Although pancreatic cancer is a relatively rare cancer, it is associated with high fatality. The etiology of pancreatic cancer remains largely unknown. There are no screening tests for early detection of pancreatic cancer. Many epidemiologic studies have been conducted to identify the risk factors for pancreatic cancer. The objective of this article was to overview the epidemiology of pancreatic cancer.

We referred the results of focusing on the (Japan Collaborative Cohort Study) JACC Study and reviewed previous studies. The reason for focusing on the JACC Study is that it is ongoing large scale population-based cohort study of a total of over 110,000 Japanese followed up.

References were mainly in a Medline search through PubMed database which have been published in English since 1994, by using keywords of pancreatic cancer, risk factor, and epidemiologic study. Reports were selected on the basis of the best available evidence for each factor discussed. Additionally, 3 papers about the JACC Study: (Mortality in the JACC Study till 1999),1 (A prospective cohort study of cigarette smoking and pancreatic cancer in Japan),2 and (Risk of pancreatic cancer in relation to alcohol drinking, coffee consumption and medical history: findings from the Japan collaborative cohort study for evaluation of
cancer risk) were quoted. In the JACC Study, the strength of associations was examined using hazard ratios (HRs) derived from the Cox proportional hazards model. The HRs were adjusted for potentially confounding factors. Risk factors data, such as life style and medical history, were obtained with self-administered questionnaire at baseline.

**Incidence and Mortality of Pancreatic Cancer**

Pancreatic cancer has demonstrated increasing trends in both incidence and mortality during the past four decades in Japan, although its morbidity and mortality in Japan had been among the lowest in the world. It is the 5th leading cause of death from cancer in males and the 6th leading cause in females in Japan according to the latest statistics in Japan. The age-adjusted mortality rate from pancreatic cancer increased 3.0-fold in males and 2.9-fold in females in Japan between 1960 and 2002. The risk of pancreatic cancer in blacks was approximately 50% higher than that in whites among the general population. High incidence of pancreatic cancer was found in New Zealand Maoris, especially in Maoris females. In the United States high incidence was occurred among Caucasian and African- American males and females.

During approximately 12 years of follow up in the JACC Study, 161 males and 156 females deaths from pancreatic cancer occurred out of a total of 46,465 males and 64,327 females. The standardized mortality ratio (SMR) of pancreatic cancer in females in the JACC Study was similar to that in Japan nationwide (0.97), whereas in males it was somewhat lower than that in Japan nationwide (0.84). This low SMR of pancreatic cancer in males might partly come from the selection of investigated subjects in the JACC Study. Because some of cohort subjects in the JACC Study were chosen out of participants in routine medical checkups or other kinds of screening, of which was regarded relating to slightly healthier lifestyles.

**Age and Sex**

The risk of pancreatic cancer increases with advancing age. Nearly 80% of the patients with pancreatic cancer were between 60 and 80 years of age. The similar founding was reflected in the JACC Study, which observed 79% of deaths aged 60 or older. Pancreatic cancer occurs more frequently in males than in females. The age-adjusted death rate of pancreatic cancer in males was approximately 1.7-fold higher than that in females in 2002 in Japan.

Hormonal factors related to pancreatic cancer in females were observed by analysis of menarche, menopause and productive history in previous studies. Although the mechanism of hormonal factors for pancreatic cancer remains unclear, pancreatic cancer is at least in part association with hormonal levels in females. It can be expected to verify the association between pancreatic cancer and hormonal factor in the JACC Study, which investigated 64,327 females over approximately 12-year follow up.

**Medical Conditions**

(1) Diabetes mellitus (DM)

A number of epidemiologic studies have shown that there is a complex relationship between DM and pancreatic cancer. In a large prospective study in the US, Calle et al. found that the risk of pancreatic cancer mortality was significantly increased not only among subjects with a history of diabetes, but also among diabetics during the second and third years of follow-up (HR = 2.05, 95% confidence interval [CI]: 1.56-2.69) (Table 1). Compared with the controls, a 70% or 50% higher risk for pancreatic cancer was observed in subjects who were diagnosed with diabetes 5-9 years prior to the diagnosis of pancreatic cancer and among subjects who were diagnosed with diabetes at least 10 years prior to the diagnosis of pancreatic cancer, respectively, in a case-control study in the US. A meta-analysis of pancreatic cancer studies found that individuals with DM for a duration of at least 5 years had an increased risk for pancreatic cancer (HR = 2.0, 95% CI: 1.2-3.2). Studies conducted in Japan, Sweden, and the US also found that patients with DM had an increased risk for pancreatic cancer (Table 1).

On the other hand, La Vecchia et al. suggested that DM was an initial symptom of pancreatic cancer rather than a cause of pancreatic cancer based on a case-control study in Italy, because the risk declined as the number of years after the diagnosis of DM increased, although the subjects with DM as a whole had a significantly elevated risk (HR = 2.1; 95% CI: 1.5-2.9). A case-control study conducted in northern Italy also obtained similar results. Gullo et al. found that there was no association between DM and pancreatic cancer among patients with diabetes of 3 or more year duration, and presumed that diabetes was caused by the pancreatic cancer and that the increasing prevalence of diabetes in patients with pancreatic cancer was mainly due to diabetes of recent onset. In a case-control study performed in hospitals in New Zealand, it was concluded that diabetes might be an epiphenomenon of pancreatic cancer, rather than a risk factor for pancreatic cancer. Furthermore, in a nested case-control study on familial pancreatic cancer in the US, the authors concluded that DM was not a risk factor for pancreatic cancer.

In order to avoid misclassification of DM, Gapstur et al. studied the postload plasma glucose level instead of self-reported diabetes as the diagnostic criterion in a cohort study conducted over a mean period of 25 years. A significant dose-response association was found between the postload plasma glucose level and pancreatic cancer mortality. Compared with the subjects with postload plasma glucose level of 119mg/dL or less, the HR of pancreatic cancer mortality was 1.65 (95% CI: 1.05-2.60) for those with 120-159 mg/dL, 1.60 (95% CI: 0.95-2.70) for those with 160-199mg/dL, and 2.15 (95% CI: 1.22 -3.80) for those with 200mg/dL or higher (Table 1). This association was stronger in males than in females. These results suggested that abnormal glucose metabolism plays an important role in the development of pancreatic cancer, and that diabetes was likely to be a risk factor for this tumor.
| Author           | Year       | Place     | Study    | Sex       | Item                                                | Risk ratio | 95% CI         | Adjusted factors                                                                 |
|------------------|------------|-----------|----------|-----------|-----------------------------------------------------|------------|----------------|--------------------------------------------------------------------------------|
| JACC Study       | 1988-1997  | Japan     | Cohort   | Male      | History of diabetes mellitus                        | 1.00       | (reference)    | age and cigarette smoking in pack-years                                         |
| Lin et al.        |            |           |          |           |                                                     |            |                |                                                                                |
| Female           |            |           |          |           | History of gallstone/cholecystitis                   | 2.12       | 1.19-3.77      |                                                                                |
| Calle et al.      | 1982-1994  | US        | Cohort   | Both      | A history of diabetes                               | 1.00       | (reference)    | age, sex, race, smoking status, body mass index, family history of pancreatic cancer, and education |
| Male             |            |           |          |           |                                                     | 1.48       | 1.30-1.68      |                                                                                |
| Female           |            |           |          |           |                                                     | 1.49       | 1.25-1.77      |                                                                                |
| Follow-up time (years) |          |           |          |           |                                                     |            |                |                                                                                |
| No               |            |           |          |           |                                                     | 1.00       | (reference)    |                                                                                |
| 1-3              |            |           |          |           |                                                     | 2.05       | 1.56-2.69      |                                                                                |
| 4-6              |            |           |          |           |                                                     | 1.44       | 1.11-1.86      |                                                                                |
| 7-9              |            |           |          |           |                                                     | 1.28       | 0.97-1.68      |                                                                                |
| 10-12            |            |           |          |           |                                                     | 1.38       | 1.08-1.77      |                                                                                |
| Silverman        | 1986-1989  | US        | Case-control | Both     | Interval between onset of diabetes and diagnosis of cancer | 1.0        | (reference)    | age at diagnosis/interview, race, gender, area, cigarette smoking, alcohol consumption, body mass index, and calories from food |
| No diabetes      |            |           |          |           |                                                     | 1.7        | 1.0-2.9        |                                                                                |
| 5-9 years        |            |           |          |           |                                                     | 1.5        | 1.02-2.2       |                                                                                |
| ≥10 years        |            |           |          |           |                                                     | 1.0        | (reference)    |                                                                                |
| Interval between onset of cholecystectomy and diagnosis of cancer |          |           |          |           |                                                     | 1.7        | 1.0-3.0        |                                                                                |
| No cholecystectomy |            |           |          |           |                                                     |            |                |                                                                                |
| 20+ years        |            |           |          |           |                                                     |            |                |                                                                                |
| La Vecchia et al. | 1983-1992  | Italy     | Case-control | Both     | A history of diabetes                               | 1.0        | (reference)    | age and sex                                                                   |
| No               |            |           |          |           |                                                     | 2.1        | 1.5-2.9        |                                                                                |
| Gapstur et al.    | 1967-1995  | US        | Cohort   | Both      | Postload plasma glucose level                        | 1.00       | (reference)    | age, race, categories of postload plasma glucose concentration, cigarette smoking status, and quartiles of body mass index |
| -119 mg/dL       |            |           |          |           |                                                     | 1.65       | 1.05-2.60      |                                                                                |
| 120-159 mg/dL    |            |           |          |           |                                                     | 1.60       | 0.95-2.70      |                                                                                |
| 160-199 mg/dL    |            |           |          |           |                                                     | 2.15       | 1.22-3.80      |                                                                                |
| 200+ mg/dL       |            |           |          |           |                                                     |            |                |                                                                                |
| Johansen et al.   | 1977-1992  | Denmark   | Cohort   | Both      | Diagnosis of gallstones                              | 1.00       | (reference)    | age, sex, and calendar year                                                    |
| No               |            |           |          |           |                                                     | 1.33       | 1.1-1.6        |                                                                                |
| Chow et al.       | 1997-1993  | Denmark   | Cohort   | Both      | cholecystectomy patients                             | 1.30       | 1.1-1.6        | age and sex                                                                   |
| Years of follow-up 5+ year |            |           |          |           |                                                     |            |                |                                                                                |
| Scherhammer et al. | 1982-1998  | US        | Cohort   | Both      | History of gallstones or cholecystectomy             | 1.00       | (reference)    | age in months, follow-up cycle, history of diabetes, smoking status, vigorous physical activity in metabolic equivalents per week, in quintiles, cohort baseline, and baseline body mass index |
| No               |            |           |          |           |                                                     | 1.11       | 0.78-1.56      |                                                                                |
| Yes              |            |           |          |           |                                                     |            |                |                                                                                |

CI: confidence interval.
In the JACC Study, an increased risk for pancreatic cancer in subjects with a history of DM was found in males and females, only in males was significant (HR = 2.12, 95% CI: 1.96-2.31).3 (Table 1) The positive association between DM and pancreatic cancer from this unique large cohort study in Japan was consistent with most of previous studies.19,20 The increasing death rates of pancreatic cancer may partly explain by the increasing of DM in Japan. Overall, DM might be both an initial manifestation of pancreatic cancer as well as a risk factor of this malignant tumor. Further investigations are required to explore the relationship between long-standing DM and pancreatic cancer.

(2) Cholecystectomy/Gallstones or Cholecystitis
A positive association between pancreatic cancer and cholecystectomy was observed.20,30 Chow reported an increased risk of pancreatic cancer for cholecystectomy 5 or more years prior to the diagnosis of pancreatic cancer43 in a cohort study. (Table 1) A case-control study also showed a 70% excess risk among subjects who underwent cholecystectomy 20 or more years prior to the cancer diagnosis.29 (Table 1) Although some studies found no evidence for an association between cholecystectomy and pancreatic cancer,25,31,32 the causality was supported by experiment study: cholecystectomy increased circulating levels of cholecystokinin, which is a promoter of pancreatic carcinogenesis in rodents.33 In the JACC Study, there was no significant relationship was observed between cholecystectomy and pancreatic cancer, but the risk of death from pancreatic cancer was significantly increased in females with gallstones or cholecystitis (HR = 2.51, 95% CI: 1.41-4.46).3 (Table 1) This result was consistent with that in a cohort study in Denmark.44 (Table 1)

(3) Others
Previous studies suggested that chronic pancreatitis plays an important role in the development of pancreatic cancer,13,35-39 but the clinical relevance of a causal relationship between chronic pancreatitis and pancreatic cancer was limited.39 Although hereditary pancreatitis resembles other types of pancreatitis, the age of onset of hereditary pancreatitis is much earlier. The risk of pancreatic cancer of hereditary pancreatitis was 50-60 times higher than expected compared with the background population.10

Two case-control studies suggested that immune function in relation to allergy might play a role in the etiology of pancreatic cancer.45,46 No association was found between regular aspirin use and pancreatic cancer in a case-control study in the US.47 In laboratory studies, aspirin inhibited the cell growth of four pancreatic cancer cell lines, and aspirin use may be a possible therapy for prevention of pancreatic cancer.48 In a recent cohort study, however, the risk of pancreatic cancer was significantly elevated with extending periods of regular aspirin use in females.49

The association between pancreatic cancer and chronic pancreatitis, hereditary pancreatitis, allergy or aspirin use can not verify in the JACC Study. Further investigations into the mechanism of these observed associations are warranted.

Family history
Family aggregation of pancreatic cancer has been found. Genetic factors played an important role of the etiology of pancreatic cancer. Among those subjects with first-degree relatives with pancreatic cancer, the risk for pancreatic cancer ranged from 1.2 to 32.0.20,21,24,45-47 In particular, the risk increased as the number of first-degree relatives with familial pancreatic cancer increased.60 Additionally, the risk of pancreatic cancer mortality was significantly increased in subjects with a family history of uterine cancer and breast cancer.46 These findings will be verified in the JACC Study.

Smoking, Alcohol, and Coffee Consumption
(1) Smoking
Table 2 shows cigarette smoking for the risk of pancreatic cancer in the JACC Study and other epidemiologic studies. According to the results of the JACC Study, upon analysis of mortality to the end of 1997, cigarette smoking was associated with pancreatic cancer mortality.2 Regarding the JACC Study, compared with non-smokers, the HR for current smokers was 1.6 (95% CI: 1.05-2.5) in males, and 1.7 (95% CI: 0.85-3.4) in females.2 The HR of death from pancreatic cancer according to the number of cigarettes smoked per day was 3.3 (95% CI: 1.38-8.1) among subjects who smoked 40 cigarettes or more per day in males.2 The age at which one started to smoke, number of years of smoking and number of pack-years were not significantly associated with an increased risk for death from pancreatic cancer.2

In many epidemiologic studies, cigarette smoking has been reported to be associated with increased risk for pancreatic cancer. A study of the cancer registry in Sweden showed that smoking increased the risk of pancreatic cancer.49 The relationship between smoking and pancreatic cancer has been studied in case-control13,20,23,25,49-50 and cohort studies.51-59 These results show that smokers have an increased risk for pancreatic cancer. Most studies showed that heavy smokers have a higher risk for pancreatic cancer than light smokers. The dose-response relationship was observed in several case-control studies.20,30,60 Although the risk of pancreatic cancer did not change after smoking cessation for more than 2 years prior to the interview (odds ratio [OR] = 1.4, 95% CI: 1.1-1.9),50 after 15 years from ceasing smoking, the risk for pancreatic cancer dropped to the level of a lifetime non-smoker regardless of the lifetime smoking amount.51

As for the previous cohort studies,52-54 the HR for pancreatic cancer ranged from 1.3 to 3.9 among current smokers, and a significant dose-response relationship was observed in 4 studies.43,50,52,54 A significant, positive trend in risk for pancreatic cancer as the number of pack-years of smoking increased was observed in another cohort study,55 especially in current smokers and when the analysis was confined to cigarette smoking within the past 15 years. Additionally, the results of a cohort study of male smokers showed that pack-years over 49 number was associated with an increased risk for pancreatic cancer compared with pack-year less than 22 number (HR = 1.66, 95% CI: 1.02-2.72).56
| Author                  | Year   | Place | Study      | Sex   | Item                          | Risk ratio | 95% CI          | Adjusted factors                                                                 |
|------------------------|--------|-------|------------|-------|-------------------------------|------------|----------------|--------------------------------------------------------------------------------|
| JACC study             | 1988-1997 | Japan | Cohort     | Male  | Never                         | 1.0        | (reference)    | age, BMI, history of DM, gallbladder diseases                                   |
| Lin Y et al.          |        |       |            | Male  | Ex-smoker                     | 1.1        | 0.61-1.9       |                                                                     |
|                        |        |       |            | Male  | Current smoker                | 1.6        | 0.95-2.6       |                                                                     |
|                        |        |       |            | Female| Never                         | 1.0        | (reference)    |                                                                     |
|                        |        |       |            | Female| Ex-smoker                     | 1.8        | 0.67-5.0       |                                                                     |
|                        |        |       |            | Female| Current smoker                | 1.7        | 0.85-3.4       |                                                                     |
| JACC study             | 1988-1997 | Japan | Cohort     | Male  | Cigarettes/day (Current smokers) | 1.0        | (reference)    |                                                                     |
| Lin Y et al.          |        |       |            | Male  | Never                         | 1.0        | (reference)    |                                                                     |
|                        |        |       |            | Male  | 1-19                          | 1.6        | 0.91-2.9       |                                                                     |
|                        |        |       |            | Male  | 20-39                         | 1.3        | 0.74-2.4       |                                                                     |
|                        |        |       |            | Male  | 40+                           | 3.3        | 1.38-8.1       |                                                                     |
| Fuch CS et al.        | 1980-1996 | US    | 2 cohorts  | both  | Never                         | 1.0        | (reference)    | age in 2-year intervals, sex, BMI, history of DM                          |
|                        | 1986-1998 |       |            | both  | 1-10                          | 1.3        | 0.3-5.4        |                                                                     |
|                        |        |       |            | both  | 11-25                         | 2.7        | 1.4-5.1        |                                                                     |
|                        |        |       |            | both  | 26-50                         | 2.8        | 1.84-4.4       |                                                                     |
|                        |        |       |            | both  | 50+                           | 2.1        | 1.2-3.8        |                                                                     |
| Stolzenberg-Solomon RZ et al. | 1985-1997 | Finland | Cohort (smokers) | Male  | Pack years                          | 1.00       | (reference)    | age, intervention(alpha-tocopherol and beta carotine supplement)            |
|                        |        |       |            | Male  | <22                           | 1.00       | (reference)    |                                                                     |
|                        |        |       |            | Male  | 22-31                         | 1.18       | 0.69-2.03      |                                                                     |
|                        |        |       |            | Male  | 32-39                         | 1.23       | 0.71-2.12      |                                                                     |
|                        |        |       |            | Male  | 30-49                         | 1.26       | 0.75-2.13      |                                                                     |
|                        |        |       |            | Male  | 49+                           | 1.66       | 1.02-2.72      |                                                                     |

CI: confidence interval.
BMI: body mass index.
DM: diabetes mellitus.
### Table 3. Alcohol consumption for the risk of pancreatic cancer.

| Author                  | Year(s)   | Place   | Study   | Sex | Daily amount (g) | Risk ratio | 95% CI       | Adjusted factors                                                                 |
|-------------------------|-----------|---------|---------|-----|------------------|------------|--------------|----------------------------------------------------------------------------------|
| JACC study, Lin Y et al. | 1988-1997 | Japan   | Cohort  | Male | Non-drinker      | 1.00       | (reference)  | age, cigarette smoking in pack year                                               |
|                         |           |         |         | Male | Ex-drinker       | 0.74       | 0.30-1.82    |                                                                               |
|                         |           |         |         | Male | Current drinkers 0-29 (g) | 1.16       | 0.66-2.04    |                                                                               |
|                         |           |         |         | Male | Current drinkers 30-59 (g) | 1.07       | 0.56-2.06    |                                                                               |
|                         |           |         |         | Male | Current drinkers 60+ (g) | 0.98       | 0.39-2.46    |                                                                               |
| Silverman et al.        | 1986-1989 | US      | Case-control | Female | Never drank      | 1.0        | (reference)  | age, area, cigarette smoking, gallbladder disease, DM                           |
|                         |           |         |         | Female | 1-8              | 1.1        | 0.5-2.2      | 1 drink=1.5 oz of hard liquor or 12 oz of beer or 4 oz of wine                  |
|                         |           |         |         | Female | 8-21             | 1.8        | 0.8-4.0*     |                                                                               |
|                         |           |         |         | Female | 21+              | 2.5        | 1.0-2.59     |                                                                               |
| Inoue M. et al.         | 1988-1999 | Japan   | Case-control | both | Never            | 1.0        | (reference)  | age, family history of pancreatic cancer, history of DM, regular physical exercise, bowel habit, raw vegetable intake |
|                         |           |         |         | both | Ever             | 0.8        | 0.57-1.12    |                                                                               |
|                         |           |         |         | both | Ever-former      | 3.7        | 2.28-6.00    |                                                                               |
|                         |           |         |         | both | Ever-current     | 0.5        | 0.34-0.73    |                                                                               |
| Michaud DS et al.       | 1980-1996 | US      | 2 cohorts | both | 0                | 1.00       | (reference)  | pack years of smoking, BMI, history of DM, cholecystectomy, energy intake and period |
|                         | 1986-1998 |         |         | both | 0.1-1.4          | 0.78       | 0.47-1.30    |                                                                               |
|                         |           |         |         | both | 1.5-4.9          | 1.15       | 0.78-1.69    |                                                                               |
|                         |           |         |         | both | 5.0-29.9         | 1.00       | 0.69-1.44    |                                                                               |
|                         |           |         |         | both | 30+              | 1.00       | 0.57-1.76    |                                                                               |

CI: confidence interval.
BMI: body mass index.
DM: diabetes mellitus.
Table 4. Coffee consumption for the risk of pancreatic cancer.

| Author            | Year          | Place         | Study       | Male | Item               | Risk ratio | 95% CI          | Adjusted factors                                                                 |
|-------------------|---------------|---------------|-------------|------|--------------------|------------|-----------------|----------------------------------------------------------------------------------|
| JACC study        | 1988-1997     | Japan         | Cohort      | 1.00 | Nondrinker         | 1.00       | (reference)     |                                                                                  |
| Lin Y et al.      | 28            |               |             | 0.74 | 1-2cups/month      | 0.74       | 0.37-1.49       | age, cigarette smoking in pack year                                              |
|                   |               |               |             | 0.58 | 1-4cups/week       | 0.58       | 0.32-1.08       |                                                                                  |
|                   |               |               |             | 0.59 | 1cup/day           | 0.59       | 0.26-1.33       |                                                                                  |
|                   |               |               |             | 0.75 | 2-3cups/day        | 0.75       | 0.36-1.59       |                                                                                  |
|                   |               |               |             | 3.19 | 4+cups/day         | 3.19       | 1.22-8.35       |                                                                                  |
| Partanen et al.   | 63            | Finland       | Case-control| 1.00 | None/occasional   | 1.00       | (reference)     | sex, birth year, smoking                                                        |
|                   | 1984-1990     |               |             | 0.83 | 1-cups/day         | 0.83       | 0.50-1.60       |                                                                                  |
|                   |               |               |             | 0.96 | 4-6cups/day        | 0.96       | 0.59-1.56       |                                                                                  |
|                   |               |               |             | 0.71 | 6+cups/day         | 0.71       | 0.41-1.20       |                                                                                  |
| Stensvold et al.  | 62            | Norway        | Cohort      | 1.00 | None               | 1.00       | (reference)     | age                                                                              |
|                   | 1977-1990     |               |             | 1.2  | 2+                 | 1.2        | (reference)     |                                                                                  |
|                   |               |               |             | 1.0  | 3+                 | 1.0        | (reference)     |                                                                                  |
| Michaud DS et al. | 64            | US            | 2 cohorts   | 1.00 | None               | 1.00       | (reference)     | pack years of smoking, BMI, history of DM, cholecystectomy, energy intake and period |
|                   | 1980-1996     |               |             | 0.94 | -1/day             | 0.94       | 0.65-1.36       |                                                                                  |
|                   | 1986-1998     |               |             | 0.60 | 1/day              | 0.60       | 0.38-0.94       |                                                                                  |
|                   |               |               |             | 0.88 | 2-3/day            | 0.88       | 0.65-1.21       |                                                                                  |
|                   |               |               |             | 0.62 | 3+/day             | 0.62       | 0.27-1.43       |                                                                                  |

CI: confidence interval.
BMI: body mass index.
DM: diabetes mellitus.
The JACC Study and most studies showed that current smokers have a higher risk than nonsmokers. The dose-response relationship was observed in the JACC Study and the other studies, however, it was not strong in these studies.

(2) Alcohol consumption
Table 3 shows alcohol consumption for the risk of pancreatic cancer in the JACC Study and other epidemiologic studies. According to the results of the JACC Study, upon analysis of mortality to the end of 1997, alcohol intake was not associated with pancreatic cancer mortality. A case-control study in the US showed that black females who drank heavily had an increased risk for pancreatic cancer (OR = 2.5, 95% CI: 1.02-5.9). Inoue et al. conducted a case-control study in Japan and showed that former drinkers had an increased risk for pancreatic cancer. In two cohort studies conducted in the US, alcohol intake was not associated with an increased risk for pancreatic cancer (30+ grams of alcohol/day versus none; HR=1.00, 95% CI: 0.57-1.76). These results are consistent with those of the JACC Study.

(3) Coffee consumption
Table 4 shows coffee consumption for the risk of pancreatic cancer in the JACC Study and other epidemiologic studies. According to the results of the JACC Study, upon analysis of the data obtained through the end of 1997, coffee intake was not associated with pancreatic cancer mortality. However, the HR significantly increased to 3.19 (95% CI: 1.22-8.35) among men who consumed a large amount of coffee, i.e., 4+ cups of coffee per day. Coffee has been studied as a cause of pancreatic cancer after the warning that coffee was related to pancreatic cancer. There was no association between coffee consumption and the risk of pancreatic cancer in a case-control study in Finland, nor in a cohort study in Norwegian men and women. Coffee intake was not associated with an increased risk for pancreatic cancer in two cohort studies conducted in the US (HR = 0.62, 95% CI: 0.27-1.43). In these two cohort studies, there were also no statistically significant associations between intake of tea, intake of decaffeinated coffee, or total caffeine intake and pancreatic cancer. Most previous studies did not find an association between coffee consumption and pancreatic cancer.

Dietary and Nutritional Factors
Many studies on the relationship between dietary intake and pancreatic cancer have been conducted. However, there are often difficulties related to ascertaining accurate dietary information from these patients. Because pancreatic cancer has a high fatality rate and due to the difficulty of dietary research, the relationship between diet and nutrition is not clear.

Many case-control studies suggested that higher cholesterol intake increases the risk of pancreatic cancer. There are few reports, intake of grilled red meat might be a risk factor for pancreatic cancer in a case-control study. In a cohort study, in male smokers the intake of butter and the intake of saturated fat increased the risk of pancreatic cancer. In a cohort of the US women, the intake of total fat, different types of fat, cholesterol, total meat, red meat, and eggs were not associated with pancreatic cancer. The relation between pancreatic cancer and intake of cholesterol and intake of fat are not clear.

In case-control studies, high caloric intake increased the risk of pancreatic cancer. The interaction between body mass index (BMI) and energy intake suggests the importance of energy balance in pancreatic carcinogenesis. However, in a cohort study of male smokers, high caloric intake reduced the risk of pancreatic cancer. The results of the relation between pancreatic cancer and caloric intake are not consistence. When the relationship between pancreatic cancer and caloric intake is analyzed, it is necessary to combine the factors of obesity and physical activities.

As to preventive factors, consumption of vegetables was protective against pancreatic cancer in a case-control study in Japan. In a cohort of male smokers, dietary folate intake and high intake of carbohydrates reduced the risk of pancreatic cancer. However, in a cohort of US women, carbohydrate intake was not associated with pancreatic cancer. A detailed analyses of the relationship between nutrition including total calorie intake, cholesterol intake, etc., and pancreatic cancer is necessary.

Obesity and Physical Activity
Most studies have shown a high incidence of pancreatic cancer among obese persons, and it may suggest that as the BMI increases, the risk of pancreatic cancer increases. Total physical activity was inversely associated with pancreatic cancer risk. A detailed analysis of the relationship between nutrition and pancreatic cancer is necessary to combine the factors of diet, obesity and physical activities.

Conclusion
The incidence and mortality of pancreatic cancer have been increasing during the past four decades in Japan. The standardized mortality ratio of pancreatic cancer in females in the JACC Study was similar to that in Japan, whereas it was little lower in males. Rates increase with an advancing age in the JACC Study. It was similar to previous studies. The relation between smoking and pancreatic cancer is most consistently described. Histories of DM and gallstones / cholecystitis were the risk of pancreatic cancer in the JACC Study. However, many studies have shown that there is a complex relationship between DM and pancreatic cancer. Further investigations will be required for DM and other medical conditions. Alcohol was not associated with and increased risk. Most previous studies did not find the association between the coffee consumption and the pancreatic cancer, although a large amount of coffee consumption increased the risk in the JACC Study. A further analysis of the relationships between family history, hormonal factors in females, dietary and nutritional factors, obesity, physical activity and pancreatic cancer is necessary.
The present investigators involved, with the co-authorship of this paper, in the JACC Study and their affiliations are as follows: Dr. Akiko Tamakoshi (present chairman of the study group), Nagoya University Graduate School of Medicine; Dr. Mitsuru Mori, Sapporo Medical University School of Medicine; Dr. Yutaka Motohashi, Akita University School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yosikazu Nakamura, Jichi Medical School; Dr. Hiroyasu Iso, Institute of Community Medicine, University of Tsukuba; Dr. Haruo Mikami, Chiba Cancer Center; Dr. Yutaka Inaba, Juntendo University School of Medicine; Dr. Yoshiharu Hoshiyama, Showa University School of Medicine; Dr. Hiroshi Suzuki, Niigata University School of Medicine; Dr. Hiroyuki Shimizu, Gifu University School of Medicine; Dr. Hideaki Toyoshima, Nagoya University Graduate School of Medicine; Dr. Shikan Tokudome, Nagoya City University Graduate School of Medical Science; Dr. Yosinori Ito, Fujita Health University School of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Akio Koizumi, Graduate School of Medicine and Faculty of Medicine, Kyoto University; Dr. Takashi Kawamura, Kyoto University Center for Student Health; Dr. Yoshiyuki Watanabe, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, Faculty of Human Environmental Sciences, Mukogawa Women's University; Dr. Kiyomi Sakata, Wakayama Medical University; Dr. Takayuki Nose, Tottori University Faculty of Medicine; Dr. Norihiko Hayakawa, Research Institute for Radiation Biology and Medicine, Hiroshima University; Dr. Takesumi Yoshimura, Institute of Industrial Science, University of Occupational and Environmental Health, Japan; Dr. Akira Shibata, Kurume University School of Medicine; Dr. Naoyuki Okamoto, Kanagawa Cancer Center; Dr. Hideo Shio, Moriyama Municipal Hospital; Dr. Yoshiyuki Ohno, Asahi Rosai Hospital; Dr. Tomoyuki Kitagawa, Cancer Institute of the Japanese Foundation for Cancer Research; Dr. Toshio Kuroki, Gifu University; and Dr. Kazuo Tajima, Aichi Cancer Center Research Foundation for Cancer Research; Dr. Toshio Kuroki, Gifu University; Dr. Kunio Aoki, Professor Emeritus, Nagoya University School of Medicine and the former chairman of the JACC Study, and Dr. Haruo Sugano, the former Director, Cancer Institute, Tokyo, who greatly contributed to the initiation of the JACC Study, and Dr. Yoshiyuki Ohno, Professor Emeritus, Nagoya University School of Medicine, who was the past chairman of the study. The authors also wish to thank Dr. Tomoyuki Kitagawa, Cancer Institute of the Japanese Foundation for Cancer Research and the former chairman of Grant-in-Aid for Scientific Research on Priority Area ‘Cancer’, for his full support of this study.

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1. Watanabe Y, Ozasa K, Nagura J, Hayashi K, Yoshimura Y, Tamakoshi A, et al. Mortality in the JACC Study till 1999. J Epidemiol 2005; 15(Suppl 1): S74-9.
2. Lin Y, Tamakoshi A, Kawamura T, Inaba Y, Kikuchi S, Motohashi Y, et al. A prospective cohort study of cigarette smoking and pancreatic cancer in Japan. Cancer Causes Control 2002; 13: 249-54.
3. Lin Y, Tamakoshi A, Kawamura T, Inaba Y, Kikuchi S, Motohashi Y, et al. Risk of pancreatic cancer in relation to alcohol drinking, coffee consumption and medical history: findings from the Japan collaborative cohort study for evaluation of cancer risk. Int J Cancer 2002; 99: 742-6.
4. Lin Y, Tamakoshi A, Wakai K, Kawamura T, Aoki R, Kojima M, et al. Descriptive epidemiology of pancreatic cancer in Japan. J Epidemiol 1998; 8: 52-9.
5. Doll R, Muir C, Waterhouse J. Cancer Incidence in Five Continents Vol. I. International Union Against Cancer by Springer-Verlag, Berlin-Heidelberg-New York, Switzerland, 1970.
6. Wynder EL, Mabuchi K, Maruchi N, Forttner JG. Epidemiology of cancer of the pancreas. J Natl Cancer Inst 1973; 50: 645-67.
7. Health and Welfare Statistics Association. J Health Welfare Stat 2004; 51: 389. (in Japanese)
8. Health and Welfare Statistics Association. J Health Welfare Stat 2001; 48: 416. (in Japanese)
9. Lowenfels AB, Maisonneuve P, Whittcomb DC. Risk factors for cancer in hereditary pancreatitis. International Hereditary Pancreatitis Study Group. Med Clin North Am 2000; 84: 565-73.
10. Phillips AR, Lawes CM, Cooper GI, Windsor JA. Ethnic disparity of pancreatic cancer in New Zealand. Int J Gastrointest Cancer 2002; 31: 137-45.
11. Price TF, Payne RL, Oberleitner MG. Familial pancreatic cancer in south Louisiana. Cancer Nurs 1996; 19: 275-82.
12. Gold EB. Epidemiology of and risk factors for pancreatic cancer. Surg Clin North Am 1995; 75: 819-43.
13. Lin Y, Tamakoshi A, Kawamura T, Inaba Y, Kikuchi S, Motohashi Y, et al. An Epidemiological Overview of Environmental and Genetic Risk Factors of Pancreatic Cancer. Asian Pac J Cancer Prev 2002; 15(Suppl 1): S74-9.
14. Kreiger N, Lacroix J, Sloan M. Hormonal factors and pancreatic cancer in women. Ann Epidemiol 2001; 11: 565-73.
15. Skinner HG, Michaud DS, Colditz GA, Giovannucci EL, Stampfer MJ, Willett WC, et al. Parity, reproductive factors, and the risk of pancreatic cancer in women. Cancer Epidemiol Biomarkers Prev 2003; 12: 433-8.
16. Kvale G, Heuch I, Nilsson S. Parity in relation to mortality and cancer incidence: a prospective study of Norwegian women. Int J Epidemiol 1994; 23: 691-9.

17. Karlson BM, Wuu J, Hsieh CC, Lambe M, Ekholm A. Parity and the risk of pancreatic cancer: a nested case-control study. Int J Cancer 1998; 77: 224-7.

18. Ji BT, Hatch MC, Chow WH, McLaughlin JK, Dai Q, Howe GR, et al. Anthropomorphic and reproductive factors and the risk of pancreatic cancer: a case-control study in Shanghai, China. Int J Cancer 1996; 66: 432-7.

19. 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: 403-10.

20. Silverman DT. Risk factors for pancreatic cancer: a case-control study based on direct interviews. Teratog Carcinog Mutagen 2001; 21: 7-25.

21. Ye W, Lagergren J, Nyren O, Ekholm A. Risk of pancreatic cancer after cholecystectomy: a cohort study in Sweden. Gut 2001; 49: 678-81.

22. La Vecchia C, Negri E, Franceschi S, D'Avanzo B, Boyle P. Risk factors for the development of pancreatic cancer in women. Int J Cancer 1996; 66: 432-7.

23. Bonelli L, Aste H, Bovo P, Cavallini G, Felder M, Gusmaroli A. Abnormal glucose metabolism and pancreatic cancer mortality: a meta-analysis. JAMA 1995; 273: 1605-9.

24. Everhart J, Wright D. Diabetes mellitus as a risk factor for chronic pancreatitis and pancreatic cancer: a population-based study. J Natl Cancer Inst 1994; 86: 625-7.

25. Bansal P, Sonnemberg A. Pancreatitis is a risk factor for pancreatic cancer. Gastroenterology 1995; 109: 247-51.

26. Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med 1993; 328: 1433-7.

27. Ekbom A, McLaughlin JK, Karlsson BM, Nyren O, Gridley G, Adami HO, et al. Pancreatitis and pancreatic cancer: a population-based study. J Natl Cancer Inst 1994; 86: 625-7.

28. Menezes RJ, Huber KR, Mahoney MC, Moysich KB. Regular use of aspirin and pancreatic cancer risk. Scand J Gastroenterol 1998; 33: 54-8.

29. Kokawa A, Kondo H, Gotoda T, Ono H, Saito D, Nakaida S, et al. Increased expression of cyclooxygenase-2 in human pancreatic neoplasms and potential for chemoprevention by cyclooxygenase inhibitors. Cancer 2002; 86: 22-8.
47. Ogren M, Hedberg M, Berglund G, Borgstrom A, Janzon L. Risk of pancreatic carcinoma in smokers enhanced by weight gain. Results from 10-year follow-up of the Malmo preventive Project Cohort Study. Int J Pancreatol 1996; 20: 95-101.

48. Poole CA, Byers T, Calle EE, Bondy J, Fain P, Rodriguez C. Influence of a family history of cancer within and across multiple sites on patterns of cancer mortality risk for women. Am J Epidemiol 1999; 149: 454-62.

49. Chiu BC, Lynch CF, Cerhan JR, Cantor KP. Cigarette smoking and risk of bladder, pancreas, kidney, and colorectal cancers in Iowa. Ann Epidemiol 2001; 11: 28-37.

50. Silverman DT, Dunn JA, Hoover RN, Schiffman M, Lillemoe KD, Schoenberg JB, et al. Cigarette smoking and pancreas cancer: a case-control study based on direct interviews. J Natl Cancer Inst 1994; 86: 1510-6.

51. Hirayama T. Epidemiology of pancreatic cancer in Japan. Jpn J Clin Oncol 1989; 19: 208-15.

52. Zheng W, McLaughlin JK, Gridley G, Bjelke E, Schuman LM, Silverman DT, et al. A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). Cancer Causes Control 1993; 4: 477-82.

53. Shibata A, Mack TM, Paganini-Hill A, Ross RK, Henderson BE. A prospective study of pancreatic cancer in the elderly. J Natl Cancer Inst 1994; 86: 469.

54. Fuchs CS, Colditz GA, Stampfer MJ, Giovannucci EL, Hunter DJ, Rimm EB, et al. A prospective study of cigarette smoking and the risk of pancreatic cancer. Arch Intern Med 1996; 156: 2255-60.

55. Engeland A, Andersen A, Haldorsen T, Tretti S. Smoking habits and risk of cancers other than lung cancer: 28 years' follow-up of 26,000 Norwegian men and women. Cancer Causes Control 1996; 7: 497-506.

56. Harmack LJ, Anderson KE, Zheng W, Folsom AR, Sellers TA, Kushi LH. Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: the Iowa Women's Health Study. Cancer Epidemiol Biomarkers Prev 1997; 6: 1081-6.

57. Shapiro JA, Jacobs EJ, Thun MJ. Cigar smoking in men and risk of death from tobacco-related cancers. J Natl Cancer Inst 2000; 92: 333-7.

58. Nilsen TI, Vatten LJ. A prospective study of lifestyle factors and the risk of pancreatic cancer in Nord-Trondelag, Norway. Cancer Causes Control 2000; 11: 645-52.

59. Coughlin SS, Calle EE, Patel AV, Thun MJ. Predictors of pancreatic cancer mortality among a large cohort of United States adults. Cancer Causes Control 2000; 11: 915-23.

60. Howe GR, Jain M, Burch JD, Miller AB. Cigarette smoking and cancer of the pancreas: evidence from a population-based case-control study in Toronto, Canada. Int J Cancer 1991; 47: 323-8.

61. Stolzenberg-Solomon RZ, Pietinen P, Barrett MJ, Taylor PR, Virtamo J, Albanes D. Dietary and other methyl-group availability factors and pancreatic cancer risk in a cohort of male smokers. Am J Epidemiol 2001; 153: 680-7.

62. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Coffee and alcohol consumption and the risk of pancreatic cancer in two prospective United States cohorts. Cancer Epidemiol Biomarkers Prev 2001; 10: 429-37.

63. Partanen T, Hemminki K, Vainio H, Kauppinen T. Coffee consumption not associated with risk of pancreas cancer in Finland. Prev Med 1995; 24: 213-6.

64. Stensvold I, Jacobsen BK. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. Cancer Causes Control 1994; 5: 401-8.

65. Anderson KE, Sinha R, Kullidorf M, Gross M, Lang NP, Barber C, et al. Meat intake and cooking techniques: associations with pancreatic cancer. Mutat Res 2002; 506-507: 225-31.

66. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. Prospective study of diet and pancreatic cancer in male smokers. Am J Epidemiol 2002; 155: 783-92.

67. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Dietary meat, dairy products, fat, and cholesterol and pancreatic cancer risk in a prospective study. Am J Epidemiol 2003; 157: 1115-25.

68. Silverman DT, Swanson CA, Gridley G, Wacholder S, Greenberg RS, Brown LM, et al. Cigarette smoking and pancreas cancer: a case-control study based on direct interviews. J Natl Cancer Inst 1994; 86: 1710-9.

69. Howe GR, Ghadirian P, Bueno de Mesquita HB, Zatonski WA, Baghurst PA, Miller AB, et al. A collaborative case-control study of nutrient intake and pancreatic cancer within the search programme. Int J Cancer 1992; 51: 365-72.

70. Michaud DS, Liu S, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Dietary sugar, glycemic load, and pancreatic cancer risk in a prospective study. J Natl Cancer Inst 2002; 94: 1293-300.

71. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. Br J Cancer 2003; 89: 519-23.

72. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. JAMA 2001; 286: 921-9.