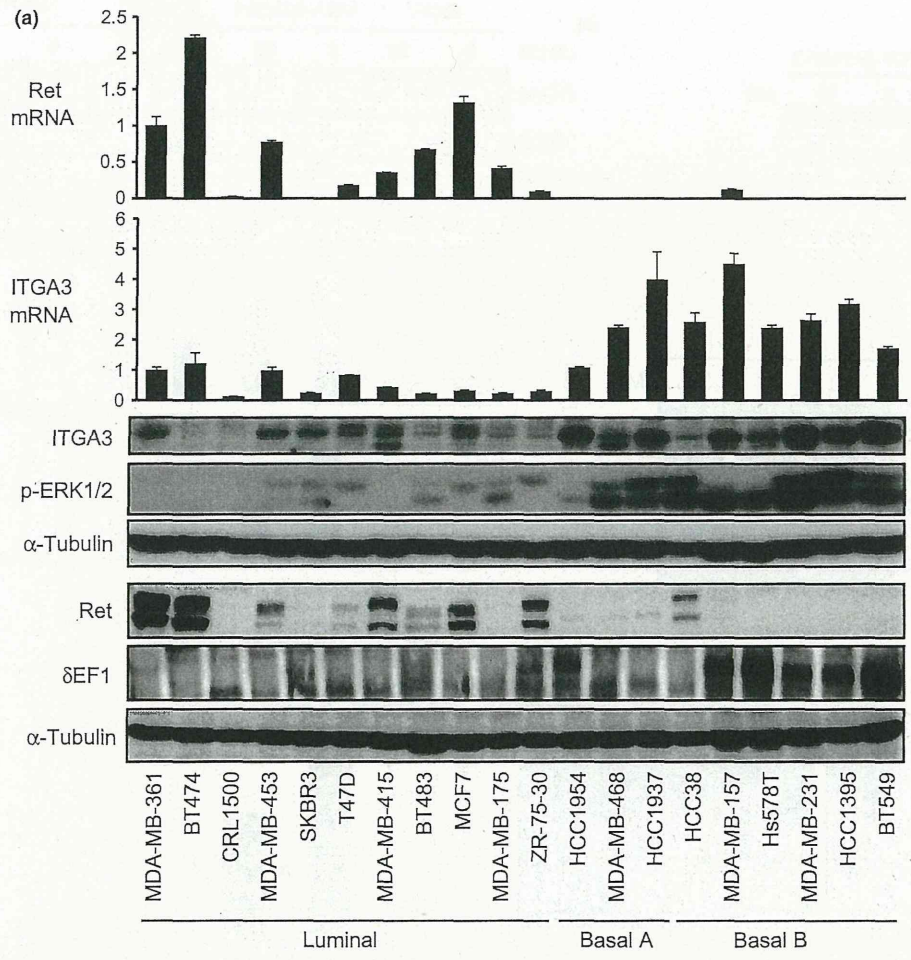

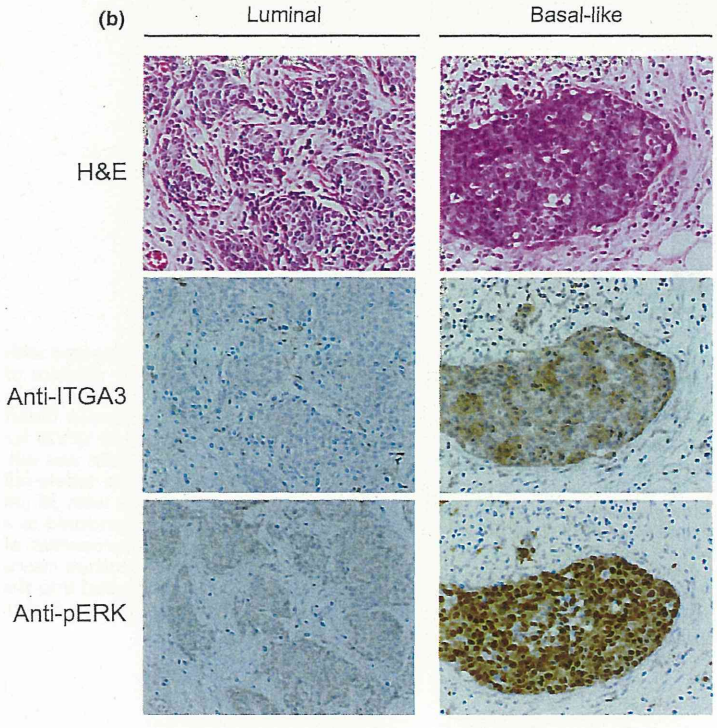

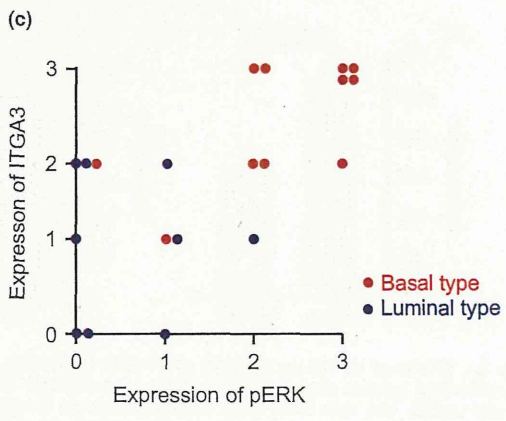

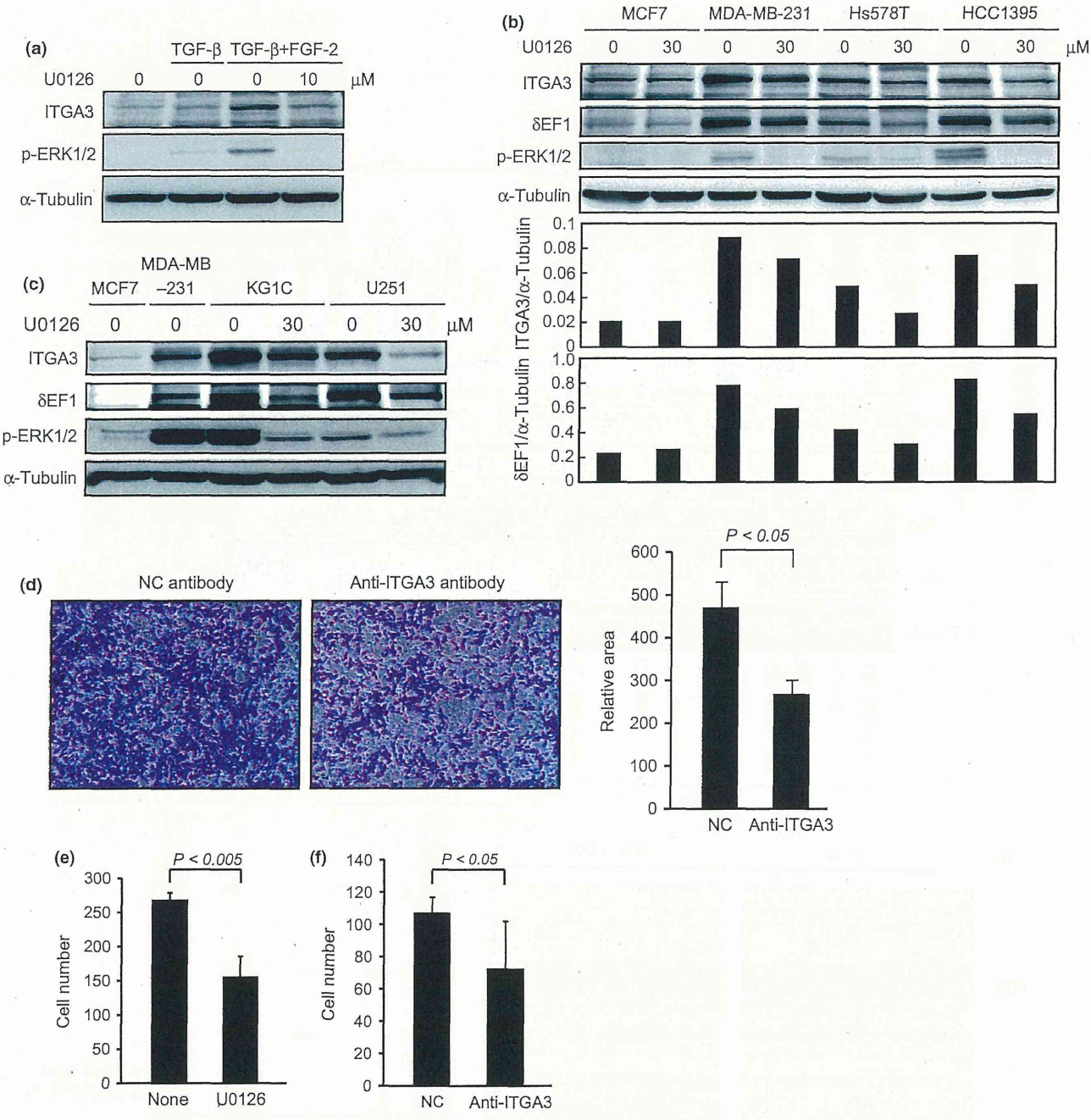

Fig. 5. *Effects of U0126 on integrin α3 (ITGA3) expression.* (a) Repression of ITGA3 by U0126 in NMuMG cells. NMuMG cells were treated with transforming growth factor (TGF)-β alone or combined TGF-β and fibroblast growth factor (FGF)-2 for 7 days in the presence or absence of 10 μM U0126. The cells were lysed and subjected to immunoblot analysis with the indicated antibodies. α-Tubulin levels were monitored as a loading control for the whole-cell extracts. p-ERK, phosphorylated ERK. (b) Inhibitory effects of U0126 on ITGA3 expression in human breast cancer cells. Luminal subtype MCF7 cells and basal-like subtype MDA-MB-231, Hs578T, and HCC1395 cells were incubated with 30 μM U0126 for 24 h. The cells were lysed and subjected to immunoblot analysis with the indicated antibodies. The ratio of ITGA3 or δEF1 to α-tubulin was validated by densitometric analysis and is shown in the lower panels. α-Tubulin levels were monitored as a loading control for the whole-cell extracts. (c) Inhibitory effects of U0126 on ITGA3 expression in human glioma cells. KG1C and U251 glioma cells were incubated with 30 μM U0126 for 24 h. The cells were lysed and subjected to immunoblot analysis with the indicated antibodies. α-Tubulin levels were monitored as a loading control for the whole-cell extracts. (d,e) Inhibitory effects of anti-ITGA3 antibody (d) and U0126 (e) on the invasive properties of NMuMG cells. NMuMG cells were pretreated with TGF-β or both TGF-β and FGF-2 for 4 days. The cells were then seeded onto cell culture inserts coated with type I collagen in the presence or absence of anti-ITGA3 antibody or 10 μM U0126. After 24 h, the cells that had invaded into the lower surface of the filters were stained with crystal violet (left), followed by quantification by measuring the area of photographed cells (right). (f) Inhibitory effects of anti-ITGA3 antibody on the invasive properties of MDA-MB-231cells. NC, control IgG.

doi: 10.1111/cas.12220

Acknowledgments

We are grateful to Ms K. Endo and Mr Y. Koshimizu for their technical assistance. We thank Drs N. Oishi, T. Kawataki, H. Kinouchi, H. Fujii, and R. Kato for their advice and discussion regarding human clinical samples. This work was supported by the Foundation for Promotion of Cancer Research and JSPS KAKENHI Grant No. 23790455 (T.S.), and Kobayashi Foundation for Cancer Research, JSPS KAKENHI Grant No. 24390419, the Cooperative Program for Graduate Student Education between the University of Yamanashi and Waseda University from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and JSPS Core-to-Core Program "Cooperative International Framework in TGF-β Family Signaling".

Disclosure Statement

The authors have no conflict of interest.

Abbreviations

EMT	epithelial–mesenchymal transition
EMyoT	epithelial–myofibroblastic transition
FGF-2	fibroblast growth factor-2
GAP	growth-associated protein
ITGA3	integrin α3
qRT-PCR	quantitative RT-PCR
α-SMA	smooth muscle α actin
TBP	TATA binding protein
TGF	transforming growth factor

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Cancer Science
The official journal of the Japanese Cancer Association JCA

Report

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

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(Received May 10, 2013/Accepted May 12, 2013)

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.

Members of the Japan Diabetes Society/Japanese Cancer Association Joint Committee on Diabetes and Cancer.
Japan Diabetes Society (JDS): Masato Kasuga, Kohjiro Ueki, Naoko Tajima, Mitsuhiko Noda, and Ken Ohashi.
Editorial assistants: Hiroshi Noto, Atsushi Goto, and Wataru Ogawa
Japanese Cancer Association (JCA): Ryuichi Sakai, Shoichiro Tsugane, Nobuyuki Hamajima, Hitoshi Nakagama, Kazuo Tajima, Kohei Miyazono, and Kohzoh Imai.

doi: 10.1111/cas.12203

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-analyses 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.

doi: 10.1111/cas.12203

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 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.

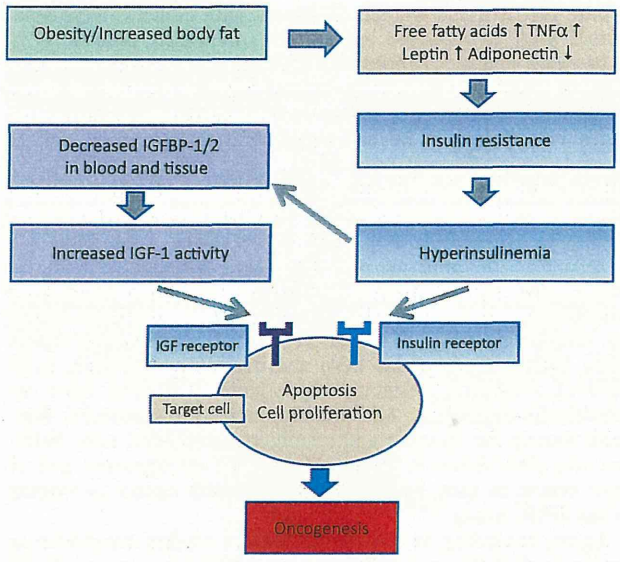

Fig. 1. Hypothetical mechanism of oncogenesis associated with insulin resistance and hyperinsulinemia. The onset of obesity leads to production of free fatty acids and tumor necrosis factor-α (TNF-α) in adipose tissue as well as to decreased adiponectin secretion, thus promoting insulin resistance. Compensatory 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).

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

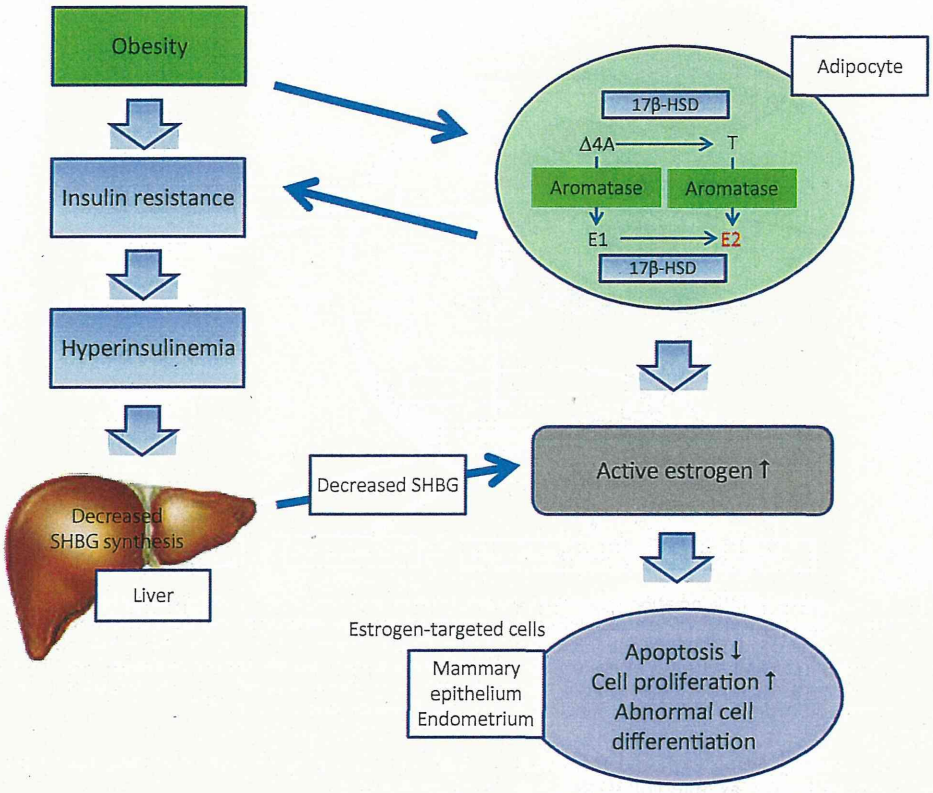

Fig. 2. Hypothetical mechanism of oncogenesis as mediated by active estrogen in hyperinsulinemia. With diabetes, conversion of 4 androstenedione(4A) to biologically active estrogen (E2) is promoted in adipocytes by aromatase and 17β-hydroxysteroid dehydrogenase (17β-HSD) via testosterone (T) or estrone (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-κB (NF-κB), 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

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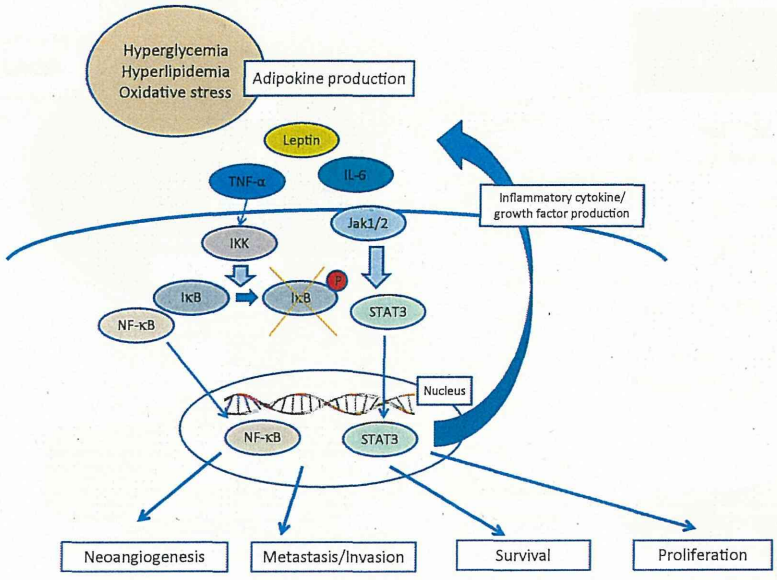

Fig. 3. Pathophysiological mechanisms of inflammation induced by hyperglycemia and their role in oncogenesis. Hyperglycemia/hyperlipidemia and associated oxidative stress induce secretion of various biologically active substances including adipokines. Tumor necrosis factor-α (TNF-α) promotes IκB phosphorylation (P) and degradation via the IκB kinase (IKK) pathway, thereby inducing nuclear factor-κB (NF-κB) activation. The other cytokines induce signal transducer and activator of transcription-3 (STAT3) activation via the Jak1/2 pathway. The NF-κB 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-κB[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, hypoadiponectinemia 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/m^2 or higher are placed at a higher risk of developing cancer than those remaining within the normal BMI range (18.5–24.9 kg/m^2)[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/m^2 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-

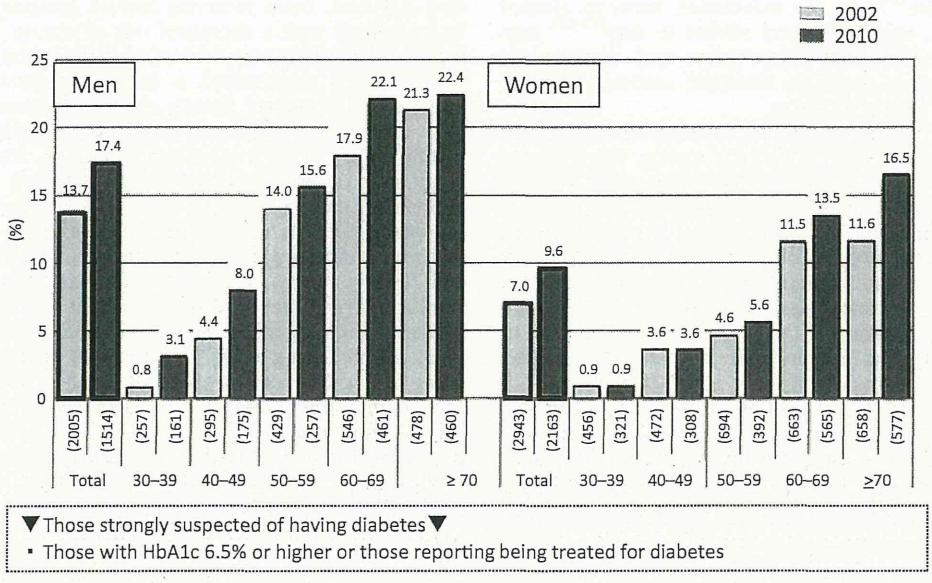

Fig. 4. Proportion of individuals in Japan strongly suspected of having diabetes, 2002 *versus* 2010. Source: Ministry of Health, Labour and Welfare of Japan. National Health/Nutrition Survey 2012.[60]

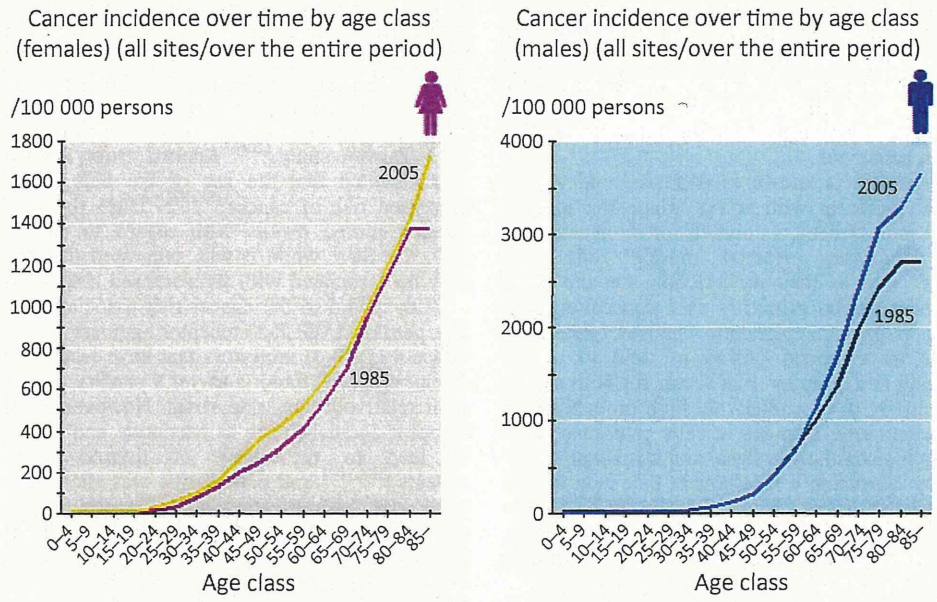

Fig. 5. Cancer incidence in Japan by age class over time, 1985 *versus* 2005. Source: Center for Cancer Control and Information Services, National Cancer Center, Japan (http://ganjoho.jp/pro/statistics/en/gdball.html).[61]

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

doi: 10.1111/cas.12203

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-κB 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