研究資料２　運動に関する質問票

身体活動についてのアンケート　厚生労働省多目的コホート班

(Appendix)　**身体活動についてのアンケート**　厚生労働省多目的コホート班
厚生労働省多目的コホート糖尿病研究班

お名前(　　)　年齢(　　)歳　生年月日 (T. S)　年　月　日
身長(　　)cm　体重(　　)kg

1、現在のお仕事は何ですか?
(　)内に具体的に記入してください。兼業や季節によって違うときはいくつでも○をつけてください。

1 農業	(① 米	②野菜	③果樹	④ 園芸	⑤ その他	)
2 林業	(				)	
3 漁業	(① 遠洋	② 近海	③ 養殖	④ その他	)	
4 勤務	(① 管理職	②事務内勤	③ 現場	④ 営業･外勤	⑤ その他	)
5 自営	(①商店	② 飲食店	③ 現場	④ 事務	⑤ その他	)
6 専門職	(				)	
7 主婦	(				)	
8 無職	(				)	
9 その他	(				)	

2、一日の労働時間はどのくらいですか?　家事労働も含めてください。

約(　　)時間

3、普段1日に仕事も含めて身体を動かす時間はどれくらいですか?○をつけてください。

1 筋肉労働や激しいスポーツは？
(①なし　②1時間未満　③1時間以上)

2 座っている時間は？
(①3時間以下　②3時間～8時間　③8時間以上)

3 歩いたり立っている時間は？
(①1時間未満　②1時間～3時間　③3時間以上)

4、普段は何時間睡眠をとりますか?

約(　　)時間

5、昨年1年間、睡眠は1日平均通常どのくらいとっていましたか?

約(　　)時間

6、仕事の他に何かスポーツや運動をする機会はどれくらいありますか？　○をつけてください。

(①ほとんどない　②月1～3日　③週1～3日　④週3～4日　⑤ほとんど毎日)

昨年1年間の「身体の動かし方」についておたずねします。

7、農繁期など、1年のほかの時期に比べて、仕事時の「身体の動かし方」が大きく変わる特に忙しい時期がありましたか。
ある場合にはその時期をお答えください。○をつけてください。

(①ない　②1ヶ月未満　③1ヶ月以上一2ヶ月未満　④2ヶ月以上一3ヶ月未満　⑤3ヶ月以上一4ヶ月未満　⑥4ヶ月以上一5ヶ月未満　⑦5ヶ月以上一6ヶ月未満)

8、1日の仕事の長さはどのくらいですか。通勤や家事の時間も含めてお答えください。
特に忙しい時期のあった方はその時期についてもお答えください。○をつけてください。

1日の仕事の長さ	①1時間未満	②1時間以上3時間未満	③3時間以上5時間未満	④5時間以上7時間未満	⑤7時間以上9時間未満	⑥9時間以上11時間未満	⑦11時間以上
1 通常の時期							
2 忙しい時期							

9、昨年1年間のうち、通常の時期の1日の仕事時間の内訳を教えてください。○をつけてください。
通勤や家事の時間も含めてお答えください。

仕事時間の内訳	①なかった	②1時間未満	③1時間以上3時間未満	④3時間以上5時間未満	⑤5時間以上7時間未満	⑥7時間以上9時間未満	⑦9時間以上11時間未満	⑧11時間以上
1 通勤、仕事、家事などで座っている時間								
2 通勤、仕事、家事などで立っている時間								
3 通勤、仕事、家事などで歩いている時間								
4 力のいる作業をしている 時間								

10、余暇での「身体の動かし方」についておたずねします。昨年、次のことを行う頻度と1回当たりの時間はどのくらいでしたか。○をつけてください。

余暇での身体の動かし方	頻度					1回当たりの時間					
	①月に1回未満	②月に1～3回	③週に1～2回	④週に3～4回	⑤ほぼ毎日	①30分未満	②30～59分	③1～2時間	④2～3時間	⑤3～4時間	⑥4時間以上
1 散歩などでゆっくり歩く											
2 ウォーキングなどで早足で歩く											
3 ゴルフ・ゲートボール・庭いじりなどの軽・中等度の運動											
4 テニス・ジョギング・エアロビクス・水泳などの激しい運動											

最近1ヶ月のおよその「身体のうごかし方」についておききします。

11、1日に歩く時間はどれくらいですか。○をつけてください。

（ ①30分未満　②30分～1時間未満　③1～2時間未満　④2～3時間　⑤3時間以上 ）

12、 平均的な1日でのおよその「身体のうごかし方」はどの程度ですか。○をつけてください。

①軽い（大部分の時間はすわって事務、勉強、談話などをしている場合）
②中程度（家事や機械の操作、接客、軽い農作業などで立ち仕事の時間が多い場合）
③やや重い（農業、漁業、建築などで、1日のうち1時間くらい重い筋作業をする場合）
④重い（木材の運搬、農繁期の農耕作業のような重い筋作業の場合）

ご協力ありがとうございました。

研究成果の刊行に関する一覧表

書籍

なし

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kayo Waki, Mitsuhiko Noda, Satoshi Sasaki, Yasuhiro Matsumura, Yoshihiko Takahashi, Akihiro Isogawa, Yasuo Ohashi, Takashi Kadowaki, Shoichiro Tsugane, for the JPHC Study Group.	Alcohol consumption and other risk factors for self-reported diabetes among middle-aged Japanese: a population-based prospective study in JPHC Study Cohort I.	Diabetic Medcine.	22	323-331	2005
Manami Inoue, Motoki Iwasaki, Tetsuya Otani, Shizuka Sasazuki, Mitsuhiko Noda, for the JPHC Study Group.	Diabetes mellitus and the risk of cancer. Results from a large-scale population-based cohort study in Japan.	Archives of Internal Medicine.	166	1871-1877	2006
野田光彦、津金昌一郎	厚生労働省研究班による多目的コホートにおける糖尿病研究.	栄養学レビュー	12	69－74	2004
野田光彦	糖尿病トピックス　日本人の飲酒はやはり危険因子　特にやせ形の男性は要注意—２型糖尿病.	メディカル朝日	33	76－78	2004
野田光彦	海外文献紹介 日本人の生活習慣と糖尿病との関係—特に飲酒との関係について—.	Diabetes Frontier	15	755－756	2004
野田光彦	２型糖尿病発症と生活習慣.	内分泌・糖尿病科	20	112－117	2005
野田光彦	糖尿病と喫煙・アルコール.	プラクティス	22	149	2005

脇　嘉代	喫煙・アルコールと２型糖尿病の発症：疫学的見地から.	プラクティス	22	181－187	2005
野田光彦	コーヒーと糖尿病の疫学.	からだの科学	244	34-38	2005
松下由実、野田光彦	メタボリックシンドローム予防策の今日	食生活	100	76-82	2006
津金昌一郎、野田光彦	糖尿病と悪性腫瘍：因果関係を証明するための研究方法	糖尿病合併症	20	119-121	2006
野田光彦	体質からみた肥満とやせ	日本体質医学会雑誌	69	99-102	2007

DOI: 10.1111/j.1464-5491.2004.01403.x

Alcohol consumption and other risk factors for self-reported diabetes among middle-aged Japanese: a population-based prospective study in the JPHC study cohort I

K. Waki, M. Noda*, S. Sasaki†, Y. Matsumura†, Y. Takahashi[1], A. Isogawa[2], Y. Ohashi‡, T. Kadowaki and S. Tsugane§ for the JPHC Study Group

Department of Metabolic Diseases, Graduate School of Medicine, University of Tokyo, *Department of Endocrinology and Metabolism, Toranomon Hospital, †National Institute of Health and Nutrition, ‡Department of Biostatistics, Graduate School of Medicine, University of Tokyo and §Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan

Accepted 15 March 2004

Abstract

Aims Few prospective studies have examined the relationship between lifestyle characteristics and the incidence of diabetes mellitus in an Asian general population. This study was undertaken to evaluate the risk factors for Type 2 diabetes in a population-based prospective study of middle-aged Japanese.

Methods We investigated 12 913 men and 15 980 women, aged 40–59 years at baseline (year 0), who participated in the Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study) Cohort I. The participants were followed for up to 10 years. Incident cases of diabetes were identified by self-reporting of a physician's diagnosis on two questionnaires sent to each participant, one at year 5 and the second at year 10.

Results During the 10-year follow-up, 703 men and 482 women reported newly diagnosed diabetes. Age, body mass index (BMI), family history of diabetes and cigarette smoking were independent risk factors in both genders by multivariate analysis. Among men with a BMI ≤ 22 kg/m^2, a significant positive association was observed between the diabetes incidence and moderate (23.0 < 46.0 g/day) to high (> 46.0 g/day) alcohol consumption, odds ratio 1.91 (95% CI, 1.05–3.46) and 2.89 (1.63–5.11), respectively. Among men with a BMI > 22 kg/m^2, a small non-significant increase in odds ratio was observed with alcohol consumption.

Conclusions Established risk factors for diabetes in western populations were also identified as predictors of the disease among Japanese. Moderate to high alcohol consumption was positively associated with the incidence of diabetes in Japanese lean (BMI ≤ 22 kg/m^2) men.

Diabet. Med. 22, 323–331 (2005)

Keywords diabetes mellitus, prospective study, risk factor

Abbreviations BMI, body mass index; CI, confidence interval; JPHC, Japan Public Health Center-based prospective study on cancer and cardiovascular diseases; OR, odds ratio; PHC, public health centre

Correspondence to: Dr Shoichiro Tsugane, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104–0045, Japan. E-mail: stsugane@ncc.go.jp
[1]The present address of Y. Takahashi is Department of Internal Medicine, Tokyo Hospital of the Printing Bureau, 2-3-6 Nishigahara, Kita-ku, Tokyo 114–0024, Japan.
[2]The present address of A. Isogawa is Department of Internal Medicine, Mitsui Memorial Hospital, 1 Kanda Izumi-cho, Chiyoda-ku, Tokyo 101–0024, Japan.

Introduction

Type 2 diabetes is associated with a genetic predisposition [1], but is also strongly influenced by lifestyle-related factors, such as eating habits and/or physical activity [2,3]. Japanese immigrants residing in the United States and Brazil, with a westernised lifestyle but a genetic background such as siblings in their homeland, have a higher prevalence of diabetes than Japanese people living in the Far East [4–7].

However, the situation may now have changed. The prevalence of diabetes has increased dramatically in many Asian nations over the past decades [8], including Japan, possibly because of changes from a traditional to a westernised lifestyle. Prevention of diabetes through suitable lifestyle modifications is an urgent health issue in this area of the world. Thus, it is important to evaluate the risk factors for diabetes in Asian general populations to determine whether the risk factors established in western populations [2,3] also apply to Asian ethnic groups. This will help to determine whether the strategies that have proven effective in Western countries can be applied to Asians. Few published studies have attempted to answer this question by a direct comparison of the influence of lifestyles on the future development of diabetes. Some have been cross-sectional [9,10] or, despite being longitudinal, were conducted in subjects who did not represent the general population [11–16]; others were too short to be reliable [17].

To quantify the risk factors for diabetes in a general Japanese population, we conducted a community-based, prospective cohort study on a relatively large number of middle-aged adults with an adequate follow-up period.

Patients and methods

The Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study) is an ongoing, longitudinal cohort study, investigating cancer, cardiovascular diseases and other lifestyle-related diseases. The total cohort has been divided into two, Cohort I and Cohort II [18], and the current study was conducted within the population-based part of Cohort I (the other smaller part consists of health check-up examinees), namely those residents who registered their address in one of 14 administrative districts supervised by four public health centres: the city of Ninohe and the town of Karumai in the Ninohe Public Health Center (PHC) area of Iwate Prefecture, the city of Yokote and the town of Omonogawa in the Yokote PHC area of Akita Prefecture, eight districts in Minami-Saku County in the Saku PHC area of Nagano Prefecture, and the city of Gushikawa and village of Onna in the Ishikawa PHC area of Okinawa Prefecture. The criteria for selecting the areas, subjects, and the methods of data collection have been reported previously [18,19]. This study was approved by the institutional review board of the National Cancer Center of Japan.

Participants

Briefly, 43 149 individuals (20 665 men and 22 484 women), aged 40–59 years at baseline, completed the baseline questionnaire upon enrolment in 1990 (year 0; response rates: 76% for men and 82% for women). Follow-up questionnaires were sent to each individual at years 5 and 10, and a total of 32 126 individuals (14 551 men and 17 575 women) returned both follow-up questionnaires (total follow-up rate: 74.5%; 70.4% for men and 78.2% for women). To construct the cohort for the current analysis, we excluded individuals who had any of the following conditions at baseline: diabetes (n = 1120; 742 men and 378 women), cardiovascular disease (n = 470; 257 men and 213 women), chronic liver disease (n = 311; 215 men and 96 women), kidney disease (n = 546; 214 men and 332 women) or cancer (n = 689; 205 men and 484 women). Individuals who had missing baseline data for any of the exposure parameters described below were also excluded (n = 298; 121 men and 177 women). After these exclusions, the remaining cohort consisted of 28 893 participants (12 913 men and 15 980 women) with data on incident diabetes.

Data collection

Each participant completed a self-administered questionnaire that included questions regarding weight and height, usual pattern of physical activity, smoking habits, alcohol intake, previously diagnosed medical conditions (including diabetes and hypertension), family history of diabetes, use of drugs, and other lifestyle factors. Subjects were classified according to smoking habit as 'never smoked', 'former smokers', and 'current smokers'; the last group was subdivided into two groups according to the number of cigarettes smoked daily: 1–19 or ≥ 20 cigarettes/day. Questions on alcohol intake included items about the types of alcoholic beverages consumed, the frequency of alcohol consumption (per week), and the usual amount of alcohol consumed daily. Total daily alcohol intake was calculated by multiplying the frequency of consumption by the alcohol content of the beverage: 23 g ethanol per 180 ml of Japanese sake (rice wine), 36 g ethanol per 180 ml of shochu or awamori (both Japanese distilled liquors), 10 g ethanol per 30 ml of whisky or brandy, 6 g ethanol per 60 ml of wine and 23 g ethanol per 633 ml of beer. According to their current drinking behaviour, the subjects were classified into two groups: 'non-drinkers and infrequent occasional drinkers (who consume alcohol on three or fewer days per month)' and 'drinkers'. The 'drinkers' category was further subdivided by the tertiles of daily ethanol consumption. We previously reported that this questionnaire was found to measure average alcohol consumption with a high degree of validity [19]. Physical activity was assessed using the replies to questions regarding the number of times per week or month that the subject engaged in sports activities during leisure time. Subjects were considered physically active if they participated in sports at least once a week; all other subjects were considered inactive. A history of hypertension was considered to exist if the subject had been informed of a diagnosis of hypertension by a doctor and/or was receiving a prescription for anti-hypertensive drug(s). The prevalence of hypertension as documented using the self-administered questionnaire was verified in a subpopulation of the cohort for whom health check-up data were available. In this subpopulation, documented hypertension was confirmed in 90.2% (1989/2204) of the subjects, i.e. those 1989 subjects fulfilled at least one of the following criteria: (i) systolic blood pressure ≥ 140

mmHg, (ii) diastolic blood pressure ≥ 90 mmHg or (iii) being prescribed anti-hypertensive drug(s). Among the 13 321 subjects without self-report-documented hypertension, 3097 had hypertension, i.e. fulfilled criterion (i) and/or (ii) and/or (iii). A subject's family history of diabetes was considered positive if at least one parent or one sibling had diabetes. Body mass index (BMI) was calculated as the weight (kg)/[height (m)]^2 and used as an index of relative weight. The subjects' weight and height acquired from the questionnaire were validated by the data obtained from the health check-up, which about one-third of the subjects voluntarily underwent [20].

Ascertainment of diabetes mellitus

Whether the subject had a prevalent disease was determined by the questions on the baseline questionnaire: i.e. 'Has a doctor ever told you that you have any of the following diseases?—diabetes (yes/no), hypertension (yes/no)', and so forth. 'Prevalent diabetes' was defined as a reply of 'yes' to the question concerning diabetes. Individuals with diabetes at baseline were excluded from this analysis. Individuals without diabetes at baseline who subsequently answered 'yes' on either or both of the follow-up questionnaires at years 5 and 10 were considered to have developed diabetes. A total of 1183 subjects (703 men and 480 women) reported the development of diabetes during the 10-year study period. We classified all incident cases of diabetes as Type 2, as the age of onset in this middle-aged cohort was 40 years or older.

To document the validity of the self-report, we examined a series of medical records as follows. For practical reasons, three of the 14 administrative districts were chosen to validate the questionnaire information. In these areas, there were 207 participants recorded as having diabetes at year 5. We sent a letter to these participants requesting permission to examine their medical records and 167 replies were received. Of these, 154 participants were confirmed as having diabetes again by self-report. Permission to review their medical records was obtained from 110 of the 154 participants, and the records of 93 participants (54 men and 39 women) of major hospitals were chosen for verification. Two specialists in diabetes (M.N. and Y.T.) reviewed the records, and diabetes was confirmed if any of the following criteria were met: (i) the World Health Organization (1985) criteria [21], (ii) a high casual plasma glucose level (≥ 11 mmol/l), or (iii) use of diabetic medication (insulin or oral hypoglycaemic agent). Thirty subjects (19 men and 11 women) met criterion (i), eight subjects (five men and three women) met criterion (ii), and 38 subjects (20 men and 18 women) met criterion (iii). When we applied the new criteria of the American Diabetes Association (1997) [22], the number of confirmed cases of diabetes did not change, as none of the subjects with a 2-h post-challenge level of < 11 mmol/l had a fasting plasma glucose level in the diabetic range specified by the new criteria alone. In summary, a diagnosis of diabetes was confirmed in a total of 76 of the 93 subjects (82%) who were screened, which we considered reasonable and sufficiently high for a large-scale study. Among the 17 subjects in whom a diagnosis of diabetes was not confirmed, the medical records of 12 subjects were unavailable (n = 9) or contained insufficient data to justify a diagnosis of diabetes (n = 3). When only subjects for whom complete medical records were available were analysed, the percentage of confirmed diagnosis increased to 94%.

We also conducted a cross-sectional survey to examine whether self-report of diabetes agreed with diagnosis based on health check-up data among Cohort I participants. We collected blood samples from 12 460 subjects (29% of the study cohort) who voluntarily participated in the health check-up examination. Participants were determined to have diabetic hyperglycaemia based on their health check-up data if at least one of the following criteria was met: (i) fasting plasma glucose ≥ 7 mmol/l, (ii) casual plasma glucose ≥ 11 mmol/l, or (iii) HbA_{1c} ≥ 6.1% [23]. In a preliminary analysis, out of 1075 subjects with diabetic hyperglycaemia, 498 reported diabetes; meanwhile, among 11 385 subjects without diabetic hyperglycaemia, 11 169 did not report diabetes. According to these results, the sensitivity and specificity of the questionnaire for diabetic hyperglycaemia was roughly 46% and 98%, respectively. Although these analyses were performed without regard to the self-reported current treatment for diabetes, the number of subjects with a self-report of pharmacological treatment without diabetic hyperglycaemia was very small (~0.4% of the total number of subjects who were without diabetic hyperglycaemia); therefore, overestimation of specificity by this was likely to be within a negligible range.

Analysis

All analyses were performed separately for men and women. The statistical significance of baseline differences with regard to diabetes status at follow-up in relation to established and suspected risk factors for Type 2 diabetes was assessed using t-tests and χ^2-tests. A P-value < 0.05 was considered significant. The cumulative incidence of diabetes over the 10-year period was selected as the outcome, (a) because risk estimates could be calculated directly, and (b) because the lack of precise dates of diabetes onset precluded the use of a person-year approach. The cumulative incidence was defined as the number of new cases of diabetes occurring during the 10-year follow-up period divided by the number of subjects at risk of developing diabetes at baseline. Multiple logistic regression analysis was used to assess the independent contributions of the risk factors to the subsequent risk for Type 2 diabetes and to obtain odds ratios that were adjusted for the other risk factors. Smoking status (four levels), alcohol intake [four levels, ALC_0 consists of non-drinkers (1349 men and 1916 women) and infrequent occasional drinkers who consume alcohol on three or fewer days a month (2449 men and 12 331 women)], physical exercise (active/inactive), family history of diabetes (positive/negative), and prevalent hypertension (positive/negative) were fitted as categorical variables in our logistic model. Because there were no significant interactions between any of the variables and the areas where the subjects resided, the geographical areas were not included as a variable in the final model and all four areas were analysed together. The 95% confidence interval for each odds ratio was calculated. The Mantel extension test was employed to analyse the trend across increasing levels of alcohol consumption. Statistical significance was determined by 95% confidence intervals not including 1.00 for logistic analyses. The statistical analyses were performed using SAS software (version 8.2; SAS Institute Inc., Cary, NC, USA).

To examine the possible existence of a significant interaction between alcohol consumption and BMI with regard to the risk

of diabetes, we conducted a stratified analysis for BMI with cut-off levels set at 22 and 25 kg/m^2; these values represent the ideal BMI and the lower BMI limit of obesity, respectively, for Japanese people as defined by the Japan Society for the Study of Obesity [24]. The former value was determined by the BMI associated with the lowest level of morbidity among middle-aged Japanese [25].

Results

Incident Type 2 diabetes mellitus (Table 1)

During the 10-year follow-up, we documented 703 incident cases (5.4%) of diabetes among men and 480 cases (3.0%) among women. There was male predominance in the incidence of diabetes.

Risk factors for diabetes at baseline (Table 2)

Subjects of both genders who converted to a diabetes-positive status were significantly older and had a higher BMI than those who remained non-diabetic. In addition, higher percentages of subjects were positive for smoking, family history of diabetes and past history of hypertension among those who became diabetic during the follow-up period than among those who remained non-diabetic. The percentage of men with moderate (ethanol intake: > 23 g/day and ≤ 46 g/day) or high (ethanol intake > 46 g/day) alcohol consumption was also higher among subjects who became diabetic during the follow-up compared with those who remained non-diabetic. There was an increasing trend for developing diabetes during the follow-up period according to alcohol consumption, and this positive trend was significant (P for trend = 0.007) by the Mantel extension test.

Table 1 Ten-year incidence of Type 2 diabetes mellitus in the JPHC Cohort according to gender

Age (years)	Men		Women	
40–49	309/6404	(4.8)	191/7698	(2.5)
	80/1471	(5.4)	52/1951	(2.7)
	80/1835	(4.4)	47/2230	(2.1)
	90/1900	(4.7)	47/2069	(2.3)
	59/1198	(4.9)	45/1448	(3.1)
50–59	394/6509	(6.1)	289/8282	(3.5)
	92/1386	(6.6)	71/1939	(3.7)
	98/1889	(5.2)	91/2650	(3.4)
	118/1955	(6.0)	81/2251	(3.6)
	86/1279	(6.7)	46/1442	(3.2)
Total	703/12 913	(5.4)	480/15 980	(3.0)

Data are incidence/total number and the per cent (in parentheses). Below the total number and per cent, incidence of diabetes and the per cent of each subcohort are shown. The data are shown for (top to bottom) the Ninohe PHC area of Iwate Prefecture, the Yokote PHC area of Akita Prefecture, the Saku PHC area of Nagano Prefecture, and the Ishikawa PHC area of Okinawa Prefecture.

BMI, family history of diabetes, smoking and risk of diabetes (Table 3)

Multiple logistic regression analysis was performed to determine which of the baseline characteristics that had been previously identified as risk factors in some of the earlier studies were independent predictors of diabetes in the present cohort. Age, BMI, a positive family history of diabetes and a past history of hypertension were strong predictors for the development of diabetes in both genders. Smoking status was also strongly associated with the development of future diabetes among former smokers and those smoking 20 cigarettes or more a day in both genders.

Alcohol consumption and risk of diabetes

Among men, daily alcohol consumption of 23 g of ethanol or more was significantly related to the future development of diabetes when compared with the group of non-drinkers and infrequent occasional drinkers; a positive trend across the increasing levels of alcohol consumption was also significant (P for trend = 0.019) according to the Mantel extension test (Table 3).

To determine whether the BMI modified the association between daily alcohol consumption and the risk of Type 2 diabetes, we stratified the subjects according to the BMI (see Table 4). Among lean men (BMI ≤ 22 kg/m^2), a significant and strong positive association with moderate to high alcohol consumption was observed and the positive trend across the increasing levels of alcohol consumption was also significant (P for trend < 0.001). The risk for heavy alcohol drinkers was 2.89 (95% CI, 1.63–5.11) times higher than that of non-drinkers and infrequent occasional drinkers. By contrast, among men with a BMI > 22 kg/m^2, only a small, non-significant increase was observed among alcohol consumers (Table 4). In addition, when we analysed non-drinkers and infrequent occasional drinkers separately in the analysis shown in Table 3 (i.e. without subdividing the subjects according to their BMI), the odds between these two groups were almost equal [odds ratio for the former to the latter: 1.01 (95% CI, 0.74–1.38)], with the significantly increased odds ratios for high (> 46 g/day) alcohol consumption compared with non- or occasional infrequent drinkers persisted in the lower (≤ 22 kg/m^2) BMI group, even in this stratified analysis (data not shown).

No significant association between alcohol intake and the future development of diabetes was observed among women.

Discussion

This study is the largest community-based prospective study in Japan with a 10-year follow-up period to quantify the risk factors for Type 2 diabetes. We identified established risk factors, such as age, BMI and family history of diabetes, as independent determinants of Type 2 diabetes in both men and women, consistent with the results of studies in western populations [26–34].

Table 2 Baseline characteristics and development of Type 2 diabetes mellitus in middle-aged Japanese men and women

Characteristics	Men			Women		
	Remained non-diabetic	Developed diabetes	*P*	Remained non-diabetic	Developed diabetes	*P*
Age (years)	49.4	50.1	0.002	49.6	50.8	< 0.001
	49.0, 49.5	49.8, 50.0		49.3, 49.9	50.3, 51.5	
	49.5, 49.4	50.1, 50.5		49.7, 49.2	51.3, 49.9	
BMI (kg/m^2)	23.4	25.0	< 0.001	23.5	25.6	< 0.001
	23.5, 23.2	25.2, 24.8		23.6, 23.2	25.6, 25.1	
	23.1, 24.4	24.4, 25.9		23.1, 24.2	25.2, 26.7	
Smoking status (%)			0.012			< 0.001
Never smokers	25.2	21.3		94.6	90.8	
	27.8, 23.2	25.0, 22.5		95.6, 96.0	93.5, 93.5	
	21.3, 31.5	15.4, 24.1		92.7, 93.6	92.2, 81.3	
Current smokers:						
1–19 cigarettes/day	15.2	13.2		3.1	2.9	
	16.7, 15.9	15.7, 10.7		2.8, 2.3	0.8, 2.9	
	15.6, 11.9	14.4, 11.7		4.5, 2.9	3.9, 4.4	
≥ 20 cigarettes/day	36.7	38.7		1.0	2.5	
	38.6, 38.3	41.3, 39.3		0.7, 0.8	1.6, 1.5	
	38.8, 29.2	39.9, 33.1		1.1, 1.6	0.8, 7.7	
Past smokers	22.8	26.7		1.3	3.8	
	17.0, 22.6	18.0, 27.5		1.0, 0.9	4.1, 2.2	
	24.3, 27.4	30.3, 31.0		1.7, 1.9	3.1, 6.6	
Alcohol intake* (%)			0.046			0.824
ALC_0	31.4	27.9		89.8	90.8	
	34.8, 21.8	29.7, 14.0		91.9, 87.2	93.5, 88.4	
	28.0, 47.2	22.6, 50.3		87.0, 95.7	87.5, 95.6	
ALC_1	25.9	24.0		3.0	3.1	
	23.4, 24.6	25.0, 20.8		2.2, 3.7	1.6, 3.6	
	28.7, 26.4	25.0, 25.5		4.4, 0.9	5.5, 1.1	
ALC_2	22.4	24.8		4.1	3.3	
	20.5, 27.6	21.5, 34.8		3.3, 5.1	2.4, 4.4	
	25.2, 12.4	27.4, 12.4		5.1, 1.8	3.9, 2.2	
ALC_3	20.3	23.3		3.1	2.7	
	21.3, 26.1	23.8, 30.3		2.6, 3.9	2.4, 3.6	
	18.1, 14.0	25.0, 11.7		3.6, 1.6	3.1, 1.1	
Leisure-time physical activity at least once a week (%)	17.2	16.4	0.588	14.2	15.2	0.528
	11.7, 15.4	13.6, 17.4		8.0, 11.8	11.4, 12.3	
	19.4, 22.6	13.0, 22.8		20.4, 17.3	19.5, 18.7	
Family history of diabetes (%)	8.2	15.1	< 0.001	8.1	18.8	< 0.001
	10.4, 8.6	18.6, 12.4		8.7, 8.4	25.2, 16.7	
	8.2, 5.0	17.3, 11.0		8.9, 5.9	21.1, 9.9	
History of hypertension (%)	15.0	22.5	< 0.001	13.9	29.0	< 0.001
	15.7, 18.1	26.7, 26.4		15.1, 15.3	34.2. 31.2	
	13.6, 11.6	20.2, 15.9		13.1, 11.5	23.4, 26.4	

Data are means (age and BMI) or percentages (all others).
*Alcohol intake (g/day of ethanol): men, ALC_1: 0 < ethanol ≤ 23.0, ALC_2: 23.0 < ethanol ≤ 46.0, ALC_3: ethanol > 46.0; women, ALC_1: 0 < ethanol ≤ 4.9, ALC_2: 4.9 < ethanol ≤ 11.5, ALC_3: ethanol > 11.5. ALC_0: non-drinkers and infrequent occasional drinkers who consume alcohol on three or fewer days a month.
The total data and data for each subcohort are shown. Data are shown for (left to right, top to bottom) the Ninohe PHC area of Iwate Prefecture, the Yokote PHC area of Akita Prefecture, the Saku PHC area of Nagano Prefecture, and the Ishikawa PHC area of Okinawa Prefecture.

The analysis revealed a significant positive association between moderate to high alcohol intake and future diabetes in lean men (BMI ≤ 22 kg/m^2) and a similar but non-significant correlation in obese men (BMI > 22 kg/m^2). This contrasts with the results for men in most previous studies in the United States and Europe conducted using a prospective design, which reported an inverse correlation between alcohol intake and Type 2 diabetes [33,35,36] or suggested no significant association with diabetes [37–39]. A few, however, showed an excess diabetes incidence only in heavy drinkers [40,41].

The results of the Osaka Health Survey of Japanese male employees [15] showed moderate alcohol consumption (21.1–

Table 3 Multivariate logistic regression analysis of the 10-year incidence of Type 2 diabetes mellitus in middle-aged Japanese according to gender

	Men (n = 12 913)		Women (n = 15 980)	
	Odds ratio (95% CI)		Odds ratio (95% CI)	
Age (1-year increase)	1.02	(1.01–1.04)	1.02	(1.01–1.04)
BMI (1 kg/m^2-increase)	1.17	(1.14–1.20)	1.17	(1.14–1.21)
Smoking status				
Never smokers	1.00 (referent)		1.00 (referent)	
Current smokers:				
1–19 cigarettes/day	1.14	(0.87–1.50)	1.07	(0.62–1.86)
≥ 20 cigarettes/day	1.37	(1.11–1.69)	2.94	(1.57–5.50)
Past smokers	1.35	(1.08–1.69)	2.77	(1.67–4.61)
Alcohol intake*				
ALC_0	1.00 (referent)		1.00 (referent)	
ALC_1	1.08	(0.87–1.34)	1.15	(0.68–1.95)
ALC_2	1.26	(1.02–1.56)	0.81	(0.48–1.35)
ALC_3	1.25	(1.00–1.56)	0.78	(0.44–1.40)
Family history (yes/no)	2.00	(1.60–2.49)	2.69	(2.12–3.43)
Leisure time physical activity (active/inactive)	0.90	(0.73–1.12)	1.06	(0.82–1.37)
Hypertension (yes/no)	1.34	(1.10–1.62)	1.79	(1.44–2.22)

*Alcohol intake (g/day of ethanol): men, ALC_1: 0 < ethanol ≤ 23.0, ALC_2: 23.0 < ethanol ≤ 46.0, ALC_3: ethanol > 46.0; women, ALC_1: 0 < ethanol ≤ 4.9, ALC_2: 4.9 < ethanol ≤ 11.5, ALC_3: ethanol > 11.5. ALC_0: non-drinkers and infrequent occasional drinkers who consume alcohol on three or fewer days a month. 95% CI, 95% confidence interval.

Table 4 Multivariate logistic regression analysis of the 10-year incidence of Type 2 diabetes mellitus in middle-aged Japanese males according to BMI

	BMI ≤ 22 kg/m^2 (n = 3845)		25 kg/m^2 ≥ BMI > 22 kg/m^2 (n = 5671)		BMI ≥ 25 kg/m^2 (n = 3397)	
	Odds ratio (95% CI)		Odds ratio (95% CI)		Odds ratio (95% CI)	
Alcohol intake*						
ALC_0	1.00 (referent)		1.00 (referent)		1.00 (referent)	
ALC_1	1.05	(0.55–2.01)	1.12	(0.80–1.56)	1.08	(0.79–1.48)
ALC_2	1.91	(1.05–3.46)	1.16	(0.83–1.61)	1.24	(0.89–1.71)
ALC_3	2.89	(1.63–5.11)	1.17	(0.83–1.66)	1.03	(0.73–1.44)

*Alcohol intake (g/day of ethanol): ALC_1: 0 < ethanol ≤ 23.0, ALC_2: 23.0 < ethanol ≤ 46.0, ALC_3: ethanol > 46.0. 95% CI, 95% confidence interval. Adjusted for age, BMI, cigarette smoking, exercise, family history of diabetes and prevalent hypertension.

50.0 ml/day) to be associated with reduced risk of Type 2 diabetes among men with BMI ≥ 22.1 kg/m^2, while heavy alcohol consumption was associated with an increased risk among lean men (BMI ≤ 22.0 kg/m^2). All the subjects of the Osaka Health Survey were employees of the same company, while the subjects of our study were composed of those living in several areas of Japan. Therefore, the study population in our analysis may be more representative of the general Japanese. However, the heterogeneity of socio-economic status in our cohort could not completely exclude potential confounding on, for example, alcohol consumption.

Recently, three more reports have been published that deal with the relationship between alcohol consumption and the risk of Type 2 diabetes among Japanese [42–44]. One of these reported a significant protective effect of a low level of alcohol consumption (23.0–45.9 g ethanol/day) against development of Type 2 diabetes, i.e. a possible U-shaped association among male employees during 7 years of follow-up [42]. Another study demonstrated a significantly positive association in lean (BMI ≤ 22.0 kg/m^2) but no significant association in obese (BMI ≥ 25.0 kg/m^2) subjects; and a significant negative association in those who had an intermediate BMI (22.1–24.9 kg/m^2) between current alcohol consumption and the incidence of Type 2 diabetes, following male (72%) and female (28%) employees for a mean of 5.7 years [43]. In addition, the Hisayama Study identified alcohol consumption as an independent risk factor for diabetes among males [44]. Summing up the literature and our data, alcohol consumption exceeding 46 g/day is concluded to have an unfavourable effect, prompting Type 2 diabetes development, especially among lean (BMI ≤ 22.0 kg/m^2) Japanese men. The apparent lack of an association in women in the present study may be due to the small number of alcohol drinkers among the women surveyed (Table 2).

No significant correlation was found between leisure-time physical activity and diabetes development, a finding somewhat different from other prospectively designed studies, most of which showed a significant association between physical inactivity and Type 2 diabetes [30,37,45–47]. In this context, it may have been a limitation in regard to assessing the association that we categorized subjects only according to frequency of leisure-time exercise in the present study.

Our study has some limitations. First, only self-reported information was available regarding the subject's diabetes status. Although the validation examination showed that self-reported diabetes reflected the true situation fairly well (more than 80%) in this general population, the number of those with undiagnosed diabetes who were in the non-diabetic category according to self-report should be estimated. For this purpose, we compared the number of self-reported diabetic subjects with the number of those who were diagnosed on the basis of plasma glucose and HbA_{1c} levels [23] in a group of approximately 14 000 health check-up examinees involved in the JPHC Cohort I. The results showed that about half of all prevalent cases (self-reported and blood-sample diagnosed combined) were undiagnosed until the health check-up. Thus, the self-report-defined non-diabetic category at follow-up is likely to have contained a substantial undiagnosed population, possibly similar in number to the diabetic category defined by self-report. This implies that the odds ratios observed in our analyses may have underestimated the effect of risk factors on the total incidence of diabetes.

Second, there may be follow-up bias between the diabetic and non-diabetic categories resulting from a presumed excess mortality of the diabetic patients during the follow-up and a possible altered response rate of the patients. We divided the total number of subjects analysed (i.e. those who replied to the baseline questionnaire) into two groups: those who responded to both follow-up questionnaires (74.5% of the initial respondents) and those who did not, and compared the two groups. There were no significant differences in representative parameters, such as BMI and lifestyle characteristics, in either men or women, and therefore estimated incidence of diabetes calculated on the basis of these parameters. This suggests that our results were not seriously affected by follow-up bias.

Third, data for alcohol consumption were obtained from self-reports. Therefore, there might be under-reporting of true alcohol consumption. In this regard, it should be commented that the levels of γ-glutamyltranspeptidase of the subjects of the group where risk for diabetes starts to increase are roughly estimated to have been ranged between ~30 and ~80 IU/l as a whole [19], which correspond to normal to moderately high levels of γ-glutamyltranspeptidase of Japanese male population. Finally, previously diagnosed medical conditions were self-reported by participants, so this study may not exclude subjects with asymptomatic chronic alcoholic liver disease at baseline.

The average annual incidence of Type 2 diabetes by self-report in the current study was calculated as 0.63% among men and 0.34% among women, incidences that, including surmised undiagnosed cases, lie in the lower middle range of the reported crude incidence rate in the Japanese general population (0.2–4.0% per year for both men and women) [48], although age range and diagnostic criteria were different from those of our study. The male predominance of the observed incidence in the present study is another interesting point. Similar results were also obtained in the Japanese Governmental investigations of diabetes conducted in 1997 [49] and in 2002 [50], which were based on 5883 and 5792 subjects from among the participants in the National Nutritional Survey of the year, respectively.

In conclusion, most variables predicting future diabetes in western populations were also found to be important predictors of the disease in our current analyses. However, greater emphasis should be placed on alcohol consumption, as it might have more of an adverse than a beneficial effect on development of diabetes, in comparison with western populations. This may be due to the difference in distribution of polymorphic ethanol-metabolizing enzymes between Japanese and western populations [51,52].

Acknowledgements

This study was supported by a grant-in-aid for Cancer Research and for the Second Term Comprehensive Ten-Year Strategy for Cancer Control, and Health Sciences Research grants (Medical Frontier Strategy Research H13-008, Clinical Research for Evidence-based Medicine H14-008) from the Ministry of Health, Labour and Welfare of Japan.

Study group members

The investigators and participating institutions in the JPHC Study Cohort I Group, a part of JPHC Study Group (principal investigator: S. Tsugane) were: S. Tsugane, S. Sasaki, Epidemiology and Biostatistics Division, National Cancer Center Research Institute East, Kashiwa; J. Ogata, S. Baba, National Center for Circulatory Diseases, Suita; K. Miyakawa, F. Saito, A. Koizumi, Iwate Prefectural Ninohe Public Health Center, Ninohe; Y. Miyajima, N. Suzuki, S. Nagasawa, Akita Prefectural Yokote Public Health Center, Yokote; H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, Nagano Prefectural Saku Public Health Center, Saku; Y. Kishimoto, E. Takara, M. Kinjo, T. Fukuyama, Okinawa Prefectural Ishikawa Public Health Center, Ishikawa; S. Matsushima, S. Natsukawa, Saku General Hospital, Usuda; S. Watanabe, M. Akabane, Tokyo University of Agriculture, Tokyo; M. Konishi, Ehime University, Matsuyama; S. Tominaga, Aichi Cancer Center Research Institute, Nagoya; M. Iida, S. Sato, Center for Adult Diseases, Osaka; the late M. Yamaguchi, Y. Matsumura, National Institute of Health and Nutrition, Tokyo; Y. Tsubono, Tohoku University, Sendai; H. Iso, Tsukuba University, Tsukuba; H. Sugimura, Hamamatsu University, Hamamatsu; and M. Kabuto, National Institute for Environmental Studies, Tsukuba.

References

1 Elbein SC. Perspective: the search for genes for type 2 diabetes in the post-genome era. *Endocrinology* 2002; **143**: 2012–2018.

2 Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393–403.

3 Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; **344**: 1343–1350.

4 Fujimoto WY, Leonetti DL, Kinyoun JL, Newell-Morris L, Shuman WP, Stolov WC *et al.* Prevalence of diabetes mellitus and impaired glucose tolerance among second-generation Japanese-American men. *Diabetes* 1987; **36**: 721–729.

5 Hara H, Egusa G, Yamakido M, Kawate R. The high prevalence of diabetes mellitus and hyperinsulinemia among the Japanese-Americans living in Hawaii and Los Angeles. *Diabetes Res Clin Pract* 1994; **24**: S37–42.

6 Tsugane S, Gotlieb SL, Laurenti R, Souza JM, Watanabe S. Mortality and cause of death among first-generation Japanese in Sao Paulo, Brazil. *Int J Epidemiol* 1989; **18**: 647–651.

7 Meguro M, Meguro K, Caramelli P, Ishizaki J, Ambo H, Chubaci RY *et al.* Elderly Japanese emigrants to Brazil before World War II. I. Clinical profiles based on specific historical background. *Int J Geriatr Psychiatry* 2001; **16**: 768–774.

8 King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998; **21**: 1414–1431.

9 Park Y, Lee H, Koh CS, Min H, Yoo K, Kim Y *et al.* Prevalence of diabetes and IGT in Yonchon County, South Korea. *Diabetes Care* 1995; **18**: 545–548.

10 Pan XR, Yang WY, Li GW, Liu J. Prevalence of diabetes and its risk factors in China, 1994. National Diabetes Prevention and Control Cooperative Group. *Diabetes Care* 1997; **20**: 1664–1669.

11 Kawakami N, Takatsuka N, Shimizu H, Ishibashi H. Effects of smoking on the incidence of non-insulin-dependent diabetes mellitus. Replication and extension in a Japanese cohort of male employees. *Am J Epidemiol* 1997; **145**: 103–109.

12 Nakanishi N, Nakamura K, Matsuo Y, Suzuki K, Tatara K. Cigarette smoking and risk for impaired fasting glucose and type 2 diabetes in middle-aged Japanese men. *Ann Intern Med* 2000; **133**: 183–191.

13 Okada K, Hayashi T, Tsumura K, Suematsu C, Endo G, Fujii S. Leisure-time physical activity at weekends and the risk of Type 2 diabetes mellitus in Japanese men: the Osaka Health Survey. *Diabet Med* 2000; **17**: 53–58.

14 Uchimoto S, Tsumura K, Hayashi T, Suematsu C, Endo G, Fujii S *et al.* Impact of cigarette smoking on the incidence of Type 2 diabetes mellitus in middle-aged Japanese men: the Osaka Health Survey. *Diabet Med* 1999; **16**: 951–955.

15 Tsumura K, Hayashi T, Suematsu C, Endo G, Fujii S, Okada K. Daily alcohol consumption and the risk of type 2 diabetes in Japanese men: the Osaka Health Survey. *Diabetes Care* 1999; **22**: 1432–1437.

16 Hayashi T, Tsumura K, Suematsu C, Endo G, Fujii S, Okada K. High normal blood pressure, hypertension, and the risk of type 2 diabetes in Japanese men. The Osaka Health Survey. *Diabetes Care* 1999; **22**: 1683–1687.

17 Shin CS, Lee HK, Koh CS, Kim YI, Shin YS, Yoo KY *et al.* Risk factors for the development of NIDDM in Yonchon County, Korea. *Diabetes Care* 1997; **20**: 1842–1846.

18 Tsugane S, Sobue T. Baseline survey of JPHC study—design and participation rate. Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases. *J Epidemiol* 2001; **11**: S24–29.

19 Tsugane S, Fahey MT, Sasaki S, Baba S. Alcohol consumption and all-cause and cancer mortality among middle-aged Japanese men: seven-year follow-up of the JPHC study Cohort I. Japan Public Health Center. *Am J Epidemiol* 1999; **150**: 1201–1207.

20 Tsugane S, Sasaki S, Tsubono Y. Under- and overweight impact on mortality among middle-aged Japanese men and women: a 10-year follow-up of JPHC study cohort I. *Int J Obes Relat Metab Disord* 2002; **26**: 529–537.

21 World Health Organization. *Diabetes Mellitus.* Report of a WHO Study Group. Technical Report Series No. 727. Geneva: World Health Organization, 1985.

22 The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 1997; **20**: 1183–1197.

23 Takahashi Y, Noda M, Tsugane S, Kuzuya T, Ito C, Kadowaki T. Prevalence of diabetes estimated by plasma glucose criteria combined with standardized measurement of HbA_{1c} among health checkup participants on Miyako Island, Japan. *Diabetes Care* 2000; **23**: 1092–1096.

24 The Examination Committee of Criteria for 'Obesity Disease' in Japan, Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J* 2002; **66**: 987–92.

25 Tokunaga K, Matsuzawa Y, Kotani K, Keno Y, Kobatake T, Fujioka S *et al.* Ideal body weight estimated from the body mass index with the lowest morbidity. *Int J Obes* 1991; **15**: 1–5.

26 Wilson PW, Anderson KM, Kannel WB. Epidemiology of diabetes mellitus in the elderly. The Framingham Study. *Am J Med* 1986; **80**: 3–9.

27 Njolstad I, Arnesen E, Lund-Larsen PG. Sex differences in risk factors for clinical diabetes mellitus in a general population: a 12-year follow-up of the Finnmark Study. *Am J Epidemiol* 1998; **147**: 49–58.

28 Meisinger C, Thorand B, Schneider A, Stieber J, Doring A, Lowel H. Sex differences in risk factors for incident type 2 diabetes mellitus: the MONICA Augsburg cohort study. *Arch Intern Med* 2002; **162**: 82–89.

29 Burchfiel CM, Curb JD, Rodriguez BL, Yano K, Hwang LJ, Fong KO *et al.* Incidence and predictors of diabetes in Japanese-American men. The Honolulu Heart Program. *Ann Epidemiol* 1995; **5**: 33–43.

30 Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS Jr. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 1991; **325**: 147–152.

31 Wei M, Gibbons LW, Mitchell TL, Kampert JB, Lee CD, Blair SN. The association between cardiorespiratory fitness and impaired fasting glucose and type 2 diabetes mellitus in men. *Ann Intern Med* 1999; **130**: 89–96.

32 Feskens EJ, Kromhout D. Cardiovascular risk factors and the 25-year incidence of diabetes mellitus in middle-aged men. The Zutphen Study. *Am J Epidemiol* 1989; **130**: 1101–1108.

33 Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *BMJ* 1995; **310**: 555–559.

34 Rimm EB, Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B *et al.* Cigarette smoking and the risk of diabetes in women. *Am J Public Health* 1993; **83**: 211–214.

35 Ajani UA, Hennekens CH, Spelsberg A, Manson JE. Alcohol consumption and risk of type 2 diabetes mellitus among US male physicians. *Arch Intern Med* 2000; **160**: 1025–1030.

36 Stampfer MJ, Colditz GA, Willett WC, Manson JE, Arky RA, Hennekens CH *et al.* A prospective study of moderate alcohol drinking and risk of diabetes in women. *Am J Epidemiol* 1988; **128**: 549–558.

37 James SA, Jamjoum L, Raghunathan TE, Strogatz DS, Furth ED, Khazanie PG. Physical activity and NIDDM in African-Americans. The Pitt County Study. *Diabetes Care* 1998; **21**: 555–562.

38 Ohlson LO, Larsson B, Bjorntorp P, Eriksson H, Svardsudd K, Welin L *et al.* Risk factors for type 2 (non-insulin-dependent) diabetes mellitus. Thirteen and one-half years of follow-up of the participants in a study of Swedish men born in 1913. *Diabetologia* 1988; **31**: 798–805.

39 Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG. Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. *Br Med J* 1995; **310**: 560–564.
40 Holbrook TL, Barrett-Connor E, Wingard DL. A prospective population-based study of alcohol use and non-insulin-dependent diabetes mellitus. *Am J Epidemiol* 1990; **132**: 902–909.
41 Kao WH, Puddey IB, Boland LL, Watson RL, Brancati FL. Alcohol consumption and the risk of type 2 diabetes mellitus: atherosclerosis risk in communities study. *Am J Epidemiol* 2001; **154**: 748–757.
42 Nakanishi N, Suzuki K, Tatara K. Alcohol consumption and risk for development of impaired fasting glucose or type 2 diabetes in middle-aged Japanese men. *Diabetes Care* 2003; **26**: 48–54.
43 Watanabe M, Barzi F, Neal B, Ueshima H, Miyoshi Y, Okayama A *et al.* Alcohol consumption and the risk of diabetes by body mass index levels in a cohort of 5636 Japanese. *Diabetes Res Clin Pract* 2002; **57**: 191–197.
44 Kiyohara Y, Shinohara A, Kato I, Shirota T, Kubo M, Tanizaki Y *et al.* Dietary factors and development of impaired glucose tolerance and diabetes in a general Japanese population: the Hisayama study. *J Epidemiol* 2003; **13**: 251–258.
45 Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH. A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA* 1992; **268**: 63–67.
46 Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS *et al.* Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 1991; **338**: 774–778.
47 Folsom AR, Kushi LH, Hong CP. Physical activity and incident diabetes mellitus in postmenopausal women. *Am J Public Health* 2000; **90**: 134–138.
48 Akazawa Y. Prevalence and incidence of diabetes mellitus by WHO criteria. *Diabetes Res Clin Pract* 1994; **24**: S23–27.
49 Editorial Board. Report of the investigation for diabetes in Japan. *J Jp Diabetes Soc* 1998; **41**: 325–331. Available from: http://www1.mhlw.go.jp/toukei/tounyou/.
50 Ministry of Health, Labour and Welfare. Report of the investigation for diabetes in Japan, 2002. Available from: http://www.mhlw.go.jp/shingi/2003/08/s0806-4.html.
51 Shibuya A, Yoshida A. Frequency of the atypical aldehyde dehydrogenase-2 gene (ALDH2(2)) in Japanese and Caucasians. *Am J Hum Genet* 1988; **43**: 741–743.
52 Sun F, Tsuritani I, Yamada Y. Contribution of genetic polymorphisms in ethanol-metabolizing enzymes to problem drinking behavior in middle-aged Japanese men. *Behav Genet* 2002; **32**: 229–236.

ORIGINAL INVESTIGATION

Diabetes Mellitus and the Risk of Cancer

Results From a Large-Scale Population-Based Cohort Study in Japan

Manami Inoue, MD, PhD; Motoki Iwasaki, MD, PhD; Tetsuya Otani, MD, PhD; Shizuka Sasazuki, MD, PhD; Mitsuhiko Noda, MD; Shoichiro Tsugane, MD, DMSc; for the Japan Public Health Center–Based Prospective Study Group

Background: An association between diabetes mellitus (DM) and cancer has long been speculated, but no conclusive evidence has been obtained.

Methods: We prospectively examined the association between a history of DM and subsequent risk of cancer in the Japan Public Health Center–Based Prospective Study. A total of 97 771 general Japanese persons (46 548 men and 51 223 women) aged 40 to 69 years who responded to the baseline questionnaire, from January 1990 to December 1994, were followed up for cancer incidence through December 31, 2003. At baseline, 6.7% of men and 3.1% of women had a history of DM.

Results: A total of 6462 cases of newly diagnosed cancer were identified. In men, a 27% increase in the risk of total cancer incidence was observed in those with a history of DM (n=3907 [366 with DM]; hazard ratio [HR], 1.27; 95% confidence interval [CI], 1.14-1.42). The HR was especially high for those with cancer of the liver (n=312 [52 with DM]; HR, 2.24; 95% CI, 1.64-3.04), pancreas (n=118 [16 with DM]; HR, 1.85; 95% CI, 1.07-3.20), and kidney (n=99 [13 with DM]; HR, 1.92; 95% CI, 1.06-3.46). We also observed a moderately increased risk of colon cancer (n=491 [46 with DM]; HR, 1.36; 95% CI, 1.00-1.85) and of stomach cancer with borderline significance (n=977 [87 with DM]; HR, 1.23; 95% CI, 0.98-1.54). In women, a borderline significant increase in risk was observed for the incidence of total cancer (n=2555 [104 with DM]; HR, 1.21; 95% CI, 0.99-1.47), while statistical significance was observed for the incidence of stomach cancer (n=362 [20 with DM]; HR, 1.61; 95% CI, 1.02-2.54) and liver cancer (n=120 [10 with DM]; HR, 1.94; 95% CI, 1.00-3.73) and borderline significance was observed for the incidence of ovarian cancer (n=74 [5 with DM]; HR, 2.42; 95% CI, 0.96-6.09).

Conclusion: Patients with DM drawn from the general Japanese population may be at increased risk of total cancer and of cancer in specific sites.

Arch Intern Med. 2006;166:1871-1877

THE POSSIBLE ASSOCIATION of diabetes mellitus (DM) with cancer risk has long been speculated, although, to our knowledge, no conclusive evidence has been obtained. This putative association has been investigated mainly by site. Many epidemiologic studies have suggested a positive link between DM and cancer of the liver[1-9] and pancreas.[5-17] Evidence from recent studies and hypothesized mechanisms suggest the possibility of associations with other sites also, including the colon[5-9,18-26] and prostate.[5-9,27-34] Evidence of links with other cancers has been sparse and inconsistent.[5-9,35-41]

As in many other countries, DM is a serious public health problem in Japan. A global estimate projects an increase in prevalence in Japanese persons 20 years and older from 6.5% in 1995 to 8.7% in 2025.[42] In a recent survey,[43] approximately 7.4 million Japanese persons were estimated to have DM in 2002, confirming a remarkable increase in recent years.

The increase in DM will likely influence trends in related health conditions, including cancer. Clarification of the association between DM and cancer in populations with an increasing prevalence, such as Japanese persons, is a crucial task, not only from the causative point of view but also with regard to the formulation of clinical strategies and public health policies for the target population.

Herein, we conducted a cohort analysis on the association between DM and cancer risk using a large-scale population-based study in Japan.

METHODS

STUDY POPULATION

The Japan Public Health Center–Based Prospective Study was launched from January 1990 to December 1994, comprising 11 prefectural

Author Affiliations: Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center (Drs Inoue, Iwasaki, Otani, Sasazuki, and Tsugane), and Department of Endocrinology and Metabolism and Clinical Laboratory Department, International Medical Center of Japan (Dr Noda), Tokyo, Japan.
Group Information: A list of the members of the Japan Public Health Center–Based Prospective Study Group appears on page 1876.

public health center areas. Details of the study design have been provided elsewhere.[44] The study protocol was approved by the institutional review board of the National Cancer Center. In the present analysis, 1 public health center area was excluded because data on cancer incidence were not available.

The study population was defined as all registered Japanese inhabitants in the 10 public health center areas, aged 40 to 69 years at the beginning of each baseline survey. Initially, 133 323 subjects were identified as the study population. After excluding 239 subjects with non-Japanese nationality (n=51), duplicate enrollment (n=4), late report of emigration occurring before the start of follow-up (n=178), and ineligibility because of incorrect birth date (n=6), a population-based cohort of 133 084 subjects was established.

QUESTIONNAIRE

A baseline self-administered questionnaire was conducted from 1990 to 1994, including various lifestyle factors, such as medical history of major diseases, smoking and alcohol drinking status, height and weight, leisure-time physical activity, beverage consumption, and food intake frequency. A total of 106 326 subjects responded to the questionnaire, giving a response rate of 79.9%. Subjects who responded after emigration (n=112) and those with a history of cancer at baseline (n=2219) were excluded from further analysis.

Information on a history of DM in the baseline questionnaire was obtained using the question, "Has a doctor ever told you that you have any of the following diseases?—diabetes mellitus (yes/no)," and was supplemented by another question, "Do you take any anti-diabetic drugs? (yes/no)." History of DM was defined as positive for a response of yes to either question.

FOLLOW-UP

Subjects were followed up from the baseline survey until December 31, 2003. Residence status, including survival, was confirmed through the residential registry. Resident and death registration are required in Japan by law, and the registries are believed to be complete. Inspection of the resident registry is available to anyone under the resident registration law. Among the study subjects, 7879 died, 8197 moved out of the study areas, 4 withdrew their participation, and 228 were lost to follow-up within the follow-up period.

The occurrence of cancer was identified by notification from the major hospitals in the study area and data linkage with population-based cancer registries. Death certificates were used as a supplementary information source. The site and histological features of each case were coded using the *International Classification of Diseases for Oncology, Third Edition*.[45] In our cancer registry system, the proportion of cases for which information was available from death certificates only was 3.7%. For the present analysis, the earliest date of diagnosis was used in cases with multiple primary cancers at different times. A total of 6947 newly diagnosed cancer cases were identified. We excluded 6224 subjects for whom information on a history of DM, cerebrovascular disease or ischemic heart disease, smoking status, alcohol drinking, height and weight, leisure-time physical activity, green vegetable intake, or coffee intake was missing. As a result, 97 771 subjects, including 6462 incident cancer cases, were used for the present analysis.

ANALYSIS

The number of person-years in the follow-up was counted from the date of the baseline survey until the date of occurrence of any cancer, the date of emigration from the study area, the date of death, or the end of the study period, whichever came first. For persons who withdrew from the study or were lost to follow-up, the date of withdrawal and the last confirmed date of presence in the study area, respectively, were used as the date of censor.

The outcome of the study was defined as cancers newly occurring during the study period. Hazard ratios and 95% confidence intervals were used to describe the relative risk of cancer occurrence associated with a history of DM at baseline. The Cox proportional hazards model was used as a control for potential confounding factors, namely, age at baseline (continuous), study area (10 public health center areas), history of cerebrovascular disease (yes or no), history of ischemic heart disease (yes or no), smoking status (0, 1-19, 20-29, 30-39, or ≥40 pack-years), ethanol intake (measured in grams per week, continuous), body mass index (calculated as weight in kilograms divided by the square of height in meters, continuous), leisure-time physical activity (<1 time per month, 1-3 times per month, and ≥1 time per week), green vegetable intake (<3 days per week, 3-4 days per week, and almost every day), and coffee intake (almost never, 1-2 days per week, 3-4 days per week, 1-2 cups per day, 3-4 cups per day, or ≥5 cups per day). These variables, obtained from the questionnaire, are either known or suspected from previous studies as risk factors for cancer. All statistical analyses were performed using Stata, version 9.[46]

RESULTS

During 1 048 474 person-years of follow-up (average follow-up, 10.7 years) for 97 771 subjects (46 548 men and 51 223 women), a total of 6462 cases of newly diagnosed cancer (3907 men and 2555 women) were identified and included in the analyses.

Characteristics of the study subjects are shown in **Table 1**. At baseline, 6.7% of men and 3.1% of women had a history of DM. In both sexes, the proportion of past smokers and nondrinkers was increased in those with a history of DM, and subjects with a history of DM tended to have a higher body mass index but more frequent leisure-time physical activities. The proportion of subjects who almost never drank coffee was higher among those with a history of DM.

In men (**Table 2**), a statistically significant increase in the risk of cancer occurrence was observed in those with a history of DM. The hazard ratio was especially high for cancer of the liver, kidney, and pancreas. We also observed a moderately increased risk of colon cancer with statistical significance and of stomach cancer with borderline significance. The exclusion of liver and pancreatic cancer cases from the analysis for total cancer risk attenuated risk values, but statistical significance was maintained. For cancer of the liver, pancreas, and kidney, estimations of the hazard ratio after the exclusion of those diagnosed as having cancer within 5 years of baseline were similar to those using all cases.

In women (**Table 3**), a borderline significant increase in risk was observed for the incidence of total cancer. Increased risk was observed for stomach and liver cancer, with statistical significance, and for ovarian cancer, with borderline significance.

Table 1. Baseline Characteristics of the 97 771 Study Subjects According to Self-reported History of DM*

Characteristic	Men†			Women‡		
	Total (N = 46 548)	Those Without a History of DM (n = 43 451)	Those With a History of DM (n = 3097)	Total (N = 51 223)	Those Without a History of DM (n = 49 652)	Those With a History of DM (n = 1571)
Age, mean ± SD, y§	51.4 ± 7.9	51.2 ± 7.9	54.0 ± 7.6	51.8 ± 8.0	51.6 ± 8.0	56.0 ± 7.6
Self-reported history of cerebrovascular disease	1.1	1.0	1.7	0.5	0.5	1.3
Self-reported history of ischemic heart disease	1.4	1.3	3.5	0.8	0.7	2.1
Smoking status, pack-years						
0	23.6	23.9	20.6	91.6	91.7	89.4
1-19	18.7	18.9	15.7	5.4	5.4	5.6
20-29	18.1	18.3	15.8	1.3	1.3	2.0
30-39	16.3	16.2	17.4	0.5	0.5	1.5
≥40	23.3	22.7	30.5	1.2	1.1	1.5
Ethanol intake, g/wk						
0	22.5	22.1	27.0	76.9	76.6	84.6
<1	8.9	9.0	8.4	10.1	10.3	6.1
1-149	25.9	26.2	22.7	10.7	10.8	7.2
150-299	21.5	21.8	18.3	1.4	1.4	1.1
300-449	12.8	12.8	13.2	0.5	0.5	0.4
≥450	8.3	8.1	10.4	0.4	0.4	0.6
Body mass index‖						
<18.0	4.3	4.3	4.3	5.9	5.9	4.9
18.0-20.9	14.7	14.7	13.6	16.4	16.5	11.9
21.0-22.9	25.8	25.9	24.2	26.4	26.6	20.2
23.0-24.9	27.9	27.9	27.9	24.0	24.1	21.9
25.0-26.9	16.5	16.4	17.5	14.8	14.6	19.7
27.0-29.9	8.8	8.8	9.6	9.5	9.3	14.5
≥30.0	2.0	2.0	2.9	3.0	3.0	6.9
Leisure-time physical activity						
Almost never	64.9	65.1	62.7	74.7	74.9	69.1
Once per month to 3-4 times per week	15.9	16.1	13.0	7.2	7.3	6.3
Almost every day	19.2	18.8	24.3	18.1	17.9	24.6
Green vegetable intake						
Almost never	14.0	14.0	13.7	9.0	8.9	10.9
1-2 Times per week	29.3	29.4	27.0	23.4	23.5	22.1
3-4 Times per week	33.6	33.7	33.4	37.2	37.3	35.3
Almost every day	23.1	22.9	25.9	30.4	30.3	31.7
Coffee intake						
Almost never	29.8	29.0	40.1	31.5	30.9	52.1
1-2 Times per week	17.7	17.6	19.3	18.3	18.3	17.4
3-4 Times per week	11.6	11.8	9.9	10.8	10.9	7.3
Almost every day						
1-2 Cups per day	26.4	26.8	20.3	29.4	29.8	19.2
3-4 Cups per day	10.8	11.1	7.9	7.9	8.0	3.2
≥5 Cups per day	3.7	3.7	2.5	2.1	2.1	0.8

Abbreviation: DM, diabetes mellitus.
*Data are given as percentage of each group unless otherwise indicated. Percentages may not total 100 because of rounding.
†Those without a history of DM comprised 93.3% of the men; and those with a history of DM, 6.7%.
‡Those without a history of DM comprised 96.9% of the women; and those with a history of DM, 3.1%.
§The age range was 40 to 69 years for all groups.
‖Calculated as weight in kilograms divided by the square of height in meters.

COMMENT

In this prospective cohort study, a past diagnosis of DM was associated with a 27% and a 21% increase in the risk of total cancer incidence in men and women, respectively. The observed risk of total cancer by DM is a "grand sum" of the various impacts of individual sites of cancer. Few studies have clarified the effect of DM on total cancer,[8,9,41] and results have been varied. The present study showed a difference in the magnitude of risk between men and women. Because of the paucity of evidence from previous studies, estimates for total cancer risk from other studies are needed to confirm the validity of our estimate.

By site, the increased risk of liver cancer seen herein is consistent with the risk in previous studies.[1-9] The increased risk of pancreatic cancer, however, was observed only in men, which is inconsistent with the positive association in both sexes suggested in most previous studies.[5-16] We also observed a higher risk in men for colon cancer, while results for women in previous studies

Table 2. Cancer Incidence According to Self-reported History of DM in 46 548 Men*

Site or Type of Cancer	*ICD-O-3* Code	Total No. of Cases	Those Without a History of DM	Those With a History of DM	HR (95% CI) for All Cases		HR (95% CI) Excluding Cases Within 5 y‡
					Adjustment 1†	Adjustment 2‡	
All sites	NA	**3907**	3541	366	1.30 (1.17-1.45)§	1.27 (1.14-1.42)§	1.16 (1.00-1.35)§
All sites excluding the liver	NA	**3595**	3281	314	1.22 (1.09-1.37)§	1.20 (1.06-1.35)§	1.08 (0.92-1.26)
All sites excluding the liver and pancreas	NA	**3477**	3179	298	1.20 (1.06-1.35)§	1.18 (1.04-1.33)§	1.05 (0.89-1.23)
Esophagus	C15	**176**	158	18	1.48 (0.91-2.41)	1.40 (0.84-2.32)	0.96 (0.45-2.09)
Stomach	C16	**977**	890	87	1.22 (0.98-1.52)	1.23 (0.98-1.54)	1.09 (0.79-1.50)
Colon	C18	**491**	445	46	1.40 (1.03-1.90)§	1.36 (1.00-1.85)§	1.14 (0.74-1.75)
Rectum	C19-C21	**243**	228	15	0.85 (0.50-1.43)	0.80 (0.47-1.36)	0.90 (0.46-1.78)
Liver	C22	**312**	260	52	2.37 (1.76-3.20)§	2.24 (1.64-3.04)§	2.30 (1.49-3.55)§
Bile duct	C23-C24	**89**	79	10	1.61 (0.83-3.12)	1.63 (0.84-3.17)	1.89 (0.85-4.21)
Pancreas	C25	**118**	102	16	2.05 (1.20-3.48)§	1.85 (1.07-3.20)§	1.97 (1.01-3.88)§
Larynx	C32	**33**	30	3	1.45 (0.44-4.79)	1.34 (0.40-4.45)	1.74 (0.39-7.66)
Lung	C33-C34	**547**	502	45	1.07 (0.79-1.46)	1.05 (0.77-1.44)	1.00 (0.67-1.50)
Leukemia	C42	**94**	88	6	0.92 (0.40-2.12)	0.99 (0.43-2.28)	1.59 (0.68-3.71)
Prostate	C61	**284**	266	18	0.81 (0.50-1.31)	0.82 (0.51-1.33)	0.50 (0.24-1.01)
Kidney	C64-C66 and C68	**99**	86	13	2.02 (1.13-3.64)§	1.92 (1.06-3.46)§	2.41 (1.22-4.78)§
Bladder	C67	**105**	93	12	1.58 (0.86-2.88)	1.63 (0.89-3.00)	0.82 (0.30-2.27)
Lymphoma	C77	**61**	56	5	1.19 (0.47-2.98)	1.27 (0.50-3.20)	1.01 (0.31-3.29)

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; *ICD-O-3, International Classification of Diseases for Oncology, Third Edition*; NA, data not applicable.

*The total person-years of follow-up was 488 914.1 (458 724.4 in those without a history of DM and 30 189.7 in those with a history of DM).

†Adjusted for age (in years) at baseline (continuous) and study area (10 public health center areas).

‡Adjusted for age (in years) at baseline (continuous), study area (10 public health center areas), history of cerebrovascular disease, history of ischemic heart disease, smoking (≤19, 20-29, 30-39, or ≥40 pack-years), ethanol intake (in grams per week, continuous), body mass index (continuous), leisure-time physical activity (<1 day per month, 1-3 days per month, or ≥1 day per week), green vegetable intake (<3 days per week, 3-4 days per week, or almost every day), and coffee intake (almost never, 1-2 days per week, 3-4 days per week, 1-2 cups per day, 3-4 cups per day, or ≥5 cups per day).

§These cases showed a significant increase in the risk of cancer occurrence.

Table 3. Cancer Incidence According to Self-reported History of DM in 51 223 Women*

Site or Type of Cancer	*ICD-O-3* Code	Total No. of Cases	Those Without a History of DM	Those With a History of DM	HR (95% CI) for All Cases		HR (95% CI) Excluding Cases Within 5 y‡
					Adjustment 1†	Adjustment 2‡	
All sites	NA	**2555**	2451	104	1.24 (1.01-1.50)§	1.21 (0.99-1.47)	1.23 (0.95-1.59)
All sites excluding the liver	NA	**2435**	2341	94	1.19 (0.96-1.46)	1.16 (0.94-1.43)	1.19 (0.91-1.56)
All sites excluding the liver and pancreas	NA	**2343**	2254	89	1.18 (0.96-1.46)	1.15 (0.93-1.43)	1.19 (0.90-1.56)
Stomach	C16	**362**	342	20	1.58 (1.01-2.49)§	1.61 (1.02-2.54)§	1.92 (1.06-3.47)§
Colon	C18	**303**	293	10	0.93 (0.49-1.75)	0.83 (0.42-1.61)	0.58 (0.21-1.57)
Rectum	C19-C21	**153**	145	8	1.58 (0.77-3.24)	1.65 (0.80-3.39)	1.22 (0.38-3.90)
Liver	C22	**120**	110	10	2.09 (1.09-4.02)§	1.94 (1.00-3.73)§	1.84 (0.79-4.30)
Bile duct	C23-C24	**91**	89	2	0.55 (0.14-2.25)	0.55 (0.13-2.24)	0.57 (0.08-4.14)
Pancreas	C25	**92**	87	5	1.30 (0.53-3.21)	1.33 (0.53-3.31)	1.32 (0.41-4.28)
Lung	C33-C34	**198**	190	8	1.13 (0.56-2.30)	1.12 (0.55-2.29)	1.24 (0.54-2.84)
Leukemia	C42	**80**	76	4	1.45 (0.53-4.00)	1.38 (0.50-3.81)	2.01 (0.61-6.58)
Breast	C50	**451**	441	10	0.84 (0.45-1.57)	0.83 (0.44-1.57)	0.93 (0.44-1.98)
Uterus							
Cervix	C53	**133**	131	2	0.60 (0.15-2.43)	0.61 (0.15-2.48)	0.66 (0.09-4.83)
Corpus	C54	**89**	85	4	1.82 (0.66-4.99)	1.68 (0.61-4.64)	1.30 (0.31-5.38)
Ovary	C56	**74**	69	5	2.49 (0.99-6.23)	2.42 (0.96-6.09)	1.70 (0.41-7.11)
Kidney	C64-C66 and C68	**35**	33	2	1.62 (0.39-6.82)	1.36 (0.32-5.78)	1.44 (0.19-11.14)
Bladder	C67	**30**	29	1	0.82 (0.11-6.07)	0.64 (0.09-4.75)	1.00 (0.13-7.62)
Thyroid	C73	**103**	100	3	1.11 (0.35-3.50)	1.08 (0.34-3.43)	1.74 (0.41-7.29)
Lymphoma	C77	**28**	26	2	2.01 (0.47-8.53)	1.89 (0.43-8.24)	3.03 (0.67-13.73)

Abbreviations: See Table 2.

*The total person-years of follow-up was 559 560.1 (543 313.4 for those without a history of DM and 16 246.7 for those with a history of DM).

†Adjusted for age (in years) at baseline (continuous) and study area (10 public health center areas).

‡Adjusted for age (in years) at baseline (continuous), study area (10 public health center areas), history of cerebrovascular disease, history of ischemic heart disease, smoking (≤19, 20-29, 30-39, or ≥40 pack-years), ethanol intake (in grams per week, continuous), body mass index (continuous), leisure-time physical activity (<1 day per month, 1-3 days per month, or ≥1 day per week), green vegetable intake (<3 days per week, 3-4 days per week, or almost everyday), and coffee intake (almost never, 1-2 days per week, 3-4 days per week, 1-2 cups per day, 3-4 cups per day, or ≥5 cups/day).

§These cases showed a significant increase in the risk of cancer occurrence.

were inconsistent.[19-22,24,25] In contrast, we observed a nonsignificant inverse association between DM and prostate cancer, which is consistent with most previous epidemiologic studies, which showed no[5-9,32] or an inverse[29-31,33,34] association. For other sites, we found a positive association for male kidney and female stomach and ovarian cancers, whereas most previous epidemiologic studies[5-9,38] found no evidence for an association with these cancers, except for a positive association with kidney cancer in diabetic patients[37] and with gastric cancer in *Helicobacter pylori*–positive subjects.[39]

Discussions on the possible biological mechanisms of the association between DM and cancer have tended to be site specific. Notably, however, these associations may be the result of metabolic and hormonal aberrations associated with DM, and common biological mechanisms may be at least partially associated with insulin and insulin-like growth factors (IGFs).[47]

The most obvious change in diabetic patients is reduced insulin sensitivity with compensatory hyperinsulinemia and elevated levels of IGF-1, which may in turn stimulate cell proliferation in the liver, pancreas, colon, prostate, ovary, breast, and other areas.[47-51] At the same time, insulin activates the IGF-1 receptor, which is known to have growth-promoting effects, including modulation of cell cycle progression. Excess insulin might also affect the development of cancer indirectly by downregulating the level of IGF-binding protein 1, which increases the level and bioavailability of total circulating IGF-1. Obesity and physical inactivity also cause hyperinsulinemia and are, thus, also ultimately associated with cancer.[47-51] This seems to be inconsistent with the baseline characteristics of our study population, among whom those with a history of DM tended to have a higher frequency of physical activity at baseline. It is likely that the subjects with a history of DM increased physical activity in response to their condition.

An experimental study[52] revealed that hepatitis C virus infection itself can induce insulin resistance via the action of the hepatitis C virus core protein in disturbing insulin's intracellular signaling pathway. It has also been speculated that *H pylori* gastritis enhances glucose- and meal-stimulated insulin release, probably by increasing gastrin secretion,[53] and that the increased reactive oxygen-related damage to DNA and genetic or epigenetic alterations in gastric mucosa induced by this hyperinsulinemia have a modifying effect on the bacteria, which may be the initial step in the cascade of gastric carcinogenesis.[39] In the present study, hepatitis C virus and *H pylori* infection status were not determined for the entire population, preventing clarification of whether these infections affect the site-specific association between DM and cancer.

Alternatively, the association between DM and cancer could also be considered in combination with the alteration in sex hormone levels occurring in some types of cancer, such as prostate and ovarian cancer. Growth of the prostate gland is controlled by testosterone,[54] and a high testosterone level is associated with prostate cancer.[55] Diabetic men have lower testosterone levels,[56,57] suggesting a decreased risk of prostate cancer. Ovarian tumor development is suggested to be enhanced by androgen, and ovarian androgen excess is related to hyperinsulinemia.[58,59] In contrast, it is also suggested that insulin resistance and chronic hyperinsulinemia induce menstrual cycle irregularity and chronic anovulation, which may reduce the risk of ovarian and breast cancer.[58-60] Because these sex hormone–related mechanisms act in an apparently opposite direction to the hyperinsulinemia and IGF mechanisms previously described, the interpretation of risk values revealed by their combination may be complicated.

Despite the biological plausibility of the association, several issues should be considered when discussing the role of DM as a cause of cancer. First, certain common health conditions are likely to cause DM and cancer. Second, some types of cancer may cause DM as a consequence. Third, it is not easy to differentiate whether DM causes cancer or whether risk factors for DM, such as obesity and physical inactivity, are associated with cancer. Last, it is likely that a diagnosis of DM and subsequent medical care increase vigilance and, thus, the possibility of a diagnosis of cancer. These issues should likely be considered as alternative factors affecting the association between DM and cancer, directly or otherwise.

The major strength of the present study is its prospective design, which avoided exposure recall bias. Other strengths include the following: study subjects were selected from the general population, the response rate of 79.9% to the baseline questionnaire is acceptable for study settings such as this, the proportion of loss to follow-up (0.2%) was negligible, the quality of our cancer registry system was satisfactory during the study period, and potential confounding factors could be adjusted to minimize their influence on risk values. With regard to the last point, however, the possible influence of residual confounding cannot be denied.

Several methodological limitations can also be identified. Assessment of a history of DM was based on self-reports. The questionnaire used for the 5- and 10-year follow-up surveys included similar questions to identify a personal history of DM as those used in the baseline survey, which previously confirmed that 94% of self-reported histories of DM in subjects sampled from our population were consistent with medical records.[61] We considered this to be a sufficiently high positive predictive value for the diagnosis of DM, and not substantially different from the value at baseline. However, the sensitivity and specificity of a past diagnosis of DM for diabetic hyperglycemia from the health checkup data were 46% and 98%, respectively.[61] Furthermore, because information on the use of antidiabetic drugs was used as complementary information, information on insulin injections or calorie restrictions could not be used to complement the primary question. For these reasons, the use of self-reports is likely to underestimate the true prevalence of DM, although such misclassification would bias the association toward the null.

According to a 1988 to 1992 survey in a general population, in which data were derived from self-reports and glycosylated hemoglobin value, the prevalence of DM in subjects 40 years and older was 9.8% in men and 6.8% in women.[62-65] By comparison, the respective baseline rates in our population, of 6.7% and 3.1%, are relatively low,

Japan Public Health Center–Based Prospective Study Group

S. Tsugane, MD, DMSc, M. Inoue, MD, PhD, T. Sobue, MD, T. Hanaoka, MD, National Cancer Center, Tokyo; J. Ogata, MD, S. Baba, MD, T. Mannami, MD, A. Okayama, MD, National Cardiovascular Center, Suita; K. Miyakawa, MD, F. Saito, MD, A. Koizumi, MD, Y. Sano, MD, I. Hashimoto, MD, Iwate Prefectural Ninohe Public Health Center, Ninohe; Y. Miyajima, MD, N. Suzuki, MD, S. Nagasawa, MD, Y. Furusugi, MD, N. Nagai, MD, Akita Prefectural Yokote Public Health Center, Yokote; H. Sanada, MD, Y. Hatayama, MD, F. Kobayashi, MD, H. Uchino, MD, Y. Shirai, MD, T. Kondo, MD, R. Sasaki, MD, Y. Watanabe, MD, Y. Miyakawa, MD, Nagano Prefectural Saku Public Health Center, Saku; Y. Kishimoto, MD, E. Takara, MD, T. Fukuyama, MD, M. Kinjo, MD, M. Irei, MD, H. Sakiyama, MD, Okinawa Prefectural Chubu Public Health Center, Okinawa; K. Imoto, MD, H. Yazawa, MD, T. Seo, MD, A. Seiko, MD, F. Ito, MD, F. Shoji, MD, Katsushika Public Health Center, Tokyo; A. Murata, MD, K. Minato, MD, K. Motegi, MD, T. Fujieda, MD, Ibaraki Prefectural Mito Public Health Center, Mito; K. Matsui, MD, T. Abe, MD, M. Katagiri, MD, M. Suzuki, MD, Niigata Prefectural Kashiwazaki and Nagaoka Public Health Center, Kashiwazaki and Nagaoka; M. Doi, MD, A. Terao, MD, Y. Ishikawa, MD, Kochi Prefectural Chuo-Higashi Public Health Center, Tosayamada; H. Sueta, MD, H. Doi, MD, M. Urata, MD, N. Okamoto, MD, F. Ide, MD, Nagasaki Prefectural Kamigoto Public Health Center, Kamigoto; H. Sakiyama, MD, N. Onga, MD, H. Takaesu, MD, Okinawa Prefectural Miyako Public Health Center, Hirara; F. Horii, MD, I. Asano, MD, H. Yamaguchi, MD, K. Aoki, MD, S. Maruyama, MD, M. Ichii, MD, Osaka Prefectural Suita Public Health Center, Suita; S. Matsushima, MD, S. Natsukawa, MD, Saku General Hospital, Saku; M. Akabane, PhD, Tokyo University of Agriculture, Tokyo; M. Konishi, MD, K. Okada, MD, Ehime University, Matsuyama; H. Iso, MD, Osaka University, Osaka; Y. Tsubono, MD, Tohoku University, Sendai; K. Yamagishi, MD, Y. Honda, MD, University of Tsukuba, Tsukuba; H. Sugimura, MD, Hamamatsu University, Shizuoka; M. Kabuto, DHS, National Institute for Environmental Studies, Tsukuba; S. Tominaga, MD, Aichi Cancer Center, Nagoya; M. Iida, MD, W. Ajiki, MD, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka; S. Sato, MD, Osaka Medical Center for Health Science and Promotion, Osaka; N. Yasuda, MD, Kochi University, Kochi; S. Kono, MD, Kyushu University, Fukuoka; K. Suzuki, MD, Research Institute for Brain and Blood Vessels Akita, Akita; Y. Takashima, MD, Kyorin University, Tokyo; E. Maruyama, PhD, Kobe University, Kobe; M. Yamaguchi, MD, S. Watanabe, MD, Y. Matsumura, PhD, S. Sasaki, MD, National Institute of Health and Nutrition, Tokyo; and T. Kadowaki, MD, Tokyo University, Tokyo.

probably because our data were based on self-reports only, in which as few as 50% to 60% of cases are detected. This estimate is supported by a subgroup analysis, in which the prevalence of DM estimated by a combination of plasma glucose and glycosylated hemoglobin values was 12.6% in men and 8.6% in women.[66]

The treatment and control of DM may also affect these associations as a result of improvements to hyperglycemia and other lifestyle factors. We could not differentiate the type of DM, although most cases among adults in Japan would be expected to be type 2. The diagnosis of DM after the start of the study may have resulted in the attenuation of the true associations.

Allowing for these methodological issues, our results suggest that a past diagnosis of DM confers an increase in the risk of total cancer incidence of 27% in the Japanese population. The remarkable increase in the diagnosis of DM in Japan in recent years may affect future trends in the incidence and type of cancer.

Accepted for Publication: June 4, 2006.
Correspondence: Manami Inoue, MD, PhD, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan (mnminoue@gan2.res.ncc.go.jp).
Author Contributions: Dr Inoue accepts full responsibility for the work and/or conduct of the study, had access to the data, and controlled the decision to publish.
Financial Disclosure: None reported.
Funding/Support: This study was supported by a Grant-in-Aid for Cancer Research and for the Third Term Comprehensive Control Research for Cancer from the Ministry of Health, Labour and Welfare, Japan.
Role of the Sponsor: The funding body had no role in data extraction and analyses, in the writing of the manuscript, or in the decision to submit the manuscript for publication.
Acknowledgment: We thank the Ibaraki, Niigata, Osaka, Kochi, Nagasaki, and Okinawa Cancer Registries for providing their incidence data.

REFERENCES

1. La Vecchia C, Negri E, Decarli A, Franceschi S. Diabetes mellitus and the risk of primary liver cancer. *Int J Cancer.* 1997;73:204-207.
2. Lagiou P, Kuper H, Stuver SO, Tzonou A, Trichopoulos D, Adami HO. Role of diabetes mellitus in the etiology of hepatocellular carcinoma. *J Natl Cancer Inst.* 2000;92:1096-1099.
3. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut.* 2005;54:533-539.
4. Balkau B, Kahn HS, Courbon D, Eschwege E, Ducimetiere P; Paris Prospective Study. Hyperinsulinemia predicts fatal liver cancer but is inversely associated with fatal cancer at some other sites: the Paris Prospective Study. *Diabetes Care.* 2001;24:843-849.
5. La Vecchia C, Negri E, Franceschi S, D'Avanzo B, Boyle P. A case-control study of diabetes mellitus and cancer risk. *Br J Cancer.* 1994;70:950-953.
6. Rousseau MC, Parent ME, Pollak MN, Siemiatycki J. Diabetes mellitus and cancer risk in a population-based case-control study among men from Montreal, Canada. *Int J Cancer.* 2006;118:2105-2109.
7. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. *Am J Epidemiol.* 2004; 159:1160-1167.
8. Batty GD, Shipley MJ, Marmot M, Smith GD. Diabetes status and post-load plasma glucose concentration in relation to site-specific cancer mortality: findings from the original Whitehall study. *Cancer Causes Control.* 2004;15:873-881.
9. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA.* 2005;293:194-202.
10. Gullo L, Pezzilli R, Morselli-Labate AM; Italian Pancreatic Cancer Study Group. Diabetes and the risk of pancreatic cancer. *N Engl J Med.* 1994;331:81-84.
11. Calle EE, Murphy TK, Rodriguez C, Thun MJ, Heath CW Jr. Diabetes mellitus and pancreatic cancer mortality in a prospective cohort of United States adults. *Cancer Causes Control.* 1998;9:403-410.
12. Silverman DT, Schiffman M, Everhart J, et al. Diabetes mellitus, other medical