

Reduced risk of colorectal cancer and regular consumption of apples: Hospital based case-control study in Poland

Research Article

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Abstract: Experimental studies in animals and epidemiological evidence supporting the health benefits from apples encouraged the authors to assess the potential protective impact of apples on the risk of colorectal cancer in the course of the hospital based case-control study. A total of 186 incident cases of colorectal cancer - for which the information on histology, anatomic location, and stage of cancer were available - have been enrolled to the study. The comparison group included 211 controls chosen from the patients of the same hospital with no history of cancer and admitted for treatment of non-neoplastic conditions. Interviews of both cases and controls were conducted in hospital settings by trained interviewers. The results showed that the risk of colorectal cancer inversely correlated with daily number of apple servings, but the significant reduction of OR estimates were observed for an intake of one or more apple servings daily (OR = 0.37, 95%CI : 0.15 – 0.91). The risk of colorectal cancer was estimated from the multivariate logistic model including a set of potential confounding variables, such as, demographic characteristics of subjects (age, gender, place of residency, marital status and occupational activity), total energy intake (in tertiles) and intake of vegetables (number of servings per day). No fruits except for apples were significantly associated with the reduced risk of colorectal cancer. The reduction of colorectal risk associated with apple consumption may result from their rich content of flavonoid and other polyphenols, which can inhibit cancer onset and cell proliferation.

Keywords: Apple consumption • Colorectal cancer risk • Case-control study

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1. Introduction

Based on the animal and human studies, it appears that apples which are rich in polyphenols may play an important role in reducing the risk of a wide variety of chronic disease and maintaining a good general health. Apples were most consistently associated with reduced risk of various cancers [1-4], cardiovascular diseases [5-9], asthma [10], and chronic obstructive pulmonary disease [11] when compared to other fruits and vegetables or other sources of polyphenols. Apple consumption was also positively associated with better lung function [12] and increased weight loss [13]. A case-control study from Uruguay found an inverse relationship

between apple consumption and colorectal cancer [14] and recent reanalysis of several case-control studies in the Mediterranean region [15] demonstrated a regular inverse association between apple consumption and risk of various cancers; colorectal cancer is among them.

Epidemiological evidence showing the health benefits from apple consumption encouraged us to assess the potential protective impact of apples on risk of colorectal cancer in the course of the recently performed hospital based case-control study in the country with dietary habits far different from that of the Mediterranean region.

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2. Material and Methods

The hospital-based case-control study of colorectal cancer was carried out between November 2005 and May 2008 among patients of the 1st Clinic of Surgery of the University Hospital in Krakow, Poland. A total of 186 incident cases of colorectal cancer - for which the information on histology, anatomic location, and stage of cancer were available - have been enrolled to the study. The comparison group consisted of 211 patients admitted to the hospital at the same period with a wide range of medical diagnoses (acute surgical conditions, traumatic lesions of various localization, cardiovascular, respiratory, blood system diseases, musculoskeletal and neurological disorders, all without dietary restrictions or history of cancer. The controls were not matched individually to cases. Interviews of both cases and controls were conducted in the hospital by trained staff from the Chair of Epidemiology and Preventive Medicine using the structured questionnaire on life style and dietary habits, which was a slightly modified version of the EPIC questionnaire [16]. The section of the questionnaire on lifestyle included information on socio-demographic characteristics, such as education and occupation, occupational and leisure activity, and personal medical history. The dietary interview focused on the reference period was five years before diagnosis for cases or the corresponding date of hospital admission for the controls. The usual dietary pattern of the subjects under study was based on answers to questions on food-frequency of 148 beverage and food items, which were combined with an assessment of quantity of foods consumed. For each food or beverage item, a commonly used unit or portion size was specified, and participants were asked about the average frequency of consumption over the course of one week per year for each item of foods. Participants chose answers ranging from "never" or "less than one serving per month" to "six or more servings per day."

Estimates of colorectal cancer risk by odds ratio (OR), and the corresponding 95% confidence intervals (CI) for consumption of apples were derived from unconditional multivariate logistic regression models, including terms for age, gender, place of birth and residence area (rural vs. urban), education, body mass index, total energy intake and vegetable consumption (without potatoes). Intake of energy was divided into tertiles of their distribution in the control group. In the preliminary analysis we used Chi² test to find statistically significant differences between the cancer cases and control group for data expressed as categorical variables and Mann-Whitney test for the difference in distribution of

continuous variables. Testing for statistical significance was based on 5% level of significance. All statistical analyses were performed using the STATA (version 10) software.

3. Results

Table 1 gives the distribution of cases and controls according to basic demographic variables. It does show that cases consisted in greater proportion of males and older patients (>50 years). Greater portion of the cases over controls have been born in rural areas, had lower education levels, and were residents of villages or small towns. On average, median numbers of fruit servings reported by cases were lower than the controls, but the difference were not statistically significant in univariate analysis. We also failed to disclose any significant differences regarding the intake of vegetables between cases and controls (Table 2).

Apples were the most frequent fruit consumed in the study population and most of the variability in the total fruit consumption resulted from consumption of apples. Table 3 displays partial correlation coefficients between average number of most commonly fruits taken by controls and cases. It does show that the strongest component of the total fruit intake results from consumption of apples and citrus fruits and it is followed by berries and stone fruits. Crude OR estimates of colorectal cancer risk were inversely associated with the number of apple servings measured in quintiles of daily consumption (Table 4), however, the effect was nonlinear and insignificant ($z = -1.35$, $p = 0.176$).

Table 5 presents the adjusted estimates of risk of colorectal cancer based on the unconditional multivariate logistic statistical model. The results show that the adjusted risk of colorectal cancer inversely correlated with daily number of apple servings, but the significant reduction of OR estimates were only observed for an intake one or more apple servings daily (OR = 0.37, 95%CI : 0.15 – 0.91). The multivariable statistical model considered the set of potential confounding variables, such as, demographic characteristics of subjects (age, gender, place of residency, marital status and occupational activity), total energy intake (in tertiles) and intake of vegetables (number of servings per day). We found out that no other fruits were significantly associated with the risk of colorectal cancer except for apples. Out of all demographic variables considered in the statistical models, the higher risk of colorectal cancer was observed among older persons and those who were residents of villages or small towns. Interestingly, unmarried subjects have shown a lower risk of colorectal cancer.

Table 1. Characteristics of the study population.

Variables	Cases N = 186	Controls N= 211	p – level for difference between cases and controls
Gender (males)	57.0%	39.8%	Chi2 = 11.691 $p = 0.001$
Age group >50 yrs	82,8%	61.6%	Chi2 = 21.788 $p = 0.000$
Place of birth (rural or small town)	72.6%	61.1%	Chi2 = 5.811 $p = 0.016$
Marital status (married)	86.0%	75.4%	Chi2 = 7.124 $p = 0.008$
Residence area (rural or small town*)	31.2%	23.2%	Chi2 = 3.182 $p = 0.074$
Education level (secondary or university diploma)	53.2%	65.9%	Chi2 = 6.590 $p = 0.014$
Occupational group:			
Clerical	44.1%	52.1%	
Manual	31.8%	25.1%	Chi2 = 2.939
Other	24.1%	22.8%	$p = 0.230$
Body mass index**	26.64 (5.20)	27.14 (8.13)	Chi2 = 2.230 $p = 0.136$
Energy intake (kcal)**	1987.58 (736.87)	1897.56 (823.84)	Chi2 = 1.667 $p = 0.197$
Fruit consumption** (number of servings)	0.99 (0.90)	1.0 (0.81)	Chi2 = 0.088 $p = 0.766$
Vegetable consumption** (number of servings)	1.56 (0.94)	1.56 (0.89)	Chi2 = 0.010 $p = 0.921$

Table 2. Consumption of fruits and vegetables (median number of servings/day with interquartile range) grouped by cases and controls.

Number of servings/day	Cases	Controls
Fruits		
Berries	0.11 (0.23)	0.12 (0.23)
Citrus	0.08 (0.16)	0.112 (0.18)
Stone fruits	0.05 (0.08)	0.07 (0.11)
Apples	0.43 (0.61)	0.54 (0.61)
Vegetables		
Fresh vegetables	0.81 (0.65)	0.81 (0.21)
Cooked vegetables	0.42 (0.31)	0.45 (0.31)
Lettuce	0.02 (0.08)	0.02 (0.14)
Cucumbers	0.11 (0.09)	0.14 (0.08)
Carrot	1.00 (0.75)	1.00 (0.75)
Tomatoes	0.50 (0.48)	0.50 (0.33)
Onions	0.02 (0.08)	0.01 (0.07)
Potatoes	1.48 (1.14)	1.35 (1.17)
Others	0.32 (0.19)	0.32 (0.21)

Table 3. Partial correlation between average number of all fruit servings per day and most common kinds of individual fruits taken by controls and cases.

Variables	Controls		Cases	
	Coeff.	p - level	Coeff.	p-level
Apples	0.901	0.000	0.878	0.000
Stone fruits	0.441	0.000	0.436	0.000
Citrus fruits	0.391	0.000	0.537	0.000
Berries	0.299	0.000	0.297	0.000

Table 4. Crude estimates of colorectal cancer risk related to level of daily consumption of apples (in quintiles).

Apple consumption in quintiles of consumption (number of servings/ day)	Controls	Cases	OR
1 st Q (< = 0.15)	37	43	1.0
2 nd Q (0.16 – 0.36)	58	50	0.742
3 rd Q (0.37 – 0.57)	30	24	0.688
4 th Q (0.58 – 1.0)	65	57	0.755
5 th Q (>1.0)	21	12	0.492

Cumulative OR = 0.783 (95%CI: 0.57 – 1.08)

Table 5. Risk of colorectal cancer (ORs) related to consumption of apple servings (in quintiles) estimated from the multivariate logistic model adjusted to potential confounding factors.

Predictor variables	Odds Ratio	z	p>z	[95% Conf.Interval]	
Gender*	0.55	-2.56	0.010	0.35	0.87
Age group**	3.26	4.61	0.000	1.97	5.38
Residence***	1.70	2.36	0.018	1.09	2.63
Occupational group****	1.25	1.00	0.317	0.81	1.96
Marital status*****Apple servings 1st Q (reference level)	0.551.00	-2.10	0.036	0.32	0.96
Apple servings 2 nd Q *****	0.79	-0.73	0.467	0.42	1.48
Apple servings 3 rd Q	0.64	-1.15	0.250	0.30	1.37
Apple servings 4 th Q	0.75	-0.91	0.361	0.41	1.39
Apple servings 5 th Q	0.37	-2.17	0.030	0.15	0.91
Number of vegetable servings (continuous)	1.19	1.11	0.265	0.88	1.61
Energy intake (kcal)*****	1.06	0.39	0.700	0.79	1.42

* / gender: 0 = female, 1 = male

** / age group: 0 <= 50 yrs, 1 > 50 yrs

*** / residence: 0 = urban area, 1 = rural area or small town

**** / occupational group: 0 non-manual, 1 = manual workers

***** / marital status: 0 = married, 1 = unmarried

*****/ apple servings in quintiles (1st Q: ≤0.15, 2nd Q: 0.16 – 0.36, 3rd Q: 0.37 – 0.57, 4th Q: 0.58 – 1.0, 5th quintile > 1 serving per day)

*****/ energy intake (kcal) in tertiles (1st tertile ≤1725.1, 2nd tertile 1725.2 – 2137.6; 3rd tertile >2137.6)

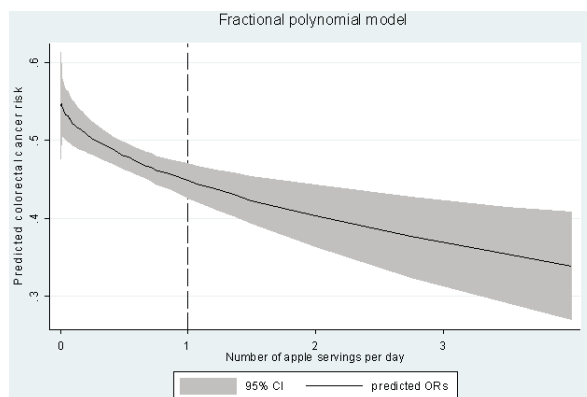
Figure 1. Predicted colorectal cancer risk (OR with 95% CI) and the number of apple servings.

Figure 1 shows graphically the predicted probability of colorectal cancer risk derived from the logistic multivariable fractional polynomial model. Even though Figure 1 shows that the predicted risk of colorectal cancer drops at a low range in the intake of apples (below 1.0 servings per day), the significant data is the important impact of apple intake noted at higher level of intake.

4. Discussion

This hospital-based case-control study showed the significant beneficial effect of apple consumption (daily number of apple servings) on risk of colorectal cancer. Out of several types of fruits in the study (apples, citrus, berries, stone fruits and others), the apple was the

only specific type of fruit associated with a significant 63% reduction of colorectal risk attributable to regular consumption of one or more apples a day. The estimated effect was adjusted to important potential confounders such as demographic variables, energy intake, and consumption of vegetables. In preliminary statistical models we also included tomatoes as a potential confounder since some authors [17,18], but not all, [19] have reported an inverse association between tomato intake and colorectal cancer risk.

We think that the reduction of colorectal risk associated with apple consumption was related to their rich content of polyphenols. As it was shown in vitro studies, the latter phytochemicals can inhibit cancer onset by protecting tissues against free oxygen radicals and inhibiting cell proliferation [20-25].

The results of our study is in very good agreement with the recently published analysis of several series of case-control studies carried out in Italy on the impact of consumption of apples on cancer occurrence in various sites [15]. In total, the Italian material 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. On the basis of this rich database, the authors found a consistent inverse association between apples and risk of cancer in various sites. Multivariate odds ratios (OR) for each cancer site 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. The results have

shown that subjects reporting consumption of one or more apples a day had OR of 0.79 (95% CI: 0.62–1.00) for cancers of the oral cavity and pharynx, 0.75 (95% CI 0.54–1.03) for esophagus, 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.

The above mentioned analysis of case-control studies was followed by another multicenter Italian study, which aimed at assessing the association between polyphenols and colorectal cancer risk [26]. The latter study included 1,953 cases of colorectal cancer (1,225 colon cancers and 728 rectal cancers) and 4,154 hospital controls admitted for acute nonneoplastic diseases. A reduced risk of colorectal cancer was found for increasing intake of isoflavones (OR = 0.76, for the highest versus the lowest quintile, p for trend = 0.001), anthocyanidins (OR = 0.67, p for trend <0.001), flavones (OR = 0.78, p for trend = 0.004, and flavonols (OR = 0.64, p for trend <0.001). It is important to mention that the estimates did not substantially differ for colon and rectal cancers, as well as in strata of sex, age and body mass index.

Similar findings were provided in the large Scottish case-control study carried out by Theodoratou et al. [27], where six main classes of flavonoids estimated from the self-administered food frequency questionnaire and the risk of colorectal cancer was examined using data from a national prospective case-control study. In total, the study included 1,456 incident cases and 1,456 population based controls matched on age, sex, and residence area. Adjusted to energy intake, reduction in colorectal cancer risk associated with the highest quartiles of intake (versus the lowest quartile) were 27% for flavonols, 32% for quercetin, 26% for epicatechin, and 22% for procyanidins. The significant dose-dependent reduction in colorectal cancer risk associated with consumption of flavonols, quercetin, catechins, and epicatechin remained strong after controlling for overall fruit and vegetable consumption or for other flavonoids.

The relationship of dietary flavonoids (catechins) and epithelial cancer was also examined in 728 men (aged 65–84) as part of the Zutphen Elderly Study and apple consumption was associated with decreased epithelial lung cancer incidence [28]. Other data from the Zutphen Elderly study also showed an inverse association between fruit and vegetable flavonoids and total cancer incidence and tumors of the alimentary and respiratory tract [1].

In the Nurses' Health Study and the Health Professionals' Follow-up Study, involving over 77,000 women and 47,000 men, fruit and vegetable intake was associated with a 21% reduced risk in lung cancer risk in women, however this association was not seen in men

[29]. Very few of the individual fruits and vegetables examined had a significant effect on lung cancer risk in women, but apples were one of the individual fruits associated with decrease risk in lung cancer. In a case control study in Hawaii, it was found that apple and onion intake was associated with a reduced risk of lung cancer in both males and females [3]. Smoking history and food intake was assessed for 582 patients with lung cancer and 582 control subjects without lung cancer. There was a 40–50% decreased risk in lung cancer in participants with the highest intake of apples, onions, and white grapefruit when compared to those who consumed the lowest amount of these fruits. The decreased risks in lung cancer were seen in both men and women and in almost all ethnic groups.

In a Finnish study involving 10,000 men and women and a 24-year follow-up, a strong inverse association was seen between flavonoid intake and lung cancer development [2]. In the sampled population, the mean flavonoid intake was 4.0 mg per day, and 95% of the total flavonoid intake was quercetin. Apples and onions together provided 64% of all flavonoid intake. The reduced risk of lung cancer associated with increased flavonoid consumption was especially strong in younger people and in nonsmokers. Apples were the only specific foods that were inversely related to lung cancer risk. Since apples were the main source of flavonoids in the Finnish population, it was concluded that the flavonoids from apples were most likely responsible for the decreased risk in lung cancer. In another cohort study of women, Arts et al. [30] observed an inverse association between certain flavonoid subgroups and risk of rectal cancer. Very big prospective cohort study carried out in USA evaluated the association between intake of flavonoids and colorectal cancer incidence in 71,976 women from the Nurses' Health Study and 35,425 men from the Health Professionals Follow-Up Study. Dietary intake of flavonoids was assessed three times over the period in 1990 – 1998 by means of a food frequency questionnaire. Between 1990 and 2000, the authors assessed 878 incident cases of colorectal cancer (498 in women and 380 in men), but total flavonoid intake was not inversely associated with colorectal cancer risk among women and men combined [31].

Finally we wanted to refer to very recent study on dietary flavonoids and colorectal adenoma recurrence in the polyp prevention trial performed in USA [32]. Intakes of flavonoids were estimated from a food frequency questionnaire. Total flavonoid intake was not associated with any or advanced adenoma recurrence. However, high intake of flavonoids being at higher concentrations in beans, onions, apples, and tea, was associated with decreased risk of advanced adenoma recurrence (OR

= 0.24, 95%CI: 0.11 – 0.53, *p* for trend = 0.0006). Similar inverse associations were observed but to a smaller extent for isoflavonoids.

Lack of consistency between case-control and cohort studies in humans raises the question of whether the protective effects of flavonoids demonstrated *in vitro* or in animal studies can be achieved in humans. A central concern in epidemiologic studies on diet and cancer is validity of the dietary assessment and in the debate on shortcomings of studies we have to keep in mind that flavonoid intake in epidemiologic studies was assessed with food frequency questionnaires (FFQ), which may express partiality in the measurement of dietary flavonoids. Virtually all dietary assessment methods in case-control studies depend on the ability of the subjects to provide accurate information on the past dietary habits. In case control studies the quality of the dietary recalls heavily rely on memory, and conceptualization skills needed to describe accurately frequency of consumption and food portion sizes. The reported diet may be a distortion of usual diet, may lack measure of day-to-day variation in diet, requires regular eating habits and depend on food composition tables.

Since flavonoids are derived from different kinds of foods their total intake varies with many factors, such as processing, storage, or species variety. Different

types of apples or other fruits are likely to have different concentrations of flavonoids. Moreover, most flavonoids present in foods are in the form of esters, glycosides, or polymers that cannot be absorbed in their indigenous form [33]. They are usually absorbed after being transformed to aglycons in the gastrointestinal tract [34-37]. The amount that is bioavailable is usually a small proportion of the ingested amount [38-39] and none of the studies included the correction of the risk estimates for the bioavailability factor. Although recent studies have suggested that the bioavailability of certain flavonoids from food may be higher than expected, it still remains unclear whether the beneficial effects of anti-proliferation and antioxidation from *in vitro* studies would also exist in humans since the beneficial effects in experimental animal studies were often obtained with much higher concentrations than can be achieved in humans through regular diet. Moreover, the colon bacteria flora catalyzes flavonoids into metabolites [40] and the inter-individual variation in the colonic microbial flora and the unpredictable influences of foods on microbial metabolite production complicates the problem concerning the impact of flavonoids on health effects in population at large.

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