Cancer Epidemiology 60 (2019) 86–92

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Cancer risk among young men with weight gain after smoking cessation: A population-based cohort study

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ARTICLE INFO

Keywords:
Smoking cessation
Weight gain
Men
Neoplasms

ABSTRACT

Background: Smoking cessation may help the current smokers to reduce cancer risk. However, weight gain following smoking cessation may attenuate the protective association of cessation with cancer.

Patients and methods: Our study included 1,278,794 men who were aged 20–39 years and underwent two consecutive health examinations by the National Health Insurance Service, without previous diagnosis of cancer. Participants were categorized into continual smokers, quitters with different degree of body weight change, and never smokers based on the biennial national health screening program (2002–2003 and 2004–2005) and were followed from January 1, 2006 to December 31, 2015. Cox proportional hazard models and restricted cubic spline model was used to evaluate the association of post-cessation weight change and cancer risk after adjustment for potential confounders.

Results: During the 10 years of follow-up, the analyses included 1,278,794 men with 21,494 cancer incidences. Compared to continual smokers, quitters without weight gain of 2.0 kg had significantly lower risk of obesity-related cancer (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.79-0.97), smoking-related cancer (HR, 0.90; 95% CI, 0.83 to 0.98), and gastrointestinal cancer (HR, 89; 95% CI, 0.80 to 0.98). Weight gain among quitters attenuated the risk reduction of cancer compared to continual smoking. Among quitters, weight gain up to 5.0 kg with smoking cessation showed protective association with cancer risk among quitters without weight gain.

Conclusion: Excessive weight gain with smoking cessation among quitters was not associated with reduced risk of several cancer types. This association should be taken into account when recommending smoking cessation to prevent cancer

1. Introduction

In the past few decades, several epidemiological studies across the globe reported the association between cigarette smoking and various types of cancer [1–6]. Analyses from multiple cohorts suggest that smoking cessation significantly reduces the risk of cancer, if continued over time without relapsing [7,8]. Despite the widely publicized health benefits of smoking cessation [9,10], weight gain following smoking cessation is known to be one of the adverse health effects that discourages smokers from quitting [11]. The severity of weight gain with smoking cessation may differ mostly by age, sex, and ethnicity, but usually occurs during half a year after quitting and persists over a period of time [12,13]. Obesity and excess body weight are also associated with elevated risk of cancer in Asian and other populations (mostly in North America and European countries) [14–16]. However, the association between post-cessation weight gain and cancer risk has not been established.

Previous observational studies have reported the association between weight gain and several cancer types, but most studies were limited to women [17–19]. Also, these epidemiological studies have not yet examined whether the post-cessation weight gain attenuates the protective effect of smoking cessation with cancer. Therefore, owing to the well-established evidence of the association between excess body weight and cancer risk, health concern on post-cessation weight gain

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https://doi.org/10.1016/j.canep.2019.03.005
Received 19 December 2018; Received in revised form 4 March 2019; Accepted 11 March 2019
Available online 30 March 2019
1877-7821/

and cancer risk could not be ruled out.

To examine the association of weight change with smoking cessation and risk of cancer, we used population-based linkage of national health screening, medical claims, and death records database of more than 1 million young men aged between 20 and 39. We report the relationship of weight change with smoking cessation with risk of cancer to update evidence on the health benefits of smoking cessation and weight management in young men.

2. Methods

2.1. Data source and study design

We obtained health screening data and medical claims of young men aged 20 to 39 in the National Health Insurance Service (NHIS) cohort database between 2002 and 2015 that were linked to death records of the National Statistical Office of the Republic of Korea. The NHIS, which is a single insurer and government-funded national health insurance system in the Republic of Korea, provides demographics, medical claims, and health screening dataset for research purpose after undergoing approval procedure from the relevant review committees. Further details of the health screening program and healthcare data of the NHIS database are available elsewhere [20]. Among 1,357,494 young men (aged between 20 and 39) identified from the NHIS database, we excluded those with unknown smoking status (N = 49,150) and missing information on weight (N = 2760) between two consecutive biennial health screening periods (2002–2003 and 2004–2005). In addition, participants who had medical claims of any cancer (ICD-10 [International Classification of Disease, 10th revision] codes: C00-C97) or died before January 1, 2006 (N = 26,790) were excluded from this study. Women were not enrolled in this study because of significantly low proportion of current smokers at baseline (below 3.0%). After applying these inclusion criteria, the final cohort included 1,278,794 young men. Since the NHIS cohort database consisted of routinely collected healthcare data, we were exempted from obtaining informed consent from the participants. Institutional Review Board (IRB) at the Seoul National University Hospital, which complies with the Declaration of Helsinki, approved the study (IRB No: 1703-039-836).

2.2. Change in smoking status and weight change

Change in smoking status were drawn from the self-reported survey between the first (2002–2003) and second (2004–2005) biennial NHIS health screening periods. Information on cigarettes smoked per day and smoking history were also collected from the same survey category. Based on the responses, we grouped the participants into continual smokers, quitters, and never smokers. We categorized quitters into quitters with weight gain (weight gain of + 2.0 kg), without weight gain (change within ± 2.0 kg), and with weight loss (loss of more than -2.0 kg) based on the average weight gain in Asian male of similar age group reported in the previous studies [21–24]. Furthermore, we created the secondary weight change categories among quitters based on the average post-cessation weight gain observed in the U.S cohort (5.0 kg) studies from the recruited study participants [25] to assess the extreme weight gain category for sensitivity analyses.

2.3. Cancer incidence follow-up

Records of cancer incidence during the follow-up from January 1, 2006 to December 31, 2015 were identified with ICD-10 codes and critical condition code for malignant neoplasm in the NHIS medical claims. The diagnostic concordance of the NHIS claims data for cancer is approximately 95% as compared to the Korea Central Cancer Registry [26]. Cancer incidences were classified as all cancer, obesity-related cancer (esophageal adenocarcinoma, gastric cardia cancer, liver cancer, kidney cancer, multiple myeloma, meningioma, pancreatic cancer, colorectal cancer, gallbladder cancer) (U.S National Cancer Institute), smoking-related cancer (U.S Surgeon General's Report, 2014) [27], gastrointestinal (GI) cancer (includes cancers of gastrointestinal tract and digestive organs), lung cancer, gastric cancer, colorectal cancer, and liver cancer. Specific cancer sites were selected for analysis according to the incidence rate among men according to the National Cancer Registry database in the Republic of Korea [28].

2.4. Assessment of covariates

Information on sociodemographic variables (age, residential area, and insurance premium [indicator of socioeconomic status]) were drawn from the insurance eligibility database of the NHIS. We abstracted data on body mass index (BMI) (weight in kilograms divided by height in meters squared [kg/m^2]), fasting serum glucose, total cholesterol, alcohol consumption, physical activity, and family history of cancer from the clinical laboratory tests and self-reported surveys performed as a part of the NHIS biennial health screening program. Charlson Comorbidity Index was calculated based on the cumulative medical claims data of the baseline period.

2.5. Statistical analysis

Beginning on January 1, 2006, each participant was censored at the first event of cancer, death from cancer or other causes, or December 31, 2015, whichever occurred first. Cancer incidences and person-years for each participant were arranged according to change in smoking status and weight change groups. We conducted one-way analysis of variance (ANOVA) to compare mean weight change across the categories of smoking status and weight change. We used Cox proportional-hazards regression models adjusted for age, residential area, insurance premium, body mass index, fasting serum glucose, total cholesterol, alcohol consumption, physical activity, family history of cancer, and Charlson Comorbidity Index to calculate hazard ratio (HR) and 95% confidence intervals (95% CI) for each type of cancers among quitters with different degrees of weight change (2.0 kg according to the average weight gain in Asian male) and never smokers as compared to continual smokers. The proportionality assumption of the Cox regression model was tested graphically using log-log plots. For secondary analyses, we used the same Cox regression model to compute adjusted HR and 95% CI for each type of cancers among quitters with different weight change category (5.0 kg adopted from the average weight gain with smoking cessation in the U.S cohort). In addition, we examined the relationship between smoking cessation and weight change (treated as a continuous variable) among quitters with restricted cubic spline with 4 knots (lowest value of Bayesian information criteria) for all cancer incidences using quitters with weight change of 0.0 kg as reference. For sensitivity analysis, we excluded cancer events up to 2 years during the follow-up to account for the possibility of undetected cancer or poor health condition among quitters with weight loss. 2-sided p-values < 0.05 was considered statistically significant and was two sided. We performed data management and statistical analysis using SAS version 9.4 (SAS Institute, Cary, NC, USA) and STATA 14 (StataCorp, College Station, TX, USA).

3. Results

3.1. Study population

Among 1,278,794 young men enrolled in this study, there were 58.7% (n = 750,060) continual smokers, 8.5% quitters (n = 106,967) and 32.8% (n = 421,767) never smokers (Table 1). About two-thirds of continual smokers had smoking history of 10–19 years and reported to smoke 10–19 cigarettes per day at baseline. Most of the quitters had weight gain of more than 2.0 kg (42.4%) or without weight change

Table 1
Baseline characteristics of young men (20–39 years) in the National Health Insurance Service database, according to change in smoking status.

Characteristics at Baseline	Continual Smokers (*N = 750,060*)	Quitters				Never Smokers (*N = 421,767*)
		All Quitters (*N = 106,967*)	Quitters with Weight gain* (*N = 45,414*)	Quitters without Weight gain† (*N = 51,072*)	Quitters with Weight loss‡ (*N = 10,481*)	
Age, years, mean (SD)	34.6 (4.84)	35.3 (4.60)	34.7 (4.64)	35.7 (4.54)	35.7 (4.45)	35.2 (4.89)
Residential Area						
Capital	120,280 (16.0)	18,547 (17.3)	7,410 (16.3)	9,126 (17.9)	2,011 (19.2)	72,346 (17.2)
Metropolitan	211,835 (28.2)	28,977 (27.1)	12,500 (27.5)	13,769 (27.0)	2,708 (25.8)	111,060 (26.3)
City/Town	417,945 (55.8)	59,443 (55.6)	25,504 (56.2)	28,177 (55.1)	5,762 (55.0)	238,361 (56.5)
Insurance Premium						
1Q	78,383 (10.5)	7,887 (7.4)	3,434 (7.6)	3,664 (7.2)	789 (7.5)	36,647 (8.7)
2Q	157,552 (21.0)	17,323 (16.2)	7,923 (17.5)	7,707 (15.1)	1,693 (16.2)	71,080 (16.9)
3Q	292,794 (39.0)	40,773 (38.1)	18,031 (39.7)	18,914 (37.0)	3,828 (36.5)	154,658 (36.7)
4Q	221,331 (29.5)	40,984 (38.3)	16,026 (35.2)	20,787 (40.7)	4,171 (39.8)	159,382 (37.7)
Prevalence of Obesity§	269,108 (35.9)	42,876 (40.1)	20.963 (46.1)	18,208 (35.7)	3,705 (35.5)	142,527 (33.8)
Body Mass Index, kg/m^2, mean (SD)	24.0 (3.5)	24.4 (2.9)	24.9 (2.9)	24.0 (2.86)	24.0 (3.0)	23.9 (2.9)
Weight Change¶						
Mean (SE) [95% CI]	0.95 (0.01) [0.94 to 0.96]	1.95 (0.01) [1.93 to 1.98]	5.35 (0.01) [5.33 to 5.37]	0.34 (0.01) [0.33 to 0.36]	−4.91 (0.03) [-4.96 to -4.86]	0.74 (0.01) [0.73 to 7.75]
Median (IQR)	1.0 (-1.0 to 3.0)	2.0 (0.0 to 4.0)	5.0 (3.0 to 6.0)	0.0 (-1.0 to 2.0)	−4.0 (-6.0 to -3.0)	1.0 (-1.0 to 3.0)
FSG, mg/dL, mean (SD)	92.4 (21.7)	92.4 (19.5)	92.1 (17.1)	92.2 (18.6)	95.4 (30.5)	91.2 (18.8)
Total Cholesterol, mg/d, mean (SD)	191.6 (40.5)	194 .2 (36.9)	196.8 (35.3)	192.7 (37.7)	190.3 (39.5)	189.2 (40.4)
Blood Pressure, mmHg, mean (SD)						
SBP	123.2 (13.2)	123.4 (13.2)	124.3 (13.0)	122.7 (13.2)	123.2 (13.6)	122.5 (13.1)
DBP	77.9 (9.7)	78.0 (9.6)	78.5 (9.5)	77.6 (9.7)	77.8 (9.9)	77.5 (9.6)
Cigarettes smoked/day						
< 10/day	118,300 (15.8)	–	–	–	–	–
10-19/day	459,377 (61.4)	–	–	–	–	–
20-39	164,678 (22.0)	–	–	–	–	–
≥40	5,701 (0.8)	–	–	–	–	–
Smoking history		–				
< 10 years	191,493 (25.5)	39,532 (37.1)	16,362 (36.0)	19,099 (37.4)	4,171 (39.8)	
10-19 years	455,731 (60.8)	45,001 (42.1)	19,474 (42.9)	21,304 (41.7)	4,223 (40.3)	
≥20 years	102,836 (13.7)	22,334 (20.8)	9,578 (21.1)	10.669 (20.9)	2,087 (19.9)	
Alcohol Consumption						
None/Barely any 2-3 times/month	113,532 (15.1) 213,989 (28.5)	18,566 (17.4)36,407 (34.0)	7,601 (16.7) 14,738 (32.5)	8,879 (17.4) 17,859 (35.0)	2,086 (19.9) 3,810 (36.4)	177,178 (42.0) 124,037 (29.4)
1-2 times/week	315,028 (42.0)	40,986 (38.3)	17,866 (39.3)	19,416 (38.0)	3,704 (35.3)	102,429 (24.3)
3-4 times/week	91,130 (12.1)	9,604 (8.9)	4,494 (9.9)	4,338 (8.5)	772 (7.4)	15,784 (3.7)
≥5 times/week	17,381 (2.2)	1,404 (1.4)	715 (1.6)	580 (1.1)	109 (1.0)	2,339 (0.6)
Physical Activity						
None	314,313 (41.9)	38,486 (35.9)	17,528 (38.6)	17,944 (35.1)	3,014 (28.8)	189,849 (45.0)
1-2 times/week	312,445 (41.7)	43,799 (40.9)	18,767 (41.3)	21,107 (41.3)	3,925 (37.4)	153,184 (36.3)
3-4 times/week	85,731 (11.4)	17,588 (16.4)	6,641 (14.6)	8,651 (16.9)	2,296 (21.9)	55,316 (3.1)
5-6 times/week	15,860 (2.1)	3,495 (3.3)	1,162 (2.6)	1,697 (3.3)	636 (6.1)	636 (6.1)
Almost everyday	21,711 (2.9)	3,499 (3.5)	1,316 (2.9)	1,673 (3.3)	610 (5.8)	12,744 (3.0)
Family History of Cancer	82,795 (11.0)	13,266 (12.4)	5,666 (12.5)	6,393 (12.5)	1,207 (11.5)	41,205 (9.7)
Charlson Comorbidity Index						
0	425,620 (56.7)	55,076 (51.5)	24,004 (52.9)	26,052 (51.0)	5,020 (47.9)	214,654 (50.9)
1	238,033 (31.7)	36,986 (34.6)	15,497 (34.1)	17,814 (34.9)	3,675 (35.1)	147,631 (35.0)
≥2	86,407 (11.6)	14,905 (13.9)	5,913 (13.0)	7,206 (14.1)	1,786 (17.0)	59,482 (14.1)

All data above are in reference to the second health examination period (2004–2005) except for weight change.
Values are presented as no. (%) unless otherwise stated.
Abbreviations: Q quartile; SD standard deviation; SE standard error; IQR interquartile range; BMI Body Mass Index; FSG Fasting Serum Glucose; SBP Systolic Blood Pressure; DBP Diastolic Blood Pressure;

* Weight gain of more than +2.0 kg in the second health examination period (2004–2005) compared to the first health checkup (2002–2003).
† Weight change within ± 2.0 kg in the second health examination period (2004–2005) compared to the first health checkup (2002–2003).
‡ Weight loss of more than -2.0 kg in the second health examination period (2004–2005) compared to the first health checkup (2002–2003).
§ Defined as BMI ≥ 25 kg/m^2 according to the Korean Society for the Study of Obesity.
¶ Change in weight between the two consecutive health examination (2002–2003 and 2004–2005) periods.

within 2.0 kg (47.8%). Continual smokers and never smokers had no significant weight change (median +1.0 kg of weight change, range -1.0 to 3.0 kg). Weight change was significantly different across the smoking status and weight change groups ($p < 0.0001$ from ANOVA test).

3.2. Smoking cessation, weight gain, and cancer risk

There were 21,494 cancer incidences among 1,278,794 young men during the 10 years of follow-up. Of the incidences of cancer in the study participants, approximately half of them were obesity-related (n = 10,314) and smoking-related (n = 12,617). After adjustment for

Table 2
Hazard ratio and 95% confidence intervals of all-cancer and specific cancer types in past-smokers as compared to continual smokers among young men (20–39 years) according to weight change (by 2.0 kg) following smoking cessation.

		Quitters				
	Continual Smokers (*N = 750,060*)	All Quitters (*N = 106,967*)	Quitters with Weight gain* (*N = 45,414*)	Quitters without Weight gain† (*N = 51,072*)	Quitters with Weight loss‡ (*N = 10,481*)	Never Smokers (*N = 421,767*)
All-Cancer						
No. of cases	12,447	1,888	751	921	216	7,159
Age-adjusted HR (95% CI)	1 (reference)	1.01 (0.96-1.06)	0.99 (0.92-1.07)	1.00 (0.93-1.07)	1.14 (0.99-1.31)	0.97 (0.94-1.00)
Multivariate adjusted§ HR (95% CI)	1 (reference)	0.97 (0.93-1.02)	0.94 (0.88-1.01)	0.97 (0.91-1.04)	1.11 (0.97-1.27)	0.95 (0.92-0.98)[a]
Obesity-related cancer¶						
No. of cases	6,439	905	372	431	102	2,970
Age-adjusted HR (95% CI)	1 (reference)	0.91 (0.85-0.98)[a]	0.95 (0.86-1.05)	0.87 (0.79-0.96)[a]	1.01 (0.83-1.23)	0.76 (0.73-0.80)[a]
Multivariate adjusted§ HR (95% CI)	1 (reference)	0.91 (0.85-0.98)[a]	0.93 (0.84-1.04)	0.88 (0.79-0.97)[a]	1.01 (0.83-1.23)	0.78 (0.75-0.82)[a]
Smoking-related cancer**						
No. of cases	7,838	1,107	441	539	127	3,672
Age-adjusted HR (95% CI)	1 (reference)	0.92 (0.87-0.98)[a]	0.93 (0.84-1.02)	0.90 (0.82-0.98)[a]	1.04 (0.87-1.24)	0.77 (0.74-0.81)[a]
Multivariate adjusted§ HR (95% CI)	1 (reference)	0.92 (0.86-0.98)[a]	0.91 (0.82-1.00)	0.90 (0.83-0.98)[a]	1.03 (0.87-1.23)	0.79 (0.76-0.82)[a]
GI-cancer††						
No. of cases	5,890	829	348	400	81	2,698
Age-adjusted HR (95% CI)	1 (reference)	0.92 (0.85-0.98)[a]	0.97 (0.87-1.08)	0.88 (0.80-0.98)[a]	0.87 (0.70-1.09)	0.76 (0.72-0.79)[a]
Multivariate adjusted§ HR (95% CI)	1 (reference)	0.92 (0.85-0.99)[a]	0.96 (0.86-1.07)	0.89 (0.80-0.98)[a]	0.87 (0.70-1.09)	0.78 (0.75-0.82)[a]
Lung cancer						
No. of cases	674	89	31	48	10	318
Age-adjusted HR (95% CI)	1 (reference)	0.86 (0.69-1.07)	0.76 (0.53-1.08)	0.93 (0.69-1.24)	0.95 (0.51-1.77)	0.78 (0.68-0.89)[a]
Multivariate adjusted§ HR (95% CI)	1 (reference)	0.86 (0.69-1.07)	0.75 (0.52-1.08)	0.91 (0.68-1.23)	0.95 (0.51-1.77)	0.77 (0.67-0.89)[a]
Gastric Cancer						
No. of cases	2,682	372	160	177	35	1,138
Age-adjusted HR (95% CI)	1 (reference)	0.90 (0.81-1.01)	0.98 (0.84-1.15)	0.86 (0.74-1.00)	0.83 (0.74-1.00)	0.70 (0.60-0.75)[a]
Multivariate adjusted§ HR (95% CI)	1 (reference)	0.91 (0.81-1.01)	0.98 (0.83-1.15)	0.86 (0.74-1.00)	0.84 (0.60-1.18)	0.73 (0.68-0.79)[a]
Colorectal Cancer						
No. of cases	2,055	304	131	144	29	1,114
Age-adjusted HR (95% CI)	1 (reference)	0.97 (0.86-1.09)	1.05 (0.88-1.25)	0.92 (0.78-1.09)	0.91 (0.63-1.31)	0.90 (0.84-0.97)[a]
Multivariate adjusted§ HR (95% CI)	1 (reference)	0.95 (0.84-1.08)	1.02 (0.85-1.21)	0.95 (0.76-1.07)	0.91 (0.63-1.31)	0.93 (0.86-1.00)
Liver Cancer						
No. of cases	1,320	161	62	82	17	551
Age-adjusted HR (95% CI)	1 (reference)	0.79 (0.67-0.93)[a]	0.77 (0.60-0.99)	0.79 (0.64-0.99)	0.81 (0.50-1.31)	0.68 (0.62-0.75)[a]
Multivariate adjusted§ HR (95% CI)	1 (reference)	0.81 (0.69-0.96)[a]	0.79 (0.61-1.02)	0.83 (0.66-1.03)	0.79 (0.59-1.28)	0.67 (0.61-0.75)[a]

Abbreviations: GI, gastrointestinal; ICD-10, international classification of disease, 10th revision.

* Weight gain of more than +2.0 kg in the second health examination period (2004–2005) compared to the first health checkup (2002–2003).

† Weight change within ± 2.0 kg in the second health examination period (2004–2005) compared to the first health checkup (2002–2003).

‡ Weight loss of more than -2.0 kg in the second health examination period (2004–2005) compared to the first health checkup (2002–2003).

§ Adjusted for age, residential area, insurance premium, body mass index, fasting serum glucose, total cholesterol, alcohol consumption, physical activity, family history of cancer, and Charlson Comorbidity Index.

¶ Includes esophageal cancer, gastric cancer, colorectal cancer, liver cancer, kidney cancer, multiple myeloma, meningioma, pancreatic cancer, and gallbladder cancer (U.S National Cancer Institute).

** Includes cancers of head and neck, esophagus, stomach, colorectum, liver, pancreas, larynx, trachea, lung, bladder, kidney, kidney pelvis, or ureter, and acute myeloid leukemia (U.S Surgeon General's Report, 2014).

†† Includes cancers of gastrointestinal tract and digestive organs (ICD-10 codes: C15-C26).

[a] $p < 0.05$.

Table 3
Sensitivity analyses for the association of smoking cessation, weight change, and risk of all-cancer in young men (20–39 years).

		Quitters				
	Continual Smokers	All Quitters	Quitters with Weight gain*	Quitters without Weight gain†	Quitters with Weight loss‡	Never Smokers
Excluding the events up to the first year of follow-up						
No. of cases	11,751	1,780	712	863	205	6,727
Age-adjusted HR (95% CI)	1 (reference)	0.78 (0.66-0.93)[a]	0.78 (0.60-1.01)	0.80 (0.63-1.00)	0.75 (0.45-1.25)	0.67 (0.60-0.74)[a]
Multivariate adjusted§ HR (95% CI)	1 (reference)	0.81 (0.68-0.96)[a]	0.80 (0.61-1.04)	0.83 (0.66-1.04)	0.74 (0.44-1.23)	0.66 (0.59-0.74)[a]
Excluding the events up to 2 years of follow-up*						
No. of cases	10,866	1,635	660	786	189	6,236
Age-adjusted HR (95% CI)	1 (reference)	0.78 (0.66-0.94)[a]	0.73 (0.55-0.97)[a]	0.83 (0.66-1.04)	0.77 (0.46-1.31)	0.65 (0.58-0.73)[a]
Multivariate adjusted§ HR (95% CI)	1 (reference)	0.81 (0.68-0.97)[a]	0.76 (0.57-1.00)	0.86 (0.68-1.09)	0.76 (0.45-1.28)	0.65 (0.58-0.73)[a]

* Exclusion of all-cancer events within 2 years of follow-up (including the cases in the first year).
[a] $p < 0.05$.

potential confounders, weight gain with smoking cessation (weight gain of more than 2.0 kg) was associated with no significant decrease in obesity-related cancer (HR, 0.93; 95% CI, 0.84–1.04), but was associated with marginal decrease in smoking-related cancer (HR, 0.91; 95% CI, 0.82–1.00) risk as compared to continual smoking. Quitters without weight gain (weight change within ± 2.0 kg) had a significantly decreased risk of obesity-related cancer (HR, 0.88; 95% CI, 0.79 to 0.97), smoking-related cancer (HR, 0.90; 95% CI, 0.83 to 0.98), and GI cancer (HR, 0.86; 95% CI, 0.89 to 0.98) compared to continual smokers. Never smokers had a significantly decreased risk of cancer as compared with continual smokers. When cancer events were excluded up to 2 years of the follow-up period, similar results were observed (Table 3).

3.3. Secondary analyses

To further explore the association between weight change with smoking cessation and risk of cancer, we categorized quitters by 5.0 kg (average weight gain observed in the U.S cohort). Protective association of smoking cessation with cancer was attenuated among quitters with weigh gain of more than 5.0 kg. Weight change within 5.0 kg with smoking cessation was associated with significantly lower risk of obesity-related cancer, smoking-related cancer, GI-cancer, and liver cancer. Quitters with weight loss of more than 5.0 kg showed a non-significant increase in cancer risk (Table S1 in the Supplementary Appendix). When we further classified quitters into quitters with severe weight gain (≥5.0 kg), quitters with moderate weight gain (2.0–5.0 kg), quitters without weight change (± 2.0 kg), and weight loss (≤-2.0 kg), risk of obesity-related cancer, smoking-related cancer, and GI-cancer were lower among quitters without weight change (Table S2 in the Supplementary Appendix). When we stratified the participants by residential area, insurance premium, presence of obesity, alcohol consumption, physical activity, and Charlson comorbidity index, the risk ratio for all-cancer, obesity-related cancer, smoking-related cancer, and GI cancer showed similar results compared to the main analyses for each subgroup (Table S3-S6 in the Supplementary Appendix). When we restricted the analysis among quitters to examine the association between weight change with smoking cessation and risk of cancer, weight gain up to approximately 5.0 kg was associated with lower risk of all cancer. No protective association of smoking cessation with cancer was observed among quitters with weight loss (Fig. 1).

4. Discussion

This large cohort study of young men in the Republic of Korea demonstrated that weight gain with smoking cessation was not associated with reduced cancer risk. After 10 years of follow-up, we found a significant decrease in risk of cancer among quitters without weight gain of more than 2.0 kg as compared with continual smokers. Weight gain of more than 2.0 kg with smoking cessation was not associated with significantly decreased risk of cancer compared to continual smoking. The risk of cancer remained significantly lower among quitters with weight gain up to approximately 5.0 kg. Although the protective association of smoking cessation with cancer is well-established, our study suggests that weight management along with smoking cessation is an important factor for successfully reducing risk of cancer in young men.

Weight gain is strongly associated with smoking cessation, and still remains as one of the factors that discourages current smokers from quitting smoking [29]. In a meta-analysis of 35 prospective cohort studies including a total of 451,835 adult participants who were followed up to 12 months after cessation found that quitters had a mean weight gain of 4.0 to 5.0 kg. Tian et al. reported that smoking cessation was associated with 2.61 kg of excess weight gain as compared to continual smoking [30] (at least 3 months from the baseline). In analysis of 1,995 Japanese male workers in the High-risk and Population Strategy for Occupational Health Promotion study, smoking cessation

was associated with approximately 2.0 kg of weight gain over a 4-year period [23]. Also, Asian male older than 30 years of age showed 1.57 kg of weight gain with quitting smoking based on the health examination records of 2,848 patients with 1 to 3 year interval between the measurements [22]. In our study, about half of the quitters had weight gain of more than 2.0 kg and approximately a quarter of them gained more than 5.0 kg. Our results are consistent with the previous findings that smoking cessation is associated with subsequent weight gain, which is mainly attributable to increased caloric intake without substantial change in physical activity [31]. Therefore, physical activity has been suggested as one of the interventions to minimize weight gain following smoking cessation [32].

Little is known about the association of weight gain attributable to smoking cessation with risk of several cancer types. In a longitudinal study of general population of Korean men over 40 years of age, smoking cessation was associated with a significant decrease in all cancer and smoking-related cancer regardless of the intensity of smoking at baseline [33]. A significant decrease in colorectal cancer risk among quitters as compared to continual smokers was observed in the Health Professionals Follow-up Study and Nurses' Health Study [34]. In addition, a pooled analysis of five contemporary cohorts in the U.S showed that cigarette smoking is related to death from stomach, esophageal, liver, pancreatic, and other types of cancer [35], some of which are included in obesity-related cancer category as suggested by the U.S National Cancer Institute. However, these cohort studies did not evaluate whether weight gain following quitting smoking attenuates the protective effect of cancer with smoking cessation. We found that the protective association of smoking cessation with cancer was attenuated among quitters with excess weight gain of more than 2.0 kg as compared to continual smoking. In contrast, those without weight gain of more than 2.0 kg had a significantly lower risk of smoking-related, obesity-related, and GI cancer. Weight loss of more than 2.0 kg with smoking cessation was associated with a non-significant increase in cancer risk, suggesting that substantial decrease in body weight with smoking cessation may be an indicator of poor general health or hidden malignancy [36], which could be a residual confounder.

Overall, weight gain with smoking cessation may attenuate to the health benefits of smoking cessation for cancer prevention. Substantial evidence from large cohort studies such as Korea National Health Insurance Corporation cohort [15] and cohort of Swedish men [37] and meta-analyses of prospective observational studies [38] suggest a positive association between excess body weight and increased risk of a wide range of cancer types. Although the biological mechanisms by which weight gain accelerates cancer develop may vary by cancer sites, excessive adipose tissue, if accumulated after smoking cessation, may induce insulin resistance, chronic hyperinsulinemia, and localized inflammation that contribute to increased cancer risk [39,40]. Despite these plausible mechanism, further studies are necessary to examine the composite health benefits and harms of smoking cessation in relation to several cancer types.

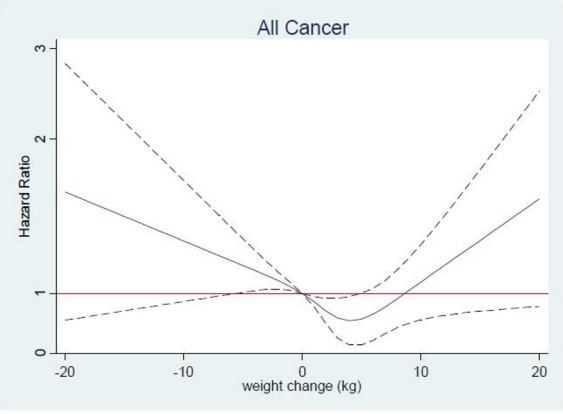

Fig. 1. Association between weight change following smoking cessation and risk of all cancer in male quitters, plotted with restricted cubic spline model. Reference group is quitters with weight change of 0.0 kg, and the model was adjusted for all the variables included in multivariable model (see Table 2 for variables).

A notable strength of this study is its large size of study population including more than 1 million young men with reliable information on health examination, medical claims, and death records. Another strength is that we were able to collect data on sociodemographic factors, health status, comorbidities, and family history from a linked database for adjustment in risk estimates for cancer. Also, classification of cancer types in the NHIS database was based on reliable medical claims and relevant codes among the participants [41], and did not rely on the secondary data source. Furthermore, we were able to conduct several sensitivity analyses with different categorization of weight change that were generally consistent with the main analysis.

There are several limitations in this study that should be noted. First, change in smoking status, especially for those who had quit smoking, was identified from self-reported survey without biochemical assays or information on nicotine dependence, which was not available in the NHIS database. However, confirmation of smoking status by laboratory assessment is rarely available in a large population-based cohort. In addition, since smoking status and weight measurement data were based on the two surveys between 2002–2003 and 2004–2005, timing and accuracy of weight change need to be considered in future studies to account for residual confounding. Second, additional risk factors for cancer, such as dietary intake, genetic mutations, and environmental carcinogen were unobtainable and not adjusted in the risk estimates because such data could not be collected in this study. Also, this study was limited to young men who were subject to the national health screening program provided by the NHIS. Therefore, further studies are needed in women and other ethnic groups of older age to confirm the association of post-cessation weight change with cancer risk observed in this study.

In conclusion, this population-based examination on weight change with smoking cessation and cancer risk showed that the protective effect of smoking cessation was attenuated among quitters with excessive weight gain in young men. Although these associations need to be examined a step further, findings of our study suggest the importance of weight management with smoking cessation to reduce cancer risk.

Ethical approval

This study was approved by the National Health Insurance Service and the Institutional Review Board (IRB) at the Seoul National University Hospital (IRB No: 1703-039-836).

Transparency

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Authors' contributions

K.K and S.M.P conceived the study. K.K and S.C collected data and performed the statistical analyses with the assistance of Y.Y.K and S.Y.P. All authors were involved in interpretation of the data. K.K wrote the first draft of the manuscript under the supervision of S.M.P. All authors provided intellectual contents and commented on the first draft for critical revisions. All authors approved the final manuscript.

Role of the sponsor

The Ministry of Health & Welfare in the Republic of Korea had no role in the study conceptualization, design, analysis, and interpretation of the data. This funding source also had no role in preparation, review, or approval of the final manuscript.

Authorship contribution statement

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Data analysis and interpretation: All authors.
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Manuscript editing: All authors.
Manuscript review: All authors.

Conflict of interest

None to declare.

Acknowledgement

We would like to thank the National Health Insurance Service for providing the dataset (NHIS-2017-1-143). Kyuwoong Kim received a scholarship from the BK21-plus education program provided by the National Research Foundation of Korea. This research was supported by the Ministry of Health and Welfare in the Republic of Korea (Grant No: 20170322652-00).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.03.005.

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