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Development of quantitative index evaluating anticancer or carcinogenic potential of diet: the anti-cancer food scoring system 1.0

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BACKGROUND/OBJECTIVE: Cancer is closely related to diet. One of the most reliable reports of the subject is the expert report from the World Cancer Research Fund & American Institute of Cancer Research (WCRF&AICR). However, majority of the studies including above were written with academic terms and in English. The aim of this study is to create a model, named Anti-Cancer Food Scoring System (ACFS), to provide a simple index of the anticancer potential of food.
SUBJECTS/METHODS: We created ACFS codes of various food groups. The evidence of the ACFS codes was provided by the literature at a level comparable to that suggested in the WCRF&AICR report or from the WCRF&AICR report. The ACFS grade was calculated considering food group, cooking, and normalization. Application was performed for Koreans' 20 common meals, which encompass multinational recipes.
RESULT: We calculated the ACFS grades of Koreans' 20 common meals. The results were not significantly different from the WCRF&AICR guidelines or information from the National Cancer Information Center of Korea. The grades were briefly interpreted as follows: grade S. ideal for cancer prevention; grade A. good for cancer prevention; grade B, might have anticancer potential; grade C, difficult to be regarded as preventive or carcinogenic; grade D, might against cancer prevention; grade E, probably against cancer prevention.
CONCLUSIONS: The ACFS provides a simple index of anticancer potential of diets. This indicator can be useful for the people without expertise, and is effective in evaluating the diets including Asian foods. The ACFS can help design of future clinical or nutritional studies of cancer prevention.

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INTRODUCTION

Cancer is a disease that might cause death and is a serious social health burden. In 2015, Approximately 90.5 million people worldwide experienced cancer, and it has led to 8.8 million deaths, accounting for 15.7% of all mortalities [1]. The risk of cancer increases with population aging, and is a more serious health problem in developed countries [2]. In the United States, cancer was the second leading cause of death following heart disease, and cancer was the leading cause of death in Japan and Korea, the East Asian countries [3-5].

The cause of cancer is deeply related to lifestyle including food consumed, and 30-35% of cancer is known to be related to diet [6]. World Cancer Research Fund (WCRF) and Ameican Institute of Cancer Research (AICR) published the second expert report in 2007, which is one of the most comprehensive literature about the association between food, nutrition, physical activity and cancer prevention [7]. In a recent prospective trial, adherence to the WCRF/AICR cancer prevention guideline was related with 61% lower cancer specific mortality [8].

The WCRF/AICR second expert report and its updated online version, which is called Continuous Updated Project (CUP) [9], are comprehensive and evidence-based. However, they contain many academics terms of medical and nutritional aspects, and the volume of reports is so large that it is difficult to understand by those who do not have medical expertise and fluency in English. The report also lacks the ability to analyze a wide range of Asian foods, with the most of the analysis taking place only on Western and some Chinese foods.

The relationship between food and cancer is well-known in common knowledge; for example, vegetable and fruits are known to prevent cancer and meat is to occur cancer. However, relying on common knowledge has risk of biased nutrition, and being shifted by commercial information without evidence. The US's healthy eating index [10] for general health promotion, and the dietary inflammatory index [11] for prevention of

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cardiovascular disease are examples of indexes that scientifically classified nutritional evidence and providing easy reference. However, there is no simple index that can easily understand the cancer potential of diets.

Food is produced and consumed by people of all socio-economic classes in all countries. Therefore, we need a simple index of anti-cancer diet that allows to analyze as many regions' diet, but which is also available for those without expertise. The aim of this study is to develop a model, named Anti-Cancer Food Scoring System (ACFS), that can provide a simple index quantitatively evaluating the anticancer or carcinogenic potential of diets.

SUBJECTS AND METHODS

Development of the ACFS codes and normalization

The ACFS codes were developed by modifying the factors in the WCRF/AICR second report [7], excluding the factors related to lifestyle rather than diet (e.g. physical activity, lactation, and sedentary living) and adding more diet related factors to assess wider range of foods including them from Asian regions. The codes were composed of 22 food groups, which were: whole grain (WG), red meat (RM), green leafy salad (GLS), fish (FISH), garlic (Ga), soy food (SF), cruciferous vegetable (CV), allium vegetable (AV), cheese (Ch), seaweed (SW), fruit (FR), non-starchy vegetable (NSV), white meat (WM), carotene-rich vegetable (CRV), processed meat (PM), selenium-rich food (SRF), milk (Mi), egg (Egg), refined grain (RG), legume (Le), Chilli (Chilli), and potato (Pot).

Each code was given cancer-specific grades (CSG) associated with its anticancer or carcinogenic potential. The CSG were assigned in five types of cancers, which have been global health burden with high mortality rates and are the cancers largely affected by diet [6,10]. These include lung, breast, colorectal, stomach, and liver cancers. The CSG was developed based on the 4 criteria for grading evidence from the WCRF/AICR second expert report; convincing, probable, limited-suggestive, and limited-no conclusion [12]. In ACFS, the evidence levels which is equal or higher than probable level from WCRF/AICR report, which briefly means the evidences supported from $\geq$ 2 cohort studies or $\geq$ 5 case control studies (which have good qualities) without substantial unexplained heterogeneity with biological plausibility, were regarded as CSG A. CSG B in ACFS was correlated with limited-suggestive level of WCRF/AICR report, which briefly means the evidences supported from $\geq$ 2 cohort studies or $\geq$ 5 case control studies with general consistency and biological plausibility. CSG C in ACFS meant the same level of evidence as the limited-no conclusion level of the WCRF/AICR report.

When CSG was A, B, and C, scores of 10, 5, and 2 were given, respectively. When CSG was related to carcinogenic potential, negative score was given. The CSGs were added for each code, and the summed code points ranged from -20 (RM) to 32 (Fr) points. These summed points were simplified and divided into five code grades; $>$ 21 for code grade A, 11 to 20 for B, 0 to 10 for C, -1 to -10 for D, and -11 to -20 for E. Theoretically, a summed code point can range from -50 to 50, but an extreme score like 50 or -50 is hard to be found in practice. CSG grading

Table 1. Anti-cancer food scoring system code table

ACFS code		Cancer specific grade					Summed code point	Code grade
		Breast	Colorectum	Stomach	Lung	Liver		
WG	Whole grain	C	A	B			17.0	B
RM	Red meat		A		B	C	17.0	E
GLS	Green leafy salad	C	B	A	B	C	24.0	A
FISH	Fish	C	B		C	B	14.0	B
Ga	Garlic	C	A	A	B		27.0	A
SF	Soy food	B	C	B[1]			12.0	B
CV	Cruciferous vegetable	C	B	A	B	C	24.0	A
AV	Alium vegetable	C	A	A	B	C	29.0	A
Ch	Cheese		B				5.0	D
SW	Seaweed	C	C				4.0	C
Fr	Fruit	C	B	A	A	B	32.0	A
NSV	Non-starchy vegetable	C	B	A	B	C	24.0	A
WM	White meat					B	5.0	C
CRV	carotene-rich vegetable			C	A		12.0	B
PM	Processed meat		A	B	B		20.0	E
SRF	Selenium-rich food		B	B	B		15.0	B
Mi	Milk		B				5.0	C
Egg	Egg						0.0	D
RG	Refined grain						0.0	D
Le	Legume			C			2.0	D
Chilli	Chilli			C			2.0	D
Potato	Potato						0.0	D

ACFS, anti-cancer food scoring system; CSG, code-specific grade.
The underlined numbers or grades in alphabet mean negative value of cancer prevention.
[1] Exclude soybean paste and miso soup

is designed considering above, distribution of summed code points, nutritional common knowledge, simplicity and ease of application. Further calculation was performed with the code grades, rather than summed code point. Above process was described in Table 1.

Evidence preparation of CSGs

We developed CSGs based on literature evidences. The main reference was the WCRF/AICR second expert report [7] and its updated online version [9].

The preventive effect of the whole grain (ACFS code: WG) for stomach cancer was supported by at least a prospective study [13] and several case-control studies with general consistency [14-21]. The fiber in the grain is potentially countering the harmful effect of N-nitroso compounds [22,23]. The relationship was considered as CSG B.

The carcinogenic effect of red meat (ACFS code: RM) consumption for liver cancer, was supported by at least 3 prospective studies [24-26], but there was heterogeneity among case-control studies [27-32]. Thus it was regarded as CSG C. The protective effect of fish (ACFS code: FISH) consumption for liver cancer was supported by at least 4 prospective studies [25,26, 33,34], and heterogeneity among case-control studies was not substantial [28,29,31,32,35,36]. Meta-analysis was performed and risk ratio of high fish intake for liver cancer was 0.78 (95% CI: 0.63-0.90) [37]. Biological plausibility was supported by studies including them about anti-inflammatory effect of poly-unsaturated fatty acids (PUFA) [38]. Therefore, protective effect of fish consumption for liver cancer was regarded as CSG B. The anticancer effect of white meat (ACFS code: WM) consumption for liver cancer was supported by at least 4 prospective and 4 case-control studies [24-29,32,34]. There was no substantial heterogeneity. The anti-inflammatory effect of PUFA also contributes to liver cancer prevention of white meat [39]. The CSG B was allotted for the anticancer effect of white meat for liver cancer.

The association between anticancer effect of soy food (ACFS code: SF) consumption and colorectal cancer was supported by at least 2 prospective studies [40,41]. A prospective study by Akhter *et al.* [42] showed no relationship, and the other prospective study by Oba *et al*. [43]. showed difference of effect according to gender. Case-control studies generally suggested protective effect [44-51]. The biological plausibility is still not robust [52]. Therefore, the CSG was regarded as C. When discussing the relationship between soy food and stomach cancer, we excluded miso soup or bean paste among the soy foods. Because they often contains significant amounts of salt, miso soup is usually served in the form of hot liquid, and salt and hot beverages are well-known risk factors for gastric cancer [9,53]. The preventive effect was supported by at least 3 prospective studies [54-56], and the result of case-control studies were generally consistent [18,46,50,57-61]. The mechanisms are explained by many hypotheses, including anti-inflammatory and antioxidative effects [62], inhibition of H.pylori growth [63], and inhibition of angiogenesis and increased apoptosis [64]. Therefore, the preventive effect of soy food on stomach cancer, except for miso soup and bean paste, was considered to be CSG B.

The relationship between soy foods and breast cancer is one of the most extensively studied areas. Biological plausibility is well known; soy isoflavone, which is a phytoestrogen of soy food similar to 17-β estradiol in structure but with weaker estrogenic effect, acts as antagonist to the cancer development of endogenous estrogens [65]. In a recent meta-analysis, a total of 35 studies including 12 prospective studies were analyzed [66]. In this study, soy food intake is preventive for breast cancer regardless of menopausal status in Asian women. The cancer preventive effect of soy food in premenopausal Asian women is supported by at least two prospective studies [67,68], and that in Asian postmenopausal women is also supported by at least two prospective studies [68,69]. The breast cancer preventive effects of soy foods in premenopausal and postmenopausal Asian women are supported by more than 10 retrospective studies respectively [66]. There is controversy about the breast cancer preventive potential of soy foods in Westerners. However, the amount of soy food intake in the studies of Western women is far lower than that of Asians. In a meta-analysis by Wu *et al*. [65], the quartile consuming the soy food the most in studies of Asian women was > 20 mg per day and the least consumed quartile was < 5 mg per day. In the studies of Western Women, the highest quartile of intake was > 0.8 mg per day and the lowest quartile was < 0.15 mg per day. The 0.8 mg of isoflavone is the amount of soy milk in < 10 cc. Considering that the soy food intake was too low in studies of Western women, a large number of studies on Asians supported the preventive effect of soy food, and biological plausibility was evident, the breast cancer preventability of soy food was classified as CSG B.

Seaweed (ACFS code: SW) is consumed as food only in limited countries, including Korea and Japan. But it is a very common food in Korea and Japan. Seaweed contains beta-carotene, fucoxanthin, and chlorophyll, which seem to be effective in preventing breast cancer [70,71]. Also, dietary fiber and digestible algae polysaccharides are abundant, which can be helpful for preventing colorectal cancer [72,73]. Many other mechanisms and possibilities of cancer prevention were suggested, but large clinical trials are warranted to draw more robust conclusion [74]. We cautiously allotted CSG C for anticancer effect of seaweed for breast and colon cancer.

The references of evidence of other CSGs are summarized in Supplement 1.

Application

Application was performed with 20 commonly consumed meals of Koreans; the composition and food exchange units (FEU) [75] of the ingredients were identified by referring to the Korean Nutrition Society database [76]. Korean lifestyle has been influenced by Asian countries such as China and Japan, and Western countries including the United States. Therefore, common meals of Korean include Chinese, Japanese, and Western food as well as Korean food. The reason for using the FEU other than the weight of the ingredient is that the former is the unit of the concept most similar to the serving, which was the more commonly used measurement than weight in reference studies.

Table 2. Examples of ingredient score calculation

Meals	Components	Weight	ACFS code	FEU	FEU ratio	FEU ratio × code grade point	Ingredient score	Cooking modification	ACFS grade
Fish soup and rice	White rice	210	RG	3	37.5%	75.0			
	Cod (fish)	100	FISH	2	25.0%	100.0			
	Raddish	50	AV	3 in total[1)]	14.3%	71.3			
	Bean sprout	30	CRV		8.6%	34.5			
	Garlic	20	Ga		5.6%	28.1			
	Water parsley	20	CRV		5.6%	22.5			
	Scallion	10	AV		3.0%	15.0			
							346.4	none	A
Chinese style fried rice	White rice	250	RG	3.5	53.8%	107.6			
	Pork	20	RM	0.5	7.7%	7.7			
	Egg	60	Egg	1	15.4%	30.8			
	carrot	30	NSV	1.5 in total[1)]	6.9%	34.7			
	Onion	40	AV		9.2%	46.2			
	Pimento	20	NSV		4.6%	23.1			
	Scallion	10	AV		2.3%	11.6			
							261.6	HF[2)]	C

ACFS, anti-cancer food scoring system; FEU, food exchange unit; RG, refined grain; FISH, fish; AV, allium vegetable; CRV, carotene-rich vegetable; Ga, garlic; RM, red meat; NSV, non-starchy vegetable; HF, high-fat cooking.
[1)] If the FEU was provided only for the whole of the vegetables, the FEU was divided according to weight and calculated.
[2)] If > 20 g of oil or > 2 g of sodium was used for cooking, it is regarded as harmful cooking and the grade is lowered one level.

Table 3. Application and ACFS codes of Koreans' common meals

Recipe name	Ingredient score	Grades before cooking modification	Harmful cooking	ACFS grade
Designed breakfast[1)]	449.5	S		S
Designed lunch[1)]	433.4	S		S
Designed dinner[1)]	427.6	S		S
Fish soup and rice	346.4	A		A
Maki roll	332.0	A		A
Chiniese-style noodles with vegetables and seafoods	367.0	A	HS	B
Vegetable and minced meat dumpling	302.0	B		B
Hand-pulled dough soup	290.8	B		B
Bibimbap	283.4	B		B
Sushi	280.0	B		B
Soybean paste stew and rice	263.8	B		B
Kimchi stew and rice	292.6	B	HS	C
Noodle with black soybean sauce	286.2	B	HF	C
Fried rice in thin omelette	277.5	B	HF	C
Chinese-style fried rice	261.6	B	HF	C
Cold buckwheat noodles	236.2	C		C
Knife-cut noodle soup	208.1	C		C
Pork cutlet and rice	223.0	C	HF	D
Ox bone soup and rice	170.0	D		D
Bulgogi	164.8	D		D
Instant noodle	200.0	C	HF,HS	E
Sweet and sour fried pork	186.3	D	HF	E
Grilled pork belly	122.0	D	HF	E

ACFS, anti-cancer food scoring system; HS, high-salt cooking; HF, high-fat cooking.
[1)] Designed meals were recipes that made ideally for cancer prevention in consideration of ACFS.

RESULTS

Calculation of the ACFS grade

The ACFS grade, which is the objective index reflecting anticancer or carcinogenic potential of the meals, is calculated in the following steps:

1) Allocate the ACFS code corresponding to the components of the meals. Auxiliary materials for cooking, including salt and cooking oil, are not considered in this step.

2) The FEU of the components given the ACFS code is summed

Table 4. Foods in the ACFS 1.0 development and the amount corresponding exchange unit

Example of food	ACFS code	Amount of 1 FEU	Practical measure
Allium vegetable	AV	70 g	1 cup
Chilli	Chilli	70 g	1 cup
Cheese	Ch	30 g	1.5 slice
Sweet potato	CRV	70 g	1/2 of middle sized sweet potato
Cruciferous vegetable	CV	50 g	1 cup
Egg	Egg	55 g	1 medium sized egg
Fish	Fish	50 g	1 small cut
Strawberry	Fr	150 g	7 strawberries
Tangerine	Fr	120 g	2 tangerines
Watermelon	Fr	150 g	1 slice
Kiwi	Fr	80 g	1 middle sized kiwi
Tomato	Fr	350 g	2 small tomatoes
Apple	Fr	100 g	1/3 of whole
Orange	Fr	100 g	1/2 of whole
Banana	Fr	50 g	1/2 of whole
Garlic	Ga	50 g	1 cup
Green-leafy salad	GLS	70 g	1 cup; 1/3 cup for boiled salad
Legume	Le	8 g	1 large spoon
Milk	Mi	200 ml	1 small cup
Non-starchy vegetable	NSV	70 g	1 cup
Ham, Sausage	PM	40 g	2 slices of ham
Potato	Potato	140 g	1 medium sized potato
Refined rice	RG	70 g	1/3 small bowl
Refined grain noodle	RG	90 g	1/2 small bowl
Red meat	RM	40 g	1 small cut
Tofu	SF	80 g	1/5 of whole tofu
Black bean	SF	20 g	2 large spoon
Natto	SF	40 g	4 large spoon
Squid, Shrimp	SRF	50 g	3 shrimp, 1/3 of squid body
Shellfish	SRF	70 g	1/3 cup
Walnut, Peanut	SRF	8	8 peanuts, 1.5 walnut
Seaweed	SW	70 g	1/3-1/2 cup
Whole grain	WG	70 g	1/3 small bowl

ACFS, anti-cancer food scorign system; FEU, food exchange unit.

up, and the fraction of the FEU of each component is calculated as a percentile.

3) Multiply the FEU percentage of each component calculated above and the point assigned to the code grade. The point assigned to the code grade is 5 for code grade A, 4 for B, 3 for C, 2 for E, and 1 for E.

4) Sum all the values of components calculated in step 3. This value is called ingredient score.

5) Theoretically, the ingredient score can range from as low as 100 to as high as 500 points. The score of > 400 is classified as grade S, 301 to 400 as A, 251 to 300 as B, 201 to 250 as D, and ≤ 200 as E. The categorization was performed considering distribution of the ingredient scores, common nutritional knowledge, simplicity and ease of use.

6) Finally, two harmful cooking factors [high salt (HS) and high fat (HF)] are used to account for the influence of the cooking method. If > 2 g of salt or > 20 g of oil was used in the cooking process, it is regarded as harmful cooking and the grade is lowered by one level.

The definition of high salt food (2 grams of salt) is made to ensure that the salt intake does not exceed the WHO recommendation (< 5 grams per day) with three meals. The definition of high fat diet was made with reference to the 'high in fat' category of Food Standard Agency of US [≥ 21 g of fat per serving (≥ 250 g)] [77] and the Coronary Prevention Group (49.5 kcal from fat/ 100 kcal of food) [78] and considering the composition of 20 Korean common meals. The example of calculating ACFS grade is described in Table 2.

Application of ACFS grades

The final result including ACFS grade of 20 common meals sampled are described in Table 3. Ingredient score ranged from 122 to 449.5. After consideration of harmful cooking method, the ACFS grades of 20 common meals are as follows:

Grade S: designed breakfast, lunch, and dinner

Grade A: fish soup and rice, Maki roll

Grade B: Chinese-style noodles with vegetables and seafood, vegetable and minced meat dumpling, Hand-pulled dough soup, Bibimbap, Sushi, Soybean paste stew and rice

Grade C: kimchi stew and rice, noodle with black soybean sauce, fried rice in thin omelette, Chinese-style fried rice, cold buckwheat noodles, knife-cut noodle soup

Grade D: pork cutlet and rice, ox bone soup and rice, bulgogi

Grade E: instant noodle, sweet and sour fried pork, grilled pork belly

The food exchange list considering the food items in 20 Korean recipes that we have used is listed in Table 4 [75].

Designed meals were recipes that made ideally for cancer prevention in consideration of ACFS. This designed meal basically refers to the composition of the meal planning as exemplified by the Korean Diabetes Association [75], takes into consideration the cancer preventive potential of ACFS, and has a variety of foods to make the meal enjoyable. The details are as follows:

Designed breakfast: steamed multi-grain rice 1.5 FEU; shredded and seasoned radish 0.5 FEU; seasoned spinach 0.5 FEU; boiled and marinated mackerel pike 2 FEU; kimchi 2.5 FEU

Designed lunch: steamed multi-grain rice 2.5 FEU; boiled tofu 1.5 FEU; white kimchi 0.5 FEU; walnuts and peanuts 1.0 FEU; boiled and marinated anchovy 0.5 FEU; tomato 0.5 FEU; broccoli 0.5 FEU; onion 0.5 FEU

Designed dinner: whole-grain bread 2.0 FEU; steamed salmon 2.0 FEU; lettuce and bokchoi salad 2.0 FEU

ACFS grades interpretation

Grade S: ideal for cancer prevention in terms of composition and cooking method.

Grade A: good for cancer prevention in terms of composition and cooking method.

Grade B: might have cancer prevention potential and some modification can be helpful.

Grade C: difficult to be regarded to have anticancer or carcinogenic potential. Modification is recommended.

Grade D: might be against cancer prevention. Modification is highly recommended.

Grade E: probably against cancer prevention.

DISCUSSION

Dolls & Peto estimated that about one-third of cancer causes are related to food [79]. Recently, the association of diets with cancer is clinically proven beyond estimation. In a recent large prospective studies, the risk of colorectal cancer and breast cancer was reduced by up to 58% and 60%, respectively, in patients who were well adhered the guidelines provided by WCRF & AICR [8,80]. These guidelines refer to diet, obesity, and lifestyle, and diet account for a significant portion. Since the ACFS model referred much of the principles from WCRF & AICR expert report, ACFS might be expected to have predictive potential for cancer prevention.

The types of cancer that occur in Asian and Western countries are very different. This might be due to racial differences, but is also largely influenced by difference in food intake. For example, it is reported that the stomach cancer, which is prevalent in East Asians countries, is associated with salt-preserved foods; and larger consumptions of soy and fish were reported to prevent cancers including breast or gastrointestinal cancer [7,36,37,41]. We systematically searched the literature and developed the ACFS code to broaden the scope of food analysis than the WCRF & AICR expert report. This will especially help to analyze Asian foods which use a wide variety of ingredients.

To our knowledge, no model has yet been published that quantifies the anticancer and carcinogenic potential of diet. We analyzed 20 Koreans' common meals encompass Korean, Chinese, Japanese, or Western styled foods, and the calculated ACFS grade was in good agreement with the generally recommended diet for cancer prevention [7,81]. The ACFS model provides estimates from calculations, but its strength is providing the grades that can be understood at a glance. Previously, in order to know the relationship between cancer prevention and diet, a comprehensive understanding of the various studies and guidelines with help of expertise was needed. With the ACFS grade, people without expertise can easily understand the relationship between diet and cancer. The ACFS will develop businesses of catering services or health food products related to cancer prevention, and evolve the cancer prevention business to more evidence-based field.

This study has several limitations. Since the ACFS is a computational estimate, it should be used for reference purposes with other nutritional epidemiologic studies and should be reinforced by future clinical studies. Because the ACFS is a model developed by an oncologist, it has limitation in terms of subjectivity. Cooperation with nutritionists, nurses, and engineers is essential to increase its reliability and utilization. The ACFS currently validates only 20 common meals, and it is necessary to analyze the diverse foods of various countries in the future to increase the reliability.

The ACFS provides a quantitative index of anticancer and carcinogenic potential of diets. This indicator is particularly useful for people without expertise, and is also effective in assessing the diets including Asian foods. This indicator should prove its effectiveness in future clinical studies. We sincerely hope that the ACFS will be able to reduce the fears and suffering caused by malignant cancer.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interests.

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