Those considered "hormonally dependent" in breast tumors (i.e., 10 fmol/mg ER) levels in two of the four men with ER-positive tumors were >7 fmol/mg and thus approached those considered hormonally dependent.

The findings from the present study suggest that preventive strategies developed for common chronic diseases may be effective also in preventing salivary gland cancer. Specifically, increasing consumption of fruits and vegetables, particularly those high in vitamin C, and limiting foods high in cholesterol may be effective in preventing such rare tumors.

Acknowledgements

This research was supported by grant R29-CA49499 from the National Cancer Institute.

References


It is generally accepted that severe air pollution episodes, such as those in Europe and North America before 1960, can cause important acute adverse effects on human health including mortality (1). Recent epidemiologic studies have indicated short-term effects of air pollution on health at relatively low levels of air pollution, even lower than current national or international air quality standards (2-11). The majority of these studies were concerned with the effects of the "classical" air pollutants, i.e., black smoke and SO2 related to combustion sources. However, due to changes in the emission sources toward road transport, the air pollution profile has gradually changed toward a more pronounced photochemical component. O3 is generally regarded as one of the most toxic components of the photochemical air pollution mix-
MATERIALS AND METHODS

Within the framework of the APHEA project (43), six European cities contributed data for evaluating the short-term effects of photochemical air pollution on the total daily number of deaths, using \( \text{NO}_2 \) and \( \text{O}_3 \) as indicators of exposure. In Table 1, the studied populations and time periods as well as the descriptive statistics of air pollutants, weather, and daily mortality series are shown for the participating cities. The cities span Central and Western Europe and comprise a population of more than 19 million. Mortality data were extracted from the national statistics records except in Athens, where the information was collected from the death certificates. In all cities except Athens and Barcelona, deaths from external causes were excluded from the total daily number of deaths. The inclusion of deaths from external causes adds random noise to the outcome variable, and, if not excluded, the estimates should be toward the null. However, the number of deaths from external causes is only a small proportion of the total number of deaths (4–5 percent). Daily mortality data have been provided by the air pollution monitoring network established in each town. Although there was no quality control program within APHEA to ensure comparability of air pollution measurements between European Union countries, a respective quality control program to conform with the European Union requirements. \( \text{NO}_2 \) is measured by the chemiluminescence method and \( \text{O}_3 \) by the ultraviolet absorption method (44, 45). The daily maximum 1-hour level for each pollutant was used, and the mean daily (24-hour) measurements of \( \text{NO}_2 \) and the maximum 8-hour values for \( \text{O}_3 \) were also considered. Urban monitoring sites were considered. For \( \text{O}_3 \), suburban data were also included. The correlation between the daily measurements at different stations in the same city ranged from 0.20 to 0.84 for \( \text{NO}_2 \) and from 0.40 to 0.97 for \( \text{O}_3 \). For each pollutant, the average daily values over all those monitoring stations that had measurements for more than 75 percent of the whole study period were estimated in each city and used for the final individual city analysis. For days with missing values in one station, values were estimated by a regression model based on the remaining stations' values, allowing also for seasonal variability. The rules adopted in the APHEA protocol about the geographic location of the monitoring stations used, the completeness criteria, and the applied methods for filling in missing values are described in more detail elsewhere (43, 46).

Although the present study is concerned with photochemical pollution, mean levels of black smoke as an indicator of ambient particulate matter are also presented in Table 1 to point out the substantial variability across cities not only in the levels but also in the mixture of air pollution. Black smoke is measured by the British black smoke filter method, which measures light reflectance from the surface of a filter. The monitor is composed of a stack of 16 filters and a calibration curve (47). Particles with a diameter less than 4 \( \mu \text{m} \) are collected with high efficiency (47). In European urban areas, black smoke is well correlated with particulate matter with a median aerodynamic diameter \( \leq 10 \mu \text{m} \) (PM10) with a reported range of cor­relations from 0.53 to 0.74, which is stronger in the winter in most areas (47). The highest levels of \( \text{NO}_2 \) and \( \text{O}_3 \) were observed in Athens and Barcelona, where there were also high levels of black smoke. London, in contrast, had relatively low levels of black smoke.

The statistical analysis in each city followed a standard approach, using the generalized linear model with the following: 1) the log link function; 2) a Poisson distribution; and 3) the ratio of the log of the mean to the log of the variance taken to be the same. This last assumption (equation 1) allowed the variance of the daily death counts to be represented as a multiple of the expected mean death rates. Parameters of interest were those associated with the logarithm of mortality, which was defined as ‘effect’.


TABLE 1. Descriptive characteristics of the APHEA cities, contributing to the analysis of photochemical air pollution

<table>
<thead>
<tr>
<th>City</th>
<th>( \text{NO}_2 ) (1-hour mean)</th>
<th>( \text{O}_3 ) (1-hour mean)</th>
<th>( \text{SO}_2 ) (24-hour mean)</th>
<th>( \text{O}_3 ) (8-hour mean)</th>
<th>Daily mean temperature</th>
<th>Daily mean relative humidity</th>
<th>Daily mean wind speed</th>
<th>Daily mean rainfall</th>
<th>Daily no. of deaths</th>
<th>Time period</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athens</td>
<td>57.4 (21.4)</td>
<td>17.4 (7.1)</td>
<td>84.4 (44.0)</td>
<td>22.0 (11.4)</td>
<td>74.0 (15.0)</td>
<td>74.0 (15.0)</td>
<td>14.8 (7.0)</td>
<td>9.0 (6.0)</td>
<td>74.0 (15.0)</td>
<td></td>
<td>400,000</td>
</tr>
<tr>
<td>Barcelona</td>
<td>10.0 (43.4)</td>
<td>17.4 (7.1)</td>
<td>46.6 (25.3)</td>
<td>74.0 (15.0)</td>
<td>74.0 (15.0)</td>
<td>74.0 (15.0)</td>
<td>14.8 (7.0)</td>
<td>9.0 (6.0)</td>
<td>74.0 (15.0)</td>
<td></td>
<td>400,000</td>
</tr>
<tr>
<td>København</td>
<td>10.0 (43.4)</td>
<td>17.4 (7.1)</td>
<td>84.4 (44.0)</td>
<td>22.0 (11.4)</td>
<td>74.0 (15.0)</td>
<td>74.0 (15.0)</td>
<td>14.8 (7.0)</td>
<td>9.0 (6.0)</td>
<td>74.0 (15.0)</td>
<td></td>
<td>400,000</td>
</tr>
<tr>
<td>Lyon</td>
<td>10.0 (43.4)</td>
<td>17.4 (7.1)</td>
<td>84.4 (44.0)</td>
<td>22.0 (11.4)</td>
<td>74.0 (15.0)</td>
<td>74.0 (15.0)</td>
<td>14.8 (7.0)</td>
<td>9.0 (6.0)</td>
<td>74.0 (15.0)</td>
<td></td>
<td>2,000,000</td>
</tr>
<tr>
<td>Zurich</td>
<td>10.0 (43.4)</td>
<td>17.4 (7.1)</td>
<td>84.4 (44.0)</td>
<td>22.0 (11.4)</td>
<td>74.0 (15.0)</td>
<td>74.0 (15.0)</td>
<td>14.8 (7.0)</td>
<td>9.0 (6.0)</td>
<td>74.0 (15.0)</td>
<td></td>
<td>2,000,000</td>
</tr>
</tbody>
</table>

* APHEA, Air Pollution and Health: An European Approach; BS, black smoke; PM10, particulate matter less than 10 \( \mu \text{m} \) (PM10); SD, standard deviation.

** The numbers refer to the populations covered by the data collection.

† Deaths from external causes were excluded.

mic scale and the RR and its inverse have the same distance from 1 (the "null"), this scale was used in the graphical presentation. The pooled regression coefficients were estimated as the weighted average of the individual ones, with the weights being the reciprocal of the local variances. The method, also called the "fixed effects model," is described in more detail elsewhere (51, 52). If significant heterogeneity among local estimates was found, random effects models were also applied. In the random effects models, we assume that the individual regression coefficients are a sample of independent observations from the normal distribution with the mean equal to the random effects pooled estimate and the variance equal to the between-cities variance. The joint estimates which data were available. The joint estimates which data were available.

number of deaths were observed in all four cities for the 1-hour maximum I-day estimated effects. The joint estimates which data were available. The joint estimates which data were available.

The fixed effect model, a 50-µg/m³ increase in the initial explanatory variable using weighted linear regression results in stronger estimates than the null hypothesis (51). If and where there was an indication of heterogeneity, several constant-over-time factors representing differences among cities in population health status (standardized mortality ratio, percentage of elderly, smoking prevalence), air pollution mixture, and/or climatic conditions were investigated as potential explanatory variables using weighted linear regression.

RESULTS
In figures 1 and 2 are shown the individual as well as the pooled (fixed and random) RRs and their 95 percent CIs associated with a 50-µg/m³ increase in the 1-day levels of NO₂ (1-hour maximum) and O₃ (1-hour maximum), respectively. The NO₂ results were consistent across cities (p for heterogeneity = 0.36). All the local estimates were positive (i.e., RR > 1), although they reached the nominal significance level (5 percent) in only three cities (Athens, Barcelona, and Paris). Significant adverse effects of O₃ on total daily number of deaths were observed in all four cities for which data were available. In terms of magnitude of the effects, London, which has predominantly photochemical air pollution, was an outlier with the largest estimated effects.

In table 2, the corresponding pooled RRs and their 95 percent CIs for NO₂ and O₃ are shown for 1-day and cumulative effects. The joint estimates were positive and highly significant for both pollutants. Under the fixed effects model, a 50-µg/m³ increase in the hourly maximum 1-day pollutant levels is associated with an increase in the total daily number of deaths of 1.3 percent (95 percent CI 0.9–1.8) for NO₂ and 2.3 percent (95 percent CI 1.4–3.3) for O₃. However, there was significant heterogeneity (p = 0.019) among local estimates for O₃, due to the extreme estimate in London. The random effects joint estimate was greater (RR = 1.029), but its 95 percent CI was still wider (95 percent CI 1.010–1.049). The cumulative effects were consistent with the 1-day estimates but somewhat greater, especially for NO₂.

Analyses by seasons showed that for both pollutants, the estimated RRs were slightly higher during the warm season. However, none of the differences between seasons was significant. Stratified analysis of NO₂ effects by high and low levels of black smoke or O₃ indicated no modification of NO₂ effects by the levels of either pollutant within each city. However, the plot of the estimated individual RRs and their 95 percent CIs (for a 50-µg/m³ increase in NO₂ 1-hour maximum) by median levels of black smoke (figure 3) revealed a tendency for larger effects of NO₂ in cities with higher levels of black smoke. This tendency was even clearer when city-specific RRs were plotted against median levels of black smoke during the cold season (data not shown). It should be noted that the correlation between daily mean PM₁₀ and black smoke is stronger in winter than in summer (47).

No similar correlation between daily mean PM₁₀ and black smoke is stronger in winter than in summer (47). No similar correlation between daily mean PM₁₀ and black smoke is stronger in winter than in summer (47). No similar correlation between daily mean PM₁₀ and black smoke is stronger in winter than in summer (47). No similar correlation between daily mean PM₁₀ and black smoke is stronger in winter than in summer (47). No similar correlation between daily mean PM₁₀ and black smoke is stronger in winter than in summer (47). No similar correlation between daily mean PM₁₀ and black smoke is stronger in winter than in summer (47). No similar correlation between daily mean PM₁₀ and black smoke is stronger in winter than in summer (47). No similar correlation between daily mean PM₁₀ and black smoke is stronger in winter than in summer (47). No similar correlation between daily mean PM₁₀ and black smoke is stronger in winter than in summer (47). 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DISCUSSION
This study summarizes the results from 10 cities (six of which participated in the APHEA project) spanning all of Central and Western Europe concerning the short-term effects of ambient oxidants exposure on total daily number of deaths. Significant positive associations were found between daily mortality and both NO₂ and O₃. Cumulative (table 2) or daily 24-hour average values (data not shown) of NO₂, indicating prolonged exposure, were substantially better predictors of total daily mortality than 1-hour maximum values. The same was observed for cumulative or 8-hour maximum values of O₃, although to a much less extent. The effects of both pollutants were found slightly greater during the warm season, although the differences of the effects during the cold season were not significant for either pollutant.

O₃ is known to have acute pulmonary effects at ambient levels. Lippmann (53) found that exposure to O₃ levels in the range 240–400 µg/m³ resulted in increased lung permeability and reactivity, decreased forced respiratory volume, and development of an inflammatory response. Kinney et al. (17) summarized the results of six studies and found an overall effect on forced expiratory volume in 1 second of 32 ml per 100 µg/m³ increase in levels of O₃ in children without respiratory complaints. Hoek et al. (54), studying 533 schoolchildren in the Netherlands, found that an increase of 100 µg/m³ in O₃ levels is associated with a decrease of 21 ml of forced expiratory volume in 1 second. Other studies also found associations between O₃ exposure and increased frequency of respiratory illness in children (23), inflammatory response of the upper airways in normal children (22), or increased frequency of hospital admissions (19, 21, 55).

Experimental exposure to high levels of NO₂ (higher than the ambient air concentrations) is known to cause acute pulmonary toxic responses. However, epidemiologic studies have given inconclusive results (56). Several studies have found significant adverse effects of NO₂ mainly in respiratory symptoms among children or hospital admissions (27, 32, 33, 57, 58) whereas others failed to find any (30, 59).

Only a few studies have specifically investigated the short-term effects of O₃ and/or NO₂ on mortality. Kinney and Orzakyan (35) found significant associations of both pollutants with total mortality as well as with the number of deaths due to cardiovascular causes in Los Angeles County. However, no signific-
TABLE 2. Estimated pooled relative risks (RRs) of total daily mortality and 95% confidence intervals (CIs) associated with a 50-µg/m³ increase in the levels of pollutants, across the APHEA* cities

<table>
<thead>
<tr>
<th>Pollutant (µg/m³)</th>
<th>RR (1-hour maximum)</th>
<th>RR (cumulative)</th>
<th>O₃ (1-hour maximum)</th>
<th>O₃ (cumulative)</th>
<th>Fixed effects model</th>
<th>Random effects model</th>
<th>Fixed effects model</th>
<th>Random effects model</th>
<th>Fixed effects model</th>
<th>Random effects model</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂ (1-hour maximum)</td>
<td>1.010 (1.000-1.018)</td>
<td>1.020 (1.017-1.026)</td>
<td>1.021 (1.027-1.034)</td>
<td>1.023 (1.014-1.033)</td>
<td>1.029 (1.010-1.049)</td>
<td>1.024 (1.012-1.037)</td>
<td>1.057 (1.042-1.074)</td>
<td>1.043 (1.025-1.062)</td>
<td>1.030 (1.010-1.051)</td>
<td>1.028 (1.009-1.047)</td>
</tr>
</tbody>
</table>

* APHEA, Air Pollution and Health: a European Approach.

TABLE 3. Summary results from two pollutant models from the APHEA* cities, including estimated pooled relative risks (RRs) of total daily mortality and 95% confidence intervals (CIs) associated with a 50-µg/m³ increase in the levels of the pollutant

<table>
<thead>
<tr>
<th>Pollutant (µg/m³)</th>
<th>Model Including black smoke</th>
<th>Model Including both NO₂ and O₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂ (1-hour maximum)</td>
<td>Fixed effects model</td>
<td>Random effects model</td>
</tr>
<tr>
<td>Fixed effects model</td>
<td>1.006 (1.000-1.012)</td>
<td>1.015 (1.009-1.020)</td>
</tr>
<tr>
<td>Random effects model</td>
<td>1.009 (1.002-1.017)</td>
<td>1.025 (1.015-1.035)</td>
</tr>
</tbody>
</table>

TABLE 4. Estimated pooled relative risks (RRs) of total daily mortality and 95% confidence intervals (CIs) associated with a 50-µg/m³ increase in the levels of pollutants after adding estimates from four non-APHEA* cities (Amsterdam, Basel, Geneva, and Zurich)

<table>
<thead>
<tr>
<th>Pollutant (µg/m³)</th>
<th>RR (1-hour maximum)</th>
<th>RR (cumulative)</th>
<th>O₃ (1-hour maximum)</th>
<th>O₃ (cumulative)</th>
<th>Fixed effects model</th>
<th>Random effects model</th>
<th>Fixed effects model</th>
<th>Random effects model</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂ (1-hour maximum)</td>
<td>1.010 (1.000-1.017)</td>
<td>1.018 (1.014-1.033)</td>
<td>1.023 (1.014-1.033)</td>
<td>1.020 (1.010-1.049)</td>
<td>1.010-1.019</td>
<td>0.001</td>
<td>0.057</td>
<td>0.010-0.014</td>
</tr>
</tbody>
</table>

* APHEA, Air Pollution and Health: a European Approach.

Figure 3. Estimated individual relative risks of total daily number of deaths and their 95% confidence intervals associated with a 50-µg/m³ increase in the levels of NO₂ (1-hour maximum) by median levels of black smoke (BS).
published studies) of our results on the O3 effect and daily mortality. However, the short-term effects of NO₂ on mortality may be confounded by other vehicle-derived pollutants. Thus, the issue of independent NO₂ effects requires additional investigation.

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