Chlorinated drinking water and pancreatic cancer
A population-based case-control study
MARJA KUKKULA, GÖRAN LÖRFOTH *

In order to examine the potential association between chlorinated drinking water and the incidence of pancreatic cancer, a population-based case-control study was performed on data obtained from the Turku area in Finland. The study base was approximately 220,000 persons. All 183 pancreatic cancer cases, diagnosed during 1989-1991, were included in the study. Each case had 2 randomly selected controls. The criterion for the exposure to chlorination by-products (CBPs) was that the subject had had chlorinated drinking water from a surface source available at home. Residential addresses with chlorinated or non-chlorinated water were obtained for up to the previous 20 years prior to diagnosis. The odds ratios (OR) varied between 0.20 and 0.66 depending on the length of the cumulative exposure time. This indicates that those exposed to chlorinated drinking water had a lower risk of contracting pancreatic cancer than the unexposed. The result is in gross agreement with earlier investigations which have mainly shown negative or inadequate associations. The side-effects of drinking water disinfection are unproven, because the published research results are inconsistent. The benefits of chlorination, however, are undeniable. Continuous water disinfection is needed in order to avoid waterborne epidemics and chlorination is the only available method in many countries.

Key words: drinking water, chlorination, chlorination by-products, pancreatic cancer, negative association

Continuous chlorination of drinking water was first introduced in some cities in Europe and the United States during the first decade of this century after which it became a widely used disinfection method. It has been demonstrated that this led to a sharp decrease of both the morbidity and mortality of many diseases known to be waterborne. It was not until 1974 that the first chlorination by-products (CBPs), trihalomethanes (THMs), were discovered in chlorinated drinking water. In 1980 this was followed by the discovery of the presence of non-volatile mutagens and the first compound of this type, MX, was identified by Holmbom et al. in Finland. Subsequently, a number of other CBPs have been detected. The discovery of mutagenic and potential carcinogenic compounds in chlorinated drinking water led to experimental animal bioassays as well as to a number of epidemiological investigations with respect to cancer of which pancreatic cancer has also been of some interest. The hitherto published studies on pancreatic cancer and exposure to chlorinated drinking water are summarized in table I. Some of these studies were reviewed by a Working Group at the International Agency for Research on Cancer resulting in the conclusion that there is inadequate evidence for the carcinogenicity of chlorinated drinking water in humans. These 6 studies have also been subjected to a meta-analysis resulting in an overall relative risk for pancreatic cancer of 1.05 with a 95% confidence interval (CI) of 0.91-1.22. Two of the studies mentioned in table I were based on the very same population and same exposure assessment method but reached different conclusions with relative risks of 0.8 and 2.2 respectively.

In the present investigation the potential association between pancreatic cancer and chlorinated drinking water has been studied in the Turku area of Finland. Turku was chosen due to the fact that the public drinking water is drawn from a local river and has been heavily chlorinated. This would enhance the possibility of detecting a carcinogenic effect if it exists.

MATERIAL AND METHODS
Geographical location and study population
The study area was 8 municipalities in the Central Hospital District of Turku, in southwestern Finland, which have been using surface water as their drinking water source. The total population of these 8 municipalities was 221,854 (table 2). The biggest city in the area is Turku with approximately 163,000 inhabitants. The municipal drinking water of Turku is produced mostly from river water (Aura) and during the 1960s and 1970s was well known for its bad quality. Increasing amounts of chlorine were used in both pre-chlorination and post-chlorination
at the Turku Water Works. The total THM concentrations in the water were often >200 µg/l at the end of the distribution system. Raw water chlorination was abandoned in 1981. By substituting alternative disinfectants for chlorine and by introducing new water treatment methods, Turku Water Works has succeeded in diminishing the concentrations of CBPs and the mutagenicity of the water considerably, since 1986 the annual mean of the total THM concentrations has been below 5 µg/l.

Methods
A matched case-control study was used for the study design. The cases were all residents of the study area, who were diagnosed as having cancer of the pancreas, ICD code 157 during 1987–1991. The selection of cases was made by the Finnish Cancer Registry.

Two population controls for each case were randomly selected by the National Population Registry from the residents of the study area. The selection of controls was subjected to the following criteria: each control had to be a resident living in the same municipality as the case at the time the pancreas cancer of the counterpart was diagnosed and each had to be of the same sex and born in the same year as the counterpart.

Exposure
Instead of the known exposure to chlorination by-products, the type of water source at the residences of subjects was used as a criterion for the exposure. The definition for exposure and exposure time in this study is that the subject has had chlorinated municipal drinking water from a surface source available at home. The exposure status of each address during the residential history of the subjects was checked at the local municipal water department by using the residence data of cases and controls from the National Population Registry, for as long as it was possible. This was most at approximately 20 years. The subjects or their relatives were not contacted because this was forbidden according to the Finnish Personal Data File Act.

For risk ratio calculations, the collected continuous exposure data were turned into dichotomous data by using the following definitions for exposed/non-exposed subjects:

i) The exposure status of cases and controls in each set (triplet or doublet) was taken at the time at which the case was diagnosed to have cancer of the pancreas. Subjects having chlorinated municipal drinking water from a surface source available at home were classified as ‘exposed’ and those without this kind of water available at home were classified as ‘non-exposed’.

ii) The 2 years before the diagnosis were excluded from the calculation of the cumulative exposure time. ‘Exposed’ subjects were those who had, according to the known residential history, been living for at least 1 year (12 months) in residence(s) with chlorinated municipal drinking water available from a surface source. Subjects whose cumulative exposure time was less than 1 year and whose exposure status was known for at least 1 year were classified as ‘non-exposed’. Otherwise, the exposure status was classified as ‘unknown’.

iii) The definition is as in ii), except that the cumulative exposure time during the known residential history of subjects was required to be at least 5 years in order to classify the subject as ‘exposed’.

iv) The definition is as in ii), but at least 10 years’ cumulative exposure was required.

v) The definition is as in ii), but at least 15 years’ cumulative exposure was required.

vi) The definition is as in ii), but at least 20 years’ cumulative exposure was required.

Statistics
Statistical tests were performed with Epi Info, Version 5 (Centers for Disease Control, Atlanta). Non-normally distributed data were tested with Kruskal-Wallis one-way analysis of variance. A p-value <0.05 was considered as the level of significance. The odds ratios and their 95% CI were estimated with the conditional logistic regression using Egret.

RESULTS
During the 5 year period 1987–1991 there were 189 cases of pancreas cancer diagnosed in the study base, which was comprised of the 8 municipalities with 221,854 inhabitants (table 2). Six of the cases were excluded from the study due to unknown residence data, so the actual case-

Table 1 A summary of the exposure assessments and results in 9 epidemiological studies concerning drinking water chlorination and pancreatic cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Exposure assessment</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvania et al.</td>
<td>Chlorinated water at address on death certificate</td>
<td>OR 1.97 (p&lt;0.005)</td>
</tr>
<tr>
<td>Brenniman et al.</td>
<td>Chlorinated water at address on death certificate</td>
<td>OR 1.02 (95% CI: 0.85–1.23)</td>
</tr>
<tr>
<td>Wilkins and Comstock</td>
<td>Cross-sectional, residence data from a past census</td>
<td>OR 0.80 (95% CI: 0.44–1.45)</td>
</tr>
<tr>
<td>Young et al.</td>
<td>Interview; data of chloroform concentrations</td>
<td>Females OR 1.15 (95% CI: 0.81–1.64)</td>
</tr>
<tr>
<td>Gottlieb et al.</td>
<td>Chlorinated/non-chlorinated water at address on death certificate and at birthplace</td>
<td>OR 1.07 (95% CI: 0.88–1.30)</td>
</tr>
<tr>
<td>Zierler et al.</td>
<td>Residence at death in a chlorinating community</td>
<td>OR 0.94 (95% CI: 0.89–0.99)</td>
</tr>
<tr>
<td>Flaten</td>
<td>Ecological classification: chlorinating/non-chlorinating municipalities</td>
<td>For females negative association, p&lt;0.05</td>
</tr>
<tr>
<td>IJsselmuiden et al.</td>
<td>Cross-sectional, residence data from a past census</td>
<td>OR 2.2 (95% CI: 1.24–4.10)</td>
</tr>
<tr>
<td>Koivusalo et al.</td>
<td>Calculated population exposure for municipalities</td>
<td>OR 1.07 (95% CI: 0.97–1.17)</td>
</tr>
</tbody>
</table>
control study was carried out with 183 cases and 360 controls. Among the 183 cases there were 71 males aged 37–86 years (mean age at the time of diagnosis 68 years and median 70 years) and 112 females aged 41–96 years (mean 74 years and median 76 years). Diagnosis was confirmed histologically in 63% of the cases.

The crude incidence rates of pancreas cancer varied between 6.6 and 19.4 per year and 100,000 inhabitants in the municipalities. The age-standardized incidence rates for females and males are given in table 3, adjusted to the 'world standard population'. The large variation is natural because of the rareness of the disease and the small size of the population in many municipalities.

The known retrospective mean residential times and their standard deviations (SD) were 20.32 years (SD 4.65) for the 183 cases and 21.08 years (SD 4.30) for the 360 controls working back from the date of diagnosis. This shows that there is no significant difference between the groups (Kruskal–Wallis test for two groups, p=0.066). The cases had shorter periods of residence than the controls. During their known residential history the cases had lived at a mean of 2.09 (SD 0.87) addresses whereas the controls at a mean of 1.88 (SD 0.88) addresses.

Table 2 The study base population, the number of new pancreas cancer cases during 1987—1991 and the type of municipal drinking water source in 8 municipalities of the Turku Central Hospital District

<table>
<thead>
<tr>
<th>Municipality</th>
<th>Population</th>
<th>Cases</th>
<th>Surface water</th>
<th>Ground-water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dragsfjärd</td>
<td>4,492</td>
<td>3</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Kaarna</td>
<td>15,262</td>
<td>5</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Kannasteen</td>
<td>2,328</td>
<td>1</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Naantali</td>
<td>9,764</td>
<td>5</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Parainen</td>
<td>11,351</td>
<td>11</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Rymättylä</td>
<td>1,795</td>
<td>1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Turku</td>
<td>163,067</td>
<td>154</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Uusikaupunki</td>
<td>13,795</td>
<td>9</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>221,854</td>
<td>189</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

*: Does not exist as municipal water source
-: Does not exist as municipal water source

Table 3 The variation of age-standardized pancreatic cancer incidences per 100,000 in the municipalities of Turku Central Hospital District during 1987–1991

<table>
<thead>
<tr>
<th>Municipality</th>
<th>Incidence per 100,000</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dragsfjärd</td>
<td>0</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Kaarna</td>
<td>8.2</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Kannasteen</td>
<td>4.6</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Naantali</td>
<td>10.4</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Parainen</td>
<td>5.2</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Rymättylä</td>
<td>0.0</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>Turku</td>
<td>10.3</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>Uusikaupunki</td>
<td>14.4</td>
<td>3.4</td>
<td></td>
</tr>
</tbody>
</table>

**DISCUSSION**

If there is any positive association between pancreatic cancer and the consumption of chlorinated drinking water from surface sources, this study has not been able to reveal it. In fact, the results indicate a negative association.
The selection bias in the study must be very small because of the effectiveness of the diagnostic system in Finland. A non-differential bias is probable as only 63% of the pancreatic cancer diagnoses were confirmed histologically. No recall bias was possible due to the study design based on registry data. The most limiting shortcoming of this study was that the residential histories available from the National Population Registry were limited to ~20 years. Due to the general late appearance of pancreatic cancer, a much longer exposure time may be necessary.

It is at least obvious that chlorinated drinking water is by no means a major factor in increased pancreatic cancer incidences. A result of this study shows indirectly that migration activity, prior to the date of diagnosis, was higher for the cases than for the controls indicating that some differences in the lifestyles of these groups may be contributing risk factors for pancreatic cancer.

The most important life style factor for increased pancreatic cancer incidence is probably tobacco smoking. Heavy smoking is presently more common among lower socioeconomic classes in Finland, in contrast to an earlier more equal distribution and this latter fact may be related to the phenomenon that there is almost no variation by social class in the incidence of pancreatic cancer. The present study, indicating a negative association between chlorinated drinking water and pancreatic cancer, can be compared to the earlier 9 studies (table 1). Wilkins and Comstock found a relative risk of 0.80 (95% CI: 0.44–1.45), Zierler et al. reported a risk ratio of 0.94 (95% CI: 0.89–0.99) and a Norwegian investigation found that the pancreatic cancer rate for females was significantly lower in chlorinating than in non-chlorinating municipalities. Several of the 9 investigations gave an inadequate or probably weak positive association whereas only 2 studies have shown a positive association.

All epidemiological studies, including the present one, have common problems concerning the exposure assessment methods. Instead of using a real individual exposure to chlorinated drinking water or CBPs, some kind of surrogate for the exposure has always been employed. This may result in the inconsistent results observed. There is no recall bias due to the study design based on registry data.

The benefits of chlorination are a fact that cannot be neglected. Proper water treatment and water disinfection are some of the most important preventive measures for public health. The positive impact of water disinfection on public health is, however, momentary. Continuous water disinfection is thus also needed in the future in order to avoid outbreaks of waterborne epidemics. Populations both in developed and developing countries are always at risk due to the potential contamination of drinking water sources or distribution systems. Disinfection by alternative methods without chlorine may be a possibility for economically advanced countries but, because of the economic situation in many developing countries, the available options for water disinfection are often either to chlorinate drinking water or not to disinfect at all.

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REFERENCES

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