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ORIGINAL REPORT

Impact of Prediagnosis Smoking, Alcohol, Obesity, and Insulin Resistance on Survival in Male Cancer Patients: National Health Insurance Corporation Study

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ABSTRACT

Purpose
Although many studies have demonstrated that smoking, alcohol, obesity, and insulin resistance are risk factors for cancer, the role of those factors on cancer survival has been less studied.

Patients and Methods
The study participants were 14,578 men with a first cancer derived from a cohort of 901,979 male government employees and teachers who participated in a national health examination program in 1996. We obtained mortality data for those years from the Korean Statistical Office. We used a standard Poisson regression model to estimate the hazard ratio (HR) for survival in relation to smoking, alcohol, obesity, and insulin resistance before diagnosis.

Results
Poor survival of all cancer combined (HR, 1.24; 95% CI, 1.16 to 1.33), cancer of the lung (HR, 1.45; 95% CI, 1.15 to 1.82), and cancer of the liver (HR, 1.36; 95% CI, 1.21 to 1.53) were significantly associated with smoking. Compared with the nondrinker, heavy drinkers had worse outcomes for head and neck (HR, 1.85; 95% CI, 1.23 to 2.79) and liver (HR, 1.25; 95% CI, 1.11 to 1.41) cancer, with dose-dependent relationships. Patients with a fasting serum glucose level above 126 mg/dL had a higher mortality rate for stomach (HR, 1.52; 95% CI, 1.25 to 1.84) and lung (HR, 1.48; 95% CI, 1.18 to 1.87) cancer. Higher body mass index was significantly associated with longer survival in head and neck (HR, 0.54; 95% CI, 0.39 to 0.74) and esophagus (HR, 0.44; 95% CI, 0.28 to 0.68) cancer.

Conclusion
Prediagnosis risk factors for cancer development (smoking, alcohol consumption, obesity, and insulin resistance) had a statistically significant effect on survival among male cancer patients.

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INTRODUCTION

Many large, population-based studies demonstrate that smoking,[1,2] alcohol consumption,[3] obesity,[4-7] and insulin resistance[8-10] are risk factors for cancer in the general population. The role of those factors in relation to prognosis, however, is less clear.

Smoking and alcohol consumption are predictors of survival in lung and head and neck cancers,[11-13] and findings of obesity[14,15] or insulin resistance[16,17] at the time of diagnosis are associated with higher mortality for colorectal and breast cancer patients. Those important prognosis predictors, as well as exercise and comorbidities, have not been considered fully. In addition, because most studies collect risk factor information after the first cancer is diagnosed,[11,13-17] results can be affected by behavior changes that follow the diagnosis. Although some studies collect information about prior health behavior,[12,18] there is a chance of recall bias. To our knowledge, no prospective study has assessed behavior risk factors before cancer development and investigated the impact of smoking, alcohol, obesity, and insulin resistance on survival.

Previously, we conducted a prospective cohort investigation, the National Health Insurance Corporation Study (NHICS), of more than one million Koreans.[1,2] During the 7 years of follow-up, more than 14,900 men were diagnosed with a first cancer. From that cohort, we identified the effect on survival of health behaviors that existed before the diagnosis.

PATIENTS AND METHODS

Study Population and Data Collection

The NHIC provides health insurance to government employees and teachers along with biennial health examinations that include height, weight, and blood pressure measurements; chest radiography; urinalysis; blood counts; and blood chemistries. Serum glucose is measured under fasting

conditions using clinical laboratories with standard quality assurance and control protocols in place. A single measurement of fasting serum glucose made for clinical purposes is used as a diagnostic standard and matches WHO recommendations.[19] In addition, a self-administered questionnaire collects information regarding medical history, current health status, family history, tobacco and alcohol use, dietary preferences, and leisure-time physical activity (frequency and duration).

We classified participants as current, former, or never smokers on the basis of their response to the following question on the 1996 baseline questionnaire: "Do you smoke cigarettes now?" (yes/had smoked but quit/never). We used body mass index (BMI), calculated as kilograms per square meter at enrollment, as a measure of relative body fat and divided the cohort into three BMI groups according to the classification proposed by WHO for the Western Pacific region.[20]

The study participants were derived from 901,979 men 20 years or older who participated in the national health examination program staring in 1996 and were in the NHICS cohort.[1,2] We restricted our analysis to men because the women were generally younger and the number with cancer was too small for analysis.

The Korean Central Cancer Registry is a nationwide hospital-based system that includes 94% of the country's university hospitals and 96% of the resident training hospitals; it covers at least 90% of the newly diagnosed malignancies in Korea.[21] Using the Korean Central Cancer Registry, we identified 14,996 men who were diagnosed with a first cancer from 1996 to 2002. We excluded patients who were diagnosed with multiple primary cancer (n = 418), and this left 14,578 patients in the study. We gathered 1996 to 2004 mortality data by linkage to the National Statistical Office. We observed participants until December 31, 2004. During the 9-year follow-up period of 44,171.34 person-years, we identified 7,271 deceased patients.

Statistical Methods

The person-years at risk accumulated for each patient were calculated from the date of diagnosis of the first primary cancer to the date of death or December 31, 2004, whichever came first.

We used a standard Poisson regression model to calculate the age-adjusted mortality rate for each category of variable and to estimate the hazard ratio (HR) for death in relation to smoking history, alcohol intake, and insulin resistance before the first primary tumor. For multivariate analyses, we used the following categories: smoking status (current, former, or never smoker); alcohol consumption (0, 1 to 124.1, ≥ 124.2 g/wk); BMI (< 23, 23 to 24.9, ≥ 25 kg/m^2); fasting glucose level (< 110, 110 to 125, ≥ 126 mg/dL); physical activity as low (active four times/wk, < 30 minutes each time), moderate (active > five times/wk, < 30 minutes each time or active > two times/wk, > 30 minutes each time), or high (active > five times/wk, > 30 minutes each time); cholesterol level (< 200, 201-239, ≥ 240 mg/dL); and food preference (vegetables, mixed, meat), adjusting for age or other variables. We tested for linear trends by testing the significance of the term in a likelihood ratio test.

All statistical tests were two sided and performed with SAS statistical package version 8.1 (SAS Institute Inc, Cary, NC). We considered $P < .05$ statistically significant.

Table 1. Baseline Characteristics of the Study Population (N = 14,578)

Characteristic	Alive		Dead	
	No.	%	No.	%
Age, years				
≤ 49	3,143	43.0	2,515	34.6
50-59	3,145	43.0	3,647	50.2
≥ 60	1,019	14.0	1,109	15.2
Place of residence				
Metropolitan area	3,304	45.2	3,307	45.5
City	2,524	34.5	2,421	33.3
Country	1,479	20.2	1,543	21.2
Job				
White collar	1,511	20.7	1,446	19.9
Blue collar	5,796	79.3	5,825	80.1
Smoking status				
Never	1,397	19.6	1,169	16.5
Former	1,296	18.1	1,146	16.2
Current	4,452	62.3	4,761	67.3
Body mass index, kg/m^2				
< 23	2,888	39.5	3,168	43.6
23-24.9	2,175	29.8	2,048	28.2
25-29.9	2,144	29.4	1,944	26.7
≥ 30	98	1.3	111	1.5
Physical activity				
Low	4,328	60.2	4,437	60.6
Moderate	2,328	32.4	2,129	30.0
High	530	7.38	528	7.4
Alcohol consumption, g/wk				
0	1,243	17.4	1,310	18.7
< 51.8	1,196	16.8	1,075	15.3
51.9-124.1	1,858	26.0	1,677	23.9
124.2-289.7	2,074	19.1	2,121	30.2
≥ 289.8	768	10.8	836	11.9
Fasting serum glucose level, mg/dL				
< 110	6,191	85.0	5,882	81.3
110-125	599	8.2	627	8.6
126-139	145	2.0	179	2.5
≥ 140	350	4.8	549	7.6
Comorbidity				
Hypertension	1,278	17.5	1,495	20.6
Heart disease	254	3.5	354	4.9
Liver disease	355	4.9	602	8.3
Cerebrovascular disease	79	1.1	52	0.7

RESULTS

The mean age of the 14,578 participants was 50.8 years. Table 1 shows the baseline characteristics of the subjects. The mean duration of follow-up was 3.03 years (maximum, 6.8 years). There were 7,271 deaths, of which only 421 (5.8%) were not related to cancer (Table 2).

Table 2. Distribution of Primary Cancer Site in Study Participants and Cause of Death

Site	No. of Patients	No. of Deaths	Cause of Death		Median Follow-Up Duration (years)
			Cancer	Other	
All	14,578	7,271	6,801	421	3.03
Head and neck	580	270	256	11	3.32
Esophagus	272	200	195	4	2.05
Stomach	3,979	1,502	1,414	69	3.54
Lung	1,548	1,179	1,124	53	1.87
Colorectal	1,882	555	524	23	3.78
Liver	2,815	2,171	2,013	155	1.89
Pancreas	348	307	293	14	1.15
Kidney	421	97	91	5	4.14
Bladder	432	53	43	9	4.69
Prostate	256	54	51	1	3.86

Smoking and Prognosis

Age- and multivariate-adjusted analyses showed significant relationships between smoking amount before the first cancer diagnosis and poor prognosis for all cancer combined (HR, 1.31; 95% CI, 1.21 to 1.42) and for cancer of the lung (HR, 1.40; 95% CI, 1.09 to 1.78), liver (HR, 1.48; 95% CI, 1.25 to 1.76), and pancreas (HR, 1.75; 95% CI, 1.12 to 2.73; Table 3). In stomach cancer patients, those with prediagnosis smoking history had better survival than nonsmokers in multivariate-adjusted analyses (HR, 0.83; 95% CI, 0.72 to 0.95).

Alcohol Consumption and Prognosis

Table 4 lists the estimated HR of death and 95% CIs by alcohol consumption. Compared with the nondrinker, patients who reported drinking at least 124.2 g alcohol per day had a significantly elevated death rate for head and neck (HR, 1.85; 95% CI, 1.23 to 2.79) and liver (HR, 1.25; 95% CI, 1.11 to 1.41) cancer, and multivariate analysis showed a dose-dependent relationship (Table 4). For patients with esophageal cancer, multivariate analysis revealed a significant trend of worse survival associated with amount of alcohol consumed ($P < .001$ for trend).

BMI and Prognosis

Compared with the reference category (BMI < 23 kg/m^2), patients with BMI ≥ 25 kg/m^2 had significantly better survival in head and neck (HR, 0.54; 95% CI, 0.39 to 0.74) and esophageal (HR, 0.44; 95% CI, 0.28 to 0.68) cancer and all cancer combined (HR, 0.90; 95% CI, 0.85 to 0.96), and multivariate analysis showed an inverse dose-dependent relationship (Table 5).

Fasting Serum Glucose Level and Prognosis

Cancer patients with the highest fasting serum glucose levels had a 38% higher risk of death than those with normal fasting serum glucose levels, even after statistical control of confounding factors.

In multivariate analysis, we observed positive linear trends for the relationship between fasting serum glucose level and mortality for head and neck (HR, 1.55; 95% CI, 0.99 to 2.42; $P < .044$ for trend), stomach (HR, 1.52; 95% CI, 1.25 to 1.84; $P < .001$ for trend), and lung cancer (HR, 1.48; 95% CI, 1.18 to 1.87; $P < .001$ for trend; Table 6).

When we repeated Poisson regression analysis to study the effects of smoking, alcohol, BMI, and insulin resistance on cancer-specific mortality, the results were similar to those for overall mortality.

Table 3. HR for Mortality by Prediagnosis Cigarette Smoking in Male Cancer Survivors

Site of Primary Cancer	Never Smoker		Former Smoker			Current Smoker			Pack-Years for Current Smokers: < 20			Pack-Years for Current Smokers: ≥ 20			*P* for Trend
	No. of Deaths	HR	No. of Deaths	HR	95% CI	No. of Deaths	HR	95% CI	No. of Deaths	HR	95% CI	No. of Deaths	HR	95% CI	
All	1,169		1,146			4,761			2,681			1,326			
Age aHR		1.0		1.00	0.92 to 1.09		1.25	1.17 to 1.33		1.25	1.17 to 1.34		1.34	1.23 to 1.45	< .001
Multivariate HR*		1.0		1.01	0.93 to 1.10		1.24	1.16 to 1.33		1.26	1.17 to 1.36		1.31	1.21 to 1.42	< .001
Head and neck	16		30			219			115			75			
Age aHR		1.0		1.53	0.93 to 2.51		2.01	1.33 to 3.06		2.08	1.35 to 3.22		2.12	1.34 to 3.34	< .001
Multivariate HR		1.0		1.18	0.71 to 1.95		1.52	0.99 to 2.34		1.63	1.04 to 2.55		1.51	0.94 to 2.43	.030
Esophagus	12		20			166			86			56			
Age aHR		1.0		0.97	0.47 to 1.99		1.67	0.93 to 3.00		1.86	1.01 to 3.42		1.58	0.84 to 2.95	.033
Multivariate HR		1.0		0.73	0.35 to 1.52		1.17	0.64 to 2.15		1.29	0.68 to 2.45		1.20	0.63 to 2.32	.146
Stomach	262		249			955			559			226			
Age aHR		1.0		0.78	0.65 to 0.92		0.88	0.76 to 1.00		0.90	0.77 to 1.04		0.85	0.71 to 1.02	.294
Multivariate HR		1.0		0.75	0.63 to 0.90		0.83	0.72 to 0.95		0.85	0.73 to 1.00		0.77	0.64 to 0.93	.048
Lung	88		165			895			427			380			
Age aHR		1.0		1.28	0.99 to 1.66		1.44	1.16 to 1.80		1.48	1.17 to 1.87		1.42	1.12 to 1.79	.004
Multivariate HR		1.0		1.34	1.02 to 1.76		1.46	1.16 to 1.83		1.53	1.20 to 1.95		1.40	1.09 to 1.78	.024
Colorectal	141		94			303			165			82			
Age aHR		1.0		0.68	0.52 to 0.88		0.93	0.76 to 1.13		0.92	0.73 to 1.15		1.08	0.82 to 1.43	.470
Multivariate HR		1.0		0.67	0.51 to 0.88		0.94	0.77 to 1.16		0.96	0.76 to 1.22		1.13	0.84 to 1.50	.268
Liver	372		357			1,387			830			282			
Age aHR		1.0		1.20	1.03 to 1.38		1.43	1.27 to 1.60		1.43	1.27 to 1.62		1.62	1.39 to 1.90	< .001
Multivariate HR		1.0		1.14	0.98 to 1.33		1.33	1.18 to 1.50		1.33	1.17 to 1.52		1.48	1.25 to 1.76	< .001
Pancreas	44		54			196			111			54			
Age aHR		1.0		1.20	0.81 to 1.79		1.18	0.85 to 1.64		1.12	0.78 to 1.61		1.73	1.15 to 2.58	.029
Multivariate HR		1.0		1.08	0.70 to 1.68		1.20	0.84 to 1.72		1.19	0.80 to 1.79		1.75	1.12 to 2.73	.018
Kidney	17		11			66			35			22			
Age aHR		1.0		0.85	0.40 to 1.81		1.59	0.93 to 2.72		1.69	0.93 to 3.08		1.64	0.86 to 3.13	.033
Multivariate HR		1.0		0.76	0.35 to 1.68		1.60	0.91 to 2.82		1.81	0.95 to 3.44		1.49	0.75 to 2.99	.056
Bladder	5		8			40			20			16			
Age aHR		1.0		1.20	0.39 to 3.67		1.55	0.61 to 3.95		1.47	0.54 to 3.99		1.91	0.70 to 5.24	.148
Multivariate HR		1.0		1.23	0.38 to 4.00		1.88	0.71 to 4.98		2.00	0.68 to 5.84		2.52	0.85 to 7.46	.054
Prostate	14		8			29			17			8			
Age aHR		1.0		1.22	0.51 to 2.90		1.63	0.86 to 3.09		2.56	1.25 to 5.25		1.58	0.66 to 3.79	.058
Multivariate HR		1.0		1.09	0.43 to 2.73		1.56	0.79 to 3.06		2.49	1.11 to 5.56		1.63	0.63 to 4.24	.076

Abbreviations: HR, hazard ratio; aHR, adjusted hazard ratio.
*Multivariate HR model used a standard Poisson regression analysis adjusted for age, alcohol consumption, body mass index, fasting serum glucose level, cholesterol level, physical activity, food preference, blood pressure, and other comorbidities (heart disease, liver disease, and cerebrovascular disease).

Table 4. Hazard Ratio for Mortality by Prediagnosis Alcohol Consumption in Male Cancer Survivors

Site of Primary Cancer	Alcohol Consumption Amount, g/wk: 0 — No. of Deaths	0 — HR	0–124.1 — No. of Deaths	0–124.1 — HR	0–124.1 — 95% CI	≥ 124.2 — No. of Deaths	≥ 124.2 — HR	≥ 124.2 — 95% CI	*P* for Trend
All	1,310		2,752			2,957			
Age aHR		1.0		0.94	0.88 to 1.00		1.05	0.98 to 1.12	.014
Multivariate HR*		1.0		0.94	0.88 to 1.01		1.02	0.95 to 1.09	.146
Head and neck	22		83			151			
Age aHR		1.0		1.30	0.87 to 1.95		2.04	1.39 to 3.01	< .001
Multivariate HR		1.0		1.26	0.83 to 1.91		1.85	1.23 to 2.79	< .001
Esophagus	15		55			122			
Age aHR		1.0		0.88	0.49 to 1.56		1.46	0.85 to 2.51	.006
Multivariate HR		1.0		0.75	0.40 to 1.39		1.44	0.81 to 2.55	.003
Stomach	232		595			623			
Age aHR		1.0		1.03	0.88 to 1.19		1.12	0.97 to 1.31	.073
Multivariate HR		1.0		1.01	0.86 to 1.18		1.13	0.96 to 1.32	.058
Lung	194		453			488			
Age aHR		1.0		1.00	0.85 to 1.19		1.07	0.90 to 1.26	.351
Multivariate HR		1.0		0.99	0.83 to 1.18		0.99	0.83 to 1.17	.869
Colorectal	92		237			209			
Age aHR		1.0		1.00	0.78 to 1.27		0.93	0.73 to 1.19	.489
Multivariate HR		1.0		0.99	0.77 to 1.27		0.92	0.72 to 1.19	.467
Liver	501		744			862			
Age aHR		1.0		1.21	1.08 to 1.35		1.37	1.23 to 1.53	< .001
Multivariate HR		1.0		1.16	1.02 to 1.31		1.25	1.11 to 1.41	< .001
Pancreas	49		129			118			
Age aHR		1.0		0.89	0.64 to 1.24		0.82	0.59 to 1.14	.238
Multivariate HR		1.0		0.98	0.68 to 1.40		0.99	0.69 to 1.43	.993
Kidney	15		49			31			
Age aHR		1.0		1.33	0.73 to 2.44		0.95	0.49 to 1.82	.552
Multivariate HR		1.0		1.40	0.71 to 2.73		0.86	0.42 to 1.76	.282
Bladder	12		23			17			
Age aHR		1.0		0.75	0.37 to 1.53		0.59	0.28 to 1.25	.168
Multivariate HR		1.0		0.57	0.27 to 1.22		0.46	0.20 to 1.02	.076
Prostate	11		18			24			
Age aHR		1.0		1.18	0.56 to 2.50		1.81	0.88 to 3.75	.087
Multivariate HR		1.0		1.31	0.57 to 3.03		1.85	0.79 to 4.34	.138

Abbreviations: HR, hazard ratio; aHR, adjusted hazard ratio.
*Multivariate HR model used a standard Poisson regression analysis adjusted for age, alcohol consumption, body mass index, fasting serum glucose level, cholesterol level, physical activity, food preference, blood pressure, and other comorbidities (heart disease, liver disease, and cerebrovascular disease).

DISCUSSION

In this large population-based cohort study, we found that among male cancer survivors, prediagnosis smoking, alcohol consumption, obesity, and insulin resistance (all risk factors for cancer development) affected cancer prognosis.

Although smoking is clearly the most preventable cause of cancer, little is known about whether smoking adversely influences cancer patients' survival,[13,22] and the impact of smoking history on survival is controversial.[11-13,23-25] Some studies have reported that smoking history is a negative prognostic factor in lung, pancreatic, breast, renal, bladder, and head and neck cancer,[12,13,23,24] whereas other studies did not find an association.[11,25] Cancer patients with smoking history are at risk of death from a spectrum of smoking-associated disease,[12] but when we adjusted for other comorbidities and repeated our analysis of the effects of smoking on cancer-specific mortality, the results were similar to those for overall mortality. This finding suggests that smoking itself has a specific role in cancer progression.

One study reported that smokers have lower cancer screening rates than nonsmokers,[26] so one possible explanation is that smoking behavior may be associated with avoidance of cancer screening and therefore delayed diagnosis. Another possibility is that smoking causes more aggressive tumors. Research has demonstrated clonal genetic alterations in the lung epithelium of smokers, and microsatellite instability is common in colon tumors of smokers. Similar changes might be present in the mammary epithelium and lung cancer tissue of smokers.[22,23]

In this study, we found an unexpected association between prediagnosis smoking and better survival in stomach cancer patients. One explanation is that the histologic subtypes of gastric cancer differ for smokers and nonsmokers; habitual male smokers are more likely to have the well-differentiated type,[27] and stomach cancer patients with well-differentiated histology survive longer than those with poorly differentiated histology.[28] Although smoking is a risk factor for stomach cancer development, our study suggests that the prognostic effect of smoking is different for stomach cancer than for other cancers.

Table 5. Hazard Ratio for Mortality by Prediagnosis Body Mass Index in Male Cancer Survivors

Site of Primary Cancer	Body Mass Index, kg/m^2								
	< 23		23–24.9			≥ 25			
	No. of Deaths	HR	No. of Deaths	HR	95% CI	No. of Deaths	HR	95% CI	*P* for Trend
All	3,168		2,048			2,055			
Age aHR		1.0		0.89	0.84 to 0.94		0.88	0.84 to 0.93	< .001
Multivariate HR*		1.0		0.90	0.85 to 0.96		0.90	0.85 to 0.96	< .001
Head and neck	159		64			47			
Age aHR		1.0		0.81	0.62 to 1.04		0.53	0.40 to 0.70	< .001
Multivariate HR		1.0		0.90	0.68 to 1.18		0.54	0.39 to 0.74	< .001
Esophagus	122		49			29			
Age aHR		1.0		0.64	0.46 to 0.90		0.52	0.35 to 0.78	< .001
Multivariate HR		1.0		0.74	0.51 to 1.07		0.44	0.28 to 0.68	< .001
Stomach	656		427			419			
Age aHR		1.0		0.95	0.82 to 1.07		0.99	0.88 to 1.12	.831
Multivariate HR		1.0		0.94	0.83 to 1.07		0.96	0.84 to 1.09	.461
Lung	578		322			279			
Age aHR		1.0		0.95	0.83 to 1.09		0.89	0.77 to 1.03	.106
Multivariate HR		1.0		0.96	0.83 to 1.11		0.88	0.76 to 1.03	.109
Colorectal	218		155			182			
Age aHR		1.0		0.91	0.74 to 1.12		1.01	0.83 to 1.24	.927
Multivariate HR		1.0		0.91	0.73 to 1.13		1.00	0.81 to 1.24	.995
Liver	890		599			685			
Age aHR		1.0		0.80	0.72 to 0.89		0.98	0.88 to 1.08	.416
Multivariate HR		1.0		0.83	0.75 to 0.93		1.03	0.92 to 1.14	.867
Pancreas	118		109			80			
Age aHR		1.0		1.15	0.88 to 1.50		1.12	0.84 to 1.49	.407
Multivariate HR		1.0		1.14	0.84 to 1.54		1.26	0.90 to 1.75	.169
Kidney	34		27			36			
Age aHR		1.0		0.72	0.43 to 1.20		0.87	0.54 to 1.40	.605
Multivariate HR		1.0		0.66	0.38 to 1.14		0.79	0.93 to 3.43	.399
Bladder	20		17			16			
Age aHR		1.0		1.14	0.59 to 2.17		1.13	0.59 to 2.19	.694
Multivariate HR		1.0		1.05	0.53 to 2.06		1.29	0.64 to 2.60	.484
Prostate	20		14			20			
Age aHR		1.0		0.84	0.42 to 1.66		1.08	0.58 to 2.01	.824
Multivariate HR		1.0		0.75	0.36 to 1.57		0.90	0.44 to 1.85	.779

Abbreviations: HR, hazard ratio; aHR, adjusted hazard ratio.
*Multivariate HR model used a standard Poisson regression analysis adjusted for age, alcohol consumption, body mass index, fasting serum glucose level, cholesterol level, physical activity, food preference, blood pressure, and other comorbidities (heart disease, liver disease, and cerebrovascular disease).

Alcohol use was significantly and independently associated with worse outcome among patients with head and neck, liver, and stomach cancers, even after adjustment for other survival predictors and comorbidities. Heavy alcohol use adversely affects survival for several types of cancer.[12,13,29,30] Alcohol abuse has been linked secondarily to a poor prognosis, with the effect attributed to increased smoking or comorbidity.[29] However, there remains the possibility that the effect of alcohol consumption on survival is not simply a function of smoking history or comorbidity, which we adjusted for in our study. Possible explanations would include more biologically aggressive tumors or impaired host defenses.[31,32] In addition, alcohol abuse increases the morbidity and mortality associated with cancer surgery.[33] Other factors that could lead to worse outcomes among alcohol drinkers include poorer response rates to chemotherapy, smaller radiation doses delivered, less multimodality treatment, and noncompliance.[29]

In this study, obesity was also significantly associated with longer survival in head and neck and esophagus cancer, and all cancer combined. Confounding risk factors for mortality, such as smoking and pre-existing medical conditions, may distort the link between BMI and cancer survival. Smoking is associated inversely with body weight,[34,35] and that must be considered when examining the effect of BMI on cancer survival, especially for cancers with smoking-related etiologies.[34] When we stratified the patients based on smoking history, the inverse association in head and neck cancer still remained in the nonsmoking group (data not shown). Although some reports show that obesity is associated with cancer recurrence and mortality in breast, colon, and prostate cancer,[14,15,36] it is associated with longer survival in esophageal and gastric cancer patients.[18] Given that breast, colorectal, or prostate cancer survivors have high long-term survival rates, obese survivors with these cancers will have a greater chance of being exposed to the effect of obesity-related comorbidities and mortality than would head and neck or esophageal cancer patients. Moreover, breast or prostate cancer patients often gain weight after diagnosis due to hormonal therapy or reduced physical activity.[37,38]

Table 6. Hazard Ratio for Mortality by Prediagnosis Fasting Blood Glucose Level in Male Cancer Survivors

Site of Primary Cancer	Fasting Serum Glucose Level, mg/dL: 0–109 No. of Deaths	0–109 HR	110–125 No. of Deaths	110–125 HR	110–125 95% CI	≥ 126 No. of Deaths	≥ 126 HR	≥ 126 95% CI	*P* for Trend
All	5,882		627			728			
Age aHR		1.0		1.08	0.99 to 1.17		1.39	1.29 to 1.50	< .001
Multivariate HR*		1.0		1.09	1.00 to 1.19		1.38	1.27 to 1.51	< .001
Head and neck	213		25			29			
Age aHR		1.0		1.12	0.77 to 1.61		1.43	1.00 to 2.04	.052
Multivariate HR		1.0		1.19	0.82 to 1.72		1.55	0.99 to 2.42	.044
Esophagus	160		20			18			
Age aHR		1.0		1.24	0.77 to 1.98		1.26	0.77 to 2.05	.248
Multivariate HR		1.0		1.39	0.86 to 2.26		1.16	0.58 to 2.29	.318
Stomach	1,222		127			150			
Age aHR		1.0		1.04	0.86 to 1.24		1.59	1.34 to 1.88	< .001
Multivariate HR		1.0		1.01	0.83 to 1.23		1.52	1.25 to 1.84	< .001
Lung	954		109			108			
Age aHR		1.0		1.26	1.04 to 1.54		1.29	1.06 to 1.58	.002
Multivariate HR		1.0		1.29	1.05 to 1.59		1.48	1.18 to 1.87	< .001
Colorectal	455		46			52			
Age aHR		1.0		0.94	0.69 to 1.27		1.23	0.92 to 1.64	.296
Multivariate HR		1.0		0.93	0.67 to 1.28		1.18	0.85 to 1.63	.512
Liver	1,731		199			227			
Age aHR		1.0		1.09	0.95 to 1.27		1.03	0.89 to 1.18	.470
Multivariate HR		1.0		1.04	0.89 to 1.21		1.04	0.89 to 1.22	.565
Pancreas	235		33			37			
Age aHR		1.0		0.94	0.65 to 1.37		1.07	0.75 to 1.51	.825
Multivariate HR		1.0		0.92	0.61 to 1.39		0.80	0.51 to 1.24	.306
Kidney	74		9			14			
Age aHR		1.0		1.39	0.70 to 2.79		2.18	1.23 to 3.87	.007
Multivariate HR		1.0		1.43	0.70 to 2.93		1.63	0.81 to 3.28	.125
Bladder	44		3			6			
Age aHR		1.0		0.57	0.18 to 1.85		1.02	0.43 to 2.41	.781
Multivariate HR		1.0		0.65	0.20 to 2.17		1.28	0.48 to 3.42	.835
Prostate	47		2			5			
Age aHR		1.0		0.37	0.09 to 1.53		1.27	0.50 to 3.21	.857
Multivariate HR		1.0		0.32	0.75 to 1.39		1.81	0.61 to 5.40	.937

Abbreviations: HR, hazard ratio; aHR, adjusted hazard ratio.
*Multivariate HR model used a standard Poisson regression analysis adjusted for age, alcohol consumption, body mass index, fasting serum glucose level, cholesterol level, physical activity, food preference, blood pressure, and other comorbidities (heart disease, liver disease, and cerebrovascular disease).

Head and neck and esophageal cancer patients, however, frequently report dysphagia and rapid weight loss. Prediagnosis BMI was one of the nutritional status markers in cancer patients, and perhaps those who were heavier before were better able to withstand treatment in several cancers.[39,40]

It is possible that the patients had been suffering from cancer before the baseline examination and that low BMI was the result of cachexia caused by head and neck or esophageal cancer. However, our finding that the mean duration between baseline data collection and cancer development was more than 3.5 years weighs against such causality. The other possibility is that those with higher BMI might have less aggressive cancer. In esophageal cancer, obesity is a risk factor for adenocarcinoma.[6,7] When we included histology type in multivariate analysis, esophageal cancer patients with adenocarcinoma had significantly better survival (HR, 0.09; 95% CI, 0.01 to 0.73) than those with other histologic types. Although the relationship between histology and survival is controversial,[41,42] these findings suggest that obesity might be associated with less aggressive esophageal cancer. In head and neck cancer, multivariate analysis did not show a significant survival difference according to histologic type. Little is known about the relationship between BMI and cancer histology or aggressiveness in head and neck cancer, and more research is needed to clarify the relationships. Our findings, however, suggest that low BMI patients with head and neck or esophageal cancer may achieve better and longer survival if given more thorough nutritional and medical support.

We found significant dose-dependent relationships between fasting serum glucose levels and risk of death in patients with head and neck, stomach, lung, or all cancer combined. In selected studies in Western populations, a history of diabetes has been associated with inferior long-term survival among patients with pancreatic, hepatocellular, colorectal, or breast cancer.[16] Another study demonstrated that a higher insulin-like growth factor-I (IGF-I) level is an independent negative predictor of prognosis in patients with renal cell carcinoma.[43] In many studies, however, diabetes status was based

exclusively on past medical history, and thus there was a chance of misclassification. Moreover, most studies did not consider other important survival predictors, such as BMI, exercise, cholesterol, alcohol consumption, and comorbidities. In the NHICS, we found that the increased cancer mortality associated with high serum glucose was unchanged when adjusted for other risk factors.

Concurrent adverse health conditions or comorbidities increase overall mortality among cancer patients.[16,44] Thus, diabetes or insulin intolerance may influence prognosis negatively because the associated comorbidities increase the risk of deaths not related to cancer. When we confined the analysis to cancer-related deaths, however, the relationship between fasting serum glucose levels and cancer-related mortality did not change. These findings suggest a specific role for insulin resistance on cancer progression. Previous studies in breast, prostate, and colorectal cancers demonstrate that insulin resistance can influence outcome through systemic consequences of hyperinsulinemia.[8-10] Insulin receptors are overexpressed in those cancer tissues, so high insulin levels could promote the selective growth advantage of cancer cells.[8-10] In lung and stomach cancer, the potential role of insulin resistance on survival has not been explored directly. To our knowledge, this is the first study to demonstrate positive linear trends in mortality with increasing prediagnosis fasting serum glucose levels for stomach and lung cancers. In some studies, high plasma levels of IGF-I are associated with a 2.75-fold increased risk of lung cancer, and IGF-I has also been shown to be an important regulator of angiogenesis in lung cancer.[45,46] In light of these previous findings, we assume that prediagnosis insulin resistance is an independent survival predictor in stomach and lung cancer patients.

In addition, when we analyzed the effect of prediagnosis blood pressure on overall cancer mortality, hypertension was significantly associated with poor prognosis in stomach, lung, and colorectal cancer (data not shown). In the current study, however, we focused on the impact of well-known cancer risk factors on cancer prognosis. Although hypertension may be a risk factor for kidney and other cancers,[47,48] its role remains unclear. We therefore just used hypertension as a confounding factor in multivariate analysis.

Our study shows that prediagnosis smoking, alcohol and insulin resistance, which are well-known risk factors for cancer development, also appear to affect cancer outcome. This suggests that patient survival could be improved by discontinuing smoking and drinking, and by reducing insulin resistance, and patients with these risk factors could be identified in clinics. Moreover, our findings suggest that groups at high risk of cancer need to be educated continually to improve their health behaviors—not only to prevent cancer, but also to improve prognosis.

Our study had several limitations. First, our sample might not represent the general population because the patients held stable, secure jobs, and also because approximately 10% of cancer patients are not in the registry in Korea.[21] Second, information about the treatment and extent (stage, lymph node involvement) of the disease was lacking, as was the status of hepatitis B virus infection. If these risk factors affected disease progression or prognosis, they would have had a confounding effect. Third, only 5.8% of the deaths were not related to cancer, which is lower than the rates reported in other studies (19.4% to 22.8%).[14,31,43] The low rate might have been due to some feature of our cohort, such as younger age (mean age, 50.8 years) than other cancer cohorts. The mean duration of follow-up also was shorter for our cohort (3.03 years).[14,31,43] Continued monitoring will be required to document whether the findings change over the long term.

In conclusion, this investigation adds to the evidence that risk factors for cancer (smoking, alcohol drinking, BMI, and insulin resistance) also affect cancer prognosis.

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