Fruit, vegetable, and fiber intake in relation to cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC)[1–4]

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ABSTRACT

Fruit, vegetables, and certain components of plant foods, such as fiber, have long been thought to protect against cancer. The European Prospective Investigation into Cancer and Nutrition (EPIC) is a prospective cohort that includes >500,000 participants from 10 European countries and has made a substantial contribution to knowledge in this research area. The purpose of this article is to summarize the findings published thus far from the EPIC study on the associations between fruit, vegetable, or fiber consumption and the risk of cancer at 14 different sites. The risk of cancers of the upper gastrointestinal tract was inversely associated with fruit intake but was not associated with vegetable intake. The risk of colorectal cancer was inversely associated with intakes of total fruit and vegetables and total fiber, and the risk of liver cancer was also inversely associated with the intake of total fiber. The risk of cancer of the lung was inversely associated with fruit intake but was not associated with vegetable intake; this association with fruit intake was restricted to smokers and might be influenced by residual confounding due to smoking. There was a borderline inverse association of fiber intake with breast cancer risk. For the other 9 cancer sites studied (stomach, biliary tract, pancreas, cervix, endometrium, prostate, kidney, bladder, and lymphoma) there were no reported significant associations of risk with intakes of total fruit, vegetables, or fiber. *Am J Clin Nutr* 2014;100(suppl):394S–8S.

INTRODUCTION

Plant foods or their components have long been thought to protect against cancer. Most prominent among the hypotheses is that fruit and vegetables or their components may protect against cancer. Fiber, which is found in high amounts in fruit, vegetables, and whole grains, is also hypothesized to protect against some cancers. The 1997 report from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) concluded, mainly on the basis of case-control studies, that there was convincing evidence that fruit and vegetables decreased the risk of cancers of the mouth and pharynx, esophagus, stomach, and lung (1). In the second report published in 2007, the judgment for fruit and vegetables was downgraded: there were no cancer sites for which the evidence of a protective effect of fruit and vegetables was deemed to be convincing (2). The downgrade was mainly due to the inclusion of results from cohort studies that became available after the first report (2). For fiber, in the 1997 report there were no cancer sites for which the evidence of a protective effect of fiber was judged to be convincing or probable (1); in the 2007 report foods containing dietary fiber were judged to probably decrease the risk of colorectal cancer (2).

The European Prospective Investigation into Cancer and Nutrition (EPIC), which was designed to investigate the relations between diet, lifestyle, and environmental factors and the incidence of different cancers, is one such cohort that has investigated fruit, vegetable, and fiber consumption in relation to cancer risk. Many articles from EPIC in this research area have been published since the 2007 WCRF/AICR report. The EPIC study recruited half a million participants, and to date >60,000 incident cases of cancer have been identified. One of the major strengths of EPIC is the inclusion of study centers in 10 European countries, giving substantial variation in dietary intakes within the cohort (3). The objective of this article is to review and summarize the studies published thus far from EPIC that report the association between total fruit, vegetable, or fiber intake and risk of cancer at any site.

DESCRIPTION OF THE EPIC COHORT

The EPIC study is a prospective cohort that includes 23 study centers in 10 countries throughout Europe (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, United Kingdom). Participants were recruited between 1992 and 2000, and most participants were recruited from the general population, with the exception of the centers in France (women recruited from a health insurance program), Utrecht (women recruited from a breast screening program), Ragusa (blood donors and their spouses), and Oxford (a health conscious sample with a large proportion of vegetarians). At baseline, country- or center-specific dietary questionnaires were used to assess the participants' diets over the previous 12 mo. To calibrate dietary intakes across centers, a random sample of 8% of the total

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cohort completed a standardized, computerized 24-h dietary recall. Most countries follow up participants via linkage to cancer registries to identify new cancer cases. In France, Germany, and Greece, a combination of active follow-up methods is used, including health insurance records and contact with study participants and their next of kin. The study population and data collection procedures for EPIC have been described in detail elsewhere (4).

For the purposes of this review, published studies from EPIC were included if they reported fruit, vegetable, or total fiber consumption in relation to incident cancer risk. Typically, results in EPIC are reported across quintiles (or occasionally quartiles) of exposure. For each study, we extracted the RRs and 95% CIs for each quantile, and the *P* value for the trend across quantiles. In addition, most studies reported RRs for cancer associated with calibrated intakes of fruit, vegetables, and fiber as continuous variables. In all cases, we used the most fully adjusted model reported. If ≥2 studies were published on the same exposure-outcome pair, we included only the most recent study with the longest follow-up and thus the greatest number of events.

A SUMMARY OF THE FINDINGS

In total, 27 published studies reported fruit, vegetable, or total fiber intake in relation to incident cancer in EPIC (5–31). Seven of these studies were superseded by subsequent studies with longer follow-up and are not discussed here (5–11). Although they varied slightly between studies, the reported fruit intakes in each quintile from lowest to highest were approximately ≤89, 90–154, 155–239, 240–355, and ≥356 g (6). For vegetables, the reported intakes in each quintile were approximately ≤99, 100–149, 150–209, 210–304, and ≥305 g (18); for fiber, these intakes were ≤16.4, 16.5–20.0, 20.1–23.5, 23.6–28.4, and ≥28.5 g (25).

The associations between fruit consumption and cancer in EPIC for 9 cancer sites are shown in **Figure 1** (14–22). There were no significant trends across quantiles of fruit intake with the risk of cancers of the stomach (683 cases; *P*-trend = 0.05) (15), pancreas (555 cases; *P*-trend = 0.93) (16), breast (3659 cases; *P*-trend = 0.11) (18), cervix (253 cases; *P*-trend = 0.19) (19), prostate (1104 cases, *P*-trend = 0.74) (20), or bladder (1015 cases; *P*-trend = 0.87) (21) or cancers of the lymphatic system (849 cases; *P*-trend = 0.63) (22). Significant inverse associations have been reported between fruit consumption and mouth, pharynx, larynx, and esophageal cancers (352 cases; RR for

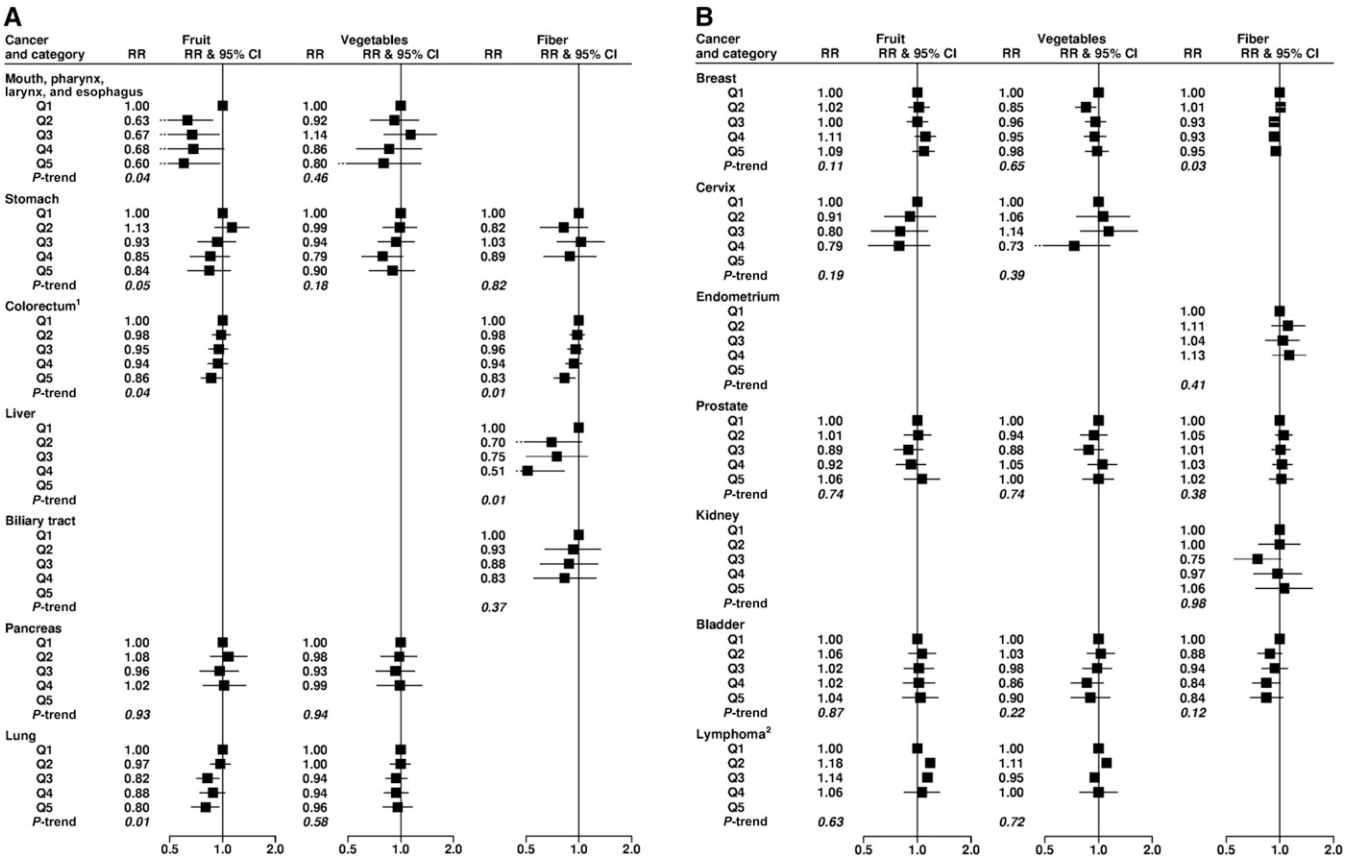

FIGURE 1. Cancer risk by quintile (or quartiles if no results are shown for Q5) of intake of fruit, vegetables, and fiber in EPIC. A: Gastrointestinal and respiratory cancers. B: Reproductive and other cancers. Data presented in the figure were extracted from the following sources: fruit and vegetables in relation to cancers of the mouth, pharynx, larynx, and esophagus (14); stomach (15); colorectum (23); pancreas (16); lung (17); breast (18); cervix (19); prostate (20); bladder (21); and lymphoma (22); and fiber intake in relation to cancers of the stomach (24), colorectum (25), liver and biliary tract (26), breast (27), endometrium (28), prostate (29), kidney (30), and bladder (31). RRs (95% CIs) were estimated by using Cox proportional hazards models. Approximately 470,000 participants were included in most of the analyses, except for analyses of cancers of the breast, cervix, and endometrium, which included ~330,000 women, and the analyses of prostate cancer, which included ~140,000 men. [1]Results shown for fruit are for the intake of fruit and vegetables combined; [2]CIs were unavailable for quartiles 2 and 3. EPIC, European Prospective Investigation into Cancer and Nutrition; Q, quintile.

highest compared with lowest quintile: 0.60; 95% CI: 0.38, 0.97; *P*-trend = 0.041) (14) and lung cancer (1830 cases; RR for highest compared with lowest quintile: 0.80; 95% CI: 0.66, 0.96; *P*-trend = 0.01) (17).

The associations between vegetable consumption and cancer in EPIC for the same 9 cancer sites are shown in Figure 1 (14–22). There were no significant trends across quantiles of vegetable intake and the risk of the following cancers: mouth, pharynx, larynx, and esophagus (352 cases; *P*-trend = 0.46) (14); stomach (683 cases; *P*-trend = 0.18) (15); pancreas (555 cases; *P*-trend = 0.94) (16); lung (1830 cases; *P*-trend = 0.58) (17); breast (3659 cases; *P*-trend = 0.65) (18); cervix (253 cases; *P*-trend = 0.39) (19); prostate (1104 cases; *P*-trend = 0.74) (20); bladder (1015 cases; *P*-trend = 0.22) (21); or cancers of the lymphatic system (849 cases; *P*-trend = 0.72) (22).

For colorectal cancer, fruit and vegetable intake was reported only as a combined variable (23). There was a significant trend across quintiles of fruit and vegetable consumption for the risk of colorectal cancer (2819 cases; RR for highest compared with lowest quintile: 0.86; 95% CI: 0.75, 1.00; *P*-trend = 0.04).

The association between total fiber consumption and cancer in EPIC has been reported for 9 cancer sites (24–31). There were no significant trends across quantiles of total fiber intake for the risk of cancers of the stomach (312 cases; *P*-trend = 0.82) (24), biliary tract (236 cases; *P*-trend = 0.37) (26), endometrium (710 cases; *P*-trend = 0.41) (28), prostate (2747 cases; *P*-trend = 0.38) (29), kidney (507 cases; *P*-trend = 0.98) (30), or bladder (1416 cases; *P*-trend = 0.12) (31). Significant inverse associations have been reported between total fiber intake and colorectal cancer (4517 cases; RR for highest compared with lowest quintile: 0.83; 95% CI: 0.72, 0.96; *P*-trend = 0.013) (25), liver cancer (191 cases; RR for highest compared with lowest quartile: 0.51; 95% CI: 0.31, 0.83; *P*-trend = 0.013) (26), and breast cancer (11,576 cases; RR for highest compared with lowest quintile: 0.95; 95% CI: 0.89, 1.01; *P*-trend = 0.03) (27). In relation to fiber type, for cancers of the gastrointestinal tract (stomach, colorectal, and liver), intake of cereal fiber was significantly inversely associated with risk, but there were no significant associations with intakes of fruit or vegetable fiber (24–26). RRs for the highest compared with the lowest quartile of intake of cereal fiber were as follows: for stomach cancer, 0.69 (95% CI: 0.48, 0.99; *P*-trend = 0.01); for colorectal cancer, 0.87 (95% CI: 0.77, 0.99; *P*-trend = 0.003); and for liver cancer, 0.48 (95% CI: 0.28, 0.80; *P*-trend = 0.012). Fiber from vegetables, but not from fruit or cereals, was inversely associated with risk of breast cancer (27). The RR for the highest compared with the lowest quintile of intake of vegetable fiber was 0.90 (95% CI: 0.84, 0.96; *P*-trend < 0.01). Fiber type was not reported in relation to risk of cancers of the endometrium, kidney, and bladder (28, 30, 31). Prostate cancer was not associated with intakes of fiber from fruit, vegetables, or cereals (29).

The results for calibrated intakes of fruit, vegetables, and fiber as continuous variables are summarized in **Table 1**. With regard to the quantile analysis, most of the associations between intakes of fruit, vegetables, and fiber and cancer were not significant. Similarly to the observed quantile analyses, in the continuous calibrated analyses there were significant inverse associations between total fiber and cancers of the colorectum (25), liver (26), and breast (27). In the continuous calibrated analyses, the inverse associations between fruit intake and cancers of the upper aerodigestive tract (14) and lung (17) and fruit and vegetable intake and colorectal cancer (23) were not significant, but there was a significant inverse association between fruit intake and cervical cancer. In addition, 2 studies reported the

TABLE 1
Adjusted RRs (95% CIs) for specified calibrated intakes of fruit, vegetables, and fiber in relation to cancer risk in EPIC[1]

Cancer site	Fruit	Vegetables	Fiber
Mouth, pharynx, larynx, and esophagus	0.93 (0.81, 1.05)[2]	0.75 (0.53, 1.04)[2]	—
Stomach	0.94 (0.87, 1.02)	0.85 (0.70, 1.02)	—
Colorectum	0.97 (0.93, 1.01)[3]	—	0.87 (0.79, 0.96)
Liver	—	—	0.65 (0.42, 0.96)
Biliary tract	—	—	0.74 (0.49, 1.10)
Pancreas	1.02 (0.92, 1.13)	1.07 (0.87, 1.33)	—
Lung	0.94 (0.88, 1.01)	0.94 (0.83, 1.07)	—
Breast	1.03 (0.98, 1.08)	1.02 (0.91, 1.14)	0.93 (0.87, 0.99)
Cervix	0.83 (0.72, 0.98)	0.85 (0.65, 1.10)	—
Endometrium	—	—	1.27 (0.99, 1.63)
Ovary	1.10 (0.99, 1.23)[4]	0.90 (0.71, 1.14)[4]	—
Prostate	—	—	0.91 (0.81, 1.02)
Kidney	1.08 (0.94, 1.23)[2]	0.93 (0.66, 1.29)[2]	0.87 (0.67, 1.11)
Bladder	0.98 (0.90, 1.05)	0.96 (0.81, 1.14)	0.93 (0.78, 1.10)
Lymphoma	0.99 (0.81, 1.19)	1.04 (0.96, 1.13)	—

[1] Values shown are per a 100-g/d increase in fruit or vegetable intake or per a 10-g/d increase in fiber intake. Data were extracted from the following sources: fruit and vegetable intake in relation to cancers of the mouth, pharynx, larynx, and esophagus (14); stomach (15); colorectum (23); pancreas (16); lung (17); breast (18); cervix (19); ovary (12); kidney (13); bladder (21); and lymphoma (22); and fiber intake in relation to cancers of the colorectum (25), liver and biliary tract (26), breast (27), endometrium (28), prostate (29), kidney (30), and bladder (31). Values were estimated by using Cox proportional hazards models. Approximately 470,000 participants were included in most of the analyses, except for analyses of cancers of the breast, cervix, endometrium, and ovary, which included ~330,000 women, and the analyses of prostate cancer, which included ~140,000 men. EPIC, European Prospective Investigation into Cancer and Nutrition; —, not available.

[2] Estimated per a 40-g/d increase in fruit or vegetable intake.

[3] Results shown are for intakes of fruit and vegetables combined.

[4] Estimated per an 80-g/d increase in fruit or vegetable intake.

association between fruit and vegetable intakes only as calibrated continuous variables and risk of cancer (12, 13). The results showed no significant associations between intakes of fruits or vegetables and cancer of the ovary (12) or kidney (13).

IMPLICATIONS OF THE FINDINGS

For cancers of the upper aerodigestive tract (mouth, pharynx, larynx, and esophagus), the intake of fruit was inversely associated with risk in the observed quintile analysis but not in the calibrated continuous analysis. There was no association with vegetable intake. This finding provides, at most, weak evidence from EPIC for an association between fruit intake and cancers of the upper aerodigestive tract. The 2007 WCRF/AICR report concluded that nonstarchy vegetables and fruit probably decrease the risk of cancers of the mouth, pharynx, larynx, and esophagus. This judgment was based on a small number of cohort studies and a much larger number of case-control studies, and the latter studies are more susceptible to bias. The report also noted that the observed associations may be due to residual confounding by smoking.

There were no significant associations between total fruit or vegetable intake and stomach cancer in EPIC. The 2007 WCRF/AICR report concluded that nonstarchy vegetables, allium vegetables, and fruit probably decrease the risk of stomach cancer. This judgment was also based on a small number of cohort studies and a large number of case-control studies. There was no significant association between total fiber and stomach cancer in EPIC, but there were significant inverse associations between cereal fiber and the risk of stomach cancer and another gastrointestinal cancer, liver cancer, although these associations were based on a small number of cases. The main sources of fiber in the EPIC cohort are cereals and cereal products, bread, fruit, and vegetables (32).

Combined fruit and vegetable intake was inversely associated with colorectal cancer in the observed quintile analysis but not in the calibrated continuous analysis. Thus, there is weak evidence from EPIC for an association between fruit and vegetable intake and colorectal cancer. The inverse association in EPIC between fiber consumption and risk of colorectal cancer is based on a large number of cases (4512). In analyses looking at different fiber types, only cereal fiber was significantly inversely associated with colorectal cancer risk (25). A review of the associations between fiber and colorectal cancer published in 2011 as part of the Continuous Update Project of the WCRF included 19 prospective studies from Europe [4 studies; including an earlier EPIC study (10)], America (11 studies), and Asia (4 studies). The results showed a significant inverse association between total dietary fiber intake and colorectal cancer (summary RR for high compared with low intake of fiber: 0.88; 95% CI: 0.82, 0.94) (33). Similarly to the results from EPIC, the inverse association was only significant for cereal fiber (33).

The inverse association between fruit intake and lung cancer in the quintile analysis in EPIC was observed in only smokers (17). One suggestion is that this association may be due to residual confounding by imperfect measurement of smoking exposure. An alternative explanation is that smokers may benefit more from consuming fruit, perhaps because the antioxidants in fruit may reduce the oxidative stress caused by smoking (34).

For reproductive cancers, with the exception of breast cancer, there was no evidence from EPIC that fruit, vegetables, or fiber were associated with any of the cancer sites reviewed. The null association between fruit and vegetable intake and breast cancer was reported in an earlier study published from EPIC, at which stage 3659 cases had accrued. The significant but small inverse association between dietary fiber intake and breast cancer in EPIC is based on a much larger number (11,576) of cases. Further analyses of subgroups of fiber and subtypes of breast cancer showed a significant inverse association between fiber from vegetables and estrogen receptor–negative and progesterone receptor–negative tumors (RR for highest compared with lowest quintile of intake of fiber from vegetables: 0.74; 95% CI: 0.59, 0.93; *P*-trend = 0.01) (27).

There are some limitations to this review. Studies from EPIC often report further analyses of subtypes of cancer and/or subgroups of fruit (citrus fruit), vegetable (fruiting vegetables, root vegetables, leafy vegetables, cabbages, and onion and garlic), or fiber (fruit fiber, vegetable fiber, cereal fiber) consumption. Although we have briefly discussed the results for different fiber types and individual cancer sites, we have focused on the results for total fruit and total vegetables. Thus, we may have overlooked specific associations between subgroups of fruit or vegetables and subtypes of cancer. However, in most cases, these subgroup analyses were secondary analyses and multiple comparisons were performed, and therefore we would expect some of these associations to be significant by chance. By focusing our review on the main results of the published studies, we avoid placing emphasis on any such associations that may be chance findings.

CONCLUSIONS

We reviewed studies published thus far in EPIC on fruit, vegetable, or total fiber intake and cancer risk. There was little evidence that vegetable intake was associated with risk of any of the individual cancer sites reviewed. The studies from EPIC have shown small inverse associations between fruit intake and cancers at some sites; for lung cancer, this inverse association was only present in current smokers. A high intake of cereal fiber was associated with a decreased risk of colorectal cancer and other gastrointestinal cancers (stomach and liver). This review is an overview of total fruit, vegetable, and fiber consumption in relation to individual cancer sites reported from EPIC, and further assessment should include the evaluation of associations with subtypes of cancer (eg, estrogen receptor–negative breast cancer) and subgroups of fruit and vegetables as well as other plant foods such as cereal grains. In addition, emerging work on biomarkers of plant food intake may help to clarify the associations between fruit, vegetables, and fiber and cancer risk.

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