INTRODUCTION

Alcoholic beverages and coffee have been part of the human diet for centuries. Norway is well known for a restrictive alcohol policy and the total alcohol consumption is relatively low and liver cirrhosis mortality is not predominant. On the other hand Norwegians are among the highest consumers of coffee in the world (1).

Alcohol has a well-established toxic and graded effect on liver, including cirrhosis. Since most heavy drinkers do not develop alcoholic cirrhosis, it is widely believed that alcoholic cirrhosis has multiple causes and that both start and progression of the process may be dependent upon predisposing factors and other causes. It has the well known effect of raising blood concentration of the liver enzyme γ-glutamyltransferase (GGT) which is widely used as a marker of alcohol intake, although it is documented that other factors also are associated with serum levels of GGT (2–4).

An inverse association between serum GGT and intake of coffee has been documented in the study of Arnesen et al. (2) in population studies in Norway. This finding has been consistently observed in population studies from other countries (3–6). Attention has recently been drawn to possible beneficial effects of coffee drinking on liver diseases. A prospective study of Klatsky et al. (7–8) reported a lower risk of hospitalization, and death from alcoholic cirrhosis in association with coffee drinking. Similar results were also observed in three case-control studies published later (9–11).

To provide further information on the issue, we utilized a cardiovascular survey in a population characterized by high coffee consumption and low risk of liver cirrhosis and did mortality follow-up with liver cirrhosis mentioned on the death certificate as endpoint.

MATERIALS AND METHODS

Between 1977 and 1983, men and women living in three countries in different parts of Norway (Finmark 1977–78, Sogn og Fjordane 1980, Oppland 1981–83) were invited to participate in a cardiovascular screening program organized by the National Health Screening Service. The screening procedures have been described in detail elsewhere (1, 12).

The survey included all residents aged 40–55, and an approximately 20% random sample of men and women aged 20–39 years. Response rate was high (87% for men and 93% for women) and it was much the same in the three counties. On the reverse side of the invitation letter was a questionnaire including questions on smoking habits, physical activity, and history of cardiovascular diseases.

The information about coffee and alcohol consumption was obtained from a self-administered food-frequency questionnaire (13). This was handed out to the person who attended the screening, and was to be returned by mail. All participants, except in 5 municipalities in Sogn Fjordane, got this additional questionnaire and about 94% returned it. A small percentage, 4%, of those who responded, did not answer the question on coffee habits.
Our study population included persons, aged 20–55 years (median 43.6 years), who answered all questions on life style habits used in the present study—a total of 25,763 men and 25,543 women. The examination comprised measurements of weight, height, systolic and diastolic blood pressure, and collection of venous non-fasting blood samples. Serum cholesterol and triglycerides were determined at the same laboratory—Central Laboratory, Ullevål Hospital, Oslo (1, 12).

The question about coffee read, “How many cups of coffee do you usually drink per day?” with preset categories: “Do not drink coffee or less than one cup”, “1–2 cups”, “3–4 cups”, “5–6 cups”, “7–8 cups”, and “9 or more cups”. These categories were coded as 1, 2, 3, 4, 5 and 6 when estimating linear trend and relative risk. No question about the method of coffee preparation was asked. Alcohol consumption was recorded using two questions: “Do you usually drink wine/spirits during one week?” and “Do you usually drink beer during one week?”. Drinkers of alcohol were defined as people who answered yes on one or both alcohol questions. Information on smoking habits was collected by the questions: “Do you smoke daily at present?” and “How many cigarettes do you or did you usually smoke daily?”

The number of observation years was calculated for each person from the time of examination at screening to the time of death, time of emigration, or at the end of the follow-up (end of 1997). Mean follow-up was 16.9 years. The total number of deaths from all causes in the studied cohort was 4207, and 173 persons emigrated from Norway during follow-up period.

The follow-up period covered three versions of the International Classification of Diseases (ICD). Liver cirrhosis was defined as ICD-8, 9: 571 and ICD10: K70 or K73 or K74. Alcoholic liver cirrhosis was defined as ICD-8, 9: 571.0–571.3 and ICD 10: K70. Up to four causes of death were recorded on the death certificate in ICD-8 and ICD-9 and up to seven causes of deaths in ICD-10. The first cause is the underlying; the others are contributory causes of death. Altogether, 33 deaths were recorded with cirrhosis as the underlying cause and 20 deaths with cirrhosis as the contributing cause; i.e. cirrhosis was mentioned on the death certificate for 53 deaths, 38 of the deaths in men and 15 in women. The corresponding figures for alcoholic cirrhosis were 25 deaths as the underlying cause and 11 deaths as the contributing cause; i.e. alcoholic cirrhosis was mentioned on the death certificate for 36 deaths, 32 of the deaths in men and 4 in women. The mean age at death was 46.3 years for cirrhosis and 45.1 years for alcoholic cirrhosis.

Relative risks were estimated by using the Cox proportional hazards regression model in SPSS (14). Interaction was tested by comparing -2 *(log likelihood) in models with and without the interaction term. Direct standardization was used to obtain age-adjusted rates/100000 person-years with the study population in five-year age-groups as the standard. Linear trend across various variables of the coffee categories was estimated by linear regression, with coffee as the dependent variable.

RESULTS

Table 1 shows biologic variables and other lifestyle factors according to different levels of coffee intake. Cholesterol levels and prevalence of the current daily smoking and alcohol use increased steadily with increasing level of coffee intake.

The mortality rates were distinctly lower among persons drinking three or more cups of coffee than in those drinking two or less (Table 2). This applies to both cirrhosis and alcoholic cirrhosis as mentioned and underlying causes. For above three cups of coffee there was no clear relationship with liver cirrhosis mortality.

When coffee intake was entered as a continuous variable in the Cox regression analysis, a distinct inverse relationship with death from liver-, total- and alcoholic cirrhosis appeared. (Table 3). The relationship persisted or became even stronger after adjustment for smoking and alcohol use. Additional adjustment for triglycerides, systolic blood pressure, BMI, and cholesterol did not change the relationship. Smoking and alcohol use were positively related to mortality from cirrhosis and alcoholic cirrhosis. When the analyses were done with cirrhosis as the underlying cause of death as endpoint, similar relative risks emerged. When number of cigarettes was used as covariate, similar relative risk of coffee consumption on death from cirrhosis was observed.

Testing for interaction between coffee and smoking, and smoking and alcohol in relation to death of liver cirrhosis produced no significance. However, our study had less than 20% power to reveal the interactions of the magnitudes that we actually found, with 5% significance level. This is based on the sample size consideration given by Schmoor et al. (15) for binary prognostic factors in survival analysis. In this case, we dichotomized coffee intake into ≤ 4 and 4+ cups/day. Hence, the existence of interactions cannot be ruled out by this study. It is mentioned that our study had close to 80% power to detect the main effect of coffee.

DISCUSSION

This study provides evidence of a favorable role of coffee intake on the risk of death from liver cirrhosis. To our knowledge, only the studies of Klatsky et al. (7–8), Corraro et al. (9–10) and Gallus et al. (11) have related the risk of cirrhosis to coffee intake. In the prospective study conducted in Northern California (7), an inverse coffee-cirrhosis relation was reported for the first time. Coffee drinking, but not tea drinking, was inversely related to alcoholic cirrhosis risk, with persons who drank four or more cups per day at one-fifth the risk of those who did not drink coffee. These find-
Coffee drinking was associated with higher levels of cholesterol. To see if the favorable effect of coffee drinking on death from liver cirrhosis was mediated through cholesterol level, we related serum cholesterol to liver cirrhosis mentioned on the death certificate in a Cox analysis. Serum cholesterol was not related to liver cirrhosis.

What agent in coffee may explain the protective effect of coffee consumption on liver cirrhosis is not clear today. The possibility that substances contained in coffee may exert a protective effect on the hepatocyte has been underlined by the study of Casiglia et al. (16), which found consistently lower liver enzymes in coffee drinkers than in non-coffee drinkers; the higher the daily number of cups of coffee, the lower the serum levels of all liver enzymes and bilirubin. Coffee intake was significantly related to decreased serum concentrations of liver enzymes also in other previous studies (5, 17).

The study of Comrø et al. (10) concluded that the inverse relationship of coffee and cirrhosis is probably not attributable to caffeine because no negative liver cirrhosis relationship was found to the other beverages containing caffeine. Studies of Urgert et al (18) and Weusten-Van der Wouw et al. (19) showed in human experimental studies that coffee oils, brews, and grounds containing cafestol and kahweol increased liver function enzymes such as alanin aminotransferase, asparate aminotransferase but reduced serum level of GGT and creatinin. The acute alteration in liver enzyme levels with intake of cafestol and kahweol as individual agents differ from the results of epidemiological studies that examined the association between coffee intake and liver enzymes other than GGT. Such findings could suggest that cafestol and kahweol are not the only agents in coffee responsible for the epidemiological findings in our study. Other ingredients contained in coffee with various biological actions may well play a role, as there are three to four-hundred pharmaceutically active substances in coffee (20).

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There seems to be a threshold in the relationship; no further decline in mortality when the intake is more than three to four cups of coffee. The size of the cups varies a lot in Norway, with an average of 1.25 dl (1). If part of the etiology, a sufficient dose seems to be in order of at least 3.7 dl per day.

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TABLE 2. Crude and age-adjusted mortality per 100,000 person-years from liver cirrhosis or alcoholic cirrhosis by coffee intake for men and women 20–55 years

<table>
<thead>
<tr>
<th>Cups of coffee/day</th>
<th>Number of deaths</th>
<th>Mortality, crude</th>
<th>Mortality, age-adjusted</th>
<th>Number of deaths</th>
<th>Mortality, crude</th>
<th>Mortality, age-adjusted</th>
<th>Number of deaths</th>
<th>Mortality, crude</th>
<th>Mortality, age-adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>5</td>
<td>12.90</td>
<td>15.50</td>
<td>4</td>
<td>10.31</td>
<td>12.29</td>
<td>3</td>
<td>7.73</td>
<td>9.04</td>
</tr>
<tr>
<td>1–2</td>
<td>12</td>
<td>15.05</td>
<td>15.64</td>
<td>9</td>
<td>11.28</td>
<td>11.60</td>
<td>9</td>
<td>11.28</td>
<td>12.07</td>
</tr>
<tr>
<td>3–4</td>
<td>11</td>
<td>4.35</td>
<td>3.89</td>
<td>7</td>
<td>2.77</td>
<td>2.57</td>
<td>6</td>
<td>2.37</td>
<td>2.19</td>
</tr>
<tr>
<td>5–6</td>
<td>15</td>
<td>5.68</td>
<td>5.59</td>
<td>10</td>
<td>3.78</td>
<td>3.72</td>
<td>10</td>
<td>3.78</td>
<td>3.76</td>
</tr>
<tr>
<td>7–8</td>
<td>6</td>
<td>4.33</td>
<td>4.60</td>
<td>2</td>
<td>1.44</td>
<td>1.66</td>
<td>6</td>
<td>4.33</td>
<td>4.60</td>
</tr>
<tr>
<td>9+</td>
<td>4</td>
<td>4.21</td>
<td>4.54</td>
<td>1</td>
<td>1.05</td>
<td>1.09</td>
<td>2</td>
<td>2.10</td>
<td>2.18</td>
</tr>
</tbody>
</table>

p (trend) < 0.01 < 0.01 < 0.001 < 0.001 < 0.05 < 0.05 < 0.01 < 0.01

TABLE 3. Relative risks (95% confidence intervals) estimated by Cox proportional hazards regression for men and women 20–55 years

<table>
<thead>
<tr>
<th>Model with sex, age and</th>
<th>Coffee or alcohol or smoking, one at time</th>
<th>Coffee, alcohol and smoking</th>
<th>Coffee, alcohol and smoking and othersa</th>
<th>Model with sex, age and</th>
<th>Coffee or alcohol or smoking, one at time</th>
<th>Coffee, alcohol and smoking</th>
<th>Coffee, alcohol and smoking and othersa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coffee drinking (per unit)</td>
<td>0.7</td>
<td>0.6 (0.5–0.8)</td>
<td>0.6 (0.5–0.8)</td>
<td></td>
<td>0.6</td>
<td>0.5 (0.4–0.7)</td>
<td>0.5 (0.4–0.7)</td>
</tr>
<tr>
<td>Alcohol use (yes/no)</td>
<td>5.3</td>
<td>4.8 (2.6–8.9)</td>
<td>4.9 (2.6–9.1)</td>
<td></td>
<td>7.6</td>
<td>6.7 (2.9–15.4)</td>
<td>6.9 (2.9–16.1)</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>2.4</td>
<td>2.8 (1.6–5.0)</td>
<td>3.0 (1.7–5.4)</td>
<td></td>
<td>2.7</td>
<td>3.4 (1.6–7.3)</td>
<td>3.7 (1.7–7.9)</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>0.7</td>
<td>0.6 (0.5–0.8)</td>
<td>0.6 (0.5–0.8)</td>
<td></td>
<td>0.6</td>
<td>0.5 (0.4–0.7)</td>
<td>0.5 (0.4–0.7)</td>
</tr>
<tr>
<td>Alcohol use (yes/no)</td>
<td>11.0</td>
<td>10.1 (3.8–26.6)</td>
<td>10.1 (3.8–27.1)</td>
<td></td>
<td>14.4</td>
<td>12.9 (3.7–44.6)</td>
<td>13.3 (3.8–46.6)</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>2.4</td>
<td>2.7 (1.3–5.5)</td>
<td>2.9 (1.4–6.0)</td>
<td></td>
<td>2.6</td>
<td>3.1 (1.3–7.5)</td>
<td>3.4 (1.4–8.2)</td>
</tr>
</tbody>
</table>

a BMI, total cholesterol, systolic blood pressure and triglycerides (log transformed); all variables in the model.
In summary, there was an inverse relationship between coffee intake and mortality from liver cirrhosis in this middle-aged Norwegian population with a high coffee intake. The mechanisms behind this relationship remain unclear.

REFERENCES