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Randomized phase II trial of sulindac for lung cancer chemoprevention

Paul J. Limburg[a,*], Sumithra J. Mandrekar[a], Marie Christine Aubry[a], Katie L. Allen Ziegler[a], Jun Zhang[a], Joanne E. Yi[a], Michael Henry[a], Henry D. Tazelaar[b], Stephen Lam[c], Annette McWilliams[c], David E. Midthun[a], Eric S. Edell[a], Otis B. Rickman[a], Peter Mazzone[d], Melvyn Tockman[e], John F. Beamis[f], Carla Lamb[f], Michael Simoff[g], Charles Loprinzi[a], Eva Szabo[h], James Jett[a], For the Cancer Prevention Network

[a] *Mayo Clinic, Rochester, MN, United States*
[b] *Mayo Clinic in Arizona, Scottsdale, AZ, United States*
[c] *British Columbia Cancer Agency, Vancouver, BC, United States*
[d] *Cleveland Clinic, Cleveland, OH, United States*
[e] *H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, United States*
[f] *Lahey Clinic Medical Center, Burlington, MA, United States*
[g] *Henry Ford Hospital, Detroit, MI, United States*
[h] *Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, United States*

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ABSTRACT

Introduction: Sulindac represents a promising candidate agent for lung cancer chemoprevention, but clinical trial data have not been previously reported. We conducted a randomized, phase II chemoprevention trial involving current or former cigarette smokers (≥30 pack-years) utilizing the multi-center, inter-disciplinary infrastructure of the Cancer Prevention Network (CPN).
Methods: At least 1 bronchial dysplastic lesion identified by fluorescence bronchoscopy was required for randomization. Intervention assignments were sulindac 150 mg bid or an identical placebo bid for 6 months. Trial endpoints included changes in histologic grade of dysplasia (per-participant as primary endpoint and per lesion as secondary endpoint), number of dysplastic lesions (per-participant), and Ki67 labeling index.
Results: Slower than anticipated recruitment led to trial closure after randomizing participants ($n = 31$ and $n = 30$ in the sulindac and placebo arms, respectively). Pre- and post-intervention fluorescence bronchoscopy data were available for 53/61 (87%) randomized, eligible participants. The median (range) of dysplastic lesions at baseline was 2 (1–12) in the sulindac arm and 2 (1–7) in the placebo arm. Change in dysplasia was categorized as regression:stable:progression for 15:3:8 (58%:12%:31%) subjects in the sulindac arm and 15:2:10 (56%:7%:37%) subjects in the placebo arm; these distributions were not statistically different ($p = 0.85$). Median Ki67 expression (% cells stained positive) was significantly reduced in both the placebo (30 versus 5; $p = 0.0005$) and sulindac (30 versus 10; $p = 0.0003$) arms, but the difference between arms was not statistically significant ($p = 0.92$).
Conclusions: Data from this multi-center, phase II squamous cell lung cancer chemoprevention trial do not demonstrate sufficient benefits from sulindac 150 mg bid for 6 months to warrant additional phase III testing. Investigation of pathway-focused agents is necessary for lung cancer chemoprevention.

1. Introduction

Lung cancer is the most common malignancy worldwide [1] with approximately one-half of all incident cases attributable to cigarette smoking [2]. Since an estimated 90 million smokers reside in the U.S. alone [3,4], there is an urgent need for novel lung cancer prevention strategies. Bronchial dysplasia can be readily identified by fluorescence bronchoscopy [5–7] and represents a plausible surrogate endpoint biomarker for early phase lung cancer chemoprevention trials [8,9]. Although change in bronchial dysplasia primarily informs the prevention of squamous cell carcinoma, this readily measurable endpoint plays a key role in chemoprevention agent development [10] and has been previously employed in several early phase clinical trials [11–14].

* Corresponding author at: 200 First Street SW, Rochester, MN 55905, United States. Tel.: +1 507 266 4338; fax: +1 507 266 0350.
E-mail address: limburg.paul@mayo.edu (P.J. Limburg).

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Nonsteroidal anti-inflammatory drugs (NSAIDs) may provide lung cancer chemopreventive benefits through multiple mechanisms that are mediated, at least in part, by cyclooxygenase (COX)-2 inhibition [15–18]. Animal studies have shown that COX inhibitors can suppress lung tumorigenesis [19,20] and three small, short-term phase II clinical trials have reported beneficial effects from celecoxib (a selective COX-2 inhibitor) on bronchial Ki67 labeling index [21–23]. However, none of the trials reported to date were designed or powered to address changes in bronchial histopathology. Ongoing concerns regarding the cardiovascular toxicity of selective COX-2 inhibitors [24,25] have prompted renewed interest in non-selective COX inhibitors, such as sulindac, for chemopreventive applications [26]. In this context, we conducted a randomized, double-blind, phase II trial of sulindac versus placebo among current or former smokers with histologically confirmed bronchial dysplasia at baseline.

2. Materials and methods

The study protocol was approved by appropriate Institutional Review Boards at each participating site (ClinicalTrials.gov, NCT00368927). Participants provided written informed consent prior to any study-related procedures. The Mayo Clinic Cancer Center Data and Safety Monitoring Board reviewed safety data every 6 months.

2.1. Subject recruitment

Subjects were enrolled at six institutions from 2006 to 2009. The target population was defined as current or former smokers, age 40–79 years, with either no history of lung cancer or stage I NSCLC resected ≥1 year prior to the baseline evaluation. General inclusion criteria were: normal organ function; no evidence of malignancy on chest X-ray; no current NSAID use (except aspirin ≤81 mg qd), or other potentially interfering compounds; and ECOG performance status ≤1. Women of childbearing potential were required to document a negative pregnancy test prior to enrollment. Exclusion criteria were: history of malignancy within the preceding 3 years (other than resected stage I NSCLC); currently breastfeeding; use of other investigational agents; or uncontrolled intercurrent illness.

2.2. Baseline evaluation

Eligible subjects were required to have at least one site of biopsy-confirmed bronchial dysplasia on bronchoscopy exam, performed <45 days prior to randomization by experienced endoscopists under white light and fluorescence settings, using an Olympus BF40D (or comparable) bronchoscope and Onco-LIFE device. At least one biopsy sample was taken from each area suspicious for intraepithelial or invasive neoplasia, with the location carefully recorded. Additional biopsies were taken from 6 pre-defined areas of visually normal epithelium: main carina, right upper lobe carina, right middle lobe carina, right lower lobe-superior segment carina, left upper lobe carina, and left lower lobe superior segment carina.

2.3. Intervention assignments and on-study assessments

Subjects were randomly assigned to receive sulindac 150 mg bid or identical placebo bid for 6 months (1:1 ratio) using a dynamic allocation procedure to balance marginal distributions of the specified stratification factors: smoking status (former versus current); history of lung cancer (yes versus no), and number of dysplastic lesions at baseline (1–3 versus >3). A telephone interview was conducted at Month 1, and a physical exam and safety assessment were performed at Month 3.

2.4. Post-intervention evaluation

Physical exam, blood work, and bronchoscopy were repeated at Month 6 using the same standardized protocol employed at baseline. Biopsies were obtained from all sites sampled at baseline, as well as from any newly identified suspicious areas.

2.5. Tissue processing and histologic interpretation

Bronchial mucosa biopsy samples were fixed in 10% neutral buffered formalin and paraffin-embedded. Two pulmonary pathologists, blinded to the intervention assignments, independently classified the histologic findings according to WHO/IASLC criteria [27]: normal, basal cell hyperplasia, or metaplasia; mild dysplasia; moderate dysplasia; severe dysplasia; carcinoma in situ; or invasive cancer. Discrepancies in biopsy interpretation were adjudicated in collaboration with a third pathologist to achieve consensus.

2.6. Mucosal proliferation

Mucosal proliferation was assessed by Ki67 immunostaining (MIB-1 clone; 1/100, Dako Antibody diluent, Dako, Carpenteria, CA). Ki67 analyses were limited to subjects with paired biopsy samples adequate for immunostaining and were assessed throughout the thickness of the bronchial epithelium. Immunoreactivity was scored as the percentage of positively staining cells (i.e., Ki67 labeling index) in 5% increments (range = 0–100%) by a pulmonary pathologist.

2.7. Compliance and adverse event monitoring

Intervention compliance was monitored using a standardized agent diary, which was reviewed during each telephone call or study visit. Adverse events were classified and graded using NCI Common Terminology Criteria, version 3.0 (www.ctep.cancer.gov), with maximum grade per subject and event type recorded across the duration of intervention.

2.8. Statistical considerations

The primary endpoint was defined as change in histologic grade of bronchial dysplasia, based on a per-participant analysis. Secondary endpoints included change in the number of bronchial dysplastic lesions, modulation of Ki67 expression, and observed adverse event profiles. Lesion-specific change in bronchial dysplasia was also analyzed as a secondary endpoint, with categories of complete response (CR), partial response (PR), progressive disease (PD), or stable disease (SD) defined as: CR = regression of a dysplastic lesion to normal, hyperplasia, or metaplasia; PR = improvement of a dysplastic lesion by at least two histologic grades (except to normal, hyperplasia or metaplasia in which case CR was recorded); PD = worsening of a dysplastic lesion by at least two histologic grades and/or the appearance of any new dysplastic lesion; and SD = any response that did not meet the lesion-specific change state criteria outlined above. Participant-specific changes in bronchial dysplasia were categorized and defined as: CR = regression of all dysplastic lesions to normal, hyperplasia or metaplasia (with no new or progressing dysplastic lesions identified); PR = regression of one or more, but not all, dysplastic lesions (with no new or progressing dysplastic lesions identified); PD = worsening of one or more dysplastic lesions by at least 2 histologic grades and/or the appearance of any new dysplastic lesion; and SD = any response that did not meet the participant-specific change state criteria outlined above.

Assuming a spontaneous regression rate of 24% for the placebo arm [11] the trial was designed to detect a bronchial dysplasia regression rate of 54% (with 90% power) among subjects assigned to receive active sulindac (2-sided chi-square test with continuity correction; type I error rate of 5%). However, due to slower than anticipated subject accrual, recruitment was closed after 61/122 (50%) participants were randomized ($n = 31$ in the sulindac arm and $n = 30$ in the placebo arm, with 26 and 27 subjects evaluable for the primary endpoint, respectively). Based on post hoc calculations, the modified sample size provided 81% power to detect a bronchial dysplasia regression rate of 66% in the sulindac arm compared to 24% in the placebo arm, with a 2-sided type I error rate of 5%.

Comparisons were made between intervention arms using a chi-square or Fisher's exact test for categorical and Wilcoxon rank sum test for continuous variables, respectively. Percent changes in the number of bronchial dysplastic lesions and Ki67 expression levels were compared between the two intervention arms using a Wilcoxon rank sum test, and within intervention arms using the Wilcoxon signed rank test. A generalized estimating equations (GEE) approach was used to compare the lesion-specific response rates between intervention arms to account for the correlation of multiple lesions within a participant. For the efficacy endpoint analyses, only those subjects with complete pre- and post-intervention bronchoscopy data were included. Otherwise, all randomized subjects who started their assigned study agent were included in the data analyses. All statistical tests were performed two-sided, unless otherwise noted, using SAS version 9.2 (SAS, Inc., Cary, NC).

3. Results

3.1. Cohort description

Four hundred nine patients were pre-registered for the baseline evaluation, of whom 172 completed the baseline bronchoscopy exam, 74 were found to have at least 1 site of histologically confirmed bronchial dysplasia, and 63 were randomized ($n = 32$ in the sulindac and $n = 31$ in the placebo arms). Two randomized participants ($n = 1$ in each arm) did not initiate their assigned study intervention, leaving 61 participants in the final intervention cohort ($n = 31$ in the sulindac and 30 in the placebo arms), as shown in the CONSORT flow diagram (Fig. 1).

Baseline participant characteristics were similarly distributed in the active and placebo intervention arms ($p > 0.05$ for each comparison; Table 1). Eighteen participants reported low dose aspirin use, with no difference between arms ($n = 11$ and $n = 7$ in the sulindac and placebo arms, respectively; $p = 0.40$). Complete baseline bronchoscopy data were available for all 61 (100%) participants in the intervention cohort. The median (range) of mucosal biopsies per participant was 7 (6–17) in the sulindac arm and 8 (6–18) in the placebo arm. The median (range) of dysplastic lesions per participant was 2 (1–12) and 2 (1–7) in the sulindac and placebo arms, respectively. By stratification levels, 89% had 1–3 dysplastic lesions and 11% had >3 dysplastic lesions, with no statistically significant difference between intervention arms ($p = 0.71$). At baseline, 45.9% had mild dysplasia and 54.1% had moderate/severe dysplasia, with no statistically significant difference between intervention arms ($p = 0.44$; Table 1).

3.2. Change in bronchial dysplasia

Post-intervention bronchoscopy data were available for 53/61 (87%) participants overall (84% and 90% participants in the sulindac and placebo arms, respectively), with missing data for 8 participants ($n = 3$ self-withdrawal, $n = 2$ adverse events, $n = 2$ lost to follow-up, and $n = 1$ investigator decision). Given the relatively small numbers of participants with PR ($n = 5$ in the sulindac arm and $n = 2$ in the placebo arm), the CR and PR categories were combined for statistical analyses. In the participant-specific analyses, the proportion with PR, SD, and PD was comparable between the sulindac and placebo arms ($p = 0.85$; Table 2 and Fig. 2). No statistically significant differences from sulindac versus placebo were observed among baseline current ($p = 0.77$) or former ($p = 1.00$) smokers. Similarly, analyses based on the most advanced histologic diagnosis at baseline (mild or moderate/severe dysplasia) demonstrated no appreciable effects from the active versus placebo interventions ($p = 1.00$ and $p = 0.57$ respectively), although these subgroup analyses were limited by small sample size.

The median percent change in number of dysplastic lesions per participant was not statistically different between intervention arms ($p = 0.63$). In the per-lesion analyses (Table 2), a total of 220 lesions in 26 participants assigned to the sulindac arm were biopsied at baseline (26.8% dysplastic) and 233 lesions in 26 participants were biopsied post-intervention (15.0% dysplastic). In the placebo arm, a total of 234 lesions in 27 participants were biopsied at baseline (25.6% dysplastic) and 251 lesions in 27 participants were biopsied post-intervention (15.9% dysplastic). In the sulindac and placebo arms, 222 and 238 lesions, respectively had either a baseline biopsy and post-intervention matched biopsy, or had a biopsy obtained during the post-intervention bronchoscopy from a mucosal site that was not biopsied at baseline (i.e., assumed to be normal). The per-lesion response rate in the sulindac arm was categorized as 15.3% with CR or PR, 81.1% with SD, and 3.6% with PD; for the placebo arm, the corresponding rates were 15.1%, 77.3%, and 7.6%. Using the GEE approach, these distributions were not significantly different between intervention arms ($p = 0.35$), adjusted for smoking status. Of note, in the PD category, 1/8 lesions in the sulindac arm (from 1 participant) and 8/18 lesions in the placebo arm (from 4 participants) represented newly identified dysplasia at the post-intervention exam, while the remainder represented lesion progression at a previously biopsied site.

3.3. Tissue proliferation

Ki67 labeling index data were available from baseline normal mucosa and site-matched, post-intervention biopsy samples for 43 participants ($n = 20$ and $n = 23$ in the sulindac and placebo arms, respectively), and from baseline bronchial dysplasia and site-matched, post-intervention biopsy samples from 39 participants ($n = 20$ and $n = 19$ in the sulindac and placebo arms, respectively). For samples taken from baseline normal mucosa, a statistically significant reduction in median Ki67 expression (% cells stained positive) was observed among participants in the placebo arm (baseline versus post-intervention: 5% versus 1%; $p = 0.005$), but not the sulindac arm (5% versus 5%; $p = 0.59$); the difference between intervention arms was also statistically significant ($p = 0.009$; Table 3). For samples taken from baseline bronchial dysplasia, statistically significant reductions in median Ki67 expression were observed among participants in both the sulindac (30% versus 10%; $p = 0.0003$) and placebo (30% versus 5%; $p = 0.0005$) arms, with no appreciable difference between the intervention arms ($p = 0.92$).

3.4. Agent compliance and adverse events

Agent compliance and adverse event data were recorded for all 61 participants in the intervention cohort. Median compliance was 95.3% and 95.1% in the active and placebo arms, respectively, with no statistically significant difference between groups ($p = 0.95$). At least one adverse event, regardless of grade or attribution, was reported by 26/31 (84%) participants in the sulindac arm and 23/30 (77%) participants in the placebo arm ($p = 0.54$ for comparison between arms). Most adverse events were classified as grade 1

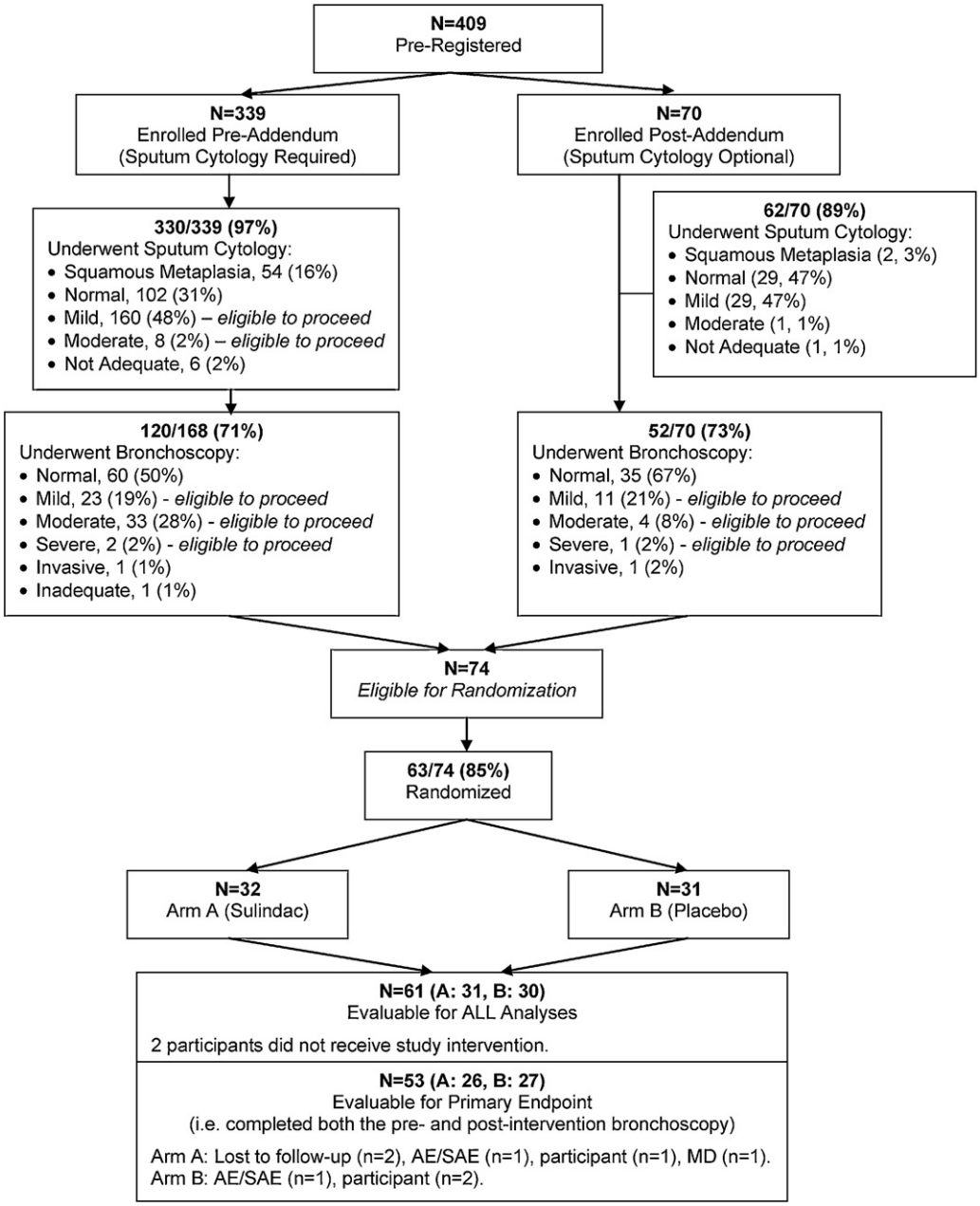

Fig. 1. CONSORT flow diagram.

(67%), with progressively fewer grade 2 (34%), and grade 3 (8%) adverse events reported. Five participants reported a total of 6 grade 3 adverse events (lower limb muscle weakness, edema, and depression in the sulindac arm; depression and joint injury/back pain in the placebo arm, respectively). No participants reported a grade 4 adverse event. Based on the judgment of the treating physician, 9.5% of the grade 2 or higher adverse events were at least possibly related to the active intervention agent.

4. Discussion

To our knowledge, we report the first randomized, placebo-controlled trial of sulindac for squamous cell lung cancer chemoprevention, as well as the first trial to assess the effects of a traditional NSAID on bronchial dysplasia as the primary endpoint. Overall, our multi-center trial found no statistically significant benefits with respect to bronchial dysplasia or mucosal proliferation from sulindac 150 mg bid versus placebo bid for 6 months. Given the smaller than anticipated sample size, the possibility that sulindac had some effects on the analyzed biomarker endpoints cannot be ruled out. However, a large effect was not missed. In view of the less-than-perfect association between bronchial premalignancy and subsequent cancer development, phase II lung cancer chemoprevention trials seek to identify agents with a large effect, not just a statistically significant one. Thus, we interpret the data from our study as demonstrating insufficient benefits from sulindac to support subsequent phase III evaluation as a squamous cell lung cancer chemoprevention agent.

Existing phase III trial data regarding the association between NSAID use and lung cancer incidence are limited to secondary analyses from studies conducted for other indications. More specifically, Peto et al. observed no statistically significant benefit from aspirin 500 mg qd for 6 years (versus control) with respect to lung cancer mortality [28]. Cook et al. detected relatively modest

Table 1
Baseline characteristics by intervention arm.

Baseline characteristic	Sulindac 150 mg BID ($N=31$)	Placebo 1 tablet BID ($N=30$)	p-Value[d]
Age, years[a]	59 (45–77)	60 (44–77)	0.87
Body mass index, kg/m^2[a]	27.5 (19.1–38.9)	28.8 (19.5–42.5)	0.64
Gender, *N* (%)			0.77
Female	7 (22.6)	8 (26.7)	
Male	24 (77.4)	22 (73.3)	
Smoking status, *N* (%)[b]			1.00
Current	20 (64.5)	20 (66.7)	
Former	11 (35.5)	10 (33.3)	
Prior NSAID use, *N* (%)			0.27
Yes	12 (38.7)	7 (23.3)	
No	19 (61.3)	23 (76.7)	
Low dose aspirin use, *N* (%)			0.40
Yes	11 (35.5)	7 (23.3)	
No	20 (64.5)	23 (76.7)	
Alcohol intake, *N* (%)			0.13
None	12 (38.7)	13 (43.3)	
≤1 drink/d	10 (32.3)	15 (50.0)	
2–3 drinks/d	6 (19.4)	2 (6.7)	
≥4 drinks/d	3 (9.7)	0 (0.0)	
Prior lung cancer, *N* (%)[b]			1.00
Yes	1 (3.2)	0 (0.0)	
No	30 (96.8)	30 (100)	
Baseline bronchoscopy exam			
Mucosal biopsies obtained[a]	7 (6–17)	8 (6–18)	0.37
Dysplastic lesions identified[a]	2 (1–12)	2 (1–7)	0.34
1–3 dysplastic lesions[b], *N* (%)	28 (90.3)	26 (86.7)	0.71
>3 dysplastic lesions[b], *N* (%)	3 (9.7)	4 (13.3)	
Most advanced histology, *N* (%)[c]			0.51
Mild dysplasia	16 (51.6)	12 (40.0)	
Moderate dysplasia	13 (41.9)	17 (56.7)	
Severe dysplasia	2 (6.5)	1 (3.3)	

[a] Median (range).
[b] Denotes stratification factor.
[c] At least one site of biopsy-confirmed bronchial dysplasia was required for randomization (subjects found to have carinoma in situ or invasive cancer were excluded).
[d] Fisher's exact test, with the exception of age and BMI which utilized the rank-sum test.

effects from aspirin 100 mg qod for an average of 10.1 years (versus placebo) on lung cancer incidence and lung cancer mortality [29]. Rothwell et al. conducted a combined analysis of individual patient level data from seven aspirin intervention trials and found a 32% decrease in deaths due to lung cancer among individuals assigned to receive the active intervention [30]. However, the inverse association with lung cancer risk was only seen after 5 years of follow up and was confined to adenocarcinomas, with no statistically significant benefits detected with respect to squamous cell carcinomas. Notably, the results from our study are actually consistent with previously reported phase III trial data, since our study was designed to evaluate the effects of sulindac on precursor lesions for bronchial squamous cell carcinoma, not adenocarcinoma.

Extensive preclinical data support the hypothesis that COX-2 and/or related proteins are functionally involved in lung carcinogenesis, as reviewed elsewhere [19,20,31–33]. However, the majority of preclinical studies have been based on bronchial adenocarcinogenesis models. Thus, the full relevance of these data for predicting agent performance in human chemoprevention trials among subjects at increased risk for squamous cell carcinoma is uncertain. Our study suggests that these animal carcinogenesis studies may not be useful to predict response in the bronchial

Table 2
Change in bronchial dysplasia, by intervention arm.

Subject group	Sulindac 150 mg BID	Placebo 1 Tablet BID	p-Value[a]
Overall			0.85
Subjects per arm, *N*	26	27	
Regression, *N* (%)	15 (57.7)	15 (55.6)	
Complete response	10 (38.5)	13 (48.2)	
Partial response	5 (19.2)	2 (7.4)	
Stable, *N* (%)	3 (11.5)	2 (7.4)	
Progression, *N* (%)	8 (30.8)	10 (37.0)	
Mild dysplasia			1.00
Subjects per arm, *N*	12	11	
Regression, *N* (%)	6 (50.0)	6 (54.6)	
Stable, *N* (%)	2 (16.7)	2 (18.2)	
Progression, *N* (%)	4 (33.3)	3 (27.3)	
Moderate or severe dysplasia			0.57
Subjects per arm, *N*	14	16	
Regression, *N* (%)	9 (64.3)	9 (56.3)	
Stable, *N* (%)	1 (7.1)	0 (0.0)	
Progression, *N* (%)	4 (28.6)	7 (43.8)	

[a] Fisher's exact test comparing regression versus stable versus progression.

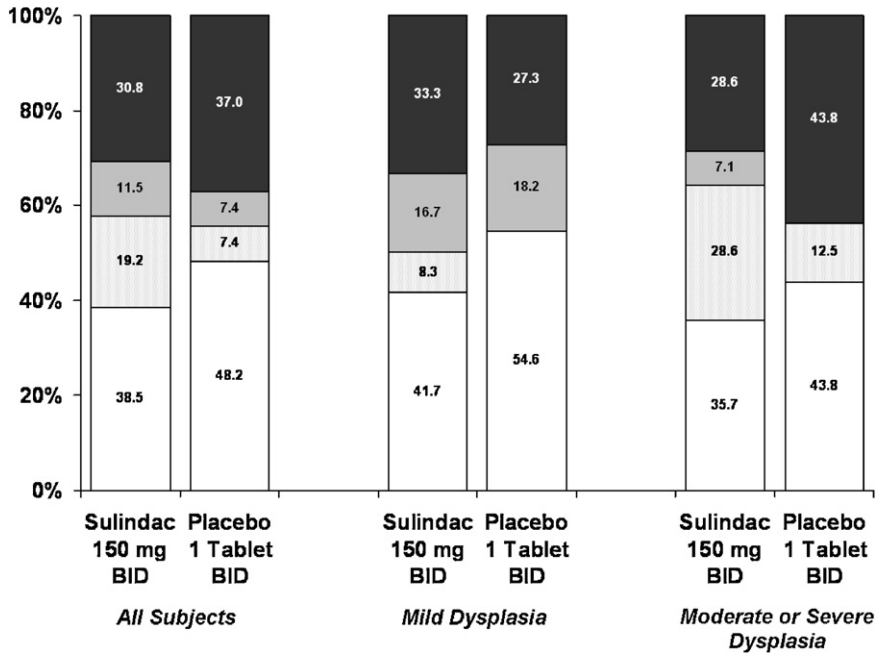

Fig. 2. Change in bronchial dysplasia, by intervention arm.

dysplasia clinical model, although they do appear to correlate with the results reported by Rothwell et al. [30]. It should be noted that our trial was designed at a time when no data existed regarding the effect of NSAIDs on lung squamous carcinogenesis and when the bronchial dysplasia model used in this study was the only available clinical trial model to test chemopreventive agents for lung cancer prevention. There was no a priori reason to believe that sulindac would be ineffective or harmful for squamous cell carcinogenesis. The increased understanding of differences in signal transduction pathways leading to squamous cell versus adenocarcinomas will

Table 3
Change in Ki67 Labeling Index (% cells stained positive) by Intervention Arm.

Subject group	Sulindac 150 mg BID	Placebo 1 tablet BID	*p*-Value[a]
Normal mucosa			
Subjects per arm, *N*	20	23	
Baseline Ki67 (%)			0.18
Median (range)	5 (0–15)	5 (0–45)	
Mean (SD)	4.9 (4.2)	9.8 (11.0)	
Post-Intervention Ki67 (%)			0.36
Median (range)	5 (1–30)	1 (1–15)	
Mean (SD)	6.2 (3.6)	3.6 (3.8)	
Difference in Ki67 (%)			0.009
Median (range)	0.0 (−9 to 25)	−4.0 (−44 to 5)	
Mean (SD)	1.4 (7.3)	−6.2 (10.8)	
p-Value[b]	0.59	0.005	
% Change in Ki67			0.02
Median (range)	0 (−90 to 500)	−58 (−98 to 100)	
Mean (SD)	83.9 (193.1)	−39.7 (50.0)	
p-Value[b]	0.28	0.01	
Bronchial Dysplasia			
Subjects per arm, N	20	19	
Baseline Ki67 (%)			0.49
Median (range)	30 (5–50)	30 (5–50)	
Mean (SD)	27.0 (14.5)	30.3 (13.3)	
Post-Intervention Ki67 (%)			0.62
Median (range)	10 (1–35)	5 (1–45)	
Mean (SD)	11.7 (9.8)	14.6 (13.5)	
Difference in Ki67 (%)			0.92
Median (range)	−17.5 (−49 to 10)	−15.0 (−44 to 5)	
Mean (SD)	−15.3 (14.8)	−15.6 (16.0)	
p-Value[b]	0.0003	0.0005	
% Change in Ki67			0.96
Median (range)	−57 (−98 to 200)	−60 (−98 to 25)	
Mean (SD)	−37.7 (73.5)	−48.3 (42.0)	
p-Value[b]	0.02	0.0003	

[a] Wilcoxon rank-sum test.
[b] Wilcoxon signed rank test.

hopefully result in improvement in our ability to identify agents that target these specific molecular lung cancer subtypes.

Strengths of our study include the multi-center design, excellent compliance, high participation rate (88%) with the post-intervention bronchoscopy exam, and reporting of per-participant, per-lesion and multiparameter biomarker data. Inclusion of fluorescence bronchoscopy further enhanced our ability to identify subtle dysplasia that may have been overlooked using standard white light evaluation alone [34]. All bronchoscopists were experienced, and it seems difficult to attribute our generally null findings solely to inter-examiner variability in mucosal inspection or interpretation. More relevant to the lack of an effect from the active intervention on bronchial dysplasia observed was the higher rate of regression in participants assigned to the inactive intervention (59%) compared to some other previously reported lung cancer chemoprevention trials that used similar criteria [11,12], emphasizing the importance of including a concurrent placebo arm in phase II lung cancer chemoprevention trials. Subject recruitment was also a challenge, despite active involvement from pulmonologists and implementation of a mixed media approach for trial promotion [35]. Exclusion of chronic NSAID use and requirement for histologically confirmed bronchial dysplasia at baseline were critical to the trial design, but proved to be recruitment barriers.

Unfortunately, few strategies are currently endorsed to reduce lung cancer risk in routine clinical practice [36,37]. Even with counseling and/or pharmacologic therapy, few smokers achieve sustained abstinence [38–40]. Data from the National Lung Screening Trial show that CT screening is associated with decreased lung cancer mortality among smokers [2,36,41]. The data reported herein should be informative for planning future NSAID-based lung cancer chemoprevention trials, as well as for prioritizing sulindac against other candidate agents.

Conflict of interest statement

Dr. Limburg served as a consultant for Genomic Health, Inc. from 8/12/08-4/19/10. Mayo Clinic has licensed Dr. Limburg's intellectual property to Exact Sciences, and he and Mayo Clinic have contractual rights to receive royalties through this agreement.

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