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Substantially increased risk of cancer in patients with diabetes mellitus☆,☆☆
A systematic review and meta-analysis of epidemiologic evidence in Japan

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Abstract

Aims: Several meta-analyses have shown that diabetes mellitus affects the risk of certain site-specific cancers. However, a meta-analysis on the overall risk of cancer has not yet been performed. **Methods:** We performed a search of MEDLINE and the Cochrane Library for pertinent articles (including their references) that had been published as of June 10, 2010. English-language, original observational cohort studies and case-control studies conducted in Japan were included for a qualitative review and a meta-analysis. **Results:** A total of 22,485 cancer cases were reported in four cohort studies and one case-control study (with a total of 250,479 subjects). With these five reports, a meta-analysis of the all-cancer risk in both men and women showed an increased risk in subjects with diabetes, compared with nondiabetic subjects (OR 1.70, 95% CI 1.38–2.10). The increase in the risk ratio adjusted for possible confounders was significant in men and borderline in women (adjusted RR 1.25, 95% CI 1.06–1.46 in men; adjusted RR 1.23, 95% CI 0.97–1.56 in women). An analysis of site-specific cancers revealed increased risks for incident hepatocellular cancer (OR 3.64, 95% CI 2.61–5.07) and endometrial cancer (OR 3.43, 95% CI 1.53–7.72). **Conclusions:** As is the case in Western countries, Asian people with diabetes have a higher risk of incident cancer than those without diabetes. Cancer prevention and early detection should be important components of diabetes management in light of the exponentially increasing prevalence of diabetes, which has substantial implications in public health and clinical practices.

Keywords: Cancer; Diabetes; Risk; Meta-analysis; Systematic review

1. Introduction

A growing body of evidence indicates that diabetes is associated with an increased risk of developing cancer. The mechanisms are yet to be elucidated but insulin resistance with secondary hyperinsulinemia is the most supported hypothesis since it may have a mitogenic effect by activating insulin-like growth factor-1 receptor (Bruning et al., 1992; Giovannucci, 1995; Hu et al., 1999; Kaaks, 1996; Kim, 1998; Le Roith, 1997; Silverman et al., 1999; White, 1997; Wolf et al., 2005; Yu, & Berkel, 1999; Zhang, Thornton, & MacDonald, 1998). Hyperglycemia may be another important factor (Barclay et al., 2008; Gapstur et al., 2000; Jee et al., 2005; Seow et al., 2006), although the possibilities of methodological issues, bias, and occult malignant tumors cannot be completely excluded.

Meta-analyses have recognized that diabetes mellitus increases the risks of site-specific cancers of the breast

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(Larsson, Mantzoros, & Wolk, 2007), endometrium (Friberg et al., 2007), bladder (Larsson et al., 2006), liver (El-Serag, Hampel, & Javadi, 2006), colorectum (Larsson, Orsini, & Wolk, 2005), and pancreas (Everhart, & Wright, 1995; Huxley et al., 2005), and decreases the risk of prostate cancer (Bonovas, Filioussi, & Tsantes, 2004; Kasper, & Giovannucci, 2006). However, the association of diabetes with all types of cancer remains uncertain.

As in other countries, the prevalence of diabetes is markedly increasing in Japan: the estimated number of persons with diabetes was about 8.9 million (prevalence 7.1%) in 2007, 7.4 million (prevalence 5.4%) in 2002, and 6.9 million (prevalence 5.5%) in 1997 (Ministry of Health, Labour, and Welfare of Japan, 2005, 2007). This trend is presumably attributable to the rapid westernization of Japanese lifestyle, a trend that is likely shared by the majority of East Asian populations (Chan et al., 2009). While cardiovascular disease is the main cause of mortality in Western countries and subjects with diabetes have a high risk of such disease, cancer is the leading cause of death in Japan (Hotta et al., 2007), and the prevalence of cancer in the general population is also increasing. In light of the current diabetes epidemic and the higher mortality in cancer patients with diabetes (Barone et al., 2008), elucidating the association of these diseases in populations with elevated risks, such as the Japanese population, is crucial for making timely, rational, and informed decisions not only in the areas of public health and socioeconomy, but also in prevention and targeted management of diabetes during daily clinical practice both domestically and globally.

These circumstances prompted us to explore the effect of diabetes on the overall cancer incidence with more precision by conducting a scrutiny of pertinent reports originating from Japan and combining their data.

2. Methods

2.1. Data sources and searches

Searches of MEDLINE and the Cochrane Library from their inceptions until June 10, 2010, were performed, and articles investigating the cancer incidence in diabetic adult patients and nondiabetic subjects were extracted. Relevant reports were identified using a combination of the following medical subject heading terms: 'diabetes,' 'cancer,' or 'neoplasms,' and 'risk' or 'risk factors,' and were limited to those originating from Japan. The reference lists of pertinent articles were also inspected.

We included observational studies evaluating type 2 diabetes but not impaired glucose tolerance/impaired fasting glucose. Cohort studies and case-control studies evaluating the risk of cancer based on original data analyses were assessed to determine their eligibility for inclusion in a qualitative analysis. Among these studies, cohort studies reporting event numbers and case-control studies providing numbers in each exposure category were eligible for inclusion in the meta-analysis. To further elucidate the magnitude of the risk of cancer in patients with diabetes, subgroup analyses for each sex- and site-specific cancers were performed.

2.2. Data extraction and quality assessment

Two independent investigators (H.N. and K.O.) reviewed each full-text report to determine its eligibility and extracted and tabulated all the relevant data. The extracted data included the characteristics of the subjects (including age, sex, and other comorbidities), study design, study years, follow-up period, and diagnosis criteria for diabetes and cancer. Disagreement was resolved by consensus between the two review authors. To ascertain the validity of eligible studies, the quality of each report was appraised in reference to the STROBE statement (von Elm et al., 2008).

2.3. Data synthesis and statistical analysis

If more than one study was published for the same cohort, the report with the information on all-cancer incidences or with the most comprehensive population was included to avoid overlapping populations. This process excluded four articles from the systematic review (Lin et al., 2002; Luo et al., 2007; Shibata et al., 2003; Washio et al., 2007). One additional investigation on atomic bomb survivors (Goododman et al., 1997) was also excluded because such a cohort is extremely atypical and its generality was deemed to be poor. If an article provided raw numbers for the risks of all cancer and site-specific cancers, the all-cancer data were included in the primary qualitative and quantitative analyses and the site-specific data were used in secondary analyses performed according to cancer site. The risks for site-specific cancers were appraised if three or more qualified reports were identified for a given cancer site. If an article reported the sex-specific risk separately, the raw data were integrated before inclusion into the systematic review and meta-analysis. Subgroup analyses for each sex with adjustment for possible confounding factors were also performed for all cancers using the available data.

The reports were summarized both qualitatively and quantitatively. In the meta-analysis, the pooled unadjusted odds ratio (OR) using raw data, the adjusted risk ratio (RR) for possible confounders, and 95% confidence interval (CI) were calculated using the Mantel–Haenszel random-effects model. Hazard ratio (HR) in cohort studies and adjusted OR in case-control studies were integrated to estimate the pooled adjusted RR. Heterogeneity between studies was evaluated using I^2 statistics. The possibility of a publication bias, which can result from the nonpublication of small trials with negative findings, was assessed visually using a funnel plot for asymmetry. A sensitivity analysis was performed by excluding the case-control studies. Subgroup analyses according to sex and cancer site were also performed. RevMan (version 5) was used for all the calculations. All the

procedures followed the guidelines for the meta-analysis of observational studies in epidemiology (Stroup et al., 2000) and the PRISMA statement (Liberati et al., 2009).

3. Results

3.1. Search results

A total of 34 citations were identified during our search; of these citations, 12 met the inclusion criteria for our review of the effect of diabetes on all-cancer or site-specific cancer incidence (Fig. 1). Most of the excluded studies did not report the RR for cancer development or did not provide original data. Of the 12 articles that met the inclusion criteria, five addressed the risk of all cancer providing original data and were included in the systematic review and meta-analysis. Eleven articles investigated site-specific cancer risks, and these articles were included in the systematic review. Among these 11 articles, one report was excluded from the meta-analysis because the event numbers used in the calculations were not provided (Mizuno et al., 1992).

The 12 selected articles consisted of seven cohort studies and five case-control studies, which were moderately heterogeneous. Table 1 shows the characteristics of each study included in our systematic review according to the study design, the site of cancer, and the year of each study's publication. There are four cohort studies (Fujino et al., 2001; Inoue et al., 2006; Khan et al., 2006; Oba et al., 2008) and one case-control study (Kuriki, Hirose, & Tajima, 2007) on all cancer. The sample sizes of these studies ranged from 7308 to 97,771 (median 56,881). 42.5% of the subjects involved in the meta-analysis of all-cancer risk were men; the majority of the age ranges were between 40 and 79 years. A total of 22,485 all-cancer cases were included among the 250,479 subjects reported in these five studies. In the four cohort studies mentioned above, the overall prevalence of diabetes was 5.0% at baseline, and 10,813 cancer cases developed among 191,039 subjects during a mean follow-up period of 9.2 years. The RRs of cancers of the liver (n=8),

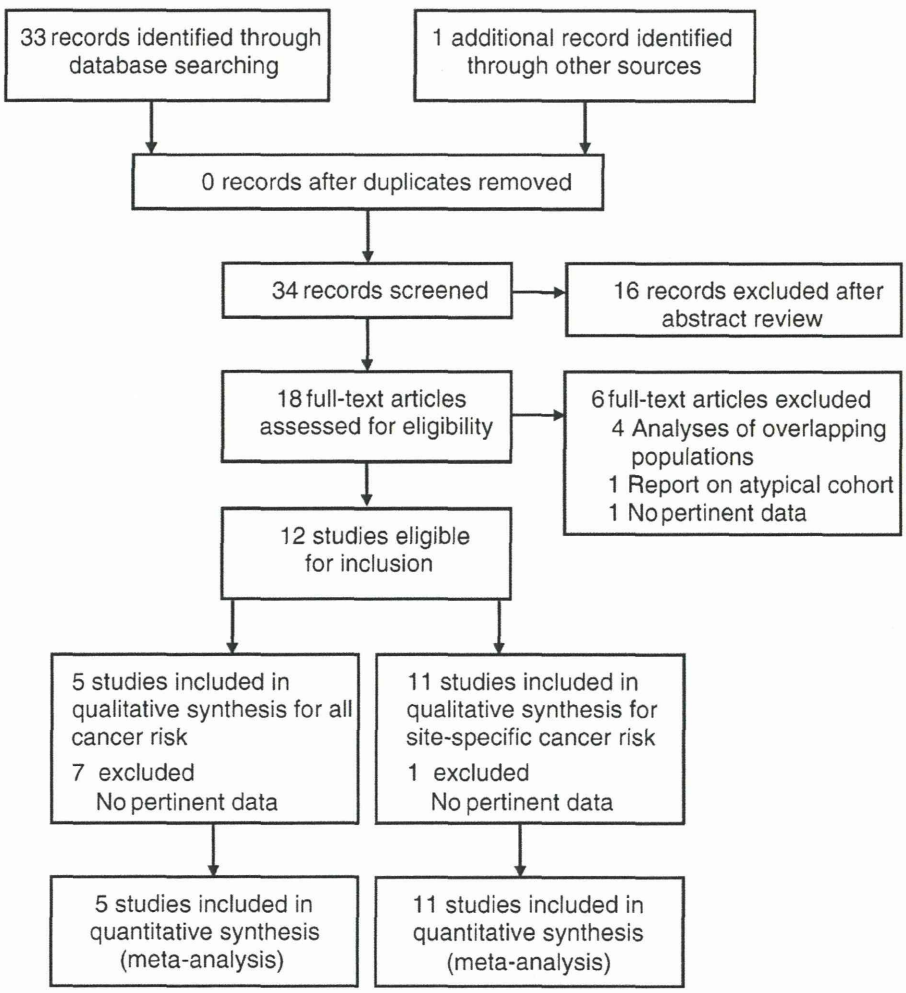

Fig. 1. Summary of the study selection.

Table 1
Characteristics of studies included in the systematic review and meta-analysis of cancer risk in subjects with diabetes

Source	Follow-up, years	Cancer Site	DM, *n* (%)	Control, *n*	Age, years	Men, %
Cohort studies						
Fujino et al., 2001	10	All, liver	364 (5.0)	6944	Mean 55.4 range 40–79	49
Khan et al., 2006	9	All, liver, pancreas	3307 (5.8)	53574	Range 40–79	41
Inoue et al., 2006	Mean 10.7	All, liver, pancreas	4668 (4.8)	93103	Mean 51.6, range 40–69	48
		Endometrium	1571 (3.1)	49652	Mean 51.8	0
Oba et al., 2008	7	All	1217 (4.2)	27862	Mean 54.6	46
Tazawa et al., 2002	Mean 5.5	Liver	23 (8.2)	256	Mean 49.4, range 23–72	68
Uetake et al., 2003	Median 5.9, range 0.5–12.5	Liver	26 (28.6)	65	Mean 50.1, range 34–72	100
Torisu et al., 2007	Median 6.8	Liver	11 (23.4)	36	Median 54, range 34–80	100
Case-control studies						
Kuriki et al., 2007		All	2491 (4.2)	56949	Mean 59.0	33
		Liver	1781 (3.7)	46383		30
		Pancreas	1748 (3.6)	46211		30
		Endometrium	793 (2.4)	33030		0
Matsuo, 2003		Liver	70 (15.8)	374	Mean 63.7	80
Inoue et al., 1994		Endometrium	20 (7.0)	265	Median 53.6, range 22–78	0
Yamazawa et al., 2003		Endometrium	12 (29.2)	152	Range 27–53	0
Mizuno et al., 1992		Pancreas	Not reported	Not reported	Range 40–79	55

The data for men and for women were combined.

pancreas (*n*=4), and endometrium (*n*=4) were evaluated in 11 reports.

The risk of bias among the studies is summarized in Table 2. Four reports investigated the RR using population-based data, while the remaining reports used hospital-based data. Diabetes was diagnosed using self-reports (*n*=6), blood tests (*n*=3), and medical records (*n*=2), and all the diagnoses had been made prior to 1999. One study did not report the method used to diagnose diabetes. The diagnosis of cancer was confirmed using medical records (*n*=7), population registries (*n*=3), and death certificates (*n*=2). One study did not adjust the estimate for potential confounders.

3.2. Qualitative summary

All of the five studies on the risk of all-type cancer were methodologically fair in quality (Tables 1 and 2). Of the four large-scale population-based cohort studies (Fujino et al., 2001; Inoue et al., 2006; Khan et al., 2006; Oba et al., 2008) and one case-control study (Kuriki et al., 2007) that reported RRs for all cancer, none reported a decreased risk among patients with diabetes. Fujino et al. (2001) reported a significantly increased risk for men and women combined in a cohort study. In four other studies that reported the risks in men and women separately, diabetes was significantly associated with elevated risks in men (Inoue et al., 2006; Kuriki et al., 2007) and women (Kuriki et al., 2007; Oba et al., 2008). The significant risk increments ranged from 27% to 88%. The estimate in a cohort study conducted by Khan et al. (2006) was not significantly elevated either in men or in women.

Among the six cohort studies and five case-control studies reporting the risks of site-specific cancers in patients with diabetes, more than one study (including subgroup analyses) recognized significantly increased risks for cancers of the liver (Fujino et al., 2001; Inoue et al., 2006; Khan et al., 2006; Kuriki et al., 2007; Matsuo, 2003; Tazawa et al., 2002; Torisu et al., 2007), endometrium (Inoue et al., 1994; Kuriki et al., 2007; Yamazawa et al., 2003), pancreas (Inoue et al., 2006; Kuriki et al., 2007), stomach (Inoue et al., 2006; Kuriki et al., 2007), and lungs (Kuriki et al., 2007), and only one article showed a significantly decreased risk of gastric cancer in diabetic men (Khan et al., 2006). Five cohort studies (Fujino et al., 2001; Inoue et al., 2006; Khan et al., 2006; Torisu et al., 2007; Tazawa et al., 2002) and two case-control studies (Kuriki et al., 2007; Matsuo, 2003) of the eight reports on hepatocellular cancer showed that diabetes was associated with a significantly increased risk in both men and women. One cohort study (Inoue et al., 2006) and one case-control study (Inoue et al., 2006; Kuriki et al., 2007) of the four reports on pancreatic cancer showed a significantly increased risk in diabetic men. Three (Inoue et al., 1994; Yamazawa et al., 2003; Kuriki et al., 2007) of the four studies on endometrial cancer showed a significantly increased risk. All these risk increments were moderate (OR range 1.85–9.30). Of note, no significant increases or decreases in the risk of cancers of the breast, colorectum, bladder, or prostate were reported (*n*=3, each) (Inoue et al., 2006; Khan et al., 2006; Kuriki et al., 2007), except for a borderline increase in the risk of colon cancer in men in one report (Inoue et al., 2006). The number of studies

Table 2
Quality assessments of the included studies

Source	Subject source	Comorbidity	Diagnosis of diabetes	Cancer ascertainment	Adjustment factor
Cohort studies					
Fujino et al., 2001	Population based		Self-reported	Death certificates	Age, sex, smoking, alcohol
Khan et al., 2006	Population based		Self-reported	Population registries	Age, BMI, smoking, alcohol
Inoue et al., 2006	Population based		Self-reported	Population registries	Age, cardiovascular disease, smoking, alcohol, BMI, physical activity, vegetable, coffee
Oba et al., 2008	Population based		Self-reported	Death certificates	Age, smoking, BMI, physical activity, education, hypertension, diet, alcohol
Tazawa et al., 2002	Hospital based	Hepatitis C	Blood tests	Medical records	None
Uetake et al., 2003	Hospital based	Alcoholic cirrhosis	Not reported	Medical records	Age, alcohol, liver function, viral antibody
Torisu et al., 2007	Hospital based	Alcoholic cirrhosis	Blood tests	Medical records	Age, sex, alcohol, smoking, family history, transfusion, liver function, tumor marker
Case-control studies					
Kuriki et al., 2007	Hospital based		Self-reported	Outpatient registries	Age, BMI, alcohol, physical activity, bowel movement, family history, diet
Matsuo, 2003	Hospital based		Medical records	Medical records	Transfusion, smoking, alcohol
Inoue et al., 1994	Hospital based		Blood tests	Medical records	Age, obesity, parity, cancer history, hypertension
Yamazawa et al., 2003	Hospital based		Medical records	Medical records	Obesity, parity, hypertension, estrogen use, psychiatric medication
Mizuno et al., 1992	Hospital based		Self-reported	Medical records	Age, sex

BMI: Body mass index.

examining other cancer sites was three or fewer, so these studies were not reviewed in the present report.

3.3. Quantitative summary (meta-analysis)

On the basis of the quality appraisal in our systematic review, all the five reports on all-cancer risk were included in the meta-analysis (Fig. 2). Subjects with diabetes had a significantly increased risk of all cancer, compared with nondiabetic subjects (OR 1.70, 95% CI 1.38–2.10; I^2=90%, P<.00001). In a sensitivity analysis, the exclusion of the single case-control study (Kuriki et al., 2007) had a minimal effect on the pooled estimate (n=191,039; OR 1.67, 95% CI 1.26–2.21; I^2=89%, P=.0003). Fig. 3 shows the sex-specific adjusted RRs among the studies with relevant data. Diabetes was associated with a significant risk increase in men (adjusted RR 1.25, 95% CI 1.06–1.46; I^2=75%, P=.007) and a borderline risk increase in women (adjusted RR 1.23, 95% CI 0.97–1.56; I^2=73%, P=.01). Significant heterogeneity was observed across these studies. No apparent publication bias was visually appreciated using a funnel plot, although this analysis was likely underpowered (data not shown).

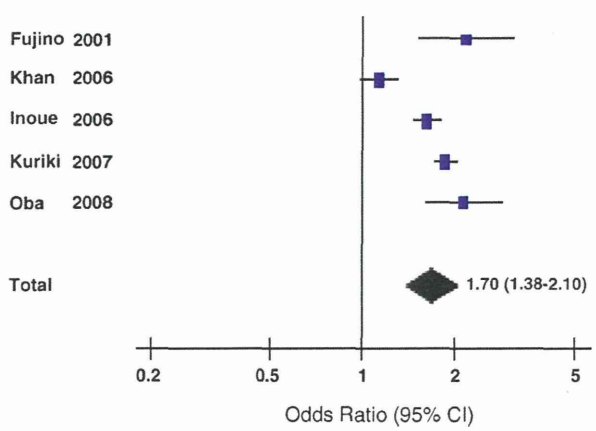

Fig. 2. Odds ratio (OR) for the all-cancer incidences among overall subjects with diabetes. Boxes, Estimated ORs; bars, 95% confidence intervals (CIs). Diamond, Mantel–Haenszel OR; width of diamond, pooled CI. The size of the box is proportional to the weight of each study in the meta-analysis.

Analyses of site-specific cancer risk using qualified data were performed for hepatocellular cancer and endometrial cancer, revealing significantly increased risks in patients with diabetes (OR 3.64, 95% CI 2.61–5.07 and OR 3.43, 95% CI 1.53–7.72, respectively) (Fig. 4). These estimates remained statistically significant after adjustment for possible confounders (adjusted RR 2.38, 95% CI 2.01–2.81; adjusted RR 2.71, 95% CI 1.19–6.19, respectively). A sensitivity analysis excluding three studies that included patients with alcoholic cirrhosis (Torisu et al., 2007; Uetake et al., 2003) or hepatitis C (Tazawa et al., 2002) resulted in an almost identical estimate (OR 3.64, 95% CI 2.93–4.52; adjusted RR 2.35, 95% CI 1.99–2.79). The risk of pancreatic cancer was not calculated because only two adequate studies (Inoue et al., 2006; Kuriki et al., 2007) were available for a meta-analysis.

4. Discussion

We found that diabetes is associated with a substantial increase in the total cancer incidence, based on a meta-

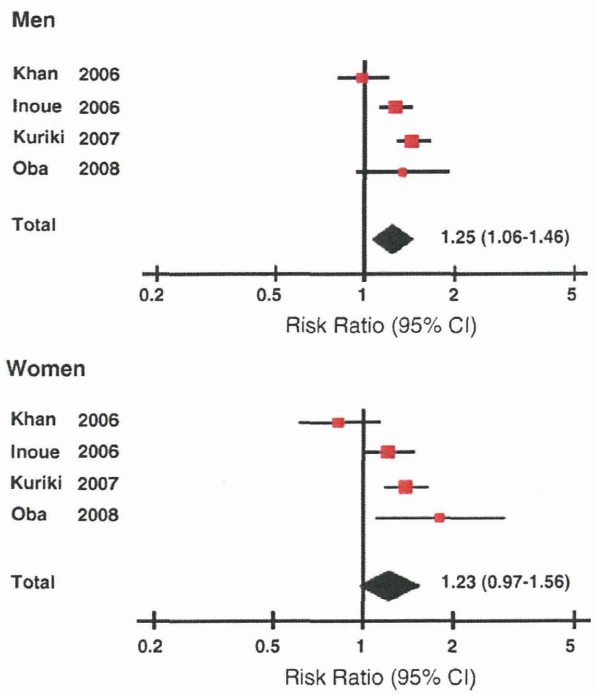

Fig. 3. Adjusted risk ratios (RRs) for the all-cancer incidences among diabetic men and women. Boxes, Estimated RRs; bars, 95% CIs. Diamonds, Mantel–Haenszel RRs; width of diamonds, pooled CIs. The size of the box is proportional to the weight of each study in the meta-analysis.

analysis of five population-based studies of epidemiological data in Japan. Our analysis also supports increased risks for hepatocellular cancer, endometrial cancer, and pancreatic cancer in patients with diabetes, consistent with previous meta-analyses examining worldwide trends (El-Serag et al., 2006; Friberg et al., 2007; Huxley et al., 2005). Reports addressing the risk of all cancer in diabetes have been scant, and our study, to our knowledge, is the first systematic review and meta-analysis. Our findings have remarkable clinical and socioeconomic implications in that the incident cancer risk proved to be significantly elevated in rapidly increasing Asian diabetic people whose beta-cell response to insulin resistance is inadequate (Boyko et al., 2000; Chan et al., 2004, 2009; Fukushima et al., 2004; Kadowaki et al., 1984; Kuroe et al., 2003).

The strength of the present research is that the analysis of overall cancer was mainly based on large population-based cohorts with high levels of precision and generality. Although the pooled OR is robust, the results of the component studies were statistically heterogeneous. This result most likely means that the dispersions fell within a narrow range but were estimated precisely because of the extremely large sample sizes, since the range of the ORs for each study result was narrow, none of the components showed a protective effect of diabetes on cancer development and the adjusted RRs in men and women were similar. A publication bias might have minimally accounted for this observation.

Insulin can exert a potentially mitogenic effect by interacting with insulin-like growth factor-1 receptor, which is the most frequently proposed hypothesis explaining the increased risk of cancer in patients with diabetes (Bruning et al., 1992; Giovannucci, 1995; Hu et al., 1999; Kaaks, 1996; Kim, 1998; Le Roith, 1997; Silverman et al., 1999; White, 1997; Wolf et al., 2005; Yu, & Berkel, 1999; Zhang et al., 1998). Type 2 diabetes is characterized by insulin resistance and secondary hyperinsulinemia. Subjects with type 2 diabetes are typically obese and inactive, which likely also contributes to hyperinsulinemia. In experimental insulin-deficient animals, the induction of pancreatic cancer with a carcinogen or with implantation of cancer cells is more effective when the animals are supplemented with insulin (Bell, McCullough, & Pour, 1988; Fisher et al., 1995). In humans, subjects with type 1 diabetes, who are deficient in insulin, reportedly have a lower risk of cancer than subjects with type 2 diabetes (Brinton et al., 1992; Lindblad et al., 1999). Hyperinsulinemia and hyperglycemia have also been reported to promote tumor cell proliferation and metastases in type 2 diabetes (Morss, & Edelman, 2007; Richardson, & Pollack, 2005). This hypothesis is supported by evidence that treatment with metformin, an insulin sensitizer, is associated with a lower incidence of cancer in diabetic patients than therapy with insulin or sulfonylurea

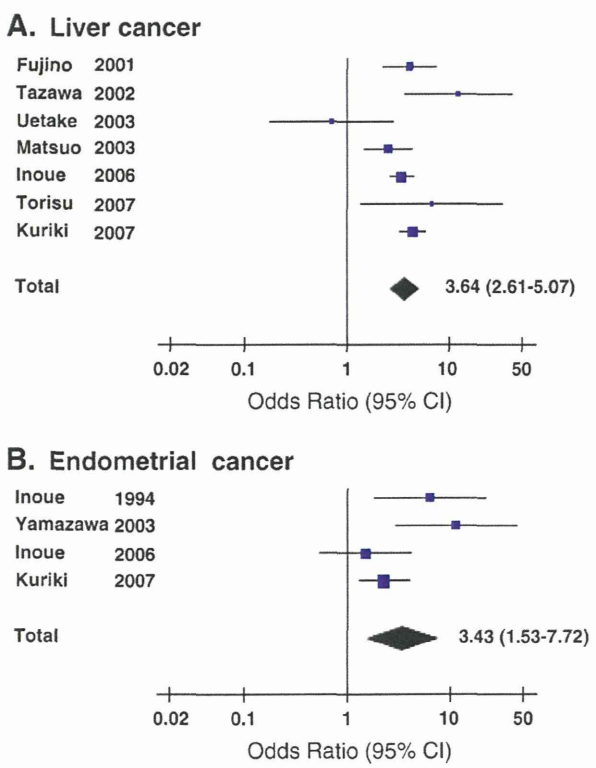

Fig. 4. Odds ratios for the site-specific cancer incidences among subjects with diabetes. (A) Liver in men and women; (B) endometrium in women. Boxes, Estimated ORs; bars, 95% CIs. Diamonds, Mantel–Haenszel ORs; width of diamonds, pooled CIs. The size of the box is proportional to the weight of each study in the meta-analysis.

(Currie, Poole, & Gale, 2009; Libby et al., 2009). Of interest, diabetes is reportedly protective against the development of prostate cancer (Bonovas et al., 2004; Kasper, & Giovannucci, 2006), which is testosterone dependent. Testosterone deficiency is common in men with diabetes or obesity secondary to low levels of sex hormone-binding globulin, and the testosterone level has been shown to be partly influenced by insulin resistance (Dhindsa et al., 2004; Ding et al., 2006; Grossmann et al., 2008). The magnitude of the decrease in cancer risk as a result of testosterone deficiency is speculated to be higher than that of the increase in cancer risk as a result of insulin resistance.

Of particular note is that the ORs of hepatocellular cancer and endometrial cancer in our present study among reportedly insulinopenic subjects were higher than those in previous reports [2.5 (El-Serag et al., 2006) and 2.1 (Friberg et al., 2007), respectively]. In addition, community-based prospective surveys including those in Asia reported associations between plasma glucose levels and cancer risks (Barclay et al., 2008; Gapstur et al., 2000; Jee et al., 2005; Seow et al., 2006). These facts point to the imminent need of understanding the role of glucose metabolism and insulin resistance in carcinogenesis (Chan et al., 2009; Karin, Lawrence, & Nizet, 2006).

Alternative explanations for the elevated risk of cancer in patients with diabetes should be noted, as the relation might not be causal. First, several potential confounders exist. For instance, coexisting obesity and physical inactivity, which induce hyperinsulinemia as mentioned earlier, might be the true causes and diabetes might merely be a risk factor (i.e., an "innocent bystander" or an "accomplice"). Cirrhosis is another possible confounding factor for diabetes and hepatocellular cancer. However, the adjusted RRs for all cancer in men, hepatocellular cancer, and endometrial cancer remained significantly elevated. The adjusted RR for women might have reached statistical significance if relevant data from the study by Fujino et al. (2001) had been available for inclusion. A second possibility is that diabetic subjects might receive medical care more frequently and have more occasions for cancer detection than nondiabetic subjects. Third, diabetes might develop as a consequence of cancer, since cancers generally cause insulin resistance and subsequent hyperglycemia by producing cytokines, such as tumor necrosis-α (McCall, Tuckey, & Parry, 1992; Noguchi et al., 1998).

Several limitations of our investigation should be noted. As with any overview, the possibility that relevant research papers were missed and the inability to adjust fully for confounders based on population-based registries must be considered. It is also important to realize that the populations of the studies were not homogenous and that the risks of site-specific cancers might have differed; therefore, an analysis of all cancer might be overly simplistic. Even with these limitations, our analysis should provide health care providers, policymakers, and patients with an important clue for assessing and managing cancer among patients with diabetes. Another limitation is that the diagnosis of diabetes in the extracted studies was mainly self-reported, which might have led to diagnostic inaccuracies. The prevalence of diabetes in our analysis was lower than the previously reported overall prevalence for Japanese individuals aged 40 years and older in the general population (5% vs. 8%) (Inoue et al., 2006), and the sensitivity and specificity of a self-reported history of diabetes in diagnosis of medically confirmed diabetes have been reported to be 46% and 98%, respectively (Waki et al., 2005). In addition, the baseline surveillance in these studies was conducted when the diagnostic cutoff value for fasting glucose was higher than the currently accepted value, and the prevalence of diabetes in the control groups most likely increased exponentially during the long follow-up interval. Thus, the true prevalence of diabetes and its impact on the associated cancer risk might have been underestimated.

In conclusion, our analysis strongly suggests that diabetes is associated with an increased risk of all cancer in the Japanese population, which should be applicable to the East Asian populations (Jee et al., 2005). It is likely applicable to diabetic people in other countries, given the consistency of increased risks in site-specific cancers and the shared insulin resistance as the underlying pathophysiology. Our findings underscore the need for diabetes prevention particularly by weight management, the implementation of effective cancer prevention and screening, and research on diabetes treatment with potentially protective effects against cancer, such as metformin (Currie et al., 2009; Li et al., 2009; Libby et al., 2009), in light of the exploding worldwide epidemic of diabetes and the subsequent socioeconomic burden of this disease on a global scale.

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発表論文

2) Noto H, Tsujimoto T, Sasazuki T, Noda M: Significantly increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis.
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Review Article

SIGNIFICANTLY INCREASED RISK OF CANCER IN PATIENTS WITH DIABETES MELLITUS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: To conduct a review and meta-analysis of the effect of diabetes mellitus on the incidence of and mortality attributable to cancer at any anatomic site.

Methods: We performed a search of MEDLINE and the Cochrane Library for pertinent articles published from the origin of these databases to July 5, 2010, and included them in a qualitative review and meta-analysis of the risk of all-cancer incidence and mortality in patients with diabetes.

Results: Among patients with diabetes (n = 257,222) in 12 cohort studies, the cancer incidence was about 7%. The cancer mortality was approximately 3% among patients with diabetes (n = 152,091) in 19 cohort studies. The pooled adjusted risk ratio (RR) of all-cancer incidence was significantly elevated—RR, 1.10 (95% confidence interval [CI], 1.04 to 1.17) overall; RR, 1.14 (CI, 1.06 to 1.23) for men; and RR, 1.18 (CI, 1.08 to 1.28) for women. Diabetes was also associated with an increased RR of mortality across all cancer types—RR, 1.16 (CI, 1.03 to 1.30) overall; RR, 1.10 (CI, 0.98 to 1.23) for men; and RR, 1.24 (CI, 1.11 to 1.40) for women.

Conclusion: Cancer prevention and early detection by appropriate screening methods in patients with diabetes should be important components of clinical management and investigation, inasmuch as the exponentially increasing prevalence of diabetes will translate into substantial clinical and public health consequences on a global scale. **(Endocr Pract. 2011;17:616-628)**

Abbreviations:
CIs = confidence intervals; **HRs** = hazard ratios; **RR** = risk ratio

INTRODUCTION

Considerable cumulative evidence suggests that diabetes is associated with an increased risk of cancer. The mechanisms are yet to be investigated, but insulin resistance with secondary hyperinsulinemia is the most frequently proposed hypothesis because insulin might have a mitogenic effect by binding the insulinlike growth factor-I receptor (1-11). In addition, hyperglycemia itself may promote carcinogenesis by increasing oxidative stress (12-18).

Meta-analyses have demonstrated that diabetes mellitus is associated with an increased risk of site-specific cancers of the breast (19), endometrium (20), bladder (21), liver (22), colorectum (23), and pancreas (24,25) and also a decreased risk of prostate cancer (26,27). The evidence for kidney cancer and non-Hodgkin lymphoma is still inconclusive. Furthermore, patients with cancer and preexisting diabetes have higher short-term (28) and long-term (29) mortalities. The association of diabetes with all-cancer incidence and mortality, however, remains uncertain.

In light of the current worldwide diabetes epidemic and the higher mortalities in patients with cancer and diabetes (28,29), elucidating the association between these diseases in general populations is crucial for making timely, rational, and informed decisions, not only in the areas of public

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health and socioeconomy but also for the prevention and targeted management of diabetes in daily clinical practice.

These circumstances prompted us to explore, with more precision, the effect of diabetes on the all-cancer incidence and mortality, by undertaking a scrutiny of the pertinent original reports and combining their data, in an attempt to obtain meaningful clues for the prevention and management of cancer.

MATERIALS AND METHODS

Data Sources and Searches

Searches of MEDLINE and the Cochrane Library from their inception until July 5, 2010, were performed, and articles investigating the cancer incidence and mortality in patients with and without diabetes were extracted. Relevant reports were identified by using a combination of the following medical subject heading terms: "diabetes," "cancer" or "neoplasms," and "risk" or "risk factors." The reference lists of the pertinent articles were also inspected.

We included observational studies evaluating type 2 diabetes, but not those focusing on impaired glucose tolerance, impaired fasting glucose, or solely type 1 diabetes. Cohort, case-control, and cross-sectional studies to evaluate the risk of cancer on the basis of original data analyses were assessed to determine their eligibility for inclusion in a qualitative analysis. Among these investigations, cohort studies reporting hazard ratios (HRs) adjusted for possible confounders and with confidence intervals (CIs) were eligible for inclusion in the meta-analysis. For further elucidation of the magnitude of the risk of all-cancer incidence and mortality in patients with diabetes, subgroup analyses for each sex were performed.

Data Extraction and Quality Assessment

We reviewed each full-text report to determine its eligibility, and we extracted and tabulated all the relevant data independently. The extracted data included the characteristics of the patients (including age, sex, and comorbidities), study design, study years, follow-up period, and methods used for ascertaining the presence or absence of diabetes and cancer. Any disagreement was resolved by consensus among the investigators. For ascertainment of the validity of the eligible studies, the quality of each report was appraised in reference to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement (30).

Data Synthesis and Statistical Analysis

If more than one study was published for the same cohort, the report with the information on the most comprehensive population was included, in an effort to avoid overlapping patient populations. This process necessitated exclusion of 2 articles from the systematic review (16,31). One other investigation among patients with diabetes and autopsy-proven nephropathy (32) was also excluded because cohorts with this condition are rare and the generalizability of the study was deemed to be poor.

The reports were summarized both qualitatively and quantitatively. Those studies that did not specify the case numbers were not included in the calculation of the incidence and mortality. In the meta-analysis, the HRs in cohort studies were combined, and the pooled risk ratio (RR) adjusted for possible confounders with 95% CI was calculated by using the random-effects model with inverse-variance weighting. The HR for the combination of men and women was estimated before pooling, if not provided in the original study. The second decimal place of the confidence interval values was estimated as needed. Heterogeneity among studies was evaluated by using I^2 statistics. The possibility of a publication bias, which can result from the nonpublication of small studies with negative findings, was assessed visually with use of a funnel plot for asymmetry. Subgroup analysis stratified by sex was also performed. Review Manager (RevMan) (version 5; the Cochrane Information Management Systems, Baltimore, Maryland) was used for all the calculations. All the procedures were in accordance with the guidelines for the Meta-analysis of Observational Studies in Epidemiology (33) and the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) statement (34).

RESULTS

Search Results

During our search, 1,314 citations were identified; after review of the material, 41 articles were assessed relative to their eligibility for inclusion in our report aimed at determining the influence of diabetes on all-cancer incidence and mortality (Fig. 1). Of these 41 articles, 32 (28 cohort studies, 3 cross-sectional studies, and 1 case-control study) were included in the systematic review and meta-analysis. More than half of the 9 excluded studies at this stage did not provide any pertinent information. Among the 28 cohort studies, 2 reports were excluded from the meta-analysis because the CIs were not provided (35,36).

In Tables 1 (15,36-47) and 2 (15,35,41,48-65) are shown the characteristics of each included study stratified by study design and the year of publication of the study. The 32 selected articles included in the systematic review were moderately heterogeneous in terms of the population demographics and assessment of the confounding factors. The diabetes sample size in these studies ranged from 224 to 109,581. About 7% of the patients with diabetes (total n = 257,222) in the 12 cohort studies developed cancer (Table 1), and approximately 3% of the patients with diabetes (total n = 152,091) in the 19 cohort studies died of cancer during the follow-up period (Table 2).

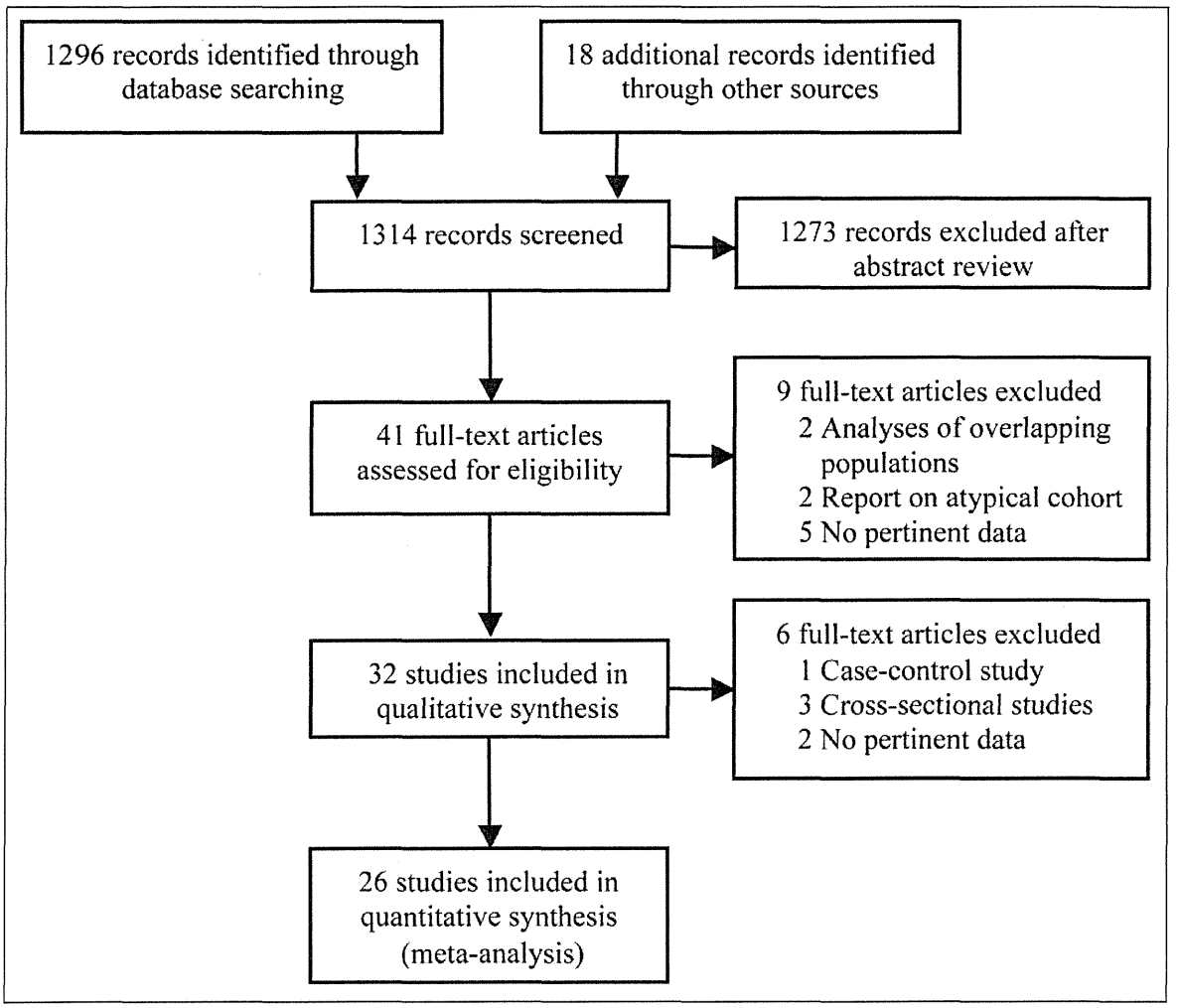

Fig. 1. Summary of the study selection.

The risk of bias among the studies is summarized in Tables 3 and 4. Among the 12 cohort studies and 1 case-control study referring to the cancer incidence, diabetes was diagnosed by using self-reports (n = 4) and prescription databases (n = 2), and 4 satisfied the current diagnostic criteria. All the diagnoses of cancer were confirmed by valid records or registries. Two published reports did not adjust the estimates for potential confounding factors, and 6 studies calculated the standardized incidence ratios. Among the 19 cohort studies and 3 cross-sectional studies on cancer mortality, diabetes was diagnosed by using self-reports (n = 9) and prescription databases (n = 4), and none satisfied the current diagnostic criteria. The diagnoses of cancer in all studies were confirmed by valid methods, except for one case ascertainment by family report. One report did not adjust the estimate for potential confounders, and 11 studies estimated the RR as the standardized mortality ratios.

Qualitative Summary

Most of the studies included were methodologically fair in quality (Tables 3 and 4). A few studies reported a significant decrease in the all-cancer mortality [1 cohort study (52) in men, none in women, and 1 cohort study (52) and 1 cross-sectional study (64) in men and women combined] and none reported a decrease in the all-cancer incidence among patients with diabetes. In contrast, several articles reported a statistically significant elevation in the risk of cancer incidence associated with diabetes [4 cohort studies (15,40,43,44) and 1 case-control study (47) in men, 5 cohort studies (15,38,40,44,45) and 1 case-control study (47) in women, and 1 case-control study (47) overall] and its mortality [3 cohort studies (15,50,57) and 2 cross-sectional studies (48,65) in men, 4 cohort studies (15,57,60,62) and 2 cross-sectional studies (48,65) in women, and 3 cohort studies (59,60,63) and 1 cross-sectional study (65) overall]. The significant increases in

Table 1
Characteristics of the Studies Included in the Systematic Review and Meta-analysis of the Cancer Incidence Risk in Patients With Diabetes[a]

Source	Follow-up (y)	Diabetes mellitus		
		No. (men, %)	Age (y)	Cancer cases (no.)
Cohort studies				
Jee et al (15), 2005	10	62,924 (60)	M: mean, 45 F: mean, 50	NS
Kath et al (36), 2000[b]	Mean, 4.3	2,720 (NS)	NS	28
Ragozzino et al (37), 1982	25	1,135 (NS)	NS	120
Adami et al (38), 1991	Range, 1-19	51,008 (45)	Mean, 45	2,417
Hjalgrim et al (39), 1997	Range, 1-19	772 (48)	≥30	101
Wideroff et al (40), 1997	Range, 1-16	109,581 (50)	M: median, 64 F: median, 69	8,831
Swerdlow et al (41), 2005	Mean, 18.0	5,066 (58)	Range, 30-49	341
Khan et al (42), 2006	9	3,307 (41)	Range, 40-79	215
Inoue et al (43), 2006	Mean, 10.7	4,668 (48)	M: mean, 54 F: mean, 51	470
Rapp et al (44), 2006	M: mean, 8.2 F: mean, 8.6	4,758 (44)	M: mean, 43 F: mean, 43	353
Stattin et al (45), 2007	M: mean, 8.3 F: mean, 8.2	1,706 (52)	M: mean, 46 F: mean, 46	110
Ogunleye et al (46), 2009	Mean, 3.9	9,577 (53)	Mean, 62	661
Case-control study				
Kuriki et al (47), 2007[b]	...	2,191 (33)	Mean, 59	766

Abbreviations: F = female patients; M = male patients; NS = not specified.
[a] The data for men and for women were combined.
[b] Not included in the meta-analysis.

the risk of all-cancer incidence and mortality calculated in these cohort studies ranged from 10% to 51% and from 11% to 88%, respectively.

Quantitative Summary (Meta-analysis)

On the basis of the quality appraisal in our systematic review, a total of 26 reports that provided sufficient information were included in the meta-analysis (Fig. 1). As depicted in Figure 2, patients with diabetes had a significantly increased risk of all-cancer incidence in comparison with those without diabetes (n = 11 studies; adjusted RR = 1.10 [95% CI, 1.04 to 1.17]; I^2 = 79%; P<.00001). The adjusted RRs for both men and women were also significantly elevated (n = 8 studies; RR = 1.14 [CI, 1.06 to 1.23]; I^2 = 81%; P<.00001 for men and n = 8 studies; RR = 1.18 [CI, 1.08 to 1.28]; I^2 = 83%; P<.00001 for women). As shown in Figure 3, diabetes was also associated with an increased RR of mortality across all cancer types (n = 14 studies; RR = 1.16 [CI, 1.03 to 1.30]; I^2 = 82%; P<.00001 overall; n = 13 studies; RR = 1.10 [CI, 0.98 to 1.23]; I^2 = 74%; P<.00001 for men; and n = 10 studies; RR = 1.24 [CI, 1.11 to 1.40]; I^2 = 65%; P = .002 for women). Significant heterogeneity was observed across these studies. No publication bias was apparent, as assessed with use of a funnel plot (data not shown).

DISCUSSION

We found that diabetes is associated with a moderately increased risk of all-cancer incidence and mortality, on the basis of our systematic review and meta-analysis of population-based observational reports of worldwide epidemiologic data. There is a paucity of analyses on the association between diabetes and any-site cancer, and our

Table 2
Characteristics of the Studies Included in the Systematic Review and Meta-analysis of the Cancer Mortality Risk in Patients With Diabetes[a]

Source	Follow-up (y)	Diabetes mellitus		
		No. (men, %)	Age (y)	Cancer deaths (no.)
Cohort studies				
Jee et al (15), 2005	10	62,924 (60)	M: mean, 45 F: mean, 50	NS
Green & Hougaard (35), 1984[b]	7	1,499 (52)	NS	39
Swerdlow et al (41), 2005	Mean, 18.0	5,066 (58)	Range, 30-49	255
Fuller et al (48), 1983[b]	Range, 11-14	5,971 (50)	NS	247
Levine et al (49), 1990	12	643 (58)	Range, 35-64	29
Balkau et al (50), 1991	15	298 (100)	Range, 44-55	22
Moss et al (51), 1991	8.5	1,772 (45)	Mean, 67	85
Wong et al (52), 1991	5	4,186 (51)	≥15	131
Smith et al (53), 1992	Range, 18-20	224 (100)	Range, 40-64	18
Sievers et al (54), 1996	7.5	1,562 (48)	≥15	27
Gu et al (55), 1998	22	710 (41)	Range, 25-75	61
Adlerberth et al (56), 1998	16	249 (100)	Mean, 56	22
Koskinen et al (57), 1998	5	58,000 (41)	Range, 30-74	1,421
Bruno et al (58), 1999	7	1,967 (68)	M: mean, 64 F: mean, 68	NS
Fujino et al (59), 2001	10	364 (49)	Mean, 59	38
Verlato et al (60), 2003	10	3,659 (47)	M: mean, 63 F: mean, 69	409
Saydah et al (61), 2003	16	427 (39)	Mean, 58	26
Oba et al (62), 2008	7	1,217 (46)	M: mean, 59 F: mean, 63	55
Landman et al (63), 2010	Median, 9.6	1,353 (42)	Mean, 68	122
Cross-sectional studies				
Fuller et al (48), 1983[b]	...	43,336 (42)	NS	3,135
Sasaki et al (64), 1985[b]	...	6,600 (NS)	Mean, 67.1	513
Tierney et al (65), 2001[b]	...	4,287 (NS)	≥18	9.7/y

Abbreviations: F = female patients; M = male patients; NS = not specified.
[a] The data for men and for women were combined.
[b] Not included in the meta-analysis.

current study, to the best of our knowledge, is the first systematic review and meta-analysis on this subject. In light of the facts that cancer is the 2nd and diabetes is the 12th leading cause of death worldwide (66) and that the number of people with diabetes is rapidly increasing, our findings have substantial clinical and public implications on a global scale and emphasize the necessity of further investigation of the interaction between these 2 conditions.

The strengths of the current research are that the analysis relative to overall cancer was mainly focused on large population-based cohorts originating from multiple nations and was performed with high levels of precision. Although the pooled RRs were robust, the results of the component studies were statistically heterogeneous. The large I^2 values indicate that the range of plausible risk estimates is wide, but there was very little evidence in our analysis to

Table 3
Quality Assessments of the Included Studies on Cancer Incidence[a]

Source	Country	Subject source	Comorbidity	Diagnosis of diabetes	Cancer ascertainment	Adjustment factors
Cohort studies						
Jee et al (15), 2005	Korea	Insurance registry-based	...	Self-report or blood test	Medical records, population registries, death certificates	Standardized incidence ratio
Kath et al (36), 2000[b]	Germany	Hospital-based	Insulin-treated DM, type 1/type 2 mixed	Blood test	Medical records	None
Ragozzino et al (37), 1982	United States	Population-based	...	Blood test	Medical records, death certificates, autopsy reports	Standardized incidence ratio
Adami et al (38), 1991	Sweden	Population-based	...	Hospital record	Population registries	Standardized incidence ratio
Hjalgrim et al (39), 1997	Denmark	Population-based	Insulin-treated DM	Prescription database	Population registries	Standardized incidence ratio
Wideroff et al (40), 1997	Denmark	Hospital-based	Type 1/type 2 mixed	Hospital record	Population registries	Standardized incidence ratio
Swerdlow et al (41), 2005	United Kingdom	Population-based	Insulin-treated DM	Prescription database	Population registries	Standardized incidence ratio
Khan et al (42), 2006	Japan	Population-based	...	Self-report	Population registries	Age, body mass index, smoking, alcohol
Inoue et al (43), 2006	Japan	Population-based	...	Self-report	Population registries	Age, cardiovascular disease, smoking, alcohol, body mass index, physical activity, green vegetable intake, coffee
Rapp et al (44), 2006	Austria	Population-based	...	Blood test	Population registries	Age, body mass index, occupation, smoking
Stattin et al (45), 2007	Sweden	Population-based	...	Blood test	Population registries	None
Ogunleye et al (46), 2009	Scotland	Hospital-based	...	Physician report	Population registries	Deprivation
Case-control study						
Kuriki et al (47), 2007[b]	Japan	Hospital-based	...	Self-report	Outpatient registries	Age, body mass index, alcohol, physical activity, bowel movement, family history, diet

Abbreviation: DM = diabetes mellitus.
[a] The data for men and for women were combined.
[b] Not included in the meta-analysis.

Table 4
Quality Assessments of the Included Studies on Cancer Mortality[a]

Source	Country	Subject source	Comorbidity	Diagnosis of diabetes	Cancer ascertainment	Adjustment factors
Cohort studies						
Jee et al (15), 2005	Korea	Insurance registry-based	…	Self-report or blood test	Medical records, population registries, death certificates	Standardized mortality ratio
Green & Hougaard (35), 1984[b]	Denmark	Population-based	Insulin-treated DM	Prescription database	Population registries	Standardized mortality ratio
Swerdlow et al (41), 2005	United Kingdom	Population-based	Insulin-treated DM	Prescription database	Population registries	Standardized mortality ratio
Fuller et al (48), 1983[b]	United Kingdom	Population-based	…	Self-report	Population registries	Standardized mortality ratio
Levine et al (49), 1990	United States	Employment registry-based	…	Self-report or medical records	Death certificates	Age, body mass index, smoking, systolic blood pressure, cholesterol, education, hypertension treatment
Balkau et al (50), 1991	France	Employment registry-based	…	Blood test	Family report, medical records	Standardized mortality ratio
Moss et al (51), 1991	United States	Population-based	…	Blood test	Death certificates	Standardized mortality ratio
Wong et al (52), 1991	United Kingdom	Clinic-based	Type 1/type 2 mixed	Medical records	Medical records	Standardized mortality ratio
Smith et al (53), 1992	United Kingdom	Population-based	…	Self-report or blood test	Death certificates	Age
Sievers et al (54), 1996	United States (Pima Indians)	Population-based	…	Blood test	Death certificates	Age, sex
Gu et al (55), 1998	United States	Population-based	…	Self-report	Death certificates	Age
Adlerberth et al (56), 1998	Sweden	Population-based	…	Self-report	Population registries	Age, cholesterol, systolic blood pressure, smoking, body mass index, coronary heart disease
Koskinen et al (57), 1998	Finland	Population-based	…	Prescription database	Death certificates	None
Bruno et al (58), 1999	Italy	Population-based	…	Medical records, prescription database	Population registries	Standardized mortality ratio
Fujino et al (59), 2001	Japan	Population-based	…	Self-report	Death certificates	Age, sex, smoking, alcohol
Verlato et al (60), 2003	Italy	Population-based	…	Medical records	Death certificates	Standardized mortality ratio
Saydeh et al (61), 2003	United States	Population-based	…	Self-report or blood test	Death certificates	Age, sex, race, education, smoking, alcohol intake, physical activity, high-density lipoprotein cholesterol, systolic blood pressure, body mass index
Oba et al (62), 2008	Japan	Population-based	…	Self-report	Death certificates	Age, smoking, body mass index, physical activity, education, hypertension, diet, alcohol
Landman et al (63), 2010	The Netherlands	Clinic-based	…	Physician report	Medical records	Standardized mortality ratio
Cross-sectional studies						
Fuller et al (48), 1983[b]	United Kingdom	Death certificates	…	Death certificates	Death certificates	Standardized mortality ratio
Sasaki et al (64), 1985[b]	Japan	Population-based	…	Death certificates	Death certificates	Standardized mortality ratio, age
Tierney et al (65), 2001[b]	United States	Population-based	…	Death certificates	Death certificates	Age

Abbreviation: DM = diabetes mellitus.
[a] The data for men and for women were combined.
[b] Not included in the meta-analysis.

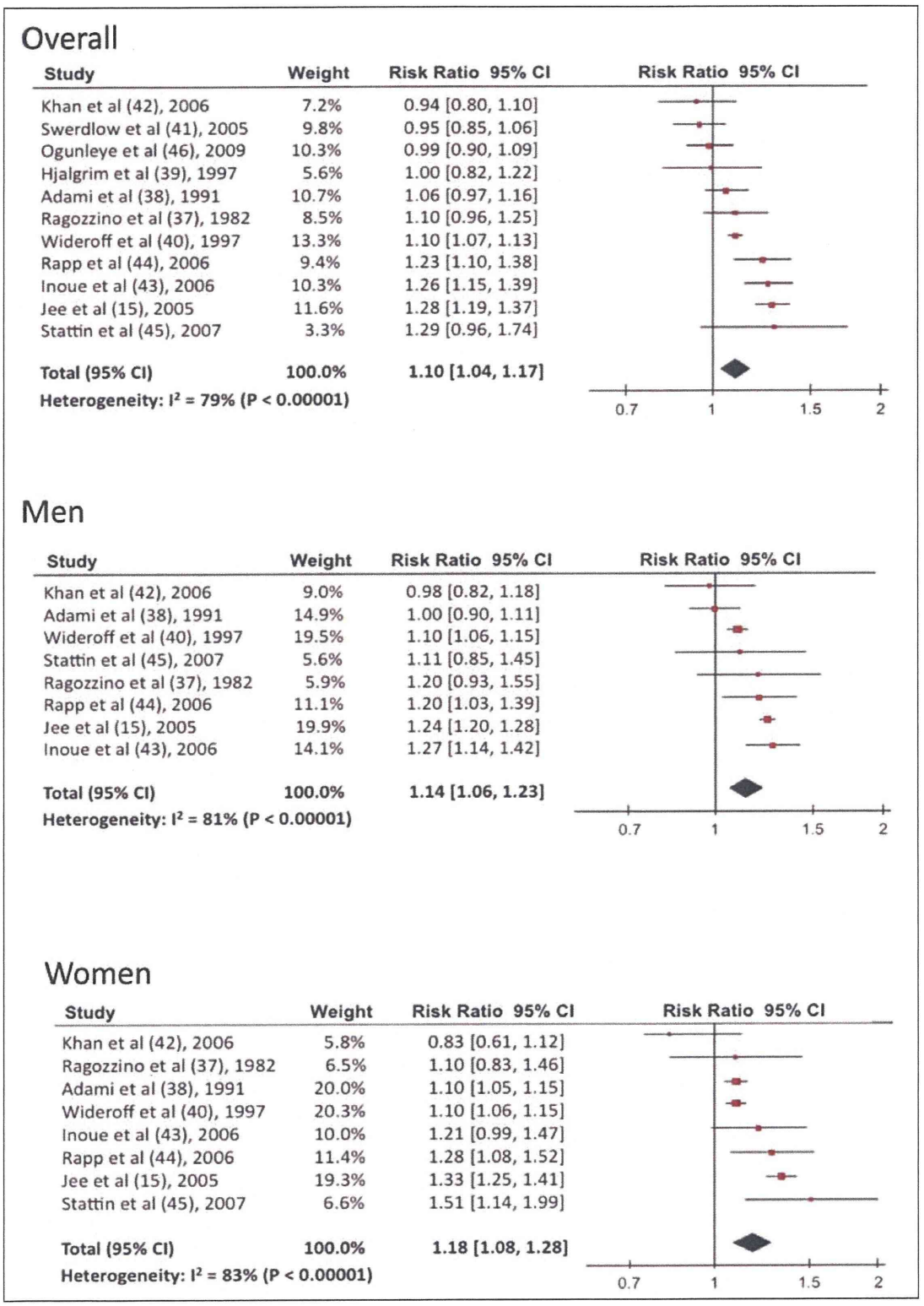

Fig. 2. Adjusted risk ratios (RRs) for the all-cancer incidence among overall patients (as well as stratified by men and women) with diabetes. *Boxes* = estimated RRs; *horizontal bars* = 95% confidence intervals (*CIs*); *diamonds* = RRs; *width of diamonds* = pooled CIs. The size of the box is proportional to the weight of each study in the meta-analysis.

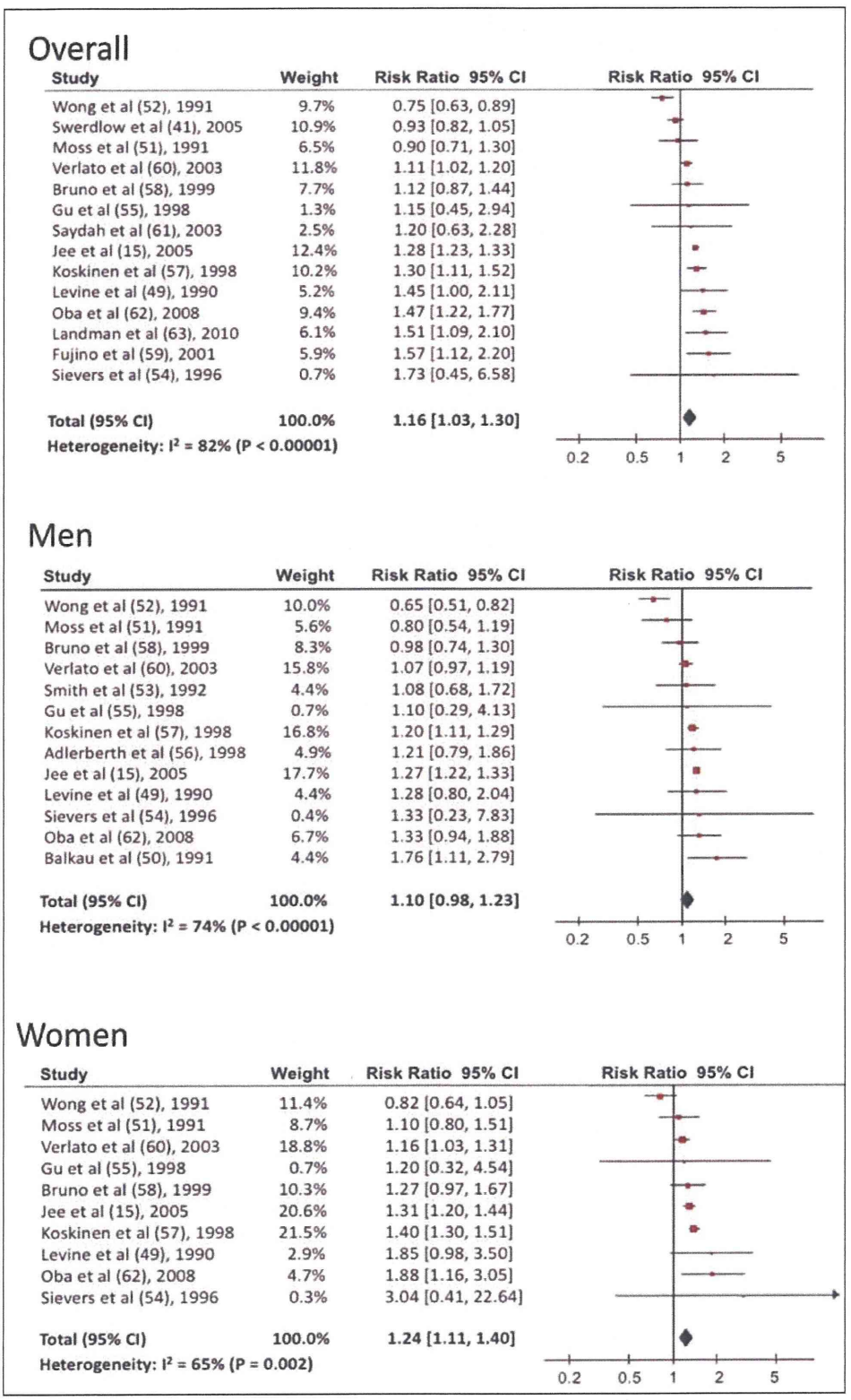

Fig. 3. Adjusted risk ratios (RRs) for the all-cancer mortality among overall patients (as well as stratified by men and women) with diabetes. *Boxes* = estimated RRs; *horizontal bars* = 95% confidence intervals (*CIs*); *diamonds* = RRs; *width of diamonds* = pooled CIs. The size of the box is proportional to the weight of each study in the meta-analysis.

support a protective effect of diabetes on all-cancer incidence and mortality. These findings might reflect the different mechanisms for development of cancer at various anatomic sites or different epidemiologic characteristics among the diverse populations included in our study (or both factors).

Investigators have suggested that insulin might have a potentially mitogenic effect by binding with insulinlike growth factor-I receptor, which is the most frequently proposed hypothesis to explain the apparently elevated risk of cancer in patients with diabetes (1-11). Type 2 diabetes is characterized by insulin resistance with compensatory hyperinsulinemia. Typically, patients with type 2 diabetes are obese and lead sedentary lives, which also contribute to the hyperinsulinemia. In experimental insulin-deficient animals, pancreatic cancer is reportedly induced more effectively with a carcinogen or implantation of cancer cells when they are supplemented with insulin (67,68). In humans, patients with type 1 diabetes, who are deficient in insulin, have a lower risk of cancer than do patients with type 2 diabetes (69,70), although the evidence of the risk in comparison with that in the general population is inconclusive (71,72). Even though these findings might support the insulin supply hypothesis, they are derived from retrospective observational studies, and because of possible confounders and biases, they do not necessarily demonstrate the causality (73,74). In fact, the data from insulin-treated patients are inconclusive (75).

Of interest, some studies have reported that diabetes protects against the development of prostate cancer (26,27), which is testosterone-dependent. Testosterone deficiency is common in men with diabetes or obesity attributable to low levels of sex hormone-binding globulin, and the testosterone level has been shown to be partly influenced by insulin resistance (76-78). The magnitude of the decrease in the cancer risk as a result of testosterone deficiency is likely higher than the magnitude of the increase in cancer risk as a result of insulin resistance. The increase in cancer mortality among men in our worldwide meta-analysis was not significant, whereas our previous meta-analysis on the cancer risk among men with diabetes in Japan, where the prevalence of prostate cancer is relatively low, showed a robust increase in the risk (adjusted RR 1.25) (79). It is speculated that this favorable effect of diabetes on prostate cancer may have contributed to the attenuation of the increase in the mortality risk found in the current study.

Hyperglycemia has also been reported to promote tumor cell proliferation and cancer metastatic involvement in patients with type 2 diabetes (80,81). This hypothesis is supported by evidence that the incidence of cancer is lower in patients with diabetes treated with metformin (82,83). In addition, hyperglycemia itself may promote carcinogenesis by generating oxidative stress (12-18), which is typically observed to be increased in diabetes, in a variety of cells. This situation would result in DNA damage, the initial step in carcinogenesis (17). Community-based prospective surveys have documented associations between plasma glucose levels and the risk of cancer (12-15). Our study supports this hypothesis in that the risks of both cancer incidence and mortality are also generally elevated among Japanese (43,47,59,62,79) and Korean (15) patients with diabetes, who are reportedly insulinopenic (84-88). These observations underscore the crucial need for understanding the role of glucose metabolism and insulin resistance in carcinogenesis (89,90).

Alternative explanations for the elevated risk of cancer in patients with diabetes should be assessed, inasmuch as the relationship might not be causal. First, several potential confounders exist. For example, coexisting obesity and a sedentary lifestyle, which induce hyperinsulinemia, may be the true causes, and diabetes might merely be a risk factor. The other confounders include age, sex, diet, alcohol habit, smoking habit, and cirrhosis, factors for which full adjustments were not made in this study. A second possibility is that patients with diabetes might receive medical care more frequently and have more opportunities for cancer detection than those without diabetes. Third, diabetes might develop as a consequence of cancer; generally, cancers cause insulin resistance and subsequent hyperglycemia by producing cytokines, such as tumor necrosis factor-α (91,92). Fourth, differences in the cancer treatment between patients with and those without diabetes may have contributed to the increased mortality among patients with diabetes. Often, patients with diabetes have other diabetes-related comorbidities that may influence the prognosis and treatment decisions. For example, diabetes may be accompanied by a high risk of infections, and the diagnosis of cancer may result in inappropriate glucose management.

Several limitations of our investigation should be noted. As with any overview, the possibility that relevant research articles were missed and the inability to adjust fully for confounding factors because of population-based databases must be taken into consideration. It is also important to realize that the populations of the various studies were heterogeneous, most likely attributable to ethnic diversity, and that the risks of site-specific cancers may have varied. Therefore, an analysis for cancer at any site might be overly simplistic and dilute the true associations. Even with these limitations, our analysis should prompt health care providers, policy makers, and patients to devise countermeasures for preventing and managing cancer among patients with diabetes. Another limitation is that the methods used to ascertain the presence of diabetes in the extracted studies included self-reports, which might have eventuated in diagnostic inaccuracies. In addition, the baseline surveillance in most of these studies was conducted when the diagnostic cutoff value for fasting plasma glucose was higher than the currently accepted value, and the prevalence of diabetes in the control groups most likely increased exponentially during the long follow-up period.