Risk Factors for Pancreatic Cancer: An Exploratory Study

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An exploratory case-control study to detect risk factors for pancreatic cancer was conducted within a large cohort of people who had received multiphasic health checkups in the San Francisco Bay Area. Four hundred and fifty who later developed pancreatic cancer were compared with 2687 who did not with respect to 779 characteristics recorded at the checkups. There was strong confirmation that cigarette smoking and diabetes mellitus were associated with risk of subsequent pancreatic cancer. Higher levels of serum iron, iron saturation and body weight were also predictive. Less striking associations of interest were with the leukocyte count, pulse rate and certain questionnaire items suggesting non-specific health impairment. Past concerns about alcohol and coffee consumption were not confirmed.

One of the most poorly controlled forms of cancer is cancer of the pancreas, which accounts for 3% of all new cancer cases and 5% of all cancer deaths in the US.¹ After diagnosis of this condition the relative 5-year survival rate is only 3% in whites and 4% in blacks;¹ it is most unusual for pancreatic cancer to be detected early enough to be cured.² Although cigarette smoking has been found to be a probable cause, leading to a moderate increase in incidence, few if any other causal factors have been identified.³⁴ Thus, at present the prospects for prevention are almost as bleak as those for cure.

It was decided, therefore, to conduct exploratory studies on a large database in the hope that additional causal or predictive factors for pancreatic cancer can be identified. Even if only one promising lead emerges among all of the chance associations that inevitably occur, the search will be worthwhile. The current study employed a large database containing characteristics measured at multiphasic health checkups given to many thousands of subscribers to a large health maintenance organization.

METHODS

Since 1945, the Kaiser Permanente Medical Care Program has provided comprehensive medical care, both inpatient and outpatient, to a growing number of subscribers in the San Francisco Bay Area. The population served is heterogeneous, both ethnically and socioeconomically, and now comprises somewhat over a quarter of the residents of the areas served. On average, subscribers are more educated than the general population and somewhat underrepresent the lowest socioeconomic group.⁵ Since 1964 a standardized multiphasic health checkup has been provided to subscribers served by the Oakland and, until 1980, the San Francisco facility. Patients obtain these checkups at various intervals on request or when referred by a physician. The checkup data collected until 1972 (when the questionnaires were greatly modified) were used for this study. If there was more than one checkup in the interval, only the first was used. The checkup consisted of physiological and laboratory tests including body measurements, chest x-ray, electrocardiogram, pulse and blood pressure, eye tests of visual acuity, pupillary escape, ocular tension, iris colour and retinal photograph, pulmonary function tests, audiogram, haematology and chemistry tests on blood, urine analysis, achilles tendon reflex test for hypothyroidism, pressure tolerance, and mammography on all women aged 48 and over. Questionnaires were also completed covering medical history and symptoms, habits and exposures, and psychological items.⁶

During the period of data collection approximately 175 000 people aged 15–94 years, received a checkup. Follow-up for cancer diagnosed during membership in the Program has been conducted for this group, using two main sources, (1) the local tumour registry that participates in the national Surveillance, Epidemiology, and End Results (SEER) programme, and (2) computer-stored diagnoses from all northern California
Kaiser Permanente hospitals. Cancers diagnosed in these hospitals in the 1960s, before the above data sources were available, were obtained from manual listings. Experience showed that the diagnoses from the SEER programme, abstracted by trained tumour registry personnel, were almost always confirmed when reviewed by our department. Thus, we accepted these as given. Diagnoses of pancreatic cancer that lacked confirmation in the SEER programme were checked by a review of the medical records. We thus identified and included in this study 450 confirmed cases that occurred in this population through 1988. The interval from checkup to diagnosis of pancreatic cancer ranged from 1 day to 24.1 years, with a mean of 12.6 and a median of 12.7 years. Two cases (0.4%) were diagnosed <1 year after the checkup; and 11 (2.4%) between 1 and 2 years. Altogether 59 or 13.1% were diagnosed <5 years after the checkup. Follow-up of all subjects ended when they left the Program, died, developed pancreatic cancer or at the end of 1988, whichever came first.

For each case we attempted to select six control subjects from the multiphasic checkup population. Controls had to have been members of the Program and free of known pancreatic cancer at the time their case was diagnosed. Controls were matched to their case for gender, examination site, age (date of birth within 5 years), and date of first checkup (closest within 6 months). Six controls were identified for 445 cases, and two to five controls each for five cases, yielding a total of 2687 controls: 50.7% of cases were male, versus 50.6% of controls; 50.9% of cases were examined in San Francisco versus 51.0% of controls. There were no discrepancies in gender or examination site within matched sets. The mean date of checkup differed by only 1 day for cases and controls. Their respective mean ages at time of checkup were 54.6 and 54.4 years. This significant difference (P = 0.012) proved to be due to the tendency for elderly cases to be matched more with controls born later than earlier due to the age distribution of the multiphasic examinees.

The search for associations employed conditional logistic regression for matched sets. Unless otherwise stated, each variable was examined in a model that also included race (white, black, Asian, other plus unknown—blacks showed higher risk of borderline significance—relative risk [RR] compared to whites = 1.34, 95% confidence interval [CI]: 0.98–1.81, P = 0.063), cigarette smoking, an established risk factor for pancreatic cancer, and age because of the residual case-control difference described above. The cigarette smoking categories were: never smoked (reference), former smoker, current smoker of <1 pack per day, of 1–2 packs, and of >2 packs per day, and unknown. Their respective RR were 1.00, 1.31, 1.83, 1.63, 2.97, and 1.90. Except for the former smokers, all other categories differed from the never smokers to a statistically significant degree (P < 0.01).

There were 903 variables that were candidates for analysis. Of these, 114 variables with fewer than 10 positives among all subjects were not analysed. For 10 others, the analysis program did not run because there were zero subjects in certain categories. All continuous variables were entered into the models as such.

RESULTS AND DISCUSSION

Of the 779 data items examined, 41 proved to be nominally statistically significant (P < 0.05) (Table 1). Some of these that were related to one another and others that were initially considered to be worth pursuing are considered below.

Cigarette Smoking

In addition to the confirmation of cigarette smoking as a predictive characteristic noted above, other questions about cigarette smoking also proved to be predictive after control for the main smoking questions and quantity smoked. These were inhalation of tobacco smoke and smoking cigarettes for >20 years (Table 1, items 20 and 21).

Cigarette smoking is probably the only exposure that has been consistently found to be associated with carcinoma of the pancreas. The results of our study are comparable to previous published studies, most of which have found the risk associated with cigarette smoking to be about 2.0 with a range of 1.2–5.4.9–27

Diabetes Mellitus

Positive answers to three questions about a history of diagnosis of, or treatment for, diabetes mellitus were all associated with about a twofold increase in risk of pancreatic cancer (Table 1, items 10, 25, and 26). Another question about a history of a bad reaction, allergy, or sensitivity to insulin or diabetes pills showed an association of borderline statistical significance (RR = 2.96, 95% CI : 0.86–10.16, P = 0.085). One-hour post-challenge serum glucose level was not predictive (RR per 10 mg/dl = 1.01, 95% CI : 0.99–1.04, P = 0.326).

The relation between diabetes and pancreatic cancer is controversial; there have been numerous positive,10,13,20,23,26–29 and negative,15,19,30,31 study findings. Our study strongly suggests that diabetes mellitus is a true predisposing factor for pancreatic cancer. This confirms findings in another study of a later cohort of our multiphasic examinees in which it did
<table>
<thead>
<tr>
<th>Data item</th>
<th>Relative risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measurements and laboratory findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(of 148 total analyses*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Weight (per 5 kg)</td>
<td>1.06 (1.01-1.11)</td>
<td>0.013</td>
</tr>
<tr>
<td>2. Vital capacity (per litre)</td>
<td>1.18 (1.01-1.39)</td>
<td>0.040</td>
</tr>
<tr>
<td>3. Diastolic blood pressure (per 10 mm Hg)</td>
<td>1.09 (1.01-1.18)</td>
<td>0.035</td>
</tr>
<tr>
<td>4. Pulse rate (per 10 beats per minute)</td>
<td>1.11 (1.02-1.21)</td>
<td>0.015</td>
</tr>
<tr>
<td>5. Serum iron (per 10 µg/dl)</td>
<td>1.14 (1.02-1.28)</td>
<td>0.026</td>
</tr>
<tr>
<td>6. Iron saturation (per 0.1 increase in ratio: iron/iron-binding capacity)</td>
<td>1.05 (1.01-1.09)</td>
<td>0.022</td>
</tr>
<tr>
<td>7. Disc changes on retinal photo (yes versus no)*</td>
<td>5.21 (1.24-21.96)</td>
<td>0.025</td>
</tr>
<tr>
<td><strong>Medical history questions (of 430 total)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Before 1 year ago had you ever had pain in your legs that forced you to stop walking?</td>
<td>1.51 (1.11-2.07)</td>
<td>0.009</td>
</tr>
<tr>
<td>9. Before 1 year ago had a doctor said you had: nervous, anxiety, or tension condition?</td>
<td>1.32 (1.06-1.64)</td>
<td>0.014</td>
</tr>
<tr>
<td>10. Diabetes (sugar disease)?</td>
<td>2.37 (1.46-3.85)</td>
<td>0.001</td>
</tr>
<tr>
<td>11. For health or medical reasons have you ever been rejected or discharged by the armed forces?</td>
<td>1.66 (1.10-2.52)</td>
<td>0.017</td>
</tr>
<tr>
<td>12. Do you have a service-connected disability?</td>
<td>1.82 (1.13-2.92)</td>
<td>0.013</td>
</tr>
<tr>
<td>13. What is the most you ever weighed (per lb.)?</td>
<td>1.01 (1.00-1.01)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>How did you happen to take this multiphasic?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular annual checkup</td>
<td>1.00 reference</td>
<td></td>
</tr>
<tr>
<td>14. Didn’t feel well</td>
<td>1.79 (1.19-2.70)</td>
<td>0.005</td>
</tr>
<tr>
<td>15. Wanted a checkup</td>
<td>1.46 (1.07-1.99)</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>In the past year how many hours did you usually spend each day for</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(categories: 0-1, 2-4, 5-7, 8-10, 11+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Sleeping or resting, ≤4 versus 8-10 hr</td>
<td>12.04 (1.06-137.33)</td>
<td>0.045</td>
</tr>
<tr>
<td>17. Self-care (dressing, eating, etc) 5-7 versus 2-4 hr</td>
<td>8.59 (1.36-54.47)</td>
<td>0.022</td>
</tr>
<tr>
<td>18. Do you usually eat and drink more than is good for you?</td>
<td>1.40 (1.09-1.79)</td>
<td>0.008</td>
</tr>
<tr>
<td>19. Mother’s mother died at age &lt;50 versus 70-79 years</td>
<td>0.10 (0.01-0.79)</td>
<td>0.029</td>
</tr>
<tr>
<td><strong>(No other comparisons for mother, father or grandparents significant)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. Do you usually inhale when you smoke?</td>
<td>1.42 (1.02-1.96)</td>
<td>0.037</td>
</tr>
<tr>
<td>21. Have you smoked altogether for more than 20 years?</td>
<td>1.58 (1.13-2.20)</td>
<td>0.007</td>
</tr>
<tr>
<td>22. In the past year have you had any bad pain in the eyeball?</td>
<td>0.60 (0.17-0.97)</td>
<td>0.036</td>
</tr>
<tr>
<td>23. In the past 6 months have you often had a sore tongue (most of the time)?</td>
<td>2.38 (1.10-5.14)</td>
<td>0.027</td>
</tr>
<tr>
<td>24. In the past 6 months has your appetite increased?</td>
<td>0.61 (0.38-0.98)</td>
<td>0.040</td>
</tr>
<tr>
<td>25. In the past year or two has a doctor said you had diabetes?</td>
<td>2.15 (1.26-3.67)</td>
<td>0.005</td>
</tr>
<tr>
<td>26. In the past year have you taken any insulin or diabetes pills?</td>
<td>1.95 (1.04-3.66)</td>
<td>0.038</td>
</tr>
</tbody>
</table>
PANCREATIC CANCER RISK FACTORS

<table>
<thead>
<tr>
<th>Data item</th>
<th>Relative risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>27. In the past year have you taken any sleeping pills?</td>
<td>1.52 (1.06-2.18)</td>
<td>0.022</td>
</tr>
<tr>
<td>28. In the past 6 months when you were not trying to did you gain more than 10 lb?</td>
<td>0.66 (0.44-0.99)</td>
<td>0.044</td>
</tr>
<tr>
<td>29. In the past year have you worked in a place where you were often or daily around insect or plant sprays?</td>
<td>1.69 (1.04-2.76)</td>
<td>0.035</td>
</tr>
<tr>
<td>Psychosocial (&quot;neuromental&quot;) questions (155 total)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30. At times I feel like smashing things</td>
<td>1.56 (1.04-2.33)</td>
<td>0.031</td>
</tr>
<tr>
<td>31. In thinking about my life it is apparent I have much of the time done something wrong or evil</td>
<td>1.96 (1.02-3.77)</td>
<td>0.043</td>
</tr>
<tr>
<td>32. In thinking about my life it is apparent I have felt useless at times</td>
<td>1.51 (1.11-2.06)</td>
<td>0.009</td>
</tr>
<tr>
<td>33. In thinking about my life it is apparent I have met problems so full of possibilities that I have been unable to make up my mind about them</td>
<td>0.56 (0.37-0.86)</td>
<td>0.008</td>
</tr>
<tr>
<td>34. Most people are not to be trusted</td>
<td>1.55 (1.04-2.31)</td>
<td>0.032</td>
</tr>
<tr>
<td>35. These days my conduct is largely controlled by the customs of others</td>
<td>1.48 (1.03-2.13)</td>
<td>0.035</td>
</tr>
<tr>
<td>36. More than most people I have trouble concentrating</td>
<td>1.58 (1.05-2.36)</td>
<td>0.027</td>
</tr>
<tr>
<td>37. Have you often found that you suddenly become scared for no good reason?</td>
<td>1.74 (1.19-2.54)</td>
<td>0.005</td>
</tr>
<tr>
<td>38. I want to accomplish things without any help and therefore to deserve full credit</td>
<td>1.44 (1.02-2.03)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Family history of disease (46 analyses)

| History of disease in mother or father (31 conditions)                     |                        |       |
| 39. Glaucoma, mother                                                      | 1.30 (1.05-1.60)       | 0.014 |
| 40. Heart attack, father                                                  | 0.66 (0.44-0.99)       | 0.044 |
| 41. Kidney stone, father                                                  | 4.05 (1.85-8.89)       | 0.001 |

* Number of analyses indicate the number of data items for which risk was assessed. For example the electrocardiogram could have up to 33 items coded of which 16 had sufficient numbers of positives to permit the risk measurement programme to run. Therefore 16 were counted in the total.

** Disc changes were coded in only four of 186 cases and four of 702 controls with retinal photographs. No common characteristics of the disc of cases were found on chart review.

not appear that diabetes-induced thirst linked beverage consumption with pancreatic cancer.27

The temporal sequence between diabetes and pancreatic cancer has not always been clear.19,26,31,32 We repeated the analyses of Table 1 items 10 and 25, excluding cases whose cancer developed within 5 years of the checkup and their matched controls. The RR were virtually unchanged (2.44 and 2.19, respectively). This indicates that diabetes mellitus is a predictor rather than a result of pancreatic cancer.

The predictive power of diabetes was not due to its association with obesity since it persisted (RR = 2.31) when body weight was added to the independent variables. Our data did not distinguish between juvenile and adult-onset diabetes.

**Weight**

There were some indications that weight or obesity might be predisposing factors for pancreatic cancer. Body weight itself was significantly related as was self-reported greatest weight (Table 1, items 1 and 13). Body mass index (kg of weight/[m of height squared]) was associated, with borderline statistical significance (RR per unit increase 1.02, 95% CI: 1.00-1.04, P = 0.096), as was subscapular skinfold (RR per cm 1.12, 95% CI: 0.98-1.28, P = 0.084). Also associated was a positive answer to a question about usually eating and drinking more than is good for one (Table 1, item 18). Several other anthropometric measurements, including height, were not related to subsequent pancreatic cancer. Perhaps somewhat contradictory to a relation
with obesity, decreased risk was noted for appetite increase and a weight gain of more than 10 lb. in the past 6 months (Table 1, items 24 and 28). In the analysis with both weight and diabetes included as independent variables the association with weight remained statistically significant (RR = 1.05 per 5 kg, 95% CI : 1.00–1.10, P = 0.030). Although others have not found weight to be associated with pancreatic cancer,\textsuperscript{19,24,26,33} this characteristic deserves further investigation.

**Blood Pressure and Pulse Rate**

Both diastolic blood pressure and pulse rate were predictive of pancreatic cancer (Table 1, items 3 and 4). Systolic blood pressure was also related at borderline significance (RR = 1.05 per 10 mm Hg, 95% CI : 1.00–1.10, P = 0.059). These three variables were re-analysed with weight added as an independent variable, resulting in a marked increase in P value for systolic blood pressure (RR reduced to 1.03, 95% CI : 0.98–1.08, P = 0.310), and for diastolic blood pressure (RR reduced to 1.04, 95% CI : 0.95–1.14, P = 0.368) but a change to borderline significance for pulse rate (RR = 1.09 per 10 beats/minute, 95% CI : 0.99–1.19, P = 0.071). It appears that blood pressure adds little once weight is known but pulse rate may still be predictive, independent of weight.

**Pulmonary Vital Capacity**

Lower vital capacity of the lungs was predictive (Table 1, item 2), as has been noted for other conditions. However, because of its association with heavy smoking, it was important to re-evaluate it among never smokers, only (101 cases, 276 controls with usable data). When this was done the association became small and non-significant (RR = 1.06, 95% CI : 0.71–1.58, P = 0.792).

**Leukocyte Count**

The leukocyte count is not listed in Table 1 because its association with subsequent pancreatic cancer was only of borderline significance (RR = 1.05 per 1000 cells/mm\textsuperscript{3}, 95% CI : 0.99–1.11, P = 0.086). However, this measure has been of interest in relation to general cancer incidence and mortality\textsuperscript{34,35} and observed associations have disappeared when attention was restricted to never smokers.\textsuperscript{35} In contrast, and unlike vital capacity, above, the association was stronger and statistically significant among the never smokers (RR = 1.20, 95% CI : 1.05–1.39, P = 0.010, 109 cases and 322 controls with usable data). Unfortunately there were no differential counts in our data that might have revealed which type(s) of leukocyte were involved.

Further study should seek a factor that both elevates the leukocyte count and increases risk for pancreatic cancer.

**Iron and Iron Binding Capacity**

Higher levels of iron in the serum and higher percentage of iron saturation (iron/iron binding capacity) were associated with increased risk of subsequent pancreatic cancer (Table 1, items 5 and 6). Re-analysis with weight and presence or absence of diabetes mellitus in the model gave almost identical results. This supports previous hypotheses and evidence that availability of iron enhances, and its relative lack inhibits the growth of tumours.\textsuperscript{36–39} Evidence in humans has supported this link for cancers of the bladder, colon, oesophagus, lung, and of all sites combined but, to our knowledge, this is the first indication that risk of pancreatic cancer may also be related to iron levels.

**Intermittent Claudication**

A history of leg pain suggestive of intermittent claudication was linked to pancreatic cancer (Table 1, item 8). However, the questionnaire included a number of other symptoms of cardiovascular disease which were not so related. In our judgement there is no clear connection between cardiovascular disease and pancreatic cancer except that which might be expected due to their common risk factors, particularly cigarette smoking and obesity.

**Psychosocial Items**

A history of anxiety-related conditions (Table 1, item 9) and nine items from a psychological questionnaire (Table 1, items 30–38)\textsuperscript{40} were related to subsequent pancreatic cancer. However, the questionnaire contained 155 items so that nine associations due merely to chance would not be unexpected, given that 5% of 155 = 7.75. Our evidence does not suggest that this is a promising avenue for further investigation.

**Occupational Exposure to Insect or Plant Sprays**

More cases than controls reported exposure to insect or plant sprays in the past year (Table 1, item 29). However, having been exposed to insect or plant sprays earlier than 1 year before was not significantly associated with pancreatic cancer (RR = 1.40, 95% CI : 0.80–2.44, P = 0.235). There is little in the literature to suggest that insecticides or pesticides may be related to pancreatic cancer.\textsuperscript{51–53} Thus, this association in our data may be due merely to chance. There were 20 other items on 10 other occupational exposures in the multiphasic questionnaire, none of which were significantly associated with pancreatic cancer.
Sleeping Pills and Tranquillizers
The use of sleeping pills in the past year was associated with a 50% increase in the risk of cancer of the pancreas (Table 1, item 27), while the use of tranquillizers in the past year was nearly significant (RR = 1.37, 95% CI : 0.99–1.88, \( P = 0.059 \)). To our knowledge, an association with sleeping pills has not been reported previously. In a recent analysis (Friedman, unpublished data) of a cohort screened for cancer following prescription drug use,\(^{12}\) no sedative or hypnotic was associated with pancreatic cancer. One unpublished earlier analysis with 7–11 year follow-up through 1980 revealed an excess risk associated with receipt of prescriptions for flurazepam hydrochloride but this lost statistical significance with longer follow-up. Specific drugs cannot be investigated in the present study.

Reason for Checkup
Two of five reasons for having the checkup—‘didn’t feel well’ and ‘wanted a checkup’—were associated with subsequent pancreatic cancer (Table 1, items 14 and 15). There was no substantial change when these analyses were repeated, omitting cases whose cancers were diagnosed within 5 years of the checkup, and their matched controls. Also, addition of weight and diabetes mellitus to the analyses of these questionnaire responses had virtually no effect on these associations.

Family History
Three rather unrelated conditions in the mother or father and a single age-at-death comparison in the maternal grandmother showed associations with pancreatic cancer (Table 1, items 19, 39, 40, and 41). These did not suggest fruitful hypotheses. A family history of pancreatic cancer was not sought in the questionnaire, and a maternal or paternal history of cancer (type not specified) was not related to pancreatic cancer.

Service Disability
Relative to controls, cases were more likely to report having been rejected or discharged by the armed forces or having a service-connected disability (Table 1, items 11 and 12). Two other related items, being in the armed forces (RR = 0.85, 95% CI : 0.63–1.15, \( P = 0.290 \) ) and receiving a disability pension (RR = 1.34, 95% CI : 0.78–2.28, \( P = 0.290 \) ), were not significantly associated with subsequent pancreatic cancer. Nor was having been refused life insurance for medical or health reasons (RR = 1.16, 95% CI : 0.73–1.87, \( P = 0.526 \) ).

Other Items
Inspection of Table 1 will reveal assorted items not described above. These seemed most likely to be chance associations.

Notable Negatives: Coffee and Alcohol Consumption
Among the most publicized cancer associations in the last decade is that between coffee drinking and pancreatic cancer.\(^{18}\) Our ability to study coffee was limited to one yes-or-no question focusing on heavy consumption. ‘Do you usually drink over 6 cups of coffee per day?’ Answering yes was associated with no increased risk (RR = 0.95, 95% CI : 0.73–1.22, \( P = 0.672 \)). Our negative results agree with the majority of later studies that have considered this question.\(^{12-14,16,20,23,27,53-57}\) Nonetheless, some studies have reported an association or found the risk to vary by smoking status\(^{18-19,58}\) and ours did not rule out this possibility. There was a slight, non-significant decrease in coffee-associated risk among never smokers (RR = 0.72, 95% CI : 0.35–1.51, \( P = 0.39 \)) or ex-smokers (RR = 0.70, 95% CI : 0.23–2.12, \( P = 0.53 \)) and a slight, non-significant increase for current smokers (RR = 1.38, 95% CI : 0.92–2.08, \( P = 0.12 \)).

Alcohol drinking was investigated in greater detail by the questionnaire (Table 2). There was no convincing association of alcohol use with subsequent pancreatic cancer. This agrees with the review by Velema\(^{59}\) and almost all subsequent studies.\(^{9,10,12-14,19,21,27,58,60}\)

Non-Specific Health Impairment
Some of the above associations suggested that some sort of health impairment that cannot now be defined.

### Table 2 Risk of pancreatic cancer associated with various indications of alcohol use

<table>
<thead>
<tr>
<th>Data item</th>
<th>Relative risk (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the past year did you drink any alcohol? No (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>If yes, how many alcoholic drinks did you usually have (wine, beer, whiskey, cocktails)? Total of ( \geq9 ) a day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–8 drinks a day</td>
<td>1.35 (0.90–2.03)</td>
<td>0.152</td>
</tr>
<tr>
<td>3–5 a day</td>
<td>1.12 (0.85–1.48)</td>
<td>0.433</td>
</tr>
<tr>
<td>( \leq2 ) a day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you sometimes get drunk on workdays? Yes versus no</td>
<td>1.25 (0.70–2.26)</td>
<td>0.451</td>
</tr>
<tr>
<td>Do you sometimes drink in the mornings? Yes versus no</td>
<td>0.95 (0.66–1.35)</td>
<td>0.759</td>
</tr>
<tr>
<td>At any time in the past were you a heavy alcohol drinker? Yes versus no</td>
<td>0.92 (0.61–1.39)</td>
<td>0.676</td>
</tr>
<tr>
<td>Does your (wife, husband) have a drinking problem? Yes versus no</td>
<td>0.69 (0.38–1.25)</td>
<td>0.219</td>
</tr>
</tbody>
</table>
further was predictive of pancreatic cancer. Items suggesting this were: reason for checkup—'didn't feel well', service connected disability, and rejection or discharge from the armed forces for health or medical reasons. The associations with pulse rate and leukocyte count may fit here, too. The association of reason for discharge from the armed forces for health or medical reasons were varied. It would yield 39 items, close to the 41 observed (Table 1). As described above, we believe that some of the findings are not due to chance and these either confirm previous hypotheses or deserve further study. Potentially the most important discoveries in this study are the associations of pancreatic cancer with increased iron levels and with increased body weight. Less striking associations of interest were with the leukocyte count, pulse rate and certain questionnaire items suggesting non-specific health impairment. The confirmation of cigarette smoking and diabetes mellitus as risk factors in this large study, which was free of recall bias, and the lack of associations with coffee and alcohol all confirmed present knowledge and added to the credibility of our other findings.

Significance of Findings
Because the data items in the multiphasic checkup were not all independent of one another, it is difficult to estimate the number of nominally statistically significant findings that would be expected by chance. If it did happen to be 5% of the 779 data items, this would yield 39 items, close to the 41 observed (Table 1). As described above, we believe that some of the findings are not due to chance and these either confirm previous hypotheses or deserve further study. Potentially the most important discoveries in this study are the associations of pancreatic cancer with increased iron levels and with increased body weight. Less striking associations of interest were with the leukocyte count, pulse rate and certain questionnaire items suggesting non-specific health impairment. The confirmation of cigarette smoking and diabetes mellitus as risk factors in this large study, which was free of recall bias, and the lack of associations with coffee and alcohol all confirmed present knowledge and added to the credibility of our other findings.

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REFERENCES
PANCREATIC CANCER RISK FACTORS


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