**Disclosure**

KKubo (Taiho, Sanofi), HS (Taiho, Chugai, Eli Lilly Japan), NK (Dainippon Sumitomo, Shionogi, Chugai Pharma, Boeringer Ingelheim, Eli Lilly, Astra Zeneca, Taiho, Sanofi), MN and AI (Taiho), HK, YT and AG (Taiho, Sanofi), KKoba (Eli-Lilly, AstraZeneca), MT (Taiho), SK (Taiho, Sanofi) received honoraria. HK (Taiho) received travel grant. MT (Taiho) received consulting fee. KKubo and MN (Taiho), NK (Eisai, Ono, Kyowa Hakko Kirin, Shionogi, Daiichi Sankyo, Chugai, Merck Serono, Astra Zeneca), HS (Chugai, Eli Lilly Japan), HO (Chugai, Dainippon Sumitomo, Takeda, Kyowa-Hakko-Kirin) and AG (Taiho, Sanofi) received research fundings. MF is shareholders of Chugai. All remaingig authors have declared no conflicts of interest.

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**Figure legends**

**Figure 1**. Overall survival (A) and progression free survival (B) for the FAS population

**Figure 2**. Quality of life assessments with EORTC-QLQ C30 (A)

Score changes of Global Health Status / QoL (items 29 & 30) in the EORTC QLQ-C30

Patients responded to EORTC QLQ-C30 3 times: 1. before each treatment, 2. 1 week after the first dose of cisplatin, and 3. at the end of the second course.

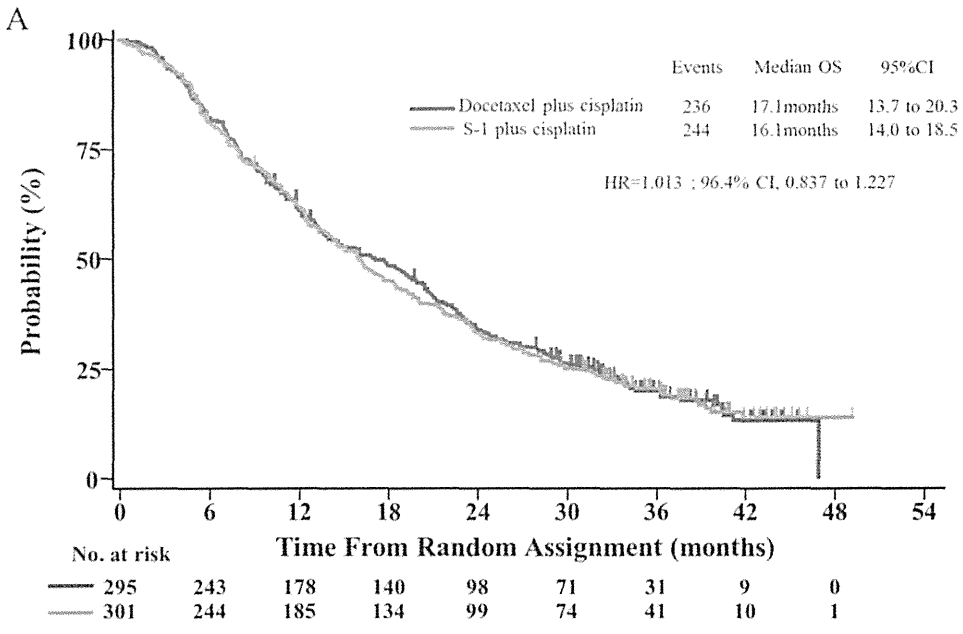
A high score for the Global Health Status/QoL represents a high QoL.

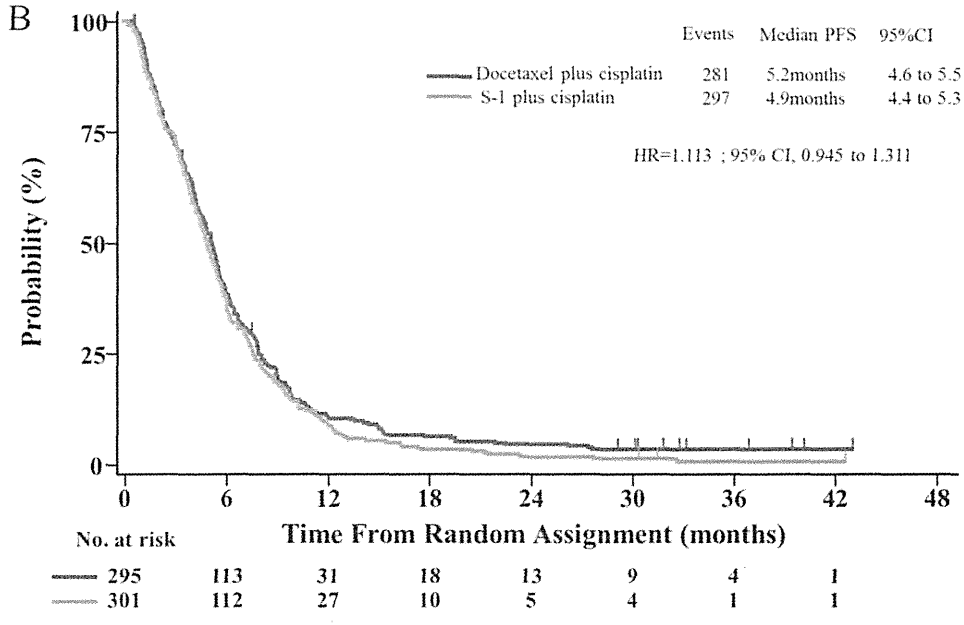
Quality of life assessments with EORTC-QLQ LC13 (B)

Score changes in the EORTC QLQ-LC13

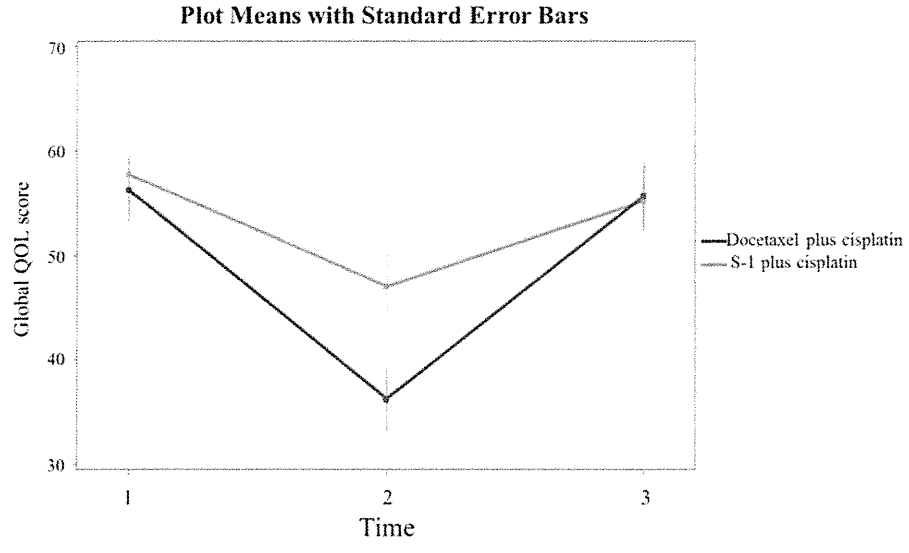
Patients responded to EORTC QLQ-LC-13 3 times: 1. before each treatment, 2. 1 week after the first dose of cisplatin, and 3. at the end of the second cycle.

A low score for the Global Health Status/QoL represents a high QoL.



A




Repeated measures ANOVA, $p<0.0001$

B

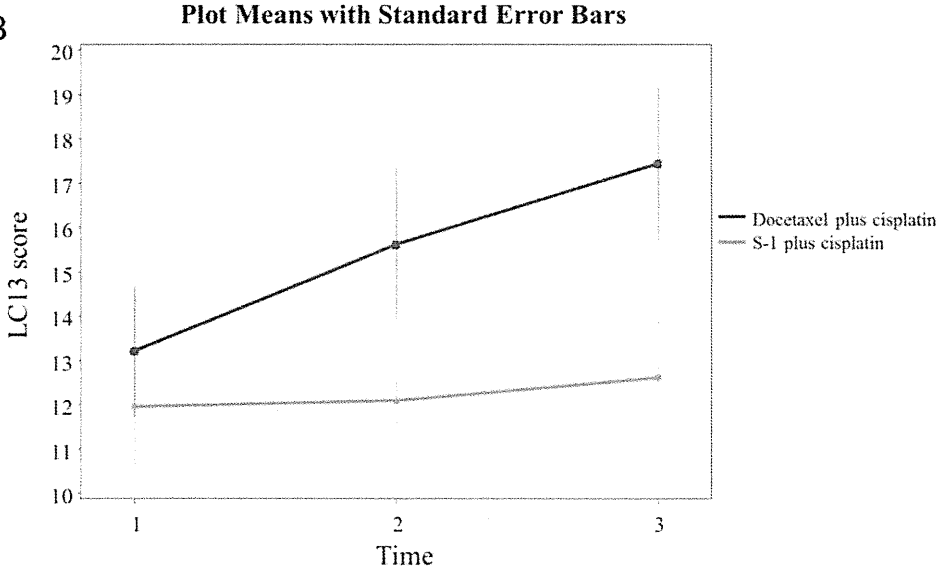


Table 1. Patient Characteristics

| *n* (%) | S-1 plus cisplatin, (*N*=301) | Docetaxel plus cisplatin (*N*=295) |
|---|---|---|
| Age, years | | |
| Average (SD) | 61.4 (8.7) | 62.8 (7.8) |
| Median (range) | 62 (25-74) | 64 (35-74) |
| Gender | | |
| Male | 211 (70.1%) | 208 (70.5%) |
| Female | 90 (29.9%) | 87 (29.5%) |
| Histology | | |
| Adenocarcinoma | 228 (75.8%) | 222 (75.3%) |
| Squamous cell carcinoma | 50 (16.6%) | 48 (16.3%) |
| Large cell carcinoma | 5 (1.7%) | 5 (1.7%) |
| Adenosquamous carcinoma | 7 (2.3%) | 1 (0.3%) |
| Other | 11 (3.7%) | 19 (6.4%) |
| Clinical stage | | |
| Stage IIIB | 79 (26.3%) | 78 (26.4%) |
| Stage IV | 201 (66.8%) | 192 (65.1%) |
| Postoperative recurrence | 21 (7.0%) | 25 (8.5%) |
| ECOG performance status | | |
| 0 | 151 (50.2%) | 152 (51.5%) |
| 1 | 150 (49.8%) | 143 (48.5%) |
| Smoking status | | |
| Previous/current smoker | 223 (74.1%) | 222 (75.3%) |
| Never smoker | 78 (25.9%) | 73 (24.8%) |
| EGFR status | | |
| Wild type | 113 (37.5%) | 115 (39.0%) |
| Mutant | 43 (14.3%) | 46 (15.6%) |
| Unknown or missing | 145 (48.2%) | 134 (45.4%) |

Table 2. Common adverse events

| CTCAE grade (*n*, %) | S-1 plus cisplatin (*N*=301) | | Docetaxel plus cisplatin (*N*=297) | | *p* value |
|---|---|---|---|---|---|
| | All grades | ≥ Grade3 | All grades | ≥ Grade3 | |
| Hematologic | | | | | (≥ Grade 3) |
| Leukocytes | 147 (48.8) | 24 (8.0) | 259 (87.2) | 164 (55.2) | < 0.001 |
| Neutrophils | 152 (50.5) | 69 (22.9) | 252 (84.8) | 218 (73.4) | < 0.001 |
| Hemoglobin | 203 (67.4) | 41 (13.6) | 249 (83.8) | 53 (17.8) | 0.178 |
| Platelets | 144 (47.8) | 17 (5.6) | 83 (27.9) | 4 (1.3) | 0.006 |
| Nonhematologic | | | | | (All grades) |
| Febrile neutropenia | 3 (1.0) | 3(1.0) | 22 (7.4) | 22 (7.4) | < 0.001 |
| Mucositis/stomatitis (clinical exam) | 41 (13.6) | 6 (2.0) | 23 (7.7) | 0 | 0.024 |
| Mucositis/stomatitis (functional/symptomatic) | 56 (18.6) | 6 (2.0) | 33 (11.1) | 1 (0.3) | 0.011 |
| Anorexia | 229 (76.1) | 53 (17.6) | 257 (86.5) | 81 (27.3) | 0.001 |
| Nausea | 201 (66.8) | 29 (9.6) | 232 (78.1) | 59 (19.9) | < 0.001 |
| Vomiting | 84 (27.9) | 12 (4.0) | 155 (52.2) | 24 (8.1) | < 0.001 |
| Diarrhea | 95 (31.6) | 18 (6.0) | 95 (32.0) | 11 (3.7) | 0.930 |
| Hair loss/ alopecia | 37 (12.3) | 0 | 176 (59.3) | 0 | < 0.001 |

# Response to bevacizumab combination chemotherapy of malignant pleural effusions associated with non-squamous non-small-cell lung cancer

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**Abstract.** Malignant pleural effusion (MPE) is a common complication of lung cancer with devastating consequences. Since vascular endothelial growth factor (VEGF) has been implicated in MPE, we hypothesized that bevacizumab, an anti-VEGF antibody, may be effective against MPE in patients with non-small-cell lung cancer (NSCLC). We analysed the records of 21 patients treated for NSCLC-associated MPE between February, 2010 and August, 2013 who consequently underwent bevacizumab combination chemotherapy at the Institute of Biomedical Research and Innovation Hospital. The results were retrospectively analysed using case records and radiographic imaging records. Three patients exhibited complete response of the pleural effusion to bevacizumab treatment, 8 patients achieved a partial response (PR) and 6 patients showed no response. When efficacy was assessed by the response of the measurable primary or metastatic lesions to the treatment, 5 patients achieved a PR, 13 patients had stable disease and 3 patients exhibited progressive disease. The response rate (RR) of the pleural effusion to the antibody treatment was 71.4% and the overall RR of measurable lesions was 23.8%. The median time-to-response for pleural effusion was 132 days. In conclusion, this study demonstrated a high RR to bevacizumab combination therapy for the MPE associated with non-squamous NSCLC. Therefore, bevacizumab therapy may be considered a therapeutic option for patients with non-squamous NSCLC who develop MPE.

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*Key words:* bevacizumab, malignant pleural effusion, non-small-cell lung cancer, vascular endothelial growth factor

## Introduction

Malignant pleural effusion (MPE) is a common and devastating complication of lung cancer, with 15% of lung cancer patients presenting with pleural effusion at the time of initial diagnosis, whereas half of the patients develop pleural effusion at a later stage of the disease (1,2). MPE may cause significant dyspnea, cough and chest pain. There are currently several management options for MPE, including chemical pleurodesis with chest tubes or medical thoracoscopy, video-assisted thoracic surgery, pleuroperitoneal shunts and chronic indwelling pleural catheter. However, all these management options have certain disadvantages (3).

Vascular endothelial growth factor (VEGF) is the founding member of an expanding family of endothelial cell growth factors. VEGF, also known as vascular permeability factor, has been implicated in MPE (4). VEGF is a powerful inducer of vascular permeability; it is 50,000 times more potent than histamine (5). In addition, VEGF expression may be induced by nearly all cell types and is often overexpressed in lung cancer cells (6,7).

Bevacizumab is a humanized monoclonal antibody against VEGF with demonstrated antitumour effects in lung cancer cell lines and animal models (8). Results from *in vitro* studies have demonstrated that this monoclonal antibody is able to effectively neutralize almost all VEGF-mediated activities (9). It was previously shown that the administration of an anti-VEGF antibody lead to a significant reduction in the amount of pleural fluid within the first week following intrapleural injection of talc or nitrate (10). This antibody was also successfully used for the treatment of recurrent pleural effusions in a patient with amyloidosis (11). Bevacizumab in combination with carboplatin/paclitaxel improved overall survival (OS) and is currently approved in the United States and Japan for use in patients with recurrent or metastatic non-squamous, non-small cell lung cancer (NSCLC) chemotherapy (12).

Therefore, we hypothesized that the administration of the anti-VEGF antibody bevacizumab may be beneficial as a treatment option for MPE in NSCLC patients. In this

study, we retrospectively analysed the efficacy of combination chemotherapies that included bevacizumab against NSCLC-associated MPE.

## Materials and methods

*Patient selection.* We analysed records from 21 patients with advanced NSCLC and MPE who consequently underwent bevacizumab combination chemotherapy between February, 2010 and August, 2013 at the Institute of Biomedical Research and Innovation Hospital, Kobe, Hyogo, Japan. Data were retrospectively collected from case records and radiographic imaging records. Written informed consent regarding bevacizumab therapy was acquired from all patients. This study was approved by the Institutional Review Board of our institute.

*Evaluation of efficacy.* Measurable lesions and the size of the MPE were determined by computed tomography (CT) scan prior to bevacizumab combination chemotherapy. Tumour response was evaluated by CT every 4-8 weeks according to the Response Evaluation Criteria in Solid Tumours Committee (13). If a patient was documented to exhibit a complete response (CR) or a partial response (PR), a confirmation with a second scan was required after an additional 4 weeks. The response of each tumour was recorded as the best tumour response observed over the entire course of treatment. Response rate (RR) was defined as CR+PR.

The size of the pleural effusion was defined as follows: Massive, effusion volume >75% of the hemithorax; large, effusion volume 50-75% of the hemithorax; moderate, effusion volume 25-50% of the hemithorax; and small, effusion volume <25% of the hemithorax. The objective response of the MPE was evaluated using chest X-rays and CT scans and a method similar to a previous report (14). CR was defined as the complete disappearance of pleural fluid for 4 weeks. PR was defined as a distinguishable decrease for 4 weeks. No response was defined as failure to meet the abovementioned criteria. CR was evaluated only by CT scans. The time-to-response was defined as the period between the initiation of bevacizumab therapy and the first detectable reduction of the pleural effusion volume by CT or chest X-ray. Time-to-response was calculated using only patients with either a CR or a PR; patients that showed no response were not included in this calculation.

## Results

*Patient characteristics.* First, we reviewed the demographics of the patients included in the study. The patient characteristics are summarized in Table I. All the patients were Japanese and included 11 men (52%) and 10 women (48%), with a median age of 46 years (range, 30-86 years). Eleven patients (52%) were never-smokers and 10 patients (48%) were current or former smokers. All the patients had stage IV adenocarcinoma according to the 7th edition of the TNM classification (15). The majority of the patients (12/21, 57.1%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2. EGFR mutations were detected in 13 of the 21 patients (61.9%) and anaplastic lymphoma kinase (ALK) rearrangement was detected in 3 cases (14.7%).

The patients were grouped based on the size of the pleural effusion; 7 patients (33.3%) had a moderate effusion size, 6 patients (28.5%) had large effusions, whereas 4 patients (19.1%) each had massive and small effusions. A total of 15 patients (71.4%) had received prior chemotherapy. The standard dose of bevacizumab (15 mg/kg) was administered to all the patients. In combination with bevacizumab, the patients received one of the following regimens: carboplatin plus paclitaxel (n=6), erlotinib (n=5), vinorelbine (n=4), carboplatin plus pemetrexed (n=2), docetaxel (n=2), or paclitaxel (n=2).

*Response to treatment.* We assessed the response of the patients to the combination therapy including bevacizumab by reviewing the change in the effusion volume over the course of the treatment. Of the 21 patients, 7 achieved a CR, 8 had a PR and 6 patients did not show a response. We next investigated the patient assessments of the primary or metastatic lesion response to the combination therapy. A total of 5 patients exhibited a PR, 13 patients had stable disease and 3 patients showed progressive disease (Table II). The RR of the pleural effusion to therapy was 71.4% and the overall RR of measurable lesions to therapy was 23.8%. Of the 6 patients who exhibited no response, 5 had no increase in the effusion volume compared to the original measurement. Of the 15 patients who achieved a CR or PR regarding the pleural effusion, 3 patients (25%) did not exhibit a re-accumulation of pleural effusion following completion of the treatment.

## Discussion

The goal of our study was to review the RR of MPE to a combination therapy that included bevacizumab. Overall, we observed that 23.8% of measurable lesions showed a response. This tumour RR is similar to those of previous reports examining a high dose bevacizumab combination therapy, which reported RRs of ~30% (12,16). However, this study also demonstrated a high RR of NSCLC-associated MPE to the high-dose bevacizumab combination therapy; 71.4% of MPE has some measurable decrease in volume.

In a number of patients with NSCLC-associated MPE, standard systemic chemotherapy was proven to be ineffective (3,18). Kitamura *et al* reported that bevacizumab in combination with chemotherapy was highly effective for the management of MPE in patients with non-squamous NSCLC (18). Combined intrapleural therapy with bevacizumab and cisplatin was found to be effective and safe in managing NSCLC-associated MPE, with a curative efficacy of 83.33% (19). According to another study, intense combination chemotherapy including cisplatin, ifosfamide, irinotecan and recombinant human granulocyte colony-stimulating factor support achieved high RRs of the pleural effusions and measurable lesions (58.8 and 73.5%, respectively) (14). Notably, our study demonstrated a higher RR of pleural effusion to a combinatorial therapy that included a high dose of bevacizumab.

Several studies demonstrated that VEGF is associated with the formation of pleural effusion, the effusion size and poor patient survival (20-24). It was also reported that VEGF receptor phosphorylation inhibited the formation of malignant effusion in mice with lung adenocarcinomas. This result was attributed to reduced vascular permeability (25).

Table I. Patient characteristics (n=21).

| Characteristics | Patient no. | % |
|---|---|---|
| Age (years) | | |
| Range | 30-86 | |
| Median | 46 | |
| Gender | | |
| Male | 11 | 52.0 |
| Female | 10 | 48.0 |
| Smoking status | | |
| Never-smoker | 11 | 52.0 |
| Current or former-smoker | 10 | 48.0 |
| ECOG PS[a] | | |
| 1 | 9 | 42.9 |
| 2 | 12 | 57.1 |
| Histology | | |
| Adenocarcinoma | 19 | 90.4 |
| Large-cell neuroendocrine cell carcinoma | 1 | 4.8 |
| Non-small-cell lung cancer NOS | 1 | 4.8 |
| Stage | | |
| IV | 21 | 100.0 |
| EGFR status | | |
| Mutation[b] | 13 | 61.9 |
| Wild-type | 7 | 33.3 |
| Unknown | 1 | 4.8 |
| ALK rearrangement | | |
| Positive | 3 | 14.7 |
| Negative | 7 | 33.3 |
| Unknown (number of EGFR mutants) | 11 (5) | 52.0 |
| Size of pleural effusion | | |
| Small | 4 | 19.1 |
| Moderate | 7 | 33.3 |
| Large | 6 | 28.5 |
| Massive | 4 | 19.1 |
| Prior chemotherapy | | |
| Yes | 15 | 71.4 |
| No | 6 | 28.6 |
| Chemotherapy schema | | |
| Carboplatin + paclitaxel + bevacizumab | 6 | 28.5 |
| Erlotinib + bevacizumab | 5 | 23.8 |
| Vinorelbine + bevacizumab | 4 | 18.9 |
| Carboplatin + pemetrexed + bevacizumab | 2 | 9.6 |
| Docetaxel + bevacizumab | 2 | 9.6 |
| Paclitaxel + bevacizumab | 2 | 9.6 |

[a]Performance status evaluated prior to the administration of bevacizumab. [b]EGFR mutation-positive; exon 19 del, exon 21 L858R, L861Q. SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; NOS, not otherwise specified; EGFR, epidermal growth factor receptor gene; ALK, anaplastic lymphoma kinase gene.

Mesiano *et al* reported that the production of ascitic fluid induced by intraperitoneal inoculation of ovarian cancer cells was almost completely inhibited by neutralizing antibodies that block the action of VEGF (26). Considering the results from those *in vitro* studies, anti-VEGF therapy may be more effective for malignant effusion rather than for primary tumours. Recombinant human endostatin (Endostar) reduced the expression of VEGF-A and MPE in mice with Lewis lung

Table II. Response to bevacizumab-containing treatment.

| Response of pleural effusion (no.)[b] | Tumour response (no.)[a] | | |
|---|---|---|---|
| | Partial response | Stable disease | Progressive disease |
| Complete response (n=7) | 3 | 3 | 1 |
| Partial response (n=8) | 0 | 7 | 1 |
| No response (n=6) | 2 | 3 | 1 |
| Total (n=21) | 5 | 13 | 3 |

[a]Tumour response rate, 23.8%. [b]Response rate of pleural effusion, 71.4%.

carcinoma (27). This result may explain the differences we observed between the response of pleural effusions and that of measurable lesions to bevacizumab.

In this study, all the patients received the standard dose of bevacizumab (15 mg/kg). Pichelmayer *et al* reported data on 4 patients with malignant effusions who received bevacizumab therapy (11). In that study, 2 patients who received low-dose bevacizumab (5 or 10 mg/kg) achieved no significant reduction of the malignant effusions. By contrast, 2 patients who received the standard dose (15 mg/kg) achieved a reduction of the malignant effusion. The results of those studies suggest that treatment of malignant effusion with bevacizumab may require administration of the standard dose.

There are currently several management options for MPE, such as chemical pleurodesis with chest tubes, medical thoracoscopy, video-assisted thoracic surgery, pleuroperitoneal shunts and chronic indwelling pleural catheter (3,17). Chemical pleurodesis is the most commonly used modality for managing MPE. However, patients with a multi-loculated effusion, trapped lung, or bronchial obstruction are unlikely to benefit from intrapleural therapy. Typically, such patients may be treated with systemic chemotherapy. Therefore, intrapleural therapy is not ideal and should be reserved for patients who are refractory to or meet the exclusion criteria for systemic chemotherapy. Based upon our results, bevacizumab therapy alone may be a treatment option for non-squamous NSCLC patients with MPE and poor performance status.

This study had certain limitations. First, there are no standard criteria to evaluate response in patients with MPE. Therefore, we used the response criteria reported by a previous study (14). Second, we were unable to confirm negative cytological findings in the pleural effusions following bevacizumab therapy, as a thoracentesis was difficult in cases where a CR or PR was observed. However, a confirmation of the response, which requires over 4 weeks and a RR of 67.0% were considered satisfactory. Finally, this study was conducted entirely by retrospectively reviewing electronic medical charts. A prospective study may improve our understanding of the potential and efficacy of anti-VEFG therapy.

In conclusion, this study demonstrated a high RR to bevacizumab combination therapy of the MPE associated with non-squamous NSCLC. Therefore, bevacizumab therapy may be a management option for patients with MPE associated with non-squamous NSCLC.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

# Multiple Primary Malignancies in Patients with Non-Small Cell Lung Cancer

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## Abstract

**Objective** Information regarding multiple primary malignancies is important, as it has the potential to clarify etiological factors and may indicate the need to refine patient follow-up to include screening for associated malignancies. Upper aerodigestive tract cancer often develops in patients with smoking-related lung cancer; however, little is known about the frequencies or types of other primary malignancies in patients with non-small cell lung cancer (NSCLC) without a history of smoking.

**Methods** We retrospectively evaluated the records of patients examined and/or treated for NSCLC at the Institute of Biomedical Research and Innovation between January 2007 and June 2012.

**Patients** In total, 938 patients, including 599 men (never-smoker/ever-smoker: 35/564) and 339 women (never-smoker/ever-smoker: 236/103), were analyzed.

**Results** Among the 209 patients (22.3%) with multiple primary malignancies, 151 had a history of smoking and 58 were never-smokers. The most common cancers were gastric (43 cases), colorectal (33 cases), and prostate (29 cases) cancer. Smoking-related cancer was more common in current smokers and ex-smokers for both men and women. Among women with NSCLC, never-smokers were more likely to have thyroid cancer than those with a history of smoking (5.1% vs. 0%, p=0.021).

**Conclusion** In this study, several differences in malignancies were observed between never-smokers and patients with a history of smoking. Thyroid cancer and NSCLC co-existed in some women without a history of smoking, implicating predisposing factors other than tobacco smoke in the onset of these cancers.

**Key words:** non-small cell lung cancer, thyroid cancer, multiple primary malignancies, smoking

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## Introduction

Lung cancer is a major cause of mortality in many developed countries. Cigarette smoking is the primary etiologic factor responsible for lung cancer; however, global statistics show that 15-25% of patients with lung cancer worldwide, in fact, are never-smokers (1). Lung cancer in those with no history of smoking has several distinct characteristics: most such patients are women, the incidence of small-cell lung cancer is extremely low, and adenocarcinoma is the most common histology (2, 3). From a biological standpoint, patients with non-small cell lung cancer (NSCLC) who have never smoked are more likely to harbor somatic activating epidermal growth factor receptor (EGFR) gene mutations, which are substantially associated with the response to EGFR tyrosine kinase inhibitors (4-6). Recently discovered rearrangements of the anaplastic large cell kinase gene resulting in the pathological expression of fusion proteins are also more frequent in adenocarcinomas in never-smokers (7, 8). Several other biological differences (e.g., chromosomal aberrations and methylation status) have also been observed between lung cancer lesions in never-smokers and smokers, and these observations support the notion that lung cancer in never-smokers deserves consideration as a distinct disease entity warranting separate investigation.

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Information regarding multiple primary malignancies is important, as it has the potential to clarify etiological factors and may indicate a need to include screening for associated malignancies during patient follow-up. Approximately 5.1% of patients with cancer in a Norwegian database had more than one cancer diagnosis (9). Upper aerodigestive tract cancer and/or urinary tract cancer often develops in patients with lung cancer, and these cancers share a common etiologic factor, that is cigarette smoking (10, 11). However, little is known about the frequencies and types of other primary malignancies in NSCLC patients with no history of smoking. We conducted this study to evaluate the clinical characteristics of multiple primary malignancies in patients with NSCLC, focusing on the effect of a history of smoking.

## Materials and Methods

From January 2007 to June 2012, 1,048 patients were pathologically confirmed to have NSCLC at the Division of Integrated Oncology in the Institute of Biomedical Research and Innovation, of whom 103 were excluded due to a lack of either a detailed family history or information regarding smoking habits. Four patients of non-East Asian ethnicity and all patients with Li-Fraumeni syndrome or Bloom's syndrome were also excluded. None of the subjects had HIV infection or a history of organ transplantation. Clinical and pathological information was collected based on patient self-reporting and physician notes available in the subjects' medical records. In this study, the smoking status was categorized as either ever-smoker or never-smoker. A "never-smoker" referred to an individual who had smoked fewer than 100 cigarettes in their lifetime. Patients with a history of occupational exposure to agents such as asbestos, nickel or arsenic (known causes of lung cancer) were not defined as never-smokers. Indoor air pollutants, such as vapors from cooking oil and smoke from burning coal, have been linked to lung cancer. However, by the mid-1960's, gas stoves had become widely popular in Japan and were thus not considered distinct causative factors in this study.

Multiple primary malignancies were defined according to the criteria of Warren and Gates, as follows: the presence of biopsy-proven malignancy with the exclusion of the possibility that one tumor resulted from the metastasis of another (12). Although patients diagnosed as having cancer based solely on imaging studies or their clinical course were eliminated, we did not exclude those with malignancies treated at other institutions if confirmation of the cancer was obtained using a pathological analysis. All premalignant lesions were excluded, although benign tumors of the brain were included.

Smoking-related cancers included head and neck squamous cell, esophageal, lung, pancreas, renal and bladder cancer (13). Although stomach, colorectal, liver, uterine cervix, ovary and bone marrow neoplasms have been shown to be associated with smoking (14), the relative risk is low, and thus these lesions were not considered to be smoking-related cancers in the current analysis.

Primary malignancies other than NSCLC were divided into antecedent, synchronous or subsequent types. Synchronous tumors were defined as other primary malignancies diagnosed less than 91 days before or after the diagnosis of NSCLC. In this study, most of the patients were diagnosed at an advanced stage and received chemotherapy or radiotherapy. Cancer treatment may result in the development of other primary cancers (15, 16). In order to lessen the effects of therapeutic intervention, subsequent malignancies identified after the diagnosis of NSCLC were not defined as multiple primary cancers in this study.

A family history of cancer was considered positive if there was any report of cancer in a genetically linked first-degree relative; however, due to the retrospective nature of chart abstraction and the non-standardized template used to assess family history, further quantitative sub-classification of familial heritage was not performed.

This study was approved by the Institute of Biomedical Research and Innovation Institutional Review Board (No. 13-05). The need for informed consent was waived given the retrospective nature of the study design.

The statistical analyses were performed using the JMP (ver. 6; SAS Institute, Cary, USA) and 'R' (R Foundation for Statistical Computing, Vienna, Austria) software programs. Categorical variables were analyzed using Fisher's exact test or the $\chi^2$ test. Continuous variables were assessed using the unpaired *t*-tests or Mann-Whitney *U*-test. All tests were two-tailed and probability values of 0.05 or less were considered to indicate statistical significance.

## Results

The patient characteristics are shown in Table 1. In total, 938 patients, including 599 men (never-smoker/ever-smoker: 35/564) and 339 women (never-smoker/ever-smoker: 236/103), were analyzed. The mean age was 68.8 years. Of the 938 patients, 209 (22.3%) had multiple primary malignancies. Of these, 178 patients had one histologically proven primary malignant tumor other than NSCLC, 27 patients had two other kinds of cancer and four patients had three other primary malignancies. These malignancies were diagnosed as antecedent to NSCLC in 198 patients and synchronous in 46 patients. Univariate differences between the group with multiple primary malignancies with NSCLC and the group with NSCLC alone were significant for age and lung cancer stage ($p<0.00001$ and $<0.0001$, respectively). As shown in Table 2, the most common types of cancer were gastric (43 cases), colorectal (33 cases), and prostate (29 cases) cancer.

Of the 209 patients with multiple primary malignancies, 151 had a history of smoking and 58 were never-smokers (Table 1, 3). As expected, smoking-related cancers were more common in current smokers or ex-smokers in both genders. Female ever-smokers were more likely to develop

Table 1. Characteristics of Patients with Multiple Primary Malignancies with Non-Small Cell Lung Cancer (MPMN) and Non-Small Cell Lung Cancer Alone

| | MPMN | NSCLC alone | p value |
|---|---|---|---|
| Number | 209 | 729 | |
| Age, years | 72 ± 9 | 68 ± 11 | p < 0.00001 |
| Gender | | | |
| Male | 132 | 467 | p = 0.875 |
| Female | 77 | 262 | |
| Smoking status | | | |
| Ever-smoker | 151 | 516 | p = 0.745 |
| Never-smoker | 58 | 213 | |
| Stage | | | |
| I - III | 157 | 425 | p < 0.0001 |
| IV | 52 | 304 | |
| Histology | | | |
| Adenocarcinoma | 127 | 494 | p = 0.085 |
| Squamous | 75 | 203 | |
| Other | 7 | 32 | |
| EGFR mutation | | | |
| Activating mutation | 37 | 161 | Not assessed |
| Exon 20 T790M | 3 | 1 | |
| Other mutation | 3 | 3 | |
| Wild-type | 90 | 332 | |
| Unknown | 76 | 232 | |
| Family history | | | |
| Yes | 45 | 173 | p = 0.568 |
| No | 164 | 556 | |

Table 2. Location of Cancers in Patients with Non-Small Cell Lung Cancer

| Primary site | Number | (%) |
|---|---|---|
| Stomach | 43 | (17.6) |
| Colon | 33 | (13.5) |
| Prostate | 29 | (11.9) |
| Breast | 22 | (9.0) |
| Lung | 17 | (7.0) |
| Bladder | 14 | (5.7) |
| Thyroid | 14 | (5.7) |
| Esophagus | 12 | (4.9) |
| Uterus | 10 | (4.1) |
| Lymphoma | 10 | (4.1) |
| Head and Neck Sq. | 7 | (2.9) |
| Liver | 5 | (2.0) |
| Skin (non-melanoma) | 5 | (2.0) |
| Brain tumor | 5 | (2.0) |
| Kidney | 5 | (2.0) |
| Sarcoma | 5 | (2.0) |
| Urether | 3 | (1.2) |
| Ovary | 1 | |
| Myeloma | 1 | |
| Carcinoid | 1 | |
| Salivary gland | 1 | |
| Gallbladder | 1 | |
| Total | 244 | (100) |

smoking-related malignancies than women without a history of smoking (7.8% and 1.7%; p=0.021).

Table 3 shows the frequencies of other primary malignancies categorized according to gender and smoking status. Among women without a history of smoking, breast, thyroid, and colorectal cancers were the most prevalent malignancies (5.9, 5.1 and 3.0%, respectively). Meanwhile, prostate cancer was the most common neoplasm among male never-smokers. Among women with NSCLC, those with a history of smoking were more likely to have lung cancer than non-smokers (3.9% and 0.4%; p=0.031), whereas never-smokers were more likely to have thyroid cancer than those with a history of smoking (5.1% and 0%; p=0.021).

Table 4 shows the clinical characteristics of 12 women with co-existing NSCLC and thyroid cancer. None of the patients had a history of environmental radiation exposure secondary to atomic bombs (e.g., Nagasaki/Hiroshima, Japan) or nuclear power plant incidents. Interstitial lung disease was not found in any of these patients. The mean age at lung cancer diagnosis was 68.3 years, and all patients developed differentiated thyroid cancer.

Regarding the treatment of thyroid cancer, 10 of 12 patients underwent curative resection, while the remaining two were monitored without treatment. In the two monitored patients, the diagnosis of thyroid cancer was synchronous with the diagnosis of NSCLC. Considering the aggressive nature of NSCLC, the doctors decided not to treat the thyroid cancer in the patients. None of the 12 patients received any chemotherapy or iodine therapy for treatment of thyroid cancer.

Seven of the 12 patients with both NSCLC and thyroid cancer had a family history of cancer and were significantly more likely to have a family history of lung cancer than female never-smokers with NSCLC without thyroid cancer (58.3% vs. 26.8%; p=0.042).

## Discussion

The reported proportion of lung cancer patients with multiple primary malignancies is 10-15%, which is relatively low compared with the 22.3% observed in our study (17). Aguilo et al. reported temporal variation in the percentage of lung cancer patients with other cancers: among patients with lung cancer, the percentage of those with primary lung cancer and certain other cancer(s) increased from 7.4% in 1990-1995 to 17.6% in 2000-2004 (18). With the development of new medical screening modalities and treatments, more patients are now diagnosed at an earlier stage of disease, and the survival rates of many patients with cancer have increased to the point at which other primary malignancies may occur. Therefore, although the proportion of

Table 3. Site of Other Malignancies in Male and Female Patients (Categorized by Smoking Status)

| Primary site | Male Smoker (n=564) | Male Never-smoker (n=35) | p | Female Smoker (n=103) | Female Never-smoker (n=236) | p |
|---|---|---|---|---|---|---|
| Stomach | 38 | 0 | 0.157 | 2 | 3 | 0.642 |
| Colon | 20 | 2 | 0.373 | 4 | 7 | 0.741 |
| Prostate | 26 | 3 | 0.236 | — | — | |
| Breast | 0 | 0 | >0.9 | 8 | 14 | 0.632 |
| Lung | 12 | 0 | >0.9 | 4 | 1 | 0.031 |
| Bladder | 12 | 1 | 0.545 | 0 | 1 | >0.9 |
| Thyroid | 1 | 1 | 0.114 | 0 | 12 | 0.021 |
| Esophagus | 11 | 0 | >0.9 | 0 | 1 | >0.9 |
| Uterus | — | — | | 5 | 5 | >0.9 |
| Lymphoma | 4 | 0 | >0.9 | 3 | 3 | >0.9 |
| Head and Neck Sq. | 4 | 0 | >0.9 | 2 | 1 | 0.221 |
| Liver | 3 | 0 | >0.9 | 0 | 2 | >0.9 |
| Skin (non-melanoma) | 3 | 0 | >0.9 | 0 | 2 | >0.9 |
| Brain tumor | 1 | 0 | >0.9 | 1 | 3 | >0.9 |
| Kidney | 3 | 0 | >0.9 | 2 | 0 | 0.091 |
| Sarcoma | 3 | 0 | >0.9 | 0 | 2 | >0.9 |
| Urether | 2 | 0 | >0.9 | 0 | 1 | >0.9 |
| Ovary | — | — | | 0 | 1 | >0.9 |
| Myeloma | 0 | 0 | >0.9 | 0 | 1 | >0.9 |
| Carcinoid | 1 | 0 | >0.9 | 0 | 0 | >0.9 |
| Salivary gland | 1 | 0 | >0.9 | 0 | 0 | >0.9 |
| Gallbladder | 1 | 0 | >0.9 | 0 | 0 | >0.9 |

our patients with multiple cancers is higher than that observed in previous reports, this value may be more accurate due to increased access to the latest technology. The effects of newly developed technology on the increased incidence of cancer is well illustrated by the use of prostate-specific antigen testing and prostate cancer, as there has been a dramatic change in the incidence of prostate cancer in developed countries over the past several decades (19) driven primarily by the increased frequency of prostate biopsies in asymptomatic men with an elevated prostate-specific antigen level.

In the present study, the proportion of never-smokers varied between men and women, reflecting gender differences in the population of smokers. The National Hospital Registry Group for Lung Cancer reported the incidence of never-smokers to be 8.9% in men and 78.4% in women in Japan (20). In France, a study of the Bas Rhin Registry reported never-smoker proportions of 1.4% and 28.9% in men and women, respectively, while the KBP-2000 study showed proportions of 2.5% and 32.3%, respectively (21, 22). Due to the small number of male never-smokers with lung cancer in our study (35 patients), it is difficult to draw any conclusions from our data regarding men.

There were significant differences in age and disease stage between the patients with NSCLC plus multiple primary malignancies and those with NSCLC alone. The average age of the NSCLC patients with other primary malignancies was higher than that of the patients with NSCLC alone. Most neoplasms in humans tend to occur as people age, and increasing survival rates may result in an increased rate of multiple primary malignancies. Regarding the tumor stage, almost all patients with cancer receive timely follow-up with their doctors; therefore, additional cancers are more likely to be detected at an early stage in such patients.

The present study demonstrated that the most common primary malignancy concurrent with NSCLC is gastric cancer. Haraguchi et al. conducted a single-institution retrospective analysis of multiple primary malignancies with NSCLC and reported gastric cancer to be the most prevalent neoplasm (33 of 938 patients) (17). In addition, Sato et al. evaluated the incidence of multiple primary malignancies involving renal cell carcinoma (319 patients) and found that the most common other malignancy was gastric cancer (11 of 319 patients) (23). However, because gastric cancer is the most frequent malignancy in men and the third most common neoplasm in women in Japan, these results may simply reflect the epidemiological prevalence of this disease.

A significant excess of female never-smokers with NSCLC with thyroid cancer was observed in this study. We excluded patients in whom the additional tumor was identi-

Table 4. **Characteristics of 12 Female Patients with Lung Adenocarcinoma and Thyroid Cancer**

| No. | Type of first cancer | Age at first cancer diagnosis, years | Type of other cancer | Age at other cancer diagnosis, years | Treatment for thyroid cancer | Stage of thyroid cancer at diagnosis | Type of EGFR mutation in lung cancer | Type of EGFR mutation in thyroid cancer | Family history of malignancy |
|---|---|---|---|---|---|---|---|---|---|
| 1 | PTC | 60 | LA | 60 | Total thyroidectomy | Unknown | Wild | Unknown | Yes |
| 2 | Acostic neuroma | 72 | PTC, LA | 72,75 | Observation | cT1N0M0 | Unknown | Unknown | No |
| 3 | PTC | 60 | LA | 60 | Thyroidectomy | pT1N0M0 | Exon 21 L861Q | Unknown | No |
| 4 | PTC | 72 | LA | 73 | Total thyroidectomy | pT1N1M0 | Exon 19 deletion | Wild | No |
| 5 | PTC | 62 | LA | 62 | Thyroidectomy | Unknown | Exon 21 L858R | Unknown | Yes |
| 6 | Breast cancer | 52 | PTC, LA | 81, 81 | Observation | cT1N0M0 | Unknown | Unknown | Yes |
| 7 | PTC | 50 | LA | 59 | Left hemilobectomy | Unknown | Exon 21 L858R | Unknown | No |
| 8 | PTC | 63 | LA | 63 | Left hemilobectomy | pT3N0M0 | Exon 21 L858R and Exon20 T790M | Wild | No |
| 9 | PTC | 62 | LA | 63 | Total thyroidectomy | Unknown | Wild | Unknown | Yes |
| 10 | PTC | 50 | LA | 68 | Total thyroidectomy | Unknown | Exon21 L858R | Unknown | Yes |
| 11 | PTC | 71 | LA | 76 | Total thyroidectomy | pT3N0M0 | Wild | Unknown | Yes |
| 12 | PTC | 72 | LA | 72 | Thyroidectomy | pT2N0M0 | Wild | Unknown | Yes |

PTC: papillary thyroid carcinoma, LA: lung adenocarcinoma, GGO: ground glass opacity

fied after a confirmed diagnosis of NSCLC in order to avoid any effects of therapeutic agents. A similar trend has been noted in previous cancer registry-based studies. For example, Teppo et al. reported the results of a Finnish nationwide study, assessing the risk of new primary cancer among 77,548 Finnish lung cancer patients from 1953 to 1995 (24). In that study, the relative risk was expressed as the standardized incidence ratio (SIR: ratio of the observed to expected number of cases), and a significantly elevated SIR was observed for thyroid cancers [SIR =3.79, 95% confidence interval (CI) =1.23-8.85] in patients with adenocarcinoma. Similar elevation was found in an international multicenter study in which the incidence of second primary cancers following lung cancer was evaluated according to histological type and gender (25). In that study of 27,502 women with adenocarcinoma, a significant excess of second thyroid cancer cases (SIR =4.87, 95% CI =2.88-7.69) was noted. Given that more than 50% of women with lung cancer are never-smokers, and adenocarcinoma is the dominant histology among never-smoking patients (26), the risk of thyroid cancer in women with lung cancer without a history of smoking appears to be increased.

The development of lung cancer in never-smokers and thyroid cancer in the general population may share common risk factors. Regarding lung cancer, known risk factors include gender, secondhand smoke, radiation exposure (including radon), environmental exposure, underlying lung disease and genetic factors (27). The most important risk factor for the development of thyroid cancer is a history of radiation exposure during childhood (28). In addition, a history of thyroid cancer in a first-degree relative and the presence of established familial cancer syndromes (e.g., Carney Complex, multiple endocrine neoplasia type 2) increase the risk of thyroid cancer. Of these factors, radiation exposure is reportedly associated with both lung and thyroid cancers; however, none of the patients who developed both of these cancers in our study had any apparent history of radiation exposure. According to a general report on the effects of radiation on the incidence of solid-organ cancers among members of the Life Span Study cohort of Hiroshima and Nagasaki atomic bomb survivors, significant radiation-associated increases in risk were seen for most sites, including the oral cavity, esophagus, stomach, colon, liver, lung, non-melanoma skin, breast, ovaries, bladder, nervous system and thyroid (29). There is a unique medical insurance status for citizens exposed to radiation fallout from the two World War II nuclear explosions in Japan. No patients in this study fell into that category, as confirmed based on insurance certificates. Moreover, considering the patients' ages and places of residence, there seems to be an extremely low probability that the nuclear explosions influenced the health status of these patients.

A lack of other environmental risks and a statistically significant excess of patients with a family history of malig-

nancy suggests the presence of underlying genetic factors. From an embryological standpoint, the thyroid and lungs originate as neighboring bud-shaped outgrowths from the midline of the anterior embryonic foregut during normal organogenesis. In addition, both of these primordial organs express the transcription factor Nkx2-1 (TTF-1). Moreover, murine models targeting the Shh and Fgf pathways indicate that some aspects of the development of these organs involve similar gene sets (30, 31).

One strength of this study is the successful exclusion of treatment effects on the development of second primary malignancies. We did not consider subsequent malignancies detected after the diagnosis of NSCLC to be multiple primary cancers. Therefore, there is no possibility that the cases of thyroid cancer reported in this study were caused by chemotherapy or radiotherapy for the treatment of NSCLC.

This study is associated with several limitations. First, this was a single-institution retrospective study conducted in Japan, and there are considerable geographical effects, particularly in women, regarding lung cancer in never-smokers. For example, lung cancer is more frequently diagnosed in Asia than in the United States and more frequently in the United States than in Europe (2). Therefore, care is needed when applying our results to patients in non-Asian countries. Second, we collected family history information from first-degree relatives only. Third, insufficient information on male never-smokers was obtained due to the small sample size. Therefore, a larger prospective study with specific guidelines on family history collection is needed to confirm the present findings.

In conclusion, this retrospective study revealed differences in second malignancies between never-smoker NSCLC patients and those with a history of smoking. A significant excess of never-smoking female NSCLC patients with thyroid cancer was observed in this study, which was quite unexpected and indicates the presence of predisposing factors other than tobacco smoke. Therefore, further research into the causes of both cancers in never-smokers is needed.

**The authors state that they have no Conflict of Interest (COI).**

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