Case-Control Study of Decaffeinated Coffee Consumption and Pancreatic Cancer

Ernst L. Wynder, Gretchen S. Dieck, and Nancy E. L. Hall

Division of Epidemiology, Mahoney Institute for Health Maintenance, American Health Foundation, [E. L. W.]; Mobil Oil Corporation, Corporate Medical Department, New York, New York 10017 [G. S. D.]; and Division of Epidemiology and Disease Control, New Jersey State Department of Health CN360, Trenton, New Jersey 08625

ABSTRACT

The relationship between decaffeinated coffee consumption and pancreatic cancer was examined using data from a hospital-based case-control study of individuals aged 20–80 years in 18 hospitals in 6 United States cities, from January 1981 to December 1984. Among the males, 127 cases and 371 controls were examined, while for females, the figures were 111 and 325 for cases and controls, respectively. Decaffeinated coffee use was not associated with an increased risk of pancreatic cancer in males (odds ratio = 0.7 for 3 or more cups/day; 95% confidence interval = 0.4–1.4). For females, an elevated risk was seen for drinkers of 1–2 cups/day (odds ratio = 1.6; 95% confidence interval = 1.0–2.7), but this finding was of borderline significance. Cigarette smoking was significantly associated with pancreatic cancer in both males and females. Factors examined and not found to be related to pancreatic cancer included education, occupation, religion, marital status, alcohol drinking, saccharin use, height, weight 5 years before hospitalization, history of previous diseases, and residence.

INTRODUCTION

Although a number of studies have investigated whether there is an association between coffee drinking and pancreatic cancer, the evidence to date is inconsistent and inconclusive (1–8). Only one study (9) has considered whether decaffeinated coffee is related to pancreatic cancer in man, a possibility, since residual amounts of the solvents used during caffeine extraction may remain in the coffee (10, 11). One solvent, trichloroethylene, commonly used until 1977 for caffeine extraction has been found to be a bacterial mutagen and may also be carcinogenic in mammals (12, 13). The present study examines the association between decaffeinated coffee drinking and pancreatic cancer using data from an ongoing, hospital-based study of tobacco and cancer.

MATERIALS AND METHODS

The study population used in this analysis is part of a large, case-control study of tobacco-related diseases which has been in progress since 1969 as described elsewhere (14). In the present study, cases are defined as individuals with primary cancer of the pancreas [islet cell excluded since the etiology may be different (15)] diagnosed within 1 year of interview, and who were between the ages of 20 and 80 at the time of interview. The diagnosis of pancreatic cancer was based on histological confirmation (or by computed tomography scan or sonogram for one male and 3 female cases). Among the male controls, 57.7% were hospitalized with a diagnosis of a non-tobacco-related cancer, while the remaining 42.3% had a non-cancer diagnosis. Of the female controls, 66.8% were hospitalized with a non-tobacco-related cancer, while 33.2% were non-cancer-related. Table 1 shows the distribution of male and female controls by diagnosis. Excluded as possible controls were individuals with an admitting diagnosis of a tobacco-related disease (who comprised the cases for the original study) as well as diagnoses possibly related to pancreatic cancer such as pancreatitis, cancers of the gallbladder and extrahepatic bile ducts, pancreatic islet cell cancer, gallbladder disease, and diabetes. Patients with gastric ulcer were also eliminated as potential controls. Individuals with self-reported diabetes but whose present hospitalization was not due to their diabetes were not excluded from either the case or control groups; instead, self-reported diabetes was controlled for in the analysis.

Cases and controls were interviewed in the hospital with a standardized, structured questionnaire administered by trained interviewers. Information was elicited on demographic factors and on lifestyle variables such as decaffeinated and caffeinated coffee consumption, usual occupation, smoking status and alcohol drinking, saccharin use, height, weight 5 years before hospitalization, history of previous diseases, and residence.

The pattern of coffee consumption, both prior to the onset of current illness and previous pattern of coffee drinking, if consumption habits had changed, was obtained for both cases and controls. Duration was ascertained by asking about years of caffeinated and decaffeinated coffee drinking.

Usual occupation was determined by establishing what job each patient had held for the longest period of time. An abbreviated list of the U. S. Bureau of Census codes was used to code self-reported usual occupation (16).

A patient was defined as a cigarette smoker if he or she had smoked at least one cigarette/day for at least 1 year or more. An ex-smoker was a patient who had not smoked cigarettes for at least a year or more. Amount of current smoking was assessed according to number of cigarettes smoked per day. Information was also obtained for pipe and cigar smokers.

Weight 5 years before the onset of current illness and height at the
time of interview were elicited by questionnaire. Body mass index, which is a measure of weight controlling for height, was calculated by

\[
\text{Weight} = \frac{\text{Height} \times 10,000}{\text{height}}
\]

Weight 5 years before hospitalization was used when calculating body mass index rather than current weight, since substantial weight loss occurs for many cancer patients.

The measure of association used to examine the relationship between decaffeinated coffee consumption and pancreatic cancer was the odds ratio which indicates the odds of exposure among the cases compared to the odds of exposure among the controls (17).

**RESULTS**

The distributions of the pancreatic cancer cases and matched controls by several demographic variables are seen in Table 2. The ages of the cases differed little from controls since matching was carried out by age. Male cases were slightly more likely to have completed fewer years of schooling, while in females, the controls were less educated. Cases and controls differed little with respect to occupation, religion, and, for females, marital status. Among males, cases were more likely to be currently married than controls. Caffeinated coffee consumption was not significantly associated with pancreatic cancer, although a greater proportion of male cases drank 3 or more cups/day than controls. Among females, the cases were more likely to be never or occasional coffee drinkers as compared to controls. Further control by these variables did not alter the results to be presented.

Table 3 shows the association between smoking status and pancreatic cancer for both males and females. For both sexes, a significantly increased risk of pancreatic cancer was found for those currently smoking at least a pack of cigarettes per day. Among males, a significantly elevated risk was also seen in those currently smoking less than a pack per day. No significant excess risk was demonstrated among ex-smokers of either sex or in smokers of pipes or cigars. Although the observed elevations in risk are consistent with the literature, these risks may be somewhat elevated because of the use of controls without tobacco-related disease.

The distribution of decaffeinated coffee consumption by sex and by case-control status is seen in Table 4. Among males, 20.5% of the cases and 25.6% of the controls drank at least 1 cup of decaffeinated coffee per day. Among females, the proportion of decaffeinated drinkers was 36.0 and 29.5% for cases and controls, respectively. A significantly elevated risk of pancreatic cancer was seen only in women who drank 1-2 cups/day or in males who drank at least 1 cup/day.
for either males or females. Because cigarette smoking was related to both decaffeinated coffee drinking and pancreatic cancer, decaffeinated coffee was stratified by smoking status (Table 5). The excess risk of cancer of the pancreas in women related to both decaffeinated coffee drinking and pancreatic cancer was apparent among those who had never smoked only. Excluding the cases and controls who had had self-reported diabetes for 3 years or more did not change the relationship between decaffeinated coffee and pancreatic cancer.

Number of years of drinking decaffeinated coffee was examined and increasing number of years of decaffeinated coffee consumption was not associated with an increased risk of pancreatic cancer in either males or females. Less than 30% of either cases or controls drank decaffeinated coffee for more than 10 years.

Cases and controls did not differ significantly with respect to which brand of decaffeinated coffee they usually drank or according to their reason for drinking decaffeinated coffee (data not shown).

Other variables examined in the present analysis and found not to be associated with an increased likelihood of pancreatic cancer were alcohol consumption, saccharin use, height, body mass index, and residence in childhood, adolescence, and adulthood.

**DISCUSSION**

Commercial extraction of caffeine from coffee began in Germany during the early 1900s and in the United States marketing of decaffeinated coffee was initiated in 1927 by the General Foods Corporation with the introduction of Sanka (18, 19). Although dozens of solvents are described in various patents for caffeine extraction, the most common solvents used until recently were méthylène chloride and trichloroethylene. In 1977, the Food and Drug Administration proposed to prohibit the use of trichloroethylene for caffeine extraction, declaring it to be a "deleterious substance" (12), since trichloroethylene has been established to be a mutagen in bacteria and may also be a carcinogen in mammals (12, 13).

Decaffeinated coffee has been reported to be mutagenic using the Ames Salmonella/Microsome Assay (20), although the mutagenic activity disappeared in the presence of S-9 rat liver enzymes; thus, normal liver enzymes may protect mammals from the possible mutagenic effect of decaffeinated coffee. Coffee decaffeinated with méthylène chloride has not been found to increase the risk of neoplasms in male and female rats (21). In addition, although measurable amounts of residual trichloroethylene and methylene chloride have been found in a few commercially available decaffeinated coffees (10, 11), it

### Table 3 Odds ratios and 95% confidence intervals for the association between smoking status and pancreatic cancer

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Case</th>
<th>Control</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>20</td>
<td>101</td>
<td>1.0*</td>
<td>0.7–2.4</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>36</td>
<td>140</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–20 cigarettes/day</td>
<td>35</td>
<td>51</td>
<td>3.5</td>
<td>1.8–6.5</td>
</tr>
<tr>
<td>21+ cigarettes/day</td>
<td>28</td>
<td>48</td>
<td>2.9</td>
<td>1.5–5.7</td>
</tr>
<tr>
<td>Pipe or cigar smoker</td>
<td>8</td>
<td>31</td>
<td>1.3</td>
<td>0.5–3.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>70</td>
<td>171</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Referent group.

### Table 4 Odds ratios and 95% confidence intervals for the association between decaffeinated coffee and pancreatic cancer

<table>
<thead>
<tr>
<th>Decaffeinated coffee consumption</th>
<th>Case</th>
<th>Control</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or &lt;1 cup/day</td>
<td>101</td>
<td>276</td>
<td>1.0*</td>
<td></td>
</tr>
<tr>
<td>1–2 cups/day</td>
<td>14</td>
<td>48</td>
<td>0.8</td>
<td>0.4–1.5</td>
</tr>
<tr>
<td>3+ cups/day</td>
<td>12</td>
<td>47</td>
<td>0.7</td>
<td>0.4–1.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>127</td>
<td>371</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Referent group.

**Table 5 Association between pancreatic cancer and current decaffeinated coffee consumption by smoking status and sex**

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Male</th>
<th>Female</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>5</td>
<td>20</td>
<td>1.4</td>
<td>0.4–4.2</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>4.5</td>
<td>37.9</td>
<td>0.9</td>
<td>0.4–2.0</td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–20 cigarettes/day</td>
<td>4.5</td>
<td>11.2</td>
<td>0.9</td>
<td>0.4–2.0</td>
</tr>
<tr>
<td>21+ cigarettes/day</td>
<td>4.5</td>
<td>24.5</td>
<td>0.9</td>
<td>0.4–2.0</td>
</tr>
<tr>
<td>Pipes/cigars</td>
<td>4.5</td>
<td>39.3</td>
<td>1.1</td>
<td>0.2–6.2</td>
</tr>
</tbody>
</table>

x²HCT* = 2.2
\[ \hat{R}_{HCT} = 0.8 \]
95% confidence interval = 0.5–1.4

\[ x²HCT* = 5.6 \]
\[ \hat{R}_{HCT} = 1.5 \]
95% confidence interval = 0.9–2.3

* Yes, at least one cup/day; No, none or less than one cup/day.

* Chi-square of heterogeneity.

* Mantel-Haenszel point estimate of the odds ratio.
would seem unlikely that an increase in risk of pancreatic cancer would be found unless the residual solvents had an extraordinarily high carcinogenic potency. Decaffeinated coffee use is a habit that starts relatively late in life so that the exposure period of many individuals is short. In the present study, less than 30% of those who drank decaffeinated coffee drank it for more than 10 years and of these only 20–30% drank more than 3 cups/day (3–4% of the entire study group).

The findings of the present study suggest that decaffeinated coffee consumption is not a factor in the etiology of pancreatic cancer in humans. Although associations of borderline significance were found when examining subgroups of women, these findings were not replicated among the men. This apparent increase in risk may, in part, be explained by differences between controls with cancer diagnoses and those whose hospitalization at the time of interview was not related to cancer. The lack of an increasing risk of pancreatic cancer, either with increased amounts of decaffeinated coffee consumed per day or with increasing duration of use is indicative of an absence of a dose-response effect. This lack, combined with the failure to replicate in men the elevated risk found in the subgroup of women, argues against a causative relationship between decaffeinated coffee drinking and pancreatic cancer.

It is unlikely that errors occurred in classifying case-control status because the large majority were histologically confirmed; however, errors in recall of decaffeinated coffee consumption could result in misclassification which, if random, would obviate the detection of a weak association between decaffeinated coffee and pancreatic cancer. Given the sample size of the present study, the power to detect a 2-fold increase in risk associated with decaffeinated coffee was 89% in males and 87% among females.

The lack of association between decaffeinated coffee consumption and pancreatic cancer found in the present study does not concur with the findings of Lin and Kessler (9) who reported a significantly greater proportion of pancreatic cancer cases (males and females combined and including 5 cases of islet cell cancer) drinking decaffeinated coffee compared to non-cancer controls (109 cases and 109 controls total). Their study was limited by several factors: (a) relative risk estimates were not given nor was decaffeinated coffee consumption assessed according to cups per day or duration of use; and (b) the effect of controlling for possible confounding variables such as smoking was not discussed.

As in the past, a positive association was found for cigarette smoking but not for coffee consumption or alcohol intake. It is clear, however, that the major determinants for pancreatic cancer are still unknown. Dietary factors may be involved, as the geographic distribution of pancreatic cancer among Japanese natives and migrants would suggest (22). The dietary factors, however, include neither coffee nor decaffeinated coffee. Further studies on the etiology of pancreatic cancer must be concerned with the role of nutrition and should make use of laboratory techniques as well as epidemiological methods.

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