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Long-term effects of inhaled budesonide on screening-detected lung nodules

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Background: A previously carried out randomized phase IIb, placebo-controlled trial of 1 year of inhaled budesonide, which was nested in a lung cancer screening study, showed that non-solid and partially solid lung nodules detected by low-dose computed tomography (LDCT), and not immediately suspicious for lung cancer, tended to regress. Because some of these nodules may be slow-growing adenocarcinoma precursors, we evaluated long-term outcomes (after stopping the 1-year intervention) by annual LDCT.

Patients and methods: We analyzed the evolution of target and non-target trial nodules detected by LDCT in the budesonide and placebo arms up to 5 years after randomization. The numbers and characteristics of lung cancers diagnosed during follow-up were also analyzed.

Results: The mean maximum diameter of non-solid nodules reduced significantly (from 5.03 mm at baseline to 2.61 mm after 5 years) in the budesonide arm; there was no significant size change in the placebo arm. The mean diameter of partially solid lesions also decreased significantly, but only by 0.69 mm. The size of solid nodules did not change. Neither the number of new lesions nor the number of lung cancers differed in the two arms.

Conclusions: Inhaled budesonide given for 1 year significantly decreased the size of non-solid nodules detected by screening LDCT after 5 years. This is of potential importance since some of these nodules may progress slowly to adenocarcinoma. However, further studies are required to assess clinical implications.

Clinical trial number: NCT01540552.

Key words: budesonide, lung cancer, chemoprevention, low-dose computed tomography, screening

introduction

Low-dose computed tomography (LDCT) is effective for the early detection of lung cancer in high-risk populations: it identifies early stage lung cancers with high sensitivity, and reduces lung cancer mortality [1, 2]. LDCT also identifies numerous indeterminate lung nodules, some of which may be preinvasive or early invasive cancers, and require investigation. In particular, CT-detected non-solid nodules are the category of nodules most likely to represent precursors of adenocarcinoma. Kim et al. [3] reported that around 80% of persistent non-solid nodules proved to be premalignant or minimally invasive adenocarcinoma.

To assess the effect of budesonide—a glucocorticoid and potential chemopreventive [4]—on CT-detected nodules, we carried out a randomized, double-blind, phase IIb trial

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(NCT00321893) of inhaled budesonide versus inhaled placebo in current and former smokers with CT-detected lung 'target' nodules (that had persisted for at least a year but did not require additional diagnostic ascertainment according to our study protocol) [5, 6]). A total of 202 individuals received inhaled budesonide, 800 μg twice daily, or inhaled placebo for 1 year. The primary end point was the effect of budesonide on target nodule size in a per-person analysis after 1 year. Although the per-person analysis did not show a significant difference between the budesonide and placebo arms (response rates 2% and 1%, respectively), per-lesion analysis revealed that budesonide was significantly ($P = 0.02$) associated with the regression of non-solid target nodules. Furthermore, both target and non-target (see definition below) non-solid nodules tended to regress in the budesonide arm, although the difference was not significant. Budesonide was well tolerated, and had no unexpected side-effects [5].

Since nodule regression after treatment was assessed after just 1 year, we continued monitoring patients, and in the present study retrospectively analyzed the size evolution of LDCT-detected nodules in the two arms of the budesonide study 4 years after the conclusion of treatment.

participants and methods

This study was nested within the ongoing prospective COSMOS screening study, whose design and participant selection criteria are described elsewhere [2, 6]. The budesonide dose and use of the Turbohaler system to administer budesonide are justified in [7]. Participants gave written informed consent to be included in the COSMOS and budesonide studies.

Nodules investigated (target nodules) in the budesonide study were those not eligible for further diagnostic ascertainment according to the COSMOS protocol. Specifically, they were present at two consecutive annual COSMOS scans and were either:

- Between 4 and 5 mm maximum diameter, and may or may not have grown.
- Between 5.1 and 8 mm maximum diameter, may or may not have grown, but if grown, volume doubling time (VDT) was >1 year.
- >8 mm maximum diameter, negative PET, and negative CT with contrast (where feasible), with VDT >1 year.

New nodules or persistent nodules below 4 mm in diameter were defined as non-target, and were also followed.

The primary end point was change in the size of target and non-target nodules in a per-lesion analysis 4 years after the end of the budesonide intervention compared with size on CT before treatment (baseline). Secondary objectives were appearance of new nodules, and the number and characteristics of lung cancers diagnosed during follow-up. We also analyzed target and non-target nodules according to the type (non-solid, partially solid, and solid). Target nodules that disappeared were considered to have a diameter of 0 mm, although they could have been larger since lesions no longer detectable on LDCT could still be present but below the resolution of the technique.

We assessed the two CT scans carried out as part of the budesonide trial (baseline and 1 year), and the four additional annual scans carried out as part of continuing COSMOS follow-up. The number, maximum and minimum diameter, volume, and type of lung nodule were recorded, although for the present analysis only maximum diameter was used. Nodules were reviewed independently by two experienced radiologists before and after the 1 year of treatment. One of the radiologists examined the LDCT scans taken over the subsequent 4 years.

A High Speed Advantage CT scanner (General Electric Corporation, Milwaukee, WI, USA) with multidetector (8 or 16 slices) was used to obtain LDCT scans in a single breath; settings were 120 kVp, 30 mA, pitch ratio 1.75 : 1, thickness 2.5 mm, and retro-reconstruction at 1.25 mm intervals.

statistical methods

Numbers of participants attending each annual CT scan according to treatment arm, and numbers of nodules detected according to type, were recorded. Age, 1-year lung cancer risk [8], and smoking status at baseline and 60 months were summarized by counts and percentages, means (with standard deviations, SD), or medians, by the treatment arm. Between-treatment comparison of changes at 60 months compared with baseline employed the two-sided two-sample Wilcoxon test (continuous variables) or χ^2 test (categorical variables). The mean maximum diameter of each type of nodule was plotted against time and analyzed using a linear mixed model for repeated measurements. Time and treatment were considered as main fixed effects together with their first-order interaction; maximum lesion diameter at baseline was a random covariate. Significance levels of *F*-tests for each effect were calculated. Between-arm comparisons for cumulative incidence of new and disappeared lesions used the log-rank test. All tests were two-sided and differences considered significant at the 5% level. We also investigated attendance versus failure to attend for annual LDCT in the 5 years after recruitment to determine whether attendance differed between the two arms and might have influenced between-arm differences in nodule size.

results

Participant and nodule characteristics are described in the original publication [5]. Table 1 summarizes the numbers of participants, nodules, and cancer cases available for analysis at yearly intervals. Supplementary Table S1, available at *Annals of Oncology* online summarizes selected characteristics of the study arms at baseline and at 60 months. The distribution of number of nodules per participant did not differ significantly between arms ($P = 0.77$), with a mean of 1.4 nodules per participant per arm. Overall, 148 participants had 1 nodule, 42 had 2, and 12 had more than 2 nodules, to a maximum of 8 nodules in 1 case. The arms did not differ for mean age, sex ratio, smoking history, nodule type, nodule size, or lung cancer risk. Of the 202 participants recruited, 198 completed the 12-month study and were included in the analysis; 3 were lost to follow-up, and 1 withdrew consent (dropout rate 2%). At 60 months, compliance was 80% (77 plus 83 of 202 participants, Table 1).

Five years after baseline, the mean size (maximum diameter) of target and non-target non-solid nodules had decreased significantly ($P = 0.029$) in the budesonide arm (Figure 1A). The size of partially solid lesions did not decrease significantly ($P = 0.252$, Figure 1B). The mean reduction in size was 2.42 mm over 60 months (5.03 mm at baseline versus 2.61 mm at 60 months) for target and non-target non-solid lesions in the budesonide arm; whereas in the placebo arm, size increased by 0.42 mm (5.26 mm at baseline versus 5.68 mm at 60 months). For partially solid nodules, the mean reduction in maximum diameter was 0.79 mm in the budesonide arm, whereas partially solid nodules in the placebo increased by 0.10 mm ($P = 0.252$, Table 2).

When partially solid and non-solid nodules were considered together, mean nodule size was significantly lower ($P = 0.030$) in the budesonide arm than the placebo arm at 60 months

Table 1. Number of participants, nodules, and cancers studied at each year, for each study arm

Time (months)	Budesonide arm					Placebo arm				
	No. of participants	No. of solid nodules	No. of partially solid nodules	No. of non-solid nodules	No. of cancers	No. of participants	No. of solid nodules	No. of partially solid nodules	No. of non-solid nodules	No. of cancers
Baseline	101	114	31	16	0	101	117	22	15	0
12	98	119 (5.0)	32 (2.1)	15 (1.2)	2	100	114 (2.5)	30 (8.0)	18 (3.0)	1
24	93	115 (0.4)	21 (0.11)	12 (0.3)	0	94	110 (0.4)	22 (0.8)	13 (0.5)	1
36	85	116 (2.1)	17 (0.4)	10 (0.2)	0	88	104 (2.8)	18 (0.4)	12 (0.1)	0
48	82	114 (0.2)	16 (0.1)	10 (0.0)	1	86	107 (3.0)	16 (0.2)	12 (1.1)	0
60	77	112 (0.2)	13 (1.4)	9 (0.1)	0	83	100 (0.7)	15 (0.1)	11 (0.1)	0

Numbers within brackets are counts for new nodules and disappeared nodules, respectively, separated by a comma; between-arm log-rank test comparisons: new solid lesions, $P = 0.490$; disappeared solid lesions, $P = 0.127$; new partially solid lesions, $P = 0.310$; disappeared partially solid lesions, $P = 0.654$; new non-solid lesions, $P = 0.127$; disappeared non-solid lesions, $P = 0.967$; cancers: $P = 0.631$.

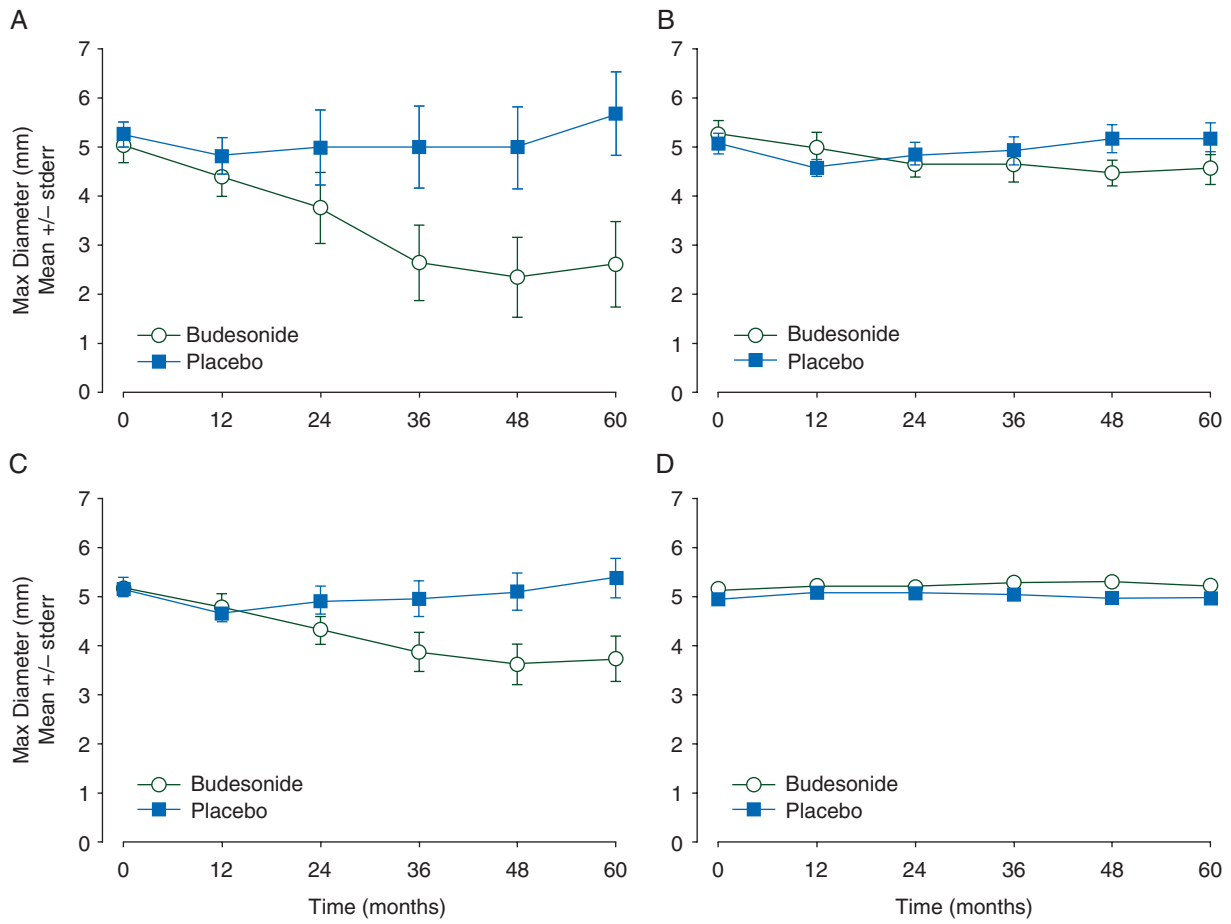

Figure 1. Evolution of mean maximum nodule diameter (mm) over time in target and non-target nodules by the treatment arm. (A) Non-solid nodules, (B) partially solid nodules, (C) non-solid plus partially solid nodules, and (D) solid nodules.

(Figure 1C). Budesonide treatment had no effect on the average size of solid nodules (Figure 1D).

Figure 2 provides a visual representation of evolution of individual non-solid nodules in the two arms over the 60 months. From this figure, it is evident that budesonide-treated nodules tended to remain stable, although many decreased in size over time. Nodules in the placebo arm also tended to remain stable, although several increased in size while two disappeared altogether.

Since participant failure to undergo the yearly CT screen could affect assessment of budesonide's effect on nodule size, we examined whether adherence to follow-up differed between

Table 2. Evolution of the number and size of all (target and non-target) non-solid, partially solid, and solid lesions over 60 months in the budesonide and placebo arms

Follow-up (months)	Arm	No. of nodules	Mean maximum nodule diameter in mm (SD)	Median maximum nodule diameter in mm
Non-solid				
Baseline	Budesonide	16	5.03 (1.39)	4.65
	Placebo	15	5.26 (0.99)	5.00
60	Budesonide	9	2.61 (2.62)	3.20
	Placebo	11	5.68 (2.81)	5.10
Partially solid				
Baseline	Budesonide	31	5.26 (1.52)	4.80
	Placebo	22	5.07 (1.00)	4.90
60	Budesonide	13	4.47 (1.18)	4.25
	Placebo	15	5.17 (1.27)	4.70
Solid				
Baseline	Budesonide	114	5.14 (0.96)	4.90
	Placebo	117	4.96 (0.87)	4.70
60	Budesonide	112	5.22 (1.38)	5.10
	Placebo	100	4.97 (1.39)	5.00

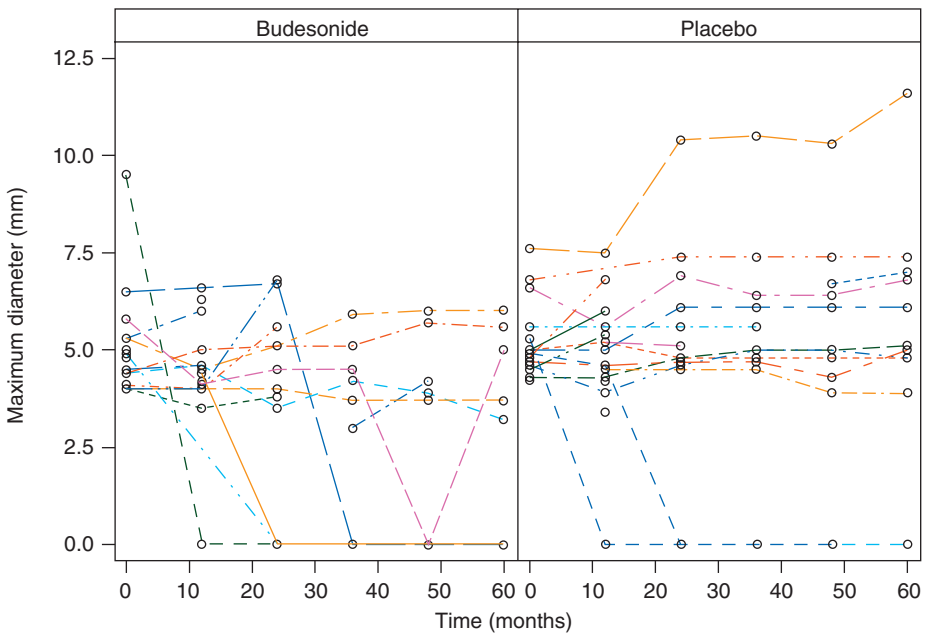

Figure 2. Size evolution of individual non-solid nodules in the two arms over 60 months.

arms. The distribution of participant non-attendance for follow-up according to nodule type is shown in supplementary Table S2, available at *Annals of Oncology* online. Follow-up was divided into complete follow-up, incomplete follow-up (complete measurements up to certain a time point but all subsequent measurements missing), and intermittent follow-up (missing measurements during follow-up in no apparent order). The two arms did not differ significantly for any of these follow-up patterns.

Supplementary Figure S1, available at *Annals of Oncology* online shows the appearance and disappearance of non-target nodules over time and by nodule type. There were no significant differences between the arms for any of the nodule types examined.

There was no difference in the distribution of lung cancers between the two arms ($P = 0.631$). Five lung cancers were diagnosed during follow-up (all adenocarcinomas); of these, four were present the previous year and were described as partially solid lesions (two in the placebo arm and two in the budesonide arm); one was described as a solid lesion of 2 mm (budesonide arm).

discussion

In this study, we show that inhaled budesonide for 1 year significantly reduced the mean size of non-solid lung nodules detected by LDCT screening, and that this effect increased 5 years after randomization, notwithstanding cessation of treatment after 1 year.

However, budesonide did not inhibit the development of new non-solid nodules, with fewer in the control than the treatment arm (not significant $P = 0.127$). Budesonide did not result in decreased lung cancer incidence, although the study was underpowered to assess this end point, and only 1 year of intervention and 5 years of follow-up may be not be enough to detect an effect on conversion of premalignant to invasive carcinoma.

The size reduction of non-solid lung nodules may have clinical implications since adenocarcinoma—the most common screening and symptoms detected lung cancer—may present as non-solid nodules (ground-glass opacities) or partially solid nodules [1, 9, 10]. However, the identity of most small CT-detected non-solid or partially solid nodules is unknown without biopsy. A recent long-term follow-up of non-calcified lung nodules identified in the National Lung Screening Trial indicated that, in contrast to ≥4 mm solid nodules, non-solid nodules were associated with a lung cancer risk that increased progressively with time from baseline [11].

In addition, there are data supporting that most persistent subsolid lesions are prone to progress to invasive adenocarcinomas [3, 12]. Several studies indicate that many LDCT-detected lesions are very slow-growing [12–14]. Thus, prolonged follow-up seems essential to determine whether and when non-solid nodules will develop into cancer [15]. It seems likely that adenocarcinoma precursors do not grow linearly, but that growth accelerates as critical molecular events leading to progression occur. For this reason, the COSMOS study is following its participants over the long term.

Pathological studies on non-solid nodules show that these lesions are frequently atypical adenomatous hyperplasia, adenocarcinoma *in situ*, or adenocarcinoma. Atypical adenomatous hyperplasia is precancerous and develops to adenocarcinoma *in situ* and eventually invasive adenocarcinoma [16, 17].

With regard to partially solid nodules in the current study, these also reduced (non-significantly) in size in the budesonide arm over the 5 years compared with the placebo arm. Again, this finding is of potential interest since these some of these lesions may be adenocarcinomas that include a solid component within the non-solid region or, alternatively, the non-solid component could represent a cancer precursor lesion next to a fibrotic or inflammatory focus [16, 17]. However, the size reduction was minimal (0.69 mm in 5 years) and its clinical significance is unclear. We were unable to measure differences in the non-solid component of these lesions, with mixed attenuation, due to small nodule size; so an effect on the non-solid component could not be assessed. Furthermore, a <2 mm change is subject to measurement error [18].

Our original study found little growth in solid nodules after a year [5]; we found a similar lack of growth in solid nodules after 5 years. It is important to emphasize that the nodules included in the study were carefully selected to exclude inflammatory nodules and clearly invasive lung cancer. Thus, the nodules investigated were highly unlikely to be cancer, given the year of stability before study enrollment.

Of the 175 primary lung cancers detected over 5 years in COSMOS participants recruited between 2004 and 2005, 16 (9%) had multifocal presentation. Multifocal lung adenocarcinoma can be difficult to manage since surgical treatment of all nodules may not be feasible and, since they tend to be slow-growing, may not respond well to cytotoxic therapy [19]. Thus, chemoprevention appears an attractive option in such patients.

Aerosol delivery is an effective administration route since the drug reaches the target yet systemic dissemination is minimal, avoiding many undesirable side-effects [20, 21]. Data (reviewed in ref. [22]) suggest that glucocorticoids may inhibit lung cancer progression.

Strengths of our study include the careful long-term follow-up of small nodules analyzed according to attenuation characteristics, and high (80%) compliance with LDCT and follow-up over the 5-year period. Furthermore, analysis of the distribution of missing data showed that drop-out rates in the two arms did not differ and could not have influenced differences in nodule evolution. Although budesonide did not produce a significant effect in the original per-person analysis, the persistent effect on non-solid nodules suggests biologic activity and the possibility that such nodules could be intermediate end points in future chemoprevention trials.

A study limitation is that nodule density was not assessed by the dedicated software, but visually by two experienced radiologists initially, and by one of the radiologists during follow-up. Future studies will need to use software to assess any effect of density variation within a nodule on size changes induced by chemoprevention. Additionally, volume change assessment might be more informative than one-dimensional measurements; however, improvements in software are required before volumes and VDT can be assessed routinely in such small lesions.

In conclusion, we have shown that inhaled budesonide for 1 year significantly reduces the size of non-solid and partially solid nodules, compared with placebo, and that this reduction remained evident 4 years after treatment cessation. Since some of these nodules may be adenocarcinoma precursors, the potential effect of budesonide on the development of lung adenocarcinomas deserves continuing investigation.

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disclosure

The authors have declared no conflicts of interest.

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