Does an apple a day keep the oncologist away?

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Background: Apples have commonly been described as a healthy food. To understand better their role on risk of cancer at several sites, we analyzed data from multicenter case–control studies conducted between 1991 and 2002 in Italy.

Patients and methods: The studies included 598 patients with incident cancers of the oral cavity and pharynx, 304 of the oesophagus, 460 of the larynx, 1953 of the colorectum, 2569 of the breast, 1031 of the ovary and 1294 of the prostate. The comparison group included a total of 6629 patients admitted to the same network of hospitals as cases for acute, non-neoplastic diseases. Multivariate odds ratios (OR) were obtained with allowance for age, sex, study center, education, body mass index, tobacco smoking, alcohol drinking, total energy intake, vegetable consumption and physical activity.

Results: Compared with subjects reporting consumption of <1 apple/day, the ORs for ≥1 apple/day were 0.79 [95% confidence interval (CI) 0.62–1.00] for cancers of the oral cavity and pharynx, 0.75 (95% CI 0.54–1.03) for oesophagus, 0.80 (95% CI 0.71–0.90) for colorectum, 0.58 (95% CI 0.44–0.76) for larynx, 0.82 (95% CI 0.73–0.92) for breast, 0.85 (95% CI 0.72–1.00) for ovary and 0.91 (95% CI 0.77–1.07) for prostate.

Conclusion: This investigation found a consistent inverse association between apples and risk of various cancers.

Key words: cancer, case–control study, diet, fruit, risk factor

Introduction

Reviewing literature until 1997, the World Cancer Research Fund [1] reported an evidence of a protective effect of fruit on cancers of the oral cavity and pharynx, oesophagus, lung and stomach, a probable evidence on cancers of larynx, breast, pancreas and bladder, and a possible evidence for ovarian, endometrial, cervical and thyroid cancer. Likewise, an International Agency for Research on Cancer (IARC) Working Group [2] concluded that fruit reduces the risk of cancers of the oesophagus, stomach and lung, and possibly of the oral cavity, pharynx, colorectum, larynx, kidney and urinary bladder. However, the issue is still open to discussion and widely debated [3], particularly after recent findings from cohort studies that showed no association between fruit intake and risk of cancer [4, 5], including the cancers of the breast [6] and of the prostate [7].

Apples are a fruit of specific interest, since they are cheap and easy to store and transport, and thus are the most frequently consumed fruit, at least in Italy. Among the studies analyzing the association between consumption of apples and cancer risk, a favourable effect was reported on lung cancer [8–11], and a pooled analysis of cohort studies including more than 350 000 women and over 7000 cases of breast cancer, found a non-significant 3% reduction in breast cancer risk per 100 g/day intake [12, 13]. A population-based case–control study from China, based on almost 1500 cases, also found a reduction of breast cancer risk across subsequent quintiles of apple intake [14]. A case–control study from Uruguay found an inverse relation between apple consumption and colorectal cancer [15], one from Southern India with oral cancer [16] and another one from Sweden with renal cancer risk [17]. Moreover, a prospective study of Swedish women found a non-significant inverse association between apple consumption and renal cell cancer [18].

To understand better the role of apples on risk of cancer at several sites, we considered data from a large and integrated network of case–control studies conducted in Italy, including detailed information on several fruit items, as well as on a large number of potential confounding factors.

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**Patients and methods**

Case–control studies on several neoplasms have been conducted between 1991 and 2002 in various regions of northern, central and southern Italy, and have been described in detail elsewhere [19–26]. The studies included 598 patients with incident, histologically confirmed cancers of the oral cavity and pharynx [19], 304 with squamous cell oesophageal cancer [20], 1953 with cancer of the colorectum (1225 of the colon and 728 of the rectum) [21, 22], 460 of the larynx [23], 2569 of the breast [24], 1031 of the ovary [25] and 1294 of the prostate [26]. The comparison group included 6629 patients (3094 men, 3535 women) admitted to the same network of hospitals as cases for acute, non-neoplastic diseases. Twenty-four per cent of controls were admitted for traumas, 31% for other non-traumatic orthopaedic conditions, 17% for acute surgical disorders and 28% for miscellaneous other illnesses. Interviews were conducted in hospital using the same structured questionnaire, including information on socio-demographic factors, anthropometric variables, tobacco and alcohol consumption, other lifestyle habits and physical activity. For the present analysis, we compared cases with corresponding controls of each study. Subjects’ usual diet before diagnosis (or hospital admission) was investigated using a validated 78-item food frequency questionnaire [27], which included a specific question on weekly consumption of apples. One portion was set as one medium-sized apple (166 g). Response rate was over 95% for both cases and controls.

Odds ratios (OR), and the corresponding 95% confidence intervals (CI), for consumption of apples were derived by unconditional multiple logistic regression models, including terms for age, sex, study center, education, tobacco smoking, alcohol drinking, body mass index, total energy intake, vegetable consumption and physical activity. In order to disentangle the role of apples on the risk of various cancers considered, we also allowed for other fruit intake.

**Results**

Table 1 gives the distribution of cases of selected cancers and corresponding controls according to age and sex. Table 2 shows the distribution of cases and controls according to the frequency of consumption of apples, and the corresponding multivariate ORs. Compared with subjects reporting consumption of <1 apple/day, the multivariate ORs for those reporting ≥1 apple/day were 0.79 for cancers of the oral cavity and pharynx, 0.75 for oesophagus, 0.80 for colorectum, 0.58 for larynx, 0.82 for breast, 0.85 for ovary and 0.91 for prostate. Corresponding estimates after further allowance for other fruit consumption were 0.82 for cancers of the oral cavity and pharynx, 0.78 for oesophagus, 0.70 for colorectum, 0.59 for larynx, 0.76 for breast, 0.76 for ovary and 0.93 for prostate.

Table 3 considers ORs for consumption of apples in strata of age, total calorie intake, and vegetable consumption. The estimates were similar across strata of the considered covariates for each cancer site. Further stratification for smoking habit and body mass index led to similar patterns.

**Discussion**

Apples are a source of several phytochemicals, including flavonoids (in particular, catechins and flavonols) and phenolic acids [8–10]. When compared with other commonly consumed fruits, apples had the second highest level of antioxidant activity (after cranberries) and phenolic compounds, and the highest level of free phenolic compounds [10]. Many phytochemicals have been shown to be biologically active and may interact to protect against cancer. Experimental studies have provided evidence for the beneficial action of flavonoids on multiple cancer-related biological pathways (carcinogen bioactivation, cell-signaling, cell cycle regulation, angiogenesis, oxidative stress, inflammation) [28]. Moreover, several epidemiological studies found inverse associations between these phytochemicals and cancers of the breast [29], stomach [30] and lung [8, 9].

Vitamin C in apples accounts for only 0.4% of the total antioxidant activity, suggesting that most of the antioxidant activity of fruit and vegetables may come from flavonoids and phenolics in apples [31, 32]. However, cold-storage times can strongly affect the antioxidant activity and potential anticancer properties of apples [33].

Apples may simply represent a non-specific indicator of a healthy diet. However, even after further allowance for consumption of vegetables and other fruit, the association with apples did not change, and become even stronger for some cancer sites.

Some cohort studies, including the Nurses’ Health Study and the EPIC cohort, found no association between intake of fruit and risk of cancer in general [4, 5], cancer of the breast [6] and of the prostate [7]. Although cohort studies are generally considered less prone to various sources of bias (mainly recall bias) [4, 5], they may have less detailed information on specific

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**Table 1. Distribution of cases with selected cancers and corresponding controls according to age and sex; Italy, 1991–2002**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Cases:controls</th>
<th>Cases:controls</th>
<th>Cases:controls</th>
<th>Cases:controls</th>
<th>Cases:controls</th>
<th>Cases:controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity and pharynx</td>
<td>222:636</td>
<td>228:474</td>
<td>148:381</td>
<td>512:1008</td>
<td>86:483</td>
<td></td>
</tr>
<tr>
<td>Colorectum</td>
<td>467:1674</td>
<td>717:1333</td>
<td>769:1147</td>
<td>1125:2073</td>
<td>828:2081</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>111:253</td>
<td>185:444</td>
<td>164:391</td>
<td>415:863</td>
<td>45:225</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>1242:1166</td>
<td>799:802</td>
<td>528:620</td>
<td>2569:2588</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>470:1058</td>
<td>325:724</td>
<td>236:629</td>
<td>1031:2411</td>
<td>1294:1451</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>63:133</td>
<td>466:657</td>
<td>765:661</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
aspects of diet on each subject [34], compared with case–control studies. However, in our studies total fruit intake was not significantly associated with cancers of the colorectum [21, 22], breast [22, 24], ovary [25] and prostate [26]. Thus, the present findings are not in contrast with those from the recent cohort studies [4–7] on total fruit intake.

This study has some limitations and several strengths of hospital-based case–control studies. Cases and controls were interviewed in the same hospitals, came from the same geographic area and were asked about their dietary habits during the 2 years before cancer diagnosis or hospital admission. With reference to selection bias, the findings of this study cannot be attributed to selectively higher response rate of health conscious controls [5], since participation was practically complete for both cases and controls. Moreover, the strengths of the study include the large number of subjects, the satisfactory validity and reproducibility of the food frequency questionnaire [27, 35], and the possibility of allowance for a large number of potential confounding factors, including total energy intake. Indeed, allowance for other fruit and total energy intake strengthened the inverse associations for several cancer sites.

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References