The authors examined the associations of glucose tolerance status and fasting and 2-hour postload glucose levels with the risk of cancer death in a 19-year follow-up study of 2,438 Japanese subjects aged 40–79 years who underwent a 75-g oral glucose tolerance test (1988–2007). During follow-up, 229 subjects died of cancer. The risk of cancer death was significantly higher in subjects with fasting plasma glucose levels of ≥5.6 mmol/L or 2-hour postload glucose levels of ≥11.1 mmol/L than in those with the lowest fasting or 2-hour postload glucose levels, after adjustment for potentially confounding factors. According to glucose tolerance status, not only diabetes but also impaired fasting glycemia and impaired glucose tolerance were significant risk factors for cancer death (for impaired fasting glycemia, multivariable-adjusted hazard ratio (HR) = 1.49 (95% confidence interval (CI): 1.05, 2.11); for impaired glucose tolerance, HR = 1.52 (95% CI: 1.05, 2.22); and for diabetes, HR = 2.10 (95% CI: 1.41, 3.12)). With regard to site-specific cancers, elevated fasting or 2-hour postload glucose levels were associated with the risks of death from stomach, liver, and lung cancer. These findings suggest that both prediabetic hyperglycemia and diabetes are significant risk factors for cancer death in the general Japanese population.

blood glucose; diabetes mellitus; glucose intolerance; glucose tolerance test; neoplasms; prediabetic state; proportional hazards models; prospective studies

Abbreviations: CI, confidence interval; HR, hazard ratio; IGF-1, insulin-like growth factor 1; NHANES II, Second National Health and Nutrition Examination Survey.

Malignant neoplasm is a major cause of death in developed countries, and its incidence continues to grow, placing a heavy burden on the community (1). Diabetes mellitus is a serious and leading health problem worldwide and is associated with severe acute and chronic complications that negatively influence both the quality of life and survival of affected persons (2). Growing epidemiologic evidence suggests that people with diabetes are at significantly greater risk for cancer in general (3–9), as well as for specific types of cancer, such as cancers of the breast, liver, pancreas, colon, rectum, and endometrium (7, 8, 10). Additionally, a recent pooled analysis using data from European prospective cohort studies demonstrated that glucose intolerance was associated with a higher risk of cancer death, beginning in the prediabetic range of glucose intolerance (11).

However, few population-based studies, especially in Asian populations, have addressed these issues or have estimated glucose intolerance status precisely using 75-g oral glucose tolerance testing. Since considerable heterogeneity in genetic background and lifestyle exists between Asian and Western populations (2), it is of value to review the influence of prediabetes and diabetes on the risk of cancer death in general Asian populations.
The purpose of this study was to investigate whether prediabetes and diabetes defined by means of a 75-g oral glucose tolerance test were associated with overall and site-specific cancer mortality in a 19-year follow-up study of a general Japanese population.

MATERIALS AND METHODS

Study population

The Hisayama Study is an ongoing population-based epidemiologic study designed to investigate the morbidity and mortality of cardiovascular disease and its risk factors in the community in the town of Hisayama, Japan. The population of Hisayama is approximately 7,500 and has been stable for 50 years. According to the 1985 census, the age and occupational distributions of the Hisayama population are almost identical to those of Japan as a whole. In 1988, a screening survey for the present study was performed in the town, and a detailed description of this survey was published previously (12). Briefly, a total of 2,587 residents aged 40–79 years (80.2% of the whole population in this age group) consented to participate in an examination and underwent a comprehensive health assessment. Since 82 subjects had already had breakfast and 15 refused glucose tolerance testing, glucose tolerance status was determined in 2,490 subjects, of whom 2,480 underwent a 75-g oral glucose tolerance test and 10 were on insulin therapy. After exclusion of 49 subjects who had a history of malignancy and 3 who died before follow-up, the remaining 2,438 subjects (1,054 men and 1,384 women) were entered into the study.

Follow-up survey

The subjects were followed prospectively for 19 years, from December 1988 to November 2007, by means of repeated health examinations and a daily monitoring system established by the study team and local physicians or members of the town’s Health and Welfare Office. Vital status was checked once yearly by mail or telephone for any subjects who did not undergo a regular examination or who moved out of town. Information about death was received through this follow-up system. When a subject died, we collected all medical information related to his/her illness and death, including hospital charts, physicians’ records, and the death certificate. Moreover, an autopsy was performed by the Department of Pathology at Kyushu University, if consent for an autopsy was obtained. All participants were followed up completely over a period of 19 years. During the follow-up period, 679 subjects died, and an autopsy was performed for 479 (70.5%). All of the medical data, including autopsy findings, were scrutinized, and the underlying causes of death were classified according to the International Classification of Diseases, Tenth Revision. During the follow-up period, 229 subjects (145 men and 84 women) died of cancer (all types), and deaths due to other causes were censored at the date of death.

Risk factors

At the baseline examination, we performed a 75-g oral glucose tolerance test between 8:00 AM and 10:30 AM after at least a 12-hour overnight fast. Plasma glucose levels were measured by means of the glucose oxidase method. Fasting plasma glucose and 2-hour postload glucose levels were divided into 4 categories: for fasting plasma glucose, <5.6, 5.6–6.0, 6.1–6.9, and ≥7.0 mmol/L; for 2-hour postload glucose, <6.7, 6.7–7.7, 7.8–11.0, and ≥11.1 mmol/L. Additionally, glucose tolerance status was defined on the basis of the 1998 World Health Organization criteria (13). We modified the lower cutpoint for impaired fasting glycemia from 6.1 mmol/L to 5.6 mmol/L according to the recent recommendation of the American Diabetes Association (14); that is, for normal glucose tolerance, fasting plasma glucose <5.6 mmol/L and 2-hour postload glucose <7.8 mmol/L; for impaired fasting glycemia, fasting plasma glucose 5.6–6.9 mmol/L and 2-hour postload glucose <7.8 mmol/L; for impaired glucose tolerance, fasting plasma glucose <7.0 mmol/L and 2-hour postload glucose 7.8–11.0 mmol/L; and for diabetes mellitus, fasting plasma glucose ≥7.0 mmol/L and/or 2-hour postload glucose ≥11.1 mmol/L. Diabetes mellitus was also subclassified into 2 groups: known diabetes, which was defined as diabetics with or without treatment diagnosed before the examination, and newly diagnosed diabetes, which was defined newly by the 75-g oral glucose tolerance test at baseline.

Each participant completed a self-administered questionnaire covering medical history, family history of cancer, anti-diabetic treatment, smoking habits, alcohol intake, and leisure-time physical activity. Smoking and alcohol intake were classified as either current use or not. Those subjects engaging in sports or other forms of exertion 3 or more times per week during their leisure time made up a “regular exercise” group. Height and body weight were measured in light clothes without shoes, and body mass index (weight (kg)/height (m)2) was calculated. Total cholesterol levels were determined enzymatically. Data on dietary factors were obtained via a semiquantitative food frequency method that had been validated in a prior study (15), and daily nutrient intakes, including total energy, total fat, salt, vitamin A, vitamin B1, vitamin B2, vitamin C, and dietary fiber, were calculated using the fourth revised edition of the Standard Tables of Food Composition in Japan (16), with adjustment for energy intake using the method of Willett and Stampfer (17).

Statistical analysis

The SAS software package, version 9.2 (SAS Institute Inc., Cary, North Carolina), was used to perform all statistical analyses. Age- and sex-adjusted mean values of possible risk factors taken as continuous variables were computed using analysis of covariance. The frequencies of risk factors taken as binary variables were adjusted for age and sex using the direct method. The statistical significance of differences in the mean values and frequencies of risk factors was estimated by means of analysis of covariance and logistic regression analysis, respectively. The mortality rate for cancer was calculated per 1,000 person-years and was adjusted for age and
sex by the direct method using 10-year age groups, where the differences in the mortality rate were tested with Cox’s proportional hazards model. Cox’s proportional hazards model was also used to estimate the multivariable-adjusted cumulative rate of mortality from cancer and the adjusted hazard ratios and 95% confidence intervals for cancer death according to glucose tolerance status.

Ethical considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research, and written informed consent was obtained from the study participants.

RESULTS

Table 1 shows baseline characteristics of the study subjects by glucose tolerance status. Compared with subjects with normal glucose tolerance, the mean values of age, body mass index, and total cholesterol and the frequencies of male sex, current alcohol intake, and family history of cancer were significantly higher in subjects with impaired fasting glycemia, impaired glucose tolerance, or diabetes.

The association between fasting plasma glucose level and the risk of death from cancer is shown in Table 2. The age- and sex-adjusted mortality rate from cancer significantly increased with elevating fasting plasma glucose levels in the whole population ($P$ for trend < 0.001). This association was substantially unchanged even after adjustment for potentially confounding factors (namely, age, sex, body mass index, total cholesterol, smoking habits, alcohol intake, physical activity, family history of cancer, and dietary factors); compared with fasting plasma glucose levels less than 5.6 mmol/L, the multivariable-adjusted hazard ratios for death from cancer were 1.38 (95% confidence interval (CI): 1.00, 1.90) for a fasting plasma glucose level of 5.6–6.0 mmol/L, 1.89 (95% CI: 1.30, 2.74) for 6.1–6.9 mmol/L, and 2.06 (95% CI: 1.35, 3.14) for ≥7.0 mmol/L. There was no evidence of heterogeneity in the association between the sexes ($P$ for heterogeneity = 0.84). As Table 3 shows, greater 2-hour postload glucose levels were also associated with a higher rate of mortality from cancer ($P$ for trend = 0.004). In the multivariate analysis, the risk of death from cancer was significantly higher in subjects with 2-hour postload glucose levels of ≥11.1 mmol/L than in those with 2-hour postload glucose levels less than 6.7 mmol/L in the whole population (hazard ratio

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Normal Glucose Tolerance (n = 1,027)</th>
<th>Impaired Fasting Glycemia (n = 648)</th>
<th>Impaired Glucose Tolerance (n = 465)</th>
<th>Diabetes Mellitus (n = 298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>Mean (SE)</td>
<td>% Mean (SE)</td>
<td>% Mean (SE)</td>
<td>% Mean (SE)</td>
</tr>
<tr>
<td>Male sex</td>
<td>36.0</td>
<td>36.0</td>
<td>36.0</td>
<td>36.0</td>
</tr>
<tr>
<td>Fasting plasma glucose level, mmol/L</td>
<td>5.2 (0.03)</td>
<td>5.9 (0.04)**</td>
<td>5.8 (0.04)**</td>
<td>5.8 (0.04)**</td>
</tr>
<tr>
<td>2-hour postload glucose level, mmol/L</td>
<td>5.8 (0.06)</td>
<td>6.2 (0.08)**</td>
<td>8.8 (0.1)**</td>
<td>15.0 (0.1)**</td>
</tr>
<tr>
<td>Body mass indexb</td>
<td>22.3 (0.1)</td>
<td>23.2 (0.1)**</td>
<td>23.7 (0.1)**</td>
<td>24.0 (0.2)**</td>
</tr>
<tr>
<td>Total cholesterol level, mmol/L</td>
<td>5.3 (0.03)</td>
<td>5.4 (0.04)**</td>
<td>5.4 (0.05)**</td>
<td>5.7 (0.06)**</td>
</tr>
<tr>
<td>Current smoking</td>
<td>26.6</td>
<td>24.5</td>
<td>24.8</td>
<td>26.4</td>
</tr>
<tr>
<td>Current alcohol intake</td>
<td>33.2</td>
<td>36.7</td>
<td>36.0</td>
<td>41.7*</td>
</tr>
<tr>
<td>Regular exercise</td>
<td>11.5</td>
<td>9.1</td>
<td>8.8</td>
<td>8.4</td>
</tr>
<tr>
<td>Family history of cancer</td>
<td>8.6</td>
<td>11.8*</td>
<td>7.6</td>
<td>8.8</td>
</tr>
<tr>
<td>Total energy intake, kcal/day</td>
<td>1,712 (11.9)</td>
<td>1,720 (14.8)</td>
<td>1,725 (17.5)</td>
<td>1,679 (21.9)</td>
</tr>
<tr>
<td>Total fat intake, g/day</td>
<td>49.6 (0.5)</td>
<td>49.3 (0.6)</td>
<td>49.9 (0.7)</td>
<td>49.0 (0.9)</td>
</tr>
<tr>
<td>Salt intake, g/day</td>
<td>13.4 (0.2)</td>
<td>13.2 (0.2)</td>
<td>13.3 (0.2)</td>
<td>12.6 (0.3)</td>
</tr>
<tr>
<td>Vitamin A intake, μg RE/day</td>
<td>970 (12.6)</td>
<td>947 (15.7)</td>
<td>977 (18.6)</td>
<td>961 (23.3)</td>
</tr>
<tr>
<td>Vitamin B1 intake, mg/day</td>
<td>0.8 (0.01)</td>
<td>0.8 (0.02)</td>
<td>0.8 (0.02)</td>
<td>0.8 (0.02)</td>
</tr>
<tr>
<td>Vitamin B2 intake, mg/day</td>
<td>1.2 (0.01)</td>
<td>1.2 (0.02)</td>
<td>1.2 (0.02)</td>
<td>1.2 (0.03)</td>
</tr>
<tr>
<td>Vitamin C intake, mg/day</td>
<td>77.3 (1.1)</td>
<td>77.1 (1.4)</td>
<td>81.0 (1.6)</td>
<td>77.2 (2.0)</td>
</tr>
<tr>
<td>Dietary fiber intake, g/day</td>
<td>11.0 (0.1)</td>
<td>10.8 (0.2)</td>
<td>11.2 (0.2)</td>
<td>11.3 (0.3)</td>
</tr>
</tbody>
</table>

Abbreviations: RE, retinol equivalents; SE, standard error.

* $P < 0.05$; ** $P < 0.01$ (vs. normal glucose tolerance).

a All data are given as age- and sex-adjusted mean values or percentages. Mean age was sex-adjusted; percentage of men was age-adjusted.
b Weight (kg)/height (m)$^2$. 

Table 1. Age- and Sex-adjusted Mean Values or Frequencies for Cancer Risk Factors by Glucose Tolerance Status in the Hisayama Study, Hisayama, Japan, 1988a
A similar tendency was observed for both sexes (P for heterogeneity = 0.80).

Table 4 presents the association between glucose tolerance status and the risk of cancer death. The multivariable-adjusted hazard ratios for death from cancer were significantly higher not only in subjects with diabetes (HR = 2.10, 95% CI: 1.41, 3.12) but also in subjects with impaired fasting glycemia (HR = 1.49, 95% CI: 1.05, 2.11) or impaired glucose tolerance (HR = 1.52, 95% CI: 1.05, 2.22), compared with subjects with normal glucose tolerance. Comparable associations were observed in both sexes (P for heterogeneity = 0.76). In the multivariate analysis in which the 2 categories of impaired fasting glycemia and impaired glucose tolerance were combined into 1 category of prediabetes, subjects with prediabetes had a 1.50-fold (95% CI: 1.10, 2.05) greater risk of death from cancer.

Furthermore, among 298 subjects with diabetes, 147 (prevalence = 6.0%) were categorized as having known diabetes and 151 (prevalence = 6.2%) as having newly diagnosed diabetes at baseline. The cumulative mortality rate from cancer over 19 years was highest in subjects with known diabetes after adjustment for the above-mentioned confounders, followed by mortality in subjects with newly diagnosed diabetes, which was close to that in subjects with impaired fasting glycemia or impaired glucose tolerance (Figure 1).

To exclude the influence of subclinical cancer on the present findings, we also performed the sensitivity analysis after excluding the first 2 years of follow-up. The significant association between glucose tolerance status and the risk of cancer death was still observed after adjusting for the confounding factors (for impaired fasting glycemia, HR = 1.46 (95% CI: 1.02, 2.10); for impaired glucose tolerance, HR = 1.59 (95% CI: 1.08, 2.34); and for diabetes, HR = 2.04 (95% CI: 1.34, 3.09)).

Finally, we examined the association of fasting plasma glucose or 2-hour postload glucose level with the risk of site-specific cancer death (Table 5). The age- and sex-adjusted hazard ratios for death from stomach cancer increased significantly in subjects with fasting plasma glucose levels of ≥5.6 mmol/L as compared with those with levels less than 5.6 mmol/L (HR = 2.13, 95% CI: 1.03, 4.45). On the other hand, subjects with 2-hour postload glucose levels of ≥7.8 mmol/L had greater risks of death from lung (HR = 1.99, 95% CI: 1.14, 3.48) and liver (HR = 2.69, 95% CI: 1.43, 5.05) cancer.

**DISCUSSION**

The present study clearly demonstrated that higher fasting plasma glucose and 2-hour postload glucose levels were significantly associated with increased risks of cancer.
death in a general Japanese population. These associations remained robust even after adjustment for other confounding factors. In particular, the risks of death from stomach, lung, and liver cancer were linked with higher fasting plasma glucose or 2-hour postload glucose levels. Intriguingly, we found that the risk of cancer death was increased significantly not only in diabetic subjects but also in prediabetic subjects as compared with subjects with normal glucose tolerance. These findings highlight the clinical value of early management of hyperglycemia, even in the prediabetic range, to prevent cancer death.

Several prospective population-based studies have assessed the association between diabetes and cancer death, but the definitions of diabetes in these studies were based on diverse parameters, such as self-reports (3, 5, 9, 18), fasting plasma glucose levels only (7, 8, 19), 2-hour postload glucose levels only (4, 6, 20, 21), and a combination of the latter two parameters (11). Most of these studies showed that diabetes exerted a major influence on cancer incidence or mortality. In contrast, the Whitehall Study in the United Kingdom (4, 20) and the NHANES II (Second National Health and Nutrition Examination Survey) Mortality Study in the United States (6) failed to reveal a significant association between diabetes diagnosed by 2-hour postload glucose levels only and cancer death. Since 2-hour postload glucose levels have been associated with the risk of cardiovascular death (22), a competing risk might have been present in these early studies, in which subjects' diabetes was thought to be less stringently managed. In the present study, all of the subjects with diabetes determined by either fasting plasma glucose level, 2-hour postload glucose level, or a combination of the two were at increased risk of cancer death. Notably, the fact that subjects with known diabetes had a greater risk of cancer death than those with newly diagnosed diabetes implies that longer exposure to diabetes may be associated with greater cancer mortality. On the whole, therefore, it might be said that diabetes is a significant risk factor for cancer.

A growing body of evidence is accumulating to show the positive association between prediabetes and cancer death. Studies conducted in South Korea (7) and Austria (19) showed a significantly elevated risk of cancer in subjects with fasting plasma glucose levels in the prediabetic range. The Emerging Risk Factors Collaboration, which conducted a meta-analysis of data from 92 cohorts, including 23,000 subjects from Asia, demonstrated that the risk of cancer death increased with fasting plasma glucose levels of ≥6.0 mmol/L among subjects without known diabetes (23). The findings from these studies suggest that higher fasting plasma glucose levels, even in the prediabetic range, are a significant risk factor for cancer.

### Table 3. Hazard Ratios for Death From Any Cancer According to 2-Hour Postload Glucose Level in the Hisayama Study, Hisayama, Japan, 1988–2007

<table>
<thead>
<tr>
<th>2-Hour Postload Glucose Level, mmol/L</th>
<th>PY at Risk</th>
<th>No. of Events</th>
<th>Age- and Sex-adjusted Mortality Rate (per 1,000 PY)</th>
<th>Age- and Sex-adjusted Risk</th>
<th>Multivariable-adjusted Risk</th>
<th>P Value</th>
<th>P for trend</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age- and Sex-adjusted Risk HR 95% CI</td>
<td>P Value</td>
<td>Multivariable-adjusted Risk HR 95% CI</td>
<td>P Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>Age- and Sex-adjusted Risk Referent HR 95% CI</td>
<td>P Value</td>
<td>Multivariable-adjusted Risk Referent HR 95% CI</td>
<td>P Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6.7</td>
<td>20,403</td>
<td>90</td>
<td>5.4</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.7–7.7</td>
<td>8,854</td>
<td>43</td>
<td>6.2</td>
<td>1.14 0.79, 1.64</td>
<td>0.48 1.17 0.80, 1.69</td>
<td>0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.8–11.0</td>
<td>8,054</td>
<td>58</td>
<td>6.7</td>
<td>1.30 0.93, 1.81</td>
<td>0.12 1.37 0.97, 1.93</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥11.1</td>
<td>3,774</td>
<td>38</td>
<td>9.2</td>
<td>1.76 1.21, 2.58</td>
<td>0.003 1.99 1.34, 2.94</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P for trend 0.004 <0.001

Men

| <6.7                                  | 8,375     | 58            | 8.4                                              | 1.00 Referent             | 1.00 Referent                |         |
| 6.7–7.7                               | 3,192     | 26            | 9.7                                              | 1.19 0.74, 1.89           | 0.47 1.23 0.77, 1.99         | 0.39    |
| 7.8–11.0                              | 3,414     | 34            | 9.7                                              | 1.19 0.78, 1.83           | 0.41 1.28 0.83, 2.00         | 0.27    |
| ≥11.1                                 | 1,975     | 27            | 14.5                                             | 1.79 1.13, 2.83           | 0.01 2.08 1.30, 3.33         | 0.002   |

P for trend 0.03 0.006

Women

| <6.7                                  | 12,028    | 32            | 3.2                                              | 1.00 Referent             | 1.00 Referent                |         |
| 6.7–7.7                               | 5,662     | 17            | 3.6                                              | 1.08 0.60, 1.95           | 0.79 1.09 0.60, 1.98         | 0.79    |
| 7.8–11.0                              | 4,641     | 24            | 4.7                                              | 1.50 0.88, 2.55           | 0.14 1.52 0.87, 2.63         | 0.14    |
| ≥11.1                                 | 1,799     | 11            | 5.1                                              | 1.72 0.86, 3.41           | 0.12 1.79 0.86, 3.72         | 0.12    |

P for trend 0.06 0.06

Abbreviations: CI, confidence interval; HR, hazard ratio; PY, person-years.

* Multivariable adjustment was made for age, sex, body mass index, total cholesterol, smoking habits, alcohol intake, family history of cancer, physical activity, and dietary factors (daily intakes of total energy, total fat, salt, vitamin A, vitamin B1, vitamin B2, vitamin C, and dietary fiber).

b In the sex-stratified analyses, the mortality rate and HR were not adjusted for sex.
range, are associated with greater cancer risk in both Western and Asian populations. However, the influence of prediabetic 2-hour postload glucose levels on the risk of cancer is still inconclusive. A longitudinal study conducted in Sweden, in which all participants underwent a 75-g oral glucose tolerance test, failed to reveal a significant association between 2-hour postload glucose levels of 8.9–12.1 mmol/L and the risk of cancer occurrence, although cancer risk was significantly increased in women with fasting plasma glucose levels of 6.1–6.9 mmol/L (24). On the contrary, in the NHANES II Mortality Study, Saydah et al. (6) reported that subjects with 2-hour postload glucose levels of 7.8–11.0 mmol/L had higher risk of cancer death. In the present study, we found that higher 2-hour postload glucose levels as well as higher fasting plasma glucose levels, even in the prediabetic range, were significant risk factors for cancer death in a Japanese population. Further longitudinal studies are needed to clarify the influence of 2-hour postload glucose level on cancer risk.

Importantly, the present study estimated the effects of impaired fasting glycemia and impaired glucose tolerance on the risks of cancer death separately. The DECODE Study revealed that prediabetes determined by 75-g oral glucose tolerance testing was a significant risk factor for cancer death (11) but did not address whether the effects of impaired fasting glycemia and impaired glucose tolerance on cancer risk were different. Impaired glucose tolerance has already been reported to be a stronger risk factor for the development of cardiovascular disease than impaired fasting glycemia (22). On the other hand, the present study


<table>
<thead>
<tr>
<th>Glucose Tolerance Status</th>
<th>PY at Risk</th>
<th>No. of Events</th>
<th>Age- and Sex-adjusted Mortality Rate (per 1,000 PY)</th>
<th>Age- and Sex-adjusted Risk</th>
<th>P Value</th>
<th>Multivariable-adjusted Risk</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT</td>
<td>18,024</td>
<td>64</td>
<td>4.8</td>
<td>1.00 Referent</td>
<td>1.00</td>
<td>Referent</td>
<td>1.00</td>
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<tr>
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<td>10,886</td>
<td>68</td>
<td>6.8</td>
<td>1.41 1.12, 2.76</td>
<td>0.049</td>
<td>1.49 1.05, 2.11</td>
<td>0.02</td>
</tr>
<tr>
<td>IGT</td>
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<td>53</td>
<td>6.8</td>
<td>1.43 0.99, 1.99</td>
<td>0.06</td>
<td>1.52 1.05, 2.22</td>
<td>0.03</td>
</tr>
<tr>
<td>DM</td>
<td>4,569</td>
<td>44</td>
<td>8.7</td>
<td>1.88 1.28, 2.77</td>
<td>0.001</td>
<td>2.10 1.41, 3.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT</td>
<td>6,302</td>
<td>40</td>
<td>7.7</td>
<td>1.00 Referent</td>
<td>1.00</td>
<td>Referent</td>
<td>1.00</td>
</tr>
<tr>
<td>IFG</td>
<td>5,108</td>
<td>43</td>
<td>9.6</td>
<td>1.20 0.78, 1.84</td>
<td>0.41</td>
<td>1.37 0.88, 2.13</td>
<td>0.16</td>
</tr>
<tr>
<td>IGT</td>
<td>3,172</td>
<td>31</td>
<td>9.6</td>
<td>1.22 0.76, 1.95</td>
<td>0.42</td>
<td>1.37 0.84, 2.23</td>
<td>0.21</td>
</tr>
<tr>
<td>DM</td>
<td>2,375</td>
<td>31</td>
<td>13.6</td>
<td>1.75 1.10, 2.80</td>
<td>0.02</td>
<td>2.07 1.28, 3.35</td>
<td>0.003</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT</td>
<td>11,722</td>
<td>24</td>
<td>2.6</td>
<td>1.00 Referent</td>
<td>1.00</td>
<td>Referent</td>
<td>1.00</td>
</tr>
<tr>
<td>IFG</td>
<td>5,778</td>
<td>25</td>
<td>4.7</td>
<td>1.85 1.05, 3.24</td>
<td>0.03</td>
<td>1.68 0.94, 2.98</td>
<td>0.08</td>
</tr>
<tr>
<td>IGT</td>
<td>4,435</td>
<td>22</td>
<td>4.6</td>
<td>1.82 1.02, 3.27</td>
<td>0.04</td>
<td>1.80 0.99, 3.28</td>
<td>0.06</td>
</tr>
<tr>
<td>DM</td>
<td>2,195</td>
<td>13</td>
<td>4.9</td>
<td>2.08 1.05, 4.10</td>
<td>0.04</td>
<td>2.04 1.00, 4.16</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; PY, person-years.

* Multivariable adjustment was made for age, (sex), body mass index, total cholesterol, smoking habits, alcohol intake, family history of cancer, physical activity, and dietary factors (daily intakes of total energy, total fat, salt, vitamin A, vitamin B1, vitamin B2, vitamin C, and dietary fiber).

† In the sex-stratified analyses, the mortality rate and HR were not adjusted for sex.

Figure 1. Multivariable-adjusted cumulative rate of mortality from cancer (all types) according to glucose tolerance status in the Hisayama Study, Hisayama, Japan, 1988–2007. Differences in the cumulative cancer mortality rate among glucose tolerance levels were tested using a Cox proportional hazards model (P < 0.01 for known diabetes vs. normal glucose tolerance (NGT) and P < 0.05 for impaired fasting glycemia (IFG), impaired glucose tolerance (IGT), and newly diagnosed diabetes vs. NGT).
demonstrated that impaired fasting glycemia had an influence on the risk of cancer death comparable to that of impaired glucose tolerance. The biologic mechanisms underlying the difference in the effects of impaired fasting glycemia and impaired glucose tolerance are unclear.

### Table 5. Hazard Ratios for Cancer at Various Sites According to Fasting or 2-Hour Postload Glucose Level in the Hisayama Study, Japan, 1988–2007

<table>
<thead>
<tr>
<th>Glucose Measure</th>
<th>No. of Events</th>
<th>Person-Years at Risk</th>
<th>Hazard Ratio*</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.6 mmol/L</td>
<td>17</td>
<td>21,002</td>
<td>1.00</td>
<td>Reference</td>
<td>0.15</td>
</tr>
<tr>
<td>≥5.6 mmol/L</td>
<td>33</td>
<td>20,083</td>
<td>1.53</td>
<td>0.85, 2.76</td>
<td></td>
</tr>
<tr>
<td>2-hour PG level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7.8 mmol/L</td>
<td>24</td>
<td>29,257</td>
<td>1.00</td>
<td>Reference</td>
<td>0.02</td>
</tr>
<tr>
<td>≥7.8 mmol/L</td>
<td>26</td>
<td>11,828</td>
<td>1.99</td>
<td>1.14, 3.48</td>
<td></td>
</tr>
<tr>
<td><strong>Stomach Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>&lt;5.6 mmol/L</td>
<td>10</td>
<td>21,002</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≥5.6 mmol/L</td>
<td>26</td>
<td>20,083</td>
<td>2.13</td>
<td>1.03, 4.45</td>
<td></td>
</tr>
<tr>
<td>2-hour PG level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>&lt;7.8 mmol/L</td>
<td>20</td>
<td>29,257</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≥7.8 mmol/L</td>
<td>16</td>
<td>11,828</td>
<td>1.59</td>
<td>0.82, 3.08</td>
<td></td>
</tr>
<tr>
<td><strong>Colorectal Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>FPG level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.6 mmol/L</td>
<td>14</td>
<td>21,002</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≥5.6 mmol/L</td>
<td>14</td>
<td>20,083</td>
<td>0.84</td>
<td>0.40, 1.78</td>
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</tr>
<tr>
<td>2-hour PG level</td>
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<td></td>
<td></td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>&lt;7.8 mmol/L</td>
<td>22</td>
<td>29,257</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≥7.8 mmol/L</td>
<td>6</td>
<td>11,828</td>
<td>0.54</td>
<td>0.22, 1.33</td>
<td></td>
</tr>
<tr>
<td><strong>Liver Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>FPG level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.6 mmol/L</td>
<td>12</td>
<td>21,002</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≥5.6 mmol/L</td>
<td>28</td>
<td>20,083</td>
<td>1.91</td>
<td>0.97, 3.76</td>
<td></td>
</tr>
<tr>
<td>2-hour PG level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>&lt;7.8 mmol/L</td>
<td>17</td>
<td>29,257</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≥7.8 mmol/L</td>
<td>23</td>
<td>11,828</td>
<td>2.69</td>
<td>1.43, 5.05</td>
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<tr>
<td><strong>Pancreatic Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>FPG level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.6 mmol/L</td>
<td>4</td>
<td>21,002</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≥5.6 mmol/L</td>
<td>11</td>
<td>20,083</td>
<td>2.27</td>
<td>0.72, 7.16</td>
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</tr>
<tr>
<td>2-hour PG level</td>
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<td></td>
<td></td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>&lt;7.8 mmol/L</td>
<td>10</td>
<td>29,257</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≥7.8 mmol/L</td>
<td>5</td>
<td>11,828</td>
<td>0.89</td>
<td>0.30, 2.60</td>
<td></td>
</tr>
<tr>
<td><strong>Other Cancer</strong></td>
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<td></td>
<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>FPG level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.6 mmol/L</td>
<td>24</td>
<td>21,002</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≥5.6 mmol/L</td>
<td>36</td>
<td>20,083</td>
<td>1.30</td>
<td>0.77, 2.19</td>
<td></td>
</tr>
<tr>
<td>2-hour PG level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>&lt;7.8 mmol/L</td>
<td>40</td>
<td>29,257</td>
<td>1.00</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≥7.8 mmol/L</td>
<td>20</td>
<td>11,828</td>
<td>1.00</td>
<td>0.58, 1.71</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FPG, fasting plasma glucose; PG, postload glucose.

* Adjusted for age and sex.
glycemia between cancer and cardiovascular disease are unclear. Nevertheless, our findings provide important information that the risk of cancer death is elevated in both impaired fasting glycemia and impaired glucose tolerance and raise the possibility that not only impaired glucose tolerance but also impaired fasting glycemia may be an important target for early intervention in patients with glucose intolerance in order to prevent cancer death.

The present study showed that higher fasting plasma glucose levels were a significant risk factor for death from stomach cancer and that higher 2-hour postload glucose levels were a significant risk factor for lung and liver cancer death. In partial support of our findings, the results from a recent pooling analysis suggested that glucose intolerance was linked with the risks of stomach and liver cancer death, from the prediabetic range upward (11). In a previous study by our research group, Yamagata et al. (25) also reported an elevated incidence of stomach cancer among subjects with fasting plasma glucose levels in the prediabetic range. An epidemiologic study demonstrated a positive relation between 2-hour postload glucose level and the risk of liver cancer death (20). In another epidemiologic study, Levine et al. (3) reported that baseline mean postload plasma glucose values were higher in lung cancer decedents than in all survivors. These findings may follow the trend of our findings. Further epidemiologic studies focusing on the site-specific effects of fasting plasma glucose and 2-hour postload glucose levels will be needed to further explore this issue. Several mechanisms may be involved in the association between glucose intolerance and cancer risk. One possible explanation is that hyperglycemia and its related conditions may act directly as a carcinogenic factor. A clinical study with diabetic subjects and healthy volunteers demonstrated that diabetes is associated with increased production of reactive oxygen species and greater oxidative damage to DNA (26). In an experimental study, a high glucose level itself was also shown to induce DNA damage (27). Thus, it is possible that increased production of reactive oxygen species or high glucose itself contributes to DNA damage, which may lead to mutational changes in oncogenes and tumor suppressor genes and thereby to the development of cancer. Another possible explanation is that hyperinsulinemia, which leads to hyperglycemia, is related to carcinogenesis. Experimental studies have found that most cancer cells express insulin receptors, and hyperinsulinemia is thought to promote carcinogenesis by directly stimulating the proliferating pathway after insulin receptors (28). Apart from the direct effects of insulin on cancer cells, it is possible that hyperinsulinemia could promote carcinogenesis indirectly via the effect of insulin-like growth factor 1 (IGF-1). Insulin reduces the production of insulin-like growth factor binding protein 1 and consequently increases levels of bioactive IGF-1. IGF-1 has more potent mitogenic and antiapoptotic activities than insulin and could act as a stimulus for growing preneoplastic and neoplastic cells. Additionally, inflammatory cytokines produced by adipose tissues, such as interleukin-6, monocyte chemoattractant protein, and plasminogen activator inhibitor 1, may play important roles in the carcinogenic process, in cancer progression, or in poor prognosis.

The strengths of our study include its longitudinal population-based design, long duration of follow-up, perfect follow-up of subjects, and accuracy in the diagnosis of the cause of death on the basis of medical records and autopsy findings. Some limitations of this study should be noted. First, the use of only a single measurement of glucose levels at baseline could have introduced some degree of misclassification of patients into the glucose tolerance categories. This limitation would have weakened the association found in the present study, biasing the results toward the null hypothesis. Second, the existence of subclinical cancer at baseline is undeniable, because no screening survey for cancer was performed at baseline. However, excluding the first 2 years of follow-up did not make any material difference in the findings of the sensitivity analysis, suggesting that the influence of this limitation would have been small. Finally, the precision of our findings may be limited, because of the small number of cancer deaths among those surveyed.

In conclusion, not only diabetes but also prediabetes defined by means of the 75-g oral glucose tolerance test was an independent risk factor for cancer death in a general Japanese population. Further large-scale prospective cohort studies and clinical trials investigating the favorable effects of intensive glucose-lowering on the risk of cancer in diabetic patients and hyperglycemic subjects are needed to clarify the role of hyperglycemia in the occurrence of cancer.

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