



Special Issue - Colorectal Carcinogenesis and Prevention Editorial Commentary

Perspective: Chemoprevention of colorectal neoplasia: Translating scientific promise into clinical practice

Peter Lance*, Patricia A. Thompson

Arizona Cancer Center, University of Arizona, Tucson, AZ, USA

E-mail: plance@azcc.arizona.edu

*Corresponding author

Published: 16 April, 2011

Journal of Carcinogenesis 2011, 10:11

This article is available from: <http://www.carcinogenesis.com/content/10/1/11>

© 2011 Lance,

Received: 20 January, 2011

Accepted: 15 February, 2011

With more than 145,000 new cases and almost 50,000 deaths each year in men and women combined, colorectal cancer (CRC) is the most common visceral cancer and the second most common of all fatal cancers in the United States.^[1] Colorectal adenomas (CRAs) are benign neoplasms and the precursors to most CRCs,^[2] with the serrated adenoma (SA) now recognized as another premalignant lesion, particularly in the proximal (right) colon.^[3] CRC prevention has focused on the detection and removal of polypoid neoplasms. However, non-polypoid, flat or depressed colorectal neoplasms are relatively common lesions and have a greater association with carcinoma compared with polypoid neoplasms.^[4,5]

In the belief that identification and removal of CRAs and early-stage CRCs will prevent many deaths from the disease, immense effort and resources have been devoted to CRC screening;^[6] currently, periodic colonoscopy is regarded as the most effective although not the only acceptable screening modality.^[6,7] However, the pre-eminence of colonoscopy for CRC prevention has recently been challenged.

Although effective for preventing distal (left-sided) CRC,

in some recent observational studies, colonoscopy was found to have conferred at best modest protection against subsequent proximal CRC.^[8-10] Other studies have shown that the colonoscopy technique is crucial:^[11] when the procedure is performed in accordance with the recommended quality measures, subsequent reduction in proximal CRC occurrence is enhanced.^[12] The effectiveness of colonoscopy will no doubt continue to be debated and, in this debate, the respectable comparative performances of other less costly and invasive screening modalities, such as fecal immunochemical testing^[13-15] and flexible sigmoidoscopy,^[16] should not be ignored. Suffice it to say that screening alone, even if fully implemented in the general population according to the current recommendations, would not prevent all CRC deaths, raising the question of what other preventive measures might or should be deployed.

Chemoprevention is the use of natural agents or synthetic drugs to halt or reverse the carcinogenesis process before the emergence of invasive cancer,^[17] and has been advocated as a potential adjunct to screening for reducing CRC morbidity and mortality. A widely used model has been to use recurrent/metachronous CRAs in patients from whom incident CRAs were previously removed as a surrogate for CRC in randomized controlled trials (RCTs) of putative chemopreventive agents. In such trials, calcium supplementation, aspirin and cyclooxygenase (COX)-2 inhibitors have reduced the risk of CRA by 15–45%;^[18-21] in most studies, somewhat greater reductions in risk – typically 30–50% – have been reported for advanced CRAs (CRAs

Access this article online

Quick Response Code:



Website:

www.carcinogenesis.com

DOI:

10.4103/1477-3163.79674

1+ cm in size or those with villous features or high-grade dysplasia).^[18,20,21] These findings demonstrate the potential for micronutrient and drug-based colorectal chemoprevention to prevent or delay the progression of CRAs to CRC.^[22] A recent trial of difluoromethylornithine (DFMO), an ornithine decarboxylase inhibitor, given in combination with sulindac, a non-steroidal anti-inflammatory drug, provides the strongest evidence to date that drug interventions can prevent or delay the development of colorectal neoplasia. The DFMO + sulindac intervention achieved remarkable reductions in CRA risk: a 70% reduction in risk of all CRAs and more than 90% reduction in risk of advanced and multiple CRAs.^[23]

Unfortunately, in individuals at average risk for CRC, the toxicity associated with the long-term administration of chemopreventive agents tempers enthusiasm for their use and has been the principle barrier to their adoption as part of clinical practice in the general population. Aspirin is associated with an enhanced risk of bleeding and other gastrointestinal side-effects.^[24,25] Depending on the agent, dose and dosing interval, coxib COX-2 inhibitors increase the risk of adverse cardiovascular events to varying degrees.^[26,27] There are concerns of ototoxicity associated with DFMO^[28,29] and cardiotoxicity with sulindac.^[30] Even calcium supplements have been questioned because some observational studies have reported an increased risk of prostate cancer^[31] and, in one randomized trial, there was an increased risk of cardiovascular disease.^[32]

With this background, the current status of chemoprevention for colorectal neoplasia (CRAs and CRC) can be summarized as follows: neither aspirin^[33] nor any other agent is recommended for this purpose as part of usual care. Thus, for clinical chemoprevention, there is a clear need for agents that are both effective and suitable for general use. However, as noted, the uncomfortable fact is that despite completion of RCTs of multiple agents in many thousands of participants over several decades, no chemopreventive agent has entered clinical practice for CRC prevention in individuals at average or increased risk for sporadic CRC. Protagonists of chemoprevention badly need a success if funding agencies and the public are not to forsake this field and quest altogether. What can be done to galvanize the field?

The DFMO + sulindac combination^[23] is potentially the success that the field badly needs, but several questions must first be answered before the combination is ready for clinical practice. The striking initial results require replication, and the question of whether either DFMO or sulindac alone is sufficient or the combination is needed must be settled. Potential ototoxicity from DFMO requires studies with careful audiology and assessment of whether a polymorphic

variation of the ornithine decarboxylase gene^[34] influences susceptibility. High-dose aspirin reduces the incidence of long-term CRC, but adverse effects limit its potential for long-term prevention;^[35] the long-term effectiveness of lower, less-toxic doses has been uncertain. A recent analysis of the effects of lower-dose aspirin (at least 75 mg daily) taken for several years provides compelling evidence for significant reductions in the CRC incidence and mortality.^[36] Should DFMO alone fail to achieve the reduction in CRA risk obtained with DFMO + sulindac, an important issue will be whether aspirin (safer and less costly) can be substituted for sulindac. Trials to address some of these questions are currently being planned.

In the absence of precise multifactorial risk assessment methods to identify those individuals who would most benefit from drugs that prevent CRC, the characteristics of previous, resected CRAs are used to predict risk for future (metachronous) CRAs. Individuals with only one or two small tubular CRAs are at modest risk (at most) for metachronous advanced CRAs,^[37] and it is unlikely that chemoprevention will ever be recommended for this group. Patients who repeatedly develop new CRAs and those with an advanced CRA or greater than two CRAs of any kind are at a substantially increased risk for metachronous advanced colorectal neoplasia.^[37] This group would be an obvious target for effective long-term chemoprevention. Compounding risk factors, such as family history of CRC (particularly at a young age)^[38] and features related to metabolic syndrome,^[39,40] are likely to increase the potential benefits of chemoprevention in patients with advanced CRAs or greater than two CRAs of any kind.

CRA chemoprevention trials have typically taken the form of phase III placebo-controlled trials conducted over periods of >5 years in a thousand or more participants. The primary trial endpoint is the metachronous CRA rate in intervention and placebo groups determined at surveillance colonoscopy performed as part of usual care. The leisurely pace at which such trials deliver results, coupled to their high cost, is likely to be a considerable challenge when funding is sought for future trials of this kind. How could the trial design be modified to provide clear, clinically relevant answers at a less cost and with greater efficiency?

In several respects, the DFMO + sulindac trial has established principles of trial design that are likely to be emulated.^[23] Relatively modest doses of agents targeted at separate cellular pathways were combined to minimize toxicity and enhance the anti-neoplastic effects. An underlying proposition was that only a large reduction in the risk of metachronous CRAs of $\geq 50\%$ would justify future introduction of the

intervention into clinical practice. Therefore, the required sample size of 375 was modest compared with many earlier CRA trials. What further refinements might be useful for the design of future chemoprevention trials?

Trial participants should be at increased risk themselves for advanced CRAs and likely candidates for future long-term chemoprevention when effective agents are introduced into clinical practice. This targets an appropriate population, which has a higher event rate than lower-risk populations, with commensurate reductions in the sample sizes that are required for trials. The consistent evidence that aspirin prevents metachronous CRAs and reduces CRC incidence and mortality at low as well as high doses justifies serious consideration of designing trials without a placebo component; a strong argument can be made that, in future trials, new interventions should be compared with aspirin or other agent(s) with known efficacy. Forgoing a placebo arm will almost certainly facilitate participant recruitment.

A major determinant of the lengthy time to completion of CRA chemoprevention trials is dependence, for compliance with practice guidelines,^[41] on surveillance intervals of 3–5 years before obtaining each trial endpoint colonoscopy; with this approach, colonoscopy costs are covered by patients' insurance as part of usual care. It is time to consider the feasibility of designing trials with a planned primary endpoint based on colonoscopy performed sooner than for usual standard of care, after 12–24 months. Costs of these "investigational" colonoscopies would have to be covered by the studies. However, savings from requiring fewer participants, each on study for shorter periods, than in traditional CRA trials, would offset procedure costs, which are trending downwards anyway in the current medical-economic climate.

This perspective will probably elicit many objections and many thorny issues that have been raised cannot be definitively addressed within this brief contribution. Substantial evidence has emerged that chemoprevention can prevent early colorectal neoplasia and delay its progression. However, the unsettling reality is that we will probably not be provided the resources to continue conducting clinical chemoprevention trials in the generously funded manner to which we have been accustomed. To reiterate, no chemopreventive strategies for the prevention of sporadic CRC have yet entered clinical practice. The unpleasant truth is that this important field may lapse into an enforced hibernation unless we find ways to conduct smaller, more efficient studies yielding results that will finally take this modality into clinical practice within a reasonable timeframe.

REFERENCES

- Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277-300.
- Leslie A, Carey FA, Pratt NR, Steele RJ. The colorectal adenoma-carcinoma sequence. *Br J Surg* 2002;89:845-60.
- Schreiner MA, Weiss DG, Lieberman DA. Proximal and large hyperplastic and nondysplastic serrated polyps detected by colonoscopy are associated with neoplasia. *Gastroenterology* 2010;139:1497-502.
- Soetikno R, Friedland S, Kaltenbach T, Chayama K, Tanaka S. Nonpolypoid (flat and depressed) colorectal neoplasms. *Gastroenterology* 2006;130:566-76.
- Soetikno RM, Kaltenbach T, Rouse RV, Park W, Maheshwari A, Sato T, et al. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. *JAMA* 2008;299:1027-35.
- USPSTF: Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008;149:627-37.
- Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS, et al. Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin* 2008;58:130-60.
- Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L: Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009;150:1-8.
- Brenner H, Hoffmeister M, Arndt V, Stegmaier C, Altenhofen L, Haug U. Protection From Right- and Left-Sided Colorectal Neoplasms After Colonoscopy: Population-Based Study. *J Natl Cancer Inst* 2010;102:89-95.
- Singh H, Nugent Z, Demers AA, Kliewer EV, Mahmud SM, Bernstein CN: The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. *Gastroenterology* 2010;139:1128-37.
- Pohl H, Robertson DJ. Colorectal cancers detected after colonoscopy frequently result from missed lesions. *Clin Gastroenterol Hepatol* 2010;8:858-64.
- Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection From Colorectal Cancer After Colonoscopy. *Ann Intern Med* 2011;54:22-30.
- Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. *Gastroenterology* 2005;129:422-28.
- Park DI, Ryu S, Kim YH, Lee SH, Lee CK, Eun CS, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. *Am J Gastroenterol* 2010;105:2017-25.
- Lane JM, Chow E, Young GP, Good N, Smith A, Bull J, et al. Interval fecal immunochemical testing in a colonoscopic surveillance program speeds detection of colorectal neoplasia. *Gastroenterology* 2010;139:1918-26.
- Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: A multicentre randomised controlled trial. *Lancet* 2010;375:1624-33.
- Sporn MB, Dunlop NM, Newton DL, Smith JM. Prevention of chemical carcinogenesis by vitamin A and its synthetic analogs (retinoids). *Fed Proc* 1976;35:1332-8.
- Arber N, Eagle CJ, Spicak J, Racz I, Dite P, Hajer J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 2006;355:885-95.
- Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, et al. Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 2006;355:873-84.
- Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, et al. Aspirin for the chemoprevention of colorectal adenomas: Meta-analysis of the randomized trials. *J Natl Cancer Inst* 2009;101:256-66.
- Baron JA, Sandler RS, Bresalier RS, Quan H, Riddell R, Lanasa A, et al. A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. *Gastroenterology* 2006;131:1674-82.
- Lance P. Chemoprevention for colorectal cancer: Some progress but a long way to go. *Gastroenterology* 2008;134:341-3.
- Meyskens FL Jr, McLaren CE, Pelot D, Fujikawa-Brooks S, Carpenter PM, Hawk E, et al. Difluoromethylornithine plus sulindac for the prevention of sporadic

- colorectal adenomas: A randomized placebo-controlled, double-blind trial. *Cancer Prev Res* 2008;1:32-8.
24. Laine L. Review article: Gastrointestinal bleeding with low-dose aspirin - what's the risk? *Aliment Pharmacol Ther* 2006;24:897-908.
 25. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006;119:624-38.
 26. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006;332:1302-8.
 27. Solomon SD, Wittes J, Finn PV, Fowler R, Viner J, Bertagnoli MM, et al. Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: The cross trial safety analysis. *Circulation* 2008;117:2104-13.
 28. Croghan MK, Aickin MG, Meyskens FL. Dose-related alpha-difluoromethylornithine ototoxicity. *Am J Clin Oncol* 1991;14:331-5.
 29. Doyle KJ, McLaren CE, Shanks JE, Galus CM, Meyskens FL. Effects of difluoromethylornithine chemoprevention on audiometry thresholds and otoacoustic emissions. *Arch Otolaryngol Head Neck Surg* 2001;127:553-8.
 30. Zell JA, Pelot D, Chen WP, McLaren CE, Gerner EV, Meyskens FL. Risk of cardiovascular events in a randomized placebo-controlled, double-blind trial of difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas. *Cancer Prev Res (Phila)* 2009;2:209-12.
 31. Chan JM, Gann PH, Giovannucci EL. Role of diet in prostate cancer development and progression. *J Clin Oncol* 2005;23:8152-60.
 32. Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, et al. Vascular events in healthy older women receiving calcium supplementation: Randomised controlled trial. *BMJ* 2008;336:262-6.
 33. Dube C, Rostom A, Lewin G, Tsertsvadze A, Barrowman N, Code C, et al. The use of aspirin for primary prevention of colorectal cancer: A systematic review prepared for the US Preventive Services Task Force. *Ann Intern Med* 2007;146:365-75.
 34. Zell JA, McLaren CE, Chen W-P, Thompson PA, Gerner EV, Meyskens FL. Ornithine decarboxylase-I polymorphism, chemoprevention with eflornithine and sulindac, and outcomes among colorectal adenoma patients. *J Natl Cancer Inst*. 2010 102:1513-16.
 35. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA* 2005;294:914-23.
 36. Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet* 2010;376:1741-50.
 37. Martinez ME, Baron JA, Lieberman DA, Schatzkin A, Lanza E, Winawer SJ, et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. *Gastroenterology* 2009;136:832-41.
 38. Taylor DP, Burt RW, Williams MS, Haug PJ, Cannon-Albright LA. Population-based family history-specific risks for colorectal cancer: Constellation approach. *Gastroenterology* 2010;138:877-85.
 39. Jacobs ET, Martinez ME, Alberts DS, Jiang R, Lance P, Lowe KA, et al. Association between body size and colorectal adenoma recurrence. *Clin Gastroenterol Hepatol* 2007;5:982-90.
 40. Ashbeck EL, Jacobs ET, Martinez ME, Gerner EV, Lance P, Thompson PA. Components of metabolic syndrome and metachronous colorectal neoplasia. *Cancer Epidemiol Biomarkers Prev* 2009;18:1134-43.
 41. Winawer SJ, Zauber AG, Fletcher RH, Stillman JS, O'Brien M J, Levin B, et al. Guidelines for colonoscopy surveillance after polypectomy: A consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *CA Cancer J Clin* 2006;56:143-59; quiz 184-145.

AUTHOR'S PROFILE

Dr. Peter Lance, Arizona Cancer Center 1515 N. Campbell Avenue Tucson, AZ 85724.

Dr. Patricia A Thompson, Arizona Cancer Center 1515 N. Campbell Avenue Tucson, AZ 85724



Journal of Carcinogenesis is published for Carcinogenesis Press by Medknow Publications and Media Pvt. Ltd.

Manuscripts submitted to the journal are peer reviewed and published immediately upon acceptance, cited in PubMed and archived on PubMed Central. Your research papers will be available free of charge to the entire biomedical community. Submit your next manuscript to Journal of Carcinogenesis.
www.journalonweb.com/jcar/