

findings, so caution is needed in interpreting our results. Indeed, the probability of mistakenly concluding that a particular association is different from nil increases with the number of hypotheses tested. A correction for multiple testing, such as the Bonferroni procedure, is often used to control the overall probability of incorrectly rejecting at least one null hypothesis under the assumption that all null hypotheses (e.g. absence of effect) are simultaneously true.^(39,40) This procedure was not conducted because this would not answer our research question; that is, the assessment of the separate relationships between diabetes and each cancer site. The diagnosis of diabetes was based on self-report in all studies. According to a validation study conducted as part of one of the studies, self-reported diabetes exhibits fairly good agreement with diabetes documented in medical records (94%).⁽⁴¹⁾ Case ascertainment based on self-reporting might result in either overreporting or underreporting, and these misclassifications would bias the association toward the null. In addition, type 1 and type 2 diabetes were not distinguished. However, because type 1 diabetes is less frequent than type 2 diabetes, especially in adult populations, it would be reasonable to suppose that most of the subjects had type 2 diabetes. Despite the large number of person-years, the number of cases of some site-specific cancers was only moderate. Finally, there may be some concerns about observational studies not providing an appropriate time reference for estimating the time-at-risk of participants. Korn *et al.*⁽⁴²⁾ recommend the use of age as a more natural and appropriate time scale that allows one to take into account the left truncated nature of the data. However, Pencina *et al.*⁽⁴³⁾ show that provided age is properly taken into account in the Cox model, the choice of one or the other time scale has no meaningful impact on the parameter estimates. In addition, Chalise *et al.*⁽⁴⁴⁾ conducted a simulation study which showed that Cox models using time-on-study as the time scale were robust to misspecification of the true underlying time scale. An analysis conducted on two of the studies included in our pooled analysis using age as the time scale showed that results in terms of relative risk of the association between diabetes and each of the considered cancer sites were very similar to those obtained using time-on-study. Therefore, we decided to present results based on time-on-study as time-scale Cox

models because this allowed us to preserve coherence with already published results.^(12,22,23)

The strength of the present study is that it includes most of the ongoing prospective studies in Japan, with overlapping birth generations and a similar survey period. Therefore, pooling of these studies allows for a stable quantitative estimate of the impact of diabetes among Japanese people. In the included studies, diabetes was measured before cancer diagnosis, which precludes the possibility of selection and recall bias. In addition, as mentioned above, the covariates were adequately controlled across studies, which removes a potential source of heterogeneity that can occur in a meta-analysis of published literature. The use of incidence rather than mortality as an end point is advantageous because it enables us to directly determine the contribution of diabetes to cancer risk.

In summary, by pooling data from eight cohort studies with a considerable number of subjects, statistically increased risk was observed for cancers at specific sites, such as colon (HR = 1.40), liver (HR = 1.97), pancreas (HR = 1.85) and bile duct (HR = 1.66; men only). Increased risk was also suggested for other sites and, as a whole, diabetes mellitus was associated with a 20% increase in the risk of total cancer incidence in the Japanese population.

The association between these two diseases has important implications for reiterating the importance of controlling lifestyle factors, and it may suggest a possible strategy for cancer screening among patients with diabetes. Furthermore, considering the increasing prevalence of diabetes worldwide and its association with cancer, studies continuously investigating the risk factors for diabetes are important.

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Disclosure Statement

The authors have no conflict of interest.

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Appendix 1

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

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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) $\mu\text{g/l}$) than in the low-dosage group (1.49 (sd 0.29) $\mu\text{g/l}$, $P < 0.001$), 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) $\mu\text{g/ml}$ and 3.85 (95% CI 0.99, 14.92) $\mu\text{g/ml}$, 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 \times 2 factorial design. A total

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

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of 1231 subjects who were aged 40–69 years and living in four municipalities of the Yokote Public Health Center District of Akita Prefecture were selected to participate in the randomised clinical trial. After the first year of participants' recruitment in 1995, β -carotene supplementation was reported to have potential harmful effects for individuals at high risk for lung cancer^(12,13), and the study protocol was modified by removing subjects who were using β -carotene and stopping recruitment of new subjects in three municipalities⁽¹⁰⁾. The primary endpoint of the trial was changed from a 10-year accumulated incidence of gastric cancer to 5-year changes of the serum levels of pepsinogen (PG) and other biomarkers⁽¹⁰⁾. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the ethics committee of the National Cancer Center and the Hiraka General Hospital. Written informed consents were obtained from all individuals willing to participate and those remaining in the study. Finally, 120 and 124 subjects in the low-dosage and high-dosage groups of vitamin C supplementation, respectively, completed the 5-year study (Fig. 1). The details of the study rationale, design, methodology and protocol amendment have been described previously^(10,11).

Eligible subjects were diagnosed with chronic atrophic gastritis by the cut-off value of PGI < 70 ng/ml and a ratio of PGI:II of < 3.0, of which the sensitivity was 80% and specificity was 70% as reported⁽¹⁴⁾. Miki⁽¹⁵⁾ reported that the values measured by the same kit showed a good correlation (correlation coefficient 0.983 for PGI, 0.991 for PGII and 0.935 for PGI:II) with those measured by RIA (PGI/PGII RIA-BEAD; Dinabot Company Limited), in which a sensitivity of 70.5% and a specificity of 97.0% for atrophic gastritis, compared with histology, have been reported⁽¹⁶⁾. Selection criteria were no history of gastric cancer or related surgery; no history of cirrhosis, liver cancer or other cancer within the last 5 years; no abnormal liver function; no use of diet supplements containing β -carotene or vitamin C; and no expectation of moving outside the study area within 1 year.

Participant follow-up and dietary intake assessment

Participants were asked to visit the community centres every 3 months where their clinical symptoms and side effects from vitamin C supplementation were assessed, compliance was checked based on the number of unconsumed capsules, and capsules for further use were dispensed^(10,11). Compliance averaged 92.6 and 92.2% in the low- and high-dosage groups,

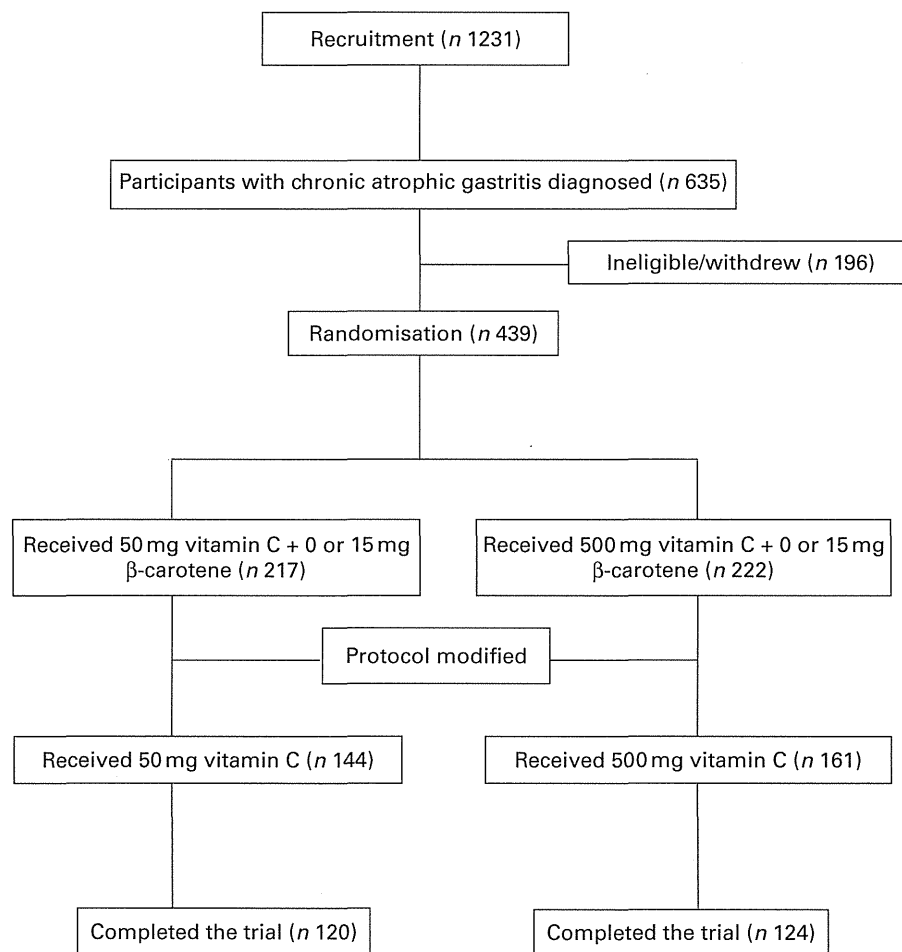


Fig. 1. Flow chart of participant recruitment before and after the protocol amendment and of participants at the 5-year follow-up.

respectively⁽¹⁷⁾. A validated 138-item FFQ was used to assess dietary intake, for which participants were asked how often they consumed individual food items and to estimate the representative size of their portions relative to the size of a standard portion. Daily intake of vitamin C and other nutrients were calculated by using the fifth revised and enlarged edition of the Standard Tables of Food Composition in Japan⁽¹⁸⁾. The details of the FFQ have been described in a previous report^(11,17).

Biochemical analysis

Fasting blood samples were collected at baseline and after 5 years and analysed for serum ascorbic acid levels, CRP and SAA. The subjects were asked not to eat or drink anything except water after 21.00 hours on the day before blood sampling. The serum was sampled between 07.00 and 10.00 hours. All samples were stored at -70 to -85°C and were analysed simultaneously after completion of the 5-year follow-up. All assays were conducted by persons who were blinded as to the intervention assignment and the questionnaire data.

Serum for ascorbic acid measurement was stabilised by the addition of metaphosphoric acid, and serum ascorbic acid concentration was measured fluorimetrically (iodine oxidation and condensation with 1,2-phenylenediamine). CRP and SAA concentrations were determined by the latex agglutination nephelometric immunoassay test (LZ test 'Eiken' CRP-HG and LZ test 'Eiken' SAA, respectively; Eiken Kagaku Company Limited). IgG antibodies to *H. pylori* were measured with a direct ELISA kit (E Plate 'Eiken' *H. pylori* antibody; Eiken Kagaku Company Limited). Levels of IgG were categorised as seropositive and seronegative for *H. pylori* according to the selected cut-off value (492 nm)⁽¹⁹⁾.

Statistical analysis

We followed the intent-to-treat analysis, which included all subjects remaining in the study after the protocol was modified. The per-protocol analysis included subjects who completed the study to the 5-year follow-up. Baseline comparisons between the low- and high-dosage groups and the dropout group as the control were examined by one-way ANOVA for continuous variables and by the χ^2 test for categorical variables. Differences of values within the low- and high-dosage groups were tested by the paired *t* test for continuous variables and by the one-sample *z* test for proportions.

CRP was categorised into positive and negative groups by using a cut-off point of 1.8 mg/l, while SAA was grouped as positive or negative based on a cut-off point of 8.0 $\mu\text{g/ml}$ ⁽³⁾. Subjects' status on combined biomarkers of CRP and SAA was determined by the defined positive and negative statuses of CRP and SAA. Log transformation was done for dietary intake of vitamin C, serum CRP and SAA, and *H. pylori* titre when conducting the comparisons between the two dosage groups; and data are presented as geometric means with their standard errors. The difference between the two

dosage groups for changes in CRP and SAA at the end of the 5-year follow-up compared with baseline was calculated by using the geometric means, respectively.

Adjusted analysis of the means of serum CRP and SAA for covariates was performed by one-way ANOVA. Results were adjusted for age (continuous), sex, dietary intake of vitamin C (quartile), alcohol consumption (never or occasional, regular), smoking status (never, ever), BMI (<25 , ≥ 25 kg/m²), *H. pylori* status (no, yes) and menopausal status (no, yes, for women). Stratified analysis was performed for age groups, alcohol consumption, smoking status, BMI and menopausal status. *P* values less than 0.05 in two-tailed tests were considered as significant, and all statistical analyses were performed using SAS version 9.1 (SAS Institute).

Results

The baseline characteristics of the trial participants are shown in Table 1. Subjects in the low-dosage group were older than those in the high-dosage group. There were more CRP-positive subjects in the high-dosage group than in the low-dosage group both in the intent-to-treat and per-protocol analyses (borderline significance). *H. pylori* titres were higher in the high-dosage group than in the low-dosage group, with a significant difference in the per-protocol analysis.

At the 5-year follow-up, serum ascorbic acid was higher in the high-dosage group (increased 0.37 $\mu\text{g/l}$) compared with the low-dosage group (increased 0.10 $\mu\text{g/l}$ from baseline, $P<0.001$) (Table 2). Correlation of the log-transformed CRP and SAA in all participants at the 5-year follow-up was 0.541 ($P<0.001$). A slight increase in the low-dose group and a decrease in the high-dose group both in CRP and SAA levels were observed at the 5-year follow-up; thus the absolute 0.07 mg/l reductions in CRP and the 0.31 $\mu\text{g/ml}$ reduction in SAA were in the high-dose group compared with those in the low-dose group, if taking consideration of the baseline values. However, there were no significant differences 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) $\mu\text{g/ml}$ and 3.85 (95% CI 0.99, 14.92) $\mu\text{g/ml}$, respectively; $P=0.61$) (Table 2). CRP status changed from positive to negative for 60% (six out of ten) of the low-dosage group and 68.4% (thirteen out of nineteen) of the high-dosage group between baseline and the 5-year follow-up ($P=0.33$), while SAA status for 57.1% (eight out of fourteen) in the low-dosage group and 70.0% (seven out of ten) in the high-dosage group of SAA-positive participants changed from positive to negative ($P=0.27$). The combined positive and negative statuses for CRP and SAA were also not significantly different between the two groups at the 5-year follow-up (47.4% (nine out of nineteen) *v.* 59.1% (thirteen out of twenty-two); $P=0.23$). When we deleted two outliers that were both CRP- and SAA-positive at baseline, similar null results for CRP and SAA were observed, respectively, between the two dosage groups at the 5-year follow-up.



Table 1. Baseline characteristics of the participants in the trial
(Mean values and standard deviations or standard errors; number of participants and percentages)

	Intent-to-treat					Per-protocol				
	Low-dosage vitamin C, 50 mg (n 144)		High-dosage vitamin C, 500 mg (n 161)		P*	Low-dosage vitamin C, 50 mg (n 120)		High-dosage vitamin C, 500 mg (n 124)		P*
	n	%	n	%		n	%	n	%	
Age (years)					0.01					0.02
Mean		58.56		56.55			58.67		56.29	
SD		6.64		8.74			6.53		8.66	
BMI (kg/m ²)					0.66					0.52
Mean		23.38		23.18			23.42		23.23	
SD		2.92		2.69			2.86		2.65	
Men	54	37.5	58	36.0	0.79	41	34.2	45	36.3	0.73
Current smoking	18	12.5	26	16.2	0.65	12	10.0	19	15.3	0.38
Alcohol consumption	62	43.1	69	42.9	0.99	53	42.2	57	46.0	0.69
Serum ascorbic acid (µg/l)	1.37	0.35	1.35	0.37	0.96	1.38	0.32	1.35	0.37	0.51
Dietary vitamin C (µg/l)					0.65					0.41
Mean		121.03		120.25			123.62		123.52	
SE		1.06		1.06			1.06		1.06	
CRP (mg/l)†					0.16					0.77
Mean		0.35		0.43			0.35		0.41	
SE		1.11		1.13			1.12		1.14	
CRP positive†	11	7.6	24	14.9	0.05	10	8.3	19	15.3	0.07
SAA (µg/ml)†					0.26					0.29
Mean		3.82		4.29			3.87		4.09	
SE		1.06		1.08			1.07		1.09	
SAA positive†	16	11.1	16	9.9	0.74	14	11.7	10	8.1	0.35
<i>Helicobacter pylori</i> titre (RU/ml)					0.15					0.01
Mean		59.19		68.73			57.13		73.73	
SE		1.07		1.07			1.08		1.07	
<i>H. pylori</i> positive	140	97.2	157	97.5	0.87	116	96.7	122	98.4	0.39
PGI (ng/ml)					0.83					0.65
Mean		38.38		39.03			38.35		39.8	
SD		17.06		16.43			17.2		16.35	
PGII (ng/ml)					0.15					0.11
Mean		19.62		20.60			19.46		20.79	
SD		7.14		7.34			7.22		7.34	
PGI:II					0.20					0.24
Mean		1.95		1.89			1.97		1.92	
SD		0.63		0.61			0.62		0.59	

CRP, C-reactive protein; SAA, serum amyloid component A; RU, relevant unit; PG, pepsinogen.

* By one-way ANOVA test or χ^2 test.

† 117 subjects in the per-protocol analysis were available in the low- and high-dosage groups, respectively.

Stratified analysis showed that there were no significant differences in the decrease in CRP or SAA levels between the two dosage groups by age categories (40s, 50s and 60s), sex, smoking or alcohol consumption. Similar results were observed after adjusting for sex, dietary intake of vitamin C (quartile), *H. pylori* titre, smoking status, alcohol consumption and BMI (data not shown).

Discussion

We did not observe any significant reduction of CRP or SAA levels in the low- or high-dosage groups after 5 years of ascorbic acid supplement use, although serum ascorbic acid concentration was higher in the high-dosage group than in the low-dosage group. We also did not observe any significant differences between the two groups in age, sex, smoking, alcohol consumption or body weight status.

The CRP and SAA levels in the present study were similar to those reported in other studies^(3,20). In the present study,

based on cut-off points of 1.8 mg/l for CRP and 8.0 µg/ml for SAA, there were small numbers of CRP- or SAA-positive participants and there was no significant difference for either between the two dosage groups at baseline, respectively. We also applied other cut-off points for CRP- and SAA-positive status such as a CRP of 10 mg/l⁽²¹⁾ or by areas under the received curve⁽²²⁾. By these criteria, the numbers of CRP- or SAA-positive participants remained similar and no significant differences existed between the two dosage groups. Nevertheless, the small number of CRP- and SAA-positive participants at baseline made it difficult to evaluate changes in CRP and/or SAA status at follow-up. It might be possible that CRP and SAA were not highly sensitive markers for measuring chronic infection status, which contributed to the null outcome in the present study. On the other hand, the 500 mg/d supplement in the present study might not be sufficient to control chronic gastric infection, although cancer chemoprevention trials with more than 500 mg/d of vitamin C

Table 2. Comparisons of serum ascorbic acid and inflammatory biomarkers between baseline and the 5-year follow-up (Mean values and standard deviations or standard errors)

	Low-dosage vitamin C, 50 mg (n 117)					High-dosage vitamin C, 500 mg (n 117)					
	Baseline		5 years		P*	Baseline		5 years		P*	P†
	Mean	SE	Mean	SE		Mean	SE	Mean	SE		
Serum ascorbic acid (µg/l)					<0.01					<0.001	<0.001
Mean	1.38		1.49			1.35		1.73			
SD	0.32		0.29			0.37		0.46			
Dietary vitamin C (µg/l)	123.62	1.06	121.14	1.06	0.79	123.52	1.06	123.11	1.06	0.88	0.78
CRP (mg/l)	0.35	1.12	0.39	1.12	0.35	0.41	1.14	0.38	1.12	0.64	0.63‡
SAA (µg/ml)	3.87	1.07	3.94	1.06	0.88	4.09	1.09	3.85	1.07	0.57	0.61‡

CRP, C-reactive protein; SAA, serum amyloid component A.

* By paired *t* test.

† By one-way ANOVA test for the difference between the two dose groups at the 5-year follow-up.

‡ Adjusted for age, sex, BMI, smoking status, alcohol consumption, dietary vitamin C, *Helicobacter pylori* status and baseline level of CRP or SAA.

supplementation have not shown consistent results on the beneficial effects^(23,24).

Human gastric carcinogenesis is a multistep and multifactorial process, with the initial stages of gastritis and atrophy linked to excessive salt intake and *H. pylori* infection^(17,25). *H. pylori* eradication can prevent the progression of precancerous gastric lesions and probably reduce the incidence of gastric cancer in those without advance lesions⁽²⁶⁾. In the present study, CRP and SAA were not significantly reduced and the positive proportions of *H. pylori* were consistently higher ($\geq 92\%$) after 5 years of follow-up in both the low- and high-dosage groups⁽¹⁷⁾. It was possible that in the achlorhydric stomach, *H. pylori* infection might disappear, although the antibodies in the serum might maintain a longer time. Nevertheless, *H. pylori* infection potentially modulates the effects of vitamin C or vice versa⁽⁹⁾. Without eradicating the infection, ascorbic acid supplementation for participants with atrophic gastritis might have fewer effects on CRP/SAA control. However, studies on changes in CRP after *H. pylori* eradication are contradictory. Some studies have reported a significant reduction of CRP levels in subjects after *H. pylori* eradication by antibiotics⁽²⁷⁾ or vitamin C supplementation⁽²⁸⁾, while others have shown no significant reduction of CRP by anti-inflammatory or antibiotic treatment^(20,29,30). A Colombian study in gastritis patients, applying a 2-week anti-*H. pylori* treatment and/or a 6-year antioxidant supplement, showed that acute inflammation disappeared soon after the *H. pylori* treatment, while chronic inflammation responded at a slower pace, and the antioxidant effect was transient and disappeared after the 6 years of follow-up, while the anti-*H. pylori* treatment effect persisted for as long as patients remained free of *H. pylori*⁽²³⁾. Also, subjects with non-metaplastic multifocal atrophic gastritis had the steepest declines if they cleared the bacteria, but had the sharpest increases if they did not⁽²³⁾. The present study results appear to support the finding that ascorbic acid supplementation does not have much beneficial effect on chronic gastric infections, particularly without assigning the anti-*H. pylori* treatment.

There are several limitations in the present study. The most critical one is that we did not have a placebo group for comparison with the 50 and 500 mg dosage groups⁽³¹⁾. However,

the mean dietary intakes of vitamin C were 151.95 (SD 111.98) µg/l and 147.93 (SD 99.81) µg/l for the high- and low-dose groups, respectively, and the low-dose supplementation group was similar to or within 1 SD of the estimated vitamin C intake level from foods. In the pilot study⁽³²⁾ for the present trial, there were no significant differences in serum vitamin C concentrations between the placebo (0 mg/d) and the low-dose groups at 1, 2 and 3 months of supplementation, respectively. Moreover, the purpose of the present study was to evaluate the effect of vitamin C supplementation (500 mg/d) compared with the normal level (the average consumption level of Japanese). Additionally, the similar mean dietary intake of vitamin C in the placebo group was seen in another trial⁽³³⁾. Therefore, the low-dose vitamin C supplementation group (50 mg/d) in the present study could be regarded as the placebo group for interpretation⁽³⁴⁾. Second, the initial sample size was considered with estimated differences in accumulated gastric cancer incidence between the two study groups in 10 years rather with the changes in these biomarkers of atrophic gastritis in 5 years⁽¹⁰⁾. For example, to detect the 0.15 µg/ml difference in SAA levels between the two dose groups at the 5-year follow-up, using the standard deviation in each group, 5% type I error and 20% type II error for estimation, 1030 subjects in each group are needed. The limited number of study subjects after changes in the initial study protocol had less statistical power for identifying the significance of CRP and SAA reductions between the two dosage groups. Third, IL-6 and other immunological factors are thought to be mediators that stimulate CRP production^(5,28,35); however, we could not evaluate the CRP reduction as modified by ascorbic acid by using these factors because the data were unavailable. Since we did not conduct endoscopy for gastritis participants, we therefore could not evaluate the progression or regression of gastric lesions after ascorbic acid supplementation at the 5-year follow-up^(23,36,37). Finally, since we only tested CRP and SAA two times, at baseline and the 5-year follow-up, any changes in their levels in the intervening time were not evaluated.

Some studies have reported that antioxidant supplementation, even at low doses, can have adverse effects on subjects at high risk for cancer or those with undiagnosed cancer^(38,39).

It should be noted that some of the well-known beneficial effects of ascorbic acid administration are still only understood at the phenomenological level⁽⁴⁰⁾. Currently, the Asia–Pacific guidelines on gastric cancer prevention do not recommend vitamin C supplementation for reducing the risk of gastric cancer⁽²⁶⁾.

In summary, we did not observe a significant reduction in CRP or SAA levels in atrophic gastritis participants with ascorbic acid supplementation of less than 500 mg/d at the 5-year follow-up. The present study suggests that ascorbic acid supplementation might not have much beneficial effect in individuals with chronic *H. pylori* infection. Further studies are needed in larger populations on the control of chronic infection and inflammation through ascorbic acid supplementation.

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Report

Report of the Japan Diabetes Society/Japanese Cancer Association joint committee on diabetes and cancer

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In recent years, diabetes has been shown to be associated with cancer risk, and this has led to a joint committee being formed, enlisting experts from the Japan Diabetes Society and the Japanese Cancer Association to address this issue. Epidemiological data in Japan provides evidence to demonstrate that diabetes is associated with increased risk for cancers, especially colorectal, liver, and pancreatic cancers. The mechanisms through which diabetes is assumed to promote oncogenesis include insulin resistance and associated hyperinsulinemia, hyperglycemia, and inflammation. Common risk factors for type 2 diabetes and cancer include aging, male sex, obesity, physical inactivity, inappropriate diet (excessive red/processed meat intake, inadequate vegetable/fruit/dietary fiber intake), excessive alcohol drinking, and smoking. Given that inappropriate diet/exercise, smoking and excessive alcohol drinking are common risk factors for diabetes and cancer, diet/exercise therapy, smoking cessation and alcohol moderation may be associated with decreased risk for cancer in diabetic patients. There is as yet limited evidence as to whether any particular antidiabetic agents may influence cancer risk. (*Cancer Sci* 2013; 104: 965–976)

Background

In recent years, evidence has gradually emerged through a series of meta-analyses of available data,^(2–14) including those from Japanese patients with diabetes, demonstrating the association between diabetes and cancer risk that has long been a focus of attention. In 2010, the American Diabetes Association (ADA) and the American Cancer Society (ACS) jointly published a consensus report on the association between diabetes and cancer, in which diverse topics were covered, including the relationship between diabetes and cancer morbidity or cancer prognosis, common risk factors for diabetes and cancer, molecular mechanisms linking diabetes and cancer, and the influence of antidiabetic treatments on cancer risk or cancer prognosis.^(15,16) Of the nine executive summaries and recommendations the American Diabetes Association and American Cancer Society provided in this report, the following are of particular note: (i) that while diabetes (mainly type 2 diabetes) is associated with an increased risk of diverse cancers which include liver, pancreatic, endometrial, colorectal, breast, and bladder cancers, it is associated with a decreased risk of prostate cancer; (ii) that healthy diet, exercise, and body weight control should be recommended as they lead to

decreased risk for diabetes and several cancers and improve prognosis; (iii) that healthcare professionals should advise diabetic patients to undergo cancer screening as appropriate to their sex and age; and (iv) that while a number of antidiabetic agents have been associated with cancer risk, at present, this cancer risk should not be counted among the major factors to be evaluated in selecting antidiabetic agents. Against this background, it appeared that diabetes and cancer needed to be examined for association through in-depth research and surveys in Japan, as well, where diabetic and cancer patients are shown to increase in numbers year by year, and this led to a joint committee being formed and convened by the Japan Diabetes Society (JDS) and the Japanese Cancer Association (JCA) on October 17, 2011, April 18, 2012, August 1, 2012, December 18, 2012, and finally on March 26, 2013, to examine diabetes for association with cancer risk/prognosis, to assess common risk factors for diabetes and cancer based on available epidemiological evidence, and to examine antidiabetic treatments for association with cancer risk based on available epidemiological evidence.

Epidemiological Evaluation of the Association between Diabetes and Cancer Risk/Prognosis

Numerous reports are available from Japan and abroad on the association between diabetes and cancer risk. Of these, the Japan Public Health Center-based Prospective Study (JPHC study) was conducted to examine the presence or absence of diabetes as a physician diagnosis for association with subsequent cancer risk during follow-up.⁽¹⁷⁾ According to this

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In 2013, the Japan Diabetes Society established The Japan Diabetes Society/Japanese Cancer Association (JDS/JCA) Joint Committee on Diabetes and Cancer, which published the final committee report in *J Japan Diab Soc* 2013; 56: 374–90 (in Japanese).¹ This is the English language translation of that report published in the official journal of the JDS, *Diabetology International*, in 2013, and has been jointly published in *Cancer Science* and *Diabetology International* by The Japanese Cancer Association and The Japan Diabetes Society.

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report, the men and women diagnosed with diabetes were associated with a 1.27-fold risk (95% confidence interval [CI], 1.14–1.42) and a 1.21-fold risk (95% CI, 0.99–1.47) of cancer at all sites (or all cancers), respectively, compared to those without the diagnosis of diabetes. By cancer site, in men, diabetes was shown to be associated with an increased risk of gastric cancer (hazard ratio [HR], 1.23; 95% CI, 0.98–1.54), colorectal cancer (HR, 1.36; 95% CI, 1.00–1.85), liver cancer (HR, 2.24; 95% CI, 1.64–3.04), pancreatic cancer (HR, 1.85; 95% CI, 1.07–3.02), and renal cancer (HR, 1.92; 95% CI, 1.06–3.46). In women, diabetes was associated with an increased risk of gastric cancer (HR, 1.61; 95% CI, 1.02–2.54) and liver cancer (HR, 1.94; 95% CI, 1.00–3.73) and tended to be associated with an increased risk of endometrial cancer (HR, 1.68; 95% CI, 0.61–4.64) and ovarian cancer (HR, 2.42; 95% CI, 0.96–6.09), although these increases in risk were not statistically significant. Additionally, metabolic syndrome, foremost among the diseases and conditions associated with diabetes, was also shown to be associated with an increased risk of liver cancer in men, as well as of pancreatic cancer in women in the JPHC study.^(18,19)

Again, according to a meta-analysis of studies conducted in Japan on diabetes and cancer risk,⁽¹³⁾ diabetes was associated with a relative risk (RR) of 1.25 (95% CI, 1.06–1.46) in men for all cancers versus an RR of 1.23 (95% CI, 0.97–1.56) in females for all cancers, which was not statistically significant but demonstrated a trend for increased risk. By cancer site, a meta-analysis of data from both men and women showed that diabetes was associated with an increased risk of liver cancer (RR, 2.38; 95% CI, 2.01–2.81) in men and women, as well as an increased risk (RR, 2.71; 95% CI, 1.19–6.19) of endometrial cancer in women.

Likewise, a meta-analysis of data from studies conducted in Japan and abroad demonstrated that diabetes was associated with an RR of 1.14 (95% CI, 1.06–1.23) and 1.18 (95% CI, 1.08–1.28) for cancer in men and women, respectively.⁽¹⁴⁾ Furthermore, a comparison of cancer risk among racial groups⁽²⁰⁾ showed that Asian men with diabetes had an RR of 1.24 (95% CI, 1.12–1.38) for cancer compared to that (RR, 1.05; 95% CI, 0.96–1.25) among non-Asian men with diabetes, while Asian women with diabetes had an RR of 1.23 (95% CI, 1.07–1.42) for cancer compared to that (RR, 1.16; 95% CI, 1.09–1.23) among non-Asian women with diabetes, suggesting that Asian patients with diabetes may be placed at a higher risk of developing cancer than their non-Asian counterparts.

Additionally, meta-analyses by cancer site of data from studies conducted in Japan and abroad demonstrated that diabetes was associated with an increased risk of colorectal cancer (RR,

1.30; 95% CI, 1.2–1.4),⁽⁹⁾ liver cancer (RR, 2.5; 95% CI, 1.8–2.9),⁽²¹⁾ pancreatic cancer (RR, 1.82; 95% CI, 1.66–1.89),⁽⁸⁾ breast cancer (RR 1.20; 95% CI, 1.12–1.28),⁽¹¹⁾ endometrial cancer (RR 2.10; 95% CI, 1.75–2.53),⁽⁷⁾ and bladder cancer (RR, 1.24; 95% CI, 1.08–1.42),⁽¹⁰⁾ while it was associated with a decreased risk of prostate cancer (RR, 0.84; 95% CI, 0.76–0.93)⁽³⁾ (Table 1). In addition, alcoholic liver disease is reported to be associated with an increased risk of liver cancer in those with diabetes.⁽²⁰⁾ However, the association between diabetes and other cancer types (e.g., skin cancer, renal cancer, non-Hodgkin's lymphoma) remains unclear. Again, diabetic patients with cancer are reported to have a poorer short- and long-term prognosis than those without diabetes.^(22,23)

While meta-analyses are used to integrate, for analysis, research data as they were available from multiple published studies that differed in research design, the heterogeneity among the studies and the potential confounding factors involved in the studies combine to make their interpretations rather difficult. In contrast, a pooled analysis of cohort studies allows for their re-evaluation based on consistent criteria or their re-integration based on available individual patient data, thus accounting for a more reliable set of findings than with meta-analyses.

Thus, a pooled analysis was conducted using data from eight cohort studies in Japan, which included: the JPHC Cohort I and the JPHC Cohort II; the Miyagi Cohort Study; the Ohsaki National Health Insurance Cohort study; the Takayama Cohort study; the Three-Prefecture Cohort Study Aichi; the Three-Prefecture Cohort Study Miyagi; and the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (Table 1).

A total of 155 345 men and 180 792 women were available for analysis. Of these, a total of 19 977 men and 13 046 women were diagnosed as having cancer during 10-year mean follow-up. In this analysis, diabetes was shown to be associated with an HR of 1.2 for all cancer incidence both in males (HR, 1.19; 95% CI, 1.12–1.27) and in females (HR, 1.19; 95% CI, 1.07–1.31) after adjusting potential confounding factors and excluding early diagnoses made within 3 years from baseline. In agreement with the meta-analyses of studies in Japan and abroad mentioned above, an analysis of the pooled data by cancer site showed that diabetes was associated with an increased risk of colon cancer (HR, 1.40; 95% CI, 1.19–1.64), liver cancer (HR, 1.97; 95% CI, 1.65–2.36), and pancreatic cancer (HR, 1.85; 95% CI, 1.46–2.34). Furthermore, diabetes was shown to be associated with an increased risk of endometrial cancer (HR, 1.84; 95% CI, 0.90–3.76) and bladder cancer (HR, 1.28; 95% CI, 0.89–1.86), although these increases in risk were not statistically significant. In contrast, diabetes was

Table 1. Results of a meta-analysis of data from studies conducted in Japan and abroad and a pooled analysis of data from studies conducted in Japan

Cancer type	Meta-analysis	Pooled analysis in Japan†	Lifetime cancer risk in Japan (2007)‡		Age-adjusted cancer incidence in Japan (/100 000 persons)§	
	RR (95% CI) (Ref.)	RR (95% CI)	Men	Women	Men	Women
Gastric cancer	1.19 (1.08–1.31) ⁽²⁴⁾	1.06 (0.91–1.22)	10.9%	5.5%	78.9	28.6
Colorectal cancer	1.3 (1.2–1.4) ⁽⁹⁾	1.40 (1.19–1.64)	8.5%	6.7%	63.4	35.9
Liver cancer	2.5 (1.8–2.9) ⁽²¹⁾	1.97 (1.65–2.36)	4.0%	2.2%	29.8	10.6
Pancreatic cancer	1.82 (1.66–1.89) ⁽⁸⁾	1.85 (1.46–2.34)	2.2%	2.1%	15.1	9.3
Breast cancer	1.20 (1.12–1.28) ⁽¹¹⁾	1.03 (0.69–1.56)	–	6.9%	–	67.1
Endometrial cancer	2.10 (1.75–2.53) ⁽⁷⁾	1.84 (0.90–3.76)	–	1.1%	–	10.5
Prostate cancer	0.84 (0.76–0.93) ⁽³⁾	0.96 (0.64–1.43)	6.6%	–	43.5	–
Bladder cancer	1.24 (1.08–1.42) ⁽¹⁰⁾	1.28 (0.89–1.86)	2.0%	0.7%	12.5	2.7

†Tsugane *et al.* (Unpublished data). ‡Lifetime cancer risk in the Japanese population.⁽²⁵⁾ §Age-adjusted cancer incidence in the Japanese population.⁽²⁶⁾ CI, confidence interval; Ref., reference; RR, relative risk.

associated with no increase in risk of breast cancer (HR, 1.03; 95% CI, 0.69–1.56) or prostate cancer (HR, 0.96; 95% CI, 0.64–1.43). In examining diabetes for association with cancer risk by cancer site, it is important to take into account the background prevalence of cancers among the Japanese population (Table 1), and the impact of the absolute increase in cancer risk associated with diabetes may be rather small, as far as cancer sites associated with relatively low incidence rates, such as bladder cancer, are concerned.

In interpreting the results of the epidemiological studies cited above, the following points (shown in italics) call for attention. (i) *Common risk factors for diabetes and cancer include age, obesity, diet, physical inactivity, and smoking.* However, data from many of the epidemiological studies cited above were not adequately adjusted for these confounding factors, and this may have contributed to an “apparently” increased risk of cancer in those with diabetes compared to that in those without diabetes (see the next section for a more detailed discussion of common risk factors). (ii) *The risk of cancer associated with diabetes may be overestimated in some types of cancer such as pancreatic cancer, where diabetes may occur as a consequence of the onset of cancer.* (iii) *The rate of detection of cancer may be increased in diabetic patients as they frequently undergo examinations.* (iv) *In many of the studies, assessment of a history of diabetes was based on self-reports, which may have led to biased estimates of the association between diabetes and cancer risk. Few people without diabetes may have reported having diabetes, while many of those with diagnosed or undiagnosed diabetes might not have reported diabetes; as a consequence, these biases may have led to an underestimation of the RR of cancer associated with diabetes.*

Mechanisms Through which the Risk of Cancer is Assumed to be Increased Due to Diabetes: Those Associated with the Pathophysiology of Diabetes

Insulin resistance and hyperinsulinemia. Insulin resistance is among the hallmark conditions that characterize type 2 diabetes and leads to hyperinsulinemia. Insulin resistance in type 2 diabetes and obesity is primarily accounted for by impaired glucose metabolism in the skeletal muscle and the liver, but not by a systemic, uniform decrease in insulin action.⁽²⁷⁾ Therefore, the presence of concurrent hyperinsulinemia may lead to excessive insulin action in some organs. Insulin receptor signaling is known to activate the PI3-kinase/Akt pathways, which, in turn, touch off an array of metabolic actions,⁽²⁷⁾ while the PI3-kinase/Akt pathways are also shown to activate a cascade of signaling responsible for oncogenesis and cell proliferation.⁽²⁸⁾ Thus, excessive insulin action associated with insulin resistance is thought to contribute to the onset of cancer (Fig. 1). Indeed, endogenous hyperinsulinemia associated with insulin resistance has been shown to promote cancer proliferation and metastasis, independently of the presence of hyperglycemia or obesity, in a breast cancer-transplant mouse model.⁽²⁹⁾

The insulin receptor is also shown to activate the Ras/MAP kinase pathways.⁽²⁷⁾ In this regard, it is of note that, in insulin-resistant states, PI3-kinase/Akt signaling-induced metabolic action may become attenuated, but Ras/MAP-kinase signaling may not be impaired, while the mechanisms involved remain to be further elucidated,⁽³⁰⁾ suggesting that the varying susceptibility of signaling pathways to impairment in insulin resistance may have a role to play in the insulin resistance-associated pathophysiology that leads to the onset of cancer.

The insulin-like growth factor-1 (IGF-1) receptor has an important role to play in the proliferation of many cancer cells.⁽³¹⁾ The insulin and IGF-1 receptors are shown to be highly similar in structure. Insulin exhibits weak cross-reactivity to the

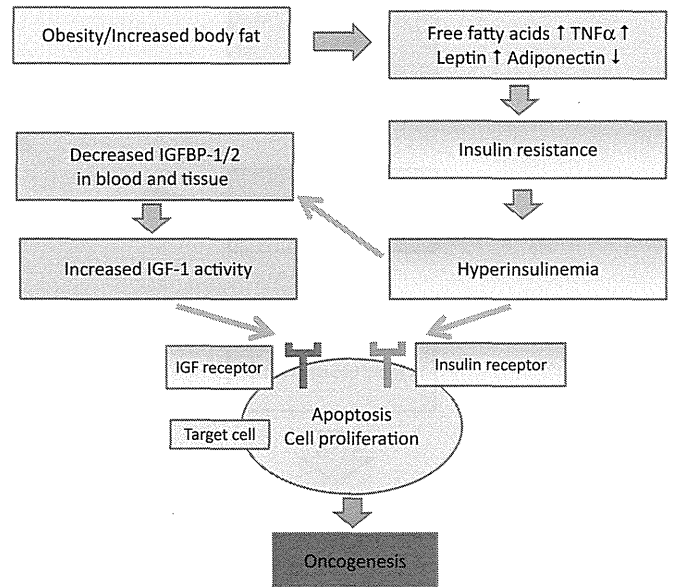


Fig. 1. Hypothetical mechanism of oncogenesis associated with insulin resistance and hyperinsulinemia. The onset of obesity leads to production of free fatty acids and tumor necrosis factor- α (TNF- α) in adipose tissue as well as to decreased adiponectin secretion, thus promoting insulin resistance. Compensatory hyperinsulinemia occurs to decrease insulin-like growth factor binding proteins-1 and -2 (IGFBP-1/2) production, which, as a consequence, leads to an elevation of insulin-like growth factor (IGF) activity. Against this background, mediated by their respective receptors, insulin and IGF-1 signaling induces cell proliferation and inhibits cell apoptosis, thus leading to the onset or progression of cancer. Adapted by permission from Macmillan Publishers Ltd: *Nat Rev Cancer*,⁽³⁵⁾ copyright (2004).

IGF-1 receptor, and, conversely, IGF-1 exhibits weak cross-reactivity to the insulin receptor, with the affinity of insulin and IGF-1 for the IGF-1 and insulin receptors being one-hundredth that for their own receptors.⁽³²⁾ Thus, the tumor-promoting effects of hyperinsulinemia may be accounted for at least in part by activation of the IGF-1 receptor. Additionally, persistent hyperinsulinemia may contribute to decreases in the synthesis of IGF-1 binding proteins such as IGFBP-1 and IGFBP-2, thus increasing the free IGF-1 level.⁽³¹⁾ Again, it is suggested that the expression of the insulin and IGF-1 receptors in target organs, which may be abundant or scarce, may contribute to the organ specificity of tumor onset in diabetes.

Furthermore, insulin is shown to inhibit the hepatic synthesis of sex hormone binding globulin and to increase the fraction of estrogen in serum known as estradiol, which is free and biologically active. Of note, estrogen is known to be implicated in the onset of breast cancer and endometrial cancer, which, coupled with the observation that serum estradiol levels are elevated in diabetic patients, appears to suggest that increases in biologically active estrogen in diabetes may contribute to the onset of cancer in patients with diabetes.^(33,34) (Fig. 2).

On the other hand, it is reported that the serum testosterone concentration decreases with the onset of diabetes,⁽³⁶⁾ which may account for the low incidence of prostate cancer in diabetes. Luteinizing hormone is reported to be decreased in neuron-specific insulin receptor-deficient mice.⁽³⁷⁾ Thus, inadequate insulin action in the central nervous system may be responsible for the decreases in testosterone associated with type 2 diabetes.

Hyperglycemia. Hyperglycemia promotes oxidative stress in the presence of mitochondrial glucose oxidation.⁽³⁸⁾ Increased oxidative stress associated with hyperglycemia is drawing attention as one of the factors responsible for micro- and macrovascular complications.⁽³⁹⁾ In this regard, increased oxidative stress

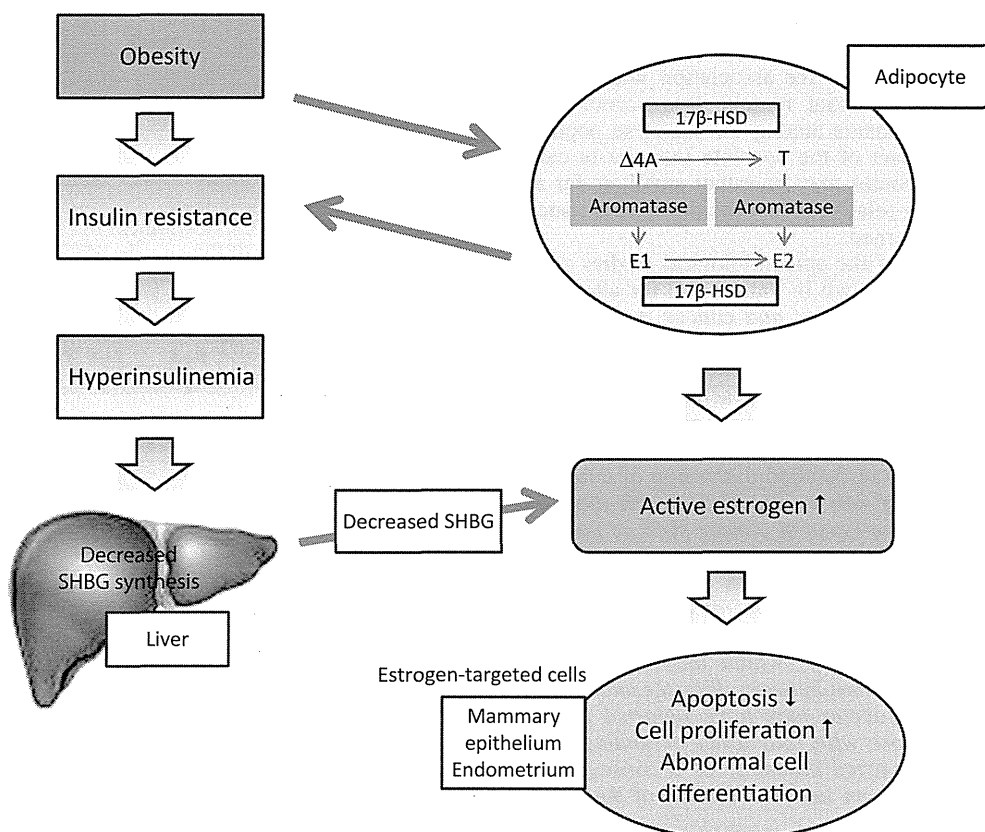


Fig. 2. Hypothetical mechanism of oncogenesis as mediated by active estrogen in hyperinsulinemia. With diabetes, conversion of 4 androstenedione (4A) to biologically active estrogen (E2) is promoted in adipocytes by aromatase and 17 β -hydroxysteroid dehydrogenase (17 β -HSD) via testosterone (T) or estrone (E1). At the same time, hyperinsulinemia leads to decreased synthesis of sex hormone binding globulin (SHBG). Thus, it is thought likely that these combine to lead to an increase in the level of biologically active estrogen. While the effects of active estrogen vary depending on the target organ, active estrogen is assumed to inhibit apoptosis and increase cell proliferation in such tissues as mammary epithelium and endometrium, thus promoting oncogenesis. Adapted by permission from Macmillan Publishers Ltd: *Nat Rev Cancer*,⁽³⁵⁾ copyright (2004).

is known to cause DNA damage,⁽⁴⁰⁾ while increased oxidative stress associated with mitochondrial dysfunction has been shown to lead to tumor growth in a *Drosophila* model.⁽⁴¹⁾ Thus, there may be a cascade of events that proceeds from hyperglycemia through increased oxidative stress to DNA modifications/mutations resulting in an increased incidence of cancer.^(38,39,42)

Furthermore, certain epigenetic changes are known to occur through increased oxidative stress and other unknown mechanisms in diabetes, and methylation changes are shown to occur in particular histone sites. Increased methylation of histone H3 lysine 4 (H3Lys4) and decreased methylation of histone H3 lysine 9 (H3Lys9) are demonstrated in endothelial cells in a high-glucose culture medium or in mice with hyperglycemia induced by intravenous glucose injection. Similar histone methylations have been observed in monocytes and other cells from diabetic patients, suggesting that these methylations may occur to favor the expression of some particular genes, such as nuclear factor- κ B (NF- κ B), thus leading to the onset of diabetes.^(43,44) In this regard, recent reports have revealed that histone/DNA methylation changes are implicated, through regulation of gene expression, in the process of oncogenesis, suggesting that such epigenetic gene modifications in diabetes may contribute to the onset of cancer through regulation of cancer-related genes.⁽⁴⁵⁾

Additionally, even in hypoxic conditions associated with tumor proliferation, cancer cells rely on the anaerobic process called glycolysis for energy production, and enhance pyruvate kinase-M expression or inhibit pyruvate dehydrogenase by

activating hypoxia-inducible factor-1 (HIF-1) to ensure nucleic acid synthesis to promote cancer cell proliferation (Warburg effect). As glycolysis is less efficient in energy production than the tricarboxylic acid cycle and calls for large amounts of glucose for energy production, the high-glucose state appears to favor cancer cell proliferation. Again, HIF-1 is activated not only by hypoxia but also via the PI-3 kinase/Akt/mTOR pathways. Indeed, insulin is known to activate HIF-1 signaling in some cells,⁽⁴⁶⁾ suggesting that excessive actions of insulin and IGF-1 may associate with the onset, proliferation and progression of cancer, via a variety of mechanisms.

Chronic inflammation and adipokines. In obesity, which is found to coexist in a considerable proportion of patients with type 2 diabetes, chronic inflammation is known to occur in adipose tissue.⁽⁴⁷⁾ While the mechanisms of onset of chronic inflammation in adipose tissue in obesity remain to be further clarified, oxidative stress, mentioned above, also contributes to aggravation of inflammation⁽⁴⁸⁾ (Fig. 3). Again, endoplasmic reticulum stress is shown to be increased in diabetes and is drawing attention as a potential cause of insulin resistance or impaired insulin secretion,^(49,50) while endoplasmic reticulum stress itself is known to aggravate inflammation.⁽⁵¹⁾ On the other hand, inflammation is known to aggravate stress in these cells, suggesting that chronic inflammation and cell stress constitute a vicious cycle in which each promotes the other.^(47,48,51) To focus on the role of inflammation in cancer, it has long been suggested that chronic inflammation is implicated in the onset of cancer in tissues where it is present, the

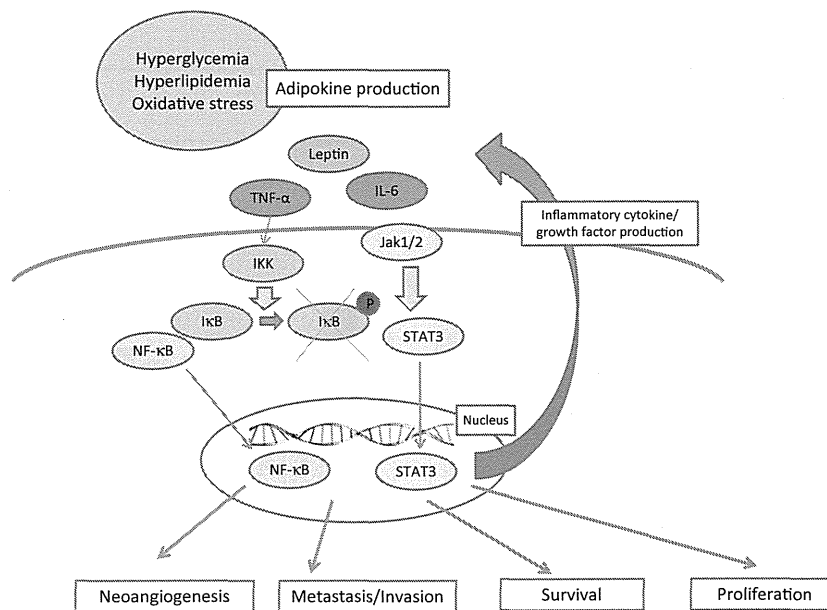


Fig. 3. Pathophysiological mechanisms of inflammation induced by hyperglycemia and their role in oncogenesis. Hyperglycemia/hyperlipidemia and associated oxidative stress induce secretion of various biologically active substances including adipokines. Tumor necrosis factor- α (TNF- α) promotes I κ B phosphorylation (P) and degradation via the I κ B kinase (IKK) pathway, thereby inducing nuclear factor- κ B (NF- κ B) activation. The other cytokines induce signal transducer and activator of transcription-3 (STAT3) activation via the Jak1/2 pathway. The NF- κ B and STAT3 activation in the nucleus leads to inflammatory cytokine production, thereby aggravating diabetes-associated inflammation, while at the same time contributing to oncogenesis through their contribution to signaling for cell proliferation and survival.^(52,53)

mechanisms of which are currently being explored from various angles, including such pathways as interleukin-6 (IL-6), tumor necrosis factor TNF- α and NF- κ B^(52,54). Thus, it is suggested that chronic multi-organ inflammation associated with diabetes is implicated, through mechanisms such as those suggested above, in the onset of cancer.

A variety of biologically active substances are secreted by adipocytes to regulate a wide range of physiological functions including nutrition and energy metabolism. These adipocyte-derived, biologically active substances are collectively called adipokines. Of these, adiponectin is of interest as an adipokine for its insulin-sensitizing and anti-atherosclerotic properties, whose serum concentration is shown to be decreased in obesity or type 2 diabetes.⁽⁵⁵⁾ Adiponectin is known to inhibit cancer cell proliferation and induce cancer cell apoptosis through mechanisms including AMP kinase (AMPK) activation, and these cancer-inhibitory effects have also been demonstrated in animal models.^(55,56) Furthermore, given that adiponectin is shown to have anti-inflammatory effects, hypo adiponectinemia may have a role to play in the onset of chronic inflammation in obesity and diabetes.^(55,57) Leptin is also of interest as an adipokine that suppresses appetite and increases energy metabolism, whose serum concentration is shown to be increased in the presence of obesity. Leptin has been shown to be implicated via various signaling pathways such as PI3 kinase, ERK1/2, and Jak2/Stat3 in cancer cell proliferation and metastasis.⁽⁵⁸⁾ Thus, hyperleptinemia in patients with obesity and type 2 diabetes may have a role to play in promoting cancer cell growth.

Epidemiological evaluation of common risk factors for diabetes and cancer. Insulin resistance and hyperinsulinemia are thought to serve as background factors for the onset and progression of cancer in diabetes.⁽⁵⁹⁾ Common risk factors for type 2 diabetes and cancer include aging, male sex, obesity, physical inactivity, inappropriate diet (excessive red/processed meat intake, inadequate vegetable/fruit/dietary fiber intake), excessive alcohol drinking, and smoking. The prevalence of diabetes (Fig. 4), as well as incidence of cancer, increases with aging (Fig. 5);

both are shown to be higher among men than among women (Figs 4 and 5).^(60,61)

Of these common risk factors, modifiable risk factors include obesity, physical inactivity, dietary habits, excessive alcohol drinking, and smoking. Given that multiple meta-analyses have demonstrated that individuals with high coffee consumption are placed at a low risk of developing both diabetes and cancer,^(62,63) coffee intake may as well be regarded as a factor that helps protect against both diabetes and cancer; however, no consensus has been reached to serve as a basis for recommending coffee intake.

Obesity is counted among the most important risk factors for type 2 diabetes^(64,65) and the International Agency for Research on Cancer (IARC) reported that there is sufficient evidence that obesity increases the risk of cancer in such sites as esophagus (adenocarcinoma), colon, pancreas, breast (postmenopausal), endometrium, and kidneys.⁽⁶⁶⁾ A report from the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan also documented that there is convincing evidence that obesity increases breast cancer risk among postmenopausal women.⁽⁶⁷⁾ Again, it is reported that individuals with a body mass index (BMI) of 25 kg/m² or higher are placed at a higher risk of developing cancer than those remaining within the normal BMI range (18.5–24.9 kg/m²)⁽⁶⁸⁾ Furthermore, gastric bypass surgery in obese individuals is shown to reduce deaths from cancer by 60% during 7-year follow-up.⁽⁶⁹⁾ However, in contrast, cancer risk has been shown to be increased in men with BMI less than 21 kg/m² in a cohort study involving a total of approximately 90 000 middle-aged and elderly men and women,⁽⁷⁰⁾ suggesting the need to maintain appropriate body weight, that is, avoid losing or gaining too much weight. In the Japanese population, obesity is less associated with cancer risk than in other populations.

With regard to the association between dietary intake and cancer, it is reported that the lower the intake of red or processed meat and the greater the intake of vegetables, fruits, and whole grains, the lower the risk for cancer.^(71,72) Addition-

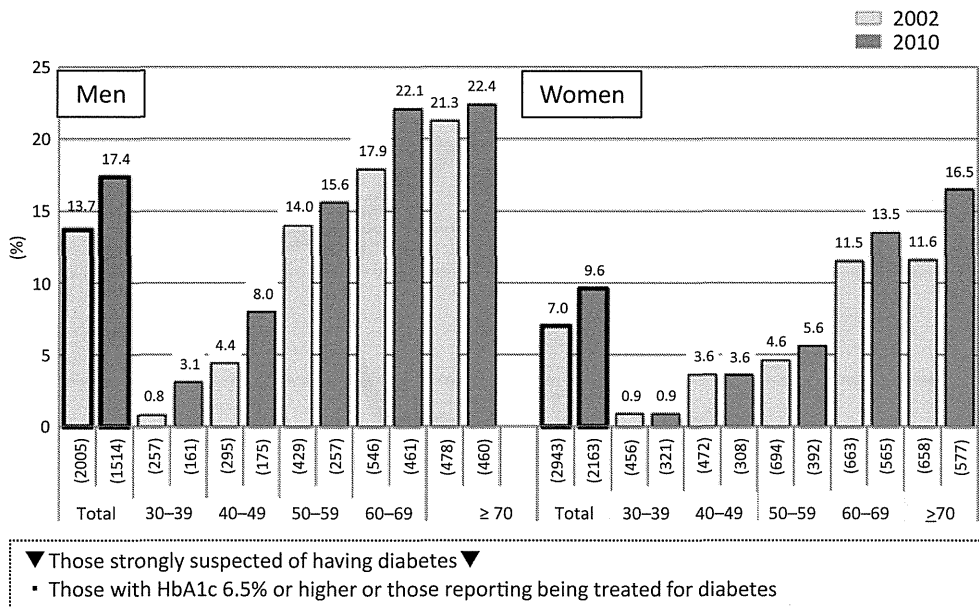


Fig. 4. Proportion of individuals in Japan strongly suspected of having diabetes, 2002 versus 2010. Source: Ministry of Health, Labour and Welfare of Japan. National Health/Nutrition Survey 2012.⁽⁶⁰⁾

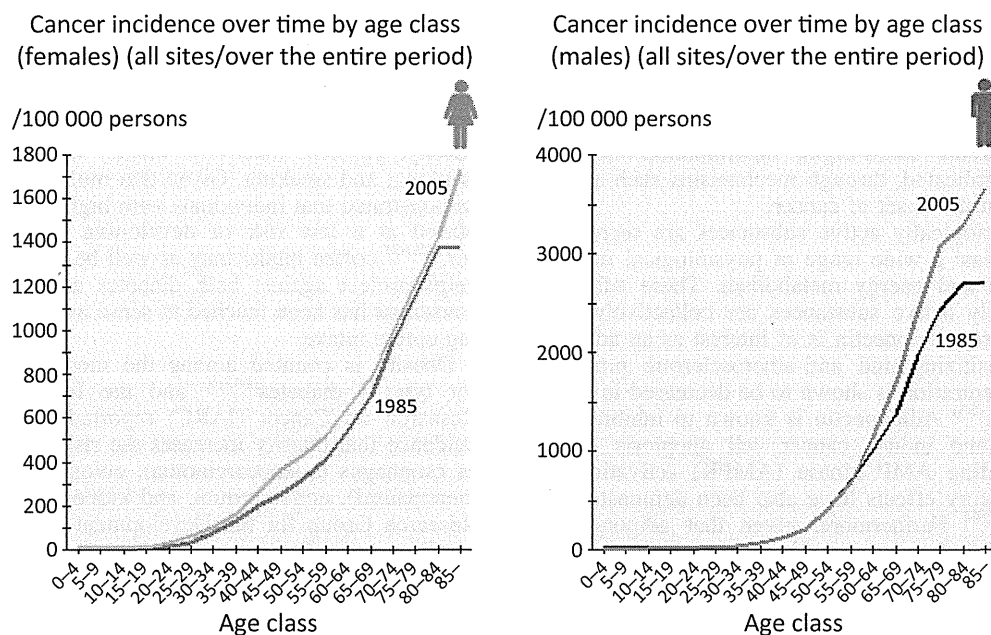


Fig. 5. Cancer incidence in Japan by age class over time, 1985 versus 2005. Source: Center for Cancer Control and Information Services, National Cancer Center, Japan (<http://ganjoho.jp/pro/statistics/en/gdball.html>).⁽⁶¹⁾

ally, diets consisting of less meat and more vegetables, fruits, and whole grains are thought to help protect against type 2 diabetes.⁽⁷³⁾

Physical activity is reported to be associated with a decreased risk of colorectal cancer, breast cancer (among postmenopausal women), and endometrial cancer in a number of epidemiological studies.^(66,74-76) Physical activity has also been associated with a decreased risk of diabetes in several epidemiological studies.⁽⁷⁷⁾ In addition, the Da Qing Study,⁽⁷⁸⁾ a randomized controlled trial, demonstrated that intervention with exercise therapy led to a 46% decrease in the risk for type 2 diabetes.

In the IARC report, smoking is identified as a factor promoting carcinogenesis not only in the lungs but in multiple organs, such as larynx, upper gastrointestinal tract, liver, pancreas, cervix, kidneys, and bladder.^(79,80) Smoking is also reported to be associated with an increased risk of type 2 diabetes.⁽⁸¹⁻⁸³⁾

With regard to the association between alcohol intake and cancer, even when moderate, alcohol intake is shown to be associated with an increased risk of cancer in studies conducted in Japan and abroad.^(84,85) In the IARC report, alcohol intake was identified as a factor promoting carcinogenesis in the oral cavity, the pharynx, the esophagus, the colon, the

liver, and the breast.⁽⁸⁶⁾ As for association between alcohol intake and diabetes, epidemiological studies to date^(87–89) suggest that, while high alcohol consumption may increase the risk of type 2 diabetes, moderate alcoholic consumption may decrease the risk of type 2 diabetes.

Mechanisms that lead to an increase in cancer risk in diabetes: common risk factors for diabetes and cancer. *Obesity and decreased physical activity level.* Obesity is a common risk factor for diabetes and cancer and accounts for many of the mechanisms of oncogenesis in diabetes associated with increased insulin resistance, chronic inflammation in adipose tissue, and adipokine abnormalities that have been discussed above. Recently, liver cancer associated with the mutagenic substance diethylnitrosamine (DEN) has been shown to increase in frequency and size in high fat diet-fed or genetically engineered, obese mice, but to be inhibited in IL-6/TNF receptor-knockout mice,⁽⁹⁰⁾ suggesting that obesity promotes carcinogenesis against the background of chronic inflammation in which IL-6/TNF signaling is implicated. Again, it is suggested that lipids accumulated in such organs as the liver may promote local inflammation and associated carcinogenesis by activating NF- κ B in such cells as Kupffer cells and by increasing production of cytokines such as IL-6 and TNF.⁽⁹¹⁾

While physical activity level and dietary habits may affect the balance between production and degradation of reactive oxygen species and reactive nitrogen species in the body to account for epigenetic changes over time and thus contribute to carcinogenesis, this association is hardly demonstrable in experimental studies with very few reports published to date. While increased lipid intake is closely associated with the onset of diabetes, feeding with high-fat diet is shown to be associated with a high incidence of liver cancer in some animal models⁽⁹²⁾; however, it remains unclear whether this is due to changes in dietary composition or secondary to obesity and increased insulin resistance.

Aging. Glucose tolerance is known to decrease, and type 2 diabetes is known to increase, with aging, where the mechanisms involved have mainly been accounted for by age-associated changes in adipocytes, skeletal muscle cells, and pancreatic β cells, as well as their dysfunction. On the other hand, given that cancer occurs primarily as a consequence of accumulated, multistep genetic/epigenetic changes, generally, carcinogenesis takes an extended period of time to occur. Again, given that aging is a common risk factor for both diabetes and cancer, the elderly have a relatively high probability of developing both. Furthermore, changes in cells or tissues associated with aging, such as oxidative stress, and hormonal/metabolic alterations, may constitute a mechanism that induces the onset of both diabetes and cancer. Again, the role of the tumor-suppressor gene *p53* has begun to be unraveled in recent years, with some reports suggesting a potential role for *p53* in insulin resistance associated with aging.^(93,94)

Epidemiological evaluation of antidiabetic treatments for their association with cancer. Given that inappropriate diet and exercise are common risk factors for diabetes and cancer, diet/exercise therapy in diabetic patients may lead to a decreased risk of cancer. Furthermore, as body weight reductions are also reported to decrease mortality from cancer,⁽⁶⁹⁾ body weight reductions may lead to a decreased risk of cancer in obese, diabetic patients.

Several studies on antidiabetic drugs and cancer risk have been reported. As mentioned earlier, as insulin has tumor-promoting effects, the use of insulin secretagogues or insulin preparations may be associated with an increased risk of cancer. As for insulin preparations, three of the four epidemiological studies published in September 2009^(95–98) reported that patients treated with insulin glargine are at an increased risk of cancer (particularly breast cancer). However, in a Dutch study

that followed, those receiving insulin glargine were shown to be associated with a decreased risk of cancer.⁽⁹⁹⁾ Furthermore, the ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial randomized a total of approximately 13 000 patients with impaired fasting glucose, impaired glucose tolerance or early-stage diabetes and cardiovascular risk factors to insulin glargine or standard therapy, demonstrating no significant difference between the treatment arms in cancer incidence and mortality after a median follow-up of 6.2 years.⁽¹⁰⁰⁾ This was followed by two more epidemiological studies of insulin glargine and cancer risk published in 2012 and 2013 in France,^(101,102) both demonstrating that the use of insulin glargine was not associated with an increased risk of cancer. Similarly, of the epidemiological studies conducted in Asia, a Hong Kong study⁽¹⁰³⁾ compared insulin users and non-users for cancer risk, irrespective of the insulin preparations used, demonstrating that insulin users have a lower risk of cancer than non-users (HR, 0.17; 95% CI, 0.09–0.32), and a Taiwan study⁽¹⁰⁴⁾ demonstrated no significant association between insulin use and bladder cancer risk (HR, 0.57; 95% CI, 0.21–1.57). Thus, at present, there is as yet no consensus as to whether or not the use of insulin preparations is associated with increased cancer risk.

Of the drugs that comprise insulin secretagogues, that is, sulfonylureas (SU) and glinides, there is as yet insufficient evidence to prove or disprove the association between the glinides and cancer risk. With regard to the cancer risk associated with the SUs, SU users were shown to be associated with decreases in cancer risk, with the HR for cancer in glibenclamide users and gliclazide users being 0.67 (95% CI, 0.51–0.89) and 0.65 (95% CI, 0.49–0.83), respectively, in an epidemiological study conducted in Hong Kong,⁽¹⁰⁵⁾ while SU users were shown to be at a 1.78-fold (95% CI, 1.41–2.26) higher risk of developing cancer compared to metformin users, in a Taiwan study.⁽¹⁰⁶⁾ Reports from the UK and Italy also demonstrated that the use of the SUs is associated with an increased risk of cancer.^(98,107) Thus, the studies to date have yielded mixed results with regard to cancer risk associated with the SUs, while it was suggested that the use of the SUs may be associated with an increased risk of cancer.

With regard to the cancer risk associated with the glucagon-like peptide-1 (GLP-1) receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors that have recently been approved in Japan, globally, there is as yet a paucity of evidence because of their relatively recent approval. However, the use of the GLP-1 receptor agonists, such as exenatide and liraglutide, was shown to lead to the onset of thyroid C-cell adenoma in rodents,^(108,109) and pancreatitis was shown in multiple clinical trials and postmarketing surveillances to develop in patients given the GLP-1 receptor agonists, such as exenatide and liraglutide, or the DPP-4 inhibitors, such as sitagliptin.^(108–112) Furthermore, an analysis of the US Food and Drug Administration's database of reported adverse events revealed that pancreatic cancer was frequently reported in patients treated with exenatide or sitagliptin, and follicular thyroid cancer was frequently reported in patients treated with exenatide.⁽¹¹³⁾ However, because analyses based on databases of reported adverse events are subject to reporting bias, information bias, selection bias, and confounding factors, it is difficult to reveal the casual relationship between drugs and cancer risk. Again, a meta-analysis of randomized controlled trials of the DPP-4 inhibitors demonstrated that the DPP-4 inhibitors were not associated with an increased risk of cancer (odds ratio [OR], 1.02; 95% CI, 0.74–1.40); however, given the short durations of the studies examined, at present, the cancer risk associated with long-term use of the DPP-4 inhibitors remains unclear.⁽¹¹⁴⁾

There is as yet insufficient data to prove or disprove the association between the α -glucosidase inhibitors and cancer

risk, while the use of the α -glucosidase inhibitors was not associated with an increased risk of bladder cancer (HR, 1.08; 95% CI, 0.46–2.56) in a Taiwan epidemiological study.⁽¹⁰⁴⁾

With regard to the cancer risk associated with the thiazolidinedione insulin-sensitizers, of which pioglitazone is covered by insurance in Japan, in recent years, studies from the USA, France, and the EU demonstrated that the use of pioglitazone was associated with an increased risk of bladder cancer.^(115–119) In this regard, in a Taiwan study, the HR for bladder cancer in pioglitazone users was 1.31 (95% CI, 0.66–2.58); although not statistically significant, the results suggest that the use of pioglitazone may be associated with an increased risk of bladder cancer in Asian populations.⁽¹²⁰⁾ In agreement with these reports, a meta-analysis of studies to date⁽¹²¹⁾ showed an increased risk of bladder cancer associated with the use of pioglitazone (RR, 1.22; 95% CI, 1.07–1.39). Additionally, rodents given pioglitazone for 2 years have been shown to develop benign or malignant transitional cell tumors.⁽¹²²⁾ In light of these reports, the package inserts for pioglitazone in Japan, the USA, and the EU have come to include a warning label “discouraging the use of pioglitazone in patients with bladder cancer”, while the impact of the absolute increase in cancer risk associated with the use of pioglitazone may be small in the Japanese population, which has a relatively low incidence of bladder cancer.

In contrast, with regard to the biguanide metformin, which is used to improve insulin resistance, metformin users have been shown to be at a lower risk of cancer than non-users.⁽¹²³⁾ A meta-analysis of six cohort studies, two randomized controlled trials, and two case-control studies has also shown that the risk of cancer associated with metformin use is 0.67-fold (95% CI, 0.53–0.85), with the risk reductions shown for colorectal cancer (RR, 0.68; 95% CI, 0.53–0.88), liver cancer (RR, 0.20; 95% CI, 0.07–0.59), and lung cancer (RR, 0.67; 95% CI, 0.45–0.99),⁽¹²³⁾ while no association was shown between metformin use and the risk of cancer in the stomach, pancreas, breast, prostate, and bladder. However, a recent meta-analysis of randomized controlled trials of metformin to date demonstrated no decrease in cancer risk with metformin (RR, 1.02; 95% CI, 0.82–1.26).⁽¹²⁴⁾ Furthermore, for many of the meta-analyses cited above which involved analyses susceptible to the influence of immortal time bias, that is, bias resulting from inappropriate handling of event-free time (immortal time) defined as a period of follow-up during which, by design, no event can occur, it was suggested that they may have overestimated the tumor-inhibitory potential of metformin.⁽¹²⁵⁾ Apart from these, given that patients with renal dysfunction or those with advanced hepatic failure, in whom metformin is contraindicated, have been excluded from metformin studies, the possibility cannot be ruled out that

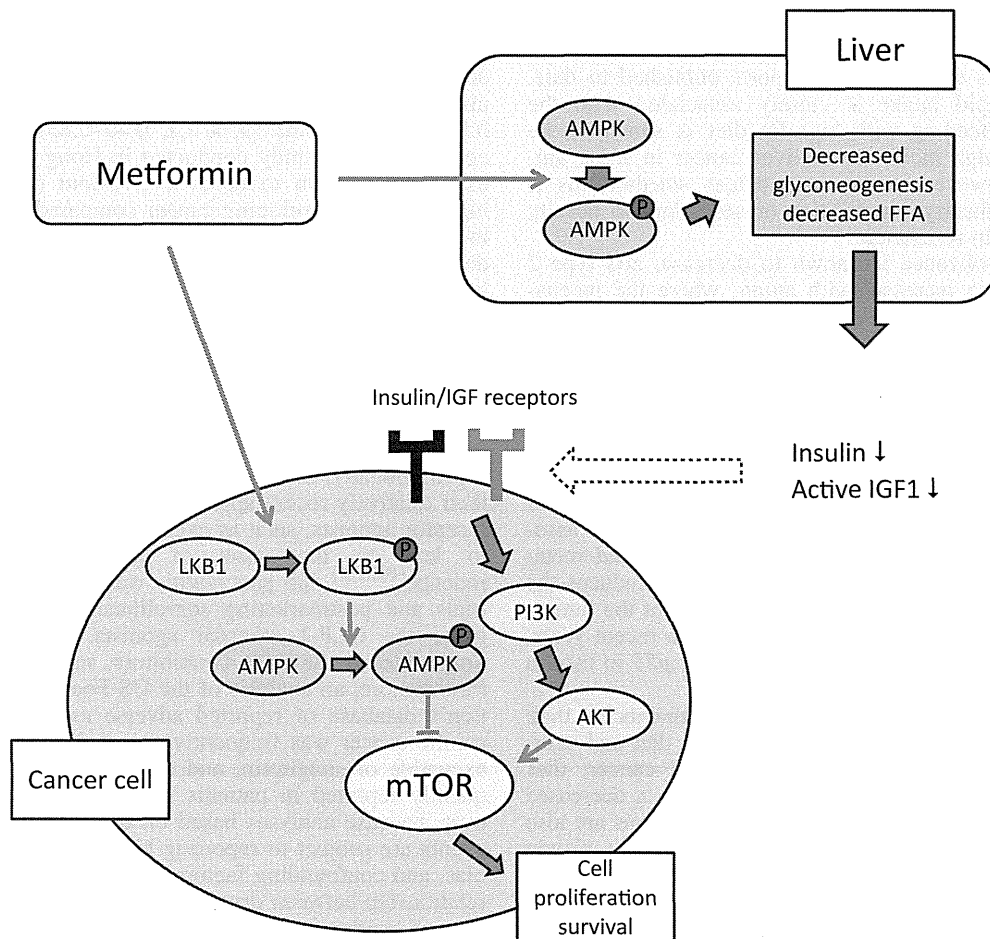


Fig. 6. Hypothetical mechanism through which metformin is assumed to inhibit carcinogenesis. Of the mechanisms of action of metformin which still remain less well elucidated, one possible mechanism through which metformin is assumed to inhibit carcinogenesis is that metformin induces AMP kinase (AMPK) phosphorylation (P) and activation via LKB1, which leads to inhibition of gluconeogenesis in the liver, thus improving insulin sensitivity. As a consequence, this leads to decreases in insulin and active insulin-like growth factor-1 (IGF-1). Additionally, metformin-activated AMPK is shown to contribute to inhibition of mTOR, which regulates cell proliferation and survival, downstream of PI3 kinase (PI3K) and AKT. By inhibiting insulin and IGF-1 signaling at the ligand level as well as at the intracellular signaling level, metformin is assumed to exert tumor-inhibitory effects.^(127,128)

this may have contributed to a decrease in cancer incidence and mortality in these studies. Thus, further research is required to determine definitely whether or not metformin is associated with decreased cancer risk.

If metformin is to inhibit carcinogenesis, it may involve the following mechanisms (Fig. 6). Metformin has the ability to activate AMPK, which is thought to mediate at least part of the antidiabetic effects of metformin,⁽¹²⁶⁾ while AMPK is assumed to suppress protein synthesis and the cell cycle by inhibiting mTOR, thus exerting its tumor-inhibitory effects.^(127, 128)

Given that diabetic patients are often found to be on poly-pharmacy with antidiabetic drugs, and that the control drugs used for comparison vary among the studies of antidiabetic drugs conducted to date, it is difficult to determine the risk of cancer associated with the use of a particular drug. Furthermore, many of the epidemiological studies cited above provide insufficient evidence to determine the casual relation between anti-diabetic drugs and cancer risk not only due to their inadequate adjustment for such confounding factors as family history and therapeutic indications, but because of not accounting for dosage and duration of medications and their short duration of follow-up. Incidentally, this appears to point to the need in Japan to align the infrastructure to allow pharmacoepidemiological studies to be appropriately designed and implemented by promoting diabetes patient registries and by linking relevant cancer patient registries with the drug databases currently in place. At present, the cancer risks associated with antidiabetic drugs still remain less clear. In drug therapy for diabetes, therefore, it seems desirable that priority should be given to maximizing the benefits of the drug(s) being used to achieve favorable glycemic control in individual patients, instead of letting them live with hyperglycemia without such benefits, with consideration also given to the warning labels for the drugs being used.

Again, while diabetic patients are often found to be receiving antihypertensive drugs (ACE inhibitors, angiotensin receptor blockers, calcium antagonists, and diuretics), statins, and aspirin for their concomitant diseases and conditions, such as hypertension, diabetic nephropathy, dyslipidemia, and atherosclerosis, to date, many studies have been conducted to determine the risk of cancer associated with the use of these drugs, with multiple meta-analyses of randomized controlled trials of antihypertensive drugs published to date demonstrating that the use of ACE inhibitors (risk ratio, 1.00; 95% CI, 0.92–1.09) and angiotensin receptor blockers (risk ratio, 1.01; 95% CI, 0.92–1.09) was not associated with an increased risk of cancer, but combination therapy with an ACE inhibitor and an angiotensin receptor blocker was associated with an increased risk of cancer (OR, 1.14; 95% CI, 1.02–1.28), while calcium antagonists were not associated with an increased risk of cancer (OR, 1.05; 95% CI, 0.96–1.13).⁽¹²⁹⁾ Again, a meta-analysis of 26 randomized controlled trials of statins demonstrated no increase in cancer risk with their use (HR, 1.00; 95% CI, 0.96–1.04).⁽¹³⁰⁾ In addition, a meta-analysis of randomized controlled trials of aspirin demonstrated cancer risk reductions with aspirin use

(HR, 0.88; 95% CI, 0.80–0.98),⁽¹³¹⁾ while the limitations of this meta-analysis were that it did not include, for analysis, such major clinical trials as the Women's Health Study or the Physicians' Health Study in which no cancer risk reductions were shown with aspirin use and that the randomized trials included for analysis were generally short in duration. Thus, at present, there is as yet no consensus as to whether or not aspirin was associated with cancer risk reductions. Again, given that all the meta-analyses cited above included diabetic and non-diabetic subjects alike for analysis, further research is required to determine the risk of cancer associated with drugs used in diabetes other than antidiabetic drugs.

Thus, in light of currently available evidence, the JDS/JCA Joint Committee on Diabetes and Cancer summarizes its recommendations for the benefit of practicing physicians, healthcare providers, and the general public, including patients, as follows.

JDS/JCA Joint Recommendations on Diabetes and Cancer for Physicians and Healthcare Providers

- Generally, it is reported that diabetes (mainly type 2 diabetes) is associated with an increased risk of colorectal, liver, pancreatic, breast, endometrial, and bladder cancers, while it is also associated with a decreased risk of prostate cancer. To focus attention on cancer risks in Japanese diabetic patients, at present, diabetes appears to be associated with an increased risk of colorectal, liver, and pancreatic cancers in these patients. Available reports suggest no increased risk of other cancers associated with diabetes or offer conflicting views.
- Diabetes may be associated with cancer partly because there are common risk factors, such as aging, obesity, and inappropriate diet/exercise.
- Hyperinsulinemia, hyperglycemia, and inflammation are suggested as potential mechanisms through which diabetes contributes to an increased risk of cancer in affected patients.
- Healthy diet, exercise, body weight control, smoking cessation, and alcohol moderation should be encouraged to reduce the risk for diabetes and cancer.
- Given that inappropriate diets, lack of exercise, smoking, and excessive alcohol drinking represent risk factors for cancer morbidity, diet/exercise therapy, smoking cessation, and alcohol moderation may lead to a decreased risk of cancer in diabetic patients.
- Diabetic patients are encouraged to undergo evidence-based cancer screening as required depending on their sex and age (Table 2). Diabetic patients are encouraged to undergo screening for liver cancer if they are hepatitis virus-positive.
- Given the insufficient evidence available for determining whether or not a particular antidiabetic drug may be associated with cancer risk, in selecting drug therapy, priority should be given to maximizing the benefits of the drug(s) being used to achieve favorable glycemic control in individual patients, following the labelings.

Table 2. Evidence-based cancer screening

Screening for	Candidates	Screening frequency	Screening procedure
Gastric cancer	Men/Women, 40 years of age or older	Once a year	History taking, stomach x-ray
Uterine cancer	Women, 20 years of age or older	Once every 2 years	History taking, inspection, cervical cytology, internal examination
Lung cancer	Men/Women, 40 years of age or older	Once a year	History taking, chest x-ray, sputum cytology
Breast cancer	Women, 40 years of age or older	Once every 2 years	History taking, inspection, palpation, breast x-ray (mammography)
Colorectal cancer	Men/Women, 40 years of age or older	Once a year	History taking, stool testing for occult blood

Source: Ministry of Health, Labour and Welfare of Japan.⁽¹³²⁾

JDS/JCA Joint Recommendations on Diabetes and Cancer for the General Public (Including Patients)

- Diabetes (mainly type 2 diabetes) in Japanese is associated with an increased risk of colorectal, liver, and pancreatic cancers. There is as yet no consensus as to whether or not diabetes is associated with an increased risk of other types of cancer.
- Healthy diet, exercise, body weight control, smoking cessation, and alcohol moderation may help prevent cancer and are therefore encouraged.
- Diet/exercise therapy, smoking cessation, and alcohol moderation may help prevent cancer in patients with diabetes as well.
- Patients with diabetes are encouraged to undergo evidence-based screening as required, depending on their sex and age (Table 2). They are also encouraged to visit a hospital to undergo screening for liver cancer if they are hepatitis virus-positive.

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- At present, there is no clear consensus as to whether or not a particular antidiabetic drug is associated with cancer risk. It is therefore essential that diabetic patients focus attention on maintaining favorable glycemic control following their physicians' instructions.

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