表S-19 イソフラボン、カロテノイド、ビタミン摂取と膵臓がんとの関連に関するケースコントロール研究（サマリーテーブル）

References			Study period	Study subjects					Strength of association
Author	Year	(Ref. No.)		Sex	Ranged age	Number of cases	Number of controls	Category	
Lin Y et al.	2005	(1)	2000-2002	Men and women	40-79	109 (sex not specified)	218 (sex not specified)	Vitamin A (IU)	-
								Carotene (μg)	-
								Vitamen C (mg)	↓ ↓ ↓
								Vitamen E (mg)	-

表S-20 カロテノイドと胃がんとの関連に関するコホート研究(サマリーテーブル)

Reference	Study period	Study population					Magnitude of association	
		Sex	Number of subjects	Age range	Event	Number of incident cases or deaths		
Ito et al	1988-2003	men+women	3204	39-85yr	death	17	α-carotene(AC)	−
							β-carotene(BC)	−
							Lycopene(LY)	−
							Total carotene(TCA=AC+BC+LY)	−
							β-cryptoxanthin(CR)	↓
							Zeaxanthin & Lutein(ZL)	↓
							Canthaxanthin(CX)	↓ ↓
							Total xanthophyll(TXA=CR+ZL+CX)	↓ ↓
							Provitamin A(PVA=AC+BC+CR)	−
							Total carotenoid(TCAR=TCA+TXA)	↓
							*Based on one unit increase of logarithmically transformed serum value (mmol/l)	
Persson et al	1990-2004	men+women	511:511 (nested case-control)	40-69	incidence	511	Lutein/Zeaxanthin	−
							Lycopene	−
		men	342:342			342	Beta-Cryptoxanthin	−
		women	169:169			169		↓ ↓
		men	342:342			342	Alpha-Carotene	↓ ↓
		women	169:169			169		−
		men	342:342			342	Beta-Carotene	↓ ↓ ↓
		women	169:169			169		−

表S-21 ビタミンと胃がんとの関連に関するコホート研究(サマリーテーブル)

Reference	Study period	Study population					Magnitude of association	
		Sex	Number of subjects	Age range	Event	Number of incident cases or deaths		
Ito et al	1988-2003	men+women	3204	39-85yr	death	17	Retinol (RE) Alpha-Tocopherol (AT) Beta-+gannma-Tocopherol (BT) Total Tocopherol (TTO=AT+BT) *Based on one unit increase of logarithmically transformed serum value (mmol/l)	— ↓ ↓ ↓ ↓ ↓
Persson et al	1990-2004	men+women	511:511 (nested case-control)	40-69	inciden	511	Retinol Alpha-Tocopherol Gannma-Tocopherol	— — —

表S-22. 糖尿病および関連要因と胃がんの関連に関するコホート研究（サマリーテーブル）

References			Study population						
Author	Year	(Ref. No.)	Study period	Sex	Number of subjects	Ranged age	Event	Number of incident cases or deaths (follow-up	Results
Yamagata	2005	(1)	1988-1997	Men+Women	2466	40+	Incidence	66	Plasma fasting glucose level ; High ↑ ↑ ↑
Inoue	2006	(2)	1990-2003	Men	46,548	40-69	Incidence	977	History of DM; —
				Women	51,223	40-69	Incidence	362	History of DM; ↑ ↑
Ikeda	2008	(3)	1988-2002	Men+Women	2603	40+	Incidence	97	HbA1c; High ↑ ↑ ↑
Inoue	2009	(4)	1990-2004	Men	9548	40-69	Incidence	233	Plasma glucose level; High —
				Women	18176	40-69	Incidence	138	Plasma glucose level; High —

表S-23. 糖尿病および関連要因と胃がんの関連に関する症例対照研究（サマリーテーブル）

Reference	Study period	Study subjects				magnitude of association
		Sex	Age range	No. of cases	No. of controls	
						Positive past/present history of DM
Kuriki K	1988-2000	Men	18yr+	1,318	14,199	-
		Women	18yr+	632	33569	↑ ↑

表S-24 イソフラボンと前立腺がんの関連に関するコホート研究（サマリーテーブル）

References		Study population						
Author	Year	Study period	Sex	Number of subjects	Ranged age	Event	Number of incident cases (follow-up period)	Results
Ozasa et al.	2004	1988-1999	men	14,105men	≧40yrs	Incidencce or Mortality	52	Serum Genistein NS Serum Daidzein NS Serum Equol ↓ ↓ ↓
Kurahashi et al.	2007	1995-2004	men	43,509men	45-74yrs	Incidence	307	Genistein NS Daidzein NS Miso soup NS Soy food NS **Localized (<60yrs)** Genistein ↓ ↓ Daidzein ↓ ↓ Miso soup ↓ Soy food ↓ ↓ **Advanced (<60yrs)** Genistein NS Daidzein NS Miso soup ↑ ↑ ↑ Soy food NS
Kurahashi et al.	2008	1990-2005	men	14,203men	40-69yrs	Incidence	201	Plasma Genistein ↓ Plasma Daidzein NS Plasma Glycitein NS Plasma Equol ↓ ↓ **Localized** Plasma Genistein ↓ Plasma Daidzein ↓ Plasma Glycitein NS Plasma Equol ↓ ↓ ↓ **Advanced** Plasma Genistein ↑ Plasma Daidzein ↑ Plasma Glycitein ↑ Plasma Equol ↑ ↑

表S-25 イソフラボンと前立腺がんの関連に関する症例対照研究（サマリーテーブル）

References		Study period	Study population				Results
Author	Year		Sex	Ranged age	No. of cases	No.of controls	
Akaza et al.	2002	?	men	?	141	112	Equol producer ↓
Nagata et al.	2007	1996-2003	men	59-73yrs	200	200	Isoflavone ↓ ↓ ↓
							Genistein NS
							Daidzein ↓

表S-26 カロテノイドと前立腺がんの関連に関する症例対照研究（サマリーテーブル）

References		Study period	Study population				Results
Author	Year		Sex	Ranged age	No. of cases	No.of controls	
Ohno et al.	1988	1981-1984	men	50-79yrs	100	100BPH	Beta-carotene ↓ ↓
						100HC	Beta-carotene ↓ ↓ ↓
Nagata et al.	2007	1996-2003	men	59-73yrs	200	200	All carotene NS
							Lycopene NS

表S-27 ビタミンと前立腺がんの関連に関する症例対照研究（サマリーテーブル）

References		Study period	Study population				Results	
Author	Year		Sex	Ranged age	No. of cases	No.of controls		
Oishi et al.	1988	1981-1984	men	50-79yrs	100	100BPH	Retinol	↓
							Vit B1	NS
							Vit B2	NS
							Niacin	↑ ↑
							Vit C	NS
						100HC	Retinol	NS
							Vit B1	NS
							Vit B2	NS
							Niacin	NS
							Vit C	NS
Nagata et al.	2007	1996-2003	men	59-73yrs	200	200	Vit B12	NS
							Vit D	NS
							Vit E	NS
							Folate	NS

引用文献リスト

全がん

カロテノイドと全がんとの関連に関するコホート研究（表 S-1）

（1） Ito Y, Suzuki K, Ishii J, Hishida H, Tamakoshi A, Hamajima N, Aoki K. A population-based follow-up study on mortality from cancer or cardiovascular disease and serum carotenoids, retinol and tocopherols in Japanese inhabitants. Asian Pac J Cancer Prev. 2006 Oct-Dec;7(4):533-46

ビタミンと全がんとの関連に関するコホート研究（表 S-2）

（1） Ito Y, Suzuki K, Ishii J, Hishida H, Tamakoshi A, Hamajima N, Aoki K. A population-based follow-up study on mortality from cancer or cardiovascular disease and serum carotenoids, retinol and tocopherols in Japanese inhabitants. Asian Pac J Cancer Prev. 2006 Oct-Dec;7(4):533-46

大腸がん

イソフラボンと大腸がんとの関連に関するコホート研究（表 S-3）

(1) Oba S, Nagata C, Shimizu N, Shimizu H, Kametani M, Takeyama N, Ohnuma T, Matsushita S. Soy product consumption and the risk of colon cancer: a prospective study in Takayama, Japan. Nutr Cancer 2007; 57: 151-157.

(2) Akhter M, Inoue M, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S. Dietary soy and isoflavone intake and risk of colorectal cancer in the Japan public health center-based prospective study. Cancer Epidemiol Biomarkers Prev 2008; 17: 2128-2135.

カロテノイドと大腸がんとの関連に関するコホート研究（表 S-4）

(1) Wakai K, Suzuki K, Ito Y, Kojima M, Tamakoshi K, Watanabe Y, Toyoshima H, Hayakawa N, Hashimoto S, Tokudome S, Suzuki S, Kawado M, Ozasa K, Tamakoshi A. Serum carotenoids, retinol, and tocopherols, and colorectal cancer risk in a Japanese cohort: effect modification by sex for carotenoids. Nutr Cancer 2005; 51: 13-24.

(2) Ito Y, Kurata M, Hioki R, Suzuki K, Ochiai J, Aoki K. Cancer mortality and serum levels of carotenoids, retinol, and tocopherol: a population-based follow-up study of inhabitants of a rural area of Japan. Asian Pac J Cancer Prev 2005; 6: 10-15.

カロテノイドと大腸がんとの関連に関するケースコントロール研究（表 S-5）

(1) Wakai K, Hirose K, Matsuo K, Ito H, Kuriki K, Suzuki T, Kato T, Hirai T, Kanemitsu Y, Tajima K. Dietary risk factors for colon and rectal cancers: a comparative case-control study. J Epidemiol 2006; 16: 125-135.

葉酸と大腸がんとの関連に関するコホート研究（表 S-6）

(1) Ishihara J, Otani T, Inoue M, Iwasaki M, Sasazuki S, Tsugane S. Low intake of vitamin B-6 is associated with increased risk of colorectal cancer in Japanese men. J Nutr 2007; 137: 1808-1814.

(2) Otani T, Iwasaki M, Sasazuki S, Inoue M, Tsugane S. Plasma folate and risk of colorectal cancer in a nested case-control study: the Japan Public Health Center-based prospective study. Cancer Causes Control 2008; 19: 67-74.

葉酸と大腸がんとの関連に関するケースコントロール研究（表 S-7）

(1) Otani T, Iwasaki M, Hanaoka T, Kobayashi M, Ishihara J, Natsukawa S, Shaura K, Koizumi Y, Kasuga Y, Yoshimura K, Yoshida T, Tsugane S. Folate, vitamin B6, vitamin B12, and vitamin B2 intake, genetic polymorphisms of related enzymes, and risk of colorectal cancer in a hospital-based case-control study in Japan. Nutr Cancer 2005; 53: 42-50.

(2) Wakai K, Hirose K, Matsuo K, Ito H, Kuriki K, Suzuki T, Kato T, Hirai T, Kanemitsu Y, Tajima K. Dietary risk factors for colon and rectal cancers: a comparative case-control study. J Epidemiol 2006; 16: 125-135.

食パターンと大腸がんとの関連に関するコホート研究（表 I-6）

(1) Kim MK, Sasaki S, Otani T, Tsugane S. Dietary patterns and subsequent colorectal cancer risk by subsite: a prospective cohort study. Int J Cancer 2005; 115: 790-798.

肺がん

ビタミン、カロテノイドと肺がんとの関連に関するコホート研究（表 S-8）

(1) Ito Y, Suzuki K, Ishii J, Hishida H, Tamakoshi A, Hamajima N, Aoki K. A population-based follow-up study on mortality from cancer or cardiovascular disease and serum carotenoids, retinol and tocopherols in Japanese inhabitants. Asian Pac J Cancer Prev. 2006;7:533-546.

ビタミン、カロテノイドと肺がんとの関連に関するケースコントロール研究（表 S-9）

(1) Ito Y, Wakai K, Suzuki K, Ozasa K, Watanabe Y, Seki N, Ando M, Nishino Y, Kondo T, Ohno Y, Tamakoshi A; JACC Study Group. Lung cancer mortality and serum levels of carotenoids, retinol, tocopherols, and folic acid in men and women: a case-control study nested in the JACC Study. J Epidemiol. 2005;15 Suppl 2:S140-9.

イソフラボンと肺がんとの関連に関するコホート研究（表 S-10）

(1) Shimazu T, Inoue M, Sasazuki S, Iwasaki M, Sawada N, Yamaji T, Tsugane S; Japan Public Health Center-based Prospective Study Group. Isoflavone intake and risk of lung cancer: a prospective cohort study in Japan. Am J Clin Nutr. 2010;91:722-728.

乳がん

イソフラボンと乳がんとの関連に関するコホート研究（表 S-11）

(1) Yamamoto S, Sobue T, Sasaki S, Kobayashi M, Sasaki S, Tsugane S. Soy, isoflavones, and breast cancer risk in Japan. J Natl Cancer Inst 2003; 95: 906-13

(2) Iwasaki M, Hamada GS, Nishimoto IN, Netto MM, Motola J Jr, Laginha FM, Kasuga Y, Yokoyama S, Onuma H, Nishimura H, Kusama R, Kobayashi M, Ishihara J, Yamamoto S, Hanaoka T, Tsugane S. Dietary isoflavone intake and breast cancer risk in case-control study in Japanese, Japanese Brazilians, and non-Japanese Brazilians. Breast Cancer Res Treat 2009; 116: 401-11.

イソフラボンと乳がんとの関連に関するケースコントロール研究（表 S-12）

(1) Hirose K, Imaeda N, Tokudome Y, Goto C, Wakai K, Matsuo K, et al. Soybean products and reduction of breast cancer risk: a case-control study in Japan. Br J Cancer 2005; 93: 15-22.

(2) Iwasaki M, Hamada GS, Nishimoto IN, Netto MM, Motola J Jr, Laginha FM, Kasuga Y, Yokoyama S, Onuma H, Nishimura H, Kusama R, Kobayashi M, Ishihara J, Yamamoto S, Hanaoka T, Tsugane S. Isoflavone polymorphisms in estrogen receptor genes and breast cancer risk in case-control studies in Japanese, Japanese Brazilians and non-Japanese Brazilians. Cancer Sci 2009; 100: 927-33.

ビタミンと乳がんとの関連に関するケースコントロール研究（表 S-13）

(1) Ma E, Iwasaki M, Kobayashi M, Kasuga Y, Yokoyama S, Onuma H, Nishimura H, Kusama R, Tsugane S.Dietary intake of folate, vitamin B2, vitamin B6, vitamin B12, genetic polymorphism of related enzymes, and risk of breast cancer: a case-control study in Japan..Nutr Cancer. 2009;61:447-56.

肝がん

肥満と肝がんとの関連に関するコホート研究（表 S-14）

(1) Ohata K, Hamasaki K, Toriyama K, Matsumoto K, Saeki A, Yanagi K, Abiru S, Nakagawa Y, Shigeno M, Miyazoe S, Ichikawa T, Ishikawa H, Nakao K, Eguchi K. Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. Cancer 2003; 97: 3036-43.

(2) Kuriyama S, Tsubono Y, Hozawa A, Shimazu T, Suzuki Y, Koizumi Y, Suzuki Y, Ohmori K, Nishino Y, Tsuji I. Obesity and risk of cancer in Japan. Int J Cancer 2005; 113: 148-57.

(3) Khan MM, Saito S, Takagi S, Ohnishi H, Izumi H, Sakauchi F, Washio M, Sonoda T, Nagata Y, Asakura S, Kobayashi K, Mori M, Shimamoto K. Relationship between hepatocellular carcinoma and impaired glucose tolerance among Japanese. Hepatogastroenterology 2006; 53: 742-6.

(4) Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, Kato M, Nakamura T, Higuchi K, Nishiguchi S, Kumada H, Ohashi Y. Overweight and obesity increase the risk for liver cancer in patients with liver cirrhosis and long-term oral supplementation with branched-chain amino acid granules inhibits liver carcinogenesis in heavier patients with liver cirrhosis. Hepatol Res 2006; 35: 204-14.

(5) Fujino Y. Anthropometry, development history and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pac J Cancer Prev 2007; 8 Suppl: 105-12.

(6) Ohki T, Tateishi R, Sato T, Masuzaki R, Imamura J, Goto T, Yamashiki N, Yoshida H, Kanai F, Kato N, Shiina S, Yoshida H, Kawabe T, Omata M. Obesity is an independent risk factor for hepatocellular carcinoma development in chronic hepatitis C patients. Clin Gastroenterol Hepatol 2008; 6: 459-64.

(7) Inoue M, Kurahashi N, Iwasaki M, Tanaka Y, Mizokami M, Noda M, Tsugane S. Metabolic factors and subsequent risk of hepatocellular carcinoma by hepatitis virus infection status: a large-scale population-based cohort study of Japanese men and women (JPHC Study Cohort II). Cancer Causes Control 2009; 20: 741-50.

肥満と肝がんとの関連に関する症例・対照研究（表 S-15）

(1) Ohishi W, Fujiwara S, Cologne JB, Suzuki G, Akahoshi M, Nishi N, Takahashi I, Chayama K. Risk factors for hepatocellular carcinoma in a Japanese population: a nested case-control study. Cancer Epidemiol Biomarkers Prev 2008; 17: 846-54.

栄養素と肝がんとの関連に関するコホート研究（表 S-16）

(1) Ito Y, Suzuki K, Ishii J, Hishida H, Tamakoshi A, Hamajima N, Aoki K. A population-based follow-up study on mortality from cancer or cardiovascular disease and serum carotenoids, retinol and tocopherols in Japanese inhabitants. Asian Pac J Cancer Prev 2006; 7: 533-46.

(2) Kurahashi N, Inoue M, Iwasaki M, Tanaka Y, Mizokami M, Tsugane S. Isoflavone consumption and subsequent risk of hepatocellular carcinoma in a population-based prospective cohort of Japanese men and women. Int J Cancer 2009; 124: 1644-9.

(3) Kurahashi N, Inoue M, Iwasaki M, Tanaka Y, Mizokami M, Tsugane S. Vegetable, fruit and antioxidant nutrient consumption and subsequent risk of hepatocellular carcinoma: a prospective cohort study in Japan. Br J Cancer 2009; 100: 181-4.

食品群と肝がんとの関連に関するコホート研究（Table III）

(1) Hirayama T. A large-scale cohort study on risk factors for primary liver cancer, with special reference to the role of cigarette smoking. Cancer Chemother Pharmacol 1989; 23 Suppl: S114-7.

(2) Iso H, Kubota Y. Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pac J Cancer Prev 2007; 8 Suppl: 35-80.

食道がん

熱い飲食物と食道がんとの関連に関するコホート研究（表 S-17）

(1) Kinjo Y, Cui Y, Akiba S, Watanabe S, Yamaguchi N, Sobue T, Mizuno S, Beral V. Mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet in Japan. J Epidemiol. 1998;8:235-243.

(2) Ishikawa A, Kuriyama S, Tsubono Y, Fukao A, Takahashi H, Tachiya H, Tsuji I. Smoking, alcohol drinking, green tea consumption and the risk of esophageal cancer in Japanese men. J Epidemiol. 2006;16:185-192.

熱い飲食物と食道がんとの関連に関するケースコントロール研究（表 S-18）

(1) Kamon SH, Hirayama T. An epidemiological study of cancer of the esophagus in Wakayama, Nara, and Miye prefecture (in Japanese). Report (1973-1975) to Japanese Cancer Association. 1976; 1-186.

(2) Takagi A, Ajiki W, Tsukuma H. A case-control study to identify risk factors for female esophageal cancer in Osaka prefecture.(in Japanese). Kousei no shihyou. 2003;50: 33-38.

(3) Yokoyama A, Kato H, Yokoyama T< Igaki H, Tsujinaka T, Muto M, Omori T, Kumagai Y, Yokoyama M, Watanabe H. Esophageal squamous cell carcinoma and aldehyde dehydrogenase-2 genotypes in Japanese females. Alcohol Clin Exp Res 2006; 30: 491-500.

イソフラボン、カロテノイド、ビタミン摂取と膵臓がんとの関連に関するケースコントロール研究（表 S-19）

(1) Lin Y, Tamakoshi A, Hayakawa T, Naruse S, Kitagawa M, Ohno Y. Nutritional factors and risk of pancreatic cancer: a population-based case-control study based on direct interview in Japan. J Gastroenterol. 2005;40:297-301.

胃がん

カロテノイドと胃がんとの関連に関するコホート研究（表 S-20）

(1) Ito Y, Suzuki K, Ishii J, Hishida H, Tamakoshi A, Hamajima N, Aoki K. A population-based follow-up study on mortality from cancer or cardiovascular disease and serum carotenoids, retinol and tocopherols in Japanese inhabitants. Asian Pac J Cancer Prev. 2006 Oct-Dec;7(4):533-46

(2) Persson C, Sasazuki S, Inoue M, Kurahashi N, Iwasaki M, Miura T, Ye W, Tsugane S; JPHC Study Group. Plasma levels of carotenoids, retinol and tocopherol and the risk of gastric cancer in Japan: a nested case-control study. Carcinogenesis. 2008 May;29(5):1042-8.

ビタミンと胃がんとの関連に関するコホート研究（表 S-21）

(1) Ito Y, Suzuki K, Ishii J, Hishida H, Tamakoshi A, Hamajima N, Aoki K. A population-based follow-up study on mortality from cancer or cardiovascular disease and serum carotenoids, retinol and tocopherols in Japanese inhabitants. Asian Pac J Cancer Prev. 2006 Oct-Dec;7(4):533-46

(2) Persson C, Sasazuki S, Inoue M, Kurahashi N, Iwasaki M, Miura T, Ye W, Tsugane S; JPHC Study Group. Plasma levels of carotenoids, retinol and tocopherol and the risk of gastric cancer in Japan: a nested case-control study. Carcinogenesis. 2008 May;29(5):1042-8.

糖尿病および関連要因と胃がんとの関連に関するコホート研究（表 S-22）

(1) Yamagata H, Kiyohara Y, Nakamura S, Kubo M, Tanizaki Y, Matsumoto T, Tanaka K, Kato I, Shirota T, Iida M. Impact of fasting plasma glucose levels on gastric cancer incidence in a general Japanese population: the Hisayama study. Diabetes Care. 2005;28:789-794.

(2) Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of

cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med. 2006;166:1871-1877.

(3) Ikeda F, Doi Y, Yonemoto K, Ninomiya T, Kubo M, Shikata K, Hata J, Tanizaki Y, Matsumoto T, Iida M, Kiyohara Y. Hyperglycemia increases risk of gastric cancer posed by Helicobacter pylori infection: a population-based cohort study. Gastroenterology. 2009;136:1234-1241.

(4) Inoue M, Noda M, Kurahashi N, Iwasaki M, Sasazuki S, Iso H, Tsugane S; Japan Public Health Center-based Prospective Study Group. Impact of metabolic factors on subsequent cancer risk: results from a large-scale population-based cohort study in Japan. Eur J Cancer Prev. 2009;18:240-247.

糖尿病および関連要因と胃がんとの関連に関するケースコントロール研究（表 S-23）

(1) Kuriki K, Hirose K, Tajima K. Diabetes and cancer risk for all and specific sites among Japanese men and women. Eur J Cancer Prev. 2007;16:83-89.

前立腺がん

イソフラボンと前立腺がんとの関連に関するコホート研究（表 S-24）

(1) Ozasa K, Nakao M, Watanabe Y, Hayashi K, Miki T, Mikami K, Mori M, Sakauchi F, Washio M, Ito Y, Suzuki K, Wakai K, Tamakoshi A; JACC Study Group. Serum phytoestrogens and prostate cancer risk in a nested case-control study among Japanese men. Cancer Sci. 2004 Jan;95(1):65-71.

(2) Kurahashi N, Iwasaki M, Sasazuki S, Otani T, Inoue M, Tsugane S; Japan Public Health Center-Based Prospective Study Group. Soy product and isoflavone consumption in relation to prostate cancer in Japanese men. Cancer Epidemiol Biomarkers Prev. 2007 Mar;16(3):538-45

(3) Kurahashi N, Iwasaki M, Inoue M, Sasazuki S, Tsugane S. Plasma isoflavones and subsequent risk of prostate cancer in a nested case-control study: the Japan Public Health Center. J Clin Oncol. 2008 Dec 20;26(36):5923-9

イソフラボンと前立腺がんとの関連に関するケースコントロール研究（表 S-25）

(1) Akaza H, Miyanaga N, Takashima N, Naito S, Hirao Y, Tsukamoto T, Mori M. Is daidzein non-metabolizer a high risk for prostate cancer? A case-controlled study of serum soybean isoflavone concentration. Jpn J Clin Oncol. 2002;32:296-300

(2) Nagata Y, Sonoda T, Mori M, Miyanaga N, Okumura K, Goto K, Naito S, Fujimoto K, Hirao Y, Takahashi A, Tsukamoto T, Akaza H. Dietary isoflavones may protect against prostate cancer in Japanese men. J Nutr. 2007;137:1974-1979.

カロテノイドと前立腺がんとの関連に関するケースコントロール研究（表 S-26）

(1) Ohno Y, Yoshida O, Oishi K, Okada K, Yamabe H, Schroeder FH. Dietary beta-carotene and cancer of the prostate: a case-control study in Kyoto, Japan. Cancer Res. 1988;48:1331-1336.

(2) Nagata Y, Sonoda T, Mori M, Miyanaga N, Okumura K, Goto K, Naito S, Fujimoto K, Hirao Y, Takahashi A, Tsukamoto T, Akaza H. Dietary isoflavones may protect against prostate cancer in Japanese men. J Nutr. 2007;137:1974-1979.

ビタミンと前立腺がんとの関連に関するケースコントロール研究（表 S-27）

(1) Oishi K, Okada K, Yoshida O, Yamabe H, Ohno Y, Hayes RB, Schroeder FH. A case-control study of prostatic cancer with reference to dietary habits. Prostate. 1988;12:179-190.

(2) Nagata Y, Sonoda T, Mori M, Miyanaga N, Okumura K, Goto K, Naito S, Fujimoto K, Hirao Y, Takahashi A, Tsukamoto T, Akaza H. Dietary isoflavones may protect against prostate cancer in Japanese men. J Nutr. 2007;137:1974-1979.

研究成果の刊行に関する一覧表

書籍

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Green tea consumption and gastric cancer in Japanese: a pooled analysis of six cohort studies

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Green tea consumption and gastric cancer in Japanese: a pooled analysis of six cohort studies

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ABSTRACT

Background: Previous experimental studies have suggested many possible anti-cancer mechanisms for green tea, but epidemiological evidence for the effect of green tea consumption on gastric cancer risk is conflicting.

Objective: To examine the association between green tea consumption and gastric cancer.

Methods: We analysed original data from six cohort studies that measured green tea consumption using validated questionnaires at baseline. Hazard ratios (HRs) in the individual studies were calculated, with adjustment for a common set of variables, and combined using a random-effects model.

Results: During 2 285 968 person-years of follow-up for a total of 219 080 subjects, 3577 cases of gastric cancer were identified. Compared with those drinking <1 cup/day, no significant risk reduction for gastric cancer was observed with increased green tea consumption in men, even in stratified analyses by smoking status and subsite. In women, however, a significantly decreased risk was observed for those with consumption of ≥5 cups/day (multivariate-adjusted pooled HR = 0.79, 95% confidence interval (CI) = 0.65 to 0.96). This decrease was also significant for the distal subsite (HR = 0.70, 95% CI = 0.50 to 0.96). In contrast, a lack of association for proximal gastric cancer was consistently seen in both men and women.

Conclusions: Green tea may decrease the risk of distal gastric cancer in women.

Green tea is one of the most popular beverages in the world and is widely consumed in Japan.[1] Green tea contains polyphenolic antioxidants, such as epigallocatechin gallate, which are thought to contribute to cancer prevention.[2] Early case–control studies found a reduced risk of gastric cancer in association with the consumption of green tea,[3–7] while previous in vitro and in vivo studies suggested many possible anti-cancer mechanisms for green tea. Together, these findings suggest that the consumption of green tea is associated with a decreased risk of gastric cancer.[2]

To date, however, epidemiological evidence for the effect of green tea consumption on cancer risk is conflicting. The recent review of the World Cancer Research Fund in 2007 did not support a possible protective effect of green tea against cancer,[8] and, presently, there is no convincing evidence to support a role for green tea in cancer prevention. In particular, several recent large-scale population-based cohort studies in Japan, established before the mid-1990s and with long-term follow-up, have actively examined the association between green tea consumption and the risk of gastric cancer.[9–14] As to results, however, these studies, which were prospective in design and thus free from recall and selection biases, provide no overall support for the idea that increased consumption of green tea protects against gastric cancer.[15]

Although Japanese tend to consume green tea in a similar manner and the studies estimated consumption dose using similar questions, the studies nevertheless varied in the factors used to adjust for potential confounders and in stratification. One finding was a difference in effect by sex. This may be noteworthy but is yet to be clarified, with some studies showing a decreasing risk tendency in women,[9 12 13] albeit that the strength of the effect appeared to be modest, if it exists at all. The null association in men may, in part, reflect insufficient adjustment for confounding factors such as cigarette smoking. Likewise, differences in the effect of green tea by subsite[12] may point to an inconsistent effect on gastric cancer overall. However, evidence for such specific issues is sparse, probably due to the relatively small number of gastric cancer cases occurring in the upper subsite among cohorts, particularly in women.

To better understand these issues, we conducted a pooled analysis of several large-scale population-based cohort studies in Japan on the association between green tea consumption and gastric cancer risk.

METHODS

Study population

In 2006, the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan initiated a pooling project using original data from major cohort studies to evaluate the association between lifestyle and major forms of cancer in Japanese. Topics for the pooled analysis were determined on the basis of discussion among all authors from the viewpoint of both scientific and public health importance. To maintain the quality and comparability of data, we set inclusion criteria for the present purpose a priori, namely population-based cohort studies conducted in Japan; started in the mid-1980s to mid-1990s; included more than 30 000 participants; obtained information on diet, including green tea consumption, using a validated questionnaire at baseline; and collected incidence data for gastric cancer during the follow-up period. Six ongoing studies that met

Table 1 Characteristics of the six cohort studies included in a pooled analysis of green tea consumption and gastric cancer risk, 1988–2004

Study	Population	Age (years) at baseline survey	Year(s) of baseline survey	Population size	Rate of response (%) to baseline questionnaire	Method of follow-up	For the present pooled analysis						
							Age (years)	Last follow-up time	Mean duration of follow-up (years)	Size of cohort		No of gastric cancer cases	
										Men	Women	Men	Women
JPHC-I	Japanese residents of five public health centre areas in Japan	40–59	1990	61595	82	Cancer registry and death certificates	40–59	2001	11.3	15111	16498	379	135
JPHC-II	Japanese residents of 6 public health centre areas in Japan	40–69	1993–1994	78825	80	Cancer registry and death certificates	40–69	2003–2004	10.6	19301	21108	565	206
JACC	Residents from 45 areas throughout Japan	40–79	1988–1990	110792	83	Cancer registry (24 selected areas) and death certificates	40–79	2001	10.2	21113	30017	639	346
MIYAGI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	47605	92	Cancer registry and death certificates	40–64	2001	11.0	19007	20596	388	173
3-pref MIYAGI	Residents of three municipalities in Miyagi Prefecture, Japan	40–98	1984	31345	94	Cancer registry and death certificates	40–98	1992	7.6	11902	14409	296	123
3-pref AICHI	Residents of two municipalities in Aichi Prefecture, Japan	40–103	1985	33529	90	Cancer registry and death certificates	40–103	2000	11.5	14045	15973	228	99
Total										100479	118601	2495	1082

JACC, The Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based prospective Study; MIYAGI, The Miyagi Cohort Study; 3-pref AICHI, The Three Prefecture Study – Aichi portion; 3-pref MIYAGI, The Three Prefecture Study – Miyagi portion.

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these criteria were identified: (1) the Japan Public Health Center-based Prospective Study (JPHC)-I;[16] (2) JPHC-II;[16] (3) the Japan Collaborative Cohort Study (JACC);[17] (4) the Miyagi Cohort Study (MIYAGI);[18] (5) the Three Prefecture Study – Miyagi portion (3-pref MIYAGI);[19] and (6) the Three Prefecture Study – Aichi portion (3-pref AICHI).[19] JPHC was treated as two independent studies (JPHC-I and JPHC-II) because of the different questionnaire used at baseline. One area in JPHC-I and one in JPHC-II, both in Okinawa Prefecture, were excluded from the analysis since tea drinking habits in these areas differed from the rest of Japan and were not comparable with other areas. Further, with regard to JACC, since information on cancer incidence was collected in only 24 of 45 study areas, data from only those 24 areas were used.

We excluded data for subjects with missing information on green tea consumption or a history of cancer at baseline. Selected characteristics of these studies are presented in table 1. Each study was approved by the relevant institutional review board. Results on the association between green tea intake and gastric cancer risk in these cohorts have been reported.[9 10 12 13] For the present analysis, we used updated data sets with an extended follow-up period.

Follow-up

Subjects were followed from the baseline survey (JPHC-I, 1990; JPHC-II, 1993–1994; JACC, 1988–1990; MIYAGI, 1990; 3-pref MIYAGI, 1984; 3-pref AICHI, 1985) to the last date of follow-up for incidence of gastric cancer in each study (JPHC-I, 2001; JPHC-II, 2003–2004; JACC, 2001; MIYAGI, 2001; 3-pref MIYAGI, 1992; 3-pref AICHI, 2000). Residence status in each study, including survival, was confirmed through the residential registry.

Case ascertainment

In all cohorts included in the present study, cancer diagnoses were identified through population-based cancer registries and active patient notification from major local hospitals. Although the quality and completeness of the case ascertainment varied by cohort, the overall percentage of cases registered from a death certificate only was 8.7% and the estimated ascertainment of cancer diagnoses was nearly 90%. Cases were coded using the International Classification of Disease, Tenth Revision,[20] or the International Classification of Diseases for Oncology, Third Edition.[21] Study outcome was defined as incident gastric cancer (code: C16) diagnosed during the follow-up period of each study. In JPHC-I, JPHC-II, MIYAGI, and 3-pref MIYAGI, in which subsite information was routinely collected, gastric cancers were also classified into proximal (C16.0–C16.1) and distal subsite (C16.2–C16.6). In epidemiological studies using Japanese populations, it is not practical to restrict "cardia (C16.0)" in the analysis because clinical site in gastric cancer diagnosis in Japan is based on the Japanese Classification of Gastric Carcinoma,[22] in which tumour location is usually described anatomically in three parts, namely upper third, middle third, and lower third. In most cases this hampers the clear division of the upper third into "cardia" and "fundus," unless the medical record provided extra information. For this reason, we used the proximal subsite and distal subsite to perform subsite-specific analysis.

Assessment of green tea consumption

In each study except JACC, the frequency and daily amounts of green tea consumption were asked about in the self-administered questionnaire in the same categories of almost none, 1–2 days/week, 3–4 days/week, and almost daily (1–2 cups/day, 3–4 cups/day, and ≥5 cups/day). In JACC, in contrast, daily consumption was asked about in terms of the actual number of cups of green tea consumed each day so these data were re-categorised into the same categories as the other studies. Spearman correlation coefficients for the correlation between green tea consumption (g/day) estimated from the questionnaire and that from the dietary record were JPHC-I, 0.57 in men and 0.63 in women;[23] JPHC-II, 0.39 in men and 0.48 in women;[12] JACC, 0.47;[24] and MIYAGI and 3-pref MIYAGI, 0.71 in men and 0.53 in women.[25] 3-Pref AICHI, for which information on the validation of green tea consumption was not available, utilised the same questionnaire as 3-pref MIYAGI.

Statistical analysis

Person-years of follow-up were calculated from the date of the baseline survey in each study to the date of diagnosis of gastric cancer, migration from the study area, death, or the end of follow-up, whichever came first. In each individual study, sex- and area-(JPHC-I, JPHC-II, and JACC) adjusted hazard ratios (HRs) (model 1) and 95% confidence intervals (95% CIs) for gastric cancer were estimated for each green tea intake category using a Cox proportional hazards model. Green tea consumption of <1 cup/day was used as reference category in consideration of the fact that green tea is a common beverage in Japan and very few people are non-consumers. Further multivariate adjustments were made by including covariates in the regression model which were either known or suspected risk factors for cancer or had previously been found to be associated with the risk of gastric cancer.[8 26] The adjustments were made in two ways: first for smoking (for men: never smoker, past smoker, current smoker of 1–19 cigarettes/day, or current smoker of ≥20 cigarettes/day; for women: never smoker, past smoker, or current smoker), ethanol intake (never/former drinker, occasional drinker (<once/week), regular drinker (≥once/week): for men: <23 g/day, 23 to <46 g/day, ≥46 g/day; for women: <23 g/day, ≥23 g/day)), rice intake (<4 bowls/day, ≥4 bowls/day), soy bean paste soup (<daily, daily), and coffee intake (<1 cup/day, 1–2 cups/day, ≥3 cups/day) in addition to adjustment in model 1 (model 2); second for pickled vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) and green–yellow vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) in addition to adjustment in model 2 (model 3). In estimation of HR by model 3, each cohort used different food items for pickled vegetables and green–yellow vegetables due to the different food items asked about in each questionnaire. We further conducted stratified analysis by smoking status, namely among never smokers and among current smokers. Also, analyses confining the outcome to the proximal or distal subsite were conducted using JPHC-I, JPHC-II, MIYAGI and 3-pref MIYAGI, for which subsite information was available. An indicator term for missing data was created for each covariate. SAS (version 9.1) or Stata (version 10) statistical software was used for these estimations.

A random-effects model was used to obtain a single pooled estimate of the hazard ratios from the individual studies for each category. The study-specific hazard ratios were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. A study that had no cases for a category was not included in the pooled estimate for that category. The trend association was assessed in a similar manner: investigators from each study calculated the regression coefficient and its standard error of linear trend for green tea consumption category treated as an ordinal variable. These values from the

Table 2 Study-specific multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) of gastric cancer incidence by green tea consumption

	Green tea consumption			
	<1 cup/day	1–2 cups/day	3–4 cups/day	≥5 cups/day
Total	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Men				
JPHC-I				
Model 2	1.00 (Reference)	0.85 (0.62 to 1.16)	0.86 (0.64 to 1.15)	0.95 (0.72 to 1.25)
Model 3	1.00 (Reference)	0.85 (0.62 to 1.17)	0.87 (0.65 to 1.16)	0.97 (0.73 to 1.28)
JPHC-II				
Model 2	1.00 (Reference)	1.11 (0.81 to 1.51)	1.08 (0.80 to 1.45)	1.06 (0.79 to 1.43)
Model 3	1.00 (Reference)	1.11 (0.82 to 1.52)	1.08 (0.80 to 1.45)	1.06 (0.78 to 1.43)
JACC				
Model 2	1.00 (Reference)	0.81 (0.60 to 1.09)	0.76 (0.58 to 1.00)	0.82 (0.64 to 1.05)
Model 3	1.00 (Reference)	0.80 (0.59 to 1.08)	0.75 (0.57 to 1.00)	0.81 (0.63 to 1.05)
MIYAGI				
Model 2	1.00 (Reference)	0.92 (0.69 to 1.22)	0.88 (0.66 to 1.18)	0.89 (0.68 to 1.16)
Model 3	1.00 (Reference)	0.90 (0.67 to 1.20)	0.87 (0.65 to 1.17)	0.88 (0.67 to 1.15)
3-pref MIYAGI				
Model 2	1.00 (Reference)	1.24 (0.82 to 1.88)	1.15 (0.76 to 1.73)	1.50 (1.06 to 2.13)
Model 3	1.00 (Reference)	1.28 (0.84 to 1.94)	1.20 (0.79 to 1.80)	1.55 (1.09 to 2.20)
3-pref AICHI				
Model 2	1.00 (Reference)	1.31 (0.76 to 2.27)	1.28 (0.77 to 2.13)	1.69 (1.03 to 2.77)
Model 3	1.00 (Reference)	1.27 (0.74 to 2.21)	1.22 (0.73 to 2.03)	1.60 (0.97 to 2.63)
Women				
JPHC-I				
Model 2	1.00 (Reference)	0.74 (0.44 to 1.23)	0.90 (0.57 to 1.41)	0.58 (0.36 to 0.95)
Model 3	1.00 (Reference)	0.75 (0.45 to 1.25)	0.90 (0.58 to 1.42)	0.58 (0.36 to 0.95)
JPHC-II				
Model 2	1.00 (Reference)	0.92 (0.55 to 1.54)	1.14 (0.72 to 1.80)	0.72 (0.45 to 1.17)
Model 3	1.00 (Reference)	0.93 (0.56 to 1.56)	1.18 (0.74 to 1.86)	0.74 (0.45 to 1.20)
JACC				
Model 2	1.00 (Reference)	1.04 (0.71 to 1.54)	0.85 (0.60 to 1.20)	0.88 (0.64 to 1.21)
Model 3	1.00 (Reference)	1.04 (0.71 to 1.53)	0.85 (0.60 to 1.19)	0.88 (0.64 to 1.21)
MIYAGI				
Model 2	1.00 (Reference)	0.83 (0.54 to 1.28)	0.95 (0.63 to 1.43)	0.73 (0.49 to 1.10)
Model 3	1.00 (Reference)	0.81 (0.53 to 1.26)	0.89 (0.59 to 1.35)	0.67 (0.44 to 1.02)
3-pref MIYAGI				
Model 2	1.00 (Reference)	0.81 (0.44 to 1.47)	0.72 (0.41 to 1.26)	0.82 (0.51 to 1.32)
Model 3	1.00 (Reference)	0.82 (0.45 to 1.49)	0.72 (0.41 to 1.27)	0.83 (0.51 to 1.35)
3-pref AICHI				
Model 2	1.00 (Reference)	1.19 (0.48 to 2.92)	1.28 (0.59 to 2.78)	1.52 (0.71 to 3.21)
Model 3	1.00 (Reference)	1.20 (0.49 to 2.95)	1.29 (0.59 to 2.80)	1.54 (0.72 to 3.28)

Model 2: Adjusted for age (continuous), area (JPHC-I, JPHC-II and JACC only), smoking (never smoker, past smoker, or current smoker), ethanol intake (never/former drinker, occasional drinker (<once/week), regular drinker (<23 g/day, ≥23 g/day)), rice intake (<4 bowls/day, ≥4 bowls/day), soy bean paste soup (<daily, daily), and coffee intake (<1 cup/day, 1–2 cups/day, ≥3 cups/day).
Model 3: Adjusted for pickled vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) and green–yellow vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) in addition to the variables included in Model 2.
JACC, The Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based prospective Study; MIYAGI, The Miyagi Cohort Study; 3-pref AICHI, The Three Prefecture Study – Aichi portion; 3-pref MIYAGI, The Three Prefecture Study – Miyagi portion.

individual studies were then combined using a random-effects model. We tested for and quantified the heterogeneity of the HRs for the highest category and the trend association of green tea consumption association among studies using the Q and I^2 statistics. Stata 10 was used for meta-analysis.

RESULTS

The present study included 219 080 subjects (100 479 men and 118 601 women) and 3577 cases of gastric cancer (2495 men and 1082 women) accumulated during 2 285 968 person-years of follow-up (table 1). Among both men and women, 80% of subjects consumed green tea every day, with 35% of men and 33% of women consuming ≥5 cups per day. Distribution of intake frequency was similar between men and women. In most cohorts, men and women with higher intake also tended to consume more rice, green–yellow vegetables, soy bean paste soup or pickled vegetables. The proportion of current smokers was also higher among men with higher green tea intake, but this characteristic was less clear among women.[9 10 12 13] The study-specific HRs and 95% CIs of total gastric cancer incidence by green tea consumption are presented in table 2.

In men (table 3), no notable association was found as a whole. No change in results was seen when subjects were stratified as never smokers and current smokers, and when outcome was confined to proximal or distal subsite. The results