Meta-analysis of studies on individual consumption of chlorinated drinking water and bladder cancer

C M Villanueva, F Fernández, N Malats, J O Grimalt, M Kogevinas

Study objective: To evaluate whether consumption of chlorinated drinking water is associated with bladder cancer.

Design: A bibliographic search was conducted and the authors selected studies evaluating individual consumption of chlorinated drinking water and bladder cancer. The authors extracted from each study risk estimates for intermediate and long term (>40 years) consumption of chlorinated water, stratified by sex when possible, and performed meta-analysis for the two exposure levels. A meta-analysis was also performed of the dose-response regression slopes.

Setting: Populations in Europe and North America.

Participants: Those included in six case-control studies (6084 incident bladder cancer cases, 10 816 controls) and two cohort studies (124 incident bladder cancer cases) fulfilling the inclusion criteria.

Main results: Ever consumption of chlorinated drinking water was associated with an increased risk of bladder cancer in men (combined OR=1.4, 95%CI 1.1 to 1.9) and women (combined OR=1.2, 95%CI 0.7 to 1.8). The combined OR for mid-term exposure in both genders was 1.1 (95% CI 1.0 to 1.2) and for long term exposure was 1.4 (95%CI 1.2 to 1.7). The combined estimate of the slope for a linear increase in risk was 1.13 (95% CI 1.08 to 1.20) for 20 years and 1.27 (95% CI 1.15 to 1.43) for 40 years of exposure in both sexes.

Conclusions: This meta-analysis of the best available epidemiological evidence indicates that long term consumption of chlorinated drinking water is associated with bladder cancer, particularly in men. The observed relative risk is only moderately high, but the population attributable risk could be important as the vast majority of the population of industrialised countries is potentially exposed to chlorination byproducts for long periods.

Chlorinated drinking water contains a complex mixture of chlorinated and brominated byproducts with mutagenic and carcinogenic properties. Several toxicological and epidemiological studies have found a positive association between chlorinated drinking water consumption and bladder cancer. An International Agency for Research on Cancer (IARC) working group evaluated the human carcinogenicity for chlorinated drinking water in 1991, concluding that there was inadequate evidence for its carcinogenicity to humans (Group 3). This evaluation was based mainly on ecological and death certificate studies. Several epidemiological studies on bladder cancer published after 1991 evaluated individual lifetime consumption to chlorinated drinking water overcoming partially the limitations of earlier studies. All of them found positive associations with bladder cancer. In 1999 the International Agency for Research on Cancer (IARC) re-evaluated individual chlorination byproducts such as chloroform and other trihalomethanes (THM) concluding that there was inadequate evidence for their carcinogenicity. It was argued that although diverse studies had associated chlorinated drinking water intake with cancer, single compounds could not be evaluated as they always occur in mixtures. A more recent report on disinfectant byproducts by the WHO considered that the evidence was insufficient to determine whether observed associations are causal and determine which specific byproducts or other contaminants play a part. Furthermore, it concludes that the health risks from disinfectant byproducts at the levels at which they occur in drinking water are extremely small in comparison with the risks associated to inadequate disinfection. Apart from bladder cancer, other health effects such as colorectal cancer and adverse pregnancy outcomes have also been associated with chlorinated drinking water. We performed a meta-analysis of results from epidemiological studies on individual consumption of chlorinated drinking water and bladder cancer following established guidelines. We provide a summary risk estimate of bladder cancer risk associated to chlorinated drinking water exposure, partially overcoming the criticisms raised in international or national evaluations of this risk.

METHODS

Literature search

A systematic bibliographic search was performed looking for studies on bladder cancer and chlorinated drinking water. We focused on those epidemiological studies with accurate exposure assessment—that is, with individual information on long term patterns of water consumption. The availability of residential history obtained from individual interviews linked with water source was defined as the inclusion criterion for the meta-analysis. This inclusion criterion was set because in previous evaluations on disinfection byproducts and cancer by the WHO, the absence of individual information was determined as crucial for the evaluation of cancer risk in humans. According to this criterion, ecological and cancer mortality based studies were excluded. Firstly, we searched in Medline all articles published without using any publication date limit. Search terms included bladder cancer, chlorine, chlorination, trihalomethanes (thm), mx, disinfectant agent, and tap water. The search was performed by consecutively entering single or combination of search terms. The search strategy is summarised as: [(chlorine & bladder cancer) or ((bladder cancer) & (disinfectant agent or chlorination or mx or thm))]. Among the 46 articles identified, 14 were review articles, seven were ecological studies, three were mortality based studies, one discussion, one editorial, one in Russian
We finally included in the meta-analysis six case-control studies. Freedman included in the meta-analysis the cohort of the study by Wilkins and Comstock. The study by Lynch was excluded from the analysis, because although it fulfilled the inclusion criteria, the population study was included in the study by Cantor 1987. The study by Freedman is a case-control study nested in the cohort of the study by Wilkins and Comstock. The study by Freedman, however, evaluated water consumption patterns of the study population only for a limited time period, precisely at the time of the same private census used in the cohort study. We included in the main meta-analysis the cohort study. Although the number of bladder cancer cases was smaller in the cohort study, the exposure assessment was more accurate and closer to the dates in which the study was conducted. The study by Freedman was considered in an alternative analysis. Death certificate based case-control studies, although have been frequently quoted, were not included in this meta-analysis because exposure information was either ecological or based on interviews of proxies.

### Statistical analysis

For each study, odds ratios (OR) or relative risks (RR) and 95% confidence intervals (95% CI) by sex and exposure category were extracted. Two studies provided only gender specific risks and overall risk estimates were calculated by us through a meta-analysis of male and female risks. One study included only men and one only women. We used Wolf’s method to combine risk estimates in all meta-analyses. This method is based on the study specific risk estimates and confidence intervals, applying the inverse of variance as the weighting factor. The exposure indices analysed were duration of chlorinated drinking water consumption in the case-control studies and water source in the cohort study. Subjects were classified as whether they ever consumed or not chlorinated drinking water. When not presented in the original papers, combined risk estimates for ever-consumers were estimated through a meta-analysis of published risk estimates for exposed subcategories. Those consuming chlorinated drinking water were further grouped according to duration of consumption. Three a priori defined exposure categories were used: no/low exposure group (reference category) including subjects not drinking chlorinated drinking water or consuming chlorinated drinking water for short time periods; an intermediate exposure group, corresponding in most studies to a consumption of chlorinated drinking water from 1 to 40 years; and the only ones partially fulfilling the inclusion criteria.”

### Table 1 Description of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Location</th>
<th>Study population</th>
<th>Exposure measurement selected for the meta-analysis</th>
<th>Exposure categories</th>
<th>Confounders considered in the statistical analysis or study designs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case-control studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cantor et al 19986</td>
<td>Iowa (USA)</td>
<td>Chlorinated surface water</td>
<td>0 years 1–39 years</td>
<td>Age, sex, study period, high risk occupation, and cigarettes.</td>
</tr>
<tr>
<td>Vyasola et al 19986</td>
<td>Finland</td>
<td>Substantially mutagenic drinking water</td>
<td>&lt;15 years 15–44 years</td>
<td>Age, socio economic status and smoking. Results stratified by sex.</td>
</tr>
<tr>
<td>King et al 199610</td>
<td>Ontario (Canada)</td>
<td>Chlorinated water</td>
<td>&lt;7 years 10–34 years</td>
<td>Age, gender, pack years of smoking, current smoking, education, and calorie intake.</td>
</tr>
<tr>
<td>McGeehin et al 19931</td>
<td>Colorado (USA)</td>
<td>Chlorinated water</td>
<td>0 years 1–30 years</td>
<td>Coffee consumption, smoking, tap water intake, family history of bladder cancer, sex, and medical history of bladder infection or kidney stones.</td>
</tr>
<tr>
<td>Vena et al 199311</td>
<td>New York state (USA)</td>
<td>Tap water</td>
<td>0–49 years consuming 0–5 glasses/day 0 years</td>
<td>Age, sex, smoking habit, high risk occupation, population size of usual residence and reporting centre.</td>
</tr>
<tr>
<td>Cantor et al 198712</td>
<td>USA</td>
<td>Chlorinated surface water</td>
<td>0–49 years consuming 0–5 glasses/day 0 years</td>
<td>Age, marital status, education, smoking history, frequency of church attendance, adequacy of housing, and persons per room.</td>
</tr>
<tr>
<td><strong>Cohort studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilkins and Comstock 198113</td>
<td>Washington County (USA)</td>
<td>Drinking water source Deep well users Chlorinated surface water users</td>
<td>Age, marital status, education, smoking history, frequency of church attendance, adequacy of housing, and persons per room.</td>
<td>Age, education, smoking status, pack years of smoking, physical activity, fruit and vegetable intake, total energy intake, body mass index, and waist to hip ratio.</td>
</tr>
<tr>
<td>Doyle et al 199716</td>
<td>Iowa (USA)</td>
<td>100% ground water source Mixed surface-ground water 100% surface water source</td>
<td>Age, marital status, education, smoking history, frequency of church attendance, adequacy of housing, and persons per room.</td>
<td>Age, education, smoking status, pack years of smoking, physical activity, fruit and vegetable intake, total energy intake, body mass index, and waist to hip ratio.</td>
</tr>
</tbody>
</table>
Table 2  Odds ratios and 95% confidence intervals from the studies included in the meta-analysis according to duration of exposure to chlorinated drinking water

<table>
<thead>
<tr>
<th>Case-control studies</th>
<th>Never exposed</th>
<th>1–19 years</th>
<th>20–39 years</th>
<th>40–59 years</th>
<th>≥60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cantor 98 Men</td>
<td>1.0</td>
<td>1.1 (0.8 to 1.3)</td>
<td>1.3 (0.9 to 1.8)</td>
<td>1.5 (0.95 to 2.3)</td>
<td>1.9 (1.1 to 3.6)</td>
</tr>
<tr>
<td>Cantor 98 Women</td>
<td>1.0</td>
<td>0.9 (0.6 to 1.4)</td>
<td>0.7 (0.3 to 1.3)</td>
<td>0.7 (0.3 to 1.4)</td>
<td>0.7 (0.2 to 2.4)</td>
</tr>
<tr>
<td>Both sexes</td>
<td>1.0</td>
<td>1.0 (0.8 to 1.2)</td>
<td>1.1 (0.8 to 1.4)</td>
<td>1.2 (0.8 to 1.7)</td>
<td>1.5 (0.9 to 2.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case-control studies</th>
<th>0 years</th>
<th>1–10 years</th>
<th>11–20 years</th>
<th>21–30 years</th>
<th>&gt;30 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCuechhin 93 Men</td>
<td>1.0</td>
<td>1.04 (0.71 to 1.53)</td>
<td>1.15 (0.86 to 1.51)</td>
<td>1.41 (1.09 to 1.81)</td>
<td></td>
</tr>
<tr>
<td>McCuechhin 93 Women</td>
<td>1.0</td>
<td>0.8 (0.6 to 1.2)</td>
<td>1.2 (0.9 to 1.7)</td>
<td>1.5 (0.95 to 2.3)</td>
<td>1.9 (1.1 to 3.6)</td>
</tr>
<tr>
<td>Both sexes</td>
<td>1.0</td>
<td>1.0 (0.7 to 1.4)</td>
<td>1.2 (0.9 to 1.7)</td>
<td>1.5 (1.0 to 2.3)</td>
<td>2.2 (1.1 to 4.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cohort studies</th>
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<th>20–39 years</th>
<th>40–59 years</th>
<th>≥60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doyle 97 Men</td>
<td>1.0</td>
<td>1.0 (0.7 to 1.4)</td>
<td>1.1 (0.7 to 1.5)</td>
<td>1.2 (0.8 to 1.7)</td>
<td>1.2 (0.7 to 2.1)</td>
</tr>
<tr>
<td>Doyle 97 Women</td>
<td>1.0</td>
<td>1.0 (0.8 to 1.4)</td>
<td>1.1 (0.7 to 1.5)</td>
<td>1.2 (0.8 to 1.7)</td>
<td>1.5 (1.0 to 2.3)</td>
</tr>
<tr>
<td>Both sexes</td>
<td>1.0</td>
<td>1.0 (0.7 to 1.4)</td>
<td>1.2 (0.9 to 1.7)</td>
<td>1.5 (1.0 to 2.3)</td>
<td>2.2 (1.1 to 4.4)</td>
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</tbody>
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<tr>
<th>Cohort studies</th>
<th>0 years</th>
<th>1–19 years</th>
<th>20–39 years</th>
<th>40–59 years</th>
<th>≥60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilkins and Comstock 81 Men</td>
<td>1.0</td>
<td>1.80 (0.8 to 4.75)</td>
<td>2.27 (1.2 to 4.31)</td>
<td>2.27 (1.2 to 4.31)</td>
<td>2.27 (1.2 to 4.31)</td>
</tr>
<tr>
<td>Wilkins and Comstock 81 Women</td>
<td>1.0</td>
<td>1.60 (0.54 to 6.32)</td>
<td>1.71 (0.8 to 3.5)</td>
<td>1.71 (0.8 to 3.5)</td>
<td>1.71 (0.8 to 3.5)</td>
</tr>
<tr>
<td>Both sexes</td>
<td>1.0</td>
<td>1.60 (0.54 to 6.32)</td>
<td>1.71 (0.8 to 3.5)</td>
<td>1.71 (0.8 to 3.5)</td>
<td>1.71 (0.8 to 3.5)</td>
</tr>
</tbody>
</table>

* Risk for both sexes obtained from a meta-analysis of men and women risk. †OR for the quartile of water consumption above the population median (1.4 litres).

RESULTS

All selected studies reported excess risks of bladder cancer ranging from 1.4 to 2.2 for the study specific highest exposure category in both sexes combined (table 2) although only in four studies were results statistically significant. In all case-control studies OR tended to increase with duration of exposure.

Ever consumption of chlorinated drinking water was associated with bladder cancer with a combined risk estimate of 1.2, (95%CI 1.1 to 1.4) for both sexes, on the basis of six studies (fig 1). Sex specific combined risk estimates were 1.4 (95%CI 1.1 to 1.9) for men on the basis of five studies and 1.2 (95%CI 0.7 to 1.8) for women, on the basis of five studies (table 3).

Results from the meta-analysis show a statistically significant increased risk for bladder cancer, associated to long term exposure to chlorinated drinking water (table 3). The combined risk estimate for both sexes and the mid-term exposure was 1.1 (95% CI 1.0 to 1.2) on the basis of five studies. The combined risk estimate for the long term exposure was 1.4 (95% CI 1.2 to 1.7) on the basis of five studies. Combined risk estimates were slightly lower in women (combined OR=1.4) for the long term exposure category, compared with men (combined OR=1.6) (table 3).
The study specific OR for both genders and the mid-term and long term exposure categories are shown in figures 2 and 3, respectively. OR for the long term exposure category are comparable and both the test for heterogeneity and the Galbraith plot, which is a more sensitive method than the $\chi^2$ statistic, do not indicate substantial differences between studies (fig 4 and 5). Heterogeneity of results among studies is, cohort study or, alternatively, of the nested case-control study by Freedman et al, modified minimally the results. The combined OR for both sexes and long term exposure category was 1.5 (95% CI 1.3 to 1.7) when including the cohort study by Wilkins and Comstock, and the combined OR was 1.4 (95% CI 1.2 to 1.6) when including the nested case-control study.

### Table 3

<table>
<thead>
<tr>
<th>Exposure category</th>
<th>Meta-OR (95% CI)</th>
<th>Number of studies</th>
<th>Test for heterogeneity p value</th>
<th>Selected method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both sexes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-term</td>
<td>1.1 (1.0 to 1.2)</td>
<td>5</td>
<td>0.84</td>
<td>Fixed effects</td>
</tr>
<tr>
<td>Long term</td>
<td>1.4 (1.2 to 1.7)</td>
<td>5</td>
<td>0.55</td>
<td>Fixed effects</td>
</tr>
<tr>
<td>Ever exposed</td>
<td>1.2 (1.1 to 1.4)</td>
<td>6</td>
<td>0.61</td>
<td>Fixed effects</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-term</td>
<td>1.3 (1.0 to 1.7)</td>
<td>4</td>
<td>0.08</td>
<td>Random effects</td>
</tr>
<tr>
<td>Long term</td>
<td>1.6 (1.2 to 2.2)</td>
<td>4</td>
<td>0.11</td>
<td>Random effects</td>
</tr>
<tr>
<td>Ever exposed</td>
<td>1.4 (1.1 to 1.9)</td>
<td>5</td>
<td>0.01</td>
<td>Random effects</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-term</td>
<td>1.0 (0.7 to 1.6)</td>
<td>3</td>
<td>0.09</td>
<td>Random effects</td>
</tr>
<tr>
<td>Long term</td>
<td>1.4 (0.6 to 3.6)</td>
<td>3</td>
<td>0.01</td>
<td>Random effects</td>
</tr>
<tr>
<td>Ever exposed</td>
<td>1.2 (0.7 to 1.8)</td>
<td>5</td>
<td>0.01</td>
<td>Random effects</td>
</tr>
</tbody>
</table>

*Includes the cohort studies that do not provide risk estimates by duration of consumption.

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**Figure 1** Odds ratios (OR), 95% confidence intervals (95% CI), study weight in the meta-analysis and combined risk estimate from meta-analysis of studies on bladder cancer and ever consumption of chlorinated drinking water. Both sexes.

**Figure 2** Odds ratios (OR), 95% confidence intervals (95% CI), study weight in the meta-analysis and combined risk estimates from meta-analysis of case control studies on bladder cancer and mid-term consumption of chlorinated drinking water. Both sexes.
however, particularly evident for results in women that are based on three studies and on comparatively small numbers (table 3). In men, the main source of heterogeneity was attributable to the inclusion of the study by Vena, particularly for mid-term exposure. Excluding this study resulted to an OR for men in the mid-term exposure category of 1.2 (95%CI 1.0 to 1.4) and p value for heterogeneity of 0.82. We explored through meta-regression whether year of publication was associated with the magnitude of the OR but found no statistically significant effect attributable to the year of publication for either of the two exposure categories.

We evaluated whether the cut off points selected could influence results, and calculated combined OR for two a priori defined “alternative” intermediate and high exposure categories. We selected as “alternative” intermediate exposure group the most comparable exposure category among studies, which corresponded to the strata including 25–26 years of consumption of chlorinated drinking water (table 2). The combined OR for this group was 1.2 (95% CI 1.0 to 1.4) with a p value for a test of heterogeneity of 0.36. The “alternative” high exposure group included the highest exposure strata in each study. The meta-OR for this group was 1.6 (95% CI 1.3 to 1.8) with a p value for a test of heterogeneity of 0.79. Similar to the overall combined OR, the gender specific combined OR calculated on the basis of these “alternative” exposure categories were slightly higher than those shown in table 3, and results for these categories were less heterogeneous.

The study by Cantor et al, 1987 reports OR by quantity of tap water consumption stratified below or above the median population level of daily water consumption (1.4 litres). Our model includes the OR of the most exposed stratum, tap water consumption above the median. We explored the effect on the combined risk estimate considering the OR from the stratum below the median. The risk estimate changed little for the overall combined risk estimate (OR=1.4, 95%CI 1.2 to 1.7); test for heterogeneity p value=0.528).

The study by Doyle reports results for three types of water source: subjects consuming 100% surface water (highest exposure), those consuming mixed surface and ground water, and those consuming 100% ground water (non-exposed). We included in our model the highest exposure category that included, however, only few subjects. We also checked for the effect on the results when using the intermediate exposure category that included the most exposed subjects. When using the intermediate category in the combined analysis, the OR increased (OR=1.4, 95%CI=0.9 to 2.2, test for heterogeneity=0.02).

![Figure 3](http://jech.bmj.com/) Odd ratios (OR), 95% confidence intervals (95% CI), study weight in the meta-analysis and combined risk estimate from meta-analysis of case-control studies on bladder cancer and long term consumption of chlorinated drinking water. Both sexes.

![Figure 4](http://jech.bmj.com/) Galbraith plot for mid-term exposure, both sexes. The Galbraith plot provides a graphical display to get a visual impression of the amount of heterogeneity from a meta-analysis. For each study, the z statistic $|\hat{b}/s.e._{\hat{b}}|$ is plotted against the reciprocal standard error $1/s.e._{\hat{b}}$. The (unweighted) regression line constrained through the origin, with its 95% confidence interval, has a slope equal to the overall log odds ratio in a fixed effects meta-analysis. The position of each study on the horizontal axis gives an indication of the weight allocated to it in a meta-analysis. The position on the vertical axis gives the contribution of each study to the Q statistic for heterogeneity. In the absence of heterogeneity we could expect all the points to lie within the confidence bounds (positioned two units over and below the regression line).

![Figure 5](http://jech.bmj.com/) Galbraith plot for long term exposure, both sexes. (See legend to figure 4 for explanation of the Galbraith plot).
Four studies applied elaborate exposure models and estimated long term level of exposure to trihalomethanes or to water mutagenicity attributable to the presence of chlorination byproducts. Risk estimates in the three studies examining both sexes were 1.4, 1.5, and 2.2 for long term exposure. The combined risk estimate for these three studies was 1.5 (95% CI 1.2 to 1.8) with a p value for the test of heterogeneity of 0.61.

The results of the dose-response analysis are shown in table 4. The combined OR for unit increase in duration of exposure is 1.006 (95%CI 1.004 to 1.009). For 20, 40, and 60 years of exposure, combined OR are respectively 1.13 (95%CI 1.08 to 1.20), 1.27 (95% CI 1.17 to 1.43), and 1.43 (95% CI 1.27 to 1.72). The comparison of “crude” and “adjusted” combined OR for the three studies that permitted the calculation of a covariance matrix, showed that adjusting for covariance led to a 20% lower combined estimate. For these three studies, the combined OR for unadjusted slopes was 1.005 per year of exposure (95%CI 1.003 to 1.008), standard error (SE)=0.000128. After adjusting for covariance, the combined OR was 1.004 (95%CI 1.001 to 1.007), SE=0.00153.

We found no evidence of publication bias. Egger’s graph showed a slight negative slope indicating that the smaller and less precise studies tended to report higher risk estimates, while the bigger and more precise studies tended to report lower risk estimates. However, the evidence of this trend is not statistically significant. We performed also the Begg’s and Egger’s tests to check for publication bias in the models stratified by sex. Because of the small number of studies, the test is not reliable as the confidence intervals very wide.

### DISCUSSION

Results of this meta-analysis indicate the presence of a moderate excess risk for bladder cancer attributable to consumption of chlorinated drinking water. A clear excess risk was observed among subjects consuming chlorinated drinking water for more than about 40 years. The risk estimate for the intermediate exposure category was only slightly increased, though it also was statistically significant. Overall, results for long term exposure to chlorinated drinking water were consistent between studies and fairly consistent exposure-response patterns were observed in all case-control studies. Previous meta-analyses or reviews had reached the same conclusions but either did not provide a quantitative summary of the effect, or did not base the analyses and conclusions on those studies with individual information.

Exposure assessment has been identified as one of the main problems when evaluating results of epidemiological studies on chlorination by products and recent studies have made considerable efforts in characterising lifetime exposure. All studies included in this meta-analysis included an individual information on water consumption. Heterogeneity of the methods used in different studies and different background levels of chlorination byproducts remains, however, a main concern. Statistical heterogeneity of the results was present for the intermediate exposure category and particularly for results stratified by gender. Small numbers, especially in women, and differences in exposure assessment are probably the most important sources of heterogeneity of results between studies. The study by Vena et al was the main source of statistical heterogeneity observed particularly in the mid-term category. In this study, OR were generally higher than in other studies, and is the least comparable to the other studies concerning various aspects of assessment of exposure including the exposure categories used.

The exposure categories used in the meta-analysis could correspond to different levels of exposure to chlorination byproducts between studies. The exposure strata used were not directly comparable between studies and also, levels of chlorination byproducts would be expected to differ between the geographical areas examined in these studies. Despite our effort to select the most comparable exposure categories identifying subjects with intermediate and long term consumption of chlorinated drinking water, exposure categories between studies differed. Even though the highly exposed group included in all studies subjects with long term consumption of chlorinated water the cut off points differed between studies. In one study the minimum was 30 years, in another 35 years, in two studies 40, in one study 45, and in two 50 years. More importantly, the groups considered as non-exposed in two studies had consumed chlorinated drinking water for a few years, which would have led to an underestimation of the risk. In an alternative analysis we examined the extent to which the definition of the cut off points could affect results. This analysis indicated that observed results are robust. Even though different estimates can be derived if the data are categorised in alternative ways, these differences are small and results tend to support a positive association between consumption of chlorination drinking water and bladder cancer.

Levels of trihalomethanes were measured and modelled only in three studies while a fourth study used a matrix of water mutagenicity that corresponds well with levels of chlorination byproducts. In the two studies measuring trihalomethanes and evaluated both sexes, risks for specific contaminant levels were comparable. The extent to which this finding can be extrapolated to the other studies included in this analysis is unknown and, in principle, one should not expect that risks by duration of exposure should be directly comparable as levels of contaminants and type of contaminants differ between areas and time periods. It should be

### Table 4 Dose-response regression slopes obtained from weighted least squares within study, and combined odds ratios (OR) with 95% confidence intervals (95% CI) obtained from the meta-analysis of the five slopes and their standard errors. Both sexes

<table>
<thead>
<tr>
<th>Study</th>
<th>Slope</th>
<th>Standard Error</th>
<th>OR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cantor 1998</td>
<td>0.0039614</td>
<td>0.0021449</td>
<td>1.006</td>
<td>1.004 to 1.009</td>
</tr>
<tr>
<td>Kivisaalo 1998</td>
<td>0.0098449</td>
<td>0.003775</td>
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<td>King 1996</td>
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<td>McGeehin 1993</td>
<td>0.0159266</td>
<td>0.0057087</td>
<td>1.004</td>
<td>1.002 to 1.006</td>
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<td>Cantor 1987</td>
<td>0.0049595</td>
<td>0.0024032</td>
<td>1.007</td>
<td>1.005 to 1.010</td>
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Combined

<table>
<thead>
<tr>
<th>Unit increase</th>
<th>Slope</th>
<th>Standard Error</th>
<th>OR</th>
<th>(95% CI)</th>
</tr>
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<tr>
<td>20 years</td>
<td>0.006</td>
<td>0.000128</td>
<td>1.006</td>
<td>1.004 to 1.009</td>
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<tr>
<td>40 years</td>
<td>1.27</td>
<td>1.17 to 1.43</td>
<td>1.27</td>
<td>1.17 to 1.43</td>
</tr>
<tr>
<td>60 years</td>
<td>1.43</td>
<td>1.27 to 1.72</td>
<td>1.43</td>
<td>1.27 to 1.72</td>
</tr>
</tbody>
</table>
noted that trihalomethanes have been traditionally used as markers of the whole mixture of chlorination byproducts because they are the most prevalent byproducts. Other chlorination byproducts such as haloacetic acids and MX, have also been shown to have mutagenic or carcinogenic properties.13–25

In one study the excess risk identified was present only among ever smokers.7 All studies adjusted for important confounding factors like age, sex, and smoking and some studies also for occupation and socioeconomic status. Residual confounding attributable to smoking could still be present but, overall, confounding seems to be an unlikely explanation for the findings of individual studies and the results of the meta-analyses. The alternative dose-response methods we used confirmed the existence of an excess risk, though they led to combined risk estimates of slightly different magnitude. According to the dose-response analysis described by Berlín26 and Greenland,27 we reached combined risk estimates slightly lower than according our intermediate term and long term exposure approach. The combined risk estimates obtained from both methods are comparable for the intermediate duration of exposure (about 20 years), and the difference seems to be larger for long term exposures. Both methodologies have their limitations. The dose-response slope approach is based on the assumption of a linear dose-response, which may be a simplification of the real dose-response trend. The mid-term, long term approach implies the combination of risk estimates from exposure categories that are not fully comparable among studies. These results obtained from different methodologies indicate the presence of an excess bladder cancer risk associated with exposure to disinfection byproducts, and also indicate that the limitations of each method are probably not producing a spurious association.

Publication bias is a concern for all meta-analyses. Our bibliographic search was limited to databases including published studies. There may exist other not published studies, for example, doctoral theses and congress communications. It is extremely difficult to identify such studies. Furthermore, their inclusion could be questioned as quality criteria are difficult to apply. A simple observation of the graphics presented (figs 1–3) indicates that there is no trend along the years. If publication bias did exist, reported risks would tend to be higher in the first published studies, and lower risks in more recent. We additionally examined with publication bias through statistical and graphical methods, showing no evidence of such bias. To conclude whether disinfection byproducts (DBP) or chlorinated drinking water exposure is a risk factor for certain cancers, evaluations could be based on an evaluation of single compounds but should also be based on the effect of the total DBP mixture, as humans are exposed to complex mixtures of DBP and it is impossible to evaluate the effect of one single compound through epidemiological studies. Results of this meta-analysis of case-control studies of bladder cancer and chlorinated drinking water exposure provide an objective summary risk for one of the cancers most consistently associated with DBP exposure.

In industrialised countries disinfection and chemical protection of drinking waters should not be considered as antagonistic. The recommendations of a recent report by the WHO9 similar to previous reports although applicable at a global level, do not correspond to the current situation of most industrialised societies where contamination of the water by microorganisms has been drastically, although not entirely,9 reduced. Traditional drinking water treatment is highly chlorine and chemical based. There exist reasonable alternatives that keep the disinfection power and produce fewer byproducts. In the long term, the most efficient approach is the protection of source waters aimed at reducing the presence of natural organic matter.10 Exposure to chlorination byproducts occurs through ingestion, inhalation, and dermal absorption.11–13 Epidemiological studies have only evaluated ingestion. Changing drinking water practices, for example consuming bottled water, would reduce exposure to trihalomethanes by only about one third.14

In conclusion, on the basis of epidemiological evidence, chronic exposure to chlorinated drinking water is associated with a moderate increased risk for bladder cancer, particularly among men. The estimated relative risks are not high, but the population attributable risk could be important, as the vast majority of the population of industrialised countries is potentially exposed for long time periods.

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Meta-analysis of studies on individual consumption of chlorinated drinking water and bladder cancer
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Multivariate regression analysis of associations between general practitioner prescribing rates for coronary heart disease drugs and healthcare needs indicators

A recent paper in the journal by the authors presented the results of bivariate correlations between prescribing rates for coronary heart disease (CHD) drugs and healthcare needs indicators (HCNIs). This paper added further weight to the suggestion that GP practice prescribing rates for statins are inequitable, although we also provided evidence for a range of other CHD drugs.

One of the letters to the journal suggested that a multivariate analysis would have helped to determine the independent associations between prescribing rates and HCNIs. We have undertaken multivariate regression analysis to determine the amount of variation in prescribing rates that can be explained by a combination of HCNIs and also to understand the strength and direction of independent associations with individual HCNIs. The main results are provided in this letter.

Between 22% to 25% of the variation in prescribing rates for statins, β blockers, and bendroflumiazide was explained in the multiple regression models. Slightly more variation was explained for ACE inhibitors (31.6%) and considerably more for aspirin (51.2%). Prescribing rates for all drug groups (except ACE inhibitors) were positively associated with CHD hospital diagnoses and procedures. Prescribing rates for statins and ACE inhibitors were negatively associated with the percentage of patients aged over 75 years in addition to the proportion of patients from minority ethnic groups. Prescribing rates for aspirin, bendroflumiazide, and all CHD drugs combined were negatively associated with deprivation.

Overall, this study found that prescribing rates were generally positively related to the rates of CHD hospital procedures and diagnoses, although they were also negatively associated with proxies of deprivation and ethnicity. These findings present further evidence of inequities of GP practice prescribing rates and the continued relevance of the inverse care law in prescribing. However, this ecological study cannot be used to infer inequitable prescribing by GPs, as the lower prescribing rates in GP practice populations with higher proportions of elderly, ethnic minority, and deprived patients may be attributable to lower utilisation of primary healthcare services because of social, psychological, economic, or cultural barriers. Therefore, further work needs to be undertaken in identified GP practice populations to understand the reasons for the low prescribing rates and ultimately to make CHD prescribing commensurate with healthcare need.

Acknowledgements

Paul Ward received a Health Services Research Training Fellowship from the North West NHS Executive to carry out the study on which this paper is based. We thank all health authority, PCT and Local Authority staff who provided access to PACT data, GP practice list data, hospital episode statistics and a variety of other data sources.

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References


BOOK REVIEW

Health


This book offers a revision of health concept and discusses different meanings of health and illness. It continues to lay definitions and enactments and concludes with speculations about the influence of contemporary trends and technological changes in health. It also explains how people contribute to enact and define these nuclear concepts of health and illness.

It is structured in six chapters. The first one, “How is health defined?” discusses the use of the definition of health as the opposite of illness. As the author points, this kind of restrictive definition is evidence of the tendency to avoid the complexity involved in these issues. In this part of the book the discussion is focused on the social consequences for communities and individuals of this lack of effort in providing more complex definitions. The first chapter finishes with the consequences of limited definitions on the measurement of health status and on the development of preventive interventions. In other words, the author discusses how the absence of integrated concepts can affect our capacity to know more about health, illness, sickness, and being healthy.

The second chapter, “How is health constructed?”, explores the social construction of health. Literature is reviewed on how the idea of illness is partly based on real facts but it is also a social construct. Moreover, health and illness constructs related with cultures and different perspectives (feminism, constructivism, relativism) are explored. The discussions on obesity, hysteria, and disability are especially interesting in this chapter.

The third chapter, “How is health lived?”, examines the way most people experience health and illness. It also gives several ideas related to health like a moral discourse and a metaphor. The discussion continues in chapter four, “How is health enacted?”, examining the way that people enact the states of being healthy or ill. Studies of illness behaviour and their criticisms are the basis of the discussion.

The book finishes with two topics related with the influence of contemporary social changes in health and illness. Chapter five, “Where is the concept of health going in the contemporary world?”, focuses on the relation between health and society. It is structured in two parts. On the one hand, theories of the relation of health and society are described. On the other hand, health inequalities and their possible explanations are carried out. Finally, chapter six, “Where is the concept of health going in the contemporary world?”, contains information about how contemporary trends may influence and promote changes in the boundaries between ill and not-ill, life and death, self and not-self, and health and illness.

To finish this review it is interesting to comment on the global significance of this book. The author mentions that it is not a textbook, but it could provide an important discussion for the academic field. The study of basic concepts related with health could be useful to improve public health professional work as well. Furthermore, this book could support the role of communities and individuals who are involved in the development of policies.
Global public goods for health; health economic public perspectives

This volume explores the applicability of the concept of global public goods to health and health related issues as well as the question of the added value—for example, in terms of new analytical insights or a better understanding of various policy approaches and initiatives. The book presents a number of chapters that focus on ‘production’, their ‘production’, and financing. Public goods and the politics of their provision through the individual chapter analyses edge) as a critical input to people’s improved medical knowledge, genomics knowledge, (2) the importance of knowledge (including mental ‘bads’ (such as the global climate change or the depletion of the ozone layer); (2) of the importance of knowledge (including medical knowledge, genomics knowledge, and public health infrastructure and knowledge) as a critical input to people’s improved health status and enhanced public health conditions; and (3) how to enable global public goods for health, such as international law and health regulations. However, running through the individual chapter analyses also are common themes. Among them are such important concepts as priority of global public goods and the policies of their provision, their ‘production’, and financing.

The discussions on these themes are analytically rigorous yet clear and focused, leading to practical and pragmatic—yet in part, also innovative—policy conclusions and recommendations. Thus, the book should be of interest to researchers and students as well as policymakers and practitioners alike.

Inge Kaul

Health inequalities: lifecourse approaches

This weighty and impressive collection describes and critically assesses the development of lifecourse approaches to understanding health inequalities over the past two decades. In part, these approaches reflect the revival of interest in early years’ influences on adult health and mortality. However, this book goes much further, showcasing several important studies that demonstrate how the social and the physical are mutually constitutive throughout the lifecourse and that trajectories and processes of influence vary with different illness conditions. Lifecourse approaches, made possible partly because of the development of longitudinal data sets that have resulted in a questioning of theories about how health inequalities develop and persist. Some of these papers show a simple cumulative lifecourse effect of exposure to health risks and insults; others examine critical time windows of exposure and influences of particular inheritances or life and lifestyle experiences. Frustations, that as products of their academic and political times, these datasets have inherent limitations, are evident in several papers. Nevertheless, this collection (39 papers, all co-authored by George Davey Smith) shows yet again that social structural factors are crucially important in generating health inequalities and includes many challenges to policy makers to tackle poverty. There are weaknesses. Although acknowledged by the editor, the gender blindness of much of this collection must still be seen as a deficit. Another is that explicit attention to culture, beliefs, and behaviour seems only to occur in the section on ethnic inequalities in health, (although the idiosyncratic “Diversions” section perhaps shows the editorial introduction of such socially important talents!). However, by highlighting the part played by social and cultural processes and clearly discussing the exceptions to notions of straightforward linear causality or general susceptibility theory, this collection should convince even the sceptical of the heuristic benefits of taking a lifecourse approach, the photographs are good too.

Kathryn Backett-Milburn

Violence against women: the health sector responds

Gender based violence (GBV) is an important public health problem with far reaching physical and mental health outcomes. Although non-governmental organisations and women’s advocacy groups have been at the forefront of the efforts to stop this epidemic, the response from the health sector has lagged behind. This book is a succinct synopsis of the Pan American Health Organisation’s (PAHO) efforts to eliminate gender based violence in Latin America. While the reader is provided with a brief overview of the scope of GBV, a significant proportion of the book is devoted to a description of the needs assessment for their project called “Critical Path”, the implementation of the multi-level PAHO Latin American Health/national) in 10 Latin American countries and the lessons learned from this project. As the healthcare sector was only one of the many levels at which this plan was implemented, the book describes more than just the health sector response to GBV; the book also describes the change effected in national policies and laws as a result of the PAHO project, as well as the extent to which the women affected by GBV. Even though the specific strategies described in this book had been tailored to the local milieu, it should be possible to use the same process in other settings; the last chapter provides a global perspective on the lessons learned from this project. The book has a comprehensive section on GBV resources; the bibliography contains selected references, and includes references to regional GBV projects. This book is a quick read; and although the tables, figures, and boxes laid out in many contrast, they do summarise relevant information for the reader and are worth paying attention to. In sum, this book provides an excellent summary of PAHO’s inter-disciplinary efforts towards eliminating GBV and is likely to be useful to other field efforts to curb GBV.

Anuradha Paranjape

MONICA monograph and multimedia sourcebook
Edited by Hugh Tunstall-Pedoe. Geneva: WHO, Swiss Fr 45, pp 244. ISBN 92-4-156223-4 (available with two CD ROMs provided)

There can be little doubt that the MONICA project represents the most significant study of the epidemiology of coronary heart disease (CHD) that the world has seen thus far. Inspired in the late 1970s by the 1950s and 1960s CHD epidemic in developed countries and by the seven countries study (among others), it was established in the early 1980s to measure trends in CHD and stroke mortality, and to relate these to changes in risk factors, lifestyle, health care, and major socioeconomic factors in defined communities in different countries. Much of our current level of understanding of cardiovascular disease is derived from the numerous reports and publications resulting from this project.

This monograph is a “must” for all those hoping to obtain an understanding of how MONICA was planned and set up; aimed to achieve, and of all the various studies, carried out under its umbrella, which contributed to its findings. However, it does not discuss these findings in the text, which is very largely descriptive, and the text describes important aspects of the project only in very general terms; it would, for example, be useful to obtain rapid access to the precise protocol for measurement of blood pressure, or collection of blood or serum cholesterol; blow by blow the details are not provided in the text itself, perhaps because such matters varied somewhat between different MONICA collaborating centres; however, two CD ROMs are provided with the book and these provide masses of background information (including on protocols), links to results, published papers, etc.

Overall, this book provides a splendid read; it is written by the leading partners in MONICA and edited by Hugh Tunstall-Pedoe, probably for the single individual who, over 23 years, has held MONICA together more than any other single person. It provides a superb overview of what MONICA was all about, and of why it remains so important to us all.

Christopher A Birt

An authors’ error occurred in this review by Drs Villanueva and others (2003;57:166–73). In figure 1 the odds ratio corresponding to the study by King et al “ever consumption” of chlorinated drinking water should be 1.2 (95%CI 1.1 to 1.3) [not 1.2 (95%CI 1.1 to 1.8)]. The correct combined odds ratio should be 1.2 (95%CI 1.1 to 1.3) [not 1.2 (95%CI 1.1 to 1.4)].