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Flavonoid intake and survival after diagnosis of colorectal cancer: A prospective study in two US cohorts

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Mingyang Song   • Show all authorsPublished: April 01, 2023 • DOI: <https://doi.org/10.1016/j.ajcnut.2023.03.026> PlumX Metrics

Abstract

Background

Although experimental evidence supports anti-cancer effects of flavonoids, the influence of flavonoids intake on colorectal cancer (CRC) survival remains unknown.

Objective

To assess the association of post-diagnostic flavonoid intake with mortality.

Methods

...spectively assessed the association of post-diagnostic flavonoid intake with CRC-specific
-cause mortality in 2,552 patients diagnosed with Stage I-III CRC in two cohorts < die >

the Nurses' Health Study and the Health Professionals Follow-up Study. We assessed the intake of total flavonoids and their subclasses using validated food frequency questionnaires. We used the inverse probability weighted multivariable Cox proportional hazards regression model to calculate the hazard ratio (HR) of mortality after adjusting for pre-diagnostic flavonoid intake and other potential confounders. We performed spline analysis to evaluate dose-response relationships.

Results



31,026 person-years of follow-up, we documented 1,689 deaths, of which 327 were due to CRC. Total flavonoid intake was not associated with mortality, but a higher intake of flavan-3-ols was suggestively associated with lower CRC-specific and all-cause mortality, with multivariable HR (95% confidence interval, CI) per 1-SD increase of 0.83 (0.69-0.99, $P=.04$) and 0.91 (0.84-0.99, $P=.02$), respectively. The spline analysis showed a linear relationship between post-diagnostic flavan-3-ol intake and CRC-specific mortality ($P=.01$ for linearity). As the major contributor to flavan-3-ol intake, tea showed an inverse association with CRC-specific and all-cause mortality, with multivariable HR per 1 cup/day of tea of 0.86 (0.75-0.99, $P=.03$) and 0.90 (0.85-0.95, $P<.001$), respectively. No beneficial associations were found for other flavonoid subclasses.

Conclusions

Higher intake of flavan-3-ol after CRC diagnosis was associated with lower CRC-specific mortality. Small, readily achievable increases in the intake of flavan-3-ol- rich foods, such as tea, may help improve survival in CRC patients.

Keywords

[flavonoids](#) • [flavan-3-ol](#) • [colorectal cancer](#) • [tea](#) • [survival](#)

ABBREVIATIONS:

[AJCC](#) (the American Joint Committee on Cancer), [AHEI](#) (Alternate Healthy Eating Index), [BMI](#) (body mass index), [CI](#) (confidence interval), [CRC](#) (colorectal cancer), [EGCG](#) (Epigallocatechin gallate), [FFQ](#) (food frequency questionnaire), [HPFS](#) (Health Professionals Follow-up Study), [HR](#) (hazard ratio), [IPW](#) (inverse probability weighting), [MET](#) (metabolic equivalent), [NHS](#) (Nurses' Health Study), [PUFA](#) (polyunsaturated fatty acids), [SD](#) (standard deviation)



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Reference

1. Sung H. • Ferlay J. • Siegel R.L. • Laversanne M. • Soerjomataram I. • Jemal A. • et al.

Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.

CA Cancer J Clin. 2021; **71**: 209-249

<https://doi.org/10.3322/caac.21660>

[View in Article](#)

[Scopus \(26639\)](#) • [PubMed](#) • [Crossref](#) • [Google Scholar](#)



2. Rock C.L. • Thomson C.A. • Sullivan K.R. • Howe C.L. • Kushi L.H. • Caan B.J. • et al.

American Cancer Society nutrition and physical activity guideline for cancer survivors.

CA Cancer J Clin. 2022; **72**: 230-262

<https://doi.org/10.3322/caac.21719>

[View in Article](#) 



3. Chang H. • Lei L. • Zhou Y. • Ye F. • Zhao G.

Dietary Flavonoids and the Risk of Colorectal Cancer: An Updated Meta-Analysis of Epidemiological Studies.

Nutrients. 2018; **10**

<https://doi.org/10.3390/nu10070950>

[View in Article](#) 

[Scopus \(67\)](#) • [Crossref](#) • [Google Scholar](#)

4. Panche A.N. • Diwan A.D. • Chandra S.R.

Flavonoids: an overview.

J Nutr Sci. 2016; **5**: e47

<https://doi.org/10.1017/jns.2016.41>

[View in Article](#) 

[Scopus \(2312\)](#) • [PubMed](#) • [Crossref](#) • [Google Scholar](#)

5. Li Y. • Zhang T. • Chen G.Y.

Flavonoids and Colorectal Cancer Prevention.

Antioxidants (Basel). 2018; **7**

<https://doi.org/10.3390/antiox7120187>

[View in Article](#) 

[Scopus \(33\)](#) • [Crossref](#) • [Google Scholar](#)

6. Deng Y. • Li S. • Wang M. • Chen X. • Tian L. • Wang L. • et al.

Flavonoid-rich extracts from okra flowers exert antitumor activity in colorectal cancer through induction of mitochondrial dysfunction-associated apoptosis, se



and autophagy.

Food Funct. 2020; **11**: 10448-10466

<https://doi.org/10.1039/d0fo02081h>

[View in Article](#) 

[Scopus \(13\)](#) • [Crossref](#) • [Google Scholar](#)



women.

J Womens Health. 1997; **6**: 49-62

<https://doi.org/10.1089/jwh.1997.6.49>

[View in Article](#) 

[Scopus \(570\)](#) • [PubMed](#) • [Crossref](#) • [Google Scholar](#)

8. Rimm E.B. • Giovannucci E.L. • Willett W.C. • Colditz G.A. • Ascherio A. • Rosner B. • et al.

Prospective study of alcohol consumption and risk of coronary disease in men.

Lancet. 1991; **338**: 464-468

[https://doi.org/10.1016/0140-6736\(91\)90542-w](https://doi.org/10.1016/0140-6736(91)90542-w)

[View in Article](#) 

[PubMed](#) • [Abstract](#) • [Google Scholar](#)

9. Liu L. • Nevo D. • Nishihara R. • Cao Y. • Song M. • Twombly T.S. • et al.

Utility of inverse probability weighting in molecular pathological epidemiology.

Eur J Epidemiol. 2018; **33**: 381-392

<https://doi.org/10.1007/s10654-017-0346-8>

[View in Article](#) 

[Scopus \(41\)](#) • [PubMed](#) • [Crossref](#) • [Google Scholar](#)

10. Amin M.B. • Greene F.L. • Edge S.B. • Compton C.C. • Gershengwald J.E. • Brookland R.K. • et al.

The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging.

CA Cancer J Clin. 2017; **67**: 93-99



<https://doi.org/10.3322/caac.21388>

[View in Article](#) ^

[Scopus \(2464\)](#) • [PubMed](#) • [Crossref](#) • [Google Scholar](#)

11. Rich-Edwards J.W. • Corsano K.A. • Stampfer M.J.

Test of the National Death Index and Equifax Nationwide Death Search.



[View in Article](#) ^

[Scopus \(419\)](#) • [PubMed](#) • [Crossref](#) • [Google Scholar](#)

12. Feskanich D. • Rimm E.B. • Giovannucci E.L. • Colditz G.A. • Stampfer M.J. • Litin L.B. • et al.

Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire.

J Am Diet Assoc. 1993; **93**: 790-796

[https://doi.org/10.1016/0002-8223\(93\)91754-e](https://doi.org/10.1016/0002-8223(93)91754-e)

[View in Article](#) ^

[Scopus \(0\)](#) • [PubMed](#) • [Abstract](#) • [Full Text](#) • [Full Text PDF](#) • [Google Scholar](#)

13. Yue Y. • Petimar J. • Willett W.C. • Smith-Warner S.A. • Yuan C. • Rosato S. • et al.

Dietary flavonoids and flavonoid-rich foods: validity and reproducibility of FFQ-derived intake estimates.

Public Health Nutr. 2020; **23**: 3295-3303

<https://doi.org/10.1017/S1368980020001627>

[View in Article](#) ^

[Scopus \(9\)](#) • [PubMed](#) • [Crossref](#) • [Google Scholar](#)

14. Willett W. • Stampfer M.J.

Total energy intake: implications for epidemiologic analyses.

Am J Epidemiol. 1986; **124**: 17-27

<https://doi.org/10.1093/oxfordjournals.aje.a114366>

[View in Article](#) ^



15. Shan Z. • Li Y. • Baden M.Y. • Bhupathiraju S.N. • Wang D.D. • Sun Q. • et al.
Association Between Healthy Eating Patterns and Risk of Cardiovascular Disease.
JAMA Intern Med. 2020; **180**: 1090-1100
<https://doi.org/10.1001/jamainternmed.2020.2176>



16. Song M. • Zhang X. • Meyerhardt J.A. • Giovannucci E.L. • Ogino S. • Fuchs C.S. • et al.
Marine omega-3 polyunsaturated fatty acid intake and survival after colorectal cancer diagnosis.
Gut. 2017; **66**: 1790-1796
<https://doi.org/10.1136/gutjnl-2016-311990>

[View in Article](#) ^

[Scopus \(71\)](#) • [PubMed](#) • [Crossref](#) • [Google Scholar](#)

17. Song M. • Wu K. • Meyerhardt J.A. • Ogino S. • Wang M. • Fuchs C.S. • et al.
Fiber Intake and Survival After Colorectal Cancer Diagnosis.
JAMA Oncol. 2018; **4**: 71-79
<https://doi.org/10.1001/jamaoncol.2017.3684>

[View in Article](#) ^

[Scopus \(94\)](#) • [PubMed](#) • [Crossref](#) • [Google Scholar](#)

18. Rimm E.B. • Giovannucci E.L. • Stampfer M.J. • Colditz G.A. • Litin L.B. • Willett W.C.
Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals.
Am J Epidemiol. 1992; **135** (; discussion 1127-36): 1114-1126
<https://doi.org/10.1093/oxfordjournals.aje.a116211>

[View in Article](#) ^

[Scopus \(1776\)](#) • [PubMed](#) • [Crossref](#) • [Google Scholar](#)

19. Cain K.C. • Harlow S.D. • Little R.J. • Nan B. • Yosef M. • Taffe J.R. • et al.
Bias due to left truncation and left censoring in longitudinal studies of developmental and disease processes.

Am J Epidemiol. 2011; **173**: 1078-1084

<https://doi.org/10.1093/aje/kwq481>

[View in Article](#) 

[Scopus \(447\)](#) • [PubMed](#) • [Crossref](#) • [Google Scholar](#)



20. Seaman S.R. • White I.R.
Review of inverse probability weighting for dealing with missing data.

Stat Methods Med Res. 2013; **22**: 278-295

<https://doi.org/10.1177/0962280210395740>

[View in Article](#) 

[Scopus \(853\)](#) • [PubMed](#) • [Crossref](#) • [Google Scholar](#)

21. Durrleman S. • Simon R.
Flexible regression models with cubic splines.

Stat Med. 1989; **8**: 551-561

<https://doi.org/10.1002/sim.4780080504>

[View in Article](#) 

[Scopus \(1850\)](#) • [PubMed](#) • [Crossref](#) • [Google Scholar](#)

22. Taylor S.R. • Falcone J.N. • Cantley L.C. • Goncalves M.D.
Developing dietary interventions as therapy for cancer.

Nat Rev Cancer. 2022;

<https://doi.org/10.1038/s41568-022-00485-y>

[View in Article](#) 

[Scopus \(19\)](#) • [Crossref](#) • [Google Scholar](#)

23. Jin H. • Leng Q. • Li C.
Dietary flavonoid for preventing colorectal neoplasms.

Cochrane Database Syst Rev. 2012; **8**: CD009350

<https://doi.org/10.1002/14651858.CD009350.pub2>



[View in Article](#) 

[Crossref](#) • [Google Scholar](#)

24. Zamora-Ros R. • Guino E. • Alonso M.H. • Vidal C. • Barenys M. • Soriano A. • et al.

Dietary flavonoids, lignans and colorectal cancer prognosis.

Sci Rep. 2015; **5**:11118



[View in Article](#) 

[Scopus \(16\)](#) • [Crossref](#) • [Google Scholar](#)

25. Song W.O. • Chun O.K.

Tea is the major source of flavan-3-ol and flavonol in the U.S. diet.

J Nutr. 2008; **138**: 1543S-1547S

<https://doi.org/10.1093/jn/138.8.1543S>

[View in Article](#) 

[PubMed](#) • [Abstract](#) • [Full Text](#) • [Full Text PDF](#) • [Google Scholar](#)

26. Bhagwat, S.; Haytowitz, D. B.; Holden, J. M. USDA Database for the Flavonoid Content of Selected Foods; U.S. Department of Agriculture 2011.

[View in Article](#) 

[Google Scholar](#)

27. Tea Association of the U.S.A. Inc. Tea Fact Sheet - 2022.

https://www.teausa.com/teausa/images/Tea_Fact_2021.pdf.

[View in Article](#) 

[Google Scholar](#)

28. Kopustinskiene D.M. • Jakstas V. • Savickas A. • Bernatoniene J.

Flavonoids as Anticancer Agents.

Nutrients. 2020; **12**

<https://doi.org/10.3390/nu12020457>

[View in Article](#) 



29. Rubert J. • Gatto P. • Pancher M. • Sidarovich V. • Curti C. • Mena P. • et al.
A Screening of Native (Poly)phenols and Gut-Related Metabolites on 3D HCT116 Spheroids Reveals Gut Health Benefits of a Flavan-3-ol Metabolite.

Mol Nutr Food Res. 2022; e2101043

<https://doi.org/10.1002/mnfr.202101043>



30. Shirakami Y. • Sakai H. • Kochi T. • Seishima M. • Shimizu M.
Catechins and Its Role in Chronic Diseases.

Adv Exp Med Biol. 2016; **929**: 67-90

https://doi.org/10.1007/978-3-319-41342-6_4

[View in Article](#)

31. Martin M.A. • Goya L. • Ramos S.
Protective effects of tea, red wine and cocoa in diabetes. Evidences from human studies.

Food Chem Toxicol. 2017; **109**: 302-314

<https://doi.org/10.1016/j.fct.2017.09.015>

[View in Article](#)

32. Fujiki H. • Sueoka E. • Watanabe T. • Suganuma M.
Primary cancer prevention by green tea, and tertiary cancer prevention by the combination of green tea catechins and anticancer compounds.

J Cancer Prev. 2015; **20**: 1-4

<https://doi.org/10.15430/JCP.2015.20.1.1>

[View in Article](#)

33. Mukherjee S. • Siddiqui M.A. • Dayal S. • Ayoub Y.Z. • Malathi K.

Epigallocatechin-3-gallate suppresses proinflammatory cytokines and chemokines induced by Toll-like receptor 9 agonists in prostate cancer cells.

J Inflamm Res. 2014; **7**: 89-101

<https://doi.org/10.2147/JIR.S61365>

[View in Article](#) ^

[Scopus \(43\)](#) • [Crossref](#) • [Google Scholar](#)



Garrett-Mayer E. • et al.

Reduction in promotor methylation utilizing EGCG (epigallocatechin-3-gallate) restores RXRalpha expression in human colon cancer cells.

Oncotarget. 2016; **7**: 35313-35326

<https://doi.org/10.18632/oncotarget.9204>

[View in Article](#) ^

[Scopus \(41\)](#) • [PubMed](#) • [Crossref](#) • [Google Scholar](#)

35. Marquez Campos E. • Stehle P. • Simon M.C.

Microbial Metabolites of Flavan-3-Ols and Their Biological Activity.

Nutrients. 2019; **11**

<https://doi.org/10.3390/nu11102260>

[View in Article](#) ^

[Scopus \(27\)](#) • [Crossref](#) • [Google Scholar](#)

36. Oteiza P.I. • Fraga C.G. • Mills D.A. • Taft D.H.

Flavonoids and the gastrointestinal tract: Local and systemic effects.

Mol Aspects Med. 2018; **61**: 41-49

<https://doi.org/10.1016/j.mam.2018.01.001>

[View in Article](#) ^

[Scopus \(152\)](#) • [Crossref](#) • [Google Scholar](#)

37. Yuan X. • Long Y. • Ji Z. • Gao J. • Fu T. • Yan M. • et al.

Green Tea Liquid Consumption Alters the Human Intestinal and Oral Microbiome.

Mol Nutr Food Res. 2018; **62**e1800178

<https://doi.org/10.1002/mnfr.201800178>



[View in Article](#) 

[Scopus \(77\)](#) • [Crossref](#) • [Google Scholar](#)

38. Dong C.

Protective Effect of Proanthocyanidins in Cadmium Induced Neurotoxicity in Mice.

Drug Res (Stuttg). 2015; **65**: 555-560

<https://doi.org/10.1055/s-0034-1305544>



[Scopus \(19\)](#) • [Crossref](#) • [Google Scholar](#)

39. Rauf A. • Imran M. • Abu-Izneid T. • lahtisham UI H. • Patel S. • Pan X. • et al.

Proanthocyanidins: A comprehensive review.

Biomed Pharmacother. 2019; **116**:108999

<https://doi.org/10.1016/j.biopha.2019.108999>

[View in Article](#) 

[Scopus \(319\)](#) • [Crossref](#) • [Google Scholar](#)

40. Ravindranathan P. • Pasham D. • Balaji U. • Cardenas J. • Gu J. • Toden S. • et al.

Mechanistic insights into anticancer properties of oligomeric proanthocyanidins from grape seeds in colorectal cancer.

Carcinogenesis. 2018; **39**: 767-777

<https://doi.org/10.1093/carcin/bgy034>

[View in Article](#) 

[Scopus \(34\)](#) • [Crossref](#) • [Google Scholar](#)

41. McQuade J.L. • Daniel C.R. • Helmink B.A. • Wargo J.A.

Modulating the microbiome to improve therapeutic response in cancer.

Lancet Oncol. 2019; **20**: e77-e91

[https://doi.org/10.1016/S1470-2045\(18\)30952-5](https://doi.org/10.1016/S1470-2045(18)30952-5)

[View in Article](#) 

[Scopus \(189\)](#) • [PubMed](#) • [Abstract](#) • [Full Text](#) • [Full Text PDF](#) • [Google Scholar](#)

42. Baky, M. H.; Elshahed, M.; Wessjohann, L.; Farag, M. A., Interactions between flavonoids and the gut microbiome: a comprehensive review. *Br J Nutr* 2021, 1

[View in Article](#) 

[Google Scholar](#)

43. Kalt W. • Cassidy A. • Howard L.R. • Krikorian R. • Stull A.J. • Tremblay F. • et al.
Recent Research on the Health Benefits of Blueberries and Their Anthocyanins.



[View in Article](#) 

[Scopus \(178\)](#) • [PubMed](#) • [Abstract](#) • [Full Text](#) • [Full Text PDF](#) • [Google Scholar](#)

44. Ranganathan P. • Pramesh C.S. • Buyse M.
Common pitfalls in statistical analysis: The perils of multiple testing.
Perspect Clin Res. 2016; **7**: 106-107
<https://doi.org/10.4103/2229-3485.179436>

[View in Article](#) 

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