease of 50% or more without quitting (reducers I) and 2) those who reported a decrease between 20% and 50% (reducers II).

In the secondary analysis, we further assessed whether there was any influence on cancer risk caused by subsequent changes in smoking behavior, such as quitting, reducing, sustaining, or resuming smoking at the third screening (2013), in comparison with the smoking behavior at the baseline (2009). The quitter, reducer I, and reducer II groups were defined as described previously. We merged participants who sustained or increased their smoking levels into nonreducers to avoid too much complexity in subgroups.

Study Outcome: Ascertainment of Cancer

The end point of the study was any newly diagnosed cancer except thyroid cancer. We excluded thyroid cancer because the current increase in the incidence of thyroid cancer in South Korea mainly has resulted from overdetection, likely as a result of widespread use of sensitive imaging tools (eg, ultrasound examination).[21,22] *ICD-10* codes C00 to C97 were used to identify cancers at all sites except the thyroid (C73), which

was also registered in the critical illness copayment reduction program for cancer (V193). Smoking-related cancer was defined in accordance with the 2014 surgeon's general report, which included the following malignancies: lip, oral cavity, and pharynx (*ICD-10* codes C00-C14); esophagus (C15); stomach (C16); colorectum (C18-C20); hepatocellular carcinoma (C22.0); pancreas (C25); larynx (C32); trachea (C33); bronchus and lung (C34); kidney, kidney pelvis, or ureter (C64-C66 and C68); bladder (C67); cervix uteri (C53); and acute myeloid leukemia (C92.0).[4]

In Korea, the NHIS provides the critical illness copayment reduction program to enhance health coverage and relieve financial burdens for patients with serious and rare diseases. For example, patients with cancer pay only 5% of the total medical bill incurred for cancer-related medical care. As enrollment in this program requires a medical certificate from a physician, the cancer diagnosis in our study is considered sufficiently reliable and has been used in previous studies.[23,24]

Covariates

We considered socioeconomic status, including income level and place of residence, as a potential covariate. Alcohol consumption was classified as none, mild (<15 g of alcohol per day), moderate (15-29.9 g of alcohol per day), or heavy (≥30 g of alcohol per day). Regular exercise was defined as >30 minutes of moderate physical activity at least 5 times per week or >20 minutes of strenuous physical activity at least 3 times per week.[25] The body mass index was calculated as the subject weight (kg) divided by the square of the subject height (m^2). Comorbidities such as diabetes mellitus were based on claims data before the screening date and health screening results.

Statistical Analysis

We performed Cox proportional hazards regression analyses to estimate hazard ratios and 95% confidence intervals (CIs) to estimate the association between smoking behavior changes and cancer risk. Sustainers were considered as the reference group. Model 1 was unadjusted. On the basis of prior studies,[3,6,12,16] model 2 was adjusted for age, sex, income, place of residence, smoking duration at the baseline, alcohol consumption, physical activity, body mass index, and diabetes mellitus. Using information on smoking behavior changes from 2 (2009 and 2011) and 3 (2009, 2011, and 2013) consecutive health screenings, we repeated the same analysis. To investigate whether the effect of smoking habit changes on cancer development was homogeneous within the strata of selected covariates, we conducted analyses stratified by smoking amount at the baseline, age (40-64 and ≥65 years), and sex.

Statistical analyses were performed with the SAS Statistical Package (version 9.4; SAS Institute, Inc, Cary, North Carolina), and a P value < .05 was considered statistically significant.

RESULTS

Baseline Characteristics of the Study Population

Table 1 shows the baseline characteristics according to changes in smoking behavior between 2009 and 2011. During the 2 years before the initiation of the study (2009-2011), 45.7% of current smokers sustained their smoking level, whereas 20.6% quit, 18.9% reduced the number of cigarettes per day (7.3% and 11.6% in the reducer I and II groups, respectively), and the remaining 14.8% became increasers (those who reported an increase in daily cigarette smoking of 20% or more) according to the study definition. Participants in the reducer I group tended to be older and female, had higher incomes, and were more likely to be heavy smokers with a longer duration and higher intensity of smoking than those in other groups. Quitters were more likely to be nondrinkers, engage in more regular exercise, and have more comorbidities than other groups.

Change in Smoking Behavior and Cancer

During a mean follow-up of 6.1 years (standard deviation, 1.0 year), there were 50,869 cancer events (9.3 per 1000 person-years): 81.0% (41,252 cases) were smoking-related cancers, and 23.3% (11,847 cases) were lung cancer. Table 2 shows the effects of changes in smoking behavior on the risk of cancer development.

In comparison with sustainers, the hazard of all cancers and smoking-related cancers decreased in the reducer I group (adjusted hazard ratio [aHR] for all cancers, 0.96; 95% CI, 0.93-0.99; aHR for smoking-related cancers, 0.95; 95% CI, 0.92-0.99) and the reducer II group (aHR for all cancers, 0.93; 95% CI, 0.91-0.96; aHR for smoking-related cancers, 0.92; 95% CI, 0.89-0.96; Fig. 2). Quitters had further reduced hazards for all cancers (aHR, 0.94; 95% CI, 0.92-0.96) and smoking-related cancers (aHR, 0.91; 95% CI, 0.89-0.93). This risk reduction was robust for lung cancer in a dose-dependent manner for the quitter (aHR, 0.79; 95% CI, 0.76-0.83), reducer I (aHR, 0.83; 95% CI, 0.77-0.88), and reducer II groups (aHR,

TABLE 1. Baseline Characteristics of the Study Participants According to Smoking Behavior Changes Between 2009 and 2011

Variable	Quitter	Reducer I	Reducer II	Sustainer	Increaser
Total	184,092 (20.6)	65,081 (7.3)	103,534 (11.6)	408,605 (45.7)	132,270 (14.8)
Age, y	52.3 ± 9.5	52.5 ± 9.8	50.4 ± 8.6	50.4 ± 8.6	50.5 ± 9.0
Male sex	165,455 (89.9)	60,613 (93.1)	99,269 (95.9)	394,228 (96.5)	124,747 (94.3)
Income					
Q1 (lowest)	33,639 (18.3)	13,555 (20.8)	19,248 (18.6)	73,013 (17.9)	24,590 (18.6)
Q2	33,214 (18.0)	13,229 (20.3)	19,316 (18.7)	75,315 (18.4)	25,843 (19.5)
Q3	48,511 (26.4)	17,280 (26.6)	28,511 (27.5)	114,959 (28.1)	36,694 (27.7)
Q4 (highest)	68,728 (37.3)	21,017 (32.3)	36,459 (35.2)	145,318 (35.6)	45,143 (34.1)
Urban residence	82,043 (44.6)	28,373 (43.6)	47,632 (46.0)	185,452 (45.4)	59,362 (44.9)
Daily smoking amount					
Light (<10 cigarettes/d)	33,891 (18.4)	2967 (4.6)	5764 (5.6)	16,785 (4.1)	29,171 (22.1)
Moderate (10-19 cigarettes/d)	73,072 (39.7)	14,084 (21.6)	35,129 (33.9)	136,209 (33.3)	74,953 (56.7)
Heavy (≥20 cigarettes/d)	77,129 (41.9)	48,030 (73.8)	62,641 (60.5)	255,611 (62.6)	28,146 (21.3)
Smoking duration					
<5 y	9348 (5.1)	1413 (2.2)	1451 (1.4)	5414 (1.3)	4051 (3.1)
5-9 y	8046 (4.4)	1712 (2.6)	1855 (1.8)	7073 (1.7)	4171 (3.2)
10-19 y	32,333 (17.6)	9743 (15.0)	14,377 (13.9)	54,675 (13.4)	24,004 (18.2)
20-29 y	68,840 (37.4)	25,473 (39.1)	48,302 (46.7)	192,746 (47.2)	57,594 (43.5)
≥30 y	65,525 (35.6)	26,740 (41.1)	37,549 (36.3)	148,697 (36.4)	42,450 (32.1)
Smoking intensity					
<10 pack-y	51,720 (28.1)	7741 (11.9)	10,632 (10.3)	44,037 (10.8)	40,175 (30.4)
10-19 pack-y	51,191 (27.8)	13,037 (20.0)	26,090 (25.2)	109,091 (26.7)	52,678 (39.8)
20-29 pack-y	40,237 (21.9)	18,205 (28.0)	27,789 (26.8)	135,467 (33.2)	23,507 (17.8)
≥30 pack-y	40,944 (22.2)	26,098 (40.1)	39,023 (37.7)	120,010 (29.4)	15,910 (12.0)
Alcohol consumption					
None	52,351 (28.4)	17,317 (26.6)	24,960 (24.1)	100,891 (24.7)	34,821 (26.3)
Mild drinker (<15 g/d)	65,497 (35.6)	20,661 (31.8)	33,754 (32.6)	135,317 (33.1)	47,419 (35.9)
Moderate drinker (15-29.9 g/d)	38,952 (21.2)	14,681 (22.6)	24,440 (23.6)	98,021 (24.0)	29,281 (22.1)
Heavy drinker (≥30 g/d)	27,292 (14.8)	12,422 (19.1)	20,380 (19.7)	74,376 (18.2)	20,749 (15.7)
Regular physical activity[a]	40,954 (22.2)	13,285 (20.4)	20,297 (19.6)	78,507 (19.2)	26,721 (20.2)
Body mass index, kg/m^2	23.9 ± 2.9	23.8 ± 3.0	23.9 ± 9.6	23.8 ± 3.0	23.9 ± 3.0
Comorbidity[b]					
Hypertension	57,810 (31.4)	20,931 (32.2)	30,255 (29.2)	117,457 (28.8)	38,353 (29.0)
Diabetes mellitus	22,240 (12.1)	8643 (13.3)	12,254 (11.8)	48,289 (11.8)	16,272 (12.3)
Dyslipidemia	36,922 (20.1)	12,920 (19.9)	19,922 (19.2)	77,927 (19.1)	25,430 (19.2)
Chronic obstructive pulmonary disease	12,279 (6.7)	4367 (6.7)	5146 (5.0)	20,880 (5.1)	7407 (5.6)

Abbreviations: *ICD-10*, *International Classification of Diseases, Tenth Revision*; Q, quartile.

Data are expressed as mean ± standard deviation or number (%).

[a]Regular exercise was defined as >30 minutes of moderate physical activity at least 5 times per week or >20 minutes of strenuous physical activity at least 3 times per week.

[b]Comorbidities were based on claims data before the screening date and health screening results. Hypertension was defined according to 1) the presence of at least 1 claim per year under *ICD-10* codes I10 to I13 or I15 and at least 1 claim per year for the prescription of antihypertensive agents or 2) a systolic/diastolic blood pressure ≥ 140/90 mm Hg. Diabetes mellitus was defined according to the following criteria: 1) at least 1 claim per year under *ICD-10* codes E11 to E14 and at least 1 claim per year for the prescription of antidiabetic medication or 2) a fasting glucose level ≥ 126 mg/dL. Dyslipidemia was defined according to 1) the presence of at least 1 claim per year under *ICD-10* code E78 and at least 1 claim per year for the prescription of a lipid-lowering agent or 2) a total cholesterol level ≥ 240 mg/dL. Chronic obstructive pulmonary disease was defined according to the presence of at least 1 claim per year under *ICD-10* codes J41 to J44.

0.84; 95% CI, 0.79-0.89). On the other hand, increasers had a higher hazard of all cancers (aHR, 1.04; 95% CI, 1.01-1.07), smoking-related cancers (aHR, 1.03; 95% CI, 1.00-1.07), and lung cancer (aHR, 1.15; 95% CI, 1.09-1.21) than sustainers. When we stratified by smoking level at the baseline (light, moderate, and heavy smokers), a similar pattern was observed.

In analyses stratified according to age and sex, these results were consistent with the main findings (Supporting Tables 1 and 2). The cancer risk reduction from smoking cessation and reduction was more prominent for younger participants (40-64 years; P for interaction < .01 for all cancers in all smokers). There was no statistically significant association with sex.

Results From 3 Consecutive Assessments of Smoking Behavior

When we followed participants whose information on smoking behavior was available from 3 consecutive health screenings (in 2009, 2011, and 2013; mean follow-up, 4.3 years), the relapse rate at the third screening was 36.5% (Table 3). Compared with sustained quitters, those who relapsed to nonreducers had an increased hazard of all cancers (aHR, 1.15; 95% CI,

1.08-1.22), smoking-related cancers (aHR, 1.23; 95% CI, 1.15-1.32), and lung cancer (aHR, 1.38; 95% CI, 1.21-1.57; Fig. 3). Those who resumed smoking even with less than half of their baseline cigarette smoking had a higher hazard of smoking-related cancers (aHR, 1.19; 95% CI, 1.06-1.33) and lung cancer (aHR, 1.48;

TABLE 2. Associations Between Smoking Behavior Changes (2009-2011) and Cancer Occurrence During 6.1 Years of Follow-Up (N = 893,582)

Smoking Behavior							
In 2009	In 2011	Subjects, No.	Events, No.	PYs	Incidence Rate per 1000 PYs	Model 1, HR (95% CI)	Model 2, HR (95% CI)
All cancers (except thyroid)							
All current smokers	Quitter	184,092	10,996	1,132,065.4	9.7	1.08 (1.05-1.10)	0.94 (0.92-0.96)
	Reducer I	65,081	4404	396,524.8	11.1	1.23 (1.19-1.27)	0.96 (0.93-0.99)
	Reducer II	103,534	5543	637,057.6	8.7	0.97 (0.94-0.99)	0.93 (0.91-0.96)
	Sustainer	408,605	22,658	2,513,285.3	9.0	1 (reference)	1 (reference)
	Increaser	132,270	7268	812,062.3	9.0	0.99 (0.97-1.02)	1.04 (1.01-1.07)
Light smokers[a] (n = 88,578)	Quitter	33,891	1859	208,034.8	8.9	0.96 (0.89-1.04)	1.01 (0.93-1.09)
	Reducer I	2967	183	18,011.6	10.2	1.09 (0.93-1.28)	1.01 (0.86-1.18)
	Reducer II	5764	365	35,136.3	10.4	1.12 (0.99-1.26)	0.98 (0.87-1.11)
	Sustainer	16,785	956	102,758.9	9.3	1 (reference)	1 (reference)
	Increaser	29,171	1824	177,897.7	10.3	1.10 (1.02-1.19)	1.15 (1.07-1.25)
Moderate smokers[a]	Quitter	73,072	4137	450,241.1	9.2	1.10 (1.06-1.14)	0.96 (0.92-1.00)
(n = 333,447)	Reducer I	14,084	858	86,051.6	10.0	1.19 (1.11-1.28)	0.92 (0.86-0.99)
	Reducer II	35,129	1896	216,274.9	8.8	1.05 (1.00-1.11)	0.96 (0.91-1.01)
	Sustainer	136,209	7012	840,213.3	8.3	1 (reference)	1 (reference)
	Increaser	74,953	3893	461,176.9	8.4	1.01 (0.97-1.05)	1.05 (1.01-1.09)
Heavy smokers[a] (n = 471,557)	Quitter	77,129	5000	473,789.5	10.6	1.13 (1.09-1.16)	0.94 (0.91-0.97)
	Reducer I	48,030	3363	292,461.7	11.5	1.23 (1.18-1.28)	0.96 (0.93-1.00)
	Reducer II	62,641	3282	385,646.5	8.5	0.91 (0.88-0.95)	0.95 (0.92-0.99)
	Sustainer	255,611	14,690	1,570,313.2	9.4	1 (reference)	1 (reference)
	Increaser	28,146	1551	172,987.8	9.0	0.96 (0.91-1.01)	1.05 (0.99-1.10)
Smoking-related cancers[b]							
All current smokers	Quitter	184,092	8593	1,138,077.6	7.6	1.02 (1.00-1.05)	0.91 (0.89-0.93)
	Reducer I	65,081	3600	398,298.5	9.0	1.22 (1.18-1.27)	0.95 (0.92-0.99)
	Reducer II	103,534	4519	639,535.9	7.1	0.96 (0.93-0.99)	0.92 (0.89-0.96)
	Sustainer	408,605	18,643	2,522,782.1	7.4	1 (reference)	1 (reference)
	Increaser	132,270	5897	815,343.9	7.2	0.98 (0.95-1.01)	1.03 (1.00-1.07)
Light smokers (n = 88,578)	Quitter	33,891	1362	209,327.6	6.5	0.93 (0.85-1.01)	0.99 (0.91-1.09)
	Reducer I	2967	139	18,122.3	7.7	1.09 (0.91-1.31)	1.02 (0.85-1.22)
	Reducer II	5764	268	35,345.3	7.6	1.08 (0.94-1.24)	0.95 (0.83-1.09)
	Sustainer	16,785	725	103,345.7	7.0	1 (reference)	1 (reference)
	Increaser	29,171	1442	178,867.3	8.1	1.15 (1.05-1.26)	1.20 (1.10-1.31)
Moderate smokers	Quitter	73,072	3237	452,491.4	7.2	1.06 (1.02-1.11)	0.93 (0.89-0.97)
(n = 333,447)	Reducer I	14,084	705	86,356.7	8.2	1.21 (1.12-1.31)	0.95 (0.88-1.03)
	Reducer II	35,129	1545	217,140.0	7.1	1.06 (1.00-1.12)	0.96 (0.91-1.02)
	Sustainer	136,209	5685	843,288.1	6.7	1 (reference)	1 (reference)
	Increaser	74,953	3162	462,918.4	6.8	1.01 (0.97-1.06)	1.05 (1.00-1.10)
Heavy smokers (n = 471,557)	Quitter	77,129	3994	476,258.5	8.4	1.08 (1.04-1.12)	0.91 (0.88-0.95)
	Reducer I	48,030	2756	293,819.6	9.4	1.21 (1.16-1.26)	0.95 (0.91-0.99)
	Reducer II	62,641	2706	387,050.5	7.0	0.90 (0.86-0.94)	0.94 (0.90-0.98)
	Sustainer	255,611	12,233	1,576,148.4	7.8	1 (reference)	1 (reference)
	Increaser	28,146	1293	173,558.2	7.4	0.96 (0.91-1.02)	1.05 (0.99-1.11)
Lung cancer							
All current smokers	Quitter	184,092	2322	1,154,295.6	2.0	0.95 (0.90-1.00)	0.79 (0.76-0.83)
	Reducer I	65,081	1114	404,509.9	2.8	1.30 (1.22-1.39)	0.83 (0.77-0.88)
	Reducer II	103,534	1262	647,806.1	1.9	0.92 (0.87-0.98)	0.84 (0.79-0.89)
	Sustainer	408,605	5405	2,556,492.9	2.1	1 (reference)	1 (reference)
	Increaser	132,270	1744	825,721.4	2.1	1.00 (0.95-1.06)	1.15 (1.09-1.21)
Light smokers (n = 88,578)	Quitter	33,891	330	212,064.4	1.6	0.91 (0.76-1.09)	0.98 (0.81-1.17)
	Reducer I	2967	34	18,368.8	1.9	1.08 (0.75-1.56)	0.96 (0.66-1.38)
	Reducer II	5764	70	35,789.1	2.0	1.14 (0.87-1.51)	0.95 (0.72-1.25)
	Sustainer	16,785	179	104,639.0	1.7	1 (reference)	1 (reference)
	Increaser	29,171	416	181,378.2	2.3	1.34 (1.13-1.60)	1.45 (1.22-1.73)
Moderate smokers	Quitter	73,072	786	458,843.2	1.7	1.06 (0.97-1.16)	0.87 (0.80-0.95)
(n = 333,447)	Reducer I	14,084	196	87,615.2	2.2	1.39 (1.20-1.61)	0.91 (0.79-1.06)
	Reducer II	35,129	419	219,913.5	1.9	1.18 (1.06-1.32)	1.00 (0.89-1.11)
	Sustainer	136,209	1374	854,262.0	1.6	1 (reference)	1 (reference)
	Increaser	74,953	907	468,549.9	1.9	1.21 (1.11-1.31)	1.32 (1.22-1.44)

TABLE 2. *Continued*

Smoking Behavior							
In 2009	In 2011	Subjects, No.	Events, No.	PYs	Incidence Rate per 1000 PYs	Model 1, HR (95% CI)	Model 2, HR (95% CI)
Heavy smokers (n = 471,557)	Quitter	77,129	1206	483,388.1	2.5	1.03 (0.97-1.10)	0.79 (0.74-0.84)
	Reducer I	48,030	884	298,525.8	3.0	1.23 (1.14-1.32)	0.81 (0.75-0.87)
	Reducer II	62,641	773	392,103.6	2.0	0.82 (0.76-0.88)	0.83 (0.77-0.90)
	Sustainer	255,611	3852	1,597,591.8	2.4	1 (reference)	1 (reference)
	Increaser	28,146	421	175,793.4	2.4	0.99 (0.90-1.10)	1.16 (1.05-1.28)

Abbreviations: CI, confidence interval; HR, hazard ratio; increaser, those who increased the number of cigarettes by 20% or more; PY, person-year; quitter, those who quit smoking; reducer I, those who reduced the number of cigarettes by 50% or more; reducer II, those who reduced the number of cigarettes by 20% to 50%; sustainer, those who reduced or increased the number of cigarettes by 20%.
Model 1 was a crude model. Model 2 was adjusted for age, sex, socioeconomic position (income level and place of residence), smoking duration at the baseline, alcohol consumption, body mass index, and diabetes mellitus.
[a]Light smokers smoked <10 cigarettes per day, moderate smokers smoked 10 to 19 cigarettes per day, and heavy smokers smoked ≥20 cigarettes per day.
[b]Smoking-related cancers included the following malignancies: lip, oral cavity, and pharynx; esophagus; stomach; colorectum; hepatocellular carcinoma; pancreas; larynx; trachea; bronchus and lung; kidney, kidney pelvis, or ureter; bladder; cervix uteri; and acute myeloid leukemia.

95% CI, 1.21-1.80) and a marginally higher risk of all cancers (aHR, 1.10; 95% CI, 1.00-1.22) than sustained quitters.

Participants who reduced their number of cigarettes smoked per day by more than 50% (reducers I) at the second screening and quit at the third screening had a lower hazard of smoking-related cancers (aHR, 0.81; 95% CI, 0.71-0.92) and lung cancer (aHR, 0.66; 95% CI, 0.52-0.84) than the sustained reducer I group. Participants who sustained or even increased their amount of smoking (nonreducers) at the second screening and quit at the third screening had a decreased hazard of all cancers (aHR, 0.93; 95% CI, 0.89-0.97) and smoking-related cancers (aHR, 0.91; 95% CI, 0.87-0.96) in comparison with sustained nonreducers.

An additional reduction in the amount smoked from the reducer II group at the second screening to the reducer I group at the third screening was associated with a decreased hazard of lung cancer (aHR, 0.74; 95% CI, 0.58-0.94), although it was not significant for all cancers or smoking-related cancers.

DISCUSSION

In this large cohort study with repetitive measurements of smoking behavior, we found that smoking reduction was associated with a decreased risk of any subsequent cancer, smoking-related cancers, and lung cancer, although the lowest risks were observed for smoking cessation over a 2-year period. Further analysis with 3 consecutive health screenings showed that an additional reduction in the number of cigarettes smoked was associated with a further reduction in lung cancer, and smoking cessation through reduction decreased the risk of all cancers, smoking-related cancers, and lung cancer in comparison with sustained smoking of a reduced amount. Participants who later resumed smoking after smoking cessation had a higher risk of all cancers, smoking-related cancers, and lung cancer in comparison with those who maintained smoking cessation.

Smoking has been linked to numerous cancers, including those of the esophagus, pancreas, larynx, trachea, bronchus and lungs, kidneys, bladder, and cervix uteri.[4] The current study further extends prior works by using a uniquely rigorous methodology featuring frequently time-updated smoking behaviors collected in person at consecutive visits to minimize bias. For example, we showed that smokers who increased their amount of smoking during 2 consecutive screenings had an increased risk of all cancers and smoking-related cancers, particularly lung cancer. In addition, heavy smokers who further increased their daily cigarette smoking had an increased risk of cancer in the larynx and cervix uteri (Supporting Table 3). These results support the causal relationship between smoking and cancers.

Smoking reduction may be used as a strategy to reduce the risk of cancer in those who are unable to quit smoking immediately. In line with previous studies,[3,6,16] our study suggests a possibly favorable effect of smoking reduction, especially for lung cancer. There are 2 possible explanations regarding reductions in cancer risk with smoking reduction. First, smoking reduction can be a waystation to permanent cessation, and the reduction in cancer risk among reducers could be partly attributable to their increased probability of cessation. People who have reduced their cigarette consumption have tended to quit smoking more frequently than nonreducing smokers in previous studies.[26,27] Second, because of the well-established linear relationship between the number of cigarettes per day and lung cancer risk,[4] it is likely that a reduction in smoking consumption could decrease the

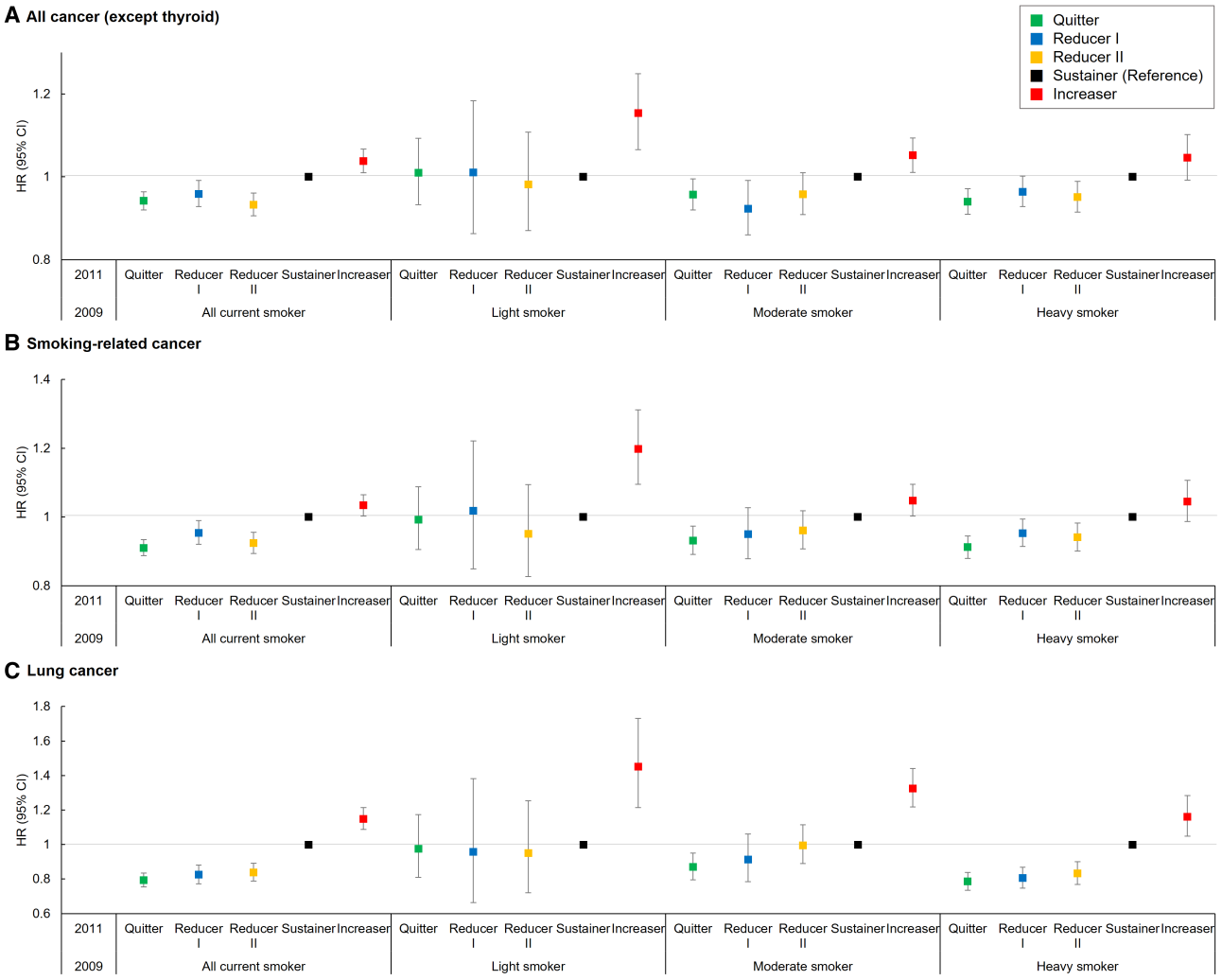

FIGURE 2. Risk of all cancers, smoking-related cancers, and lung cancer according to changes in smoking behavior between 2009 and 2011. HRs are adjusted for age, sex, socioeconomic position (income level and place of residence), alcohol consumption, physical activity, body mass index, and diabetes mellitus. CI indicates confidence interval; HR, hazard ratio; increaser, those who increased the number of cigarettes by 20% or more; quitter, those who quit smoking; reducer I, those who reduced the number of cigarettes by 50% or more; reducer II, those who reduced the number of cigarettes by 20% to 50%; sustainer, those who reduced or increased the number of cigarettes by less than 20%.

risk of lung cancer, probably through the lowered level of tobacco-specific carcinogens. Thus, any reduction in the number of cigarettes could explain the decreased risk of cancer among reducers.

Those who further reduced the number of cigarettes smoked per day at the third health examination showed an even lower risk of lung cancer than those who maintained their smoking level, and this further suggests a dose-response relationship between smoking and lung cancer. However, further risk reduction for all cancers and smoking-related cancers was not evident. This might be due to compensatory smoking, which means that the intensity at which the reducer inhales his or her cigarette may compensate for the decrease in the number of cigarettes.[28] These findings suggest that just a reduction in the amount of smoking is not comparable to risk reduction by smoking cessation.

Undoubtedly, smoking cessation decreases the risk of all cancers, smoking-related cancers, and lung cancer. The current study is consistent with earlier works reporting that quitting smoking reduces the risk of smoking-related cancers,[3,16,29] such as lung,[3,6,7,16] larynx,[8] kidney,[30] and bladder cancer,[31] in comparison with those who persistently smoke.

To the best of our knowledge, this is the first study to investigate the effects of subsequent resumption of

TABLE 3. Associations Between Additional Changes in Smoking Behavior (2009-2013) and Cancer Occurrence During 4.3 Years of Follow-Up (N = 682,966)

Smoking Behavior							
2009-2011	2013[a]	Subjects, No.	Events, No.	PYs	Incidence Rate per 1000 PYs	Model 1, HR (95% CI)	Model 2, HR (95% CI)
All cancers (except thyroid)							
Quitter (n = 145,528)	Quitter	90,570	3829	389,483.5	9.8	1 (reference)	1 (reference)
	Reducer I	8478	414	36,220.3	11.4	1.16 (1.05-1.29)	1.10 (1.00-1.22)
	Reducer II	8784	343	37,815.1	9.1	0.92 (0.83-1.03)	1.05 (0.94-1.18)
	Nonreducer[a]	34,696	1477	148,740.6	9.9	1.01 (0.95-1.07)	1.15 (1.08-1.22)
Reducer I (n = 48,582)	Quitter	10,139	487	43,341.9	11.2	0.94 (0.84-1.05)	0.90 (0.80-1.00)
	Reducer I	17,237	872	73,265.4	11.9	1 (reference)	1 (reference)
	Reducer II	7185	310	30,846.4	10.0	0.84 (0.74-0.96)	0.98 (0.86-1.11)
	Nonreducer	14,021	649	59,937.7	10.8	0.91 (0.82-1.01)	1.02 (0.92-1.13)
Reducer II (n = 79,117)	Quitter	12,241	523	52,410.8	10.0	1.15 (1.04-1.28)	0.95 (0.86-1.05)
	Reducer I	10,271	420	43,845.5	9.6	1.11 (0.99-1.24)	0.92 (0.83-1.03)
	Reducer II	31,619	1169	135,319.7	8.6	1 (reference)	1 (reference)
	Nonreducer	24,986	924	107,126.3	8.6	1.00 (0.92-1.09)	0.97 (0.89-1.06)
Nonreducer (n = 412,739)	Quitter	61,248	2604	262,030.6	9.9	1.12 (1.07-1.16)	0.93 (0.89-0.97)
	Reducer I	22,627	1141	96,272.2	11.9	1.33 (1.25-1.41)	1.04 (0.98-1.10)
	Reducer II	39,208	1559	167,788.9	9.3	1.04 (0.99-1.10)	1.02 (0.97-1.08)
	Nonreducer	289,656	11,051	1,240,773.7	8.9	1 (reference)	1 (reference)
Smoking-related cancers							
Quitter (n = 145,528)	Quitter	90,570	2826	391,341.7	7.2	1 (reference)	1 (reference)
	Reducer I	8478	332	36,386.8	9.1	1.26 (1.13-1.42)	1.19 (1.06-1.33)
	Reducer II	8784	278	37,938.6	7.3	1.02 (0.90-1.15)	1.15 (1.02-1.30)
	Nonreducer[a]	34,696	1177	149,282.5	7.9	1.09 (1.02-1.17)	1.23 (1.15-1.32)
Reducer I (n = 48,582)	Quitter	10,139	363	43,554.2	8.3	0.85 (0.75-0.96)	0.81 (0.71-0.92)
	Reducer I	17,237	722	73,514.0	9.8	1 (reference)	1 (reference)
	Reducer II	7185	238	30,953.1	7.7	0.78 (0.68-0.91)	0.91 (0.78-1.05)
	Nonreducer	14,021	535	60,115.7	8.9	0.91 (0.81-1.01)	1.02 (0.91-1.14)
Reducer II (n = 79,117)	Quitter	12,241	405	52,636.0	7.7	1.09 (0.97-1.23)	0.91 (0.81-1.02)
	Reducer I	10,271	348	43,977.0	7.9	1.12 (0.99-1.27)	0.94 (0.83-1.06)
	Reducer II	31,619	956	135,706.9	7.0	1 (reference)	1 (reference)
	Nonreducer	24,986	746	107,465.2	6.9	0.99 (0.90-1.08)	0.96 (0.87-1.06)
Nonreducer (n = 412,739)	Quitter	61,248	2053	263,109.1	7.8	1.08 (1.03-1.13)	0.91 (0.87-0.96)
	Reducer I	22,627	939	96,645.0	9.7	1.35 (1.26-1.44)	1.06 (0.99-1.13)
	Reducer II	39,208	1246	168,327.0	7.4	1.03 (0.97-1.09)	1.01 (0.95-1.07)
	Nonreducer	289,656	8983	1,244,377.7	7.2	1 (reference)	1 (reference)
Lung cancer							
Quitter (n = 145,528)	Quitter	90,570	749	395,176.8	1.9	1 (reference)	1 (reference)
	Reducer I	8478	115	36,768.4	3.1	1.65 (1.36-2.01)	1.48 (1.21-1.80)
	Reducer II	8784	72	38,303.1	1.9	0.99 (0.78-1.26)	1.16 (0.91-1.48)
	Nonreducer[a]	34,696	341	150,826.8	2.3	1.19 (1.05-1.36)	1.38 (1.21-1.57)
Reducer I (n = 48,582)	Quitter	10,139	99	44,030.6	2.2	0.71 (0.56-0.89)	0.66 (0.52-0.84)
	Reducer I	17,237	237	74,401.8	3.2	1 (reference)	1 (reference)
	Reducer II	7185	74	31,268.7	2.4	0.74 (0.57-0.97)	0.94 (0.72-1.22)
	Nonreducer	14,021	174	60,783.4	2.9	0.90 (0.74-1.09)	1.07 (0.88-1.30)
Reducer II (n = 79,117)	Quitter	12,241	124	53,219.8	2.3	1.16 (0.94-1.44)	0.87 (0.70-1.08)
	Reducer I	10,271	87	44,504.1	2.0	0.98 (0.77-1.24)	0.74 (0.58-0.94)
	Reducer II	31,619	274	136,942.2	2.0	1 (reference)	1 (reference)
	Nonreducer	24,986	208	108,467.5	1.9	0.96 (0.80-1.15)	0.90 (0.75-1.08)
Nonreducer (n = 412,739)	Quitter	61,248	645	265,840.2	2.4	1.18 (1.08-1.28)	0.92 (0.84-1.00)
	Reducer I	22,627	315	97,753.2	3.2	1.56 (1.39-1.76)	1.09 (0.97-1.23)
	Reducer II	39,208	343	169,977.7	2.0	0.98 (0.88-1.10)	0.96 (0.86-1.07)
	Nonreducer	289,656	2587	1,256,139.9	2.1	1 (reference)	1 (reference)

Abbreviations: CI, confidence interval; HR, hazard ratio; nonreducer, those who were either a sustainer (those who reduced or increased the number of cigarettes by 20%) or an increaser (those who increased the number of cigarettes by 20% or more); PY, person-year; quitter, those who quit smoking; reducer I, those who reduced the number of cigarettes by 50% or more; reducer II, those who reduced the number of cigarettes by 20% to 50%.

We observed cancer occurrence according to the smoking status change from 2009 to 2013 (the third screening) in 682,996 persons with available data. Model 1 was a crude model. Model 2 was adjusted for age, sex, socioeconomic position (income level and place of residence), smoking duration at the baseline, alcohol consumption, body mass index, and diabetes mellitus.

[a]Smoking behavior in 2013 was defined on the basis of 2009.

smoking after smoking cessation on cancer risk. When past smokers resumed smoking, they no longer had the beneficial effect of smoking cessation, but the risk of cancer increased again. We showed that smoking-related cancer risk increased with the resumed smoking dose in a dose-response manner. Moreover, smoking resumption

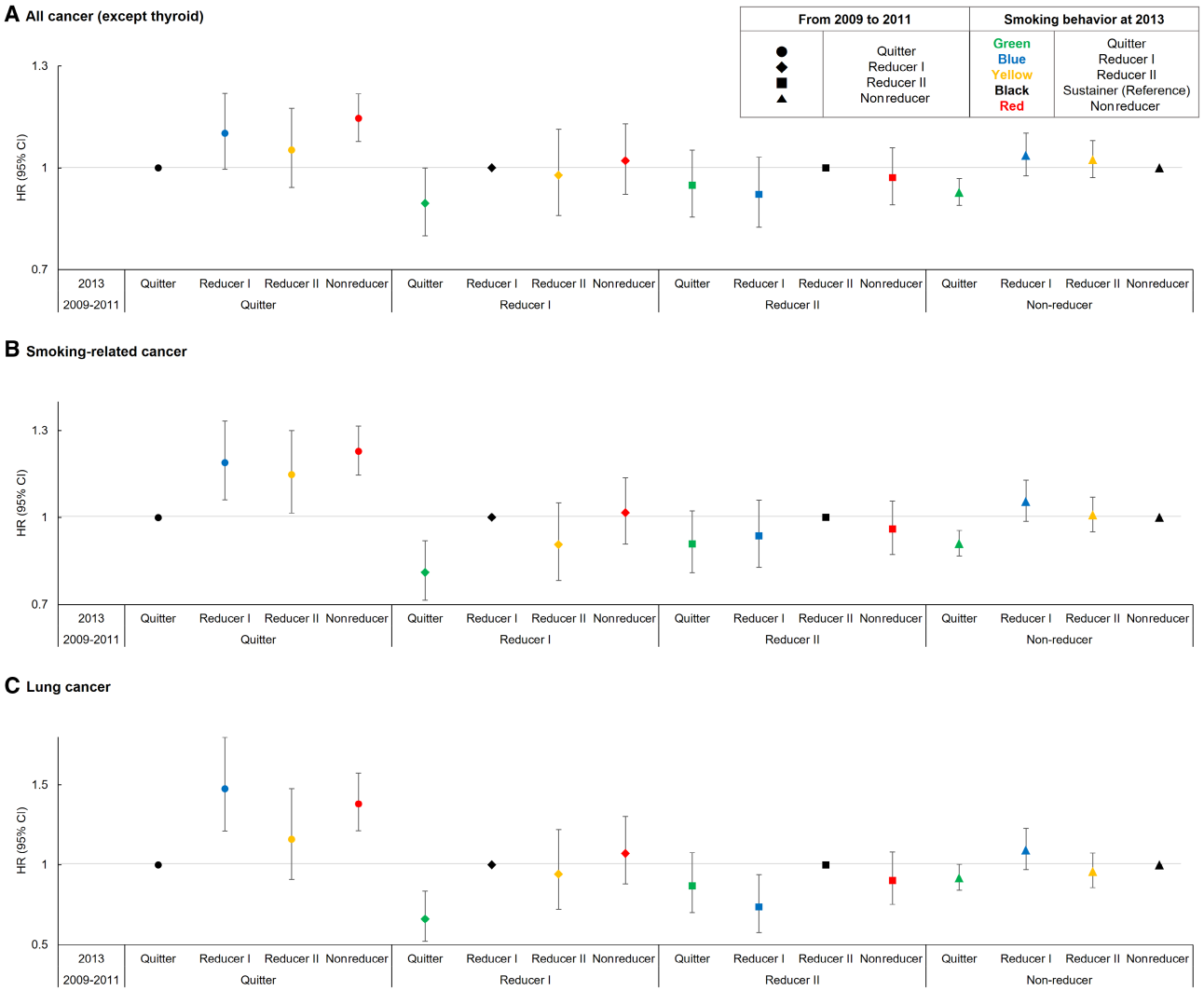

FIGURE 3. Risk of all cancers, smoking-related cancers, and lung cancer according to changes in smoking behavior between 2009 and 2013. Smoking behavior in 2013 was defined on the basis of 2009. HRs are adjusted for age, sex, socioeconomic position (income level and place of residence), alcohol consumption, physical activity, body mass index, and diabetes mellitus. CI indicates confidence interval; HR, hazard ratio; nonreducer, sustainers (those who reduced or increased the number of cigarettes less than 20%) and increasers (those who increased the number of cigarettes by 20% or more); quitter, those who quit smoking; reducer I, those who reduced the number of cigarettes by 50% or more; reducer II, those who reduced the number of cigarettes by 20% to 50%.

even at a reduced amount in comparison with the original smoking level increased the risk of smoking-related cancers and lung cancer. This highlights the importance of sustained smoking cessation.

In the current study, the beneficial effect of smoking cessation on cancer risk reduction was more prominent in younger participants compared with older ones. Although smoking cessation was beneficial at all ages, the greatest benefit was seen in those who quit earliest in life. According to previous studies, even people who stopped smoking at the age of 50 or 60 years avoided most of their subsequent risk of developing lung cancer, but those who stopped at the age of 30 years avoided more than 90% of the risk attributable to tobacco of those who continued to smoke.[32,33] In addition, stopping at the ages of 30, 40, 50, and 60 years resulted in gains of approximately 10, 9, 6, and 3 years of life expectancy, respectively,[34] and past smokers who quit before the age of 45 years did not significantly differ in mortality from never smokers.[35] These findings emphasize that smoking cessation as early as possible is important.

Though not statistically significant, the cancer risk reduction from smoking cessation and smoking reduction seemed to be more prominent in women than men (aHR for smoking cessation, 0.89 vs 0.94; aHR for smoking reduction, 0.92 vs 0.96). The lack of statistical significance for this sex difference might be due to the low number of women (<10%) in our study population. Women may be more susceptible to tobacco smoke and potentially more vulnerable to smoking-related cancer development. Several studies have indicated that for a given number of cigarettes smoked, women may be at higher risk for lung,[36-38] oral,[39] and bladder cancers[40] in comparison with men. Several studies have shown that women may be more susceptible to the molecular aberrations caused by tobacco smoke. For instance, an increased frequency of TP53, K-ras, c-erbB-2, or EGFR mutations has been observed in women who smoke compared with men who smoke.[38] It has been reported that GRPR expression may underlie women's increased susceptibility to the carcinogenic effects of cigarette smoke.[41] However, women tend to have less success than men in quitting smoking,[42] and our study suggests the needs for a greater focus on specific interventions for smoking cessation in women.

Our study has important public health implications. We clearly have shown a substantial benefit from smoking reduction for cancer risk, and this also might be meaningful for those who are unable to quit smoking. On the other hand, we also have shown that smoking cessation is the best way to cancer prevention. In addition, our results also emphasize the need to maintain quitting after cessation, as smoking resumption even at a lower level increased cancer risk.

There are several limitations to our study. First, because smoking behaviors were based on self-reported questionnaires without biochemical verification, a misclassification bias could exist. However, using biochemical verification such as urine cotinine levels in a large population study is infeasible. Self-reported smoking behavior has been considered relatively accurate with 87.5% sensitivity and 89.2% specificity according to a systematic review.[43] Second, because we used administrative data, we did not have sufficient clinical information, such as the self-reported reasons for changes in smoking behavior. For example, some participants might have quit smoking because of symptoms of an undiagnosed cancer-related illness. In that case, the effect of smoking cessation might have been underestimated.[44]

In conclusion, in this large population-based cohort study, smoking cessation and, to a lesser extent, smoking reduction were associated with a decrease in the risk of cancer. Smoking resumption was associated with a higher cancer risk than sustained quitting. These findings suggest that although smoking reduction has substantial benefit for cancer prevention, especially for those who cannot quit, smoking cessation should be encouraged whenever possible, and quitters should be carefully monitored to ensure that they do not resume smoking.

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CONFLICT OF INTEREST DISCLOSURES
The authors made no disclosures.

AUTHOR CONTRIBUTIONS
Jung Eun Yoo: Conceptualization, investigation, methodology, visualization, roles/writing–original draft, and writing–review and editing. **Kyungdo Han:** Conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, supervision, and writing–review and editing. **Dong Wook Shin:** Conceptualization, investigation, methodology, project administration, supervision, visualization, roles/writing–original draft, and writing–review and editing. **Wonyoung Jung:** Investigation and writing–review and editing. **Dahye Kim:** Data curation, formal analysis, methodology, project administration, software, and writing–review and editing. **Cheol Min Lee:** Investigation and writing–review and editing. **Hyuktae Kwon:** Investigation and writing–review and editing. **Kyu-Won Jung:** Investigation and writing–review and editing. **Yun-Mi Song:** Investigation and writing–review and editing.

DATA AVAILABILITY
The data sets used and/or analyzed during this study are available from the corresponding authors on reasonable request.

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