RESEARCH COMMUNICATION

Nutritional Epidemiology of Cancer in Korea: Recent Accomplishments and Future Directions

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Abstract

Because diet is closely related to cancer incidence and mortality, recent studies in cancer epidemiology have focused on dietary factors. The results of studies on nutritional cancer epidemiology in Korea are discussed in this research paper. Most studies have used a case-control design focused on breast or gastric cancer patients. Antioxidants were associated with a reduced risk of gastric cancer in most studies, but this association was not observed for breast cancer. Most diets consumed by Koreans that included fruits and vegetables were associated with reduced cancer risk, but high concentrations of salt in food were positively associated with gastric cancer risk. Genetic susceptibility was considered in several studies, and food contaminants were assessed to estimate life-time cancer risk. Recent studies have made advances in understanding the relationship between diet and cancer among Korean populations. However, because the history of nutritional cancer epidemiology in Korea is relatively short, the subjects covered and methodology of the research have been limited. A cohort design with a large sample size and appropriate methods to assess subjects' usual intake may be needed to determine the true association between diet and cancer in the future.

Keywords: Korean - nutrition - diet - cancer - epidemiology

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Introduction

Cancer is a leading cause of death in Korea. The cancer mortality rate was 146.6 per 100,000 population in 2010, an increase of 18.7 percent from 2000 to 2010 and 59.7 percent from 1990 to 2010 (Statistics Korea, 2011). Dietary and lifestyle changes can affect cancer incidence and mortality, and the nutritional epidemiology of cancer has become an important part of cancer prevention. The World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR, 2007) specifies recommendations for food, nutrition, physical activity, and body composition to prevent cancer, largely based on nutritional epidemiology research. However, there are several issues in the study of the nutritional epidemiology of cancer. Measurement errors in diet exposure, especially associated with food frequency questionnaires (FFQ), complicate the identification of an association between diet and cancer (Bingham et al., 2008; Michels, 2001). Extreme diets are rare in the general population, and assessing diets with small variances among subjects makes it difficult to detect accurate associations between diet and cancer. Minor associations between diet and cancer can be easily confounded by other lifestyle factors. Nevertheless, the nutritional epidemiology of cancer has achieved notable accomplishments.

Although most types of cancers are closely related to nutrition and other lifestyle factors, the history of nutritional cancer epidemiology in Korea is relatively short. Previous studies on nutrition and cancer have primarily focused on the nutritional status of cancer patients, who are likely to suffer from malnutrition. Because of the importance of nutrition in cancer epidemiology and the fact that the Korean diet is considerably different from the diet in western countries, studies on the association between diet and cancer risk have recently received increased attention from Korean researchers. Korean diets are rich in fruits and vegetables, which have an inverse association with cancer risk, but the vegetables are generally consumed as pickled vegetables mixed with various condiments, which tend to have high sodium content. Cooking methods that vary based on cultural differences are considered an important part of the nutritional epidemiology of cancer. This study aims to summarize previous reported results and discuss future aspects of the nutritional epidemiology of cancer for Korean populations.

Materials and Methods

Various keywords, including 'Korean', 'Korea', 'food', 'diet', 'intake', 'nutrition', 'cancer', and 'risk', were used to search for studies on the nutritional aspects of cancer risk among Korean populations on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), KoreaMed (http://

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Table 1. Summary OR/RR of Nutrient Intake for Different Cancer Sites

	OR/RR[a]		OR/RR[b]		
	Breast	Gastric	Breast	Gastric	Cervix
Energy			1.04	1.35	1.13
Carbohydrate			1.59	1.24	1.37
Carbohydrate_GI	0.44				
Carbohydrate_GL			0.85		
Protein				0.6	0.61
Protein_animal				0.63	
Protein_vegetable			0.39		
Protein_soy	0.51				
Fat			1.15	0.62	0.67
Fat_animal				0.93	
Fat_vegetable		0.49			
Fatty acid			1.02, 1.65	0.55-0.75	
Fatty acid	0.44-0.50				
Fiber		0.37			

[a]Statistically significant results; [b]Non-significant results; Reference list: Do et al., 2003, Kim et al., 2005, 2008a, 2009b, 2010a, Yun et al., 2010

koreamed.org/SearchBasic.php), and KMBase (http://kmbase.medric.or.kr/). Various micro- and macronutrients, foods, and contaminants in food were examined as risk factors for cancer. Several studies were included on the genetic influence in the association between nutrition and cancer risk.

Results

Macronutrients and food intakes

Carbohydrate, protein and fat intake, as well as total energy intake, have not been associated with cancer risk (Do et al., 2003; Kim et al., 2005; Kim et al., 2010a). However, protein or fat from vegetable sources have been found to reduce the risk of gastric cancer (Kim et al., 2005) (Table 1). Fruits and vegetables, which have been widely studied, have been inversely associated with cancer risk, whereas pickled vegetables significantly increased breast and gastric cancer risk (Table 2). Mushroom intake has been associated with reduced cancer risk (Kim et al., 2002a; Lee et al., 2004; Hong et al., 2008; Shin et al., 2010), but one study reported an association with a significant increase in breast cancer risk (Lee et al., 2003a). It seems that the selection of cases in this study was not restricted to newly diagnosed cancer patients; mushrooms are frequently consumed by cancer patients because mushrooms are considered by Korean cancer patients to be a beneficial food for breast cancer. Intakes of meats, especially charcoal grilled meats, and eggs have been found to increase cancer risk (Lee et al., 2003a; Kim et al., 2002a). The results of soybean intake have been inconsistent. Soybean curd, fermented soy and soybean milk reduced cancer risk (Park et al., 2000; Kim et al., 2002a; 2008a; Lee et al., 2002; 2003b; Cho et al., 2010a), whereas soybean paste and soybean paste stew increased gastric cancer risk (Park et al., 2000; Nan et al., 2005; Zhang et al., 2009). Fish intake showed an

Table 2. Summary OR/RR of Food Intake for Different Cancer Sites

	OR/RR[a]			OR/RR[b]		
	Breast	Gastric	Colon	Breast	Gastric	Colon
Fruits	0.7	0.20, 0.30		0.74-1.00		
Fruit juice		0.4		0.55-0.83	0.55	
Vegetables	0.22			0.76		0.8
Fresh vegetables	0.09	0.2			0.92	
Green vegetables	0.3	0.24		0.6		
Light-colored vegetables	0.3			1.1		
Seasoned raw vegetables		0.20, 0.30				
Pickled vegetables	2.47	1.57-4.10				
Kimchi_cabbage				0.83	0.5	
Kimchi_radish		1.96		0.77	1.78	
Mushroom	0.40-1.50	0.3				
Meats	0.40-1.70		1.72		0.94, 1.67	
Meat_charcoal grilled		2.11			1.58	
Eggs	1.6			0.71		
Soybeans	0.36, 0.67	0.57		0.70-1.41	0.85	1.11
Soybean curd	0.37, 0.45	0.30-0.51		0.71		
Soybean paste		1.62, 1.63				
Fermented soy	0.31			0.72, 0.76		
Soybean milk		0.5				
Soybean paste stew		2.73				
Fish	0.55, 1.50				0.43	
Salt-fermented fish		2.4			2.1	
Other seafood		0.13, 0.66			0.7	
Seaweed	0·43	0.41, 0.52		0.70, 0·89	0.78	
White rice				1.51		
Boiled rice with assorted mixture	0.42	0.26		0.97	1.7	
Cereals	1.8					

[a]Statistically significant results; [b]Non-significant resultsReference list: Lee et al., 2003a, Lee et al., 2003b, Cho et al., 2010a, Do et al., 2007, Hong et al., 2008, Kim et al., 2002a, Kim et al., 2003, Kim et al., 2008a, Kim et al., 2009b, Lee et al., 2002, Lee et al., 2003a, Lee et al., 2003b, Lee et al., 2004, Nan et al., 2005, Park et al., 2000, Shin et al., 2010, Yang et al., 2010b, Yu et al., 2010, Yun et al., 2010, Zhang et al., 2009

inverse association with cancer risk, but salt-fermented fish increased the risk of gastric cancer (Lee et al., 2002; Lee et al., 2003b). These results suggest that typical Korean diets are generally associated with reduced cancer risk. However, high concentrations of salt in food are a major problem in Korean diets and, are associated with an increased incidence of gastric cancer.

Because foods are not consumed in isolation, the association between a single food and cancer risk cannot be assessed accurately. Therefore, analyses of dietary patterns are necessary to assess the interactions between food components in the nutritional epidemiology of Cancer. The 'vegetable-seafood' pattern and the 'well-being diet' pattern have been associated with a reduced risk of breast cancer (Table 5). Increased risks of cancer have been identified in the 'pork and alcohol' and 'coffee and cake' patterns. Consistent with the results for salted food items, salt preference has been associated with increased gastric cancer risk (Bae et al., 2001; Kim et al., 2010b). A preference for well-done meat and broiled food consumption increased the risk of gastric cancer (Bae et al., 2001; Zhang et al., 2009).

Micronutrients

The effects of dietary antioxidant intake on cancer risk have been extensively studied among Korean populations (Table 3). Antioxidants, mainly vitamins, were associated with reduced risk of cancer, but numerous studies have failed to show statistically significant results. Dietary antioxidant intakes from food were inversely associated with the risk of gastric cancer, but not breast cancer. High consumption of vitamins A, B1, B2, E, β-carotene (Kim et al., 2005), B6 (Kim et al., 2005; Zhang et al., 2009) and folic acid (Kim et al., 2005, Kim et al., 2009) have

Table 3. Summary OR/RR of Dietary Intake and Serum Concentrations of Antioxidants for Different Cancer Sites

	OR/RR[a]			OR/RR[b]		
	Breast	Gastric	Gynecologic	Breast	Gastric	Gyneclogic
Dietary intake						
Vitamin A		0.36	0.36	0.72-1.03		
Retinol				0.62-0.88	0.57	0.81
Vitamin B1		0.42		0.79, 2.77		
Vitamin B2		0.37		0.47, 0.68		
Vitamin B3				1.84	0.6	
Vitamin B6		0.35, 0.71				
Folic acid		0.4		0.82, 0.83		0.92
Vitamin B12						0.94
Vitamin C	0.37		0.36	0.76, 1.07	0.55, 0.79	
Vitamin E	0.22, 0.49	0.48		0.81		0.58
β-carotene	0.42	0.35	0.48	0.8		
Isoflavones				0.81		
Dietary & supplement						
Vitamin A	0.63	0.37	0.35			
Vitamin B1		0.41		0.72		
Vitamin B2		0.42		1.32		
Vitamin C		0.35	0.35	0.7		
Vitamin E		0.47	0.53	0.67		
Serum concentrations						
Vitamin A	0.5					
Retinol				0.74		
Vitamin B1				0.6		
Vitamin B2	0.5					
Vitamin B3				0.7		
Vitamin B6				0.5		
Folic acid	0.5					0.45
Vitamin B12			0.29			
Vitamin C	0.4					
α-tocopherol	0.3		0.19	0.32		
γ-tocopherol			0.18			
Lycopene			0.15, 0.16	1.03		
Zeaxanthin+lutein	0.14		0.33			
α-carotene				0.37		
β-carotene	0.08		0.10, 0.12			
Cryptoxanthin				1.31		
Genistein		0.54				
Daidzein		0.21				
Equol		0.5				
Enterolactone					0.87	

[a]Statistically significant results; [b]Non-significant results; Reference list: Cho et al., 2009, Cho et al., 2010a, Do et al., 2003, Jeong et al., 2009, Kim et al., 2002b, Kim et al., 2005, Kim et al., 2009a, Kim et al., 2010a, Ko et al., 2009b, Lee et al., 2008a, Lee et al., 2008b, Lee et al., 2010, Lee et al., 2011, Zhang et al., 2009

Table 4. Summary OR/RR of Dietary Mineral Intake for Different Cancer Sites

	OR/RR[a]		OR/RR[b]	
	Breast	Gastric	Breast	Gastric
Calcium	0.33	0.43		
Iron			0.76	0.49, 0.77
Phosphorous		0.38	0.98	
Potassium		0.36	0.64	
Selenium			0.98	
Sodium		2.14		0.56
Zinc				0.51

[a]Statistically significant results; [b]Non-significant results; Reference list: Kim et al., 2005, Lee et al., 2008a, Zhang et al., 2009

been associated with a reduced risk of gastric cancer compared to low consumption groups, but the effects of vitamin A, retinol (Lee et al., 2011; Do et al., 2003; Lee et al., 2008a), vitamins B1 and B2 (Do et al., 2003; Lee et al., 2008a), vitamin B3 (Lee et al., 2008a), folic acid, vitamin C, β-carotene (Lee et al., 2008a; 2011a), vitamin E (Do et al., 2003), and isoflavones (Cho et al., 2010a) showed no statistically significant results. Although few studies have assessed antioxidant intakes from both food and supplements or serum concentrations, antioxidants significantly reduced cancer risk, except for breast cancer, in most studies. The results were not statistically significant in many studies assessing only dietary intake of antioxidants. Therefore, the assessment of antioxidant concentrations using serum specimens or the inclusion of supplement use in dietary intake might contribute to the identification of an association between antioxidants and cancer risk. Overall, the results showed that dietary intake or serum concentration of antioxidants decreased gastric cancer risk, but breast cancer showed little association with antioxidant intake.

The effects of mineral intake on cancer risk were similar to the results for antioxidants (Table 4). Intake of most minerals was associated with reduced risk of gastric cancer, but not breast cancer. High intake of calcium, phosphorous, and potassium reduced gastric cancer risk (Kim et al., 2005), but there was no significant association between iron intake and either gastric or breast cancer risk. Sodium, which is consumed in large amounts in Korea, was positively associated with gastric cancer risk (Zhang et al., 2009)

Gene-diet interactions

Diet alone can influence the etiology of cancer, but its effect can differ according to genetic susceptibility. Because diet can affect the association between genetics and cancer risk, gene-diet interactions have become an important part of the study of cancer etiology. Ataxia telangiectasia mutated (ATM) diplotype has been associated with breast cancer in women with low intake of antioxidant vitamins based on a recessive model. However, this association was not observed in the high intake group, suggesting that the effect of ATM diplotype on breast cancer risk could be modified by intakes of antioxidant vitamins (Lee et al., 2010). The p53 mutation did not affect the association between antioxidant vitamin intake and breast cancer risk (Kim et al., 2002b). A C677T base change in methylenetetrahydrofolate reductase (MTHFR) gene, an enzyme of folate metabolism, was associated with reduced enzyme activity, resulting in a mild increase in plasma homocysteine. Women with the MTHFR TT genotype in the low green vegetable intake group showed increased breast cancer risk compared to women with the CC/CT genotype. Breast cancer risk did not increase significantly in the high green vegetable consumption group for women with the TT genotype (Lee et al., 2004). People with low consumption of soybeans with risk gene variants of IL10, an anti-inflammatory cytokine, had an increased risk of gastric cancer compared to people with high consumption of soybeans and no risk gene variants (Ko et al., 2009a).

N-Acetyltransferase (NAT), which is a key enzyme in the activation and detoxification of chemical carcinogens, acted as an important modifier of the doneness of meat on gastric cancer risk. People with a preference for well-done meat had a higher risk of gastric cancer. This association increased, among people with slow/intermediate acetylators, and the association was not observed in people with rapid acetylators (Zhang et al., 2009). The hOGG1 gene is involved in the removal of 8oxoG adducts, the DNA lesions induced by reactive oxygen species. Thus,

Table 5. Summary OR/RR of Dietary Pattern and Habit for Different Cancer Sites

		OR/RR[a]			OR/RR[b]	
	Breast	Gastric	Colon	Breast	Gastric	Colon
Vegetable-seafood	0.14					
Well-being diet			0.16			
Meat-starch				0.69		
Meat & fish						0.55
Pork & alcohol						1.92
Milk & juice			0.4			
Rice & kimchi						1.22
Coffee & cake			2.18			
Animal food preference					1.01	
Salt preference		1.10, 9.80				
Well-done meat preference		1.24				
Frequent broiled food consumption		3.33				
Meal regularity					1.04	

[a]Statistically significant results; [b]Non-significant results; Reference list: Bae et al., 2001, Cho et al., 2010b, Kim et al., 2010b, Oh et al., 2004, Zhang et al., 2009, Kim et al., 2010b

the Ser326Cys polymorphism of hOGG1 might have different effects on the association between dietary factors and cancer risk. Meat intake was not associated with increased colon cancer risk in Ser/Ser or Ser/Cys carriers, but frequent consumption of meat increased the risk for colon cancer in Cys/Cys carriers. However, polymorphism of the hOGG1 gene did not affect other dietary factors, such as vegetables and soybeans (Kim et al., 2003).

Chemicals in food

Various chemicals have been introduced into the body by environmental contaminants in food and food preservatives. Because of increases in environmental pollutants and processed food intake, people are exposed to numerous hazardous chemicals. Thus, the contaminants in food that have adverse health effects have become a public health concern. Several contaminants in the Korean diet have been investigated, and their effects on cancer risk have been assessed.

Nitrates are naturally present in human diets, but high levels of nitrate concentrations lead to high concentrations of nitrites, which form potent carcinogenic N-nitroso compounds. Nitrate intake from food has not been associated with breast or gastric cancer risk, but a higher ratio of nitrates to folate intake has been found to increase both breast and gastric cancer risk. Furthermore, the nitrate/vitamin E ratio has been associated with gastric cancer risk, suggesting that the availability of antioxidant vitamins, such as folate and vitamin E, might moderate the harmful effects of nitrates on cancer risk (Yang et al., 2010a; Kim et al., 2007). The polycyclic aromatic hydrocarbons (PAHs) can be found in various food items, such as grilled meat, vegetables, seafood and oils. Benzo[a]pyrene (BaP), a member of the PAH class, is used as a surrogate marker for PAH contamination. Humans are exposed to BaP primarily through dietary intake, and the detectable levels of BaP can differ by cooking procedures. Pyrolytic formation by cooking method and the estimated dietary intake of BaP has been analyzed. High concentrations of BaP were detected in fried chicken and smoked dried beef, and low concentrations were detected in nonmeat food items (Lee and Shim, 2007). BaP was not detected in raw foods, but higher concentrations were formed by broiling food (Choi and Lee, 1994). The estimated dietary BaP-related cancer risk was $1.52\times 10\text{-}5$, and the lifetime cancer risk of eating cooked foods was estimated to be $1.77\times10\text{-}6$ for broiled foods and $1.65\times10\text{-}7$ for boiled foods (Choi and Lee, 1994; Lee and Shim, 2007). Sixteen PAHs from commonly consumed seafood in Korea were measured, and the lifetime cancer risk was estimated to be $2.85\times10\text{-}6$ (Moon et al., 2010).

Nutritional status of cancer patients

Malnutrition is a common problem among cancer patients. Severe malnutrition is often responsible for the death of cancer patients, and well-nourished cancer patients had better prognoses. Various methodologies have been used to assess the nutritional status of cancer patients in Korean populations. Among oncology outpatients receiving chemotherapy, patients with gastrointestinal cancer had a 50% likelihood nutritional risk, whereas only 6.3% of breast cancer patients without oral intake difficulties were at nutritional risk (Kim et al., 2008b). Gastric cancer patients who had undergone gastrorectomy were at a higher risk for malnutrition (Sohn, 2010), but the nutritional status of gastric cancer patients returned to pre-surgical status 12 months after surgery (Ryu and Kim, 2010). Malnutrition was negatively correlated with the survival time of metastatic cancer patients (Choi et al., 2006), and patients at advanced stages of cancer had significant nutritional deficiencies (Wie et al., 2009).

Discussion

Studies of the nutritional epidemiology of cancer among Korean populations have usually been performed using a case-control design. However, case-control studies of diet are vulnerable to selection and recall biases, which may produce misleading results. Two cohort studies have been conducted to determine the association between dietary preference and cancer risk (Yun et al., 2008; Kim et al., 2010b), but the cohorts used in the studies were not specifically designed for the research. These studies used dietary data obtained from a regular health examination of Korean government employees and the Korean Central Cancer Registry to identify the incidence of cancer. Thus, the dietary information was limited to a few questions about dietary habits and preferences. Two nested case-control studies were conducted to examine the association between diet and gastric cancer risk, using subjects from the Korean Multicenter Cancer Cohort (KMCC). The KMCC, a community-based prospective cohort, was started in 1993 for genomic epidemiological studies on cancer etiology (Yoo et al., 2002). A self-administered FFQ with 4 frequency categories and 3 portion sizes has been collected since 1995. A nested case-control study using this FFQ data showed an association between diet and cancer, indicating that the association between IL10 genetic polymorphisms and the risk of gastric cancer was modified by soybean product intake (Ko et al., 2009). Several other genomic cohorts in Korea, such as the Korean National Cancer Center Cohort (KNCCC), the Korean Health Examinees Cohort (KOEX), the Korean Health and Genome Epidemiology Study (KHGES), and Korean Hydro-Nuclear Power (KHNP) have included dietary information, but no studies using this dietary information have been reported. Cohort studies are less susceptible to bias than case-control studies, but the timing of dietary data collection is important. Dietary intake has usually been assessed using data collected at the baseline of the cohort, but this is insufficient for assessing long-term exposure. Thus, dietary information should be updated regularly and consistently.

The follow-up time for the cohorts in Korea was relatively short, and the sample size was limited. Furthermore, these cohorts have not focused primarily on the effects of diet on health. Large cohorts with valid and accurate dietary assessment methods, such as European Prospective Investigation into Cancer and Nutrition (EPIC), are needed for future research on the nutritional epidemiology of cancer. The association between dietary factors and cancer risk has been inconsistent. It is difficult to accurately assess individual nutritional status, and errors in the measurement of dietary intake in epidemiological studies often lead to biased findings. The FFQ, which is frequently used in epidemiological studies, introduces both systemic and random error. Despite its crude assessment, the FFQ is believed to be able to accurately detect an association between diet and cancer risk (Michels, 2005; Schatzkin et al., 2009). However, minor associations between dietary factors and cancer risk can easily be compromised by measurement errors. The assessment of plasma concentration levels in individual diets will be useful in the future study of the nutritional epidemiology of cancer. Ongoing cohort studies have mostly collected biospecimens. The availability of both dietary assessments and biospecimens for gene expression data facilitate nutrigenomics, the study of nutritional influence on gene expression. Our recent research has shown that high intake of soy isoflavones may be associated with increased risk of cancer recurrence in HER2-positive breast cancer patients, but not in HER2-negative patients (Woo et al., 2012). Thus, the same diet can have different effects on the risk of cancer incidence and cancer survival. Gene-diet interaction data have been reported in Korea, but bioactive food constituents can influence multiple processes of carcinogenesis. Therefore, nutrigenomics, can suggest personalized, optimal nutrition (WCRF/AICR, 2007). Suitable biomarkers at reasonable costs should be made available, and technological methods are

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