

11:00 - 11:30

Nutrient - gene Interactions in Cancer Prevention

Carcinogenesis Branch National Cancer Center

Mi Kyung Kim

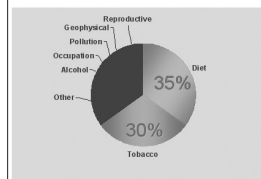
Outline of the talk

1. Diet and nutrition in carcinogenesis
2. Nutrient-gene interaction in carcinogenesis
 - 1) Folate and MTHFR, MTR, MTRR
 - 2) Antioxidant and MnSOD, catalase
3. Public health implications of nutrient-gene interactions

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The Largest Cancer Risk Factors are the Ones We Can Control

Proportions of Cancer Deaths attributed to Various Different Factors



Doll & Peto, JNCI, 1981

Causes of cancer (IARC)

Causes	% of all cancers
Tobacco	15-30%
Chronic infections	10-25%
Nutrition	30%

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CANCER DEATHS AVOIDABLE BY DIETARY CHANGE

Type of cancer	Deaths% ^a	Percent avoidable	
		Doll-Peto, 1981	Willett, 1994
Lung	28	20	20 (10-30)
Colon/rectum	11	90	70 (50-80)
Breast	8	50	50 (20-80)
Prostate	7	(with other)	75 (20-80)
Pancreas	5	50	50 (10-50)
Stomach	5	35	35 (30-70)
Endometrium	1	50	50 (50-80)
Gallbladder	1	50	50 (50-80)
Larynx, cervix, mouth, esophagus	6	20	20 (10-30)
Other types	28	10	10
Overall estimate		35	32 (20-42)

^a Percent estimated deaths, 1993.

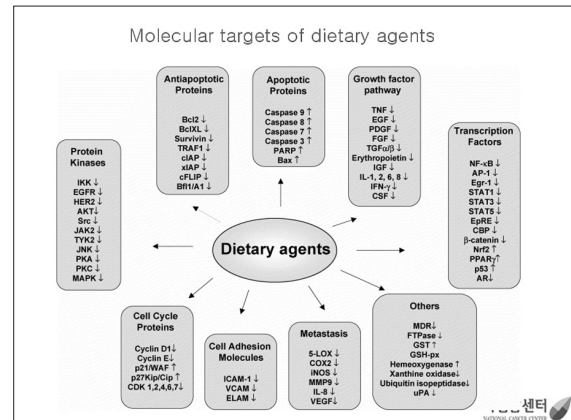
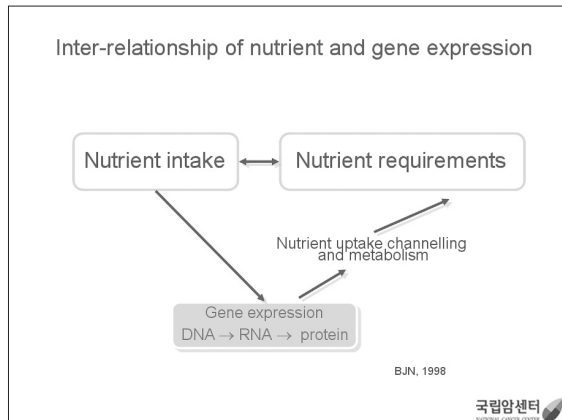
Doll & Peto, JNCI, 1981; Willett W, Environ Health Perspect 103:165-70, 1995

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Diet as a causal factor in carcinogenesis?

- Diet and nutrition in carcinogenesis
- Traditional epidemiological approaches
 - remain unanswered
- How genetic and nutritional factors interact to influence the risk of various cancers
- Integration of genomics into epidemiologic studies

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Single Nucleotide Polymorphism (SNP)

- A tiny change in the gene sequence
: only a single nucleotide change
- Allele frequency: 1/1000 to 1/2 in populations
- Functional consequences:
 - alteration in protein function, thus metabolic pathway
 - alteration in promotor activity, thus metabolic pathway
 - no known alteration but association with parameter level

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Nutrient-gene interaction in carcinogenesis

- ❑ The action of nutrient may differ according to specific genotypes in a physiological or metabolic pathway related to carcinogenesis.

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Folate

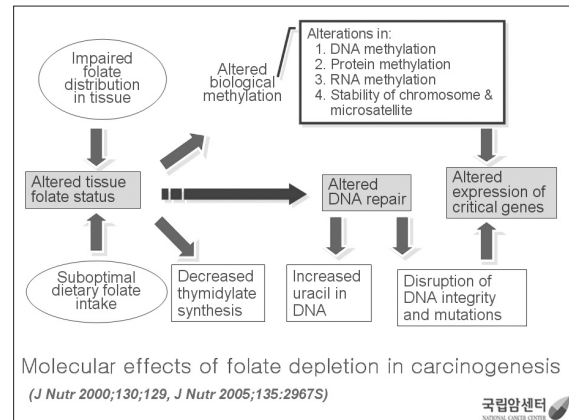
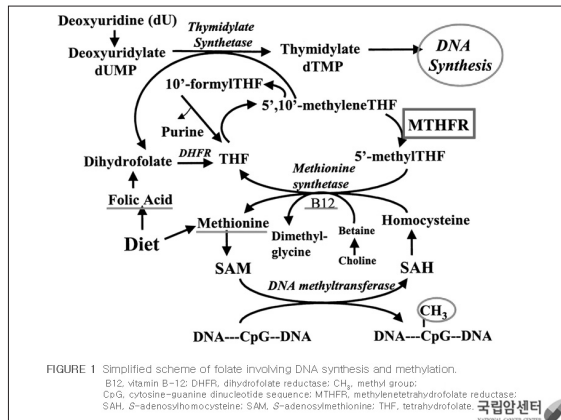
- water-soluble B vitamin, one-carbon transfer
- macrocytic anemia, neural tube defects, cardiovascular diseases, and many cancers
- functions of folate
 - nucleic acid synthesis
 - red blood cell maturation
 - plays an important part in DNA metabolism
→ DNA methylation & DNA synthesis

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Food sources of folate

- Vegetables—Excellent Source!
 - Asparagus
 - Green leafy vegetables
- Fruits
 - Oranges
 - Strawberries
 - Cantaloupes and other melons
- Beans, sunflower seeds

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Interaction between folate and methylenetetrahydrofolate reductase (MTHFR) gene in cancer

Methylenetetrahydrofolate reductase (MTHFR)

- MTHFR
 - 5,10-methyl THF → 5-methyl THF
- C677T
 - cytosine to thymidine conversion at 677
 - alanine → valine
 - enzyme activity: CC(100%), CT(65%), TT(30%)
 - frequency of TT: 10-15%
- A1298C
 - adenine to cytosine conversion at 1298
 - glutamate → alanine

Folate, MTHFR, and the risk of cancer: epidemiologic findings

- More than 30 epidemiologic evidences
 - : overwhelming consensus on association of folate and cancer
- Diminished folate status & enhanced risk of cancer
- Nurses' Health Study & Physician's Health Study
 - MTHFR genotype can modify the association of folate with cancer (Cancer Res, 1997)
 - MTHFR TT vs CT/CC : OR=0.49(0.27 - 0.87)
 at adequate folate, OR=0.32(0.15 - 0.68)
 at folate deficiency, OR=1.78(0.93-3.42)

Shanghai Breast Cancer Study

- Population-based case-control study, Shanghai, China, 1996-1998
- 1,144 incident cancer cases, 1,236 control from resident registry

MTHFR genotypes and adjusted ORs

genotype	Cases, n(%)	Controls, n(%)	OR(95% CI)
C677T			
CC	374(33.6)	387(33.4)	1.00
CT	555(49.9)	577(49.7)	1.01(0.84-1.22)
TT	183(16.5)	196(16.9)	0.97(0.76-1.25)
A1298C			
AA	768(68.5)	824(68.2)	1.00
AC	311(27.7)	344(28.5)	0.96(0.80-1.16)
CC	42(3.8)	40(3.3)	1.14(0.73-1.79)

CEBP, 2004

MTHFR genotypes and folate intake with breast cancer risk

Shanghai Breast Cancer Study

genotype	Dietary folate intake				p for interaction
	Q4	Q3	Q2	Q1	
C677T					
CC	1.00	1.76	1.75	1.94 (1.15-3.26)	0.048
CT	1.16	1.50	1.73	2.17 (1.34-3.51)	
TT	0.70	1.66	2.17	2.51 (1.37-4.60)	
A1298C					
AA	1.00	1.59	1.94	2.18 (1.46-3.25)	0.71
AC/CC	1.05	1.80	1.59	1.94 (1.23-3.05)	
CEBP, 2004					

CEBP, 2004

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Association between MTHFR and high- and low-risk diet as determined by combined levels of folate, methionine and alcohol

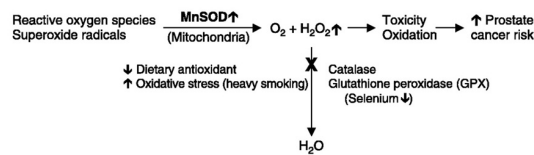
Colon cancer: case-control study Potter JD, CEBP, 1999

C677T	Cases, n	Controls, n	OR(95% CI)	OR (95% CI)		
				High risk	Intermediate	Low risk
All subject						
CC/CT	673	827	1.0	1.0	0.8 (0.6-1.0)	0.6 (0.4-1.0)
TT	139	207	0.9 (0.7-1.1)	1.0 (0.4-2.4)	0.7 (0.5-1.0)	0.4 (0.1-0.9)
Distal						
CC	316	827	1.0			
CT	329	787	1.1 (0.9-1.3)			
TT	73	207	1.0 (0.7-1.3)			
Proximal						
CC	339	827	1.0			
CT	319	787	1.0 (0.8-1.2)			
TT	64	207	0.8 (0.6-1.1)			

High risk: low folate, low methionine, high alcohol
Low risk: high folate, high methionine, low alcohol

High risk: low folate, low methionine, high alcohol
Low risk: high folate, high methionine, low alcohol국립암센터
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Potential mechanism for the interaction between MnSOD and antioxidant status in cancer



Li, H. et al. Cancer Res 2005;65:2498-2504

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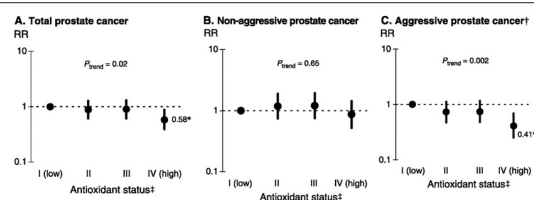
MnSOD polymorphism, antioxidant status, and the risk of prostate cancer

- MnSOD: manganese superoxide dismutase
 - primary antioxidant in the mitochondria
- polymorphism of MnSOD (V→A at bp16)
 - may alter secondary structure of enz.
 - A-variant
 - 1) higher enzyme activity
 - 2) allele frequency : 18%(Korean)
12%(Japanese)
41-55%(Caucasian)

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Association between plasma antioxidant status and risk of prostate cancer

Nested case-control study in Physicians' Health Study



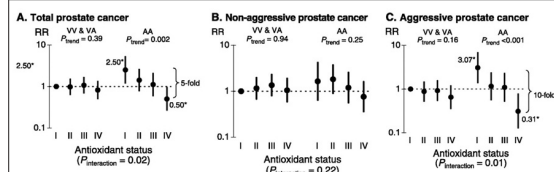
Antioxidant status: antioxidant score was estimated based on quartiles of combination of plasma lycopene, a-tocopherol, and selenium.

Li, H. et al. Cancer Res 2005;65:2498-2504

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Risk of prostate cancer associated with MnSOD genotype modified by prediagnostic levels of plasma antioxidant combinations

Nested case-control study in Physicians' Health Study

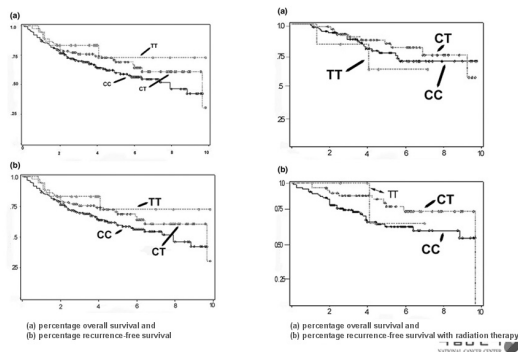


- intervention studies (β-carotene supplementation)
 - not lower prostate cancer risk, we found that β-carotene treatment was
 - significantly protective for fatal prostate cancer for men with the AA genotype.

Li, H. et al. Cancer Res 2005;65:2498-2504

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Association between MnSOD promoter gene polymorphism and breast cancer survival



Potential role of folate supplementation in the chemoprevention of CRC

- strong evidence for a true cause-and-effect relationship between folate and colorectal carcinogenesis
- folate supplementation user(>400ug/day, >15yrs)
 - marked reduction in the risk of CRC (RR=0.25, 0.13-0.51) (Nurses Health Study, Ann Intern, Med, 1998)
- small, placebo-controlled, intervention trial of folate supplementation on colorectal adenoma recurrence (1mg/d, for 2 yr)
 - 46% reduction (Dis, Colon Rectum, 1995)

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On-going Project on Diet, Nutrition, Genetic susceptibility in Cancer

- Breast Cancer
 - Hospital-based case-control study (2 hospital in Seoul)
 - 250 cases, 250 controls (as of August, 2006)
- Female Reproductive Cancers (cervix, endometrium, ovary)
 - Hospital-based case-control study
 - multicenter study (9 medical center)
 - subjects: (as of August, 2006)
 - normal controls(250), CIN(300),
 - cancer-cervix(150), endometrium(50), ovary(70)
- Dietary and plasma level
 - Folate and B vitamins
 - Antioxidant(b-carotene, lycopene, tocopherol, cryptoxanthin, retinol)
- SNPs
 - MTHFR, MTR, MnSOD, Catalase

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Public Health Implications of Nutrient-Gene Interactions for Cancer Prevention

- Gene-environment interaction study have provided so far important insight into whether a nutrient is causally associated with cancer risk
- If nutrient-gene interaction is established, should individuals be genotyped and their diets targeted based on the results?

Still unanswered !

- more carefully designed studies and scientific evidences are needed

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Conclusion

- Environmental and genetic factors contribute to cancer
- Environmental factors are most important
- Integration of genetics into epidemiologic study
 - clarify causal relation to cancer
- Evidence of effective means to prevent cancer
- Identification specific groups in the population who could benefit from specific recommendations, given their specific susceptibility to dietary compounds

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