Summary

Cancer chemoprevention strategies are not widely implemented in clinical practice. Targeting biomarkers in patients with elevated risk of developing cancer using short-term administration of certain agents may be a strategy to minimize toxicities while maintaining efficacy in clinical trials that can be completed in years rather than decades.
In this issue of *Clinical Cancer Research*, Takayama and colleagues address two major limitations in cancer chemoprevention clinical trial designs: the selection of surrogate endpoints of cancer and the long-term administration of agents to at-risk populations(1).

Strong clinical evidence supports colorectal adenoma (CRA) as a biological intermediate for colorectal cancer (CRC)(2). In randomized studies, long-term (years) continuous use of COX2-selective inhibitors of non-steroidal anti-inflammatory drugs (NSAIDs) as well sulindac, a non-selective NSAID, has been shown to prevent CRA in average-risk and genetically high-risk groups (3, 4). The prevention of CRA with NSAIDs, along with extensive evidence for the prostanoid pathway in epithelial tumorigenesis, justifies enthusiasm for NSAIDs as a class of drugs with cancer preventive properties. However, concern over agent-related toxicity (*i.e.*, gastrointestinal [GI] and cardiovascular) and tolerability with prolonged use challenges the acumen of NSAIDs as clinically viable research endeavors.

An estimated 60 million Americans annually are prescribed an NSAID (5, 6) and, with over-the-counter availability, a large fraction report regular use for more than 30 days. Given their cancer prevention activity, a need exists to clarify agent-specific potency, including study designs that allow iterative testing to find the lowest effective dose and duration. The Takayama study on the use of NSAIDs for eradicating aberrant crypt foci (ACF) is an important example of one such design. This small, double-blinded, placebo-controlled study of 300 mg/day sulindac or 400 mg/day etodolac for 2 months for ACF prevention has a number of notable strengths that include a focus on short-term, discontinuous NSAID use and shorter time to endpoint analysis. To select a maximally effective, shortest drug duration schedule, the investigators first estimated the effect of 1, 2, 3, and 5 months of 300 mg/day sulindac on ACF in a few subjects. In a larger, placebo-controlled study, the investigators demonstrated a significant effect of 2 months’ sulindac treatment on ACF. Importantly, they show 2 months’ daily sulindac followed by no drug was sufficient to reduce risk of colorectal polyps of any type at 12 months. In contrast, treatment with etodolac (a COX2 inhibitor) for 2 months showed no effect on ACF or polyp formation. Takayma et al. postulate that short-duration sulindac eradicates ACF, resulting in fewer total polyps. Perhaps the lack of COX2 expression in ACF and off-target (non-COX2) activity of sulindac explain the differential effect between the agents. These results suggest that
short, discontinuous treatment with sulindac may be sufficient to achieve a chemopreventive effect. If better understood, this finding would allow for more measured use of sulindac in moderate-risk groups to offset harms associated with long-term use.

Using surrogate endpoints for CRC remains controversial. In 2003, Levin (7) raised issues with the use of CRA citing the low frequency of conversion to cancer and concern that drug effects on lesions with low inherent malignant potential may not be informative for prevention of invasive carcinoma. This criticism has been raised more strongly for ACF, particularly the more common non-dysplastic type, where neither the presence nor number changed with celecoxib treatment, nor were ACF correlated with risk of CRA in a substudy of patients in the Adenoma Prevention with Celecoxib (APC) trial (8). Takayama et al. acknowledge the field’s criticism of ACF as a surrogate endpoint for cancer and note the lack of power to assess effects on dysplastic-type ACF. However, they emphasize that sulindac efficacy for the prevention of polyp and CRA at 12 months was greater in individuals who showed eradication of ACF with sulindac intervention. This finding lends support to the ACF lesion as a precursor for colorectal polyps that is eradicated by sulindac but not etodolac therapy.

We believe this study raises two important issues. First, short, discontinuous use of sulindac appears as effective in suppressing polyp formation (by eradicating the ACF precursor) as longer (1-2 year), continuous treatments. This noteworthy observation contrasts with evidence from the APC Trial, wherein celecoxib showed no treatment effect for ACF(8). Second, Takayama et al. distinguish between preventing adenoma versus treating earlier precursors (ACF). Both conclusions provide an opportunity to discuss trial design modifications that would accelerate answers to questions about agent dose and duration and possibly differential action of COX2 inhibitors and sulindac.

We adapted Levin’s Figure 1 (7) on the "timeline of evaluation of surrogate endpoints associated with chemoprevention studies" to address the issues raised by the Takayama study. In the classic chemoprevention trial design for CRA, patients who have undergone polypectomy (at-risk population with clean colon) are recruited, randomized to treatment or placebo, and followed to colonoscopy as dictated clinically by surveillance guidelines. This approach has the advantages of having a fairly large population of eligible subjects (persons with adenoma), follows standard-of-care practices (endpoint colonoscopy covered by insurers), and does not
introduce additional harm to subjects with non-standard use of colonoscopy. Disadvantages include exposing predominantly average-risk subjects to long interventions, decreasing the benefit to risk ratio.

Takayama's study represents an alternative to the classic design, involving a trial with planned colonoscopy at shorter intervals. The authors advocate for the ACF endpoint, but a strength of their study is the endoscopy results at 12 months. We support similar designs and suggest consideration of only large effect size (50% risk reduction) and implementation as a Phase II agent screening approach similar to those conducted in the therapeutic setting (9). This includes loosening the alpha level for significance testing in order to fast-track agent(s) dose/duration combinations to Phase III testing. The advantages of this approach would be smaller, faster studies with reduced exposure to study participants to identify best dose, duration, and drug combinations. The disadvantage of this design is the introduction of a non-standard endoscopy procedure, which increases patient risk and study costs.

With regard to distinguishing preventive versus treatment effects, we propose recruiting subjects with a history of polyp that are due for surveillance endoscopy at some near future date (12-18 months) to intervention studies. Many of these patients will have prevalent CRA, which can be estimated from published studies for sample size and power estimates, and are ideal candidates for short-term treatment to test agent effect (alone or in combination) on existing adenoma. For this and all intervention studies, we reiterate the cautionary note raised by Levin (7) that post-treatment endpoints should be integrated as part of the formal clinical trial design (see modification to Figure 1). Partial reduction in growth, as opposed to eradication, could result in altered kinetics such that existing lesions fall just below the limits of endoscopy detection. This could adversely increase surveillance intervals post-intervention in at-risk individuals.

In these short 'prevention' and 'treatment' designs, the timeline for completion of primary (effect on surrogate endpoint) and immediate secondary (toxicities and adenoma rates after stopping treatment) endpoints could conceivably occur within a 5-year grant cycle. Complementary to this discussion, Robert Temple, Director of the Office of Medical Policy of the FDA’s Center for Drug Evaluation and Research, recently discussed parallels between the development of drugs for cardiovascular disease and cancer (10). “It seems clear that effective
cancer prevention drug development will depend on finding clinical features and biomarkers that identify high-risk states…” He emphasized the importance of choosing populations in which drug benefit clearly exceeds drug risk. Perhaps increased effort to identify moderate-to-high-risk populations, combined with focus on determining the minimum necessary dose/duration for drug effect, will provide a way to move NSAIDs from use in the familial high-risk setting to additional patient populations.

Acknowledgements. The authors acknowledge Betsy Wertheim for her help editing the commentary. Drs. Thompson and Gerner acknowledge the support from the National Institutes of Health (CA095060 and CA123065).

Disclosure of Potential Conflict of Interest. Dr. Gerner has an ownership interest in Cancer Prevention Pharmaceuticals, Tucson, Arizona.
References


Figure 1. Fast tracking the timeline of evaluation of chemoprevention studies of NSAIDS. Integration of the common surrogate endpoints of aberrant crypt foci or any polyp allows design considerations for short interventions with shorter time to follow-up. Truncation of this timeline in the ongoing evaluation of the NSAIDs for prevention would allow formal inclusion of post intervention evaluation to determine persistency of effect or emergence of latent harmful effects for establishing informed delivery of NSAIDs for chemoprevention.
Outcomes of persistent benefit or latent harmful effect

<table>
<thead>
<tr>
<th>Time (months to years)</th>
<th>Drug stopped</th>
<th>Trial stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agent(s) 2, 3, 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Surrogate endpoints of agent anti-neoplastic effect in colorectum (Benefit)**

1. Advanced colorectal neoplasia (rare/most relevant to life-threatening invasive cancer)
2. Any colorectal adenoma (common/reduced relevance to invasive cancer)
3. Aberrant Crypt foci (common/non-dysplastic type questionable relevance to invasive cancer)
4. Biomarkers
   a) effect on proliferation, apoptosis, or other oncogenic molecules (questionable for anti-cancer effect)
   b) effect on target molecules (no information for anti-cancer effect)
clinical cancer research

of timing and surrogates - a way forward for cancer chemoprevention

patricia thompson and eugene w gerner

clin cancer res published onlinefirst april 15, 2011.

updated version
access the most recent version of this article at:
doi: 10.1158/1078-0432.ccr-11-0643

supplementary material
access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2011/05/27/1078-0432.ccr-11-0643.dc1

author manuscript
author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

email alerts
sign up to receive free email-alerts related to this article or journal.

reprints and subscriptions
to order reprints of this article or to subscribe to the journal, contact the aacr publications department at pub@aacr.org.

permissions
to request permission to re-use all or part of this article, contact the aacr publications department at permissions@aacr.org.