表7. ピロリ菌感染と背景要因

	H. pylori 陰性 n=550	%	陽性 n=367	%
性				
男	266	48.4%	205	55.9%
女	284	51.6%	162	44.1%
年齢				
<=30	149	27.1%	29	7.9%
31-40	137	24.9%	33	9.0%
41-50	86	15.6%	63	17.2%
51-60	72	13.1%	105	28.6%
61-70	67	12.2%	94	25.6%
71-	39	7.1%	43	11.7%
喫煙				
PY<5	354	64.4%	206	56.1%
5 <= PY <20	92	16.7%	64	17.4%
20 <= PY <40	60	10.9%	43	11.7%
PY >=40	44	8.0%	54	14.7%

表8.萎縮性胃炎の有無と背景要因

	萎縮性胃炎 陰性 n=657	%	陽性 n=259	%
性				
男	346	52.7%	125	48.3%
女	311	47.3%	134	51.7%
年齢				
<=30	166	25.3%	12	4.6%
31-40	160	24.4%	10	3.9%
41-50	114	17.4%	35	13.5%
51-60	102	15.5%	75	29.0%
61-70	88	13.4%	73	28.2%
71-	27	4.1%	54	20.8%
喫煙				
PY<5	402	61.2%	157	60.6%
5 <= PY <20	118	18.0%	38	14.7%
20 <= PY <40	79	12.0%	24	9.3%
PY >=40	58	8.8%	40	15.4%

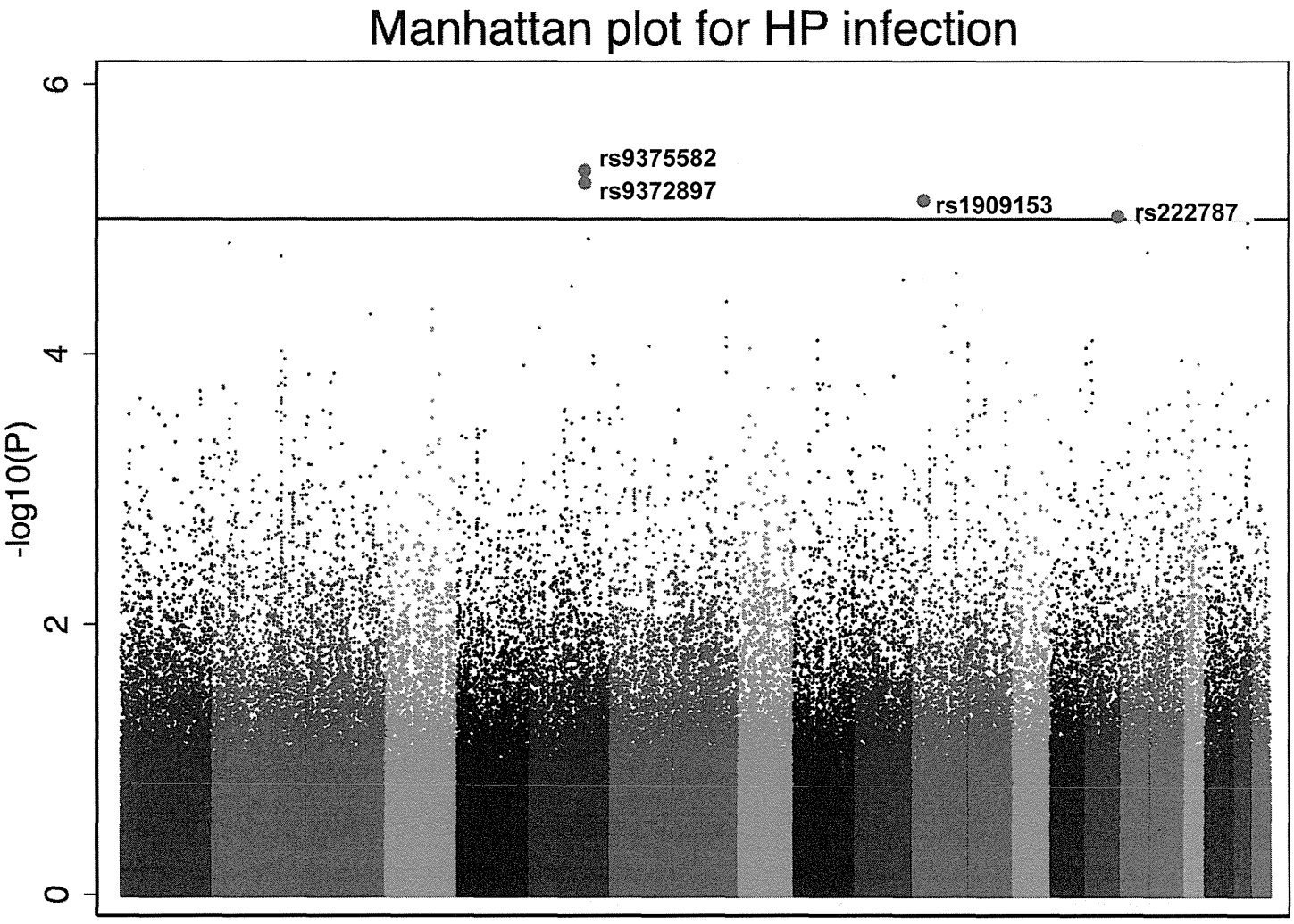

図 4. ピロリ菌感染に関するマンハッタンプロット

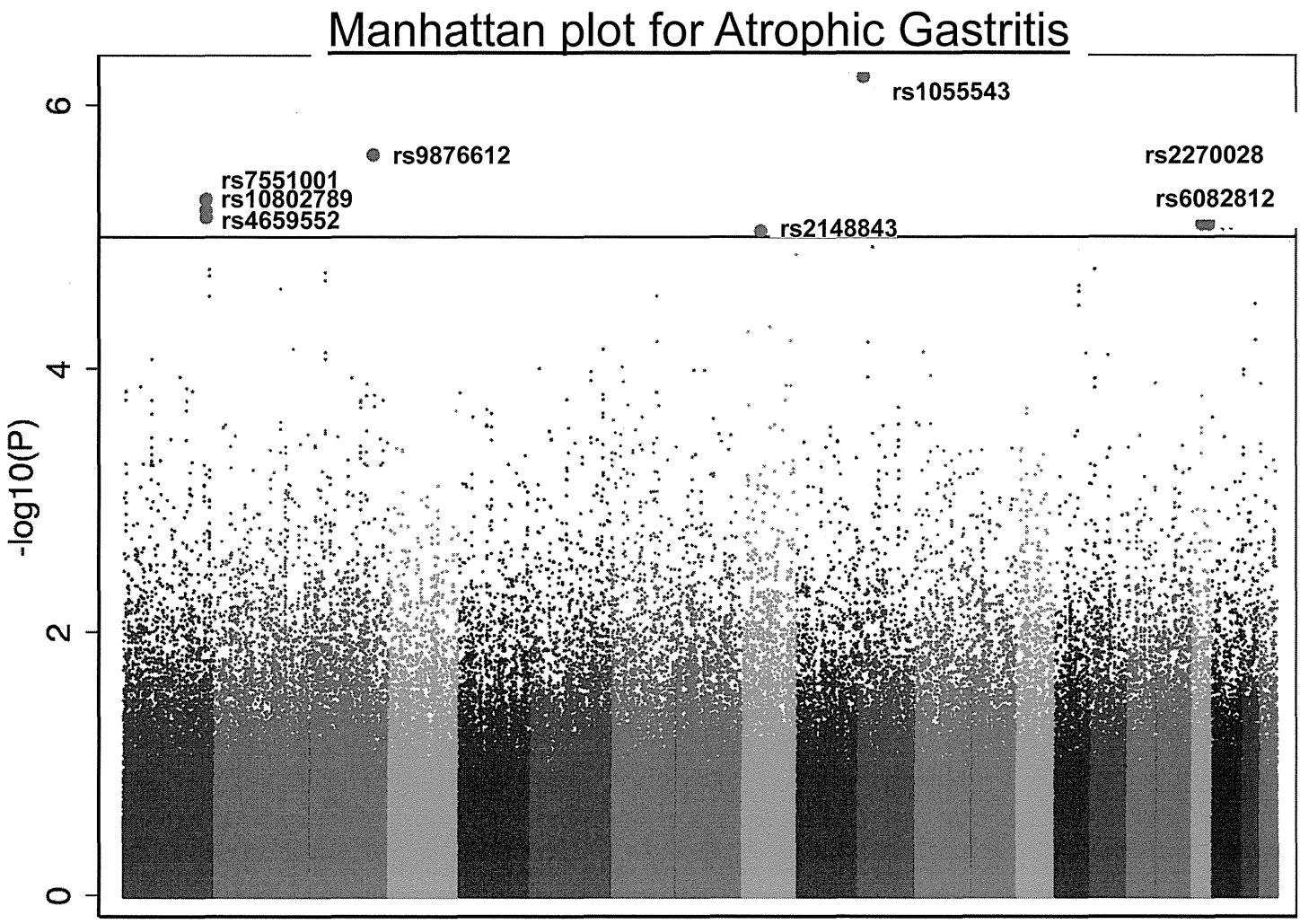

図 5.萎縮性胃炎に関するマンハッタンプロット

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
Sasazuki S, Tamakoshi A, Matsuo K, Ito H, Wakai K, Nagata C, Mizoue T, Tanaka K, Tsuji I, Inoue M, Tsugane S	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
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FOCUS REVIEW

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

Insulin resistance and cancer: epidemiological evidence

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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

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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 ≥ 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.

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Green Tea Consumption and Gastric Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence Among the Japanese Population

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Objective: Numerous *in vitro* and animal studies have shown that green tea has a protective effect against cancer. However, results from epidemiologic studies are conflicting. We evaluated the association between green tea consumption and risk for gastric cancer risk among the Japanese population based on a systematic review of epidemiologic evidence.
Methods: Original data were obtained from MEDLINE searches using PubMed or from searches of the *Ichushi* database, complemented with manual searches. Evaluation of associations was based on the strength of evidence and the magnitude of association, together with biologic plausibility.
Results: Eight cohort studies and three case–control studies were identified. Overall, we found no preventive effect on gastric cancer for green tea intake in cohort studies. However, a small, consistent risk reduction limited to women was observed, which was confirmed by pooling data of six cohort studies (hazard ratio = 0.79, 95% confidence interval 0.65–0.96 with $\geq$5 cups/day of green tea intake). Case–control studies consistently showed a weak inverse association between green tea intake and gastric cancer risk.
Conclusions: We conclude that green tea possibly decreases the risk of gastric cancer in women. However, epidemiologic evidence is still insufficient to demonstrate any association in men.

Key words: systematic review – epidemiology – green tea – gastric cancer – Japanese

BACKGROUND

Although the age-standardized mortality rate has been continuously declining, gastric cancer is still the second leading cause of cancer deaths among men and women in Japan (1). In addition to *Helicobacter pylori* infection or cigarette smoking, dietary factors are suggested to be associated with gastric carcinogenesis (2).

Numerous *in vitro* and animal studies have shown that green tea has a protective effect against cancer (3). These experimental studies have suggested that green tea polyphenols might have a protective effect against gastric cancer through its apoptosis-inducing, antimutagenic and antioxidant activities. In 1997, a review of the World Cancer Research Fund, based on the results of case–control studies and several animal models that showed a protective effect of green tea, stated that 'green tea possibly reduce the risk of stomach cancer' (4). Since then, results from cohort studies generally have not supported the findings from case–control studies, and the more recent 2007 report concluded that 'the evidence was so limited that no firm conclusion can be made' (5).

In Japan, green tea is one of the most commonly consumed beverages, and therefore, the effect of green tea on the risk for gastric cancer may be of particular concern. We reviewed epidemiologic studies of green tea consumption and gastric cancer risk among Japanese. This work was conducted as a systematic review of epidemiologic studies on lifestyle factors and cancer based on previous publications targeting Japanese (6).

METHODS

Research Review

Details of the evaluation method have been described previously (6). Briefly, original data for this review were identified through searches of the MEDLINE (PubMed) and *Ichushi (Japana Centra Revuo Medicina)* databases, complemented by manual searches of references from relevant articles where necessary. All epidemiologic studies on the association between green tea intake and gastric cancer incidence/mortality among the Japanese from 1950 (or 1983 for the *Ichushi* database) to June 2011 were identified using the search terms 'green tea', 'tea', 'gastric cancer', 'stomach cancer', 'cancer', 'cohort study', 'case-control study', 'Japan' and 'Japanese' as key words. In addition, we manually searched through references from relevant articles where necessary. Papers written in either English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included. In the case of multiple publications of analyses of the same or overlapping data sets, only data from the largest or the most recent studies were included. The individual results were summarized in the tables separately as cohort or case–control studies. Pooled data of Japanese cohort studies, including some of the individual studies already listed, were also available through the review process. To better understand the results from individual studies and finally evaluate the evidence for green tea intake and gastric cancer risk in Japanese, findings from recent pooled analyses were also listed and considered in this report.

Evaluation of Strength of Association Between Green Tea Intake and Gastric Cancer Risk

The evaluation was made based on the magnitude of association and the strength of evidence. First, the former was assessed by classifying the relative risk (RR) in each study into the following four categories, while considering statistical significance (SS) or no statistical significance (NS), as strong (symbol ↓↓↓ or ↑↑↑), <0.5 or >2.0 (SS); moderate (symbol ↓↓ or ↑↑), either (i) <0.5 or >2.0 (NS), (ii) >1.5–2 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↓ or ↑), either (i) >1.5–2 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association (symbol –), 0.67–1.5 (NS). In cases where the frequency or amount of green tea intake had been separated into levels in a study, we used the RR derived from comparing the highest intake with the lowest. To consider the intermediate categories of intake, however, the *P* value for the trend was also considered when judging the statistical significance. After this process, the strength of evidence was evaluated in a manner similar to that used in the WHO/FAO Expert Consultation Report, where evidence was classified as convincing, probable, possible and insufficient (7). We assumed that biologic plausibility was based on evidence in experimental models, human studies and other relevant data.

MAIN FEATURES AND COMMENTS

Through the review process, we identified eight cohort studies (8–15), one pooled analysis of six cohort studies (16) (Table 1) and three case–control studies (17–19) (Table 2). Among cohort studies, the events followed were death in five studies (8,10,12,14,15) and incidence in the other three studies (9,11,13). Five studies showed the results for men and women separately (9,10–14), whereas three studies showed combined results only (8,13,15). The pooled analysis included four cohorts (9,10 and two cohorts in 11) listed in Table 1 and two other cohorts (20,21). For all case–control studies, the results were shown for men and women combined.

The summary of the magnitudes of association for the cohort study and the case–control study is presented in Tables 3 and 4, respectively. As shown in Table 3, among eight cohort studies, one study showed a weak positive association between green tea intake and gastric cancer risk in men (9). Women in the study and all other studies showed no association at all. When the anatomic subsite was considered, one study observed a moderate inverse association for distal cancer in women (11). On the other hand, case–

Table 1. Gastric cancer risk and consumption of green tea in cohort studies of Japanese populations

References	*Study period*	*Study population*				Category	No. among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	*Comments*
Author		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths						
Nakachi et al. (8)	1986–99	8552	Population-based Saitama Prefecture	Death	140	Green tea, cups/day				Sex and lifestyle factors	
						≤3		1.0			
						≥10		0.69 (0.23–1.88)			
Tsubono et al. (9)	1984–92	26 311	Population-based Miyagi Prefecture	Incidence	419	Green tea, cups/day				Age, sex, types of health insurance, history of peptic ulcer, smoking status, alcohol consumption, daily consumption of rice, black tea, coffee, meat, green or yellow vegetables, pickled vegetables, other vegetables, fruits and bean-paste soup	
		11 902 men			296 men	Total					
		14 409 women			123 women	<1	66	1.0			
						1–2	68	1.1 (0.8–1.6)			
						3–4	79	1.0 (0.7–1.4)			
						≥5	206	1.2 (0.9–1.6)	0.13		
						Men					
						<1	41	1.0			
						1–2	49	1.3 (0.8–1.9)			
						3–4	55	1.2 (0.8–1.8)			
						≥5	151	1.5 (1.0–2.1)	0.03		
						Women					
						<1	25	1.0			
						1–2	19	0.8 (0.5–1.5)			
						3–4	24	0.7 (0.4–1.3)			
						≥5	55	0.8 (0.5–1.3)	0.46		
Hoshiyama et al. (10)	Mean 8 years	72 851	Population-based 45 areas of Japan	Death	359	Green tea, cups/day				Age, smoking status, history of peptic ulcer, family history of stomach cancer, consumption of rice, miso soup, green– yellow vegetables, white vegetables, fruits and preference for salty foods	
		30 370 men			240 men	Men					
		42 481 women			119 women	<1	24	1.0			
						1–2	51	1.6 (0.9–2.9)			
						3–4	51	1.1 (0.6–1.9)			
						5–9	76	1.1 (0.6–1.9)			
						≥10	38	1.0 (0.5–2.0)	0.634		
						Women					
						<1	20	1.0			
						1–2	18	1.1 (0.5–2.5)			
						3–4	40	1.0 (0.5–2.1)			
						5–9	32	0.8 (0.4–1.6)			
						≥10	9	0.7 (0.3–2.0)	0.476		

Continued

Table 1. *Continued*

References	Study period	Study population				Category	No. among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
Author		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths						
Sasazuki et al. (11)	1990–2001	72,943	Population-based	Incidence	892	Green tea, cups/day				Age, area, cigarette smoking, consumption of fruits, green or yellow vegetables, fishgut, miso soup, black tea and coffee	
		34,832 men			665 men	Men					
		38,111 women			227 women	All sites					
						<1		1.0			
						1–2		0.95 (0.72–1.22)			
						3–4		0.84 (0.65–1.08)			
						≥5		0.98 (0.77–1.25)	0.65		
						Upper-third including cardia					
						<1		1.0			
						1–2		1.06 (0.51–2.18)			
						3–4		0.73 (0.34–1.57)			
						≥5		1.17 (0.60–2.30)	0.75		
						Distal					
						<1		1.0			
						1–2		0.88 (0.64–1.20)			
						3–4		0.79 (0.59–1.07)			
						≥5		0.92 (0.69–1.22)	0.37		
						Women					
						All sites					
						<1		1.0			
						1–2		0.85 (0.53–1.38)			
						3–4		1.04 (0.68–1.58)			
						≥5		0.67 (0.43–1.04)	0.08		
						Upper-third including cardia					
						<1		1.0			
						1–2					
						3–4		0.89 (0.34–2.33)			
						≥5			0.81		
						Distal					
						<1		1.0			
						1–2		0.88 (0.52–1.49)			
						3–4		1.00 (0.63–1.59)			
						≥5		0.51 (0.30–0.86)	0.01		

Khan et al. (12)	1984–2002	3158	Population-based Hokkaido	Death	51	Men				Age, smoking, health status, health education, health screening
		1524 men			36 men	Green tea ≤ several times/month		1.0		
		1634 women			15 women	Green tea ≥ several times/week		1.1 (0.4–2.5)		
						Women				
						Green tea ≤ several times/month		1.0		
						Green tea ≥ several times/week		0.7 (0.2–2.9)		
Sauvaget et al. (13)	1980–99	38 576	Atomic-bomb survivors: Hiroshima, Nagasaki	Incidence	1270	Green tea, cups/day				Sex, sex-specific age, city, radiation dose, sex-specific smoking habits and education level
		14 885 men				<2	242	1.0		
		23 691 women				2–4	680	1.03 (0.89–1.19)		
		34–98 years old				≥5	348	1.06 (0.89–1.25)	>0.50	
Kuriyama et al. (14)	All-cause	40 530	Population-based	Death	193	Green tea, cups/day				Age, sex, job status, years of education, BMI, sports or exercise, walking duration, history of HT, DM, GU, smoking, alcohol, total energy, rice, miso soup, soy bean product, total meat, total fish, dairy products, total fruits, total vegetables, oolong tea, black tea, and coffee
	1995–2005 (11 years)	19 060 men				<1	44	1.0		
		21 470 women				1–2	44	1.33 (0.86–2.04)		
	Cause-specific					3–4	38	1.00 (0.64–1.58)		
	1995–2001 (7 years)					5≤	67	1.17 (0.78–1.76)	0.72	
					138 men	<1	32	1.0		
						1–2	30	1.29 (0.78–2.16)		
						3–4	30	1.19 (0.71–2.00)		
						≥5	46	1.20 (0.74–1.95)	0.55	
					55 women	<1	12	1.0		
						1–2	14	1.32 (0.59–2.94)		
						3–4	8	0.64 (0.26–1.63)		
						≥5	21	1.08 (0.50–2.33)	0.84	
Suzuki et al. (15)	1999–2006	12 251	Population randomly chosen from all 74 municipalities in Shizuoka Prefecture	Death	68	Green tea, cups/day				Age, sex, smoking, alcohol, BMI, and physical activity
		6231 men				<1	2	1.0	Test for trend: HR = 1.04 (0.95–1.13)	
		6020 women				1–3	14	0.49 (0.11–2.28)		
		65–84y old				4–6	32	0.78 (0.19–3.30)		
						≥7	20	0.81 (0.18–3.54)		

Continued

Table 1. *Continued*

References	Study period	Study population				Category	No. among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
Author		No. of subjects for analysis	Source of subjects	Event followed	No. of incident cases or deaths						
Pooled analysis of 6 cohort studies including those listed above (9,10, cohort I of 11, cohort II of 11) or mentioned in the text (20 and 21)											
Inoue et al. (16)	1985–2004	219 080	Population-based	Incidence	3577	Green tea, cups/day					
		100 479 men			2495 men	Men				Age, area (for three cohorts only), smoking, alcohol drinking, rice, soy bean paste soup, coffee, pickled vegetables, and green-yellow vegetables intake	
		118 601 women			1082 women	All sites					
						<1	420	1.0			
						1–2	452	0.97 (0.83–1.12)			
						3–4	610	0.93 (0.81–1.08)			
						≥5	1013	1.06 (0.86–1.30)	0.74		
						Proximal (upper third)					
						<1	38	1.0			
						1–2	41	1.10 (0.70–1.73)			
						3–4	42	0.79 (0.46–1.35)			
						≥5	96	1.43 (0.96–2.14)	0.08		
						Distal (lower two-thirds)					
						<1	185	1.0			
						1–2	185	0.91 (0.73–1.12)			
						3–4	249	0.95 (0.77–1.16)			
						≥5	328	0.96 (0.79–1.17)	0.86		
						Women					
						All sites					
						<1	215	1.0			
						1–2	174	0.90 (0.73–1.10)			
						3–4	303	0.92 (0.76–1.11)			
						≥5	390	0.79 (0.65–0.96)	0.04		
						Proximal (upper third)					
						<1	8	1.0			
						≥1	45	1.17 (0.52–2.60)	0.87		
						Distal (lower two thirds)					
						<1	83	1.0			
						1–2	64	0.80 (0.57–1.13)			
						3–4	117	0.96 (0.71–1.30)			
						≥5	106	0.70 (0.50–0.96)	0.04		

NS, not significant; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; GU, gastric ulcer.

Table 2. Gastric cancer risk and consumption of green tea in case–control studies of Japanese populations

References	Study time	Study subjects				Category	Relative risk (95% CI)	*P* for trend	Confounding variables considered	Comments
Author		Type and source	Definition	No. of cases	No. of controls					
Tajima and Tominaga (17)	1981–83	Hospital-based (Aichi Cancer Center)	Cases:	93	186	Green tea, times/day			Matched for age (±5 years), sex, time of interviews (±6 months)	
			Histologically confirmed cases			≥4	0.64	NS		
			Controls:			≤3	1.0			
			Patients without stomach cancer							
Kono et al. (18)	1979–82	Hospital-based (Karatsu Stomach Institute)	Cases:	139	Hospital controls: 2574	vs. hospital controls				
			Newly diagnosed as having gastric cancer at the Institute	74 men		Green tea, cups/day				
				65 women	1171 men	None or 1–4	1.0		Age, sex	
					1403 women	5–9	1.1			
						≥10	0.6	NS		
			Hospital controls:		General controls;					
			Patients without gastric cancer		278	≤9	1.0		Age, sex, smoking, oranges, fruits	
					148 men	≥10	0.5 (0.3–1.1)			
			General population controls:		130 women					
			Random sampling from the computerized file of residents			vs. general controls			General population:	
						Green tea, cups/day			Matched (1:2) for	
						None or 1–4	1.0		Sex	
						5–9	1.2		Age	
						≥10	0.4*	NS		
						≤9	1.0		Smoking, oranges, fruits	
						≥10	0.3 (0.1–0.7)†			

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