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ORIGINAL ARTICLE

Case Control Study

Colors of vegetables and fruits and the risks of colorectal cancer

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Abstract

AIM
To investigate the relationship between the colors of vegetables and fruits and the risk of colorectal cancer in Korea.

METHODS
A case-control study was conducted with 923 colorectal cancer patients and 1846 controls recruited from the National Cancer Center in Korea. We classified vegetables and fruits into four groups according to the color of their edible parts (*e.g.*, green, orange/yellow, red/purple and white). Vegetable and fruit intake level was classified by sex-specific tertile of the control group. Logistic regression models were used for estimating the odds ratios (OR) and their 95% confidence intervals (CI).

RESULTS
High total intake of vegetables and fruits was strongly associated with a reduced risk of colorectal cancer in women (OR = 0.32, 95%CI: 0.21-0.48 for highest *vs* lowest tertile) and a similar inverse association was observed for men (OR = 0.60, 95%CI: 0.45-0.79). In the analysis of color groups, adjusted ORs (95%CI) comparing the highest to the lowest of the vegetables and fruits intake were 0.49 (0.36-0.65) for green, and 0.47 (0.35-0.63) for white vegetables and fruits in men. An inverse association was also found in women for green, red/purple and white vegetables and fruits. However, in men, orange/yellow vegetables and fruits (citrus fruits, carrot, pumpkin, peach, persimmon, ginger) intake was linked to an increased risk of colorectal cancer (OR = 1.61, 95%CI: 1.22-2.12).

CONCLUSION
Vegetables and fruits intake from various color groups may protect against colorectal cancer.

Key words: Vegetable and fruits; Colorectal cancer; Korea

Core tip: Although many studies have focused on the associations between vegetable and fruit intake and health, few studies have classified vegetables and fruits by their colors, which reflect their unique contents of phytochemicals and micronutrients. In the current study, most color groups of vegetables and fruits showed protective benefits against colorectal cancer regardless of the anatomical subsites.

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INTRODUCTION

Vegetables and fruits contain nutrients such as vitamins, minerals, folate, dietary fiber, plant sterols, carotenoids and various phytochemicals[1,2] . These nutrients may reduce mortality and prevent chronic diseases, including various cancers, cardiovascular diseases and even mental illnesses, through their antitumor activity as well as their anti-obesity, anti-oxidant and anti-inflammatory agents[1,3-7].

According to the latest research on the prevention of colorectal cancer from the Continuous update project of the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), which was published in 2011, non-starchy vegetables and fruits have been evaluated as a "limited-suggestive" preventive factor[8]. A recent meta-analysis of 15 cohort studies of vegetable and fruit intake and the risk of colorectal cancer found that there was a small (8%) reduction and a nonlinear inverse association between colorectal cancer risk and the intake of vegetables and fruits[9]. The relationship between cruciferous vegetables, citrus fruits, brassica vegetables, leafy vegetables, root vegetables and total vegetables and fruits consumption were not consistent[10-15].

Phytochemicals from vegetables and fruits contain many colorful and dark pigments, such as flavonoid and polyphenols, and may be distinguished (in terms of their various physiological effects and actions) by their specific colors. A previous study suggested classifying vegetables and fruits according to their nutritional phytochemicals when providing guidelines for the public[16]. Pennington and Fish have classified 9 color groupings of vegetable and fruit subgroups based on a consideration their unique nutritional values, features and potential correlations[17,18].

There have been studies of vegetable and fruit classification, by color, for stroke[19], coronary heart disease[20], and colorectal cancer[15]. Our present case-control study, therefore, explored the association between vegetables and fruits color groups and colorectal cancer risk in the Korean population.

MATERIALS AND METHODS

Study subjects

The colorectal cancer cases were recruited from the Center for Colorectal Cancer of the National Cancer Center in Korea between August 2010 and August 2013. Among 1427 eligible patients, 1070 agreed to participate in the study. Colorectal cancer cases with incomplete semi-quantitative food frequency questionnaire (SQFFQ) data (145 cases) and those with implausible energy intakes below 500 Kcal/d or above 4000 Kcal/d (2 cases) were excluded. Controls were persons who received health screenings provided by the National Health Insurance Corporation between October 2007 and December 2014 at the same institute. Among 14201 potential control participants, individuals with incomplete SQFFQ (n = 5044) and with implausible energy intakes (n = 120) were excluded. Patients and eligible controls were matched in a 1:2 ratio according to their sex and 5 year age groups. Ultimately, there were 923 cases and 1846 controls whose data were used in the final analysis. All the participants provided written informed consent, and this study's protocol was approved by the Institutional review board of the National Cancer Center (IRB No. NCCNCS-10-350 and No. NCC 2015-0202).

Data collection

A trained dietitian performed questionnaire surveys through face-to-face interviews. Information on

Table 1 Classification of vegetables and fruits according to type and color group[1]

Color group	Vegetables and fruits type	Vegetables and fruits item
Green (23.2%)[2]	Dark green leafy vegetables (27.1%)[3]	Water dropwort, mugwort, crown daisy, spinach, perilla leaf, chicory, kale, pumpkin leaf, leak beet
	Lettuces (10.6%)	Lettuce
	Other green fruits and vegetables (62.3%)	Melon, zucchini, green cucumber, green pepper, cabbages, broccoli, celery
Orange/yellow (17.5%)	Citrus fruits (57.5%)	Citrus fruits juices, orange, mandarin orange, kumquat
	Other orange/yellow fruits and vegetables (42.5%)	Carrot, pumpkin, peach, persimmon, ginger
Red/purple (19.0%)	Berries (38.3%)	Strawberry , grape
	Other red fruits and vegetables (61.7%)	Watermelon, tomato, red cabbage, red pepper, plum
White (40.3%)	Allium family bulbs (15.1%)	Garlic, leek, onion
	Hard fruits (41.8%)	Apple, pear
	Cauliflower (13.4%)	Asian radish
	Other white fruits and vegetables (29.7%)	Oriental melon, mushroom, banana, deodeok, burdock, lotus root, balloon flower root

[1]Vegetables and fruits were classified into subgroup as proposed by Pennington and Fisher; [2]Proportion of color group to total vegetables and fruits; [3]Proportion of vegetables and fruits type to vegetables and fruits by color group.

general characteristics, family history of cancer, alcohol consumption, cigarette smoking, and exercise habits was obtained using a structured questionnaires. Dietary information was assessed using the semi-quantitative food frequency questionnaire (SQFFQ) developed by the Korea Centers for Disease Control and Prevention[21]. The SQFFQ was designed to measure typical food intake habits during the course of one year. The reliability and validity of this questionnaire have been previously reported[21]. Subjects were queried by a trained dietitian on their usual intake amount of 106 food items during the last 12 mo before the interview. Daily vegetable and fruit intake and calorie intake were calculated using the Nutritional Analysis Program for Professionals ver. 4.0 (CAN-Pro 4.0 the Korean Nutrition Society, 2012, Seoul, Korea). Vegetables and fruits were classified into 4 color groups according to Pennington and Fish's[17,18] categories (*e.g.*, green, orange/yellow, red/purple and white) (Table 1). On the basis of outcomes form the Food Balance Wheels (Ministry of Health and Welfare, Dietary Reference Intakes for Koreans, 2015), potatoes and sweet potatoes, which have high starch content, were not included as vegetables. Additionally, we did not include kimchi, pickled vegetables and jam as vegetables and fruits, because of their high salt and sugar content. And the fruit juice beverages were included in the analysis. We have performed an analysis according to the anatomical location of the origin of cancer: proximal colon (cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure); distal colon (descending colon, sigmoid-descending colon junction, sigmoid colon); and rectum (rectosigmoid colon, rectum).

Statistical analysis

Chi-square tests were used to compare the distribution of general characteristics and health related behavior factors among cases and controls. Intake levels of vegetables and fruits were categorized into sex-specific tertiles according to the distribution among control groups. The potential confounding variable considered were age, education, alcohol consumption, regular exercise, body mass index (BMI), fiber intake, red meat consumption, processed meat consumption, and energy intake, all of which were selected based on the literature[9,13,22-24]. After considering multi-collinearity, we finally adjusted age, education level, alcohol consumption, BMI, regular exercise, red meat consumption, processed meat consumption, and total energy intake by residual methods. Nutrient intakes were adjusted for total individual energy intakes using the residual method[25]. Binary and polytomous logistic regression models were used to assess the ORs and their 95%CIs for the association between the colors of the vegetables and fruits consumed and the risk of colorectal cancer. All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc. Cary, NC, United States).

RESULTS

The characteristics of the study subjects are presented in Table 2. Male colorectal cancer patients showed differences compared to controls in marital status, education level, household income, obesity, smoking status, alcohol consumption and regular exercise. The female subjects showed a similar pattern, but the cancer patients had a higher percentage of obese individuals and current smokers.

Table 3 presents consumption of vegetables and fruits for the cases and controls, separated by sex. Total energy intake was higher among controls in both sexes; thus, the energy adjusted average intake levels of vegetables and fruits were compared. Among cancer cases, consumption of total vegetables and fruits, vegetables, fruits, color group vegetables and fruits and even red meat was lower than controls.

Table 4 shows the ORs and the 95%CIs for the colors of the vegetables and fruits consumed and the

Table 2 General characteristics of the study subjects *n* (%)

Variable	Male (*n* = 1875)		*P* value[1]	Female (*n* = 894)		*P* value[1]
	Case (*n* = 625)	Control (*n* = 1250)		Case (*n* = 298)	Control (*n* = 596)	
Age group (yr)			0.997			0.994
-49	128 (20.5)	258 (20.6)		82 (27.5)	166 (27.9)	
50-59	227 (36.3)	453 (36.2)		111 (37.3)	221 (37.1)	
60+	270 (43.2)	539 (43.1)		105 (35.2)	209 (35.1)	
Missing	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Marital status			< 0.001			< 0.001
Married	557 (89.1)	1162 (93.0)		216 (73.0)	493 (83.4)	
Single	66 (10.6)	72 (5.8)		80 (27.0)	98 (16.6)	
Missing	2 (0.3)	16 (1.3)		2 (0.7)	5 (0.8)	
Education level			< 0.001			< 0.001
Under middle school	183 (29.3)	175 (14.0)		138 (46.3)	106 (18.1)	
High school	266 (42.6)	329 (26.3)		103 (34.6)	258 (44.0)	
College or more	176 (28.2)	712 (57.0)		57 (19.1)	223 (38.0)	
Missing	0 (0.0)	34 (2.7)		0 (0.0)	9 (1.5)	
Income (10000won/mo)			< 0.001			< 0.001
< 200	222 (35.5)	254 (20.3)		99 (33.2)	134 (25.0)	
200-400	253 (40.5)	534 (42.7)		134 (45.0)	218 (40.7)	
> 400	150 (24.0)	363 (29.0)		65 (21.8)	184 (34.3)	
Missing	0 (0.0)	99 (7.9)		0 (0.0)	60 (10.1)	
Body mass index (kg/m^2)			< 0.001			0.270
< 25	432 (69.1)	734 (58.7)		207 (69.5)	435 (73.0)	
≥ 25	192 (30.7)	516 (41.3)		91 (30.5)	161 (27.0)	
Missing	1 (0.2)	0 (0.0)		0 (0.0)	0 (0.0)	
Smoking status			0.076			< 0.001
Non-smoker	145 (23.2)	245 (19.6)		264 (88.6)	571 (95.8)	
Ex-smoker	303 (48.5)	671 (53.7)		15 (5.0)	16 (2.7)	
Current smoker	177 (28.3)	334 (26.7)		19 (6.4)	9 (1.5)	
Missing	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Alcohol consumption			< 0.001			0.186
Non-drinker	107 (17.1)	199 (15.9)		172 (57.7)	362 (60.7)	
Ex-drinker	103 (16.5)	136 (10.9)		26 (8.7)	33 (5.5)	
Current drinker	415 (66.4)	915 (73.2)		100 (33.6)	201 (33.7)	
Missing	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Regular exercise			< 0.001			< 0.001
No	387 (61.9)	490 (39.2)		225 (75.5)	262 (44.0)	
Yes	238 (38.1)	715 (57.2)		73 (24.5)	333 (56.0)	
Missing	0 (0.0)	45 (3.6)		0 (0.0)	1 (0.2)	
Family history of cancer			0.002			0.141
No	392 (62.7)	686 (54.9)		171 (57.4)	311 (52.2)	
Yes	233 (37.3)	560 (44.8)		127 (42.6)	285 (47.8)	
Missing	0 (0.0)	4 (0.3)		0 (0.0)	0 (0.0)	
Family history of colorectal cancer			< 0.001			0.926
No	560 (89.6)	1188 (95.0)		277 (93.0)	555 (93.1)	
Yes	65 (10.4)	58 (4.6)		21 (7.1)	41 (6.9)	
Missing	0 (0.0)	4 (0.3)		0 (0.0)	0 (0.0)	

[1]*P* values were calculated by χ^2 test.

risks of colorectal cancer. After adjustments for the confounding variables, we found that higher intake of total vegetables and fruits (OR = 0.60, 95%CI: 0.45-0.79, highest *vs* lowest tertiles); vegetables (OR = 0.48, 95%CI: 0.36-0.64); green vegetables and fruits (OR = 0.49, 95%CI: 0.36-0.65); and white vegetables and fruits (OR = 0.47, 95%CI: 0.35-0.63) reduced the risks of colorectal cancer for men. However, for orange/yellow vegetables and fruits, a significant association with the risks of colorectal cancer was found (OR = 1.61, 95%CI: 1.22-2.12). In women, all categories of vegetables and fruits intake showed decreased risk of colorectal cancer (OR = 0.32, 95%CI: 0.21-0.48 for total vegetables and fruits; OR = 0.37, 95%CI: 0.24-0.57 for vegetables; OR = 0.41, 95%CI: 0.27-0.63 for fruits; OR = 0.25, 95%CI: 0.16-0.40 for green vegetables and fruits; OR = 0.66, 95%CI: 0.44-0.99 for red/purple vegetables and fruits; OR = 0.34, 95%CI: 0.22-0.52 for white vegetables and fruits).

In the analysis of orange/yellow vegetables and fruits separately, orange/yellow fruits intake reduced the risks of colorectal cancer in women (OR = 0.64, 95%CI: 0.43-0.97). We found that higher intake of orange/yellow vegetables elevated the risks of colorectal cancer in both sexes (OR = 2.41, 95%CI:

Table 3 Intake of vegetables and fruits between cases and controls

Total energy adjusted intake (g/d), mean ± SD	Male (*n* = 1875)		Female (*n* = 894)	
	Case (*n* = 625)	Control (*n* = 1250)	Case (*n* = 298)	Control (*n* = 596)
Total energy intake (kcal/d)	2127.7 ± 509.1	1731.6 ± 545.8	1814.4 ± 523.5	1604.6 ± 577.4
Total vegetables and fruits	279.4 ± 155.7	350.2 ± 236.7	343.1 ± 192.8	470.7 ± 383.4
Total vegetables	148.5 ± 77.3	186.7 ± 126.2	155.8 ± 85.4	205.3 ± 138.2
Total fruits	125.0 ± 115.3	174.5 ± 197.8	185.9 ± 152.1	271.7 ± 230.0
Green vegetables and fruits	64.8 ± 38.0	86.2 ± 69.6	72.7 ± 52.1	105.5 ± 84.5
Orange/yellow vegetables and fruits	49.4 ± 45.4	54.2 ± 66.8	75.4 ± 71.2	95.2 ± 97.7
Orange/yellow vegetable	10.1 ± 12.1	9.3 ± 17.0	13.0 ± 16.3	11.7 ± 23.1
Orange/yellow fruits	37.7 ± 46.2	57.0 ± 109.1	65.0 ± 84.7	94.7 ± 117.0
White vegetables and fruits	105.9 ± 65.4	149.8 ± 120.4	128.8 ± 100.3	186.2 ± 135.0
Red/purple vegetables and fruits	55.2 ± 65.9	66.1 ± 88.8	66.0 ± 62.6	89.1 ± 89.8
Red meat	56.0 ± 36.2	64.4 ± 41.9	40.9 ± 26.9	43.7 ± 28.7
Processed meat	0.5 ± 1.8	3.5 ± 25.1	1.9 ± 13.8	1.7 ± 6.1

Mean of vegetables and fruits intake were adjusted for the total individual energy intakes using the residual method.

1.83-3.16 for men; OR = 2.28, 95%CI: 1.55-3.34 for women). In the subsite analysis (Table 5), similar associations by subsite were observed for both men and women.

DISCUSSION

In this case control study, we investigated the relationship between vegetables and fruits groups categorized by color and the risks of colorectal cancer. The investigation revealed that the green vegetables and fruits and white vegetables and fruits color groups and total vegetables and fruits intake were strongly related to a reduced risk of colorectal cancer in men and women. In addition, it was shown that in women, the total amount of fruit consumed, as well as consumption of the red/purple color groups, attenuated colorectal cancer risk. However, no significant association was found for the red/purple color groups in men. Surprisingly, a high intake from the orange/yellow vegetables and fruits color group was associated with a higher risk of colorectal cancer in men.

The protective effect of total vegetables and fruits intake as related to colorectal cancer risk was consistent with previous case-control studies[12,26-28] and meta-analysis[9]. However, recent cohort studies[13,14,23,29], and a recent case- control study[12], do not comply with our results.

In the present study, green vegetables and fruits intake was shown to be inversely associated with the risk of CRC in both sexes. Green vegetables and fruits are thought to decrease the risk of CRC through their high folate, fiber, lutein, sulforaphane and indole level, which induce apoptosis in cancer cells and inhibit cell damage and the growth of cancer cells[30,31]. The Netherlands Cohort Study[10], as well as a case-control study for Guangzhou (in men)[15] and the NIH-AARP study[11] reported the beneficial effects of green vegetables and fruits. However, other cohort studies and case control studies have produced null findings[12,13,32,33].

This study suggested that high white vegetables and fruits intake has protective effects on colorectal cancer risk. White vegetables and fruits contains various phytochemicals and nutrients, such as the polysaccharides of apples, theglucans of mushroom, saponins of root and bulb vegetables, and the quercetin of onions and apples, which play important roles in antioxidant activity, reduction of DNA damage, and anticancer activity[34]. However, epidemiological studies of white vegetables and fruits intake are still contradictory. In the case of apples, with the exception of one study[33], most research has shown a beneficial significant association[12,35] or no association between apple intake and colorectal cancer risk. Several recent meta-analyses have been published[36-39] on bulbs in the allium family, and the results of these papers show that garlic consumption is not associated with colorectal cancer.

Studies that classify vegetables and fruits by color are rare regardless of the disease. One case-control study was conducted in China[15]. In a case-control study from Switzerland, citrus fruit, a main component of the orange/yellow vegetables and fruits category, was found to be significantly inversely associated with colorectal cancer risk[40]. However, most studies show no significant associations with orange/yellow vegetables and fruits consumption[10,12,13,29,32,33]. In two case control studies conducted in China and Hawaii, it was found that high orange/yellow vegetables and fruits intake reduces colorectal cancer risk[15,41]. Orange/yellow vegetables and fruits are known to be rich in carotene, which can function as provitamin A[42]. Vitamin A may have a positive effect by controlling the growth and metastasis of cancer cells and may act as an antioxidant in reducing cancer[43]. However, our study found that high orange/yellow vegetable and fruit intake was significantly associated with increased risk of colorectal cancer for men. The Nurse' Health Study and Health Professionals Follow-Up Study conducted in the United States suggested that citrus

Table 4 Odds ratios and 95% confidence intervals for colorectal cancer risk in relation to intake of vegetables and fruits

Total energy adjusted vegetables and fruits intake	Male (n = 1875)				Female (n = 894)			Total (n = 2769)		
	Controls /cases (n)	Age-adjusted OR (95%CI)	Multivariate OR[1] (95%CI)		Controls /cases (n)	Age-adjusted OR (95%CI)	Multivariate OR[1] (95%CI)	Controls /cases (n)	Age-adjusted OR (95%CI)	Multivariate OR[1] (95%CI)
Total vegetables and fruits (g/d)										
T1 (< 224.2)	417/275	1.00	1.00	T1 (< 317.7)	199/166	1.00	1.00	616/441	1.00	1.00
T2 (224.2-< 380.0)	416/230	0.83 (0.67-1.04)	0.94 (0.74-1.21)	T2 (317.7- < 534.8)	199/91	0.55 (0.39-0.75)	0.60 (0.42-0.85)	615//321	0.72 (0.60-0.87)	0.81 (0.67-0.99)
T3 (≥ 380.0)	417/120	0.43 (0.34-0.56)	0.60 (0.45-0.79)	T3 (≥ 534.8)	198/41	0.25 (0.17-0.37)	0.32 (0.21-0.48)	615/161	0.36 (0.29-0.45)	0.50 (0.40-0.63)
P for trend[2]		< 0.001	< 0.001			< 0.001	< 0.001		< 0.001	< 0.001
Total vegetables (g/d)										
T1 (< 123.0)	416/256	1.00	1.00	T1 (< 135.9)	198/143	1.00	1.00	614/399	1.00	1.00
T2 (123.0-< 203.6)	418/270	1.05 (0.84-1.30)	1.19 (0.93-1.52)	T2 (135.9- < 219.1)	200/110	0.76 (0.55-1.04)	0.89 (0.62-1.26)	618/380	0.94 (0.79-1.13)	1.05 (0.86-1.28)
T3 (≥ 203.6)	416/99	0.38 (0.29-0.50)	0.48 (0.36-0.64)	T3 (≥ 219.1)	198/45	0.31 (0.21-0.46)	0.37 (0.24-0.57)	614/114	0.36 (0.29-0.45)	0.43 (0.34-0.55)
P for trend		< 0.001	< 0.001			< 0.001	< 0.001		< 0.001	< 0.001
Total fruits (g/d)										
T1 (< 68.3)	416/224	1.00	1.00	T1 (< 135.0)	198/129	1.00	1.00	614/353	1.00	1.00
T2 (68.3-< 178.1)	418/265	1.18 (0.94-1.47)	1.36 (1.06-1.74)	T2 (135.0- < 307.1)	199/124	0.96 (0.70-1.31)	1.03 (0.73-1.46)	617/389	1.09 (0.91-1.31)	1.21 (1.00-1.48)
T3 (≥ 178.1)	416/136	0.61 (0.47-0.78)	0.77 (0.58-1.02)	T3 (≥ 307.1)	199/45	0.35 (0.23-0.51)	0.41 (0.27-0.63)	615/181	0.51 (0.41-0.63)	0.67 (0.53-0.84)
P for trend		< 0.001	0.017			< 0.001	< 0.001		< 0.001	< 0.001
Green vegetables and fruits (g/d)										
T1 (< 48.8)	417/238	1.00	1.00	T1 (< 61.0)	199/151	1.00	1.00	616/389	1.00	1.00
T2 (48.8-< 93.6)	417/280	1.17 (0.94-1.46)	1.21 (0.94-1.54)	T2 (61.0-< 114.2)	198/115	0.76 (0.56-1.04)	0.89 (0.63-1.27)	615/395	1.01 (0.84-1.21)	1.06 (0.87-1.30)
T3 (≥ 93.6)	416/107	0.45 (0.34-0.58)	0.49 (0.36-0.65)	T3 (≥ 114.2)	199/32	0.21 (0.14-0.32)	0.25 (0.16-0.40)	615/139	0.35 (0.28-0.44)	0.39 (0.31-0.50)
P for trend		< 0.001	< 0.001			< 0.001	< 0.001		< 0.001	< 0.001
Red/purple vegetables and fruits (g/d)										
T1 (< 22.1)	416/191	1.00	1.00	T1 (< 39.5)	199/112	1.00	1.00	615/303	1.00	1.00
T2 (22.1- < 62.2)	417/266	1.39 (1.10-1.75)	1.63 (1.26-2.11)	T2 (39.5-< 98.5)	199/121	1.08 (0.78-1.49)	1.21 (0.84-1.73)	616/387	1.27 (1.06-1.54)	1.46 (1.19-1.79)
T3 (≥ 62.2)	417/168	0.88 (0.68-1.12)	1.10 (0.83-1.44)	T3 (≥ 98.5)	198/65	0.58 (0.41-0.84)	0.66 (0.44-0.99)	615/233	0.77 (0.63-0.94)	0.96 (0.77-1.20)
P for trend		0.042	0.706			0.002	0.027		< 0.001	0.033
Orange /yellow vegetables and fruits (g/d)										
T1 (< 21.1)	416/162	1.00	1.00	T1 (< 40.7)	199/89	1.00	1.00	615/251	1.00	1.00
T2 (21.1- < 54.0)	417/264	1.63 (1.28-2.07)	1.91 (1.47-2.49)	T2 (40.7- < 100.6)	198/140	1.58 (1.14-2.20)	1.77 (1.23-2.56)	615/404	1.61 (1.33-1.95)	1.78 (1.45-2.20)
T3 (≥ 54.0)	417/199	1.23 (0.96-1.58)	1.61 (1.22-2.12)	T3 (≥ 100.6)	199/69	0.77 (0.53-1.12)	0.85 (0.56-1.27)	616/268	1.07 (0.87-1.31)	1.33 (1.06-1.66)
P for trend		0.618	0.021			0.051	0.163		0.286	0.576
Orange /yellow fruits (g/d)										
T1 (< 15.9)	416/230	1.00	1.00	T1 (< 32.5)	199/105	1.00	1.00	615/335	1.00	1.00
T2 (15.9- < 47.9)	417/230	1.00 (0.79-1.25)	1.17 (0.91-1.51)	T2 (32.5- < 90.6)	198/130	1.24 (0.90-1.72)	1.43 (1.00-2.06)	616/360	1.07 (0.89-1.29)	1.20 (0.98-1.47)
T3 (≥ 47.9)	417/165	0.72 (0.56-0.91)	0.98 (0.75-1.28)	T3 (≥ 90.6)	199/63	0.60 (0.42-0.87)	0.64 (0.43-0.97)	615/228	0.68 (0.56-0.83)	0.85 (0.69-1.06)
P for trend		0.003	0.003			0.002	0.002		< 0.001	< 0.001
Orange /yellow vegetable (g/d)										
T1 (< 2.7)	416/144	1.00	1.00	T1 (< 3.2)	198/77	1.00	1.00	614/221	1.00	1.00
T2 (2.7- < 7.7)	417/188	1.30 (1.01-1.68)	1.47 (1.11-1.95)	T2 (3.2- < 9.1)	200/69	0.89 (0.61-1.30)	1.14 (0.75-1.73)	617/257	1.16 (0.94-1.43)	1.30 (1.04-1.64)
T3 (≥ 7.7)	417/293	2.09 (1.63-2.67)	2.41 (1.83-3.16)	T3 (≥ 9.1)	198/152	2.01 (1.43-2.83)	2.28 (1.55-3.34)	615/445	2.06 (1.69-2.51)	2.19 (1.77-2.73)
P for trend		< 0.001	< 0.001			< 0.001	< 0.001		< 0.001	< 0.001

White vegetables and fruits (g/d)										
T1 (< 87.9)	416/301	1	1	T1 (< 109.9)	199/156	1	1	615/457	1	1
T2 (87.9- < 153.9)	418/219	0.72 (0.57-0.90)	0.84 (0.66-1.08)	T2 (109.9- < 198.0)	199/99	0.63 (0.46-0.87)	0.78 (0.55-1.11)	617/318	0.69 (0.58-0.83)	0.8 (0.66-0.98)
T3 (≥ 153.9)	416/105	0.34 (0.27-0.45)	0.47 (0.35-0.63)	T3 (≥ 198.0)	198/43	0.28 (0.19-0.41)	0.34 (0.22-0.52)	614/148	0.32 (0.26-0.40)	0.43 (0.34-0.55)
P for trend		< 0.001	< 0.001			< 0.001	< 0.001		< 0.001	< 0.001

[1]Adjusted by age, education, alcohol consumption, BMI, regular exercise, red meat, processed meat and total energy intake; [2]Test for trend calculated with the median intake for each category of vegetables and fruits as a continuous variable.

Table 5 Odds ratios and 95% confidence intervals for colorectal cancer subsites in relation to intake of vegetables and fruits

	Control	Proximal colon			Distal colon			Rectum		
	No.	No.	Age-adjusted OR (95%CI)	Multivariate OR[1] (95%CI)	No.	Age-adjusted OR (95%CI)	Multivariate OR[1] (95%CI)	No.	Age-adjusted OR (95%CI)	Multivariate OR[1] (95%CI)
Men										
Total vegetables and fruits (g/d)										
T1 (< 224.2)	417	46	1.00	1.00	76	1.00	1.00	145	1.00	1.00
T2 (224.2- < 380.0)	416	45	0.97 (0.63-1.49)	1.08 (0.68-1.69)	73	0.95 (0.67-1.35)	1.10 (0.76-1.58)	107	0.74 (0.55-0.98)	0.82 (0.61-1.12)
T3 (≥ 380.0)	417	22	0.47 (0.28-0.80)	0.63 (0.36-1.09)	29	0.38 (0.24-0.59)	0.50 (0.32-0.80)	68	0.47 (0.34-0.64)	0.67 (0.47-0.94)
P for trend[2]			0.004	0.086		< 0.001	0.003		< 0.001	0.018
Total vegetables (g/d)										
T1 (< 123.0)	416	40	1.00	1.00	66	1.00	1.00	142	1.00	1.00
T2 (123.0-< 203.6)	418	46	1.13 (0.72-1.77)	1.26 (0.79-2.01)	88	1.32 (0.93-1.87)	1.50 (1.04-2.16)	130	0.91 (0.69-1.20)	1.05 (0.77-1.41)
T3 (≥ 203.6)	416	27	0.67 (0.40-1.11)	0.80 (0.47-1.37)	24	0.36 (0.22-0.59)	0.44 (0.27-0.74)	48	0.34 (0.24-0.48)	0.43 (0.29-0.63)
P for trend			0.089	0.34		< 0.001	0.002		< 0.001	< 0.001
Total fruits (g/d)										
T1 (< 68.3)	416	37	1.00	1.00	69	1.00	1.00	113	1.00	1.00
T2 (68.3- < 178.1)	418	52	1.38 (0.89-2.16)	1.59 (1.01-2.52)	76	1.09 (0.76-1.55)	1.26 (0.88-1.83)	129	1.14 (0.85-1.52)	1.30 (0.96-1.78)
T3 (≥ 178.1)	416	24	0.64 (0.38-1.09)	0.83 (0.47-1.44)	33	0.47 (0.31-0.74)	0.59 (0.38-0.94)	78	0.69 (0.50-0.95)	0.90 (0.63-1.27)
P for trend			0.035	0.269		< 0.001	0.01		0.008	0.318
Green vegetables and fruits (g/d)										
T1 (< 48.8)	417	39	1.00	1.00	64	1.00	1.00	129	1.00	1.00
T2 (48.8- < 93.6)	417	49	1.24 (0.80-1.94)	1.26 (0.79-1.99)	87	1.35 (0.95-1.92)	1.43 (0.99-2.07)	136	1.05 (0.80-1.39)	1.08 (0.79-1.46)
T3 (≥ 93.6)	416	25	0.63 (0.38-1.07)	0.67 (0.39-1.16)	27	0.42 (0.26-0.67)	0.46 (0.28-0.74)	55	0.43 (0.30-0.60)	0.47 (0.32-0.68)
P for trend			0.048	0.092		< 0.001	< 0.001		< 0.001	< 0.001
Red/purple vegetables and fruits (g/d)										
T1 (< 22.1)	416	34	1.00	1.00	60	1.00	1.00	91	1.00	1.00
T2 (22.1- < 62.2)	417	48	1.40 (0.88-2.22)	1.63 (1.01-2.04)	73	1.21 (0.84-1.75)	1.39 (0.95-2.04)	138	1.52 (1.13-2.04)	1.84 (1.33-2.53)
T3 (≥ 62.2)	417	31	0.90 (0.55-1.50)	1.12 (0.66-1.88)	45	0.75 (0.50-1.13)	0.92 (0.60-1.41)	91	1.00 (0.72-1.38)	1.28 (0.90-1.81)
P for trend			0.371	0.895		0.067	0.379		0.355	0.666
Orange/yellow vegetables and fruits (g/d)										
T1 (< 21.1)	416	28	1.00	1.00	47	1.00	1.00	86	1.00	1.00
T2 (21.1- < 54.0)	418	43	1.52 (0.93-2.50)	1.80 (1.08-3.01)	73	1.55 (1.05-2.29)	1.86 (1.24-2.80)	138	1.61 (1.19-2.18)	1.86 (1.34-2.59)
T3 (≥ 54.0)	416	42	1.49 (0.90-2.45)	1.94 (1.16-3.27)	58	1.23 (0.82-1.85)	1.60 (1.04-2.46)	96	1.12 (0.81-1.55)	1.47 (1.04-2.09)
P for trend			0.217	0.03		0.683	0.121		0.837	0.178

Orange /yellow fruits (g/d)										
T1 (< 15.9)	416	38	1.00	1.00	69	1.00	1.00	120	1.00	1.00
T2 (15.9-< 47.9)	417	46	1.20 (0.77-1.89)	1.43 (0.90-2.27)	61	0.88 (0.61-1.27)	1.04 (0.71-1.52)	115	0.96 (0.72-1.28)	1.11 (0.82-1.52)
T3 (≥ 47.9)	417	29	0.76 (0.46-1.25)	1.04 (0.62-1.75)	48	0.69 (0.47-1.02)	0.92 (0.61-1.38)	85	0.71 (0.52-0.96)	0.97 (0.69-1.36)
P for trend			0.155	0.849		0.065	0.625		0.02	0.724
Orange /yellow vegetable (g/d)										
T1 (< 2.7)	416	31	1.00	1.00	38	1.00	1.00	70	1.00	1.00
T2 (2.7-< 7.7)	417	27	0.87 (0.51-1.48)	1.01 (0.59-1.75)	55	1.44 (0.93-2.23)	1.68 (1.07-2.63)	101	1.44 (1.03-2.01)	1.64 (1.15-2.34)
T3 (≥ 7.7)	417	55	1.79 (1.12-2.86)	2.15 (1.32-3.51)	85	2.28 (1.51-3.44)	2.72 (1.77-4.18)	149	2.19 (1.59-3.02)	2.51 (1.77-3.54)
P for trend			0.003	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001
White vegetables and fruits (g/d)										
T1 (< 87.9)	416	51	1.00	1.00	87	1.00	1.00	156	1.00	1.00
T2 (87.9- < 153.9)	418	46	0.88 (0.58-1.35)	1.04 (0.67-1.61)	68	0.77 (0.54-1.09)	0.89 (0.62-1.28)	100	0.63 (0.48-0.84)	0.76 (0.55-1.03)
T3 (≥ 153.9)	416	16	0.31 (0.17-0.55)	0.40 (0.22-0.73)	23	0.26 (0.16-0.42)	0.34 (0.21-0.56)	64	0.41 (0.29-0.56)	0.58 (0.41-0.83)
P for trend			< 0.001	0.003		< 0.001	< 0.001		< 0.001	0.002
Women										
Total vegetables and fruits (g/d)										
T1 (< 317.7)	199	29	1.00	1.00	64	1.00	1.00	70	1.00	1.00
T2 (317.7-< 534.8)	199	19	0.65 (0.35-1.20)	0.66 (0.35-1.25)	28	0.44 (0.27-0.71)	0.47 (0.28-0.79)	41	0.58 (0.38-0.90)	0.65 (0.41-1.03)
T3 (≥ 534.8)	198	5	0.17 (0.07-0.45)	0.22 (0.08-0.58)	21	0.33 (0.19-0.56)	0.41 (0.23-0.71)	13	0.19 (0.10-0.35)	0.25 (0.13-0.47)
P for trend			< 0.001	0.002		< 0.001	0.001		< 0.001	< 0.001
Total vegetables (g/d)										
T1 (< 135.9)	198	26	1.00	1.00	51	1.00	1.00	61	1.00	1.00
T2 (135.9-< 219.1)	200	22	0.83 (0.45-1.51)	1.02 (0.53-1.95)	41	0.80 (0.50-1.26)	0.97 (0.59-1.57)	45	0.73 (0.47-1.12)	0.82 (0.52-1.31)
T3 (≥ 219.1)	198	5	0.19 (0.07-0.50)	0.22 (0.08-0.61)	21	0.41 (0.29-0.71)	0.50 (0.28-0.89)	18	0.29 (0.17-0.51)	0.36 (0.20-0.65)
P for trend			< 0.001	0.003		0.001	0.018		< 0.001	< 0.001
Total fruits (g/d)										
T1 (< 135.0)	198	21	1.00	1.00	46	1.00	1.00	59	1.00	1.00
T2 (135.0-< 307.1)	199	27	1.29 (0.70-2.35)	1.37 (0.73-2.58)	46	1.00 (0.63-1.57)	1.05 (0.65-1.69)	48	0.81 (0.53-1.25)	0.88 (0.56-1.38)
T3 (≥ 307.1)	199	5	0.24 (0.09-0.64)	0.27 (0.10-0.76)	21	0.45 (0.26-0.79)	0.52 (0.29-0.93)	17	0.29 (0.16-0.51)	0.35 (0.19-0.64)
P for trend			0.003	0.002		0.004	0.006		< 0.001	< 0.001
Green vegetables and fruits (g/d)										
T1 (< 61.0)	199	26	1.00	1.00	60	1.00	1.00	60	1.00	1.00
T2 (61.0- < 114.2)	198	23	0.87 (0.48-1.59)	1.03 (0.55-1.93)	39	0.65 (0.42-1.02)	0.78 (0.49-1.26)	51	0.85 (0.56-1.29)	0.98 (0.62-1.54)
T3 (≥ 114.2)	199	4	0.15 (0.05-0.43)	0.18 (0.06-0.54)	14	0.23 (0.12-0.43)	0.28 (0.15-0.53)	13	0.21 (0.11-0.40)	0.26 (0.14-0.50)
P for trend			< 0.001	0.002		< 0.001	< 0.001		< 0.001	< 0.001
Red/purple vegetables and fruits (g/d)										
T1 (< 39.5)	199	20	1.00	1.00	41	1.00	1.00	47	1.00	1.00
T2 (39.5- < 98.5)	199	26	1.30 (0.70-2.41)	1.54 (0.81-2.95)	44	1.07 (0.67-1.71)	1.19 (0.72-1.95)	49	1.04 (0.67-1.63)	1.18 (0.73-1.89)
T3 (≥ 98.5)	198	7	0.35 (0.15-0.85)	0.43 (0.17-1.06)	28	0.69 (0.41-1.15)	0.75 (0.43-1.30)	28	0.60 (0.36-1.00)	0.71 (0.41-1.21)
P for trend			0.013	0.052		0.118	0.232		0.035	0.157
Orange/yellow vegetables and fruits (g/d)										
T1 (< 40.7)	199	16	1.00	1.00	33	1.00	1.00	40	1.00	1.00
T2 (40.7- < 100.6)	198	22	1.38 (0.70-2.71)	1.58 (0.78-3.20)	50	1.52 (0.94-2.47)	1.72 (1.03-2.87)	62	1.56 (1.00-2.43)	1.74 (1.08-2.80)
T3 (≥ 100.6)	199	15	0.93 (0.45-1.93)	1.05 (0.49-2.24)	30	0.91 (0.53-1.55)	0.98 (0.56-1.72)	22	0.55 (0.32-0.96)	0.61 (0.34-1.09)
P for trend			0.674	0.891		0.461	0.634		0.013	0.041

Orange/yellow fruits (g/d)										
T1 (< 32.5)	199	18	1.00	1.00	38	1.00	1.00	48	1.00	1.00
T2 (32.5- < 90.6)	199	22	1.22 (0.63-2.34)	1.44 (0.72-2.85)	47	1.24 (0.77-1.98)	1.43 (0.87-2.35)	56	1.17 (0.76-1.80)	1.35 (0.85-2.15)
T3 (≥ 90.6)	198	13	0.72 (0.35-1.52)	0.79 (0.37-1.70)	28	0.74 (0.44-1.25)	0.77 (0.44-1.35)	20	0.42 (0.24-0.73)	0.44 (0.25-0.80)
P for trend			0.281	0.37		0.15	0.198		< 0.001	0.002
Orange/yellow vegetable (g/d)										
T1 (< 3.2)	198	13	1.00	1.00	27	1.00	1.00	34	1.00	1.00
T2 (3.2- < 9.1)	200	11	0.84 (0.37-1.91)	1.17 (0.49-2.75)	28	1.03 (0.59-1.81)	1.35 (0.75-2.46)	28	0.82 (0.48-1.40)	1.04 (0.59-1.84)
T3 (≥ 9.1)	198	29	2.21 (1.11-4.40)	2.87 (1.36-6.03)	58	2.20 (1.33-3.64)	2.54 (1.48-4.36)	62	1.85 (1.16-2.95)	2.05 (1.24-3.40)
P for trend			0.005	0.002		< 0.001	< 0.001		0.001	0.002
White vegetables and fruits (g/d)										
T1 (< 109.9)	199	31	1.00	1.00	60	1.00	1.00	61	1.00	1.00
T2 (109.9- < 198.0)	199	15	0.49 (0.25-0.93)	0.59 (0.30-1.16)	36	0.60 (0.38-0.95)	0.75 (0.46-1.22)	45	0.74 (0.48-1.14)	0.93 (0.59-1.48)
T3 (≥ 198.0)	198	7	0.22 (0.10-0.50)	0.25 (0.10-0.59)	17	0.28 (0.16-0.50)	0.35 (0.19-0.63)	18	0.30 (0.17-0.52)	0.37 (0.21-0.67)
P for trend			0.001	0.002		< 0.001	0.001		< 0.001	< 0.001

[1]Adjusted by age, education, alcohol consumption, BMI, regular exercise, red meat, processed meat and total energy intake; [2]Test for trend calculated with the median intake for each category of vegetables and fruits as a continuous variable.

consumption can contribute to the development of melanoma[44]. Citrus is rich in psoralens and furocoumarins, which raise melanoma risk through photocarcinogens. However, negative health effects of psoralens and furocoumarins on colorectal cancer have not been found in epidemiologic studies. Therefore, we cannot explain the association and possible mechanism for the increased risk of colorectal cancer.

This study shows that high orange/yellow vegetables intake elevates the risk of colorectal cancer. Orange/yellow vegetables include carrot, pumpkin, and ginger. In a case control study from Western Australia[12] and Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial study[45] reported the protective effects of dark yellow vegetables (carrot, pumpkin) for colorectal cancer risk. Gingerol and supplementation with ginger root extract inhibit colorectal carcinoma progress in vivo and humans[46,47]. However, safrole, ingredients that generated when ginger rotted, and group 2B carcinogen classified by the IARC[48], is known to induce cancer in rodents[49,50]. Also, the remaining chemical additives (fertilizer, preservatives, pesticide) after washing are likely to cause cancer. We have no definite explanation that orange/yellow vegetables intake increase the risk of developing colorectal cancer. More research is needed to verify this observation.

Our results showed a sex difference. Although the underlying mechanism for the sex difference of our study between sexes is not clearly known, few possibilities can be considered from various aspects. Previous studies have suggested that estrogen exposure[51] and the use of oral contraception[52] prevented the development of colorectal cancer. Also, taking hormonal replacement therapy (HRT) in postmenopausal women showed reduced colorectal cancer risks in Women's Health Initiative (WHI) study[53] and a meta-analysis[54]. Another reason is that women tend to prefer vegetables and fruits than men. Because usually women are responsible in buying and cooking foods in Korean culture, they tend to have more information about beneficial health effects of vegetable/fruits and consume more of them[55]. Other factors such as prevalence of diabetes, physical activity, education and income levels, and lifestyle differences between sexes may influence the relationship between vegetables and fruits intake and colorectal cancer risk.

Korean diet has a unique synchronic serving method/style of which all dishes are served at one time on a table. On the other hand, Western or Chinese diet is diachronic (course meal), serving dishes at different points of time[56]. A Typical and common Korean table is set with bap (steamed rice), kuk or chigae (broth, stew), banchan (side dishes) and kimchi[57]. Bap is the main Korean dish that gives a major source of energy. Kuk or chigae, which are different than the Western soups[58] are eaten with bap. Usually, banchan (side dishes) are composed of more than three kinds of foods such as namul, legumes, fish, meat, and kimchi, and are seasoned with jang, sesame or perilla seed/oil, vinegar, and herbs. Korean diet is usually well-balanced and nutritious. Based on these features, the health benefits of the Korean diet are reported in many cases of diseases[59,60]. Currently, peoples believe that colorful vegetables and fruits are the most nutritious and indicate that the distinction between the color of vegetables and fruits is a powerful factor in food selection[61]. The information presented in this study could be used to advise members of the general Korean public who are interested in the phytochemicals of vegetables and fruits. However, it is difficult to generalize to the population of many countries in the world. Because each country has its own traditional recipe and the unique vegetables and fruits that are naturally grown in each climate and topography.

The present study has several limitations. First, because the design of our study relied on hospital-based case-control groups, and the control group was recruited from participants in the health check-up program of the National Health Insurance Corporation, the results of our study may not be representative of the source population of the cases[62]. The control group could have had healthy behaviors and habits compared to the patients. Second, recall bias is an inherent weakness in case-control study design. Case and control groups tend to have differences in recall. Colorectal cancer patients are likely to overestimate or underestimate their poor eating habits compared to the control group[25]; therefore, there is the possibility of exaggerating of the association. To reduce this problem, we tried to survey the case group as soon as their cancer was diagnosed or just before surgery. Third, we did not evaluate the manufacturing method (cooked, raw, or frozen) or extra ingredients (seasoning, dressing, *etc*.). The majority of study suggested that the inverse relationship for cancer may be stronger for raw vegetables, in which destruction of nutrients is minimized compared to cooked vegetables. But, compared to other cancers, colorectal cancer showed similar results between raw vegetables and cooked vegetables[63]. Lastly, we could not further consider the molecular characteristics such as microsatellite Instability or CpG island methylator phenotype of colorectal cancer patients, which could be related with differential risk.

In conclusion, our results suggest that total vegetables and fruits intake by color was inversely related to colorectal cancer risk. However, the orange/yellow vegetables and fruits color group showed an elevated risk for colorectal cancer. Further studies are necessary to confirm the relationship between vegetable and fruit intake by color and colorectal cancer risk.

COMMENTS

Background

The colors of vegetable and fruit reflect their contents of unique phytochemicals and micronutrients. In this case-control study, the authors investigated the relationship between the colors of vegetable and fruit and the risk of colorectal cancer.

Research frontiers

The authors conducted a case-control study to investigate the association between the vegetable and fruit color group and colorectal cancer risk in the Korea population.

Innovations and breakthroughs

Methods that classify vegetables and fruits by color are rare in most studies of disease including colorectal cancer. Vegetables and fruits that are consumed by Koreans were classified according to the criteria.

Applications

Results of this study may be used to advise the general Koreans who are interested in prevention of colorectal cancer.

Terminology

The color of vegetables and fruits reflect the contents of unique phytochemicals and micronutrients. Vegetables and fruits intake in various color groups may protect against colorectal cancer.

Peer-review

Presented manuscript depicts interesting way of seeing of diet-factors impact to colorectal cancer genesis. Discrimination of vegetables and fruits according to only their colour and hypothetical natural consent is substantially difficult in light of reliable statistical analysis. However, there are consistent preventive data of cruciferous vegetables, garlic or fiber-rich plants. The meaning of achieved results should be very careful. Available vegetables and fruits include diversified values of chemical additives, various preservatives and chemical fertilizers as well. Vast used, *e.g.,* to citrus preservation, fungicides such as enilkonasol and also tiabendasol have documented pro-cancerous action. Because of that, estimation of influence of dietary plants to cancer is especially difficult in the age of chemically modified plants.

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