A Review of the Epidemiological Evidence on Tea, Flavonoids, and Lung Cancer$^{1–3}$

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Abstract

Tea and its main bioactive ingredients, the flavonoids, have been associated with human cancer for several decades. In this article, an overview is provided of observational epidemiological studies of lung cancer incidence in relation to intake of green tea, black tea, flavonols/flavones, and catechins. A PubMed search was conducted in September 2007. Articles were selected if they provided risk ratios (relative risk or odds ratio) for lung cancer and were of observational design (cohort, case-control, or case-cohort). Three of 12 studies reported a significantly lower risk of lung cancer with a high intake of flavonoids, whereas 1 study reported a significantly increased risk. After stratification by type of flavonoid, catechin intake was no longer associated with lung cancer risk in 3 of 4 studies available. For tea, 4 of 20 studies reported significantly reduced risks with high intake. Two studies found significantly increased risk ratios, but both were older studies. Findings were similar for green and black tea but became more significant when only methodologically sounder cohort studies were considered. When tea intake and lung cancer were studied among never- or former smokers to eliminate the confounding effect of smoking, 4 of 7 reported associations were significantly protective. In general, the studies on tea, flavonoids, and lung cancer risk indicate a small beneficial association, particularly among never-smokers. More well-designed cohort studies, in particular for catechins, are needed to strengthen the evidence on effects of long-term exposure to physiological doses of dietary flavonoids.


Introduction

Tea consumption has been associated, both positively and negatively, with human cancer for several decades. The first epidemiological report on tea and cancer was published in 1966 (1). Since then, an increasing number of epidemiological studies on tea intake and cancer have appeared. A PubMed search conducted in September 2007 with the keywords “tea and cancer and epidemiology” yielded 556 hits. In recent years the collective evidence available for several types of cancer has been summarized in systematic reviews and meta-analyses (2–4), but to date, no such review has been published for lung cancer.

Tea, from a biological standpoint, is not a clearly defined substance. All tea is produced from the leaves of *Camellia sinensis*, but differences in processing result in several types of tea, of which green and black tea are the most consumed worldwide. Moreover, tea is a complex mixture of a large number of bioactive components, including catechins, flavonols, lignans, and phenolic acids. Theaflavins and thearubigins are present only in black tea as a result of oxidative processes (5). All types of tea and the major phenolic compounds present in tea have been the subject of epidemiological studies. The debate is still open as to which of these phenolic compounds might be of primary importance, whether the combination of compounds is essential, or if perhaps unknown components might be responsible for any health-modulating effects of tea.

An earlier review on flavonoids and chronic diseases (6) found evidence suggestive of a lower risk of lung cancer with a higher intake of flavonols/flavones. However, at the time, only 4 cohort studies were available. Data from studies on asthma incidence (7) and lung function (8) also suggested beneficial effects from flavonoids. In an animal study, where rats were given the major flavonol quercetin for 11 wk, the highest tissue...
concentrations were found in the lung (9). Taken together, these data suggested a beneficial effect of tea and/or flavonoids on lung health. This article provides an overview of observational epidemiological studies considering lung cancer incidence or mortality in relation to intake of green tea, black tea, flavonols/flavones, and catechins.

Methods

A search in the PubMed database was conducted in September 2007 using the keywords tea, flavon*, flavan*, catechin, polyphenol, cancer, tumor, cohort, case-control, case-cohort, intervention, meta-analysis, and epidemiology*. Reference lists of original articles on tea or flavonoids and lung cancer and reviews on tea or flavonoids and cancer were checked for relevant studies. Articles were selected for this review if they provided risk ratios [relative risk or odds ratio (OR)] for lung cancer and were of observational design (cohort, case-control, or case-cohort). Two studies were excluded because no risk ratios were presented (10,11). Studies on both incidence and mortality were included, but only 2 articles used lung cancer mortality data (12,13). From the articles, we retrieved the number and gender of the participants, years of follow-up (cohort and case-cohort studies only), and type of tea and/or flavonoids studied. The most adjusted risk estimates, comparing the highest versus the lowest intake category, corresponding 95% confidence intervals (CI), and P-values for dose-response trend tests were extracted for this review. If the original article did not present aggregated risk estimates, data for subgroups (e.g., male/female, smokers/nonsmokers) were taken instead. If the 3 studies that did not specify the type of tea were from the United States, Canada, and Sweden and were assumed to pertain to black tea. Flavonols and flavones were grouped together because the intake of flavonols is minor compared with the intake of flavonoids.

Case-control studies are vulnerable to recall bias, a phenomenon that leads to attenuation of associations and that occurs because diseased subjects may remember their diet differently from control subjects. Therefore, results from cohort studies and case-control studies were also discussed separately. A second major methodological issue in the analysis of observational studies is confounding. Confounding is particularly important when weak associations are studied in the presence of strong confounders. In the case of the tea/flavonoid-lung cancer association, smoking is one such strong confounder. Even after meticulous adjustment for smoking behavior, residual confounding may exist. To reduce the residual confounding presented by the strong smoking confounder, we also summarized studies that only considered never- or former smokers who had quit >20 y ago.

### Results

Twelve studies, including 8 cohort studies, reported on the association between intake of flavonoids and lung cancer incidence (Table 1). None of the flavonoid studies considered lung cancer mortality. All studies, except those by Arts et al. (18,19) reported risk estimates for flavonols/flavones. More recent studies have started to include catechins as well. Three articles reported a significantly lower risk of lung cancer with a high intake of flavonoids (15,17,20), whereas 1 article (24) reported a significantly increased risk. The association between flavonol/flavone intake and lung cancer incidence was similar to that for flavonoids as a whole, but leaving out the methodologically less strong case-control studies allowed a stronger suggestion of a protective association to emerge. Of the 6 cohort studies, 3 showed a significant inverse association, and 3 showed no effect. Only 1 of 4 studies on catechins and lung cancer found a significant effect, with a risk ratio of 0.94 and a 95% CI of 0.91–0.98 (20). Leaving out the case-control study by Lagiou et al. (24) did not change the findings for catechins.

On the association of tea and lung cancer, 20 studies were published, including 6 cohort studies (Table 2). Two of the cohort studies used data for cancer mortality instead of incidence (12,13). Two studies were excluded from this overview because they did not report a risk ratio estimate: Heilbrun et al. (10), who were the first to report on tea and lung cancer in 1986, found no significantly different age-adjusted lung cancer proportion for frequent consumers of black tea. Huang et al. (11) only mentioned that the association between green tea and jasmine tea and lung cancer in their small case-control study was not significant. The overview of all studies on tea and lung cancer is fairly symmetrical, although it appears slightly skewed toward a protective association of tea intake (Fig. 1). Four risk ratios reported were significantly below 1 (27,34–36). Two studies reported risk ratios that were significantly higher than 1 (12,31). Both were older studies, and Kinlen et al. (12) did not report a CI. Stratifying by type of tea consumed did not substantially change the distribution of risk estimates (data not shown). When the case-control studies were omitted from consideration, few studies remained. Of the 3 cohort studies on black tea, only the study by Kinlen et al. (12) showed a significantly increased risk for lung cancer. For green tea, the

### Table 1

<table>
<thead>
<tr>
<th>First author (ref)</th>
<th>Country</th>
<th>Year</th>
<th>Participants, n</th>
<th>Sex</th>
<th>Follow-up time, y</th>
<th>Type of flavonoids</th>
<th>RR</th>
<th>(95% CI)</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hertog (14)1</td>
<td>Netherlands</td>
<td>1994</td>
<td>740 M</td>
<td>5</td>
<td>Flavonoids</td>
<td>1.02 (0.51 – 2.04)</td>
<td>0.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knekt (15)</td>
<td>Finland</td>
<td>1997</td>
<td>9,959 MF</td>
<td>24</td>
<td>Flavonols</td>
<td>0.53 (0.29 – 0.97)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldbohm (16)</td>
<td>Netherlands</td>
<td>1998</td>
<td>120,852 MF</td>
<td>4</td>
<td>Flavonols</td>
<td>0.99 (0.69 – 1.42)</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hirvonen (17)</td>
<td>Finland</td>
<td>2001</td>
<td>27,110 M</td>
<td>6</td>
<td>Flavonols</td>
<td>0.56 (0.45 – 0.69)</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arts (18)</td>
<td>Netherlands</td>
<td>2001</td>
<td>728 M</td>
<td>10</td>
<td>Catechins</td>
<td>0.92 (0.41 – 2.07)</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knekt (7)</td>
<td>Finland</td>
<td>2002</td>
<td>5,218 M</td>
<td>30</td>
<td>Flavonols</td>
<td>0.64 (0.39 – 1.04)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arts (19)</td>
<td>U.S.A.</td>
<td>2002</td>
<td>34,651 F</td>
<td>13</td>
<td>Catechins</td>
<td>0.94 (0.72 – 1.23)</td>
<td>0.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wright (20)</td>
<td>Finland</td>
<td>2004</td>
<td>27,111 M</td>
<td>11</td>
<td>Catechins + flavonols</td>
<td>0.94 (0.91 – 0.98)</td>
<td>0.005</td>
<td></td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Case-control studies</th>
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<tbody>
<tr>
<td>Garcia-Closas (21)</td>
</tr>
<tr>
<td>De Stefani (22)</td>
</tr>
<tr>
<td>Le Marchand (23)</td>
</tr>
<tr>
<td>Lagiou (24)</td>
</tr>
</tbody>
</table>

| Flavonols | 1.83 (1.22 – 2.72) | 0.003 |

1 RR: relative risk for prospective cohort studies; OR for case-control studies; 95% CI in parentheses.
2 Lung cancer and gastrointestinal tract cancer combined.
3 Number of cases/controls.
study by Nakachi et al. (27) was the only 1 of 3 cohort studies that found a significantly decreased risk for lung cancer.

To study the association between tea intake and lung cancer incidence without the confounding effect of smoking, studies reporting risk estimates for never- or former smokers are summarized in Figure 2. Four of seven studies that reported associations among nonsmokers showed a significant protective association for a high intake of tea. The other 3 associations were not significantly different from 1. All studies were among women, presumably because in most countries there are too few never-smoking men to conduct meaningful analyses. In the studies by Kubik et al. (37,40), nonsmokers were defined as women who had never smoked and women who had quit 20 y ago. The other 3 studies included never-smokers only. Only 2 studies on flavonoid intake and lung cancer incidence presented risk estimates for never-smokers. Garcia-Closas et al. (21) reported that findings were similar to those for the whole sample (i.e., a nonsignificant risk ratio of 0.98). Lagiou et al. (24) likewise found no significant interaction between smoking status and flavonoid intake, with risk estimates that were comparable to those for the whole group.

Discussion

The collective evidence available so far from observational epidemiological studies on tea, flavonoids, and lung cancer risk tends toward a small beneficial association for green and black tea, particularly among never-smokers, and for flavonols/flavones but not for catechins. Studies that report increased risks with a high intake of tea are mostly older studies that were published at a time when tea was considered a possible car-
cinogenic and mutagenic (10,31). Several authors found that in the Ames test, 1 cup of black or green tea was more mutagenic than the smoke condensate of 1 cigarette (31,41). Epidemiological data published later have not confirmed these concerns. Peters et al. (42) found evidence for publication bias in a meta-analysis on tea consumption and risk of stroke. We have not examined publication bias. However, it seems unlikely that studies finding increased lung cancer risks with increased tea or flavonoid consumption would remain unpublished, given the increased risk ratios reported in early studies and also in the light of more recent reports regarding the increased mortality risks that seem to be associated with taking antioxidant supplements, particularly among smokers (43,44). Studies that found increased risks with higher tea or flavonoid intake were mostly of the case-control design. Only 1 cohort study found a risk estimate that was significantly above 1; the 1988 study by Kinlen et al. (12). In this study, tea intake was adjusted for smoking only but not for other risk factors.

Accurate assessment of exposure to tea and/or flavonoids is not easy. In general, food frequency questionnaires were not designed to assess tea or flavonoid intake. In recent years, assessment of tea consumption has received more attention (45), but certainly baseline measurements of the older epidemiological studies have yielded imprecise exposure estimates. Even if the level of tea consumption is assessed accurately, differences in cultivars and production methods and in brewing methods at home also significantly influence the tea composition (46) and, consequently, the internal exposure to bioactive ingredients. Several databases have been used to estimate flavonoid intake from dietary data. The Dutch values (46–49) that were most frequently used in epidemiological studies are now part of the comprehensive USDA flavonoid database (50), which has rigorous quality control. It is my hope that more studies will be added to this database in the near future. Inaccurate assessment of exposure to tea/flavonoids has probably led to nondifferential misclassification and an underestimation of the true associations in the epidemiological studies presented here.

Although lung cancer is treated here as a single disease, etiologically and histologically clearly distinct types of lung cancer can be distinguished. Yet few authors of articles on this subject have stratified their data by type of lung cancer. Le Marchand et al. (23) found a stronger inverse trend with quercetin intake among cases with squamous cell carcinoma (OR in the highest quartile = 0.5; 95% CI = 0.2–1.9) compared with cases with adenocarcinoma (OR = 0.9; 95% CI = 0.4–2.0). Similarly, Zhong et al. (35) also reported a lower OR for nonsmoking women with nonadenocarcinomas compared with adenocarcinomas, but the numbers of cases were small, and trends were not significant. Baker et al. (39), on the other hand, found similar associations for black tea intake with different subtypes (adeno-, squamous cell, small cell, and large cell carcinoma) of lung cancer. More research is needed to determine whether lung cancer type is of importance.

Residual confounding occurs if confounders, extraneous factors that are associated with both the outcome and the exposure under study, are not or insufficiently accounted for in the statistical analysis. Studying associations in never-smokers is an effective way of ruling out residual confounding by smoking. Zhong et al. (35) have elegantly shown that the manner in which models are adjusted for confounding by smoking can greatly influence the results. The OR between green tea drinking and lung cancer among women was 1.69 (95% CI = 0.78–3.62) without adjustment for smoking. When 4 categories of pack-years were added to the model, the OR changed to 1.09, whereas adding the number of cigarettes per day (as 3 categories) instead gave an OR of 1.23. A smoothing technique, which allows more precise adjustment for confounding, changed the estimated OR to 1.23 and 0.94 for pack-years and number of cigarettes per day, respectively. So, with use of different techniques to adjust for smoking, the effect estimate changed significantly from 1.69 to 0.94, although none of the estimates was significant. In the same article, Zhong and co-workers (35) also reported the OR for never-smokers, which was 0.65 (95% CI = 0.45–0.93) and significant. Thus, residual confounding for strong confounders such as smoking can lead to higher risk estimates in populations where smoking is associated with tea drinking. Our overview of studies among nonsmokers suggests that, indeed, protective associations become more distinct in this group. On the other hand, when tea drinking is associated with a healthy lifestyle, associations may become more beneficial as a result of residual confounding. More research among never-smokers is needed to resolve this issue, taking into account exposure to environmental smoke and other determinants of lung cancer among never-smokers.

In tea-drinking populations, the correlation between tea intake and flavonoid intake is high. For example, in the Zutphen Elderly Study in The Netherlands, the correlation between catechins and tea was 0.98, making the 2 variables essentially interchangeable (18). Which approach is preferred then, the food-based one or the component-based approach? Of course that depends on the hypothesized mechanism: if flavonoids are considered to be the active compounds in tea, then it makes more sense to look at flavonoids directly. In countries where tea intake is low, such as many Mediterranean countries, other sources of flavonoids will become important. However, if other compounds in tea, or combinations of compounds, are believed to be important, then tea would be the preferred exposure. In that case, calculating flavonoid intake will merely introduce additional error. The results presented in this overview show that a similar picture emerges, whether tea or flavonoids are used as exposure estimates. For catechins, too few studies have been published to draw any conclusions. Despite its drawbacks, observational epidemiology is the only type of research that is able to assess the effects of long-term exposure to physiological doses of bioactive compounds on real disease endpoints. It therefore has great value in the study of the association between intake of tea and flavonoids and lung cancer risk. Accumulating more data from well-designed studies, together with more

![FIGURE 2](#) Risk estimates from observational epidemiological case-control studies on intake of tea and risk of lung cancer among never-or former (≥20 y ago) smokers. Plotted are the most adjusted RR with 95% CI (if reported) for the highest versus the lowest category of intake, sorted by increasing RR. G, green tea; B, black tea.
mechanistic intervention studies, will bring us closer to firm conclusions about the health effects of tea and its bioactive ingredients.

Other articles in this supplement include references (51–60).

**Literature Cited**


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