Dietary flavonoid intake and colorectal cancer: a case–control study

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(Received 25 February 2009 – Revised 21 July 2009 – Accepted 27 July 2009 – First published online 7 September 2009)

Dietary flavonoids may reduce the risk of developing colorectal cancer. Flavonoids are widely distributed in foods of plant origin, though in the UK tea is the main dietary source. Our objective was to evaluate any independent associations of total dietary and non-tea intake of four flavonoid subclasses and the risk of developing colorectal cancer in a tea-drinking population with a high colorectal cancer incidence. A population-based case–control study (264 cases with histologically confirmed incident colorectal cancer and 408 controls) was carried out. Dietary data gathered by FFQ were used to calculate flavonoid intake. Adjusted OR and 95 % CI were estimated by logistic regression. Stratification by site of cancer and assessment of individual flavonoids showed a reduced risk of developing colon but not rectal cancer with increasing non-tea quercetin intake (OR 0·5; 95 % CI 0·3, 0·8; Ptraj < 0·01). We concluded that flavonols, specifically quercetin, obtained from non-tea components of the diet may be linked with reduced risk of developing colon cancer.

Flavonoids: Flavonols: Quercetin: Colorectal cancer: Case–control studies: Epidemiology

Colorectal cancer is the third most common cancer in the developed world(1) with incidence in Scotland being among the highest in Europe(2). Critical assessment of potential risk factors suggests that diets rich in plant-based foods, such as fruit and vegetables, may reduce the risk of developing colorectal cancer(3,4). Though the mechanism by which these foods exert a protective effect is unclear, one hypothesis is the presence of high levels of potentially anti-carcinogenic phytochemicals(5). Flavonoids are a large and diverse group of phytochemicals and research into their anti-carcinogenic potential with animal and cellular model systems supports a protective role(6,7). Structurally distinct subclasses of flavonoids have varying capacities to modulate the progression of colorectal cancer, acting as antioxidants(8,9), anti-inflammatory agents(10–13), anti-proliferative agents(14–16) or as regulators of signal transduction pathways(17,18). Of all the tissues in the human body, the large intestine may be exposed to the presence of high levels of potentially anti-carcinogenic phytochemicals(5). Flavonoids are a large and diverse group.
of flavonoid intake may be misleading, with black tea being
the major source of flavonoids in the Scottish population(26).
Additionally, when assessing associations between flavonoid
intake and disease risk in populations where high levels of
te are commonly consumed, misclassification of risk may
occur if non-tea dietary sources are neglected(24).

The present study investigated the associations between
dietary flavonoid intake and the risk of developing colorectal
cancer in the North East of Scotland. The aim was to assess
whether this relationship varied when considering total dietary
and non-tea intake of four flavonoid subclasses (flavonols,
catechins (flavon-3-ols), procyanidins and flavanones).

Materials and methods

Subjects and study design

Participants were recruited as part of a population-based
case–control study of colorectal cancer investigating colorec-
tal cancer and genetic polymorphisms in xenobiotic metabolis-
ing enzymes in the North East of Scotland(33). Patients (cases)
presenting with their first primary cancer, diagnosed between
September 1998 and February 2000, and resident in the
Grampian Health Board area were approached after histologi-
cal confirmation of incident invasive tumours of the colon
or rectum. Population-based controls, frequency matched to
cases, were selected from the Grampian Community Health
Index (a list of all those registered with a general practitioner
in the National Health Service). Controls who declined to
participate were replaced. The present study was conducted
according to the guidelines laid down in the declaration of
Helsinki and all procedures involving human subjects and
patients were approved by the Joint Ethical Committee of
the Grampian Health Board and the University of Aberdeen.
Written consent was obtained from all participants.

Dietary assessment and analysis

With the permission of their general practitioner, subjects
were contacted by mail and asked to complete the Scottish
Collaborative Group FFQ version 6.31 (www.foodfrequen-
cy.org.uk) and a questionnaire which included questions on
a range of sociodemographic and lifestyle factors relevant to
colorectal cancer aetiology. Of those invited to participate,
62 % of cases and 61 % of controls completed and returned
our questionnaires (264 cases and 408 controls). Of these,
seven subjects (three cases and four controls) were excluded
because their FFQ were returned incomplete(33).

Dietary data were converted into estimates of nutrient
intakes using the UK McCance and Widdowson’s food com-
position tables(34). Twelve subjects (six cases and six controls)
were excluded on the basis of implausible total energy intakes
(≥ 3 SD of mean intake)(35). Total dietary and non-tea flavonol,
flavon-3-ol, procyanidin and flavanone intakes were computed
using a flavonoid food composition database compiled by
systematic review of the available composition literature
representing foods consumed in the UK(26). In this database,
as numerous conjugated forms of flavonoids are commonly
present in foods, all food content and intake values are
expressed in their free (aglycone) form. Additionally, each
subclass is a summary of individual flavonoid compounds
as outlined: flavonols – quercetin, kaempferol and myricetin;
flavones – lutein and apigenin; flavon-3-ols – catechin,
epigallocatechin, epigallocatechin gallate, epicatechin gallate and gallocatechin; procyanidins – types
BI-IV; flavanones – hesperidin and naringenin. The
150-item semi-quantitative FFQ was previously tested in the
local population and compared with 4 d weighed intake
records for macro- and micronutrients as well as each
flavonoid subclass(35,36). Relatively good Spearman rank
correlation and agreements were found for flavonols, procya-
nidins and flavon-3-ols (correlations 0·70–0·94), but not for
flavanones and flavones, 0·33 and 0·18 respectively. As a
result, flavone data were not used. The FFQ included
questions on frequency of consumption of each food item in
the last year as ‘rarely or never’, ‘monthly’ or 1, 2, 3, 4, 5,
6, 7 d per week and amount (‘measures’) of consumption of
a range of food items. The measure for each food was
designed to be a small portion or unit measure such as a
tablespoon; hence a single standard portion of a particular
food might be two measures(36).

Statistical analysis

SPSS (version 13; SPSS, Inc., Chicago, IL, USA) and Stata 8
(StataCorp LP, College Station, TX, USA) were used for sta-
tistical analysis. Case and control demographic and lifestyle
factors were summarised. Independent t tests and χ² tests
assessed the significance of any differences. The mean
values and standard deviations of measures of tea, fruit and
vegetables were calculated. The measure for tea was a cup,
while fruit and vegetable measures were the total number of
single portions per d as reported on the FFQ.

The distributions of flavonoid variables were checked. Log
transformation normalised the non-tea flavonoid intake, but
not total flavanone intake. Median intake and interquartile
range of flavonoid subclasses and individual compounds
were computed for cases and controls before investigating
any significant differences by applying the non-parametric
Wilcoxon rank-sum test. The correlation between flavonoid
intakes and other dietary and non-dietary factors (for example,
BMI) were calculated using the Spearman rank correlation
coefficients.

Flavonoid, tea, fruit and vegetable intakes were adjusted
for total energy using the nutrient residual method(37) before
division of subjects into quartiles of intake (lowest to highest).
The odds of developing colorectal cancers with increasing
intake of flavonoids were then computed. Multivariate
adjusted OR were adjusted for sex, age, correlated dietary
variables and potential confounders; factors making a
significant contribution (likelihood ratio test P<0·1) were
retained in the regression model, including variables with
significant correlations with flavonoid intake. The likelihood
ratio test was used to assess trends across the quartiles of
flavonoid intake (P trend). The primary analysis was for all
colorectal cancers combined; secondary analyses were carried
out for colon and rectal cancers separately.

Results

A total of 261 colorectal cancer patients (cases) (186 and
seventy-five with colon and rectal cancer, respectively)
and 404 population-based control subjects were included in the full analysis of the present investigation (Table 1). Cases (age range 39–92 years) tended to be older than controls (age range 32–88 years) and a higher proportion of cases were male. Although fewer cases were current smokers ($P<0.01$), more were ex-smokers ($P<0.01$) than controls. A higher percentage of cases reported a family history of colorectal cancer compared with controls, while non-steroidal anti-inflammatory drugs were more frequently taken by controls.

When stratified by sex, energy intake of cases and controls did not differ significantly, though energy intake in men ($10.5 \pm 3.8$ MJ/d) was significantly higher than in women ($9.1 \pm 3.9$ MJ/d) for both cases and controls ($P<0.05$). Significantly higher total dietary intake of flavonoids, procyandins and flavanones was recorded for cases than controls. The converse was observed for non-tea flavonol, procyanidin and flavon-3-ol intake, with controls reporting higher intakes (Table 2).

Tea intake was highly correlated with flavonol, procyanidin and flavon-3-ol intakes ($r > 0.90; P<0.001$). Exclusion of tea as a potential source of flavonoids yielded markedly lower estimates of intake (Table 2), with black tea consumption accounting for between 71 and 93% of total flavonol, procyanidin and flavon-3-ol intakes. After exclusion of tea flavonoids, gallated catechin esters (epigallocatechin gallate, epicatechin gallate and epigallocatechin) were replaced with catechin and epicatechin as the main contributors to dietary flavon-3-ol intake, while quercetin remained the main flavonol consumed before and after adjustment for tea consumption.

Colorectal cancer patients consumed more tea than control subjects ($P<0.01$), drinking an average of 3-7 (SD 0-1) and 3-3 (SD 0-1) cups per d, respectively. There were no significant differences between reported fruit and vegetable intake between cases and controls ($1.9 \pm 1.8$ and $1.9 \pm 1.9$ SD 1-9) measures of fruit per d and 3-1 (SD 4-2) and 3-6 (SD 3-9) measures of vegetables per d for cases and controls, respectively). Controls under the age of 55 years consumed less tea and more vegetables than controls over 55 years ($P<0.01$), but this effect was not seen in cases. This had an impact on intake of both total and non-tea flavonoids, with controls reporting a lower intake of flavonols ($P<0.05$) and a higher intake of procyanidins ($P<0.05$) and flavon-3-ols ($P<0.01$) than cases.

Increasing energy-adjusted black tea consumption demonstrated a weak increased risk of developing colorectal cancer (OR 1.5; 95% CI 1.0, 2.4; highest v. lowest quartile; $P_{\text{trend}} = 0.08$), but this was attenuated after adjustment for confounding variables. Energy-adjusted vegetable intake was significantly associated with colon cancer (highest quartile of energy-adjusted intake OR 0.6; 95% CI 0.3, 0.9; $P_{\text{trend}} = 0.03$). Again this association was not seen after multivariate adjustment (highest v. lowest quartile of energy-adjusted intake OR 1.0; 95% CI 0.6, 1-8; $P_{\text{trend}} = 0.52$). No effect was seen with rectal cancer. There was also no evidence of a relationship between fruit consumption and colorectal cancers (data not shown).

No association between total dietary flavonol, procyanidin or flavon-3-ol intake and risk of developing colorectal cancer was observed (Table 3). There was a weak ($P_{\text{trend}} = 0.04$) trend towards increased risk of colorectal cancer with higher levels of flavanone intake. Stratification by cancer site (Table 4) strengthened this observation, with a significant trend apparent for colon cancer (multivariate OR 1.3; 95% CI 0.7, 2.4; highest v. lowest quartile; $P_{\text{trend}} < 0.01$).

Analysis of non-tea flavonoid intake indicated a significant inverse association between non-tea flavonol intake and risk of colorectal cancer ($P<0.05$), but not for non-tea procyanidin or flavon-3-ol intake (Table 3). Separate analyses of colon and rectal cancer cases demonstrated that non-tea flavonol intake was significantly associated with a reduced risk of developing colon (OR 0.5; 95% CI 0.3, 0.8; highest v. lowest quartile; $P_{\text{trend}} < 0.01$), but not rectal cancer in the adjusted model (Table 4). Further assessment of the relationship with intake of individual non-tea flavonol compounds highlighted an association between quercetin (highest v. lowest quartile multivariate adjusted OR 4.0; 95% CI 0.2, 0.8; $P_{\text{trend}} < 0.01$) and colon cancer (Table 5).

### Discussion

Associations between dietary intake of four different flavonoid subclasses and colorectal cancer risk were assessed in the present case–control study amongst men and women from the North East of Scotland. Total dietary flavonol, flavan-3-ol or procyanidin intakes were not associated with colorectal cancer risk. However, there was a weak negative trend with flavanone intake and colon cancer risk. Black tea and its flavonoids did not appear to be related to colorectal cancer risk in this population. An inverse association between colorectal cancers, more specifically colon cancer, and non-tea quercetin intake was observed.

While the retrospective nature of the case–control design of the present study makes it potentially susceptible to recall bias, the fact that the study has a population-based study design helps to minimise selection biases. A similar participation rate was achieved as in a previous UK postal...
contact study(38). In addition, response rates and the quality of completion of the dietary questionnaires in the cases and controls were comparable. Moreover, it is worth noting that assessment of known risk factors resulted in associations consistent with previous evidence(33), while reported energy intake was comparable with previous observations for this population. Multiple testing may also be a potential source of bias, though due to the relatively small sample size, the present study’s aim was hypothesis generating rather than hypothesis testing.

Table 2. Dietary flavonoid intakes of cases and controls (Medians and interquartile ranges (IQR))

<table>
<thead>
<tr>
<th>Flavonoid</th>
<th>Total dietary intake (mg/d)</th>
<th>Non-tea dietary intake (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases Median IQR</td>
<td>Controls Median IQR</td>
</tr>
<tr>
<td>Flavonols</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flavonols</td>
<td>32.5*** 22.6–40.3</td>
<td>28.6 17.4–40.5</td>
</tr>
<tr>
<td>Quercetin</td>
<td>20.2 14.7–24.9</td>
<td>18.1 11.9–25.0</td>
</tr>
<tr>
<td>Kaempferol</td>
<td>10.2* 5.7–12.9</td>
<td>8.0 5.0–12.8</td>
</tr>
<tr>
<td>Myricetin</td>
<td>2.1*** 5.7–12.9</td>
<td>1.9 1.1–2.8</td>
</tr>
<tr>
<td>Procyanidins B1–B4</td>
<td>39.3*** 25.8–40.9</td>
<td>34.1 19.2–50.0</td>
</tr>
<tr>
<td>Catechins</td>
<td>141.0** 83.6–180.6</td>
<td>119.2 73.3–188.8</td>
</tr>
<tr>
<td>(-)Epigallocatechin</td>
<td>25.7 12.9–32.2</td>
<td>19.3 6.7–32.2</td>
</tr>
<tr>
<td>(+)Catechin</td>
<td>7.5** 5.5–9.8</td>
<td>6.7 4.7–9.6</td>
</tr>
<tr>
<td>(-)Epicatetechin gallate</td>
<td>34.6 19.8–42.5</td>
<td>29.7 9.0–49.5</td>
</tr>
<tr>
<td>(-)Epicatechin gallate</td>
<td>39.0 19.6–48.8</td>
<td>29.0 10.0–48.7</td>
</tr>
<tr>
<td>(-)Gallocatechin</td>
<td>12.5* 6.3–15.7</td>
<td>9.4 3.5–15.7</td>
</tr>
<tr>
<td>Flavonoids 1–3-ols</td>
<td>19.0*** 5.4–36.4</td>
<td>13.4 2.7–32.1</td>
</tr>
<tr>
<td>(-)Naringenin</td>
<td>8.9*** 2.5–16.7</td>
<td>6.6 1.4–15.2</td>
</tr>
<tr>
<td>(-)Hesperidin</td>
<td>9.8*** 3.0–19.3</td>
<td>7.2 1.4–16.6</td>
</tr>
</tbody>
</table>

Median was significantly different from that of the controls: * P<0.05, ** P<0.01, *** P<0.001.

Table 3. Total dietary and non-tea flavonoid intakes by quartile of intake and risk of colorectal cancer (261 cases and 404 controls) (Odds ratios and 95 % confidence intervals)

<table>
<thead>
<tr>
<th>Flavonoids</th>
<th>Total dietary flavonoids</th>
<th>Non-tea flavonoids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Energy adjusted†</td>
<td>Multivariate adjusted‡</td>
</tr>
<tr>
<td>Intake (mg)</td>
<td>OR 95 % CI</td>
<td>OR 95 % CI</td>
</tr>
<tr>
<td>Flavonols</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 &lt; 19.30</td>
<td>1.0 Reference</td>
<td>1.0 Reference</td>
</tr>
<tr>
<td>2 19.31–30.40</td>
<td>1.2 0.7, 1.9</td>
<td>1.0 0.6, 1.7</td>
</tr>
<tr>
<td>3 30.41–40.40</td>
<td>1.5 1.0, 2.3</td>
<td>1.3 0.8, 2.1</td>
</tr>
<tr>
<td>4 &gt; 40.41</td>
<td>1.0 0.6, 1.6</td>
<td>0.8 0.5, 1.3</td>
</tr>
<tr>
<td>R²rand</td>
<td>0.20 0.37</td>
<td>0.03</td>
</tr>
<tr>
<td>Procyanidins B1–B4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 &lt; 21.30</td>
<td>1.0 Reference</td>
<td>1.0 Reference</td>
</tr>
<tr>
<td>2 21.31–36.40</td>
<td>1.1 0.7, 1.7</td>
<td>0.9 0.6, 1.5</td>
</tr>
<tr>
<td>3 36.41–49.80</td>
<td>1.4 0.9, 2.1</td>
<td>1.2 0.7, 1.9</td>
</tr>
<tr>
<td>4 &gt; 49.81</td>
<td>0.9 0.6, 1.4</td>
<td>0.7 0.4, 1.2</td>
</tr>
<tr>
<td>R²rand</td>
<td>0.19 0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>Flavanones 1–3-ols</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 &lt; 67.10</td>
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<td>1.0 Reference</td>
</tr>
<tr>
<td>2 67.11–119.20</td>
<td>0.8 0.5, 1.2</td>
<td>0.7 0.4, 1.1</td>
</tr>
<tr>
<td>3 119.21–188.80</td>
<td>1.7* 1.1, 2.7</td>
<td>1.3 0.8, 2.2</td>
</tr>
<tr>
<td>4 &gt; 188.81</td>
<td>0.8 0.5, 1.3</td>
<td>0.6 0.4, 1.0</td>
</tr>
<tr>
<td>R²rand</td>
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<td>0.08</td>
</tr>
<tr>
<td>Flavanones</td>
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<td></td>
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<tr>
<td>1 &lt; 2.73</td>
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<td>1.0 Reference</td>
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<tr>
<td>2 2.74–13.40</td>
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<td>1.5 0.9, 2.5</td>
</tr>
<tr>
<td>3 13.41–32.18</td>
<td>1.2 0.8, 1.9</td>
<td>1.4 0.9, 2.4</td>
</tr>
<tr>
<td>4 &gt; 32.19</td>
<td>1.3 0.9, 2.1</td>
<td>1.6 1.0, 2.6</td>
</tr>
</tbody>
</table>

* P<0.05.
† Energy adjusted.
‡ Adjusted for energy, age at diagnosis, family history, non-steroidal anti-inflammatory drugs, aspirin, Mn, riboflavin, vitamin C, folate.
Our estimates of intake of flavonols and catechins are comparable with other tea-drinking populations and higher than non-tea-drinking countries such as Italy and America (20–25), while flavanone intake was comparable with a Finnish study (23), but lower than an Italian population study (28). Intakes of flavonols, procyanidin and flavon-3-ols were higher among controls, but not cases, when compared with another recently published Scottish colorectal cancer study (29). One reason for this may be a difference in the age distribution of subjects between the studies; in the present study.

### Table 4. Association between total dietary and non-tea flavonoid intakes by quartile of intake and colon and rectal cancers†

(Odds ratios and 95% confidence intervals)

<table>
<thead>
<tr>
<th>Flavonoids...</th>
<th>Total dietary</th>
<th>Non-tea</th>
<th>Total dietary</th>
<th>Non-tea</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
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<tr>
<td>Flavonols</td>
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<tr>
<td>2</td>
<td>0.9</td>
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<td>0.4, 1.1</td>
</tr>
<tr>
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<td>0.7</td>
<td>0.4, 1.2</td>
</tr>
<tr>
<td>4</td>
<td>0.7</td>
<td>0.4, 2.1</td>
<td>0.5*</td>
<td>0.3, 0.8</td>
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<tr>
<td></td>
<td><strong>P</strong>&lt;0.05</td>
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<td>0.96</td>
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<tr>
<td>Procyanidins B1–B4</td>
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<td>1.4</td>
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<td>0.5, 1.9</td>
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<tr>
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<td><strong>P</strong>&lt;0.05</td>
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<td></td>
<td><strong>P</strong>&lt;0.05</td>
<td>0.01</td>
<td>0.51</td>
<td></td>
</tr>
</tbody>
</table>

*P*<0.05.
†Multivariate adjusted for energy, age at diagnosis, family history, non-steroidal anti-inflammatory drugs, aspirin, Mn, riboflavin, vitamin C, folate.

Our estimates of intake of flavonols and catechins are comparable with other tea-drinking populations and higher than non-tea-drinking countries such as Italy and America (20–25), while flavanone intake was comparable with a Finnish study (23), but lower than an Italian population study (28). Intakes of flavonols, procyanidin and flavon-3-ols were higher among controls, but not cases, when compared with another recently published Scottish colorectal cancer study (29). One reason for this may be a difference in the age distribution of subjects between the studies; in the present study.

### Table 5. Association between non-tea flavonol intake by quartile of intake and colorectal cancers†

(Odds ratios and 95% confidence intervals)

<table>
<thead>
<tr>
<th>Flavonoids...</th>
<th>Intake (mg)</th>
<th>Colorectal cancer (261 cases)</th>
<th>Colon cancer (186 cases)</th>
<th>Rectal cancer (75 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Quercetin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&lt;4.76</td>
<td>1.0  Reference</td>
<td>1.0  Reference</td>
<td>1.0  Reference</td>
</tr>
<tr>
<td>2</td>
<td>4.77–6.87</td>
<td>0.8  0.5, 1.3</td>
<td>0.8  0.5, 1.4</td>
<td>0.7  0.4, 1.5</td>
</tr>
<tr>
<td>3</td>
<td>6.88–9.55</td>
<td>0.6*  0.4, 1.0</td>
<td>0.4*  0.2, 0.8</td>
<td>0.9  0.5, 1.7</td>
</tr>
<tr>
<td>4</td>
<td>&gt;9.56</td>
<td>0.6**  0.4, 0.9</td>
<td>0.4**  0.2, 0.8</td>
<td>0.9  0.4, 1.9</td>
</tr>
<tr>
<td></td>
<td><strong>P</strong>&lt;0.05</td>
<td>0.01</td>
<td>0.01</td>
<td>0.38</td>
</tr>
<tr>
<td>Kaempferol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&lt;0.50</td>
<td>1.0  Reference</td>
<td>1.0  Reference</td>
<td>1.0  Reference</td>
</tr>
<tr>
<td>2</td>
<td>0.51–0.80</td>
<td>1.2  0.7, 1.9</td>
<td>1.2  0.7, 2.1</td>
<td>1.1  0.5, 2.3</td>
</tr>
<tr>
<td>3</td>
<td>0.81–1.10</td>
<td>1.3  0.8, 2.0</td>
<td>1.2  0.7, 2.1</td>
<td>1.3  0.6, 2.8</td>
</tr>
<tr>
<td>4</td>
<td>&gt;1.11</td>
<td>1.1  0.6, 2.0</td>
<td>1.2  0.7, 1.1</td>
<td>1.0  0.4, 2.3</td>
</tr>
<tr>
<td></td>
<td><strong>P</strong>&lt;0.05</td>
<td>0.01</td>
<td>0.01</td>
<td>0.98</td>
</tr>
<tr>
<td>Myricetin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&lt;0.04</td>
<td>1.0  Reference</td>
<td>1.0  Reference</td>
<td>1.0  Reference</td>
</tr>
<tr>
<td>2</td>
<td>0.05–0.20</td>
<td>0.6  0.4, 0.9</td>
<td>0.6*  0.4, 1.0</td>
<td>0.6  0.3, 1.2</td>
</tr>
<tr>
<td>3</td>
<td>0.21–0.44</td>
<td>0.7  0.5, 1.1</td>
<td>0.6*  0.3, 0.9</td>
<td>1.2  0.6, 2.3</td>
</tr>
<tr>
<td>4</td>
<td>&gt;0.45</td>
<td>0.7  0.5, 1.1</td>
<td>0.7  0.4, 1.2</td>
<td>0.8  0.4, 1.7</td>
</tr>
<tr>
<td></td>
<td><strong>P</strong>&lt;0.05</td>
<td>0.27</td>
<td>0.13</td>
<td>0.94</td>
</tr>
</tbody>
</table>

*P*<0.05, **P**<0.01.
†Adjusted for energy, age, education, family history, non-steroidal anti-inflammatory drugs, aspirin, vitamin C, folate, fruit and vegetables.
study both cases and controls were on average 6 years older than in the other study. Though a relatively small difference, in the UK tea consumption by the 64- to 74-year age group is 25 % higher than by the 50- to 64-year-olds(39).

The results of our regional North East of Scotland study are only partially consistent with those of the larger Scottish study of Theodoratou et al. (29). In their study, increasing total dietary flavonol (OR 0.73; P_trend < 0.02), quercetin (OR 0.68; P_trend < 0.001), catechin (OR 0.68; P_trend < 0.001), epicatechin (OR 0.74; P_trend < 0.05) and procyanidins (OR 0.78; P_trend < 0.05) intake significantly reduced the risk of developing colorectal cancer, while no effect was found for total flavonones or flavon-3-ols. The latter result is consistent with our findings; however, in contrast to Theodoratou et al. we did not observe a trend in risk with total flavonols, catechin or epicatechin intakes and colorectal cancer. One explanation may be that our findings may reflect the smaller sample size or the different age distribution of subjects. Alternatively it may be that, due to regional variations in diet within Scotland, our population drank more tea and consumed less fruit and vegetables, providing relatively lower non-tea sources of flavonoids. Our findings with regard to non-tea flavonoid intake reflect those of a large Italian case–control study(26). Researchers in the Italian study identified a positive trend against colorectal cancers with increasing intake of flavonols (OR 0.64; P_trend < 0.001), but not flavon-3-ols or flavonones in a population with high fruit and vegetable intake and infrequent tea consumption. Each of the now three case–control studies have utilised recently compiled and relatively comprehensive flavonoid composition databases, one developed in the UK reflecting the flavonoid content of foods commonly consumed in Europe(26) and the USA(40), unlike the previously published cohort studies, in which an earlier more limited Dutch database with regional additions were employed(27,41–43). Of earlier studies, only one reported significant associations between flavonoid intake and risk of colorectal cancer(23). The Iowa Women’s Health study, a cohort of 34,651 postmenopausal women, observed a significant inverse association between total flavon-3-ol intake and rectal cancer. The present study did not replicate these findings even when the analysis was limited to females only, but there were only twenty-eight women with rectal cancer in the present study. Black tea is not commonly consumed in America, and comparison of the US intake with the Scottish non-tea flavon-3-ol intake indicates that the Scottish non-tea intake (>8.5 mg/d) may be too low to detect a protective effect.

The lack of an association between black tea consumption and colorectal cancer risk is in agreement with previous findings(3). As total dietary flavonol, procyanidin and flavon-3-ol intakes were highly correlated with black tea consumption, a case has been made to study total and non-tea flavonoid intake separately(24). Assessment of these independent associations with risk of developing colorectal cancer suggests that flavonoids from dietary sources other than tea may modulate colorectal cancer risk.

Previous dietary flavonoid intake assessment in the North East of Scotland revealed that the main dietary sources of flavonoids were tea (46 % of the intake), onions (14 %), apples (10 %) and processed foods and beverages (13 %) for flavonols(44). This suggests that flavonoid intake from a diverse combination of fruit- and vegetable-based foods may be responsible for the observed inverse association.

Individual flavonoid compounds and their dietary sources have differing relative bioavailability(45). Consequently, when assessing several flavonoid subclasses in relation to disease, the sources and types of flavonoids could have different potential relationships with colorectal cancer. The structure–activity relationship of flavonoids provides an analytical example to support this observation. Ranking of the ability of flavonoids to scavenge different reactive oxygen and nitrogen species in both aqueous and lipophilic environments indicates that quercetin is a potent antioxidant in vitro(46,47). As large amounts of flavonoids remain unabsorbed in the lower gastrointestinal tract, they may exert their antioxidant effects at that site(46). An imbalance between cellular levels of reactive oxygen species and antioxidants can result in damage to DNA, leading to mutation and dysregulation of oncogenes or tumour-suppressor genes(46). Quercetin, as one of the most potent antioxidants in vitro, may act to minimise mutations. Suppression of cellular proliferation may also be structure dependent. For example, quercetin, but not catechin, can suppress proliferation of colon cancer cell lines(48). More recently quercetin has been reported to modulate cell growth signalling pathways(16,49–52). Finally, chronic inflammation is an important target for preventive measures against colon cancer, with non-steroidal anti-inflammatory drugs and aspirin, for example, being thought to reduce risk by up to 50 % (53,54). This is principally achieved through modulation of arachidonic acid release and its subsequent metabolism by cyclo-oxygenase and lipoxygenase, mediators of the inflammatory response(54). Flavonoids are known to modulate expression of these enzymes with quercetin, in particular, inhibiting their activity(8,12,13).

The inverse association observed between colorectal cancer risk and non-tea flavonol intake but not tea flavonoids in the present study is interesting and highlights the importance of assessing their different dietary sources in relation to disease risk. It is only the non-tea dietary sources of flavonols that are significantly associated with a protective effect against colorectal cancer. This may circumstantially suggest that other dietary factors in fruit and vegetables in addition to flavonols have important roles in preventing the pathogenesis of the disease. Further investigation of the effect of flavonols from different fruit and vegetables and their processed products is required to determine whether the observed association is due to flavonols per se or to the other as yet unidentified components of fruit and vegetables which are co-associated with flavonoids. Intervention studies comparing the effects of individual flavonoids with flavonoid-rich diets may be required to elucidate whether the main protective effects are actually due to these phytochemicals.

Acknowledgements

The original case–control study was funded by a grant from the National Hospitals Trust. The flavonoid analysis was financially supported by the Scottish Executive Environment and Rural Affairs Department and the Food Standards Agency.

J. A. M. K. led the development of the flavonoid database and analysis, contributed to the interpretation of results and
References


