Research Article

Cancer Prevention Research

Randomized Phase II Trial of Inhaled Budesonide versus Placebo in High-Risk Individuals with CT Screen–Detected Lung Nodules

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Abstract

Screening CT identifies small peripheral lung nodules, some of which may be pre- or early invasive neoplasia. Secondary end point analysis of a previous chemoprevention trial in individuals with bronchial dysplasia showed reduction in size of peripheral nodules by inhaled budesonide. We performed a randomized, double-blind, placebo-controlled phase IIb trial of inhaled budesonide in current and former smokers with CT-detected lung nodules that were persistent for at least 1 year. A total of 202 individuals received inhaled budesonide, 800 μg twice daily or placebo for 1 year. The primary endpoint was the effect of treatment on target nodule size in a per person analysis after 1 year. The per person analysis showed no significant difference between the budesonide and placebo arms (response rate 2% and 1%, respectively). Although the per lesion analysis revealed a significant effect of budesonide on regression of existing target nodules ($P = 0.02$), the appearance of new lesions was similar in both groups and thus the significance was lost in the analysis of all lesions. The evaluation by nodule type revealed a nonsignificant trend toward regression of nonsolid and partially solid lesions after budesonide treatment. Budesonide was well tolerated, with no unexpected side effects identified. Treatment with inhaled budesonide for 1 year did not significantly affect peripheral lung nodule size. There was a trend toward regression of nonsolid and partially solid nodules after budesonide treatment. Because a subset of these nodules is more likely to represent precursors of adenocarcinoma, additional follow-up is needed. *Cancer Prev Res; 4(1); 34–42. ©2010 AACR.*

Introduction

There were 100 million tobacco-related deaths in the 20th century, and of the 1 billion deaths that are expected in the 21st century, one-third will be due to lung cancer, which is the world's leading cause of cancer death (1), primarily due to late diagnosis at regionally advanced or metastatic stages when cure is not currently possible (2). The increased risk of developing lung cancer persists many years after smoking cessation (3) and smoking is increasing among young people and women in Western countries, as well as in all populations in developing countries (4, 5). Thus, lung cancer will continue to be a major source of morbidity and mortality for years to come.

In addition, to smoking cessation, chemoprevention may have a role in the prevention of lung cancer in as much as it has the potential to arrest or reverse carcinogenic progression. Although clinical studies have not provided striking results thus far (6), the majority of phase II preliminary efficacy prevention trials performed to date have focused on modulation of bronchial dysplasia, the precursor to squamous cell carcinoma (7). To our knowledge, no phase II studies have directly addressed the peripheral lung, where most lung cancers actually arise.

Inhaled steroids are a promising chemopreventive strategy. In mouse carcinogenesis model systems, budesonide, a glucocorticoid widely used for the treatment of asthma, inhibited all stages of progression from hyperplasia formation to cancer (8) and was able to delay the appearance of lung tumors and to decrease their growth and progression to carcinoma (9, 10). An epidemiologic study of

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chronic obstructive pulmonary disease showed that patients treated with inhaled steroids had a dose-dependent decreased risk of lung cancer (11). However, in a phase IIb clinical trial of 6 months of inhaled budesonide versus placebo treatment, budesonide had no effect on bronchial dysplasia, although a significantly greater number of CT-detected peripheral lung nodules decreased in size after budesonide treatment (12). Similarly, a clinical trial of fluticasone versus placebo for 6 months in subjects with squamous metaplasia or dysplasia also showed that in the fluticasone arm, more subjects had a decrease and fewer had an increase in number of nodules detected on chest CT, although this trend did not reach statistical significance (13). Of note, both of these studies focused on individuals with histologic abnormalities in the bronchial epithelium of the central airways, raising the question whether inhaled steroid treatment should rather be focused on a cohort selected for the presence of peripheral lung abnormalities, some of which are presumably adenocarcinoma precursors.

With the evolution of helical CT technology, CT screening for lung cancer is under evaluation in high-risk individuals (former and current smokers), with encouraging results in single-arm studies and phase III randomized trials underway (14–16). At the European Institute of Oncology (EIO), a single-center screening trial recruited 5,203 high-risk volunteers (current or former smokers) to undergo an annual multidetector low-dose CT (ld-CT) for 5 or more years, beginning in 2004 (15). The screening CT, a noninvasive test with low radiation exposure and no contrast medium, affords the opportunity to serially examine the peripheral lung for the first time, albeit with the limitation that small lesions cannot be biopsied and thus their identity remains unknown. We, therefore, nested a phase IIb chemoprevention clinical trial into the screening trial to ask whether 1 year of treatment with inhaled budesonide or placebo significantly reduces the size of peripheral lung nodules identified by ld-CT.

Subjects and Methods

Subjects

Study design and methodology for subjects' selection have been published elsewhere (17). Participants were individuals with persistent nodules detected at low-dose thoracic CT scan during the second or third year of the ongoing EIO CT screening trial. The study was restricted to asymptomatic current smokers or former smokers who stopped within the last 15 years, all of whom had a smoking history of more than 20 pack-years, were older than 50 years, and had normal organ function. Subjects had to have a persistent lung nodule more than 4 mm in size detected by 2 serial yearly screening ld-CT scans. Subjects with solid nodules larger than 8 mm had to have a negative FDG-PET (^{18}F-fluorodeoxyglucose positron emission tomography) scan. Subjects with lung nodules with clearly benign morphologic features (e.g., homogenous calcification, solid nodules with regular and round or polygonal margins, and distance from the pleura <1cm), subjects currently suffering from malignant disease or having had malignant disease within the last 5 years, and regular/chronic users of oral or inhaled corticosteroids were excluded.

Potential participants whose CT scans showed nodules with the required characteristics were contacted by telephone by trained personnel and were invited to participate in the chemoprevention trial.

Trial design and treatment

The trial was a randomized, double-blind phase IIb study in which participants received either budesonide or placebo. Subjects underwent CT screening as part of their participation in the annual CT screening trial at the EIO. Randomization was performed within 2 months (61 days) of the qualifying CT scan. Subjects were stratified according to sex, smoking status (current vs. former smoker), and type of nodule (nonsolid and partially solid vs. solid). If a subject had both solid and nonsolid nodules, he or she was stratified in the nonsolid group.

Budesonide 800 μg twice daily or placebo using a Turbuhaler device was self-administered on an outpatient basis for 1 year. A repeat ld-CT was performed after 12 months of treatment. Toxicity was evaluated at each clinic visit using the NCI toxicity criteria (CTCAE Version 3.0). Dose modifications were performed according to severity and attribution of toxicity to treatment. Compliance was evaluated by counting the doses left in the inhaler.

CT scan evaluation

Investigations were performed using low-dose technology, with a multidetector (8 or 16 slices) High-Speed Advantage CT scanner (General Electric Corporation), with 140 kVp, 30 mA, pitch 1.75, 2.5-mm thickness, single-breath, retro-reconstruction at 3-mm interval, and an effective dose equivalent to patient estimated to be 0.7 mSv. Number, minor and maximum diameter, volume, and type of lung nodules were registered before and after 12 months of treatment. All nodules were independently reviewed by 2 radiologists.

Quantitative analysis of emphysema was based on attenuation values of CT numbers expressing Hounsfield units (HU) calculated over the entire lung volume. Multiplanar reconstruction and 3-dimensional volume reconstruction were performed on the workstation (Advantage Windows 4.2; General Electric medical system). Lung parenchyma was isolated using a −200 HU threshold. Lung representation of voxel values were calculated on the voxel between −1,023 and −200 HU. A graphic representation of voxel values was calculated and minimum and maximum densities, volume, and percentage of emphysema were automatically calculated (18, 19).

Pulmonary function tests

All subjects underwent pulmonary function tests (PFT), single-breath DLCO (carbon monoxide lung diffusion) and percutaneous arterial saturation. Lung volumes and flow

rate were measured in the sitting position according to the American Thoracic Society recommendations (20). Values were expressed as absolute and a percentage of predicted normal values. The single-breath DLCO was measured by infrared CO analyzer and corrected for barometric pressure and temperature according to the American Thoracic Society recommendations. Results were expressed as percentage of the predicted values forced expiratory flow in 1 second (FEV_1%; ref 21). Percutaneous arterial saturation was assessed by a continuous pulse oximeter.

Sample size and statistical analysis

The primary endpoint was the shrinkage of lung nodules in a per person analysis according to the RECIST (Response Evaluation Criteria in Solid Tumors) criteria (22). A partial response was considered a reduction of 30% or more of the longest diameter for single nodules 5 mm or greater. For single nodules with longest diameter less than 5 mm, thought to be less precisely measurable, complete disappearance was considered as a treatment response. In case of multiple lesions, treatment was considered successful when complete or partial response occurred according to RECIST criteria. Specifically, a complete response was the disappearance of all target lesions; partial response was at least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum longest diameter; progressive disease was at least a 20% increase in the sum of the longest diameter of all target lesions, taking as reference the baseline sum longest diameter, or the appearance of one or more new lesions; and stable disease was neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the baseline measurements.

The sample size was calculated to show a treatment effect in 20% of subjects in the budesonide arm, that is, a nodule shrinkage in 30% in the treated arm versus 10% in the placebo arm ($\alpha = 0.05$, $1 - \beta = 0.90$, χ^2 2-sided test). These assumptions were based on previous data on a pilot early detection study with ld-CT, where the rate of spontaneous regression of undetermined lung nodules in the follow-up was as high as 10% (23). The sample size was adjusted for a 10% noninformative dropout rate. Subjects were considered compliant if at least 50% of the drug was taken. Participants who dropped out or had missing final CT scans were considered treatment failures. Participant characteristics and the average 1-year lung cancer risk as per the Bach risk assessment model (24) at baseline, with 95% CIs, at study entry were summarized and tabulated according to treatment arm. Both per person and per lesion analyses were conducted following an intent-to-treat approach.

Between group response rates as well as categorical variables for primary and secondary endpoints were compared using the χ^2 test, the Cochran–Mantel–Haenszel χ^2 test, or the 2-sided Fisher's exact test, as appropriate. Secondary endpoints included a per lesion analysis, effect of budesonide on pulmonary function as assessed by PFTs and CT, and toxicity analysis. Tests for normality on continuous variables were done using the Shapiro–Wilk test (25). Between-group comparison for nonnormal continuous data was done using either the 2-sample, 2-sided Wilcoxon test or a repeated-measures ANOVA on ranks using treatment, gender, and smoking status as main effects. Percent changes in maximum diameters at 12 months by treatment arm were plotted according to lung nodule type. All analyses were performed with the SAS software release 9.1.3. All *P* values were 2-sided.

Results

Participant characteristics

Among the 4,821 participants who underwent the second yearly ld-CT screening in the EIO screening trial, a total of 527 participants were eligible according to nodule characteristics and 135 were subsequently excluded because of other eligibility criteria. The flow diagram of study participants as they progressed through the phases of the randomized trial is shown in Figure 1. Two hundred two individuals were randomized in a 16-month period (from April 2006 to July 2007), with an average accrual of 13 participants per month. One hundred one participants were allocated to each study arm. The characteristics of the participants are shown in Table 1. Frequency distribution of lesions per participant was not significantly different between arms ($P = 0.77$). Overall, 148 participants had 1 lesion only, 42 had 2 lesions, and 12 participants had more than 2 lesions, with a maximum of 8 lesions in 1 person. The average number of lesions per participant was 1.4, both for the placebo and budesonide arms. There was no statistically significant difference in median age, sex, smoking history, types of nodules, size of nodules, and lung cancer risk between arms.

Overall, 198 participants completed the 12-month study and were included in the analysis. Three were lost to follow-up, and 1 participant withdrew consent to the trial (dropout rate: 2%).

Person-specific analysis

There was no significant difference in response rate between the treated or placebo arms (Table 2). Subgroup analysis comparing participants with nonsolid or partially solid nodules with participants with purely solid nodules or current smokers with former smokers similarly did not reveal any differences between the budesonide- and placebo-treated groups. Specifically, in the nonsolid and partially solid nodule subgroup, complete or partial response occurred in 6.1% of cases in the budesonide arm versus 3.3% in the placebo arm. Stable disease was also similar in the two groups (84.8% and 86.7% in the budesonide and placebo arms, respectively). Progressive disease occurred in 9.1% in the budesonide group compared with 10% in the placebo group. In the solid nodule subgroup, no complete or partial response occurred in either arm, stable disease occurred in 92% and 90% of cases in the budesonide and placebo groups, respectively, and progressive disease was noted in 7.7% of participants in the budesonide arm versus 10% of participants in the control group. At 12 months, 4

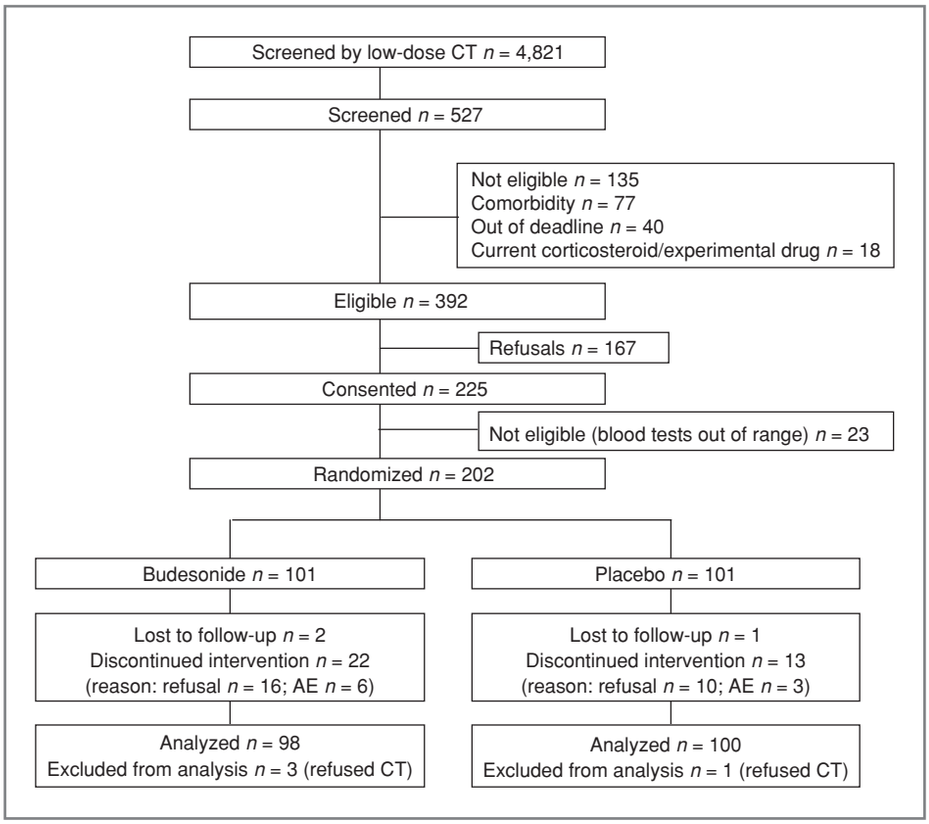

Figure 1. Flow diagram for subjects who were accrued into the study. AE, adverse event.

patients were diagnosed with resectable stage I adenocarcinomas and were equally distributed in the two arms.

Lesion-specific analysis

The lesion-specific analysis of target nodules existing at baseline showed a significant difference between the two arms in terms of response rate according to RECIST criteria (Table 3). In particular, no target lesions in the budesonide arm showed disease progression, whereas 5% of target lesions in the placebo arm progressed ($P = 0.02$). However, the appearance of new nodules after 12 months was not different between the two arms ($P = 0.41$). Therefore, the progressive disease rate, defined as growth in existing nodules or appearance of new nodules, was not significantly different between the budesonide- and placebo-treated groups.

The analysis of absolute and relative changes in nodule diameter after treatment did not show a significant difference between the two arms. Analysis by nodule type, however, showed that budesonide appeared to be more effective in reducing nodule size in nonsolid nodules (Fig. 2), although this difference was not statistically significant. Specifically, the mean diameter reduction was −22% in nonsolid lesions in the budesonide arm compared with −5% in the placebo arm, it was −5% in partially solid lesions in the budesonide arm versus −2% in the placebo arm, and it was −0.2% in solid lesions in the budesonide arm versus +0.3% in the placebo arm.

Respiratory function

The presence and amount of emphysema were assessed through pulmonary function testing and from CT scans. The FEV_1% was not significantly modified by budesonide treatment after 12 months compared with placebo. It changed from 94.7% to 98% in the budesonide arm and from 96% to 98% in the placebo arm ($P = 0.62$; data not shown).

The percentage of emphysema assessed from CT scans after 1 year of treatment slightly but statistically significantly worsened in the budesonide arm compared with the placebo arm. Mean% ± SE% emphysema changed from 1.21 ± 0.12 to 1.51 ± 0.14 in the budesonide arm and from 1.29 ± 0.12 to 1.41 ± 0.15 in the placebo arm ($P = 0.002$; data not shown).

Adverse events

The treatment was well tolerated. Compliance was similar in the two randomized groups, with 84.6% of the participants receiving at least half of the dose (83.1% in the budesonide arm and 86% in the placebo arm; $P = 0.697$). The toxicity profile was consistent with the published literature, with the only adverse events significantly related to the drug (almost all grade 1) being altered taste, voice changes, and asymptomatic cortisol suppression (Table 4). There were 8 serious adverse events, all of which were considered to be unrelated to drug use.

Table 1. Participant demographic characteristics

Characteristics	Budesonide ($n = 101$)	Placebo ($n = 101$)	Overall ($N = 202$)
Age, y			
Median	59	59	59
Range	52–72	51–75	51–75
Sex, *n* (%)			
Male	76 (75.2)	77 (76.2)	153 (75.7)
Female	25 (24.8)	24 (23.8)	49 (24.3)
Smoking history, pack-years			
Median	47	42	45
Range	10–156	6–129	6–156
Smoking status, *n* (%)			
Current smoker	84 (83.2)	83 (82.2)	167 (82.7)
Former smoker	17 (16.8)	18 (17.8)	35 (17.3)
Nodules type, *n* (%)			
Nonsolid	12 (8.7)	14 (9.9)	26 (9.3)
Partially solid	26 (19.0)	19 (13.4)	45 (16.1)
Solid	99 (72.3)	109 (76.7)	208 (74.6)
Nodules size, *n* (%)			
4–5 mm	94 (68.6)	100 (70.4)	194 (69.5)
5–8 mm	40 (29.2)	42 (29.6)	82 (29.4)
>8 mm	3 (2.2)	0	3 (1.1)
1-y lung cancer risk[a] (%)	0.36 (0.07–1.43)	0.35 (0.07–1.17)	0.35 (0.07–1.43)

[a]Risk assessment using the algorithm by Bach et al. (24), assuming that current smokers stopped smoking at enrollment.

Discussion

Progress in preventing lung cancer has been hampered by the lack of well-established clinical trial models to provide preliminary evidence of efficacy in humans before proceeding to definitive efficacy phase III trials. Whereas multiple phase II lung cancer prevention trials have focused on bronchial dysplasia (the precursor to squamous cell carcinoma), the peripheral lung, which is beyond the reach of the bronchoscope, has previously been inaccessible to study. The current trial represents the first phase II study of a chemopreventive intervention focusing on the peripheral lung, where the majority of lung cancers arise. In addition to assessing the intervention, the study aimed to determine whether serial follow-up of CT-detected lung nodules is feasible and interpretable. We show that within the context of an ongoing CT screening study, 202 participants were accrued within a 16-month period in a single institution and 98% of these highly motivated individuals (198 participants) were evaluable. Using RECIST criteria modified to include very small lesions less than 1 cm in size, we were able to categorize nodule response rates and thereby assess the efficacy of the intervention.

The present study did not show a difference in nodule response rate in a per person analysis. After excluding participants with nodules that were suspicious for lung cancer due to size or other characteristics, it is noteworthy that more than 70% of the remaining nodules identified by CT was solid and that there was essentially no change in these nodules over the period of 1 year. On the contrary, the nonsolid and, to a lesser extent, partially solid lesions, decreased in size after budesonide treatment, although this trend was not significant, possibly due to the small number of lesions. Furthermore, none of the preexisting lesions in the budesonide arm grew, in contrast to growth in approximately 5% of nodules in the placebo-treated arm. Nonsolid nodules, which manifest as ground-glass opacities on CT scans, are increasingly being identified during CT screening studies. Accumulating data (26) suggest that such ground-glass nodules are more likely to be malignant (59%–73% of cases) than solid nodules (7%–9% of cases).

The actual identity of CT-detected ground-glass opacity cannot be ascertained without histologic analysis, but this is the category of nodule that is most likely to represent atypical alveolar hyperplasia, the putative precursor of pulmonary adenocarcinoma (27). Kim et al. reported that of 53 persistent ground-glass opacities in 49 patients who underwent resection, 68% proved to be bronchoalveolar carcinoma, 7.5% were adenocarcinoma with predominant brochoalveolar components, 6% were atypical adenomatous hyperplasia, and 19% were nonspecific fibrosis or organizing pneumonia (28). Similarly, Ohtsuka et al. reported that of 26 patients who underwent resection, bronchoalveolar carcinoma was diagnosed in 10 patients (38%), atypical adenomatous hyperplasia was diagnosed in 15 patients (58%), and focal scar was seen in 1 patient (4%; ref. 29). Although criteria such

Table 2. Per person analysis of overall response as measured by RECIST criteria at 12 months ($n = 198$)

	CR/PR	SD	PD	Total
Overall,[a] *n* (%)				
Budesonide	2 (2.0)	88 (89.8)	8 (8.2)	98
Placebo	1 (1.0)	89 (89.0)	10 (10.0)	100
Subsolid,[b] *n* (%)				
Budesonide	2 (6.1)	28 (84.8)	3 (9.1)	33
Placebo	1 (3.3)	26 (86.7)	3 (10.0)	30
Solid, *n* (%)				
Budesonide	0	60 (92.3)	5 (7.7)	65
Placebo	0	63 (90.0)	7 (10.0)	70
Current smoker,[c] *n* (%)				
Budesonide	1 (1.2)	74 (90.2)	7 (8.5)	82
Placebo	1 (1.2)	72 (87.8)	9 (11.0)	82
Overall	2 (1.2)	146 (89.0)	16 (9.8)	164
Former smoker, *n* (%)				
Budesonide	1 (6.2)	14 (87.6)	1 (6.2)	16
Placebo	0	17 (94.4)	1 (5.6)	18
Overall	1 (2.9)	31 (91.2)	2 (5.9)	34

Abbreviations: CR/PR, complete response/partial response; PD, progressive disease; SD, stable disease.
[a]Fisher's exact test: $P = 0.85$.
[b]Cochran–Mantel–Haenszel χ^2 test: $P = 0.80$.
[c]Cochran–Mantel–Haenszel χ^2 test: $P = 0.75$.

as size, the presence of air bronchograms, and nodule sphericity on CT scan have been used to differentiate carcinomas from atypical alveolar hyperplasia, histologic analysis remains the gold standard for definitive categorization of nodules and there continues to be debate regarding the overlap between small bronchoalveolar carcinomas and atypical alveolar hyperplasia (30, 31).

Because resected nodules represent lesions that are suspicious enough to merit surgery, it is possible and even likely that the smaller nodules identified in the context of our CT screening study represent less advanced neoplasia than described in the above-cited studies as well as nonneoplastic etiologies. To exclude from our intervention trial the small inflammatory lesions that resolve spontaneously, we instituted the requirement for persistence of nodules over 2 successive yearly CT scans. One would hypothesize that the persistent nonsolid and partially solid nodules would, therefore, be enriched for preneoplasia and possibly for neoplasia. However, the lack of pathologic correlation remains a significant limitation of this study design.

Significant growth on CT scan is a well-described feature of malignancy. Little is known, however, about differences in growth rates throughout the entire process of carcinogenesis and, specifically, about growth rates of premalignant lesions. Hasegawa et al. calculated the volume doubling time of cancers identified in a CT screening program (32). These authors found that the mean volume doubling time ranges from 813 days for tumors characterized as ground-glass opacities (which were well-differentiated adenocarcinomas) to 149 days for purely solid cancers (which included a range of adenocarcinoma differentiation as well as squamous and small cell lung cancers). The very early rates of growth of these lesions, however, cannot be ascertained from such cross-sectional studies that examine lesions that are pathologically identified as true cancers, and therefore by definition, represent the late stages of carcinogenesis. Presumably, rapidly growing tumors once started as slowly growing clones that eventually acquired the capacity for rapid uncontrolled

Table 3. Per lesion analysis of response as measured by RECIST criteria at 12 months

Nodules type	CR/PR	SD	PD, existing lesions	New lesions
Overall,[a] *n* (row %)				
Budesonide	3 (2.1)	130 (90.9)	0	10 (7.0)
Placebo	2 (1.4)	132 (89.2)	7 (4.7)	7 (4.7)
Nonsolid, *n* (row %)				
Budesonide	2 (15.4)	9 (69.2)	0	2 (15.4)
Placebo	1 (6.7)	10 (66.7)	3 (20.0)	1 (6.7)
Partially solid, *n* (row %)				
Budesonide	1 (3.4)	25 (86.2)	0	3 (10.3)
Placebo	0	19 (82.6)	0	4 (17.4)
Solid,[b] *n* (row%)				
Budesonide	0	96 (95.0)	0	5 (5.0)
Placebo	1 (0.9)	103 (93.6)	4 (3.6)	2 (1.8)

Abbreviations: CR/PR, complete response/partial response; PD, progressive disease; SD, stable disease.
[a]Between-group comparison (Fisher's exact test): all lesions, $P = 0.04$; target lesions only, $P = 0.02$; new lesions only, $P = 0.41$; all lesions with new lesions included as PD, $P = 0.66$.
[b]Between-subgroup comparison with the lowest Fisher's exact test $P = 0.07$.

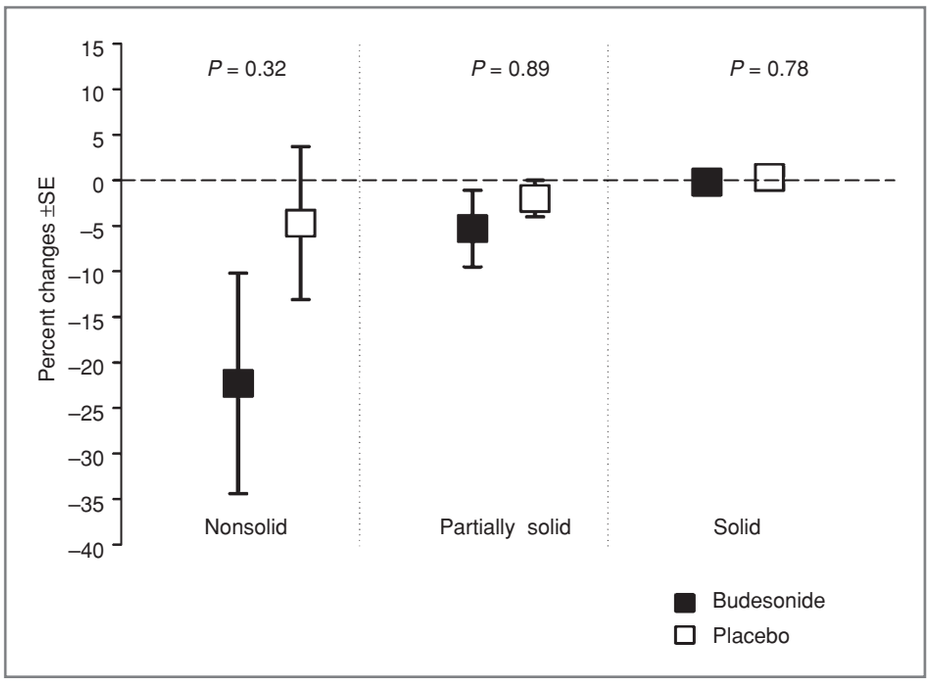

Figure 2. Percent changes in maximum diameters of lung nodules according to the type of nodule by treatment arm.

proliferation. If, at least in some cases, the evolution of pulmonary adenocarcinoma does proceed from atypical adenomatous hyperplasia through the *in situ* bronchoalveolar carcinoma phase to invasive adenocarcinoma (27), then serial CT scanning offers the opportunity to study the growth patterns during the early phases of carcinogenesis until well-accepted clinical and radiologic criteria indicate the need for resection. The implication for a study such as ours, in which small lesions were followed over a relatively short period of time, is that the lack of growth cannot necessarily be interpreted to mean that the CT-detected lesion is not premalignant or even malignant. Given the suggestion that approximately one quarter of ground-glass opacities (GGO) may represent benign lesions, further follow-up of the present trial is underway to determine the association between nonsolid lesions and subsequent lung cancer in light of the expected long doubling time.

The clinical intervention using budesonide was predicated on a body of consistent literature, suggesting that glucocorticoids could inhibit cancer progression (8–12,

Table 4. Adverse events by treatment arms

	Budesonide (n = 101)				Placebo (n = 101)				
Symptom	**Grade 1**	**Grade 2**	**Grade 3**	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Total**	**P[a]**
Dry throat	6	2	0	8	4	0	0	4	0.373
Sore mouth	4	0	0	4	10	0	0	10	0.164
Bad taste	8	0	0	8	1	0	0	1	0.035
Throat irritation	0	0	0	0	1	0	0	1	1.000
Voice change	22	1	0	23	4	1	0	5	<0.001
Hoarse voice	11	2	0	13	0	0	0	0	<0.001
Thrush	7	0	0	7	3	0	0	3	0.331
Cough	15	0	0	15	16	1	0	17	0.847
Headache	4	0	0	4	1	0	1	2	0.683
Fatigue	2	1	1	4	3	2	1	6	0.748
Nausea	4	0	0	4	1	0	0	1	0.369
Skin bruising	1	0	0	1	2	0	0	2	1.000
Cortisol suppression	15	0	0	15	2	1	0	3	0.005
Hyperglycemia	2	0	1	3	4	0	0	4	1.000

[a]Comparison using Fisher's 2-sided exact test.

33). The mechanisms of action for this are not well understood (34). Glucocorticoids have potent anti-inflammatory properties and profoundly affect the cellular microenvironment as well as epithelial cells. Direct effects mediated through the glucocorticoid receptor result in transactivation and cis- and transrepression of multiple genes, thereby affecting signal transduction pathways involved in inflammation. The animal and human data suggested that budesonide is most likely to be effective in the prevention of peripheral lung adenocarcinomas. However, our results do not confirm the multiple animal carcinogenesis studies, nor the positive preliminary data from the clinical trial by Lam and colleagues (12). There are several potential reasons for this. In the study by Lam et al., a smaller number of individuals with bronchial premalignancy were studied and the nodules identified by CT scanning were mainly very small (<4 mm), frequently new, and only rarely nonsolid. Such new nodules may well represent acute inflammation that resolves spontaneously or with inhaled corticosteroids. In contrast, our study showed that the solid lesions that persisted from a previous year showed little tendency to change over the course of an additional year of follow-up and we excluded participants with new nodules specifically to avoid the potential fleeting small inflammatory lesions. The disadvantage of this choice, however, was the decrease in likelihood that the nodules, in particular the solid ones, were malignant or premalignant.

As discussed earlier, the relatively short time frame of our trial as well as the preponderance of solid nodules that are less likely to represent premalignancy or invasive malignancy may be responsible for the difference between the animal models and the human trials. In contrast to animal studies in which the intervention occurs early after carcinogen exposure, the human intervention is delivered relatively late, after lesions (in this case, nodules) already exist. It is possible that earlier intervention may be more efficacious, but it is difficult to identify the appropriately high-risk population and therefore it is difficult to know how to best design such studies. It also remains possible that inhaled budesonide does not penetrate adequately into the peripheral lung (35). To increase peripheral diffusion of budesonide, nanocluster technology is under development (36).

Our trial also presented the opportunity to compare CT assessment of emphysema with spirometric determination of pulmonary function. It is known from the literature (37, 38) that treatment with inhaled corticosteroids has no effect in improving FEV_1%, but has a significant effect in reducing the number acute exacerbations in patients with severe chronic obstructive pulmonary disease (COPD). CT assessment of emphysema showed a slight worsening in the treated group that was not appreciated by spirometry. Although it is highly unlikely that this small effect is clinically significant, a speculative explanation can be that the effect of budesonide decreased the degree of inflammation even at the alveolar level, reducing the density of the lung and not, *per se*, increasing emphysema. Because resistance to steroids is well documented in patients with COPD (34), it is conceivable that CT is more sensitive than spirometry in the detection of ongoing deterioration of lung function in individuals who continue to smoke, as is true of the majority of our cohort.

In summary, this study for the first time showed the feasibility of performing a chemoprevention trial addressing the prevention of lung adenocarcinoma, measuring the effect of the intervention on persistent indeterminate CT-detected lung nodules. Lesion measurement performed using RECIST criteria allowed categorization of participants into responding versus nonresponding categories. As volumetric nodule assessment becomes more feasible, assessment of response is likely to become more precise. Although this study did not show a significant response to budesonide, subgroup analysis showed an intriguing decrease in the size of nonsolid and partially solid nodules. As these are the nodules that are the most likely to represent premalignant lesions or overt cancer, these results suggest that subsequent trials should focus exclusively on the subgroup of participant with such nodules. Improved risk assessment, based on demographic, CT, and, eventually, molecular information, is needed to optimize the identification of individuals with the highest short-term lung cancer risk who stand to benefit the most from chemopreventive interventions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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