4.37(1.49-12.81)であり、有意な関連を示した。しかし一方で、年齢、H.pylori 感染など既知の要因はそれぞれ相対危険度が 1.06, 2.16 であったが有意には至らなかった。性別と飲酒はともに喫煙との相関が強く、モデルに入れると喫煙自体の関連は消失することから、性別と飲酒は共変量としなかった。

D. 考察

結果は過去の知見と同様の傾向であるが、得られた相対危険度の 95%信頼区間は広く、また、既知の要因である年齢、H.pylori 感染は有意に至らなかった。これはサンプルサイズ不足が原因と考えられ、今後胃がん発生に関する予測モデルを構築するためには十分なサンプルにおける分析が必至である。

E.結論

胃がん発生の予測モデルの構築を試みたが、安定したモデルの構築のためにはより多くのサンプルの分析が必要であることが明らかとなった。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

1) Ma E, Sasazuki S, Sasaki S, Tsubono Y, Okubo S, Tsugane S. Vitamin C supplementation in relation to inflammation in individuals with atrophic gastritis: a randomised controlled trial in Japan. Br J Nutr. 2013;109:1089-95.

2) Sasazuki S, Tamakoshi A, Matsuo K, Ito H, Wakai K, Nagata C, Mizoue T, Tanaka K, Tsuji I, Inoue M, Tsugane S; Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Green tea consumption and gastric cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol. 2012;42:335-46.

3) Hara A, Sasazuki S, Inoue M, Iwasaki M, Shimazu T, Sawada N, Yamaji T, Tsugane S; Japan Public Health Center–Based Prospective Study Group. Isoflavone intake and risk of gastric cancer: a population-based prospective cohort study in Japan. Am J Clin Nutr. 2012 ;95:147-54.

2. 学会発表

1) 原 梓、笹月静、井上真奈美、岩崎基、島津太一、澤田典絵、山地太樹、津金昌一郎:イソフラボン摂取と胃がんリスクとの関連:多目的コホート研究より、第23 回日本疫学会学術総会、2013 年 1 月 24 日-26 日、大阪府吹田市

H. 知的財産権の出願・登録状況

特に無し

表.H.pylori 感染などの要因と胃がんとの関連(n=1,368)

	Coefficient	相対危険度*	95%信頼区間下限	95%信頼区間上限
年齢	0.0547	1.06 (NS)	0.99	1.13
過去喫煙	1.6718	5.32	1.92	14.74
現在喫煙、<20 本/日	0.8914	2.44 (NS)	0.70	8.44
現在喫煙、>20 本/日	1.3902	4.02	1.63	9.45
胃がんの家族歴	0.8481	2.34	1.00	5.45
H. pylori 感染	0.7705	2.16 (NS)	0.51	9.23
萎縮性胃炎	1.4745	4.37	1.49	12.81

*互いに補正。

厚生労働科学研究費補助金(第3次対がん総合戦略研究事業)
分担研究報告書

新規バイオマーカー開発による胃がんのハイリスクグループ同定のための研究

研究分担者　伊藤秀美　愛知県がんセンター研究所 疫学・予防部 室長

研究要旨

本研究は、胃がんにおいて、頭頸部がん・食道がんと同様に、飲酒とアセトアルデヒド代謝酵素である ALDH2 の rs671 遺伝子多型の遺伝子環境要因交互作用が存在するか否かを検討することを目的とする。

愛知県がんセンターにおける 697 名の胃がん患者並びに、1372 名の非がん対照者を用いた症例対照研究を実施し、飲酒習慣と rs671 多型並びに両者の交互作用を既知の交絡要因を考慮した多変量解析により検討した。

アセトアルデヒド活性が高い *ALDH2* Glu/Glu 群に比べ、Glu/Lys 群、Lys/Lys 群の調整オッズ比は、1.40 (95%信頼区間: 1.11-1.76)、1.73 (1.12-2.68)であった。飲酒状況と組み合せた解析では、ALDH2 Lys+群での高飲酒群のオッズ比は、3.03 (1.59-5.79)であった一方、Glu/Glu 群では 1.28 (0.77-2.12)であった。遺伝子環境要因交互作用に関する P 値は 0.0054 であり、有意なものであった。

本研究は、胃がんにおいてアセトアルデヒド由来の発癌の可能性を強く示唆するとともに、遺伝子型によって取るべき飲酒行動が異なる可能性を示した意味で重要である。今後、国内の他研究による追試が望まれる。

A. 研究目的

胃がんは我が国における主要ながん種で有り、変容可能なリスク要因を同定することは重要である。既存の疫学研究において、胃がんに対する飲酒の影響は認められて来なかった。頭頸部がん・食道がんでは、飲酒とアセトアルデヒド代謝酵素である ALDH2 の rs671 遺伝子多型の遺伝子環境要因交互作用が知られている。このことはアセトアルデヒドによる発がんを強く示唆するものであるが、胃がんにおいて本視点に立った検討はなされて来なかった。本研究では、*ALDH2* rs671 遺伝子多型と飲酒行動の間の遺伝子環境要因交互作用を検討するのが目的である。

B. 研究方法

本研究の研究デザインは症例対照研究である。対象者は 2001ー2005 年に愛知県がんセンター病院を受診し大規模病院疫学研究(Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC))に、遺伝子測定用の DNA 検体を提供の上参加した患者より選択された。患者は同期間に組織学的に胃がんと診断された 697 名である。また同時期に HERPACC に参加し、受信後 1 年以内にいかなるがんとも診断されていない患者を非がん対照者として 1392 名抽出した。

飲酒状況【非飲酒、低飲酒群(週 5 日未満飲酒)、中等飲酒群(週 5 日以上飲酒、一回辺りエタノール量 46g 未満飲酒)、高飲酒群(週5日以上飲酒、一回

辺り 46g 以上飲酒)に分類した。Rs671 遺伝子多型は TaqMan 法により測定し、Glu/Glu, Glu/Lys, Lys/Lys の遺伝子型を決定した。

飲酒状況、rs671 多型並びに両者の交互作用は、ロジスティック回帰分析により、性、年齢、喫煙状況、野菜果物摂取、胃がんの家族歴、ヘリコバクター・ピロリ菌感染状況、IgG 抗体によるペプシノーゲン I/II による萎縮性胃炎状況を調整した上で評価を行った。

(倫理面での配慮)

本研究の参加者に対しては、目的、個人情報の保護、参加拒否による不利益がないこと、いつでも参加を取りやめることが出来ること等を十分に説明の上、文書による同意を取得した。愛知県がんセンターのヒトゲノム倫理審査委員会により承認済みである。

C. 研究結果

表 1 に対象者の特性を示す。症例の方が現在喫煙者が多く、Pack-yearも高い傾向であった。また、高度飲酒者も症例群で多かった。野菜・果物摂取は低摂取者が症例群で多かった。胃がん家族歴も症例群で高かった。Helicobacter pylori 感染者、萎縮性胃炎の有病者は、感染者で明瞭に高かった。

表 2 に飲酒状況、ALDH2 遺伝子型の胃がんリスクへの影響を示す。どのモデルにおいても、ALDH2 Lys アリル保持者は統計学的に有意に高いリスクを示した。また、高度飲酒は、特にALDH2 遺伝子型を考慮した場合には非飲酒群と比べて、1.72 (95%信頼区間: 1.17-2.52)と高い数値を示した。

表 3 には、飲酒状況とALDH2 遺伝子型の交互作用を検討した結果を示す。ALDH2 Glu/Glu において、飲酒が増えることは明瞭なリスク上昇にはつながっていない一方、ALDH2 Lys アリル保持者においては、用量依存性のリスク上昇傾向を認めた。ALDH2 Glu/Glu 且つ非飲酒に比べ、ALDH2 Lys+且つ高度飲酒の調整オッズ比は 3.03 (95%信頼区間: 1.59-5.79)と有意な上昇を示した。また、交互作用に関するP値も0.0054と強い交互作用を示唆する結果が得られた。

表4には非がん対照者のみを対象として ALDH2 遺伝子型と飲酒の組合わせの萎縮性胃炎の有病率に対する影響を横断的に検討した結果を示す。胃がんリスクの時と同様、ALDH2 Lys アリル保持者において明確な用量依存性を示唆する関連が認められた。非飲酒且つ ALDH2 Glu/Glu に比して、高度飲酒且つ ALDH2 Lys アリル保持の調整オッズ比は 4.50 (95%信頼区間: 1.51-13.43)であった。ただしこの ALDH2 Glu/Glu と Lys アリル保持の間における飲酒状況の交互作用は統計学的には有意なものではなかった。

D. 考察

ALDH2 rs671 遺伝子多型は、アミノ酸の置換をもたらす遺伝子多型で有り、Glu/Glu のアセトアルデヒド代謝活性を 100%とすると、Glu/Lys で 6-7%、Lys/Lys でほぼ 0%の活性低下という dominant negative な機能変化をもたらすものである。本多型は日本人を含む東アジア人でアリル頻度が高く、同地域の食道がん、頭頸部がん、肝臓がんに対して、飲酒と組み合わさることにより遺伝子環境要因交互作用を示すことが報告されてきた。この遺伝子環境要因交互作用が示唆するのはアセトアルデヒドの発癌性であり、これらのがんにおける、飲酒による発がんの背景要因にアセトアルデヒドが存在することを強く示唆してきた。

本研究では胃がんにおける飲酒と ALDH2 多型の遺伝子環境要因交互作用を検討し、頭頸部がん・食道がんと同様の結果を得た。これまで疫学研究において胃がんは飲酒関連がんとは考えられてこなかったが、本研究の結果は、アセトアルデヒドが胃がん発生に影響することを示したものであり、予防を考える上で意義が大きい。さらに、頭頸部・食道がんが、扁平上皮癌が主たる組織型であるのに対し、腺癌が主体の胃がんでも同様の傾向が認められたことも、今後の飲酒由来の発癌を考える上で示唆的なものと考えられる。

また表 4 における非がん対照のみでの横断解析に

おいて、Lys アリル保持者において、萎縮性胃炎のオッズ比が高い事実は、アセトアルデヒドが萎縮性胃炎の進展の前の段階で寄与していることを意味していると考えられ、これまでの *Helicobacter pylori* 感染、食塩、喫煙で説明されていたメカニズムに新たな一面を加えたという意義があると考えられる。

E.結論

本研究により、アセトアルデヒド代謝能の低い ALDH2 Lys アリル保持者において、飲酒が用量依存的に胃がんリスクを挙げていることを示した。アセトアルデヒドは、萎縮性胃炎を発生する段階から影響を与えている可能性を示したことは、胃がん発癌メカニズムを考える上で新たな視点をもたらした。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

1) Matsuo K, Oze I, Hosono S, Ito H, Watanabe M, Ishioka K, Ito S, Tajika M, Yatabe Y, Niwa Y, Yamao K, Nakamura S, Tajima K, Tanaka H. The aldehyde dehydrogenase 2 (*ALDH2)* Glu504Lys polymorphism interacts with alcohol drinking in the risk of stomach cancer. Carcinogenesis (in press)

2. 学会発表

(特になし)

H. 知的財産権の出願・登録状況

特に無し

表1. 対象者の特性

		胃がん		非がん対照	
Overall	697	%	1,372	%	
性	男性	521	74.7	1,028	74.9
	女性	176	25.3	344	25.1
年齢	<40	34	4.9	146	10.6
	40-49	72	10.3	154	11.2
	50-59	245	35.2	429	31.3
	60-69	210	30.1	435	31.7
	>70	136	19.5	208	15.2
喫煙	非喫煙	222	31.9	538	39.2
	過去喫煙	181	26	403	29.4
	現在喫煙	294	42.2	430	31.3
Pack-years					
	非喫煙	222	31.9	539	39.3
	<20	99	14.2	286	20.9
	<40	160	23.0	272	19.8
	<60	117	16.8	153	11.2
	60 or more	92	13.2	113	8.2
飲酒	非飲酒	228	32.7	452	32.9
	軽度飲酒	167	24.0	412	30.0
	中等度飲酒	159	22.8	316	23.0
	高度飲酒	132	18.9	177	12.9
野菜・果物摂取3分位					
最低(<114.0 g/day)		263	37.7	446	32.5
中等(<199.96 g/day)		208	29.8	445	32.4
最高(≥199.96 g/day)		209	30	445	32.4
胃がんの家族歴					
	有り	153	22	239	17.4
	無し	544	78	1133	82.6
Helicobacter pylori IgG抗体検査					
	陽性	124	17.8	628	45.8
	陰性	573	82.2	744	54.2
ペプシノーゲンによる慢性胃炎の有無					
	陰性	262	37.6	893	128.1
	陽性	434	62.3	479	68.7
	不詳	1	0.1	0	0

表2. 飲酒とALDH2 遺伝子型と胃がんリスクの関連

	Case	Control	モデル 1*1 OR(95%CI)*2	モデル 2 *2 OR(95%CI)*2	モデル 3 *3 OR(95%CI)*2
飲酒状況					
非飲酒	228	452	Reference	Reference	Reference
軽度飲酒	167	412	0.81 (0.63-1.04)	0.89 (0.67-1.17)	1.04 (0.77-1.40)
中等度飲酒	159	316	1.03 (0.79-1.34)	0.92 (0.68-1.24)	1.15 (0.82-1.61)
高度飲酒	132	177	1.52 (1.14-2.04)	1.29 (0.92-1.80)	1.72 (1.17-2.52)
不詳	11	15			
ALDH2 遺伝子型 *4					
Glu/Glu	310	683	Reference	Reference	Reference
Lys+	386	689	1.24 (1.03-1.49)	1.27 (1.04-1.56)	1.42 (1.13-1.79)
Glu/Lys	323	580	1.23 (1.02-1.49)	1.25 (1.01-1.54)	1.40 (1.11-1.76)
Lys/Lys	63	109	1.27 (0.91-1.78)	1.42 (0.98-2.08)	1.73 (1.12-2.68)

*1 Crude ORs by the conditional logistic regression model.

*2 ORs were calculated by a conditional logistic regression model adjusted for pack-years of smoking, fruit and vegetable intake, family history of gastric cancer, gastric atrophy defined by serological pepsinogen testing, and *Helicobacter pylori* status.

*3 ORs were calculated by unconditional logistic regression model adjusted for age, sex, pack-years of smoking, fruit and vegetable intake, family history of gastric cancer, gastric atrophy defined by serological pepsinogen testing, *Helicobacter pylori* status, levels of drinking, and ALDH2 genotypes.

*4 One case was excluded because ALDH2 genotype was not defined.

表3. 胃がんリスクと飲酒・ALDH2 遺伝子型の組合わせの関連

	ALDH2 Glu/Glu			ALDH2 Lys+			
飲酒状況	症例	対照	OR(95%CI)*2	症例	対照	OR(95%CI)*2	交互作用P
非飲酒	49	112	Reference	179	340	1.24 (0.82-1.90)	0.0054
軽度飲酒	87	208	1.07 (0.67-1.70)	80	204	1.03 (0.63-1.67)	
中等度飲酒	79	208	0.89 (0.54-1.44)	80	108	1.57 (0.94-2.64)	
高度飲酒	87	145	1.28 (0.77-2.12)	44	32	3.03 (1.59-5.79)	
不詳	8	10		3	5		

*1 One case was excluded because ALDH2 genotype was not defined.

*2 ORs were calculated by an unconditional logistic regression model adjusted for age, sex, pack-years of smoking, fruit and vegetable intake, family history of gastric cancer, gastric atropy defined by serological pepsinogen testing, and *Helicobacter pylori* status.

表 4. 非がん対照者におけるALDH2 遺伝子型と飲酒量の組合わせと、萎縮性胃炎の関連

	Overall			Combined with ALDH2 genotype					
				ALDH2 Glu/Glu			ALDH2 Lys+		
	AG	non-AG	OR(95%CI)*2	AG	non-AG	OR(95%CI)*2	AG	non-AG	OR(95%CI)*2
非飲酒	163	289	Reference	39	73	Reference	124	216	1.65 (0.92-2.93)
軽度飲酒	128	284	0.99 (0.68-1.44)	68	140	1.71 (0.90-3.25)	60	144	1.27 (0.66-2.44)
中等度飲酒	119	197	1.20 (0.81-1.79)	76	132	1.67 (0.88-3.17)	43	65	2.10 (1.00-4.41)
高度飲酒	66	111	1.19 (0.73-1.92)	51	94	1.48 (0.74-2.98)	15	17	4.50 (1.51-13.43)
不詳	3	12		1	9		2	3	

*1 One case was excluded because ALDH2 genotype was not defined.

*2 ORs were calculated by an unconditional logistic regression model adjusted for age, sex, pack-years of smoking, fruit and vegetable intake, family history of gastric cancer, and *Helicobacter pylori* status

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Inoue M, Tsugane S	Insulin resistance and cancer: epidemiological evidence.	Endocr Relat Cancer	19	F1-8.	2012
Ma E, Sasazuki S, Sasaki S, Tsubono Y, Okubo S, Tsugane S.	Vitamin C supplementation in relation to inflammation in individuals with atrophic gastritis: a randomised controlled trial in Japan.	Br J Nutr	109	1089-95.	2013
Sasazuki S, Tamakoshi A, Matsuo K, Ito H, Wakai K, Nagata C, Mizoue T, Tanaka K, Tsuji I, Inoue M, Tsugane S; Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan.	Green tea consumption and gastric cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population.	Jpn J Clin Oncol	42	335-46	2012
Hara A, Sasazuki S, Inoue M, Iwasaki M, Shimazu T, Sawada N, Yamaji T, Tsugane S; Japan Public Health Center–Based Prospective Study Group.	Isoflavone intake and risk of gastric cancer: a population-based prospective cohort study in Japan.	Am J Clin Nutr	95	147-54	2012

Matsuo K, Oze I, Hosono S, Ito H, Watanabe M, Ishioka K, Ito S, Tajika M, Yatabe Y, Niwa Y, Yamao K, Nakamura S, Tajima K, Tanaka H.	The aldehyde dehydrogenase 2 (ALDH2) Glu504Lys polymorphism interacts with alcohol drinking in the risk of stomach cancer.	Carcinogenesis	In press		

FOCUS REVIEW

Endocrine-Related Cancer (2012) **19** F1–F8

Insulin resistance and cancer: epidemiological evidence

Manami Inoue and Shoichiro Tsugane

Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

(Correspondence should be addressed to M Inoue; Email: mnminoue@ncc.go.jp)

Abstract

Epidemiological research into insulin resistance has focused on excess body weight, type 2 diabetes mellitus (DM), physical activity, and coffee consumption. These common modifiable factors have also been suggested to play a role in the process of carcinogenesis via associations with insulin resistance. Findings of systematic literature reviews and meta-analyses have generally supported an association between excess body weight and DM with an increased risk of colon cancer in males, and of liver, pancreatic, and endometrial cancers. Inverse relationships between these cancers and physical activity and coffee consumption have been shown, both of which are known to reduce the risk of DM. Interventions directed at or involving these variables should contribute to decreasing the risk of insulin resistance-associated cancer.

Endocrine-Related Cancer (2012) **19** F1–F8

Introduction

A substantial body of epidemiological evidence over recent decades has suggested a positive link between excess bodyweight and type 2 diabetes mellitus (DM) and many types of cancer. Studies have also suggested an inverse association between these cancers and physical activity and coffee consumption, both of which are suggested to decrease the risk of DM. These findings share the common keyword 'insulin resistance', and each factor plays a role in the carcinogenic process via this condition (Tsugane & Inoue 2010). Various recent systematic reviews and meta-analyses have helped establish the quantitative evaluation of these associations. Here, we review epidemiological evidence for the association between factors involved in insulin resistance and cancer risk, with a focus on the four factors commonly targeted in epidemiological research, namely excess body weight, DM, physical activity, and coffee consumption. Further, we summarize several possible mechanisms of insulin resistance-associated carcinogenesis.

Risk factors related to insulin resistance and cancer

Excess body weight and cancer risk

In its second report, the World Cancer Research Fund/American Institute for Cancer Research (WCRF report 2007) assessed causal link between several factors and individual cancers using systematic reviews of epidemiological evidence, and also interpretations of relevant mechanisms and animal experimental data (WCRF/AICR 2007). This report states that excess body weight convincingly increases the risk of esophageal adenocarcinoma, colorectal cancer, pancreatic cancer, postmenopausal breast cancer, endometrial cancer, and kidney cancer. Further, it probably increases the risk of gallbladder cancer, and possibly increases the risk of liver cancer. The WCRF report also indicates that increased abdominal fatness, as assessed by waist circumference and/or waist–hip ratio, confers a convincing increase in the risk of colorectal cancer, as well as a probable increase in risk of pancreatic cancer, postmenopausal breast cancer, and endometrial cancer. As shown in Table 1, meta-analysis of a number of cohort studies from North America, Europe, Australia, and Asia-Pacific, with geometric mean follow-up periods from 8.4 years (breast cancer) to 14.4 years (multiple myeloma) (Renehan *et al.* 2008*b*), showed the magnitude of risk with a 5 kg/m^2 increase in body mass index (BMI) greater for esophageal adenocarcinoma (relative risk (RR) = 1.5); and cancers of thyroid (RR = 1.3), colon (RR = 1.2), kidney (RR = 1.2), and liver (RR = 1.2) in men; and for endometrial cancer

Endocrine-Related Cancer (2012) **19** F1–F8
1351–0088/12/019–F1
DOI: 10.1530/ERC-12-0142
Online version via http://www.endocrinology-journals.org

Table 1 Summary results from recent meta-analyses of the association between factors related to insulin resistance and cancer risk

	Excess body weight (per 5 kg/m^2 increase of BMI)							**Type 2 diabetes** (diabetes vs nondiabetes)				**Pysical activity** (highest vs lowest)				**Coffee consumption** (highest vs lowest)			
	Men			**Women**															
Cancer site	**SRR**	**(95% CI)**	**Number of studies (CH/CC)**	**SRR**	**(95% CI)**	**Number of studies (CH/CC)**	**Ref.**	**SRR**	**(95% CI)**	**Number of studies (CH/CC)**	**Ref.**	**SSR**	**(95% CI)**	**Number of studies (CH/CC)**	**Ref.**	**SRR**	**(95% CI)**	**Number of studies (CH/CC)**	**Ref.**
Oral pharynx																0.64	(0.51–0.80)	9 (1/8)	[19]
Esophageal squamous cell carcinoma	0.71	(0.60–0.85)	3	0.57	(0.47–0.69)	2	[1]	1.30	(1.12–1.50)	17 (11/6)	[2]					0.87	(0.65–1.17)	7 (1/6)	[19]
Esophageal adenocarcinoma	1.52	(1.33–1.74)	5	1.51	(1.31–1.74)	3	[1]									1.18	(0.81–1.71)	3 (0/3)	[19]
Stomach	0.97	(0.88–1.06)	8	1.04	(0.90–1.20)	5	[1]	1.01	(0.90–1.11)	10 (10/0)	[3]								
Colorectum								1.26	(1.20–1.31)	24 (16/8)	[4]								
Colon	1.24	(1.20–1.28)	22	1.09	(1.05–1.13)	19	[1]					0.76	(0.72–0.81)	52 (28/24)	[14]	0.90	(0.78–1.04)	11 (11/0)	[20]
Rectum	1.09	(1.06–1.12)	18	1.02	(1.00–1.05)	14	[1]									0.98	(0.80–1.20)	10 (10/0)	[20]
Liver	1.24	(0.95–1.62)	4	1.07	(1.00–2.08)	1	[1]	2.31	(1.87–2.84)	49 (32/17)	[5]					0.45	(0.38–0.53)	10 (4/6)	[21]
Biliary tract	1.09	(0.99–1.21)	4	1.59	(1.02–2.47)	2	[1]	1.43	(1.18–1.72)	21 (13/8)	[6]								
Pancreas	1.07	(0.93–1.23)	12	1.12	(1.02–1.22)	11	[1]	1.94	(1.66–2.27)	35 (35/0)	[7]	0.72	(0.52–0.99)	5 (5/0)	[15]	1.13	(0.99–1.29)	54 (17/37)	[22]
Lung	0.76	(0.70–0.83)	11	0.80	(0.66–0.97)	6	[1]					0.70	(0.62–0.79)	11 (8/3)	[16]	1.27	(1.04–1.54)	13 (5/8)	[23]
Malignant melanoma	1.17	(1.05–1.30)	6	0.96	(0.92–1.01)	5	[1]												
Breast								1.20	(1.12–1.28)	20 (15/5)	[8]					0.95	(0.90–1.00)	18 (9/9)	[24]
Postmenopausal breast				1.12	(1.08–1.16)	31	[1]												
Premenopausal breast				0.92	(0.88–0.97)	20	[1]												
Endometrium				1.59	(1.50–1.68)	19	[1]	2.10	(1.75–2.53)	16 (3/13)	[9]					0.71	(0.62–0.81)	16 (6/10)	[25]
Ovary				1.03	(0.99–1.08)	13	[1]					0.81	(0.72–0.92)	13 (6/7)	[17]				
Prostate	1.03	(1.00–1.07)	27				[1]	0.84	(0.76–0.93)	19 (12/7)	[10]	0.90	(0.84–0.95)	43 (19/24)	[18]	1.16	(1.01–1.33)	12 (4/8)	[26]
Kidney	1.24	(1.15–1.34)	11	1.34	(1.25–1.43)	12	[1]	1.42	(1.06–1.91)	9 (9/0)	[11]								
Bladder								1.24	(1.08–1.42)	16 (9/7)	[12]								
Thyroid	1.33	(1.04–1.70)	4	1.14	(1.06–1.23)	3	[1]												
Non-Hodgkin's lymphoma	1.06	(1.03–1.09)	6	1.07	(1.00–1.14)	7	[1]	1.19	(1.04–1.35)	16 (5/11)	[13]								
Multiple myeloma	1.11	(1.05–1.18)	7	1.11	(1.07–1.15)	6	[1]												
Leukemia	1.08	(1.02–1.14)	7	1.17	(1.04–1.32)	7	[1]												

Sources: Ref., references: [1] Renehan *et al.* (2008*b*), [2] Huang *et al.* (2012), [3] Marimuthu *et al.* (2011), [4] Deng *et al.* (2012), [5] Wang *et al.* (2012), [6] Ren *et al.* (2011), [7] Ben *et al.* (2011), [8] Larsson *et al.* (2007), [9] Friberg *et al* (2007), [10] Kasper & Giovannucci (2006), [11] Larsson & Wolk (2011), [12] Larsson *et al.* (2006), [13] Mitri *et al.* (2008), [14] Wolin *et al.* (2009), [15] O'Rorke *et al.* (2010), [16] Tardon *et al.* (2005), [17] Olsen *et al.* (2007), [18] Liu *et al.* (2011), [19] Turati *et al.* (2011), [20] Je *et al.* (2009), [21] Bravi *et al.* (2007), [22] Turati *et al.* (2012), [23] Tang *et al.* (2010), [24] Tang *et al.* (2009), [25] Je & Giovannucci (2011), [26] Park *et al.* (2010).
Abbreviations: CC, case-control study; CH, cohort study; SRR, summary relative risk; 95%CI, 95% confidence interval.

(RR = 1.6), gallbladder cancer (RR = 1.6), esophageal adenocarcinoma (RR = 1.5), and kidney cancer (RR = 1.3) in women. A statistically significant sex difference has been observed for the risk of colon cancer, for which the RR was 1.1 in women. In that study, the duration of follow-up or the mean age at baseline had little effect on the positive association between BMI and cancer, and populations in the Asia-Pacific regions showed a stronger association with breast cancer, independently of menopausal status. Since then, two pooled analyses of over one million Caucasian (Berrington de Gonzalez *et al.* 2010) and Asian subjects (Zheng *et al.* 2011) reported an increased risk of cancer mortality with increased BMI in both white and East Asian populations, but not in Indian or Bangladeshi populations. No good explanation for this difference has appeared, but it is suggested that the lack of association in these two populations may be partly due to confounding by socioeconomic status; namely, subjects with a high BMI in less developed countries are more likely to have a high socioeconomic status and thus better access to health care.

In the United States, the population attributable fraction of excess body weight (BMI $\geq$25 kg/m^2) has been estimated at 4% of male and 14% of female total cancer deaths (Calle *et al.* 2003), and in Europe at 3% of male and 4% of female total cancer incidence in 2002, and 3 and 9% in 2008 respectively (Renehan *et al.* 2010). In comparison, Japanese estimates for 2005 indicate that excess body weight was responsible for <1% of male and 1–2% of female cancer incidence and mortality (Inoue *et al.* 2011).

Type 2 DM and cancer risk

Accumulating epidemiological evidence over decades supports a positive link between DM and site-specific cancers in different populations, which are unrelated to excess body weight. Recent systematic reviews and meta-analyses in both Western and Asian populations showed a strong positive association for DM and pancreatic cancer (RR = 1.8–1.9; Huxley *et al.* 2005, Ben *et al.* 2011), hepatocellular carcinoma (RR = 2.3; Wang *et al.* 2012), and endometrial cancer (RR = 2.1; Friberg *et al.* 2007), while weaker but nevertheless positive links were seen for kidney (RR = 1.4; Larsson & Wolk 2011), biliary tract (RR = 1.4; Ren *et al.* 2011), bladder (RR = 1.2; Larsson *et al.* 2006), colorectal (RR = 1.3; Deng *et al.* 2012), esophageal (RR = 1.3; Huang *et al.* 2012), and breast cancers (RR = 1.2; Larsson *et al.* 2007), and also non-Hodgkin's lymphoma (RR = 1.2; Mitri *et al.* 2008). By comparison, an inverse association was reported for prostate cancer (RR = 0.8; Kasper & Giovannucci 2006; Table 1). Links with other types of cancer, less common than those consistently associated with DM, have been unclear due to limited evidence and have yet to be elucidated.

Possible mechanism for the link between excess body weight, DM, and cancer

The mechanism by which excess body weight increases cancer risk is possibly explained by insulin and insulin-like growth factor (IGF), sex steroids, and adipokines, which are connected through insulin (Calle & Kaaks 2004, Renehan *et al.* 2008*a*). Their roles might differ among cancer types.

A chronic excess body weight condition increases production of free fatty acids, cytokines such as tumor necrosis factor-α and interleukin 6, and leptin from adipose tissue, while it decreases adiponectin production, which together lead to the development of insulin resistance and chronic hyperinsulinemia (Calle & Kaaks 2004, Gallagher & LeRoith 2010). Chronic hyperinsulinemia decreases IGF-binding protein 1 (IGFBP1) and IGFBP2 concentrations in blood and other local tissues, which results in an increase in bioavailable free IGF1. Circulating total IGF1, a major element of free IGF1, increases the risk of colorectal, prostate, and premenopausal breast cancers. The sex difference in colorectal cancer risk might be partly explained by the higher concentration of circulating total IGF1 in men than in women (Juul *et al.* 1994, Renehan *et al.* 2008*b*).

The increased risk for breast cancer in postmenopausal women might be accounted for by the increased conversion of precursors of androgens to estradiol (E_2) via increased activity of aromatase enzyme in adipose tissue (Key & Verkasalo 1999). With regard to endometrial cancer, elevated E_2 leads to an increase in endometrial cell proliferation and inhibition of apoptosis (Graham & Clarke 1997, Calle & Kaaks 2004), simultaneously it also stimulates local IGF1 synthesis in the endometrium (Murphy 1994). Moreover, chronic hyperinsulinemia might promote carcinogenesis in tissues which are sensitive to estrogen by reducing sex-hormone-binding globulin concentrations in blood, as well as by increasing bioavailable estrogen (Calle & Kaaks 2004). In men, adiposity and testosterone concentration are inversely associated (Derby *et al.* 2006), whereas in women, they have a positive association (Key *et al.* 2003). This difference might explain sex differences in the association between BMI and cancer risk.

Adipokines are mainly produced from adipose tissue. The most abundant adipokines are leptin and adiponectin, which are implicated as mediators of the effects of obesity on cancer development. Leptin is secreted from adipocytes and involved in appetite control and energy metabolism. Circulating levels of this factor are high in obese conditions. Epidemiological studies suggest an association between circulating leptin levels and cancer progression, with the strongest link for colon, prostate, and breast cancers (Hursting & Berger 2010). Adiponectin is produced by adipocytes and involved in the regulation of carbohydrate and lipid metabolism, and insulin sensitivity. In contrast to other adipokines, plasma levels of adiponectin are decreased in response to several metabolic impairments, including DM, dyslipidemia, and extreme obesity. Plasma concentration of adiponectin shows an inverse association with excess body weight (Renehan *et al.* 2006), and levels are substantially higher in women than in men. The anti-angiogenic and anti-inflammatory activities of this agent may inhibit tumor growth (Barb *et al.* 2007).

While the association between DM and cancer differs among different cancer types, several mechanisms for the association have been hypothesized to date, such as the effect of hyperglycemia or insulin resistance and endogenous hyperinsulinemia (Giovannucci *et al.* 2010). In addition, excess body weight increases the risk of DM, which in the early stages is characterized by insulin resistance, followed by subsequent hyperinsulinemia (Tabak *et al.* 2009) before the development of hyperglycemia. Moreover, hyperinsulinemia may promote tumor cell growth directly via insulin receptors (Giovannucci *et al.* 2010). However, the association between DM and cancer may be partly due to shared risk factors between the two diseases, such as excess body weight, physical activity, smoking, and so on. Also, whether DM is associated with both cancer incidence and prognosis/mortality remains to be solved, and the answer may influence the screening and treatment strategies of both diseases.

Protective factors associated with insulin resistance and cancer

Physical activity and cancer risk

Substantial evidence supports an inverse association between physical activity and cancer risk at several sites, and physical activity is now regarded as an important cancer prevention target. The second WCRF/AICR report concluded that all types of physical activity (occupational, household, transport, and recreational) convincingly decrease the risk of colon cancer, and probably also reduce the risk of postmenopausal breast cancer and endometrial cancer, either in association with excess body weight or independent of it (WCRF/AICR 2007). Evidence for a decrease in risk for lung, pancreatic, and premenopausal breast cancers is limited. Meta-analysis has been limited due to difficulty in harmonizing the physical activity measures used by each study. In contrast, several recent meta-analyses reported inverse associations between physical activity and colon (RR=0.8; Wolin *et al.* 2009), pancreas (RR=0.7; O'Rorke *et al.* 2010), lung (RR=0.7; Tardon *et al.* 2005), ovary (RR=0.8; Olsen *et al.* 2007), and prostate cancers (RR=0.9; Liu *et al.* 2011; Table 1). The recent systematic review with meta-analysis by Jeon *et al.* (2007) showed that regular physical activity of moderate intensity produced a substantial decrease in the risk of DM (RR=0.7) independently of excessive body weight.

A variety of mechanisms have been put forward to explain the association of physical activity for these cancers, including changes in insulin and IGF or sex hormones, immune modulation, alterations in free radical generation, and changes in body weight. Direct effects on these cancers have also been proposed (Lee 2003, Westerlind 2003). Exercise increases insulin sensitivity and reduces fasting insulin and C-peptide levels (Regensteiner *et al.* 1991), thereby improving insulin resistance. Physical activity appears to lower the levels of biologically available sex hormones, which could lead to decreased risk of hormone-related cancers such as the breast, endometrium, ovary, and prostate. Physical activity also induces increases in antitumor immune defenses by increasing the number and activity of macrophages, lymphokine-activated killer cells, and their regulating cytokines. Strenuous exercise increases the production of free radicals, whereas chronic exercise improves free radical defenses by upregulating the activities of free scavenger enzymes and antioxidant levels. Physical activity prevents cancer development through a reduction in abdominal fat mass (Friedenreich & Orenstein 2002). Overall, there appears to be a wide variety of potential mechanisms, and it is unknown to what degree the pathway between physical activity and cancer is attributable to insulin resistance. Also, even though physical activity has benefit in reducing the risk of cancer, an optimal level of physical activity to prevent or promote cancer remains to be elucidated. Nevertheless, it is reasonable to suggest that moderate but not strenuous physical activity potentially reduces the risk of cancer by improving insulin resistance.

Coffee consumption and cancer risk

The second WCRF/AICR report in 2007 (WCRF/AICR 2007) reviewed the association between coffee and risk for pancreatic and kidney cancers. While the effect of coffee on cancer risk remains controversial, many epidemiological studies have reported a strong protective effect in hepatocellular carcinoma and endometrial cancer (Arab 2010). A meta-analysis supported the association between coffee consumption and risk reduction in liver (RR = 0.54; Bravi *et al.* 2007) and endometrial cancers (RR = 0.71; Je & Giovannucci 2011; Table 1), while a borderline protective effect was also shown for colon cancer. This effect was stronger in women (RR = 0.79) than in men (RR = 1.00), particularly in Japanese populations (RR = 0.62), although a plausible explanation for this sex difference deserves further investigation (Je *et al.* 2009). A recently large-scale prospective study in the US reported a null association for total cancer mortality (Freedman *et al.* 2012), which suggests that the effect of coffee varies by cancer site, likely depending on whether it is associated with insulin resistance or not.

The favorable effects of coffee intake on carcinogenesis are suggested to result from three predominant constituents, namely chlorogenic acid, caffeine, and diterpenes. Chlorogenic acid, a potent antioxidant and inhibitor of glucose-6-phosphate translocase in the liver, reduces gluconeogenesis and inflammation in the liver and the glucose absorption in the gut, which leads to an improvement in insulin resistance by elevating insulin sensitivity (Tunnicliffe & Shearer 2008). This effect may not be in conflict with the finding that higher coffee intake is related to lower postload glucose concentrations, rather than to fasting concentrations (van Dam *et al.* 2004, Yamaji *et al.* 2004). Like chlorogenic and caffeic acid, coffee diterpenes in coffee oil, such as cafestol and kahweol, might also decrease mutagenesis, tumorigenesis, and the genotoxicity of carcinogens, and also decrease DNA adduct formation.

Recent studies provide evidence that coffee has a protective effect against DM (van Dam & Hu 2005) and various cancers. Acute caffeine ingestion decreases glucose disposal (Greer *et al.* 2001, Keijzers *et al.* 2002, Lee *et al.* 2005). Meanwhile, US studies show that decaffeinated coffee decreases the risk of DM, and a cross-sectional analysis showed that coffee had a stronger inverse association with hyperglycemia than caffeine (Isogawa *et al.* 2003). Coffee constituents other than caffeine might thus also have favorable effects on DM. Perhaps, importantly, coffee is also rich in magnesium, which has known to improve insulin sensitivity and insulin secretion (Larsson & Wolk 2007).

This large body of evidence, along with biological plausibility, indicates that coffee consumption has a protective effect against insulin resistance, and may decrease the risk of colon, liver, pancreatic and endometrial cancers associated with DM.

Conclusion

A substantial body of epidemiological evidence leaves little doubt that insulin resistance is an important factor in the development of cancer at various sites, including colon, liver, pancreas, and endometrium. The factors covered in this review – excess body weight, DM, physical activity, and coffee consumption – play a role in the carcinogenic process through their association with insulin resistance. Interventions based around these factors should accordingly help decrease the risk of insulin resistance-associated cancer.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

Funding

This work was supported by the National Cancer Center Research and Development Fund and by funds for the Third Term Comprehensive Control Research for Cancer from the Ministry of Health, Labour, and Welfare, Japan.

References

Arab L 2010 Epidemiologic evidence on coffee and cancer. *Nutrition and Cancer* **62** 271–283. (doi:10.1080/01635580903407122)

Barb D, Williams CJ, Neuwirth AK & Mantzoros CS 2007 Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. *American Journal of Clinical Nutrition* **86** s858–s866.

Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, Zhang H & Li Z 2011 Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. *European Journal of Cancer* **47** 1928–1937. (doi:10.1016/j.ejca.2011.03.003)

Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, Moore SC, Tobias GS, Anton-Culver H, Freeman LB *et al.* 2010 Body-mass index and mortality among 1.46 million white adults. *New England Journal of Medicine* **363** 2211–2219. (doi:10.1056/NEJMoa1000367)

Bravi F, Bosetti C, Tavani A, Bagnardi V, Gallus S, Negri E, Franceschi S & La Vecchia C 2007 Coffee

drinking and hepatocellular carcinoma risk: a meta-analysis. *Hepatology* **46** 430–435. (doi:10.1002/hep.21708)

Calle EE & Kaaks R 2004 Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nature Reviews. Cancer* **4** 579–591. (doi:10.1038/nrc1408)

Calle EE, Rodriguez C, Walker-Thurmond K & Thun MJ 2003 Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *New England Journal of Medicine* **348** 1625–1638. (doi:10.1056/NEJMoa021423)

van Dam RM & Hu FB 2005 Coffee consumption and risk of type 2 diabetes: a systematic review. *Journal of the American Medical Association* **294** 97–104. (doi:10.1001/jama.294.1.97)

van Dam RM, Dekker JM, Nijpels G, Stehouwer CD, Bouter LM & Heine RJ 2004 Coffee consumption and incidence of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes: the Hoorn Study. *Diabetologia* **47** 2152–2159. (doi:10.1007/s00125-004-1573-6)

Deng L, Gui Z, Zhao L, Wang J & Shen L 2012 Diabetes mellitus and the incidence of colorectal cancer: an updated systematic review and meta-analysis. *Digestive Diseases and Sciences* **57** 1576–1585. (doi:10.1007/s10620-012-2055-1)

Derby CA, Zilber S, Brambilla D, Morales KH & McKinlay JB 2006 Body mass index, waist circumference and waist to hip ratio and change in sex steroid hormones: the Massachusetts Male Ageing Study. *Clinical Endocrinology* **65** 125–131. (doi:10.1111/j.1365-2265.2006.02560.x)

Freedman ND, Park Y, Abnet CC, Hollenbeck AR & Sinha R 2012 Association of coffee drinking with total and cause-specific mortality. *New England Journal of Medicine* **366** 1891–1904. (doi:10.1056/NEJMoa1112010)

Friberg E, Orsini N, Mantzoros CS & Wolk A 2007 Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia* **50** 1365–1374. (doi:10.1007/s00125-007-0681-5)

Friedenreich CM & Orenstein MR 2002 Physical activity and cancer prevention: etiologic evidence and biological mechanisms. *Journal of Nutrition* **132** 3456S–3464S.

Gallagher EJ & LeRoith D 2010 Insulin, insulin resistance, obesity, and cancer. *Current Diabetes Reports* **10** 93–100. (doi:10.1007/s11892-010-0101-y)

Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG & Yee D 2010 Diabetes and cancer: a consensus report. *Diabetes Care* **33** 1674–1685. (doi:10.2337/dc10-0666)

Graham JD & Clarke CL 1997 Physiological action of progesterone in target tissues. *Endocrine Reviews* **18** 502–519. (doi:10.1210/er.18.4.502)

Greer F, Hudson R, Ross R & Graham T 2001 Caffeine ingestion decreases glucose disposal during a hyperinsulinemic–euglycemic clamp in sedentary humans. *Diabetes* **50** 2349–2354. (doi:10.2337/diabetes.50.10.2349)

Huang W, Ren H, Ben Q, Cai Q, Zhu W & Li Z 2012 Risk of esophageal cancer in diabetes mellitus: a meta-analysis of observational studies. *Cancer Causes & Control* **23** 263–272. (doi:10.1007/s10552-011-9874-9)

Hursting SD & Berger NA 2010 Energy balance, host-related factors, and cancer progression. *Journal of Clinical Oncology* **28** 4058–4065. (doi:10.1200/JCO.2010.27.9935)

Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A , Barzi F & Woodward M 2005 Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *British Journal of Cancer* **92** 2076–2083. (doi:10.1038/sj.bjc.6602619)

Inoue M, Sawada N, Matsuda T, Iwasaki M, Sasazuki S, Shimazu T, Shibuya K & Tsugane S 2011 Attributable causes of cancer in Japan in 2005 – systematic assessment to estimate current burden of cancer attributable to known preventable risk factors in Japan. *Annals of Oncology* **23** 1362–1369. (doi:10.1093/annonc/mdr437)

Isogawa A, Noda M, Takahashi Y, Kadowaki T & Tsugane S 2003 Coffee consumption and risk of type 2 diabetes mellitus. *Lancet* **361** 703–704. (doi:10.1016/S0140-6736(03)12586-X)

Je Y & Giovannucci E 2011 Coffee consumption and risk of endometrial cancer: findings from a large up-to-date meta-analysis. *International Journal of Cancer* **131** 1700–1710. (doi:10.1002/ijc.27408)

Je Y, Liu W & Giovannucci E 2009 Coffee consumption and risk of colorectal cancer: a systematic review and meta-analysis of prospective cohort studies. *International Journal of Cancer* **124** 1662–1668. (doi:10.1002/ijc.24124)

Jeon CY, Lokken RP, Hu FB & van Dam RM 2007 Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. *Diabetes Care* **30** 744–752. (doi:10.2337/dc06-1842)

Juul A, Bang P, Hertel NT, Main K, Dalgaard P, Jorgensen K, Muller J, Hall K & Skakkebaek NE 1994 Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. *Journal of Clinical Endocrinology and Metabolism* **78** 744–752. (doi:10.1210/jc.78.3.744)

Kasper JS & Giovannucci E 2006 A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiology, Biomarkers & Prevention* **15** 2056–2062. (doi:10.1158/1055-9965.EPI-06-0410)

Keijzers GB, De Galan BE, Tack CJ & Smits P 2002 Caffeine can decrease insulin sensitivity in humans. *Diabetes Care* **25** 364–369. (doi:10.2337/diacare.25.2.364)

Key TJ & Verkasalo PK 1999 Endogenous hormones and the aetiology of breast cancer. *Breast Cancer Research* **1** 18–21. (doi:10.1186/bcr7)

Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, Stanczyk FZ, Stephenson HE Jr, Falk RT, Miller R *et al.* 2003 Body mass index, serum sex

hormones, and breast cancer risk in postmenopausal women. *Journal of the National Cancer Institute* **95** 1218–1226. (doi:10.1093/jnci/djg022)

Larsson SC & Wolk A 2007 Magnesium intake and risk of type 2 diabetes: a meta-analysis. *Journal of Internal Medicine* **262** 208–214. (doi:10.1111/j.1365-2796.2007.01840.x)

Larsson SC & Wolk A 2011 Diabetes mellitus and incidence of kidney cancer: a meta-analysis of cohort studies. *Diabetologia* **54** 1013–1018. (doi:10.1007/s00125-011-2051-6)

Larsson SC, Orsini N, Brismar K & Wolk A 2006 Diabetes mellitus and risk of bladder cancer: a meta-analysis. *Diabetologia* **49** 2819–2823. (doi:10.1007/s00125-006-0468-0)

Larsson SC, Mantzoros CS & Wolk A 2007 Diabetes mellitus and risk of breast cancer: a meta-analysis. *International Journal of Cancer* **121** 856–862. (doi:10.1002/ijc.22717)

Lee IM 2003 Physical activity and cancer prevention – data from epidemiologic studies. *Medicine and Science in Sports and Exercise* **35** 1823–1827. (doi:10.1249/01.MSS.0000093620.27893.23)

Lee S, Hudson R, Kilpatrick K, Graham TE & Ross R 2005 Caffeine ingestion is associated with reductions in glucose uptake independent of obesity and type 2 diabetes before and after exercise training. *Diabetes Care* **28** 566–572. (doi:10.2337/diacare.28.3.566)

Liu Y, Hu F, Li D, Wang F, Zhu L, Chen W, Ge J, An R & Zhao Y 2011 Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis *European Urology* **60** 1029–1044. (doi:10.1016/j.eururo.2011.07.007)

Marimuthu SP, Vijayaragavan P, Moysich KB & Jayaprakash V 2011 Diabetes mellitus and gastric carcinoma: Is there an association? *Journal of Carcinogenesis* **10** 30. (doi:10.4103/1477-3163.90481)

Mitri J, Castillo J & Pittas AG 2008 Diabetes and risk of non-Hodgkin's lymphoma: a meta-analysis of observational studies. *Diabetes Care* **31** 2391–2397. (doi:10.2337/dc08-1034)

Murphy LJ 1994 Growth factors and steroid hormone action in endometrial cancer. *Journal of Steroid Biochemistry and Molecular Biology* **48** 419–423. (doi:10.1016/0960-0760(94)90189-9)

Olsen CM, Bain CJ, Jordan SJ, Nagle CM, Green AC, Whiteman DC & Webb PM 2007 Recreational physical activity and epithelial ovarian cancer: a case–control study, systematic review, and meta-analysis. *Cancer Epidemiology, Biomarkers & Prevention* **16** 2321–2330. (doi:10.1158/1055-9965.EPI-07-0566)

O'Rorke MA, Cantwell MM, Cardwell CR, Mulholland HG & Murray LJ 2010 Can physical activity modulate pancreatic cancer risk? a systematic review and meta-analysis *International Journal of Cancer* **126** 2957–2968.

Park CH, Myung SK, Kim TY, Seo HG, Jeon YJ & Kim Y 2010 Coffee consumption and risk of prostate cancer: a meta-analysis of epidemiological studies. *BJU International* **106** 762–769. (doi:10.1111/j.1464-410X.2010.09493.x)

Regensteiner JG, Mayer EJ, Shetterly SM, Eckel RH, Haskell WL, Marshall JA, Baxter J & Hamman RF 1991 Relationship between habitual physical activity and insulin levels among nondiabetic men and women. San Luis Valley Diabetes Study. *Diabetes Care* **14** 1066–1074.

Ren HB, Yu T, Liu C & Li YQ 2011 Diabetes mellitus and increased risk of biliary tract cancer: systematic review and meta-analysis. *Cancer Causes & Control* **22** 837–847. (doi:10.1007/s10552-011-9754-3)

Renehan AG, Frystyk J & Flyvbjerg A 2006 Obesity and cancer risk: the role of the insulin–IGF axis. *Trends in Endocrinology and Metabolism* **17** 328–336. (doi:10.1016/j.tem.2006.08.006)

Renehan AG, Roberts DL & Dive C 2008*a* Obesity and cancer: pathophysiological and biological mechanisms. *Archives of Physiology and Biochemistry* **114** 71–83. (doi:10.1080/13813450801954303)

Renehan AG, Tyson M, Egger M, Heller RF & Zwahlen M 2008*b* Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* **371** 569–578. (doi:10.1016/S0140-6736(08)60269-X)

Renehan AG, Soerjomataram I, Tyson M, Egger M, Zwahlen M, Coebergh JW & Buchan I 2010 Incident cancer burden attributable to excess body mass index in 30 European countries. *International Journal of Cancer* **126** 692–702. (doi:10.1002/ijc.24803)

Tabak AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimaki M & Witte DR 2009 Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. *Lancet* **373** 2215–2221. (doi:10.1016/S0140-6736(09)60619-X)

Tang N, Zhou B, Wang B & Yu R 2009 Coffee consumption and risk of breast cancer: a metaanalysis. *American Journal of Obstetrics and Gynecology* **290** e291–e299.

Tang N, Wu Y, Ma J, Wang B & Yu R 2010 Coffee consumption and risk of lung cancer: a meta-analysis. *Lung Cancer* **67** 17–22. (doi:10.1016/j.lungcan.2009.03.012)

Tardon A, Lee WJ, Delgado-Rodriguez M, Dosemeci M, Albanes D, Hoover R & Blair A 2005 Leisure-time physical activity and lung cancer: a meta-analysis. *Cancer Causes & Control* **16** 389–397. (doi:10.1007/s10552-004-5026-9)

Tsugane S & Inoue M 2010 Insulin resistance and cancer: epidemiological evidence. *Cancer Science* **101** 1073–1079. (doi:10.1111/j.1349-7006.2010.01521.x)

Tunnicliffe JM & Shearer J 2008 Coffee, glucose homeostasis, and insulin resistance: physiological mechanisms and mediators. *Applied Physiology, Nutrition, and Metabolism* **33** 1290–1300. (doi:10.1139/H08-123)

Turati F, Galeone C, La Vecchia C, Garavello W & Tavani A 2011 Coffee and cancers of the upper digestive and respiratory tracts: meta-analyses of observational studies. *Annals of Oncology* **22** 536–544. (doi:10.1093/annonc/mdq603)

Turati F, Galeone C, Edefonti V, Ferraroni M, Lagiou P, La Vecchia C & Tavani A 2012 A meta-analysis of coffee consumption and pancreatic cancer. *Annals of Oncology* **23** 311–318. (doi:10.1093/annonc/mdr331)

Wang P, Kang D, Cao W, Wang Y & Liu Z 2012 Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. *Diabetes/Metabolism Research and Reviews* **28** 109–122. (doi:10.1002/dmrr.1291)

WCRF/AICR Ed 2007 *World Cancer Research Fund/ American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective.* Washington DC: AICR.

Westerlind KC 2003 Physical activity and cancer prevention – mechanisms. *Medicine and Science in Sports and Exercise* **35** 1834–1840. (doi:10.1249/01.MSS.0000093619.37805.B7)

Wolin KY, Yan Y, Colditz GA & Lee IM 2009 Physical activity and colon cancer prevention: a meta-analysis. *British Journal of Cancer* **100** 611–616. (doi:10.1038/sj.bjc.6604917)

Yamaji T, Mizoue T, Tabata S, Ogawa S, Yamaguchi K, Shimizu E, Mineshita M & Kono S 2004 Coffee consumption and glucose tolerance status in middle-aged Japanese men. *Diabetologia* **47** 2145–2151. (doi:10.1007/s00125-004-1590-5)

Zheng W, McLerran DF, Rolland B, Zhang X, Inoue M, Matsuo K, He J, Gupta PC, Ramadas K, Tsugane S *et al.* 2011 Association between body-mass index and risk of death in more than 1 million Asians. *New England Journal of Medicine* **364** 719–729. (doi:10.1056/NEJMoa1010679)

Received in final form 3 July 2012
Accepted 31 July 2012
Made available online as an Accepted Preprint
31 July 2012

British Journal of Nutrition (2013), **109**, 1089–1095
doi:10.1017/S0007114512002954

Vitamin C supplementation in relation to inflammation in individuals with atrophic gastritis: a randomised controlled trial in Japan

Enbo Ma[1], Shizuka Sasazuki[2]*, Satoshi Sasaki[3], Yoshitaka Tsubono[2], Shunji Okubo[4] and Shoichiro Tsugane[2]

[1]*Department of Epidemiology, Faculty of Medicine, University of Tsukuba, Ibaraki 305-8575, Japan*
[2]*Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Research Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*
[3]*Department of Social and Preventive Epidemiology, Graduate School of Medicine, University of Tokyo, Tokyo 113-0033, Japan*
[4]*Hiraka General Hospital, Akita 013-8610, Japan*

(Submitted 7 March 2012 – Final revision received 17 May 2012 – Accepted 17 May 2012 – First published online 24 July 2012)

Abstract

Evidence has shown that both C-reactive protein (CRP) and serum amyloid component A (SAA) are increased in individuals with gastritis and stomach cancer. Controlling the level of these biomarkers by inhibiting the gastric infection with high doses of ascorbic acid may reduce the risk of carcinogenesis. A population-based double-blind randomised controlled trial in a Japanese population with atrophic gastritis in an area of high stomach cancer incidence was conducted between 1995 and 2000. Daily doses of 50 or 500 mg vitamin C were given, and 120 and 124 participants completed the 5-year study, respectively. Although serum ascorbic acid was higher in the high-dosage group (1·73 (SD 0·46) μg/l) than in the low-dosage group (1·49 (SD 0·29) μg/l, $P<0·001$), at the end of the study, no significant difference was observed for CRP between the low- and high-dosage groups (0·39 (95 % CI 0·04, 4·19) mg/l and 0·38 (95 % CI 0·03, 4·31) mg/l, respectively; $P=0·63$) or for SAA between the low- and high-dosage groups (3·94 (95 % CI 1·04, 14·84) μg/ml and 3·85 (95 % CI 0·99, 14·92) μg/ml, respectively; $P=0·61$). Vitamin C supplementation may not have a strong effect on reducing infections in individuals with atrophic gastritis.

Key words: Ascorbic acid: C-reactive protein: Serum amyloid component A: Atrophic gastritis

Chronic gastritis, caused by *Helicobacter pylori* infection, is an early-stage precursor for gastric adenocarcinoma[1,2]. However, gastric carcinogenesis may result from a combination of factors, particularly in individuals who react strongly to inflammation or demonstrate a strong immune response[3]. C-reactive protein (CRP) and serum amyloid component A (SAA) are acute-phase inflammatory reactants in the human body that increase in parallel[3,4]. Evidence has shown that both CRP and SAA are increased in individuals with gastritis and stomach cancer[3,5,6]. Vitamin C has been suggested to have roles in inhibiting the growth of *H. pylori*, inhibiting intragastric formation of nitrosamines and regulating the immune response[7–9]. Controlling the level of these biomarkers may reduce the risk of carcinogenesis in the stomach. Therefore, we hypothesise that a high serum level of ascorbic acid may reduce stomach cancer risk via control of the inflammatory markers CRP and SAA.

A population-based double-blind randomised controlled trial in a Japanese population with gastritis in an area of high stomach cancer incidence was conducted between 1995 and 2000, with the aim of examining the effect of vitamin C supplementation on the primary prevention of gastric cancer[10,11]. We report the impact of vitamin C supplementation on CRP and SAA status in trial subjects at the end of the 5-year period.

Materials and methods

Study participants

The trial was initially intended to examine the effects of supplementation with β-carotene (0 or 15 mg/d) and vitamin C (50 or 500 mg/d) on the incidence of gastric cancer, whereby participants were randomised in a double-blind manner to one of four groups by using a 2 × 2 factorial design. A total

Abbreviations: CRP, C-reactive protein; PG, pepsinogen; SAA, serum amyloid component A.

* **Corresponding author:** S. Sasazuki, fax +81 3 3547 8578, email ssasazuk@ncc.go.jp