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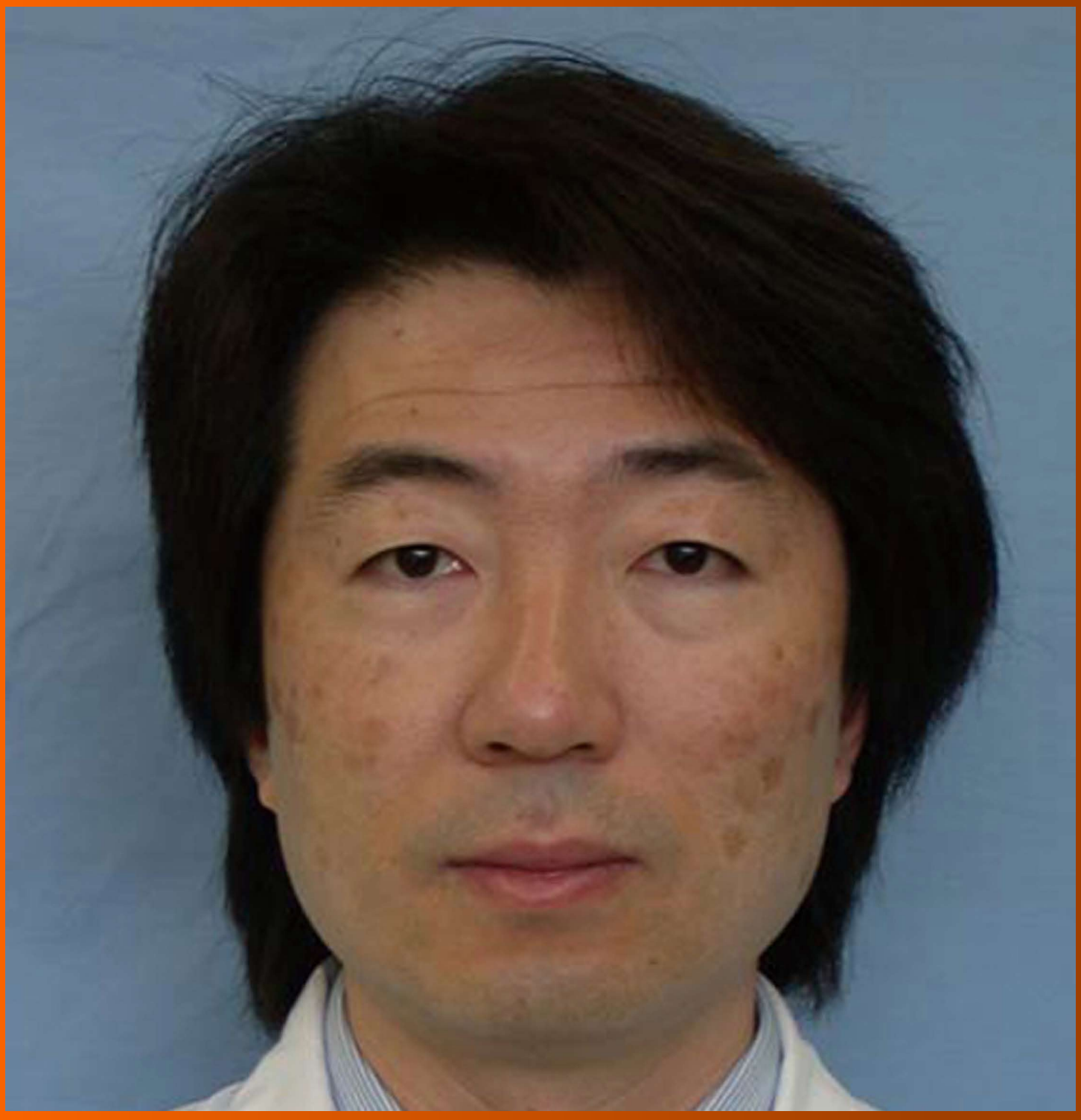

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REVIEW

Lung cancer screening: Should we be excluding people with previous malignancy?

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Abstract

The National Lung Screening Trial (NLST) was a large, randomized, controlled study showing a 20% reduction of lung cancer mortality and 7% reduction of all cause mortality using annual low dose computed tomography (LDCT) in a high risk population. NLST excluded people with a previous history of cancer treatment within the past 5 years and all people with a history lung cancer. The aim of this work is to review how lung cancer screening trials addressed the confounding effect of previous malignancy. We also review the subsequent recommendations by the United States Preventative Task Force Services, multiple professional societies and the Center for Medicaid and Medicare Services which defer either to NLST criteria or, clinician judgment or refrain from asserting any recommendation on the topic, respectively. Implications of lung cancer screening in the setting of previous malignancies, specifically lung, head and neck, esophageal, gastric, breast, colorectal cancer and lymphoma are also discussed. With lung cancer screening, an antecedent malignancy introduces the possibility of discovering metastasis as well as lung cancer. In some circumstances diagnosis and treatment of oligometastatic disease may confer a survival benefit. The survival benefit of treating either lung cancer or oligometastatic disease as result of lung cancer screening has yet to be determined. Further studies are needed to determine the role of lung cancer screening in the setting of previous malignancy.

Key words: Lung cancer screening; Criteria; Previous malignancy; Antecedent malignancy; Lung metastasis; Guidelines; Head and neck cancer; Lung cancer; Low dose computed tomography; Gastric cancer; Breast cancer; Colorectal cancer; Lymphoma; Esophageal cancer

Core tip: Most lung cancer screening trials, including the National Lung Screening Trial, exclude those with a history of a previous malignancy as it may introduce confounding factors that influence survival. However,

people with previous malignancy may benefit from the discovery of treatable lung cancer as well as treatable metastasis. In this review, we summarize the consideration that studies and national guidelines give in regards to lung cancer screening in patients with previous malignancy. Furthermore, we address the implications of lung cancer screening in the setting of specific malignancies, namely lung, head and neck, esophageal, gastric, breast, colorectal cancer and lymphoma.

Erkmen CP, Kaiser LR, Ehret AL. Lung cancer screening: Should we be excluding people with previous malignancy? *World J Respirol* 2016; 6(1): 1-13 Available from: URL: http://www.wjgnet.com/2218-6255/full/v6/i1/1.htm DOI: http://dx.doi.org/10.5320/wjr.v6.i1.1

INTRODUCTION

According the National Cancer Institute, lung cancer is the most common cause of cancer death among both men and women, accounting for more deaths than breast, colorectal, prostate and pancreatic cancer combined. Nearly 75% of lung cancers are diagnosed at stage Ⅲ or Ⅳ[1], thus contributing to the dismal average five-year survival of 17.4% to 18.5%[2,3]. Though early detection through lung cancer screening should be expected to confer a survival benefit, several studies have failed to prove this, even in large randomized trials[4]. In 2011, the National Lung Screening Trial (NLST) compared a low dose computed tomography (LDCT) scan to chest radiography (CXR) as a modality of lung cancer screening. LDCT reduced the risk of lung cancer death by 20% and death from all causes by 7%[5]. This was a multi-institutional, randomized study of over 53000 patients. The NLST restricted eligibility to those with greater than 30 pack years of smoking, active smokers or those who quit smoking within the past 15 years who were between the ages of 55 to 74. In addition to including those at high risk of lung cancer, NLST excluded people who were not likely to benefit from lung cancer screening, namely those who were unwilling to undergo surgical resection, those with major health problems that would preclude lung cancer treatment, and those with obvious symptoms of lung cancer. The combination of a sufficiently powered study, inclusion of only those at highest risk of lung cancer and exclusion of people unlikely to benefit from early lung cancer detection contributed to the unprecedented mortality risk reduction of NLST. LDCT, applied to the United States population could potentially avert 12000 lung cancer deaths per year[6].

However, Pinsky *et al*[7] utilized data from Surveillance, Epidemiology and End Results (SEER), the United States Census and the National Health Interview Survey to determine that only 6.2% of the United States population over 40 years old was eligible for lung cancer screening. Additionally, only 26.7% of people with lung cancers would have been eligible for lung cancer screening by NLST criteria Farjah *et al*[8] used a risk-prediction model to review resected lung cancer patients. The authors concluded that NLST lung cancer screening criteria may exclude people who have a predicted risk greater than or equal to those who are currently eligible. Many people excluded by NLST criteria could benefit from lung cancer screening. This study prompts scrutiny of the exclusion criteria of lung cancer screening.

Looking at the design of NLST, is important to categorize the exclusion criteria into exclusion because people will not likely benefit from lung cancer screening, and exclusion that confounds a clinical trial. Patients presenting with symptoms of lung cancer such as, weight loss or, hemoptysis, and those who are unwilling to undergo lung cancer surgery are not likely to benefit from lung cancer screening[9]. However other NLST exclusion criteria such as "patients participating in another screening trial or cancer prevention study" may benefit from lung cancer screening, but were not included to avoid confounding scenarios. Similarly, the NLST exclusion of patients with metallic implants or devices in the chest or back, patients with a chest computed tomography (CT) within the past 18 mo, patients with a recent pneumonia or respiratory tract infection, or patients with removal of any portion of the lung excluding needle biopsy could all possibly benefit from the lung cancer mortality risk reduction of LDCT. More controversially, NLST excluded those on home oxygen and those with previous malignancy. Though unclear if these people will benefit from LDCT, they at least deserve further study.

EXCLUSION OF PATIENTS WITH PREVIOUS MALIGNANCY

NLST excluded people with a history of lung cancer and those who were treated for a malignancy within five years of the initial screen. People with non-melanomatous skin cancer were still eligible for lung cancer screening. From the perspective of study design, previous malignancy introduces confounding challenges to the study of lung cancer screening: (1) A lung nodule has a 40%-60% chance of being a metastasis from a previous malignancy. Radiologists may interpret a nodule differently with the knowledge of a previous malignancy[10,11]; (2) The management of a lung nodule in a patient with a previous cancer history varies from that in patients without a cancer history. For instance, a lung nodule in the setting of previous cancer may prompt a PET scan to look for other metastasis or recurrence of the primary cancer. The recommendation for management of the same nodule in a patient without previous malignancy may be a follow up CT scan. It is difficult to establish the benefit and harms of screening when work-up and treatment varies within the study group; (3) The etiology of a malignant nodule

cannot always be determined. For instance, a squamous cell cancer found in the lung may be a lung primary or a metastasis from a head and neck cancer. Even immunohistochemistry and genetic analysis may not be able to distinguish the cancer's origin; (4) Previous malignancy introduces wide variability in survival. The type, stage and disease free interval of a previous malignancy all influence overall survival. It would be difficult to interpret if screening for lung cancer with a LDCT improved survival in these patients; and (5) It can be challenging to determine the contribution a lung cancer, another distinct malignancy or the combination of the two has on mortality.

Previous studies of lung cancer screening had similar concerns about including patients with previous malignancy. We have summarized findings of index trials in lung cancer screening in Table 1. In 1993, Henschke and colleagues concluded that CT screening for lung cancer detected disease at an earlier stage than CXR in their Early Lung Cancer Action Project (ELCAP)[12]. Patients with prior cancer were excluded from the study. The ongoing International I-ELCAP study continues to limit enrollment to people with no previous history of lung cancer[13]. The Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) was a longitudinal, population-based study of 335441 people proved that lung cancer screening with CT scanning and a volumetric lung nodule management algorithm was feasible[14]. The NELSON trial excluded persons with current or past renal cancer, melanoma or breast cancer were not included, "because these tumors give rise to lung metastasis even after long follow up. People with lung cancer within 5 years of diagnosis, and lung cancer diagnosed greater than 5 years from randomization, but still undergoing treatment were also excluded[15]. The Detection and Screening of Early Lung Cancer with Novel Imaging Technology (DANTE) Trial published their results comparing lung cancer mortality in those undergoing LDCT compared to no screening in May of 2014[16]. Unlike NLST, there was no reduction in lung cancer or all cause mortality in 2532 patients randomized to LDCT *vs* no screening. Similar to NLST and NELSON, persons with a previous malignancy within 10 years of recruitment were ineligible. The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial was a population study of over 154000 patients looking at lung cancer death as a primary outcome[17]. There was no reported difference in lung cancer mortality with CXR as a screening modality[4,18]. This study excluded patients with prior cancer of the colon, rectum, lung, prostate, ovary or individuals undergoing treatment for cancer at the time of the study, excluding basal-cell and squamous-cell skin cancer.

At the time of this writing, 15 studies of lung cancer screening are registered as "active" with ClinicalTrials.gov. Of these 15 studies, 13 have exclusion criteria for people with a history of previous malignancy, including lung cancer. These studies have varying exceptions, but all allowed people with non-melanomatous skin cancer to be eligible for lung cancer screening. Only two studies made no mention of excluding people with previous malignancy. Only one study aims to look at lung cancer screening in the setting of previous malignancy, namely Hodgkin's lymphoma[19].

RECOMMENDATIONS FOR LUNG CANCER SCREENING

Though the exclusion of a previous malignancy makes sense in the setting of a randomized trial, it does not necessarily translate to the logic of excluding these patients as a policy. In 2014, the United States Preventative Services Task Force (USPSTF) updated their recommendations regarding lung cancer screening[20]. The previous recommendation, published in 2004, found insufficient evidence to recommend LDCT for lung cancer screening. With compelling evidence from four randomized controlled studies NLST, DANTE (Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays)[13,21], DLCST (Danish Lung Cancer Screening Trial)[22], and MILD (Multicentric Italian Lung Detection)[23] the USPSTF "concludes with moderate certainty that annual screening for lung cancer with LDCT is of moderate net benefit[16]".

Interestingly, USPSTF departed from the NSLT in its recommendations by expanding eligibility. Based on comparative modeling studies calibrated to both NLST and PLCO Cancer Screening Trial data, de Koning *et al*[24] found that annual LDCT has a favorable benefit-harm ratio for individuals aged 55 through 80, not 55 to 74 as defined by NLST. USPSTF does not mention excluding people with a history of previous malignancy. Even though both NLST and PLCO had exclusion criteria of lung cancer and restrictions on any previous malignancy, USPSTF did not recommend including or excluding people with previous malignancy from lung cancer screening. This leaves clinicians to interpret the USPSTF recommendation to screen patients in a fashion "similar to NLST".

The American Lung Association (ALA) in 2012 published guidance on lung cancer screening addressing both patients and physicians in 2012[25]. Though the ALA did not specifically address screening people with previous malignancy, they did acknowledge that lung cancer screening requires future refinement of the criteria. In the absence of randomized control data for all clinical scenarios of criteria, they suggest relying on risk stratification models. They cite Tammemagi and colleagues' use of PLCO participants to develop a lung cancer risk prediction model[26] which performed better than the NLST criteria. Unfortunately, risk prediction models rely on existing data about lung cancer screening, which excludes those with a history of previous malignancy.

The American College of Chest Physicians (ACCP) released their evidence-based clinical practice guidelines in 2013[27]. Regarding the inclusion and exclusion

Table 1 Index trials of lung cancer screening

Ref.	Participants	Exclusion criteria	Design	Results
Aberle *et al*[5]	53454 participants Age 55 to 74 At least 30 pack-year smoking history Former smokers must have quit within previous 15 yr	Previous lung cancer diagnosis CT scan within previous 18 mo	Randomized Control Trial Participants randomized to three annual screenings with LDCT (26722) *vs* single view PA CXR (26732)	Rate of positive screening was 24.2% in LDCT and 6.9% with CXR group The majority of positive screening results were false positives, 96.4% in the LDCT group and 94.5% in the CXR group Lung cancer mortality decreased by 20% (P = 0.004) and all cause mortality decreased by 6.7% in LDCT group (P = 0.02)
van Iersel *et al*[14]	15822 participants Age 50-74 Determined to be high risk based on answers to heath questionnaire Good overall health (able to climb 2 flights of stairs, weight less than 140 kg)	Hemoptysis or unexplained weight loss of 15 lbs or more in last year Current or past diagnosis of renal cancer, melanoma or breast cancer Lung cancer diagnosis within last 5 yr or current treatment CT scan within past year	Randomized Control Trial Participants randomized to either LDCT screening (7915) or no screening (7907)	Ongoing - 10 yr follow up planned
Infante *et al*[16]	2472 participants Males aged 60-74 20 pack-year smoking history	History of previous malignancy treated within 10 yr (exceptions: Early laryngeal cancer and nonmelanoma skin cancer with a 5-yr disease-free interval) Comorbid conditions with life expectancy less than 5 yr	Randomized Control Trial Randomized to 5 yr of annual screening with LDCT (1276) or clinical follow up (1196)	Ongoing. 3 yr results: Lung cancer detected in 4.7% of patients in LDCT group and 2.8% in controls (P = 0.016) There was a 1.6% lung cancer mortality in the LDCT group and 1.7% in the control group (P = 0.84). No difference in all cause mortality (P = 0.83) to this point in the study
Saghir *et al*[22]	4104 participants Age 50-70 At least 20 pack-year smoking history Former smokers who quit after age 50 and quit less than 10 yr prior FEV1 of at least 30% predicted value Good overall health (able to climb 2 flights of stairs, weight less than 130 kg)	Previous cancer diagnosis and treatment Comorbid illness that would shorten life expectancy to < 10 yr CT scan within previous year	Randomized control trial Participants randomized to five annual LDCT screenings (2052) or no screening (2052)	There was a higher rate of invasive procedures performed in the LDCT group compared with controls (P < 0.0001) Ongoing. 5 yr results: Lung cancer was diagnosed in 69 patients in the LDCT group, compared with 24 in the control group (P < 0.001) Stage Ⅰ-ⅡB lung cancer was diagnosed more frequently in the LDCT group (P = 0.002), however there was no difference in frequency of Stage ⅢA-Ⅳ lung cancer (P = 0.509) There was no difference in mortality from lung cancer (P = 0.428) or overall mortality (P = 0.059) to this point of follow up
Pastorino *et al*[23]	4099 participants Age 49 or older At least 20 pack-year smoking history - current smoker or had quit within 10 yr	History of cancer within the previous 5 yr	Randomized Control Trial Randomized participants to annual LDCT screening (1190), biennial LDCT screening (1186), or observation alone (1723)	The cumulative 5-yr lung cancer incidence rate was 0.0031% in the control group, 0.0046% in the biennial, and 0.0062% in the annual LDCT group (P = 0.036) Rates of mortality from lung cancer were 0.0011% in the control group, 0.0011% in the biennial group, and 0.0022% in the annual group (P = 0.21) There was also no difference in all cause mortality between the three groups (P = 0.13)

LDCT: Low dose CT; CXR: Chest radiography; CT: Computed tomography.

criteria of the NLST, the authors state, "Expanding screening to cohorts other than those included in the NLST is probably not warranted at this time unless it is in the context of a research study". They also look

to risk prediction models to assist with establishing screening criteria, however they must account for competing causes of death. More specifically, for those with a previous malignancy, further studies are needed to understand how a previous malignancy impacts lung cancer death. Though there are no clear recommendations about lung cancer screening in those with previous malignancy, the ACCP and their collaborative, multi-society statement with the American Cancer Society (ACS), the American Society of Clinical Oncology (ASCO) and the NCCN emphasizes the need to balance the benefits and harms of lung cancer screening on an individual basis[28].

The Centers for Medicare and Medicaid Services released their final national coverage determination for lung cancer screening with LDCT in February of 2015[29]. The supporting data cites the Cochrane Database Systematic Review[30] and a systematic review by Prosch and Schaefer-Prokop[31]. Both of these reviews included studies like NLST, DANTE, DLCST and PLCO which all excluded people with previous malignancy. However there is no recommendation on either including or excluding patients with previous malignancy.

In the 2015 review of current ACS guidelines for cancer screening in the United States, the authors advise that clinicians should initiate a discussion about lung cancer screening in people who meet the criteria of the NLST. "Clinicians should not discuss LDCT lung cancer screening with patients who do not meet the recommended criteria", including those with previous malignancy. The ACS allows for judgment of the clinician to discuss lung cancer screening when the risk "seems to approximate" NSLT eligibility criteria. They note that the uncertainty of harms and benefits outside the NLST criteria are too great to recommend screening.

In contrast, in the most recent 2015 update of the National Comprehensive Cancer Network (NCCN) guidelines for lung cancer screening[32], the panel members do not exclude patients with previous cancer from lung cancer screening. In fact, the NCCN guidelines include a personal cancer history as a significant risk factor for developing lung cancer. The guidelines highlight that those who survive lung cancer, lymphomas, cancers of the head and neck and other smoking-related cancers such as esophageal cancer. The panel recommends that with one additional risk factor (category 2A), like previous malignancy, lung disease, family history of lung cancer, radon exposure and occupational exposure to carcinogens, individuals aged 50 or older with a 20 pack-year history of smoking tobacco should undergo lung cancer screening.

The most comprehensive evaluation of lung cancer screening in patients with previous malignancy is found in the American Association for Thoracic Surgery guidelines[33]. These guidelines note that people with previous cancer, lung cancer in particular, are at increased risk of developing a lung malignancy. Complex environmental and genetic factors that predispose someone to the first malignancy are still relevant for the development of a second lung cancer. Additionally, treatment with radiation therapy or alkylating agents for a previous cancer may also contribute to the risk of developing lung cancer. The consensus opinion is that a previous malignancy should not exclude patients from lung cancer screening. Furthermore, a previous malignancy is an indication to start lung cancer screening at an earlier age and in those with less tobacco exposure than currently recommended by NLST criteria. With regard to patients who have been successfully treated for lung cancer, they should receive high resolution CT scans for 4 years followed by annual LDCT screening for the rest of their life, or until functional status or refusal to undergo lung cancer treatment precludes the potential benefit of lung cancer screening. Jaklitsch *et al*[33] recommend lung cancer screening in patients with level 2 evidence (*i.e.,* data from case-controlled or nonrandomized clinical trials).

In the absence of specific data about lung cancer screening in the setting of previous malignancy, risk prediction models can guide recommendations. Tammemägi *et al*[26] have developed a lung cancer risk prediction model (www.brocku.ca/lung-cancer-risk-calculator). This model incorporates multiple variables including smoking (intensity, duration, quit time), social circumstances and personal health history[34,35]. Selecting individuals for lung cancer screening based on accurate lung cancer risk prediction models can increase sensitivity (83.0% *vs* 71.1%; $P < 0.001$) and positive predictive value (4.0% *vs* 3.4%; $P = 0.01$) without loss of specificity (62.9% and 62.7%; $P = 0.54$) compared to NLST or USPSTF criteria[36]. Accurate modeling can lead to smaller numbers of individuals being screened, identification of more lung cancers and an increased positive predictive value[37]. Early data of lung cancer screening in patients with antecedent malignancy suggests that such screening may contribute to developing personalized risk prediction models.

LUNG CANCER SCREENING IN PATIENTS WITH HISTORY OF SPECIFIC MALIGNANCY

The benefit that lung cancer screening can confer on a patient with previous malignancy depends on the antecedent cancer. Benefit may be in the form of finding lung cancer in a high risk population, or in the form of finding treatable metastasis. We summarize the existing knowledge of lung cancer screening in the setting of previous lung, head and neck, esophageal, gastric, breast, colorectal cancer and lymphoma (Table 2).

Lung cancer

A history of lung cancer is one of the strongest risk factors for developing a new lung cancer. In a study of 1294 patients undergoing resection for early stage

Table 2 Prior malignancy and lung cancer

Prior malignancy	Ref.	Method	Results
Lung	Lou *et al*[38]	1294 participants with early-stage NSCLC underwent resection and then were followed with surveillance CT screening	Recurrence was diagnosed in 20% of patients and second primary lung cancer was diagnosed 7% of patients. The risk of second primary lung cancer diagnosis did not decrease over time Of the second primary cancers that were diagnosed, 93% were identified by scheduled surveillance CT. Of the recurrences that were diagnosed, 61% were identified by surveillance CT. Twenty five percent of patients required additional invasive testing, but less than 1% experienced complications from these procedures
Head and Neck	Milano *et al*[50]	61883 patients with SCC of the head and neck were identified *via* the SEER database. Of those, 4522 developed a second primary lung cancer. A retrospective data analysis was performed	The risk of developing a primary lung cancer after HNSCC was 5.8%, 11.4%, and 16.4% at 5, 10, and 15 yr These rates are higher compared to the general population
Head and Neck	Baxi *et al*[51]	35958 three-year survivors of SCC of the head and neck were identified *via* SEER database. A competing-risks proportional hazards regression was used to estimate probabilities of death from different causes	Second primary malignancy was the second leading cause of death (second only to primary head and neck squamous cell carcinoma) in this population Of these, 53% of second primary malignancies were lung cancer
Head and Neck	Pagedar *et al*[54]	Data was collected and retrospectively analyzed. Survival estimates were generated for patients with lung cancer with and without a history of head and neck cancer	The median survival of patients with only primary lung cancer was 38 mo, compared to 22 mo in those with a history of head and neck cancer with lung cancer as a second primary malignancy. This statistically significant difference suggests that survival outcomes after lung cancer diagnosis are worse in patients who have a history of head and neck malignancy
Breast	Kitada *et al*[63]	Data was collected an analyzed on 1226 patients who underwent surgical resection of breast cancer, 49 of whom were found to have at lease one pulmonary lesion during or after workup	14 patients underwent surgical resection of the pulmonary lesion. Primary lung cancer was the diagnoses in 3 of these patients, metastases in 8 cases. Of those diagnosed with second primary lung cancer, the stage was Ⅰ A in all
Breast	Kerendi *et al*[67]	35 patients with breast cancer and second primary lung cancer were identified and retrospective analysis of survival was performed	More than half of patients had their lung cancer diagnosed during workup or follow-up. 54% of these patients were successfully treated with surgery. There was a statistically significant survival benefit when the cancer was detected early (stage Ⅰ A, asymptomatic)
Breast	Milano *et al*[68]	3529 women with NSCLC diagnosis after breast treatment were identified in the SEER database. Data on these patients was retrospectively analyzed and compared to data on 151628 women diagnosed with NSCLC alone	Patients with a history of breast cancer were diagnosed at significant earlier stage, although surgical resection was used more frequently in the NSCLC only group History of breast cancer history did not affect overall survival in localized NSCLC. Overall survival was significantly greater in patients with regional and distant NSCLC that had a history of breast cancer
Bladder	del Rey *et al*[72]	Data from 231 patients with non-muscle invasive bladder cancer were retrospectively analyzed	Lung cancer was the most common second primary malignancy in this population. The risk of lung cancer in patients with non-muscle invasive bladder cancer is 10 fold higher than the regional general population
Lymphoma	Das *et al*[75]	Authors used a decision-analytic model to estimate potential benefits of annual low-dose CT screening *vs* no screening in a hypothetical cohort of patients (early stage lymphoma diagnosed at age 25, lung cancer screening starting at age 30). Model parameters were generated from SEER	In this simulated model, annual CT screening increased survival by 0.64 yr for smokers and 0.16 yr for non-smokers. The difference in quality of life and cost effectiveness was also more pronounced in smokers
Lymphoma	Milano *et al*[77]	Survival data of 187 patient with history of Hodgkins lymphoma diagnosed with NSCLC was compated to data from 178431 patients diagnosed with NSCLC only	Hodgkins lymphoma survivors had significantly inferior overall survival across all lung cancer stages (estimated to be between 30% to 60% decrease in overall survival) Patients with younger age at lymphoma diagnosis, younger age at lung cancer diagnoses, and those with longer latency between cancer diagnoses were more likely to be diagnosed with late stage disease
Colorectal	Hattori *et al*[34]	A retrospective analysis of lung cancer patients with (123) or without (4431) a previous history of colorectal cancer treated with surgical resection	There is no statistically significant difference in overall survival comparing patients with lung cancer *vs* lung cancer with a history of surgery for colorectal cancer. Prior history of colorectal cancer was not a poor prognostic indicator on multivariate analysis Of those patients who had been diagnosed with both lung and colorectal cancer, those who are older and those who underwent treatment with adjuvant chemotherapy had poorer outcomes

CT: Computed tomography; NSCLC: Non-small-cell lung cancer; SEER: Surveillance, epidemiology and end results; SCC: Squamous cell cancer; HNSCC: Head and neck squamous cell cancer.

lung cancer, 7% presented with a second primary lung cancer within a median follow up of 35 mo[38]. People with lung cancer have a 3%-6% risk per year of developing a second lung cancer, a risk that actually

increases with time[31,39,40]. This increased risk of a second lung cancer persists to even 10 years after the initial diagnosis[41]. By comparison, in the NLST high-risk population, the incidence of lung cancers was less than 1% per patient year[5]. Screening lung cancer patients should be at least as successful in discovering a new lung cancer as screening those who fit the NLST criteria. Second primary lung cancers found during surveillance are diagnosed in stage Ⅰ (92%) or stage Ⅱ (4%), suggesting a survival benefit[31]. However, the survival benefit of long term, annual LDCT to screen for second primary lung cancers is unknown. Special consideration should be given to the possibility of false positives (25%) and unnecessary invasive procedures (3%) and complications from unnecessary invasive procedures (0.3%) from nodules found in the setting of CT scanning after lung cancer treatment[31].

Surveillance following the treatment of lung cancer consists of a history and physical and chest CT every 6 to 12 mo for two years, then a history and physical with a LDCT annually, according to NCCN guidelines[31]. Locoregional recurrence occurs in 10%-30% of patients[42], and metastatic spread occurs in 15%-39% of patients[33]. A majority of these occur within the first 2 years of diagnosis[43]. For the first 4 years after surgery, the risk of recurrence is 6% to 10% per patient year but decreases thereafter to 2%[31]. In a review of 9 studies looking at lung cancer recurrence following surgical resection[44], Mollberg *et al*[44] found that only 0.9% to 4.4% of patients with lung cancer recurrence were candidates for repeated resection. A more recent study by Crabtree *et al*[45] showed that 40%-41% of subsequent malignancies were treated with curative intent. Data on five-year survival following recurrence varies widely from 8.3% to 40.0% with improved survival in those receiving curative treatment[37,38]. Though it would seem that early detection of recurrent lung cancer would improve survival, several studies comparing intense surveillance for lung cancer with clinic visits and CT scans failed to demonstrate a survival benefit[38,46]. A randomized trial in France comparing lung cancer surveillance with CXR *vs* CT and bronchoscopy is underway. Hopefully these results will clarify which surveillance techniques improve survival[47]. Regardless of whether a CT following lung cancer treatment is for surveillance for recurrence or early diagnosis of a new lung cancer, the impact on survival is still unclear. Advances in targeted therapy, novel chemotherapeutic regimens and palliative care give promise toward improved survival, even with a diagnosis of metastatic disease.

Perhaps the greatest value of surveillance and screening in lung cancer survivors is ensuring that patients are smoke free. Parsons *et al*[48] found that continued smoking following treatment for lung cancer was associated with a significant increased risk of recurrence and an almost threefold increase risk of all cause mortality. Even recent quitters enjoy a significant improvement in disease free and overall survival compared to those who continue to smoke[49]. Smoking cessation confers a benefit for lung cancer patients at any time.

Head and neck cancer

Head and neck cancer and lung cancer share the risk factors of smoking and age. Up to 15%-20% of head and neck cancer patients develop a second primary malignancy[50]. Lung cancer accounts for 50% of these second primary malignancies and 50% of second primary malignancy-related deaths in patients with head and neck cancer[51]. With proactive follow up with a CT scan, oro-nasopharyngeal and esophageal endoscopy, Wolf *et al*[52] found a second primary malignancy in 18% of head and neck squamous cell cancer patients. Almost half of the second primary malignancies turned out to be primary lung cancer. Of the patients found to have a second primary malignancy, 86% were diagnosed at an early stage and were able to undergo therapy with curative intent. Though this study demonstrated that a lung cancer can be found and treated in patients with head and neck cancer, they did not study the influence of lung cancer treatment on survival.

To date, there are no controlled trials of head and neck cancer patients comparing survival with and without LDCT screening for lung cancer. In the absence of controlled trials, a recent survey of Canadian Head and Neck Surgeons showed that a majority of surgeons believe lung screening can improve patient mortality, and 31% currently screen high-risk patients for lung cancer with a LDCT[53]. However, Pagedar *et al*[54] found that the median survival of patients with lung cancer was 38 mo compared to 22 mo in patients with an antecedent history of head and neck cancer. These authors suggest that screening patients with a history of head and neck cancer with LDCT may not have the same survival benefit as those without this cancer history.

Additional questions arise when screening head and neck cancer patients for lung cancer. For instance, it is not always possible to determine if a pulmonary nodule is a primary lung cancer or a metastasis. Previously, Geurts *et al*[55] found that there is no difference in overall survival between patients who had surgical resection of a metastasis *vs* a lung cancer[55]. This would argue for screening in the setting of head and neck cancer. However a directed study looking at survival in the setting of screening has yet to be done. As second question is when to start screening head and neck cancer patients, at the time of diagnosis or some interval following successful treatment? Patients presenting with synchronous second primary lung cancer are more likely to have treatable, early-stage disease, as compared to patients with metachronous malignancy[56]. Five-year survival is higher in patients with synchronous head and neck and lung cancer compared to metachronous malignancies[57]. The improved 5-year survival is likely due to increased detection of early stage disease and earlier intervention.

It is possible that lung cancer screening may aid in detecting metachronous malignancy at an earlier stage and thus may improve survival, but this is yet to be demonstrated in the literature. These questions and controversies will hopefully lead to controlled trials looking at lung cancer screening in the setting of head and neck cancer. Clinicians must evaluate the value of lung cancer screening in head and neck cancer survivors on an individual basis, taking into consideration the patient's expected survival, risk of lung cancer, and potential benefit of treatment for either lung primary or metastasis. As with all cancer patients with a smoking history, a discussion of lung cancer screening should also include a discussion about smoking cessation.

Esophageal cancer and gastric cancer

Patients with esophageal cancer, gastric cancer and lung cancer share smoking as a common risk factor. In a study of 116 consecutive cases of esophageal cancer, 19% had a solitary pulmonary nodule[58]. Of these, 68% were benign nodules, 18% were new primary lung cancers and none were metastatic esophageal cancer. In patients with gastric cancer, 9.2% had secondary primary malignancies, of which lung was the most common (18.4%)[59]. In this same study, logistic regression analysis failed to show a significant association between age, gender, smoking, alcohol and *Helicobacter pylori* infection and the development of a second primary malignancy. The authors propose that clinicians consider the possibility for secondary primary malignancies during diagnosis and surveillance. However, there are no studies addressing the value of lung cancer screening. Furthermore, there are no evidence-based guidelines on who to screen and when to screen for lung cancer in those with previous esophageal and gastric cancer. Clinicians have to judge on an individual basis if the risk of lung cancer is great enough to screen, and if treatment of a discovered lung cancer will favorably impact survival. In sharing this decision with active smokers, clinicians must emphasize that risk reduction achieved by smoking cessation will likely surpass any risk reduction from lung cancer screening.

Breast cancer

Breast cancer is the most commonly diagnosed malignancy in females. Current recommendations in breast cancer surveillance recommend frequent physical exams and post-treatment yearly mammograms[60]. Given the rarity of lung metastasis, the ASCO guidelines do not recommend routine CT screening for metastatic disease of the lung[61]. Even during initial breast cancer workup, routine use of CT staging is thought to have limited value, low sensitivity, and considerable rate of false positives, and thus is recommended only in the setting of symptoms concerning for distal metastases[62]. However, excluding women with a history of breast cancer from LDCT lung cancer screening eliminates a large number of women who may otherwise benefit from early detection of malignancy. Almost 4% of breast cancer patients have pulmonary lesions during workup or identified during follow up[63]. In addition, while radiation therapy is an effective treatment for breast malignancy, it leads to a well-documented increase in risk for second primary malignancy of the lung[64,65]. This risk of treatment related lung cancer is significantly higher in patients with a smoking history[66].

Earlier diagnosis of lung cancer in a patient with a history of breast cancer carries an improved prognosis. Kerendi *et al*[67] reviewed the records of 35 patients with known breast cancer found to have a second primary malignancy of the lung. Of these patients 54% were asymptomatic at the time of diagnoses, and the malignancy was found during workup or routine follow up. Pre-operative biopsy yielded a diagnosis in 82% of cases and 54% of these lung cancers were successfully treated with surgery. They documented an improved prognosis if the lung cancer was diagnosed when the patient was asymptomatic and if the patient was a non-smoker. In addition, it has been demonstrated that treatment of non-small cell lung cancer in the setting of a history of breast cancer paradoxically may convey an improved prognosis compared to patients diagnosed with non-small cell lung cancer alone. Data gathered from the SEER-18 registry indicated that non-small cell lung cancer was diagnosed at an earlier stage in patients with a breast cancer history, and these patients were more likely to undergo surgical resection[68]. Breast cancer history did not affect overall survival in local disease, but portended an improved overall survival in regional or distant lung cancer. Thus, it appears as though this patient population would certainly be ideal for inclusion in a LDCT lung cancer screening program.

While CT screening may identify a solitary pulmonary nodule, it is notoriously difficult to distinguish between primary lung malignancy and breast metastasis radiologically. Evidence suggests that over 50% of solitary pulmonary nodules detected in the setting of treated breast malignancy are primary lung cancer[69]. Kinoshita *et al*[70] reviewed records of 64 breast cancer patients who had undergone surgical resection of a pulmonary nodule. Of these, 37 patients (58%) were found to have a primary lung cancer. Retrospectively reviewing pre-operative CT scans after surgical diagnosis suggested that primary lung malignancy was significantly associated with the following radiologic findings: Air bronchograms, increased size, and ill defined nodule border. However, these can still be non-specific findings and radiologic diagnosis continues to be a challenge.

This begs the question, does survival differ between patients with a solitary pulmonary nodule found to be lung cancer *vs* breast metastasis? Tanaka *et al*[69] studied 30 patients who underwent surgical resection for a solitary pulmonary nodule after curative surgery for breast cancer. They found that 93% of pulmonary nodules were malignant, 67% of these being primary lung cancer. Five-year survival after surgical resection was 100% in cases of breast metastasis and 61%

in cases of primary lung cancer[62]. In another study, 84% of patients found to have a solitary breast cancer metastasis to the lung were able to undergo complete metastatic resection[71]. Thus, in the setting of a history of breast cancer a Solitary pulmonary nodule is almost uniformly malignant. Again, given high 5-year survival rates regardless of pathologic diagnosis, LDCT screening is likely to be beneficial in breast cancer survivors who meet all other NLST criteria.

Bladder cancer

Lung cancer also shares an association with bladder cancer. A recent study examined 231 patients with non-muscle-invasive bladder cancer and found that 4% of these patients were found to have a second primary lung malignancy during follow up, a rate 10-fold higher than the local population[72]. Of those found to have a lung malignancy, 9 were found at late stage and only 1 was found at an early stage. In the 5 years following diagnosis, all patients with late stage lung cancer died; however the patient with early stage lung cancer was still alive after undergoing chemotherapy. In those patients with both primary lung and primary bladder cancer, the cause of death was uniformly attributed to lung cancer. Thus, the authors suggest early detection of a primary lung malignancy in a patient with history of non-invasive bladder cancer may contribute to improved survival. People with a history of bladder cancer who otherwise meet all other NLST criteria are likely to benefit from a discussion of lung cancer screening and smoking cessation, if applicable.

Lymphoma

Hodgkin's lymphoma is associated with a significantly increased risk of treatment related lung cancer. According to American College of Radiology (ACR) recommendations within the first 5 years of follow up, the imaging goal is to detect lymphoma recurrence. After this time the focus shifts towards detecting complications of treatment. The current ACR recommendations state that after 5 years there is no longer a need for follow up imaging, although mammography and LDCT can be considered despite a lack of evidence of their benefit[73]. The incidence of lung cancer in patients with a history of Hodgkin's lymphoma is over 1% by 15 year follow up, with a relative risk of 4.62 (95%CI: 3.18-6.70)[74]. The risk is greater in patients diagnosed and treated for Hodgkin's lymphoma at an earlier age, especially 15-24.

Das *et al*[75] performed a cost-effectiveness estimate of annual lung cancer screening in patients with Hodgkin's lymphoma. Hypothetical patients for the model analysis were diagnosed with stage ⅠA-ⅡB Hodgkin's lymphoma at age 25, with screening starting 5 years after initial diagnosis. Annual CT screening was predicted to increase survival by 0.64 years for smokers and 0.16 years for non-smokers, with improvement in quality of life and cost effectiveness greater in the population of smokers with lymphoma. Wattson *et al*[76] reported similar cost and survival benefits in smokers compared to non-smokers with Hodgkin's lymphoma. While non-smokers were predicted to experience a slightly improved survival and quality of life, LDCT scanning does not appear to be cost effective in this population.

In clinical practice it is unclear if this survival benefit of lung cancer screening is observed. Milano *et al*[77] examined overall survival in patients with Hodgkin's lymphoma diagnosed with NSCLC compared to controls diagnosed with only NSCLC. Lung cancer stage at diagnosis did not differ significantly between the groups. Despite this, Hodgkin's lymphoma survivors had a 30%-60% decrease in overall survival. This suggests that annual LDCT lung cancer screening may aid in identifying a second lung malignancy in this high-risk population, especially in current or heavy smokers. However, lung cancer screening may not provide as robust of a survival benefit in patients with a history of Hodgkin's lymphoma compared to the general population. There is currently a trial looking at lung cancer screening in people with a history of Hodgkin's lymphoma, which is expected to conclude by 2015[78]. Hopefully these results will define the benefit of lung cancer screening in this population.

Colorectal cancer

Low-dose CT may have a role in both colon cancer surveillance and screening for lung cancer. There have been many studies of postoperative surveillance programs following surgical resection of colon cancer. Aside from screening colonoscopy and CEA testing, there is little consensus opinion on the use of additional modalities that may detect colorectal cancer recurrence[79]. The purpose of these surveillance programs is to detect asymptomatic recurrences so intervention may occur at an earlier stage. A meta-analysis of 11 studies looking at intensity of surveillance determined that overall survival was significantly improved in patients who underwent more intense follow up (more frequent, additional imaging modalities). CT scanning of the pelvis and frequently the chest, lead to improved overall survival[80]. Thus, while not currently part of the surveillance guidelines, patients with a history of colorectal cancer would likely benefit from more frequent imaging of the chest.

Additionally, patients with colorectal cancer are more likely to be diagnosed with a primary lung cancer then the general population[81]. There is no difference between lung cancer incidence in patients with a history of colon or a history of rectal cancer[73]. A recent multicenter study in Japan examined whether a history of surgically resected colorectal cancer affected prognosis in patients diagnosed with lung cancer[34]. They compared 123 lung cancer patients with a history of colorectal cancer to 4431 controls with lung cancer alone. Patients with a history of colorectal cancer were more likely to be diagnosed at stage ⅠA, however there was no difference between the groups in overall survival

or lung cancer mortality. This relationship did not vary with colorectal cancer stage. Thus, a previous history of surgically resectable colon cancer does not portend an improved nor diminished overall survival in patients diagnosed with a primary lung malignancy. These patients may still benefit from LDCT screening similar to the general population, so long as they fulfill all other accepted criteria for lung cancer screening. As with the majority of the previous malignancies discussed, there is a great need for prospective studies to examine clinical disease features, treatment response, and overall survival in these patients after lung cancer is detected by screening exam.

CONCLUSION

NLST demonstrated a reduction of lung cancer mortality and all cause mortality with annual screening LDCT. With regard to lung cancer screening in people with previous cancer, there is no data, as most lung cancer screening trials have excluded this population. Implementation of LDCT in the general population has proven complicated as USPSTF, professional societies and CMS have published slightly different recommendations on this and other criteria. The potential benefit of diagnosing early stage lung cancer or treatable metastatic disease is at least compelling enough to justify future study. Future directions include defining which malignancies at which stage are likely to benefit. The type of screening (routine CT dose or low dose), the interval of screening, and when to initiate and end screening after previous cancer treatment remain unanswered questions.

Until randomized, controlled studies can direct recommendations on lung cancer screening for people with antecedent malignancy, clinicians will need to consider screening on an individual basis. To be eligible for lung cancer screening, patients with previous malignancy should at least fulfill other lung cancer screening eligibility criteria. The previous malignancy, like any comorbidity, "should not substantially limit life expectancy or the ability or willingness to have curative (lung cancer) surgery" as defined by USPSTF. The prediction of survival benefit of lung cancer treatment and metastatic cancer treatment should outweigh the risks of screening. Clinicians should have a detailed, personalized discussion about these survival benefits of annual LDCT, as wells as the risks of false positive, overdiagnosis, anxiety, radiation, and the possibility what we know from all existing data may be insufficient to guide any individual decision. As with all lung cancer screening LDCT, a shared decision making tool should be used to address the issues of lung cancer screening that matter most to the individual. As patients with previous malignancy present complex scenarios, screening should be done within a setting with access to multidisciplinary evaluation and treatment. Most importantly, lung cancer screening in the setting of previous malignancy should include a discussion of smoking cessation in active smokers and a discussion with previous smokers of staying smoke free. Smoking cessation is critical in this population as these patients face the increased risk of recurrence, metastasis as well as lung cancer. When available, lung cancer screening of patients with previous malignancy should be done within a clinical trial.

In conclusion, though patients with previous malignancy have been excluded from lung cancer screening trials, they are a unique population that may enjoy a survival benefit from diagnosis of not only lung cancer, but of metastatic disease. Hopefully future clinical studies in this population will clarify the risks and benefits of lung cancer screening in the setting of antecedent malignancy.

REFERENCES

1 **Siegel R**, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin* 2011; **61**: 212-236 [PMID: 21685461 DOI: 10.3322/caac.20121]

2 **Centers for Disease Control**. Unites States Cancer Statistics: Cancer Survival Data. [accessed 2015 Sept]. Available from: URL: http://nccd.cdc.gov/uscs/SurvivalData.aspx

3 **National Cancer Institute**. Surveillance, epidemiology and end results program: Lung and bronchus cancer facts sheet. [accessed 2015 Sept]. Available from: URL: http://seer.cancer.gov/statfacts/html/lungb.html

4 **Prorok PC**, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, Fogel R, Gelmann EP, Gilbert F, Hasson MA, Hayes RB, Johnson CC, Mandel JS, Oberman A, O'Brien B, Oken MM, Rafla S, Reding D, Rutt W, Weissfeld JL, Yokochi L, Gohagan JK. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials* 2000; **21**: 273S-309S [PMID: 11189684 DOI: 10.1016/S0197-2456(00)00098-2]

5 **Aberle DR**, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; **365**: 395-409 [PMID: 21714641 DOI: 10.1056/NEJMoa1102873]

6 **Ma J**, Ward EM, Smith R, Jemal A. Annual number of lung cancer deaths potentially avertable by screening in the United States. *Cancer* 2013; **119**: 1381-1385 [PMID: 23440730 DOI: 10.1002/cncr.27813]

7 **Pinsky PF**, Berg CD. Applying the National Lung Screening Trial eligibility criteria to the US population: what percent of the population and of incident lung cancers would be covered? *J Med Screen* 2012; **19**: 154-156 [PMID: 23060474 DOI: 10.1258/jms.2012.012010]

8 **Farjah F**, Wood DE, Zadworny ME, Rusch VW, Rizk NP. Resected Lung Cancer Patients Who Would and Would Not Have Met Screening Criteria. *Ann Thorac Surg* 2016; **101**: 274-279 [PMID: 26298169 DOI: 10.1016/j.athoracsur.2015.06.010]

9 **Aberle DR**, Berg CD, Black WC, Church TR, Fagerstrom RM, Galen B, Gareen IF, Gatsonis C, Goldin J, Gohagan JK, Hillman B, Jaffe C, Kramer BS, Lynch D, Marcus PM, Schnall M, Sullivan DC, Sullivan D, Zylak CJ. The National Lung Screening Trial: overview and study design. *Radiology* 2011; **258**: 243-253 [PMID: 21045183 DOI: 10.1148/radiol.10091808]

10 **Mery CM**, Pappas AN, Bueno R, Mentzer SJ, Lukanich JM, Sugarbaker DJ, Jaklitsch MT. Relationship between a history of antecedent cancer and the probability of malignancy for a solitary pulmonary nodule. *Chest* 2004; **125**: 2175-2181 [PMID: 15189939]

11 **Rena O**, Davoli F, Boldorini R, Roncon A, Baietto G, Papalia E, Turello D, Massera F, Casadio C. The solitary pulmonary nodule in patients with previous cancer history: results of surgical treatment. *Eur J Surg Oncol* 2013; **39**: 1248-1253 [PMID: 24035503 DOI: 10.1016/j.ejso.2013.08.014]

12 **Henschke CI**, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, Libby D, Pasmantier M, Koizumi J, Altorki N, Smith JP. Early lung cancer action project: a summary of the findings on baseline screening. *Oncologist* 2001; **6**: 147-152 [PMID: 11306726 DOI: 10.1634/theoncologist.6-2-147]

13 **University Health Network Toronto**. Lung cancer screening in high-risk smokers using low-dose computed tomography. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). 2000-2015. Available from: URL: http://clinicaltrials.gov/ct2/show/NCT00188734?term=elcap&rank=2 NLM Identifier: NCT00188734

14 **van Iersel CA**, de Koning HJ, Draisma G, Mali WP, Scholten ET, Nackaerts K, Prokop M, Habbema JD, Oudkerk M, van Klaveren RJ. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). *Int J Cancer* 2007; **120**: 868-874 [PMID: 17131307 DOI: 10.1002/ijc.22134]

15 **van Klaveren RJ**, Oudkerk M, Prokop M, Scholten ET, Nackaerts K, Vernhout R, van Iersel CA, van den Bergh KA, van 't Westeinde S, van der Aalst C, Thunnissen E, Xu DM, Wang Y, Zhao Y, Gietema HA, de Hoop BJ, Groen HJ, de Bock GH, van Ooijen P, Weenink C, Verschakelen J, Lammers JW, Timens W, Willebrand D, Vink A, Mali W, de Koning HJ. Management of lung nodules detected by volume CT scanning. *N Engl J Med* 2009; **361**: 2221-2229 [PMID: 19955524 DOI: 10.1056/NEJMoa0906085]

16 **Infante M**, Lutman FR, Cavuto S, Brambilla G, Chiesa G, Passera E, Angeli E, Chiarenza M, Aranzulla G, Cariboni U, Alloisio M, Incarbone M, Testori A, Destro A, Cappuzzo F, Roncalli M, Santoro A, Ravasi G. Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. *Lung Cancer* 2008; **59**: 355-363 [PMID: 17936405 DOI: 10.1016/j.lungcan.2007.08.040]

17 **National Cancer Institute**. Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). 2000-2015. Available from: URL: http://clinicaltrials.gov/ct2/show/study/NCT01696968?term=plco lung&rank=1§=X3457016 NLM Identifier: NCT01696968

18 **Oken MM**, Hocking WG, Kvale PA, Andriole GL, Buys SS, Church TR, Crawford ED, Fouad MN, Isaacs C, Reding DJ, Weissfeld JL, Yokochi LA, O'Brien B, Ragard LR, Rathmell JM, Riley TL, Wright P, Caparaso N, Hu P, Izmirlian G, Pinsky PF, Prorok PC, Kramer BS, Miller AB, Gohagan JK, Berg CD. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. *JAMA* 2011; **306**: 1865-1873 [PMID: 22031728 DOI: 10.1001/jama.2011.1591]

19 **University Health Network Toronto**. Low dose chest CT for lung cancer screening in survivors of Hodgkin's disease. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). 2000-2015. Available from: URL: http://clinicaltrials.gov/ct2/show/NCT01180010?term=lung cancer screening&rank=18 NLM Indentifier: NCT01180010

20 **Humphrey LL**, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, Zakher B, Fu R, Slatore CG. Screening for lung cancer with low-dose computed tomography: a systematic review to update the US Preventive services task force recommendation. *Ann Intern Med* 2013; **159**: 411-420 [PMID: 23897166 DOI: 10.7326/0003-4819-159-6-201309170-00690]

21 **Infante M**, Cavuto S, Lutman FR, Brambilla G, Chiesa G, Ceresoli G, Passera E, Angeli E, Chiarenza M, Aranzulla G, Cariboni U, Errico V, Inzirillo F, Bottoni E, Voulaz E, Alloisio M, Destro A, Roncalli M, Santoro A, Ravasi G. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. *Am J Respir Crit Care Med* 2009; **180**: 445-453 [PMID: 19520905 DOI: 10.1164/rccm.200901-0076OC]

22 **Saghir Z**, Dirksen A, Ashraf H, Bach KS, Brodersen J, Clementsen PF, Døssing M, Hansen H, Kofoed KF, Larsen KR, Mortensen J, Rasmussen JF, Seersholm N, Skov BG, Thorsen H, Tønnesen P, Pedersen JH. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. *Thorax* 2012; **67**: 296-301 [PMID: 22286927 DOI: 10.1136/thoraxjnl-2011-200736]

23 **Pastorino U**, Rossi M, Rosato V, Marchianò A, Sverzellati N, Morosi C, Fabbri A, Galeone C, Negri E, Sozzi G, Pelosi G, La Vecchia C. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prev* 2012; **21**: 308-315 [PMID: 22465911 DOI: 10.1097/CEJ.0b013e328351e1b6]

24 **de Koning HJ**, Meza R, Plevritis SK, ten Haaf K, Munshi VN, Jeon J, Erdogan SA, Kong CY, Han SS, van Rosmalen J, Choi SE, Pinsky PF, Berrington de Gonzalez A, Berg CD, Black WC, Tammemägi MC, Hazelton WD, Feuer EJ, McMahon PM. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. *Ann Intern Med* 2014; **160**: 311-320 [PMID: 24379002 DOI: 10.7326/M13-2316]

25 **American Lung Association**. Providing guidance on lung cancer screening to patients and physicians. [accessed 2015 Sept]. Available from: URL: http://www.lung.org/lung-disease/lung- cancer/lung-cancer-screening-guidelines

26 **Tammemägi MC**, Katki HA, Hocking WG, Church TR, Caporaso N, Kvale PA, Chaturvedi AK, Silvestri GA, Riley TL, Commins J, Berg CD. Selection criteria for lung-cancer screening. *N Engl J Med* 2013; **368**: 728-736 [PMID: 23425165 DOI: 10.1056/NEJMoa1211776]

27 **Detterbeck FC**, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; **143**: e78S-e92S [PMID: 23649455 DOI: 10.1378/chest.12-2350]

28 **Bach PB**, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, Byers T, Colditz GA, Gould MK, Jett JR, Sabichi AL, Smith-Bindman R, Wood DE, Qaseem A, Detterbeck FC. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA* 2012; **307**: 2418-2429 [PMID: 22610500 DOI: 10.1001/jama.2012.5521]

29 **Centers for Medicare & Medicaid Services**. Final National Coverage Determination on Screening for Lung Cancer with Low Dose Computed Tomography (LDCT) (CAG-00439N). [accessed 2015 Mar]. Available from: URL: http://www.cms.gov/medicare-coverage-database/details/nca- decision-memo.aspx?NCAId=274

30 **Manser R**, Lethaby A, Irving LB, Stone C, Byrnes G, Abramson MJ, Campbell D. Screening for lung cancer. Cochrane Database Syst Rev, 2013

31 **Prosch H**, Schaefer-Prokop C. Screening for lung cancer. *Curr Opin Oncol* 2014; **26**: 131-137 [PMID: 24441507 DOI: 10.1097/CCO.0000000000000055]

32 **National Comprehensive Cancer Network**. Clinical Practice Guidelines in Oncology, Lung cancer screening: Version 2. [accessed 2015 Sept]. Available from: URL: http://www.nccn.org

33 **Jaklitsch MT**, Jacobson FL, Austin JH, Field JK, Jett JR, Keshavjee S, MacMahon H, Mulshine JL, Munden RF, Salgia R, Strauss GM, Swanson SJ, Travis WD, Sugarbaker DJ. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. *J Thorac Cardiovasc Surg* 2012; **144**: 33-38 [PMID: 22710039 DOI: 10.1016/j.jtcvs.2012.05.060]

34 **Hattori A**, Suzuki K, Aokage K, Mimae T, Nagai K, Tsuboi M, Okada M. Prognosis of lung cancer patients with a past history of colorectal cancer. *Jpn J Clin Oncol* 2014; **44**: 1088-1095 [PMID: 25156681 DOI: 10.1093/jjco/hyu122]

35 **Kovalchik SA**, Tammemagi M, Berg CD, Caporaso NE, Riley TL, Korch M, Silvestri GA, Chaturvedi AK, Katki HA. Targeting of low-dose CT screening according to the risk of lung-cancer death. *N Engl J Med* 2013; **369**: 245-254 [PMID: 23863051 DOI: 10.1056/NEJMoa1301851]

36 **Smetana GW**, Boiselle PM, Schwartzstein RM. Screening for lung cancer with low-dose computed tomography: grand rounds discussion from the Beth Israel Deaconess Medical Center. *Ann Intern Med* 2015; **162**: 577-582 [PMID: 25894026 DOI: 10.7326/

M15-0055]
37 **Tammemägi MC**, Church TR, Hocking WG, Silvestri GA, Kvale PA, Riley TL, Commins J, Berg CD. Evaluation of the lung cancer risks at which to screen ever- and never-smokers: screening rules applied to the PLCO and NLST cohorts. *PLoS Med* 2014; **11**: e1001764 [PMID: 25460915 DOI: 10.1371/journal.pmed.1001764]
38 **Lou F**, Huang J, Sima CS, Dycoco J, Rusch V, Bach PB. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. *J Thorac Cardiovasc Surg* 2013; **145**: 75-81; discussion 81-82 [PMID: 23127371 DOI: 10.1016/j.jtcvs.2012.09.030]
39 **Griffioen GH**, Lagerwaard FJ, Haasbeek CJ, Slotman BJ, Senan S. A brief report on outcomes of stereotactic ablative radiotherapy for a second primary lung cancer: evidence in support of routine CT surveillance. *J Thorac Oncol* 2014; **9**: 1222-1225 [PMID: 25157777 DOI: 10.1097/JTO.0000000000000218]
40 **Hanna WC**, Keshavjee S. How to follow up patients after curative resection of lung cancer. *Semin Thorac Cardiovasc Surg* 2013; **25**: 213-217 [PMID: 24331143 DOI: 10.1053/j.semtcvs.2013.07.005]
41 **Surapaneni R**, Singh P, Rajagopalan K, Hageboutros A. Stage I lung cancer survivorship: risk of second malignancies and need for individualized care plan. *J Thorac Oncol* 2012; **7**: 1252-1256 [PMID: 22627646 DOI: 10.1097/JTO.0b013e3182582a79]
42 **Pepek JM**, Chino JP, Marks LB, D'amico TA, Yoo DS, Onaitis MW, Ready NE, Hubbs JL, Boyd J, Kelsey CR. How well does the new lung cancer staging system predict for local/regional recurrence after surgery?: A comparison of the TNM 6 and 7 systems. *J Thorac Oncol* 2011; **6**: 757-761 [PMID: 21325975 DOI: 10.1097/JTO.0b013e31821038c0]
43 **Choi PJ**, Jeong SS, Yoon SS. Prognosis of recurrence after complete resection in early-stage non-small cell lung cancer. *Korean J Thorac Cardiovasc Surg* 2013; **46**: 449-456 [PMID: 24368972 DOI: 10.5090/kjtcs.2013.46.6.449]
44 **Mollberg NM**, Ferguson MK. Postoperative surveillance for non-small cell lung cancer resected with curative intent: developing a patient-centered approach. *Ann Thorac Surg* 2013; **95**: 1112-1121 [PMID: 23352418 DOI: 10.1016/j.athoracsur.2012.09.075]
45 **Crabtree TD**, Puri V, Chen SB, Gierada DS, Bell JM, Broderick S, Krupnick AS, Kreisel D, Patterson GA, Meyers BF. Does the method of radiologic surveillance affect survival after resection of stage I non-small cell lung cancer? *J Thorac Cardiovasc Surg* 2015; **149**: 45-52, 53.e1-3 [PMID: 25218540 DOI: 10.1016/j.jtcvs.2014.07.095]
46 **Benamore R**, Shepherd FA, Leighl N, Pintilie M, Patel M, Feld R, Herman S. Does intensive follow-up alter outcome in patients with advanced lung cancer? *J Thorac Oncol* 2007; **2**: 273-281 [PMID: 17409797 DOI: 10.1097/01.JTO.0000263708.08332.76]
47 **Westeel V**, Lebitasy MP, Mercier M, Girard P, Barlesi F, Blanchon F, Tredaniel J, Bonnette P, Woronoff-Lemsi MC, Breton JL, Azarian R, Falcoz PE, Friard S, Geriniere L, Laporte S, Lemarie E, Quoix E, Zalcman G, Guigay J, Morin F, Milleron B, Depierre A. [IFCT-0302 trial: randomised study comparing two follow-up schedules in completely resected non-small cell lung cancer]. *Rev Mal Respir* 2007; **24**: 645-652 [PMID: 17519819 DOI: 10.1016/S0761-8425(07)91135-3]
48 **Parsons A**, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. *BMJ* 2010; **340**: b5569 [PMID: 20093278 DOI: 10.1136/bmj.b5569]
49 **Sardari Nia P**, Weyler J, Colpaert C, Vermeulen P, Van Marck E, Van Schil P. Prognostic value of smoking status in operated non-small cell lung cancer. *Lung Cancer* 2005; **47**: 351-359 [PMID: 15713518 DOI: 10.1016/j.lungcan.2004.08.011]
50 **Milano MT**, Peterson CR, Zhang H, Singh DP, Chen Y. Second primary lung cancer after head and neck squamous cell cancer: population-based study of risk factors. *Head Neck* 2012; **34**: 1782-1788 [PMID: 22319019 DOI: 10.1002/hed.22006]
51 **Baxi SS**, Pinheiro LC, Patil SM, Pfister DG, Oeffinger KC, Elkin EB. Causes of death in long-term survivors of head and neck cancer. *Cancer* 2014; **120**: 1507-1513 [PMID: 24863390 DOI: 10.1002/cncr.28588]
52 **Wolff HA**, Wolff CR, Hess CF, Jung K, Sennhenn-Kirchner S, Hinterthaner M, Müller-Dornieden A, Körber W, Marten-Engelke K, Roedel R, Christiansen H, Engelke C. Second primary malignancies in head and neck cancer patients: high prevalence of curable-stage disease. *Strahlenther Onkol* 2013; **189**: 874-880 [PMID: 23842636 DOI: 10.1007/s00066-013-0404-4]
53 **Madana J**, Morand GB, Barona-Lleo L, Black MJ, Mlynarek AM, Hier MP. A survey on pulmonary screening practices among otolaryngology-head & neck surgeons across Canada in the post treatment surveillance of head and neck squamous cell carcinoma. *J Otolaryngol Head Neck Surg* 2015; **44**: 5 [PMID: 25649793 DOI: 10.1186/s40463-015-0057-7]
54 **Pagedar NA**, Jayawardena A, Charlton ME, Hoffman HT. Second Primary Lung Cancer After Head and Neck Cancer: Implications for Screening Computed Tomography. *Ann Otol Rhinol Laryngol* 2015; **124**: 765-769 [PMID: 25881583 DOI: 10.1177/0003489415582259]
55 **Geurts TW**, Balm AJ, van Velthuysen ML, van Tinteren H, Burgers JA, van Zandwijk N, Klomp HM. Survival after surgical resection of pulmonary metastases and second primary squamous cell lung carcinomas in head and neck cancer. *Head Neck* 2009; **31**: 220-226 [PMID: 18972427 DOI: 10.1002/hed.20952]
56 **Griffioen GH**, Louie AV, de Bree R, Smit EF, Paul MA, Slotman BJ, Leemans CR, Senan S. Second primary lung cancers following a diagnosis of primary head and neck cancer. *Lung Cancer* 2015; **88**: 94-99 [PMID: 25662386 DOI: 10.1016/j.lungcan.2015.01.011]
57 **Atabek U**, Mohit-Tabatabai MA, Raina S, Rush BF, Dasmahapatra KS. Lung cancer in patients with head and neck cancer. Incidence and long-term survival. *Am J Surg* 1987; **154**: 434-438 [PMID: 3661848 DOI: 10.1016/0002-9610(89)90019-6]
58 **Margolis ML**, Howlett P, Bubanj R. Pulmonary nodules in patients with esophageal carcinoma. *J Clin Gastroenterol* 1998; **26**: 245-248 [PMID: 9649002]
59 **Kim JW**, Jang JY, Chang YW, Kim YH. Clinical features of second primary cancers arising in early gastric cancer patients after endoscopic resection. *World J Gastroenterol* 2015; **21**: 8358-8365 [PMID: 26217087 DOI: 10.3748/wjg.v21.i27.8358]
60 **Khatcheressian JL**, Hurley P, Bantug E, Esserman LJ, Grunfeld E, Halberg F, Hantel A, Henry NL, Muss HB, Smith TJ, Vogel VG, Wolff AC, Somerfield MR, Davidson NE. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013; **31**: 961-965 [PMID: 23129741 DOI: 10.1200/JCO.2012.45.9859]
61 **Smith TJ**. Breast cancer surveillance guidelines. *J Oncol Pract* 2013; **9**: 65-67 [PMID: 23633975 DOI: 10.1200/JOP.2012.000787]
62 **James JJ**, McMahon MA, Tennant SL, Cornford EJ. CT staging for breast cancer patients with poor prognostic tumours. *Breast* 2012; **21**: 735-738 [PMID: 22959310 DOI: 10.1016/j.breast.2012.08.001]
63 **Kitada M**, Sato K, Matsuda Y, Hayashi S, Miyokawa N, Sasajima T. Role of treatment for solitary pulmonary nodule in breast cancer patients. *World J Surg Oncol* 2011; **9**: 124 [PMID: 21989021 DOI: 10.1186/1477-7819-9-124]
64 **Grantzau T**, Overgaard J. Risk of second non-breast cancer after radiotherapy for breast cancer: a systematic review and meta-analysis of 762,468 patients. *Radiother Oncol* 2015; **114**: 56-65 [PMID: 25454172 DOI: 10.1016/j.radonc.2014.10.004]
65 **Kirova YM**, De Rycke Y, Gambotti L, Pierga JY, Asselain B, Fourquet A. Second malignancies after breast cancer: the impact of different treatment modalities. *Br J Cancer* 2008; **98**: 870-874 [PMID: 18268495 DOI: 10.1038/sj.bjc.6604241]
66 **Grantzau T**, Thomsen MS, Vaeth M, Overgaard J. Risk of second primary lung cancer in women after radiotherapy for breast cancer. *Radiother Oncol* 2014; **111**: 366-373 [DOI: 10.1016/j.radonc.2014.05.004]
67 **Kerendi F**, Gal A, Corvera JS, Halkos ME, Miller JI. Characteristics of second primary lung malignancy in patients with known breast cancer. *South Med J* 2009; **102**: 269-274 [PMID: 19204611 DOI: 10.1097/SMJ.0b013e318197fec6]
68 **Milano MT**, Strawderman RL, Venigalla S, Ng K, Travis LB. Non-

small-cell lung cancer after breast cancer: a population-based study of clinicopathologic characteristics and survival outcomes in 3529 women. *J Thorac Oncol* 2014; **9**: 1081-1090 [PMID: 25157761 DOI: 10.1097/JTO.0000000000000213]

69 **Tanaka K**, Shimizu K, Ohtaki Y, Nakano T, Kamiyoshihara M, Kaira K, Rokutanda N, Horiguchi J, Oyama T, Takeyoshi I. Diagnosis and surgical resection of solitary pulmonary nodules in patients with breast cancer. *Mol Clin Oncol* 2013; **1**: 117-123 [PMID: 24649133 DOI: 10.3892/mco.2012.21]

70 **Kinoshita T**, Yoshida J, Ishii G, Hishida T, Wada M, Aokage K, Nagai K. The availability of pre- and intraoperative evaluation of a solitary pulmonary nodule in breast cancer patients. *Ann Thorac Cardiovasc Surg* 2015; **21**: 31-36 [PMID: 24835922 DOI: 10.5761/atcs.oa.14-00025]

71 **Friedel G**, Pastorino U, Ginsberg RJ, Goldstraw P, Johnston M, Pass H, Putnam JB, Toomes H. Results of lung metastasectomy from breast cancer: prognostic criteria on the basis of 467 cases of the International Registry of Lung Metastases. *Eur J Cardiothorac Surg* 2002; **22**: 335-344 [PMID: 12204720 DOI: 10.1016/S1010-7940(02)00331-7]

72 **del Rey J**, Placer J, Vallmanya F, Pujol N, Prat E, Miró R, Gelabert A. Are patients with non-muscle-invasive bladder cancer a suitable population for a lung cancer screening trial? *BJU Int* 2010; **106**: 49-52 [PMID: 19922541 DOI: 10.1111/j.1464-410X.2009.09081.x]

73 **Ng A**, Constine LS, Advani R, Das P, Flowers C, Friedberg J, Hodgson DC, Schwartz CL, Wilder RB, Wilson LD, Yunes MJ. ACR Appropriateness Criteria: follow-up of Hodgkin's lymphoma. *Curr Probl Cancer* 2010; **34**: 211-227 [PMID: 20541059 DOI: 10.1016/j.currproblcancer.2010.04.007]

74 **Ibrahim EM**, Kazkaz GA, Abouelkhair KM, Al-Mansour MM, Al-Fayea TM, Al-Foheidi M, Bayer AM, Elmasri OA. Increased risk of second lung cancer in Hodgkin's lymphoma survivors: a meta-analysis. *Lung* 2013; **191**: 117-134 [PMID: 23053567 DOI: 10.1007/s00408-012-9418-4]

75 **Das P**, Ng AK, Earle CC, Mauch PM, Kuntz KM. Computed tomography screening for lung cancer in Hodgkin's lymphoma survivors: decision analysis and cost-effectiveness analysis. *Ann Oncol* 2006; **17**: 785-793 [PMID: 16500905 DOI: 10.1093/annonc/mdl023]

76 **Wattson DA**, Hunink MG, DiPiro PJ, Das P, Hodgson DC, Mauch PM, Ng AK. Low-dose chest computed tomography for lung cancer screening among Hodgkin lymphoma survivors: a cost-effectiveness analysis. *Int J Radiat Oncol Biol Phys* 2014; **90**: 344-353 [PMID: 25104066 DOI: 10.1016/j.ijrobp.2014.06.013]

77 **Milano MT**, Li H, Constine LS, Travis LB. Survival after second primary lung cancer: a population-based study of 187 Hodgkin lymphoma patients. *Cancer* 2011; **117**: 5538-5547 [PMID: 21692074 DOI: 10.1002/cncr.26257]

78 **University Health Network Toronto**. Low dose chest CT for lung cancer screening in survivors of Hodgkin's disease. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-2015. Available from: URL: http://clinicaltrials.gov/ct2/show/NCT01180010?term=lung cancer screening&rank=18 NLM Indentifier: NCT01180010

79 **Steele SR**, Chang GJ, Hendren S, Weiser M, Irani J, Buie WD, Rafferty JF. Practice Guideline for the Surveillance of Patients After Curative Treatment of Colon and Rectal Cancer. *Dis Colon Rectum* 2015; **58**: 713-725 [PMID: 26163950 DOI: 10.1097/DCR.0000000000000410]

80 **Pita-Fernández S**, Alhayek-Aí M, González-Martín C, López-Calviño B, Seoane-Pillado T, Pértega-Díaz S. Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis. *Ann Oncol* 2015; **26**: 644-656 [PMID: 25411419 DOI: 10.1093/annonc/mdu543]

81 **Lee YT**, Liu CJ, Hu YW, Teng CJ, Tzeng CH, Yeh CM, Chen TJ, Lin JK, Lin CC, Lan YT, Wang HS, Yang SH, Jiang JK, Chen WS, Lin TC, Chang SC, Chen MH, Teng HW, Liu JH, Yen CC. Incidence of Second Primary Malignancies Following Colorectal Cancer: A Distinct Pattern of Occurrence Between Colon and Rectal Cancers and Association of Co-Morbidity with Second Primary Malignancies in a Population-Based Cohort of 98,876 Patients in Taiwan. *Medicine* (Baltimore) 2015; **94**: e1079 [PMID: 26131831 DOI: 10.1097/MD.0000000000001079]

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MINIREVIEWS

Prognostic scoring systems for clinical course and survival in idiopathic pulmonary fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is the most common and rapidly fatal among idiopathic interstitial pneumonias. Its clinical course is variable. A significant fraction of the population of patients display a slow disease course and can remain stable for years, while other patients show a rapid progressive course and may die within few months from diagnosis. For these reasons estimating prognosis of IPF patients is extremely difficult and has important clinical repercussions on optimal patients management including patients referral for lung transplantation. Several studies have tried to address this key point in the course of the two last decades analyzing different clinical, functional, radiological and biological variables. The purpose of this review is to assess relevant studies published on this subject and to examine the variety of prognostic predictors proposed along with staging systems.

Key words: Idiopathic pulmonary fibrosis; Prognosis; Survival; Scoring systems

Core tip: Idiopathic pulmonary fibrosis (IPF) is the most common and rapidly lethal among interstitial lung disease. Its clinical course is highly variable and estimating prognosis of patients with IPF is extremely difficult with important impacts on the best clinical management of patients, including the referral of patients for lung transplantation. In this review article we evaluate relevant studies published on this subject and examine the variety of proposed prognostic predictors along with staging systems.

Puxeddu E, Rogliani P. Prognostic scoring systems for clinical course and survival in idiopathic pulmonary fibrosis. *World J Respirol* 2016; 6(1): 14-23 Available from: URL: http://www.wjgnet.com/2218-6255/full/v6/i1/14.htm DOI: http://dx.doi.org/10.5320/wjr.v6.i1.14

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is the most common and rapidly fatal among idiopathic interstitial pneumonias (IIP), a group of interstitial disorders of

unknown origin limited to the lung[1]. IPF is characterized by the pattern of usual interstitial pneumonia (UIP) defined by the presence of areas of reticular opacities and honeycomb cysts alternating with areas of apparently unaffected parenchyma at high resolution computerized tomography (HRCT) of the chest and of focal fibroblast proliferation resulting from microscopic foci of acute lung injury at histological evaluation of lung biopsy specimens[2].

Although the pathogenesis of IPF remains largely unknown, recent works has shed light on the molecular mechanism involved in the disease shifting the current pathogenic concept from a traditional inflammatory paradigm to a model centered on alveolar epithelia cell (AEC) dysfunction. In this view a number of potential risk factors, including environmental factors and among them tobacco smoke[3], would lead to repetitive (AEC) injury with subsequent abnormal wound healing in genetically predisposed subjects[4]. According to this concept, the alveolar epithelium is subject to clinically silent microinjuries over a prolonged period of time with activation of pro-fibrotic signaling pathways that lead to interstitial matrix remodeling through the up regulation of specific molecules, such as metalloproteinases[5], and migration, proliferation and activation of mesenchymal cells with aberrant extracellular matrix deposition[4]. It is believed that abnormal release of oxidants and various cytokines and growth factors by alternatively activated alveolar macrophages (AM) is also involved in the constitution of the alveolar mileu that characterize this fibro-proliferative disorder[6-8].

Epidemiological studies conducted in different geographical areas estimate IPF prevalence and incidence in the range of 20 to 40 cases per 100000 inhabitants and of 6.8 to 16 new cases per 100000 per year inhabitants respectively, although, given the complexity of IPF diagnosis, those data might underestimate the real burden of this disease[9,10]. In fact, the diagnosis of IPF is difficult and requires the recognition on HRCT scans or on lung biopsy specimen of the typical UIP pattern in the absence of clinical feature suggesting alternative diagnosis that may be associated to the UIP pattern, *i.e.,* connective tissue diseases or exposure to known environmental agents like asbestos. For this reason current guidelines[2] recommend that the diagnosis is performed in centers experienced in the field of interstitial lung diseases in a process defined multidisciplinary discussion that should take place with the participation of different specialists, the pulmonologist, the radiologist, the rheumatologist and, in those cases where biopsy is performed, of the thoracic surgeon and the pathologist. Albeit recent data enforce the role of HRCT in the diagnosis of IPF, that in the appropriate setting allows the diagnosis combined with a detailed clinical picture in the large majority of IPF patients[11], biopsy is still required in a fraction of patients with non typical UIP radiological presentation. Given the significant morbidity and mortality associated with traditional surgical lung biopsy approach, less invasive approaches have been recently proposed with success[12,13].

IPF clinical course is variable. A significant fraction of the population of patients display a slower and less aggressive disease course, with longer survivals[14] and these patients can remain stable for years even without any medical intervention. On the other hand, other patients show a rapid progressive course and may die within few months from diagnosis. Furthermore, the course of disease can change, with patients who originally displayed a slow and stable disease course progressing to a rapid decline in lung function[14].

For these reasons, predicting the clinical course of the disease is crucial for the optimal management of IPF patients, especially for a prompt referral to lung transplantation of those patients with worst prognosis. Albeit the extensive research in the field, predicting IPF clinical course remains a challenging task. To this end, several biological and functional variables have been evaluated as predictors of outcome. Furthermore a number of multi-dimensional scoring systems, based on the combination of different variables have been recently proposed and validated in cohorts of IPF patients. The purpose of this review is to assess relevant studies published on this subject and to examine the variety of prognostic predictors proposed along with staging systems.

BIOMARKERS

The term "biomarker" stands for an objectively quantifiable biological measurement, *i.e.,* the level of a serum protein or a specific genetic mutation or polymorphism, that gives clinical meaningful information about the disease state of an individual patient[15]. Biomarkers can be divided into several classes based on the type of the information they offer. Diagnostic biomarkers allow the distinction of affected subjects from healthy individuals and to distinguish one disease from the other, and therefore can be used in disease diagnosis and classification. Disease susceptibility markers, that are often included with diagnostic markers, are those markers that in the healthy individual indicate an increased risk to develop the disease and therefore their diagnostic value in complex disease like IPF is not fully accepted. Prognostic biomarkers are markers that allow the prediction of outcome, usually at the time of presentation[16]. Several molecular signature belonging to this last group has been evaluated for their prediction ability in cohorts of IPF patients.

Krebs van den Lungen-6 (KL-6) is a mucin-like glycoprotein expressed into alveolar and bronchiolar lumen by activated alveolar type Ⅱ alveolar epithelial cells (AEC-Ⅱ) and bronchiolar epithelial cells where it acts as a chemotactic factor favoring circulating mesenchymal cell migration in the lungs and resident lung fibroblasts proliferation[17-20]. When the integrity of alveolar capillary barrier is compromised, KL-6 can leak into the circulation and can therefore be detected. Serum KL-6 levels

are significantly elevated in patients with IPF. Similar results are described in other ILDs such as non-specific interstitial pneumonia and systemic sclerosis-related ILD and as a result this marker does not show high specificity for IPF[21,22]. Nevertheless, KL-6 has been evaluated as a prognostic marker in multiple forms of ILD, including IPF. A prospective study by Satoh *et al*[21] conducted in a cohort of 152 patients with idiopathic interstitial pneumonias and 67 patients with ILD associated to connective tissue disease, demonstrated that patients with high KL-6 levels had a worst survival compared with those with lower levels. However, this results were not replicated in one of the largest study involving IPF patients where baseline KL-6 did not improve the prediction ability of traditional clinical variables[23].

Matrix metalloproteinase (MMP) are a structurally and functionally related superfamily of 23 zinc-dependent proteases that are thought to play an important role in the tissue fibrogenic process promoting interstitial matrix remodeling, cell migration and activation of profibrotic pathways[24,25]. MMP7, the smallest member of the MMP family, is thought to degrade multiple components of the extra cellular matrix playing a pivotal role in the fibrogenic process[24]. Elevated serum MMP7 levels have been reported in studies comparing IPF patients with patients affected by sarcoidosis and COPD, but MMP7 concentrations in IPF patients do not differ from those observed in other forms of ILD[26,27]. Nevertheless, Rosas *et al*[28] evaluating serum levels of both MMP7 and MMP1 were able to distinguish IPF from hypersensitivity pneumonitis, that represent one of the more complex differential diagnosis of IPF, with high sensitivity and specificity. The same study demonstrated that serum MMP7 concentrations were inversely correlated with lung function measurements proposing MMP7 as a possible prognostic biomarker. Coherently, in a subsequent study Richardson and al. demonstrated that levels of MMP7, analyzed together with other variables in a multidimensional index, were significantly associated with patients' outcome[29].

Pulmonary surfactants proteins are lipoprotein complexes synthesized by AEC-Ⅱ that play in the alveoli the essential function of decreasing the surface tension at the air-liquid interface. The reduction in surface tension allows lung expansion during inspiration with lower transpulmonary pressures and prevents alveoli from collapsing during expiration[30]. Surfactant proteins A (SP-A) and D (SP-D) have shown interesting potentiality both as diagnostic and prognostic markers in IPF and other forms of ILD. Abnormal surfactant proteins synthesis is thought to play a role in AEC-Ⅱ cell dysfunction activating endoplasmic reticulum stress and the unfolded protein response[31]. Interestingly, defects in the genes encoding SP-A1 and SP-A2 have been associated with familial forms of pulmonary fibrosis, suggesting that these proteins may be involved in IPF pathogenesis. However only a minority of sporadic forms of IPF carry these mutations[32-40]. Levels of SP-A and SP-D have been found to be elevated in IPF patients due to increased permeability of the alveolar-capillary barrier or for increased secretion by AEC-Ⅱ[41]. Increased serum levels of either surfactant protein at the time of diagnosis has been demonstrated to be independent predictor of survival and has been proposed as a tool for patients referral to lung transplantation[41-43]. However, similarly to KL-6, ancillary studies conducted during recent clinical trials showed no difference in serum surfactant protein levels between treatment and placebo groups[44]. For this reason further evidences are required for their implementation into routine clinical practice.

CC chemokine ligand 18 (CCL18) is a chemokine protein that stimulates collagen production and fibroblasts differentiation[45]. It is produced by alternative activated AM and it has been reported to be elevated in a variety of fibrotic lung diseases, including IPF, sarcoidosis and systemic sclerosis-related ILD limiting its role as diagnostic biomarker for IPF[46,47]. However, Prasse *et al*[48] in a prospective cohort of 72 IPF patients were able to demonstrate correlation between serum CCL18 levels and physiological variables. In fact, in this cohort of patients baseline serum CCL18 levels were able to predict subsequent functional decline, and CCL18 serum levels > 150 ng/mL were independently associated with death in the follow up period.

In 2011 Seibold *et al*[49] by means of a genome wide linkage approach detected linkage between idiopathic interstitial pneumonia and a 3.4-Mb region of chromosome 11p15 in 82 families. Further analysis revealed that common polymorphism in the promoter region of the Mucin 5B (MUC5B) is associated with both familial interstitial pneumonia and IPF, being the minor-allele of the single-nucleotide polymorphism rs35705950 present at a frequency of 34% among subjects with familial interstitial pneumonia, 38% among subjects with IPF and 9% among controls. The association between the MUC5B promoter variant and IPF is the most consistently reproduced in the literature since studies conducted in other cohorts have independently confirmed these results[50]. Interestingly no association has been found with systemic sclerosis related ILD or sarcoidosis[51]. The MUC5B promoter variant appears to have prognostic value, as it is associated with decreased mortality when compared with the wild-type allele in IPF patients[52]. This observation seems to be independent of clinical factors and stratification of patients based on the presence of this polymorphism significantly improves the accuracy of previously validated prediction index[52].

PHYSIOLOGIC VARIABLES

Baseline pulmonary function test values poorly predict survival in IPF. Baseline forced vital capacity (FVC) shows an unclear predictive value[53,54] probably due to the confounding effect of comorbid conditions such as emphysema, pulmonary vascular disease and obesity[2].

Baseline diffusing capacity for carbon monoxide (DLCO) appears to be a better survival predictor compared to FVC, and a threshold of approximately 40 percent of predicted values has been associated with an increased risk of mortality[54-57]. Studies conducted in small IPF patients cohorts suggest that baseline total lung capacity (TLC) and alveolar-arterial oxygen difference in partial pressures [P(A-a)O_2] may predict outcome in IPF. In particular change in P(A-a)O_2 greater than 15 mmHg after 12 mo has been shown to correlate with patients survival[55]. However, these results were not replicated in large cohorts of IPF patients.

Longitudinal functional trends have shown strong prognostic value in IPF. Serial change in FVC is an accepted measure of the disease course and decline in FVC has been used as the primary endpoint in several randomized controlled drug trials[58-63]. A decline in FVC greater than 10% has been consistently correlated with worse survival time in IPF and recent evidence-based guidelines recommend that an absolute decrease in FVC greater than 10% can be used as a surrogate marker of mortality[2]. Recent data indicate that in IPF even declines in FVC of 5% may be predictive of mortality[64] and that using the relative change instead of the absolute change when calculating the decline in FVC allows to identify clinically meaningful information preserving prognostic efficiency[65]. A decline in DLCO and 6-mo change in TLC and P(A-a)O_2 have also been associated with decreased survival[54,55,57,66].

The 6-min walk test (6MWT) is a measure of exercise tolerance, that has been widely used in a variety of cardiac and pulmonary conditions to asses patients performance status and to evaluate the need for oxygen supplementation[67,68]. The 6MWT is a practical, inexpensive and reliable test that requires no special equipment or advanced training and can be performed by all but the most severely impaired IPF patients[69]. A number of studies have evaluated at prognostic utility of the 6MWT in IPF, however, until recently, these studies were limited by the small size of the analyzed cohorts or by the lack of standardization in the procedure[70-72]. However, in a recent study conducted analyzing data from the database of a large randomized controlled study evaluating interferon-gamma 1b in IPF, the 6MWT demonstrated to be a reliable, valid, and responsive clinical measure and to efficiently predict one-year mortality[73]. In a subsequent study, the investigators found that both baseline 6MWT distance (6MWD) and 24-wk change in 6MWD were independent predictors of short-term mortality in an analysis of 748 patients with IPF[74].

MULTI-DIMENSIONAL SCORING SYSTEMS

Published studies on multi-dimensional scoring systems are summarized in Table 1. In 1986 Watters *et al*[75] developed a composite clinical-radiographic-physiologic (CRP) scoring system based on several parameters as dyspnea, radiology, spirometry, lung volume, diffusion capacity, resting alveolar-arterial PO_2, and O_2 saturation corrected for maximal achieved VO_2max in 26 biopsy-proven IPF patients. Scores ranged from 0 to 100 (100 being the most severe disease). The authors looked at the relationship between CRP scores and histopathologic findings, including a cellular pathology score based on abnormalities considered potentially reversible, a fibrotic pathology score based on abnormalities thought to be mainly irreversible, and an overall index defined as "total pathology score". The CRP score determined after 6 mo of corticosteroid treatment correlated with the fibrotic pathology score on open lung biopsy and the change in CRP after 6 mo of corticosteroid therapy correlated with the cellular histopathologic component at biopsy.

In a subsequent study Gay *et al*[76] tested pre-treatment features that could be used to predict short-term improvement in pulmonary function and long term survival in a population of 38 biopsy-proven IPF patients. The CPR, a high-resolution CT scan (HRCT) scores, and histopathologic scores were available in all patients. In a first phase of the study, patients were treated with high-dose steroids for 3 mo and thereafter CRP scoring was repeated. Patients were divided into three groups: Responders with a greater than 10-point drop in CRP, stable with a change in CRP within 10 point, and non-responders with rise in CRP greater than 10 or death. Patients showing improvement continued the steroids treatment for 18 mo tapering the drug dose. In all others patients, steroids therapy was interrupted and oral cyclophosphamide prescribed. Only the HRCT fibrotic score ($P < 0.009$) and the fibrotic pathology score ($P < 0.03$) independently predicted survival in the analyzed population. Addition to the HRCT fibrotic score of physiologic measures, CRP score, or pathologic findings did not improve its predictive value.

King *et al*[77] elaborated an updated of the CRP scoring system in order to predict survival in newly diagnosed cases of IPF. Study population included 238 biopsy-proven IPF patients divided by smoking status into current smokers, former smokers and never smokers.

For each patient, clinical manifestations, chest radiographs, and pulmonary physiology were prospectively assessed by means of Cox proportional hazards models and the effect of these parameters on survival was evaluated. Survival was related to age, smoking status, clubbing, the extent of interstitial opacities on the chest radiograph, presence of pulmonary hypertension, reduced lung volume, and abnormal gas exchange during maximal exercise. Based on these results the authors updated the CRP scoring system elaborated by Watters *et al*[75] and developed an abbreviated model which excluded pulmonary mechanics and exercise variables that was demonstrated to be superior to the original model proposed by Watters *et al*[75].

In an English study by Mogulkoc *et al*[78] a model

Table 1 Summary of characteristics and main results of the studies published on Multidimensional-scoring systems

Ref.	Type of study (number of patients)	Variables included in the model	Summary of results
Gay *et al*[76]	Prospective (38)	HRCT score Pathology fibrotic score	HRCT fibrotic score ⩾ 2: 80% sensitive and 85% specific in predicting death (34 mo average follow-up). The CRP does not add predicting value
King *et al*[77]	Retrospective (91)	Age Smoking status Clubbing HRCT score HRCT score for PH TLC % pred PaO_2 at max exercise	Only prediction results of single variables are reported by the authors. No direct data about performance of the CRP are reported
Mogulkoc *et al*[78]	Retrospective (95)	HRCT score DLCO % pred	HRCT and DLCO% combined model: AUC 0.91; sensitivity 84%, specificity 82% in predicting 2 yr survival
Wells *et al*[79]	Retrospective (212)	DLCO % pred FVC % pred FEV1 % pred	5 yr survival CPI regression coefficient: 0.092 (0.043, 0.141). $P < 0.0005$
du Bois *et al*[80]	Prospective (830)	Age Respiratory hospitalization FVC % pred 24 wk in FVC % pred	Combined scoring system AUC: 0.75. 1 yr survival
Richards *et al*[29]	Prospective (241)	Gender FVC %pred DLCO %pred MMP-7	PCMI ⩾ 330: AUC 0.74-0.84 in predicting survival. Average follow-up 1.8 yr
Mura *et al*[82]	Prospective (138)	MRCDS 6MWD % pred CPI	ROSE > 2:HR 11.4, $P < 0.0001$; AUC 0.76; sensitivity 39%, specificity 100% in predicting survival. 3 yr follow-up
Ley *et al*[83]	Retrospective (558)	Gender Age FVC % pred DLCO % pred	GAP: c-index 69.3. Stages Ⅰ, Ⅱ and Ⅲ 1-yr mortality of 6%, 16%, and 39%, respectively

HRCT: High resolution computerized tomography; CRP: Clinical-radiographic-physiologic; TLC: Total lung capacity; DLCO: Diffusing capacity for carbon monoxide; CPI: Composite physiologic index; PCMI: Personal clinical molecular mortality index; MMP: Matrix metalloproteinase; MRCDS: Medical research council dyspnea score; 6MWD: 6 min walking distance; ROSE: Risk stratificatiOn ScorE; HR: High-resolution; GAP: Gender, age, physiology; PaO_2: Pulmonary arterial oxygen tension; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 s.

based on DLCO percent predicted and HRCT-fibrosis score was developed in order to estimate survival and to optimize the timing of lung transplant referral in IPF patients. Study population was composed of 115 patients under 65 years 38% of which with biopsy proven IPF. The primary endpoint of this study was 2-year survival. Authors found that HRCT-fibrosis score, based on fibrotic and ground glass changes, and DLCO expressed as percent of predicted values were independent predictors of survival and they also determined a cut-off for both measures. The model yielded a specificity and sensitivity of 84% and 82%, respectively.

In 2003 a study by Wells *et al*[79] proposed the Composite Physiologic Index (CPI) as a determinant of prognosis in IPF patients with and without concomitant emphysema. The CPI was derived against a quantitative radiographic score of pulmonary fibrosis and provided an accurate estimate of the disease extent on HRCT. The CPI was calculated in a derivation population of 106 patients, 36 with biopsy-proven IPF, and was eventually tested in a validation population of the same size. Stepwise regression was used to generate a combination of lung function variables reflecting the extent of pulmonary fibrosis on HRCT. Parameters examined included FEV1, FVC, TLC, residual volume, DLCO, carbon monoxide transfer coefficient, PO_2, and A-aO_2. The extent of IPF on HRCT was independently associated to percent predicted DLCO, FVC and FEV1 that were included in the final CPI formula as follows:

Extent of disease on CT = 91.0- (0.65 × percent predicted DLCO)- (0.53 × percent predicted FVC)+ (0.34 × percent predicted FEV1).

In the validation population, when compared to the single variables, the CPI showed the best correlation to the HRCT disease extent. In terms of survival, five years retrospective mortality analysis demonstrated that the CPI had the greatest prognostic power in both the singles and combined cohorts, including a separate cohort of 36 patients with biopsy proven IPF (CPI, P = 0.0005; FVC, P = 0.002; PO2, P = 0.002).

A risk scoring system for 1-year mortality was proposed by du Bois *et al*[80] in 2011. The authors analyzed clinical data of 830 patients with mild to moderate disease without emphysema included in two large international clinical trials aimed to test the efficacy of IFN-g1b in IPF[58,81].

The endpoint was 1-year survival and the mortality was found to be 9.7% at one year. The following variables were found to be independent predictors of all-cause mortality and were included in a clinical model: Age, history of respiratory hospitalizations, percent

Table 2 Risk stratification Score[82]

Low risk (all of the following conditions)	Intermediate risk (1 or 2 of the following conditions)	High risk (all the following conditions)
MRCDS ⩽ 3	MRCDS > 3	MRCDS > 3
6MWD > 72% predicted	6MWD 72% ⩽ predicted	6MWD 72% ⩽ predicted
CPI ⩽ 41	CPI > 41	CPI > 41

MRCDS: Medical research council dyspnea score; 6MWD: 6 min walking distance; CPI: Composite physiologic index.

predicted FVC, 24-wk change in percent predicted FVC, percent predicted DLCO, 24-wk change in percent predicted DLCO and 24-wk change in health related quality of life questionnaire. A second simplified model was developed based on age, history of respiratory hospitalization, percent predicted FVC and 24-wk change in percent predicted FVC. Both the original and simplified models had comparable discriminatory power. Based on the simplified clinical model a scoring system able to estimate the probability of 1-year mortality in patients with IPF was developed.

A personal clinical molecular mortality index (PCMI) was proposed in a prospective study by Richards *et al*[29]. This multi-dimensional index incorporated for the first time serum biomarkers with pulmonary function test measures. Study population included 241 patients divided into a derivation cohort of 140 patients, 85 with biopsy proved IPF, and a validation cohort of 101, 41 with biopsy. The primary endpoints of the study were mortality, transplant-free survival, and progression-free survival. Sera samples from the 241 patients were tested for the concentrations of more than 90 different proteins. The association of serum biomarkers with primary endpoints were tested in the derivation and validation cohorts using nonparametric methods of survival analysis and the Cox proportional hazards model, and an integrated risk prediction score including FVC and DLCO was derived and tested.

Although concentrations of MMP-7, ICAM-1, IL-8, VCAM-1, and S100A12 were all associated with the primary endpoints in the derivation cohort, the Akaike information criterion (AIC) that was applied for variable selection in the Cox proportional hazards model, included only MMP-7 in the final equation defining PCMI as follows: 114 × I(Male) + 2 (100% - FVC% Predicted) + 3 (100% - DLCO%Predicted) + 111 × I (MMP-7 ⩾ 4.3 ng/mL) where I has to be considered equal to 1 if and only if the condition inside the parentheses is true. With a PCMI cut-off of 330, low-risk patients showed a median survival of 5.13 years while high risk patients had a median survival of 1.56 years.

In an Italian study Mura *et al*[82] elaborated an index, defined as Risk stratificatiOn ScorE (ROSE). This study was conducted on an overall population of 138 newly diagnosed patients, 55 (40%) of those had a biopsy-proven diagnosis, and the rest had a clinical-radiological diagnosis reviewed by three different expert radiologists. The study population comprised a prospective derivation population of 70 patients and a retrospective validation population of 68 patients used for comparative analysis. Minimum follow-up was 3 years and the primary end-point was survival defined as time to death or to lung transplantation. Incidence of acute exacerbation was also addressed in this study. Examination of clinical variables collected at time of diagnosis and at six month from diagnosis by means of ROC curve and multivariate analysis allowed the definition of three independent predictors of 3-year survival: (1) Medical research council dyspnea score (MRCDS) > 3 (HR = 6.77, $P < 0.0005$), (2) 6 min walking distance (6MWD) ⩽ 72% predicted (HR = 3.27, $P < 0.0162$) and (3) CPI > 41 (HR = 5.36, $P < 0.0071$).

The ROSE predicted 3-yr survival with 39% sensitivity and 100% specificity. A ROSE of 3 (Table 2) carried a hazard ratio of 11.4 towards 3-year mortality. Importantly, advancement to ROSE 3 of patients with an initial score of 1 or 2 six months after diagnosis predicted 3-yr mortality with 94% sensitivity and 41% specificity.

In their retrospective study Ley *et al*[83] developed an index defined as GAP (gender, age, physiology), in order to predict mortality in IPF. United States and Italian patients included in this study were divided in three groups: 228 patients, 44.3% of which with biopsy proven IPF, were included in the derivation cohort and 555, 54.7% of which with biopsy, in two validation cohorts of 330 and 325 patients. Mean follow-up was 1.7 and 2.4 in the derivation and the validation cohorts, respectively. The primary endpoint of the study was time to death or lung transplantation. Overall mortality was 49% in the derivation cohort and 62% in the validation cohorts. A competing-risk regression model was used to screen potential predictors of mortality in the derivation cohort including age, sex, body mass index, smoking status, supplemental oxygen use, FVC, FEV1, TLC and DLCO. Age, sex, FVC% predicted and DLCO% predicted were identified as independent predictors and were used to develop the GAP individual risk calculator towards mortality and staging system. Three stages (stages Ⅰ, Ⅱ, and Ⅲ) were identified based on the GAP index with 1-year mortality of 6%, 16%, and 39%, respectively (Table 3).

CONCLUSION

Predicting clinical course of IPF is extremely difficult and despite the progress in the field reviewed in this article, survival prediction in the single IPF patient remains an unmet clinical need. This task is limited by multiple factors. On one hand diagnostic delays related to

Table 3 Gender, age, physiology index[83]

Stage	I	II	III
Points	0-3	4-5	6-8
	Predictor		Points
	Gender		
G	Female		0
	Male		1
	Age		
A	⩽ 60		0
	61-65		1
	⩾ 65		3
	FVC% predicted		
	> 75		0
	50-75		1
P	< 50		2
	DLCO% predicted		
	> 55		0
	36-55		1
	⩽ 35		2
	Cannot perform		3
	Total possible points		8

FVC: Forced vital capacity; DLCO: Diffusing capacity for carbon monoxide.

different patients symptoms perception and healthcare operators awareness, but also different biological disease characteristics might cause a high variability of disease presentation at time of diagnosis. Furthermore, largely unknown triggers might dramatically affect disease course, with patients who originally displayed a stable disease progressing to rapid decline in lung function. In this respect, recent data suggest that even medical interventions considered standard therapy until few years ago might have contribute to disease progression in a significant fraction of IPF patients[84,85]. On the other hand, the complex pathophysiology of IPF, that is characterized by a combination of gas exchange, ventilatory and cardiovascular response abnormalities, limits the correlation between single traditional clinical measures such as pulmonary function tests, exercise capability and radiological or histopathological disease extent affecting their clinical utility at time of diagnosis. Observation of trends in clinical variables have shown a better prediction ability compared to baseline measures. However this approach presents the major limitation of the need of follow-up periods ranging from 6 to 12 mo in a disease with a median survival of about 3 years. Recent data suggest that shorter term observations and the validation of clinical meaningful differences in clinical variables of lesser magnitude might improve the clinical utility of this approach[64,74].

Multiple-dimensional scoring systems have significantly improved the prediction of survival in IPF. These scoring systems have the advantage to take into account different aspects of the disease at the same time increasing the amount of information on the status of the single patient. However, to date none of the proposed systems can be considered extent of limitations. In fact, some of the published studies are limited by their retrospective nature or by the relative small numbers of analyzed prospective cohorts. Availability of prospective data from the large database of recent clinical trials has partially overcame these limitations. However, these studies have generally enrolled mild or moderate patients that might not represents the "real life" clinical setting missing advanced and rapidly progressing disease forms and therefore might underestimate the real disease burden of IPF.

In our opinion the search for the optimal survival prediction tool should take into account the increasing information coming from basic studies on the genetics, pathogenetic mechanisms and more in general biology of IPF, some of which have already provided useful hints in form of molecular signature that should be incorporated in old and new clinical models and eventually validated in large prospective cohorts of IPF patients. Such consistent and improved survival tool might be particular useful in the next future to guide the clinicians in patients management with particular regard to the choice of the increasing available effective therapeutic strategies for IPF patients.

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REFERENCES

1 **Travis WD**, Costabel U, Hansell DM, King TE, Lynch DA, Nicholson AG, Ryerson CJ, Ryu JH, Selman M, Wells AU, Behr J, Bouros D, Brown KK, Colby TV, Collard HR, Cordeiro CR, Cottin V, Crestani B, Drent M, Dudden RF, Egan J, Flaherty K, Hogaboam C, Inoue Y, Johkoh T, Kim DS, Kitaichi M, Loyd J, Martinez FJ, Myers J, Protzko S, Raghu G, Richeldi L, Sverzellati N, Swigris J, Valeyre D. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; **188**: 733-748 [PMID: 24032382 DOI: 10.1164/rccm.201308-1483ST]

2 **Raghu G**, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schünemann HJ. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; **183**: 788-824 [PMID: 21471066 DOI: 10.1164/rccm.2009-040GL]

3 **Baumgartner KB**, Samet JM, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1997; **155**: 242-248 [PMID: 9001319 DOI: 10.1164/ajrccm.155.1.9001319]

4 **Wolters PJ**, Collard HR, Jones KD. Pathogenesis of idiopathic pulmonary fibrosis. *Annu Rev Pathol* 2014; **9**: 157-179 [PMID: 24050627 DOI: 10.1146/annurev-pathol-012513-104706]

5 **Rogliani P**, Mura M, Mattia P, Ferlosio A, Farinelli G, Mariotta S, Graziano P, Pezzuto G, Ricci A, Saltini C, Orlandi A. HRCT and histopathological evaluation of fibrosis and tissue destruction in IPF associated with pulmonary emphysema. *Respir Med* 2008; **102**: 1753-1761 [PMID: 18723334 DOI: 10.1016/j.rmed.2008.07.010]

6 **Stahl M**, Schupp J, Jäger B, Schmid M, Zissel G, Müller-Quernheim J, Prasse A. Lung collagens perpetuate pulmonary fibrosis via CD204 and M2 macrophage activation. *PLoS One* 2013; **8**: e81382 [PMID: 24278429 DOI: 10.1371/journal.pone.0081382]

7 **Sangiuolo F**, Puxeddu E, Pezzuto G, Cavalli F, Longo G, Comandini A, Di Pierro D, Pallante M, Sergiacomi G, Simonetti G, Zompatori M, Orlandi A, Magrini A, Amicosante M, Mariani F, Losi M, Fraboni D, Bisetti A, Saltini C. HFE gene variants and iron-induced oxygen radical generation in idiopathic pulmonary fibrosis. *Eur Respir J* 2015; **45**: 483-490 [PMID: 25504993 DOI: 10.1183/09031936.00104814]

8 **Puxeddu E**, Comandini A, Cavalli F, Pezzuto G, D'Ambrosio C, Senis L, Paci M, Curradi G, Sergiacomi GL, Saltini C. Iron laden macrophages in idiopathic pulmonary fibrosis: the telltale of occult alveolar hemorrhage? *Pulm Pharmacol Ther* 2014; **28**: 35-40 [PMID: 24365112 DOI: 10.1016/j.pupt.2013.12.002]

9 **Raghu G**, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2006; **174**: 810-816 [PMID: 16809633 DOI: 10.1164/rccm.200602-163OC]

10 **Agabiti N**, Porretta MA, Bauleo L, Coppola A, Sergiacomi G, Fusco A, Cavalli F, Zappa MC, Vignarola R, Carlone S, Facchini G, Mariotta S, Palange P, Valente S, Pasciuto G, Pezzuto G, Orlandi A, Fusco D, Davoli M, Saltini C, Puxeddu E. Idiopathic Pulmonary Fibrosis (IPF) incidence and prevalence in Italy. *Sarcoidosis Vasc Diffuse Lung Dis* 2014; **31**: 191-197 [PMID: 25363218]

11 **Raghu G**, Lynch D, Godwin JD, Webb R, Colby TV, Leslie KO, Behr J, Brown KK, Egan JJ, Flaherty KR, Martinez FJ, Wells AU, Shao L, Zhou H, Pedersen PS, Sood R, Montgomery AB, O' Riordan TG. Diagnosis of idiopathic pulmonary fibrosis with high-resolution CT in patients with little or no radiological evidence of honeycombing: secondary analysis of a randomised, controlled trial. *Lancet Respir Med* 2014; **2**: 277-284 [PMID: 24717624 DOI: 10.1016/S2213-2600(14)70011-6]

12 **Pompeo E**, Rogliani P, Cristino B, Schillaci O, Novelli G, Saltini C. Awake thoracoscopic biopsy of interstitial lung disease. *Ann Thorac Surg* 2013; **95**: 445-452 [PMID: 23245450 DOI: 10.1016/j.athoracsur.2012.10.043]

13 **Casoni GL**, Tomassetti S, Cavazza A, Colby TV, Dubini A, Ryu JH, Carretta E, Tantalocco P, Piciucchi S, Ravaglia C, Gurioli C, Romagnoli M, Gurioli C, Chilosi M, Poletti V. Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. *PLoS One* 2014; **9**: e86716 [PMID: 24586252 DOI: 10.1371/journal.pone.0086716]

14 **Martinez FJ**, Safrin S, Weycker D, Starko KM, Bradford WZ, King TE, Flaherty KR, Schwartz DA, Noble PW, Raghu G, Brown KK. The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med* 2005; **142**: 963-967 [PMID: 15968010 DOI: 10.7326/0003-4819-142-12_Part_1-200506210-00005]

15 **Zhang Y**, Kaminski N. Biomarkers in idiopathic pulmonary fibrosis. *Curr Opin Pulm Med* 2012; **18**: 441-446 [PMID: 22847105 DOI: 10.1097/MCP.0b013e328356d03c]

16 **Hambly N**, Shimbori C, Kolb M. Molecular classification of idiopathic pulmonary fibrosis: personalized medicine, genetics and biomarkers. *Respirology* 2015; **20**: 1010-1022 [PMID: 26109466 DOI: 10.1111/resp.12569]

17 **Ishikawa N**, Hattori N, Yokoyama A, Kohno N. Utility of KL-6/MUC1 in the clinical management of interstitial lung diseases. *Respir Investig* 2012; **50**: 3-13 [PMID: 22554854 DOI: 10.1016/j.resinv.2012.02.001]

18 **Bandoh S**, Fujita J, Ohtsuki Y, Ueda Y, Hojo S, Tokuda M, Dobashi H, Kurata N, Yoshinouchi T, Kohno N, Takahara J. Sequential changes of KL-6 in sera of patients with interstitial pneumonia associated with polymyositis/dermatomyositis. *Ann Rheum Dis* 2000; **59**: 257-262 [PMID: 10733471]

19 **Hirasawa Y**, Kohno N, Yokoyama A, Inoue Y, Abe M, Hiwada K. KL-6, a human MUC1 mucin, is chemotactic for human fibroblasts. *Am J Respir Cell Mol Biol* 1997; **17**: 501-507 [PMID: 9376125 DOI: 10.1165/ajrcmb.17.4.2253]

20 **Ohshimo S**, Yokoyama A, Hattori N, Ishikawa N, Hirasawa Y, Kohno N. KL-6, a human MUC1 mucin, promotes proliferation and survival of lung fibroblasts. *Biochem Biophys Res Commun* 2005; **338**: 1845-1852 [PMID: 16289035 DOI: 10.1016/j.bbrc.2005.10.144]

21 **Satoh H**, Kurishima K, Ishikawa H, Ohtsuka M. Increased levels of KL-6 and subsequent mortality in patients with interstitial lung diseases. *J Intern Med* 2006; **260**: 429-434 [PMID: 17040248 DOI: 10.1111/j.1365-2796.2006.01704.x]

22 **Ohnishi H**, Yokoyama A, Kondo K, Hamada H, Abe M, Nishimura K, Hiwada K, Kohno N. Comparative study of KL-6, surfactant protein-A, surfactant protein-D, and monocyte chemoattractant protein-1 as serum markers for interstitial lung diseases. *Am J Respir Crit Care Med* 2002; **165**: 378-381 [PMID: 11818324 DOI: 10.1164/ajrccm.165.3.2107134]

23 **Song JW**, Do KH, Jang SJ, Colby TV, Han S, Kim DS. Blood biomarkers MMP-7 and SP-A: predictors of outcome in idiopathic pulmonary fibrosis. *Chest* 2013; **143**: 1422-1429 [PMID: 23715088 DOI: 10.1378/chest.11-2735]

24 **Pardo A**, Selman M. Role of matrix metaloproteases in idiopathic pulmonary fibrosis. *Fibrogenesis Tissue Repair* 2012; **5**: S9 [PMID: 23259796 DOI: 10.1186/1755-1536-5-S1-S9]

25 **Pardo A**, Selman M. Matrix metalloproteases in aberrant fibrotic tissue remodeling. *Proc Am Thorac Soc* 2006; **3**: 383-388 [PMID: 16738205 DOI: 10.1513/pats.200601-012TK]

26 **Vuorinen K**, Myllärniemi M, Lammi L, Piirilä P, Rytilä P, Salmenkivi K, Kinnula VL. Elevated matrilysin levels in bronchoalveolar lavage fluid do not distinguish idiopathic pulmonary fibrosis from other interstitial lung diseases. *APMIS* 2007; **115**: 969-975 [PMID: 17696954 DOI: 10.1111/j.1600-0463.2007.apm_697.x]

27 **Huh JW**, Kim DS, Oh YM, Shim TS, Lim CM, Lee SD, Koh Y, Kim WS, Kim WD, Kim KR. Is metalloproteinase-7 specific for idiopathic pulmonary fibrosis? *Chest* 2008; **133**: 1101-1106 [PMID: 18071010 DOI: 10.1378/chest.07-2116]

28 **Rosas IO**, Richards TJ, Konishi K, Zhang Y, Gibson K, Lokshin AE, Lindell KO, Cisneros J, Macdonald SD, Pardo A, Sciurba F, Dauber J, Selman M, Gochuico BR, Kaminski N. MMP1 and MMP7 as potential peripheral blood biomarkers in idiopathic pulmonary fibrosis. *PLoS Med* 2008; **5**: e93 [PMID: 18447576 DOI: 10.1371/journal.pmed.0050093]

29 **Richards TJ**, Kaminski N, Baribaud F, Flavin S, Brodmerkel C, Horowitz D, Li K, Choi J, Vuga LJ, Lindell KO, Klesen M, Zhang Y, Gibson KF. Peripheral blood proteins predict mortality in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2012; **185**: 67-76 [PMID: 22016448 DOI: 10.1164/rccm.201101-0058OC]

30 **Goerke J**. Pulmonary surfactant: functions and molecular composition. *Biochim Biophys Acta* 1998; **1408**: 79-89 [PMID: 9813251]

31 **Tanjore H**, Blackwell TS, Lawson WE. Emerging evidence for endoplasmic reticulum stress in the pathogenesis of idiopathic pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol* 2012; **302**: L721-L729 [PMID: 22287606 DOI: 10.1152/ajplung.00410.2011]

32 **Bridges JP**, Wert SE, Nogee LM, Weaver TE. Expression of a human surfactant protein C mutation associated with interstitial lung disease disrupts lung development in transgenic mice. *J Biol Chem* 2003; **278**: 52739-52746 [PMID: 14525980 DOI: 10.1074/jbc.M309599200]

33 **Chibbar R**, Shih F, Baga M, Torlakovic E, Ramlall K, Skomro R, Cockcroft DW, Lemire EG. Nonspecific interstitial pneumonia and usual interstitial pneumonia with mutation in surfactant protein C in familial pulmonary fibrosis. *Mod Pathol* 2004; **17**: 973-980 [PMID: 15133475 DOI: 10.1038/modpathol.3800149]

34 **Lawson WE**, Cheng DS, Degryse AL, Tanjore H, Polosukhin VV, Xu XC, Newcomb DC, Jones BR, Roldan J, Lane KB, Morrisey EE, Beers MF, Yull FE, Blackwell TS. Endoplasmic reticulum stress enhances fibrotic remodeling in the lungs. *Proc Natl Acad Sci USA* 2011; **108**: 10562-10567 [PMID: 21670280 DOI: 10.1073/pnas.1107559108]

35 **Selman M**, Lin HM, Montaño M, Jenkins AL, Estrada A, Lin Z, Wang G, DiAngelo SL, Guo X, Umstead TM, Lang CM, Pardo A, Phelps DS, Floros J. Surfactant protein A and B genetic variants predispose to idiopathic pulmonary fibrosis. *Hum Genet* 2003; **113**: 542-550 [PMID: 13680361 DOI: 10.1007/s00439-003-1015-4]

36 **Nogee LM**, Dunbar AE, Wert SE, Askin F, Hamvas A, Whitsett JA. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. *N Engl J Med* 2001; **344**: 573-579 [PMID:

11207353 DOI: 10.1056/NEJM200102223440805]
37 **Lawson WE**, Crossno PF, Polosukhin VV, Roldan J, Cheng DS, Lane KB, Blackwell TR, Xu C, Markin C, Ware LB, Miller GG, Loyd JE, Blackwell TS. Endoplasmic reticulum stress in alveolar epithelial cells is prominent in IPF: association with altered surfactant protein processing and herpesvirus infection. *Am J Physiol Lung Cell Mol Physiol* 2008; **294**: L1119-L1126 [PMID: 18390830 DOI: 10.1152/ajplung.00382.2007]
38 **Lawson WE**, Grant SW, Ambrosini V, Womble KE, Dawson EP, Lane KB, Markin C, Renzoni E, Lympany P, Thomas AQ, Roldan J, Scott TA, Blackwell TS, Phillips JA, Loyd JE, du Bois RM. Genetic mutations in surfactant protein C are a rare cause of sporadic cases of IPF. *Thorax* 2004; **59**: 977-980 [PMID: 15516475 DOI: 10.1136/thx.2004.026336]
39 **Maitra M**, Wang Y, Gerard RD, Mendelson CR, Garcia CK. Surfactant protein A2 mutations associated with pulmonary fibrosis lead to protein instability and endoplasmic reticulum stress. *J Biol Chem* 2010; **285**: 22103-22113 [PMID: 20466729 DOI: 10.1074/jbc.M110.121467]
40 **Markart P**, Ruppert C, Wygrecka M, Schmidt R, Korfei M, Harbach H, Theruvath I, Pison U, Seeger W, Guenther A, Witt H. Surfactant protein C mutations in sporadic forms of idiopathic interstitial pneumonias. *Eur Respir J* 2007; **29**: 134-137 [PMID: 17005585 DOI: 10.1183/09031936.00034406]
41 **Greene KE**, King TE, Kuroki Y, Bucher-Bartelson B, Hunninghake GW, Newman LS, Nagae H, Mason RJ. Serum surfactant proteins-A and -D as biomarkers in idiopathic pulmonary fibrosis. *Eur Respir J* 2002; **19**: 439-446 [PMID: 11936520]
42 **Kinder BW**, Brown KK, McCormack FX, Ix JH, Kervitsky A, Schwarz MI, King TE. Serum surfactant protein-A is a strong predictor of early mortality in idiopathic pulmonary fibrosis. *Chest* 2009; **135**: 1557-1563 [PMID: 19255294 DOI: 10.1378/chest.08-2209]
43 **Takahashi H**, Fujishima T, Koba H, Murakami S, Kurokawa K, Shibuya Y, Shiratori M, Kuroki Y, Abe S. Serum surfactant proteins A and D as prognostic factors in idiopathic pulmonary fibrosis and their relationship to disease extent. *Am J Respir Crit Care Med* 2000; **162**: 1109-1114 [PMID: 10988138 DOI: 10.1164/ajrccm.162.3.9910080]
44 **Azuma A**, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, Taguchi Y, Nagai S, Itoh H, Ohi M, Sato A, Kudoh S. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2005; **171**: 1040-1047 [PMID: 15665326 DOI: 10.1164/rccm.200404-571OC]
45 **Prasse A**, Pechkovsky DV, Toews GB, Jungraithmayr W, Kollert F, Goldmann T, Vollmer E, Müller-Quernheim J, Zissel G. A vicious circle of alveolar macrophages and fibroblasts perpetuates pulmonary fibrosis via CCL18. *Am J Respir Crit Care Med* 2006; **173**: 781-792 [PMID: 16415274 DOI: 10.1164/rccm.200509-1518OC]
46 **Kodera M**, Hasegawa M, Komura K, Yanaba K, Takehara K, Sato S. Serum pulmonary and activation-regulated chemokine/CCL18 levels in patients with systemic sclerosis: a sensitive indicator of active pulmonary fibrosis. *Arthritis Rheum* 2005; **52**: 2889-2896 [PMID: 16142750 DOI: 10.1002/art.21257]
47 **Prasse A**, Pechkovsky DV, Toews GB, Schäfer M, Eggeling S, Ludwig C, Germann M, Kollert F, Zissel G, Müller-Quernheim J. CCL18 as an indicator of pulmonary fibrotic activity in idiopathic interstitial pneumonias and systemic sclerosis. *Arthritis Rheum* 2007; **56**: 1685-1693 [PMID: 17469163 DOI: 10.1002/art.22559]
48 **Prasse A**, Probst C, Bargagli E, Zissel G, Toews GB, Flaherty KR, Olschewski M, Rottoli P, Müller-Quernheim J. Serum CC-chemokine ligand 18 concentration predicts outcome in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009; **179**: 717-723 [PMID: 19179488 DOI: 10.1164/rccm.200808-1201OC]
49 **Seibold MA**, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE, Fingerlin TE, Zhang W, Gudmundsson G, Groshong SD, Evans CM, Garantziotis S, Adler KB, Dickey BF, du Bois RM, Yang IV, Herron A, Kervitsky D, Talbert JL, Markin C, Park J, Crews AL, Slifer SH, Auerbach S, Roy MG, Lin J, Hennessy CE, Schwarz MI, Schwartz DA. A common MUC5B promoter polymorphism and pulmonary fibrosis. *N Engl J Med* 2011; **364**: 1503-1512 [PMID: 21506741 DOI: 10.1056/NEJMoa1013660]
50 **Zhang Y**, Noth I, Garcia JG, Kaminski N. A variant in the promoter of MUC5B and idiopathic pulmonary fibrosis. *N Engl J Med* 2011; **364**: 1576-1577 [PMID: 21506748 DOI: 10.1056/NEJMc1013504]
51 **Stock CJ**, Sato H, Fonseca C, Banya WA, Molyneaux PL, Adamali H, Russell AM, Denton CP, Abraham DJ, Hansell DM, Nicholson AG, Maher TM, Wells AU, Lindahl GE, Renzoni EA. Mucin 5B promoter polymorphism is associated with idiopathic pulmonary fibrosis but not with development of lung fibrosis in systemic sclerosis or sarcoidosis. *Thorax* 2013; **68**: 436-441 [PMID: 23321605 DOI: 10.1136/thoraxjnl-2012-201786]
52 **Peljto AL**, Zhang Y, Fingerlin TE, Ma SF, Garcia JG, Richards TJ, Silveira LJ, Lindell KO, Steele MP, Loyd JE, Gibson KF, Seibold MA, Brown KK, Talbert JL, Markin C, Kossen K, Seiwert SD, Murphy E, Noth I, Schwarz MI, Kaminski N, Schwartz DA. Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. *JAMA* 2013; **309**: 2232-2239 [PMID: 23695349 DOI: 10.1001/jama.2013.5827]
53 **Schwartz DA**, Helmers RA, Galvin JR, Van Fossen DS, Frees KL, Dayton CS, Burmeister LF, Hunninghake GW. Determinants of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1994; **149**: 450-454 [PMID: 8306044 DOI: 10.1164/ajrccm.149.2.8306044]
54 **Collard HR**, King TE, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003; **168**: 538-542 [PMID: 12773325 DOI: 10.1164/rccm.200211-1311OC]
55 **King TE**, Safrin S, Starko KM, Brown KK, Noble PW, Raghu G, Schwartz DA. Analyses of efficacy end points in a controlled trial of interferon-gamma1b for idiopathic pulmonary fibrosis. *Chest* 2005; **127**: 171-177 [PMID: 15653980 DOI: 10.1378/chest.127.1.171]
56 **Egan JJ**, Martinez FJ, Wells AU, Williams T. Lung function estimates in idiopathic pulmonary fibrosis: the potential for a simple classification. *Thorax* 2005; **60**: 270-273 [PMID: 15790978 DOI: 10.1136/thx.2004.035436]
57 **Latsi PI**, du Bois RM, Nicholson AG, Colby TV, Bisirtzoglou D, Nikolakopoulou A, Veeraraghavan S, Hansell DM, Wells AU. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. *Am J Respir Crit Care Med* 2003; **168**: 531-537 [PMID: 12791580 DOI: 10.1164/rccm.200210-1245OC]
58 **Raghu G**, Brown KK, Bradford WZ, Starko K, Noble PW, Schwartz DA, King TE. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2004; **350**: 125-133 [PMID: 14711911 DOI: 10.1056/NEJMoa030511]
59 **Demedts M**, Behr J, Buhl R, Costabel U, Dekhuijzen R, Jansen HM, MacNee W, Thomeer M, Wallaert B, Laurent F, Nicholson AG, Verbeken EK, Verschakelen J, Flower CD, Capron F, Petruzzelli S, De Vuyst P, van den Bosch JM, Rodriguez-Becerra E, Corvasce G, Lankhorst I, Sardina M, Montanari M. High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2005; **353**: 2229-2242 [PMID: 16306520 DOI: 10.1056/NEJMoa042976]
60 **King TE**, Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, Stähler G, Leconte I, Roux S, Raghu G. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008; **177**: 75-81 [PMID: 17901413 DOI: 10.1164/rccm.200705-732OC]
61 **Raghu G**, Brown KK, Costabel U, Cottin V, du Bois RM, Lasky JA, Thomeer M, Utz JP, Khandker RK, McDermott L, Fatenejad S. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. *Am J Respir Crit Care Med* 2008; **178**: 948-955 [PMID: 18669816 DOI: 10.1164/rccm.200709-1446OC]
62 **Daniels CE**, Lasky JA, Limper AH, Mieras K, Gabor E, Schroeder DR. Imatinib treatment for idiopathic pulmonary fibrosis: Randomized placebo-controlled trial results. *Am J Respir Crit Care Med* 2010; **181**: 604-610 [PMID: 20007927 DOI: 10.1164/rccm.200906-0964OC]

63 **Noble PW**, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, King TE, Lancaster L, Sahn SA, Szwarcberg J, Valeyre D, du Bois RM. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; **377**: 1760-1769 [PMID: 21571362 DOI: 10.1016/S0140-6736(11)60405-4]

64 **Zappala CJ**, Latsi PI, Nicholson AG, Colby TV, Cramer D, Renzoni EA, Hansell DM, du Bois RM, Wells AU. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. *Eur Respir J* 2010; **35**: 830-836 [PMID: 19840957 DOI: 10.1183/09031936.00155108]

65 **Richeldi L**, Ryerson CJ, Lee JS, Wolters PJ, Koth LL, Ley B, Elicker BM, Jones KD, King TE, Ryu JH, Collard HR. Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis. *Thorax* 2012; **67**: 407-411 [PMID: 22426899 DOI: 10.1136/thoraxjnl-2011-201184]

66 **Flaherty KR**, Mumford JA, Murray S, Kazerooni EA, Gross BH, Colby TV, Travis WD, Flint A, Toews GB, Lynch JP, Martinez FJ. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003; **168**: 543-548 [PMID: 12773329 DOI: 10.1164/rccm.200209-1112OC]

67 **Nathan SD**, du Bois RM, Albera C, Bradford WZ, Costabel U, Kartashov A, Noble PW, Sahn SA, Valeyre D, Weycker D, King TE. Validation of test performance characteristics and minimal clinically important difference of the 6-minute walk test in patients with idiopathic pulmonary fibrosis. *Respir Med* 2015; **109**: 914-922 [PMID: 25956020 DOI: 10.1016/j.rmed.2015.04.008]

68 **Ora J**, Calzetta L, Pezzuto G, Senis L, Paone G, Mari A, Portalone S, Rogliani P, Puxeddu E, Saltini C. A 6MWT index to predict O2 flow correcting exercise induced SpO2 desaturation in ILD. *Respir Med* 2013; **107**: 2014-2021 [PMID: 24161677 DOI: 10.1016/j.rmed.2013.10.002]

69 **ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories.** ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; **166**: 111-117 [PMID: 12091180 DOI: 10.1164/ajrccm.166.1.at1102]

70 **Hallstrand TS**, Boitano LJ, Johnson WC, Spada CA, Hayes JG, Raghu G. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. *Eur Respir J* 2005; **25**: 96-103 [PMID: 15640329 DOI: 10.1183/09031936.04.00137203]

71 **Lama VN**, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, Murray S, Kazerooni EA, Gross BH, Lynch JP, Martinez FJ. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003; **168**: 1084-1090 [PMID: 12917227 DOI: 10.1164/rccm.200302-219OC]

72 **Enright PL**. The six-minute walk test. *Respir Care* 2003; **48**: 783-785 [PMID: 12890299]

73 **du Bois RM**, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Sahn SA, Szwarcberg J, Thomeer M, Valeyre D, King TE. Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. *Am J Respir Crit Care Med* 2011; **183**: 1231-1237 [PMID: 21131468 DOI: 10.1164/rccm.201007-1179OC]

74 **du Bois RM**, Albera C, Bradford WZ, Costabel U, Leff JA, Noble PW, Sahn SA, Valeyre D, Weycker D, King TE. 6-Minute walk distance is an independent predictor of mortality in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2014; **43**: 1421-1429 [PMID: 24311766 DOI: 10.1183/09031936.00131813]

75 **Watters LC**, King TE, Schwarz MI, Waldron JA, Stanford RE, Cherniack RM. A clinical, radiographic, and physiologic scoring system for the longitudinal assessment of patients with idiopathic pulmonary fibrosis. *Am Rev Respir Dis* 1986; **133**: 97-103 [PMID: 3942381]

76 **Gay SE**, Kazerooni EA, Toews GB, Lynch JP, Gross BH, Cascade PN, Spizarny DL, Flint A, Schork MA, Whyte RI, Popovich J, Hyzy R, Martinez FJ. Idiopathic pulmonary fibrosis: predicting response to therapy and survival. *Am J Respir Crit Care Med* 1998; **157**: 1063-1072 [PMID: 9563720 DOI: 10.1164/ajrccm.157.4.9703022]

77 **King TE**, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med* 2001; **164**: 1171-1181 [PMID: 11673205 DOI: 10.1164/ajrccm.164.7.2003140]

78 **Mogulkoc N**, Brutsche MH, Bishop PW, Greaves SM, Horrocks AW, Egan JJ. Pulmonary function in idiopathic pulmonary fibrosis and referral for lung transplantation. *Am J Respir Crit Care Med* 2001; **164**: 103-108 [PMID: 11435247 DOI: 10.1164/ajrccm.164.1.2007077]

79 **Wells AU**, Desai SR, Rubens MB, Goh NS, Cramer D, Nicholson AG, Colby TV, du Bois RM, Hansell DM. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. *Am J Respir Crit Care Med* 2003; **167**: 962-969 [PMID: 12663338 DOI: 10.1164/rccm.2111053]

80 **du Bois RM**, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Raghu G, Sahn SA, Szwarcberg J, Thomeer M, Valeyre D, King TE. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; **184**: 459-466 [PMID: 21616999 DOI: 10.1164/rccm.201011-1790OC]

81 **King TE**, Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, Noble PW, Sahn SA, Szwarcberg J, Thomeer M, Valeyre D, du Bois RM. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet* 2009; **374**: 222-228 [PMID: 19570573 DOI: 10.1016/S0140-6736(09)60551-1]

82 **Mura M**, Porretta MA, Bargagli E, Sergiacomi G, Zompatori M, Sverzellati N, Taglieri A, Mezzasalma F, Rottoli P, Saltini C, Rogliani P. Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study. *Eur Respir J* 2012; **40**: 101-109 [PMID: 22241745 DOI: 10.1183/09031936.00106011]

83 **Ley B**, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, Poletti V, Buccioli M, Elicker BM, Jones KD, King TE, Collard HR. A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Ann Intern Med* 2012; **156**: 684-691 [PMID: 22586007 DOI: 10.7326/0003-4819-156-10-201205150-00004]

84 **Rogliani P**, Mura M, Assunta Porretta M, Saltini C. New perspectives in the treatment of idiopathic pulmonary fibrosis. *Ther Adv Respir Dis* 2008; **2**: 75-93 [PMID: 19124361 DOI: 10.1177/1753465808089363]

85 **Raghu G**, Anstrom KJ, King TE, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012; **366**: 1968-1977 [PMID: 22607134 DOI: 10.1056/NEJMoa1113354]

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ORIGINAL ARTICLE

Basic Study

Pulmonary effects of intermittent, seasonal exposure to high concentrations of cotton dust

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Abstract

AIM: To quantify the exposure levels and to assess pulmonary reactions associated with exposure to cotton dust and its biological contaminants.

METHODS: All employees (51 male workers) of a ginning industry as well as 51 referent unexposed subjects from clerical staff of an educational center were investigated. Atmospheric concentrations of cotton dust and bioaerosols were measured. Furthermore, bacterial and fungal genera and species were identified by an expert microbiologist and an experienced mycologist. A standard respiratory symptom questionnaire was filled out for the subjects and they underwent multiple spirometry tests, at the beginning and at the end of work season as well as prior to (pre-exposure base line values) and at end of the first shift of workweek (post exposure).

RESULTS: Gram negative bacteria including *Enterobacter agglomerans* and *Pseudomonas spp*. were found to be the dominant bacterial species and genera, respectively. Similarly, dominant fungi were identified to

be *Mucor* sp. *Rhizopus* sp. and *Aspergillus niger*. Mean atmospheric concentrations of cotton dust in ginning and outdoor areas were found to be 35.2 and 6.8 mg/m^3, respectively. The prevalence rates of cough, phlegm, wheezing, dyspenea and grade 1/2 byssinosis among the exposed subjects were significantly higher than their corresponding values for the unexposed employees ($P < 0.05$). Additionally, significant differences were noted in the mean baseline value (preshift) of vital capacity, forced expiratory volume in the first second (FEV1)and FEV1/forced vital capacity ratio of the exposed subjects when compared with those of their referent counterparts. Similarly, significant cross shift decrements were noted in most parameters of pulmonary function of the exposed subjects.

CONCLUSION: Seasonal exposure to cotton dust induces both acute, partially reversible, and chronic irreversible decrements in the lungs' functional capacities as well as increased prevalence of respiratory symptoms.

Key words: Cotton dust; Bioaerosols; Byssinosis; Lungs' functional impairments; Respiratory symptoms

Core tip: It is not known whether long term seasonal exposure to high concentrations of cotton dust for a few months per year followed by several months of exposure free period in ginning industry is associated with any pulmonary effects. Findings of the present study indicate that even seasonal exposure to high concentrations of this organic dust is a risk factor for byssinosis manifested by acute partially reversible and chronic irreversible significant decrements in lungs' functional capacities and increased prevalence of respiratory symptoms.

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INTRODUCTION

Cotton dust-induced asthma was first described about 300 years ago. Harvested cotton consists of a mixture of plant materials including leaves, bracts and stems, fiber, bacteria, fungi, and other contaminants[1]. Primarily, lint within unopened cotton bolls is free from any contamination[2]. However, it quickly becomes contaminated with different germs after the bolls open[3]. Endotoxins which originate from gram negative bacteria have been implicated as causal factors in the pathogenesis of byssinosis. Findings of a number of epidemiological and toxicological studies have shown that exposure to bioaersolos has been associated with inflammatory pathogenic pulmonary effects[4-6]. Drummond and Hamlin[7] believe that soil is a major source from which cotton dust bacteria originate. Other potential sources include the seeds, insects, airborne microorganisms and germs which are deposited on the plants by the cultivation. Although it seems that more than one of these could be the reservoir, it won't be possible to ascertain where exactly the organisms which colonize the lint come from before the normal flora of the lint are known. Inhalation of cotton dust from textile mills (and also flax dust and soft hemp dust) produces gradual awareness of chest tightness or difficulty getting air into the chest. This generally occurs three or four hours after entering the cotton textile working area. It is accompanied by shortness of breath during periods of exertion and frequently by cough, usually without phlegm[8,9].

From a clinical point of view, byssinosis is initially manifested by complaints described as chest tightness which is sometimes associated with a continual cough, dyspenea, and wheezing. These symptoms normally occur on the first day of the work week. At early stages of the disease, symptoms occur only occasionally and most often when the humidity is very high (grade 1/2 byssinosis). If exposure continues, symptoms progress to grade Ⅰ byssinosis. At this stage patients complain from chest tightness on most workdays or at least on all first workdays of the week. Several years later, symptoms may progress to grade Ⅱ byssinosis. At this stage, symptoms are present on days other than Monday and they still are generally worse at the beginning of the week, with many patients noting some degree of improvement at the end of the week. Improvement of the symptoms as the week progresses differentiates byssinosis from nonspecific airway reactivity in which symptoms actually worsen as the work week progresses. Symptoms of grade Ⅱ byssinosis are reversible, provided that exposure to dust is entirely eliminated or significantly reduced. Otherwise, they progress to grade Ⅲ byssinosis. Grade Ⅲ byssinosis continues to worsen to the point where it is clinically irreversible. At this stage, significant chronic airway obstruction has developed[10].

Significant variations exist in the prevalence rates of byssinosis in different parts of the world, ranging from about 1% to 50%[11-15]. It is known that washing and steaming of raw cotton significantly decrease the population of bioaerosols and eliminate water soluble chemicals responsible for acute byssinosis. This practice, which significantly reduces the biological activity of byssinosis, explains the low prevalence rate of byssinosis (1.1%) in some countries such as Australia[1].

Additionally, other factors such as differences in the levels and duration of exposure to cotton dust, smoking habits of workers, presence or absence of local exhaust ventilation system in the workplace, and whether employees wear respiratory protective devices[14,16] also may explain, at least in part, why

byssinosis does not have a uniform distribution in the world. While byssinosis has shown a descending trend in recent two decades[11,17,18], it has remained high in developing countries[14,18,19]. The precise mechanisms by which exposure to cotton dust induces byssinosis are not known. However, it has been proposed that bacterial endotoxins, immune-mediated IgE stimulation, non-immunological release of histamine and fungal (*Alternaria tenuis*, *Aspergillus niger* and *Fusarium solani*)[1] proteolytic enzymes may play a role in the pathogenesis of the disease[8,20-23].

Higher prevalence of byssinosis and respiratory symptoms as well as reduced lung functional capacities have been reported in workers who are continuously exposed to high concentrations of cotton dust[15,24-28]. However, it is not known whether the same is true for intermittent, seasonal exposure to cotton dust. Ginning process is a seasonal activity which takes place for a few months per year followed by several months of exposure free period. Whether this long-term intermittent seasonal exposure to cotton dust is associated with any acute and/or chronic changes in the parameters of pulmonary function and the prevalence of respiratory symptoms, is not known. Additionally, it is not clear whether bioaerosols contaminating the cotton are similar in different parts of the world. Darab city in Fars province, south of Iran, is a place where cotton is cultivated and harvested at a relatively large scale and then it is processed in a local ginning industry. To date, no study has been carried out to evaluate respiratory health of the subjects exposed to cotton dust in this local plant, the level of exposure of employees of this industry to cotton dust and its bioaerosol contaminants is not known and the types of the cotton bioaerosols have not been determined.

This study was, therefore, undertaken to address these issues and identify employees with different grades of byssinosis, if any, particularly, those with reversible grades (1/2 and 1) whose progression could be prevented by appropriate interventions.

MATERIALS AND METHODS

Studied population

This cross sectional study was carried out in a local ginning industry in Darab (latitude and longitude 28.7519° N and 54.5444° E, respectively) city in Fars Province, south of Iran. Darab has a generally warm climate reaching 45 Celsius degrees in the summer. Darab's major agricultural products include wheat, citrus fruit, cotton, maize and palm. Cotton is cultivated and harvested at a relatively large scale and then it is processed in a local ginning industry. The studied population consisted of all employees (51 male subjects) of the plant as well as a group of 51 unexposed referent subjects from clerical staff of an educational center. The plant consisted of three separate sections, of feed, ginning and seed separator. The workers were equally distributed in these sections and frequently traveled between them, without wearing any respiratory protective equipment, to perform their duties. In the feed section, cotton is manually fed by the workers to the gin machines where cotton is transferred to a dryer to reduce its moisture and then passes through cleaning equipment for its foreign materials to be removed. In the seed separator section, revolving circular saws pull the lint through closely spaced ribs that prevent the seed from passing through. The lint is removed from the saw teeth by air blasts or rotating brushes, and then compressed into bales. Finally, cotton is stored in a warehouse until it is transferred to a textile mill.

Prevalence of respiratory symptoms

Standard respiratory symptom questionnaires, as suggested by the American Thoracic Society[29], with some additional specific questions for classification of different grades of byssinosis[10], were filled out for both groups. The questionnaire contained questions regarding the employees' job, work history, symptoms and signs of respiratory diseases and smoking habits.

Pulmonary function tests

The parameters of pulmonary function including vital capacity, forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and FEV1/FVC ratio were measured at the beginning of work season (November), at the end of work season (January), prior to first shift of workweek (pre-exposure base line values) and at end of the first shift of workweek (post exposure). Spirometry was performed with a calibrated Vitalogragh (Spiro Analyzer ST-150, Japan) according to the standard method[30], details of which are to be found elsewhere[31]. The mean percentage predicted value was based on the subjects' age, weight, standing height, sex and ethnic group as calculated and adjusted by spirometer device.

Measurement of cotton dust concentrations, fungi and bacteria

In order to determine the atmospheric concentrations of cotton dust, several samples were collected from different parts of the plant and the mean concentrations were expressed in mg/m^3. Samples were collected by SKC personal air sampling pumps equipped with PVC filters (5 μm pores). Pretest experiments showed that the appropriate sampling time and flow rate to avoid overloading of the filters were about 30 min and 2.4 L/min, respectively. To assess the extent to which the workers were exposed to bioaerosols, atmospheric concentrations of bacteria and fungi were determined according to NIOSH method 0800, by a single-stage Anderson sampler using Sabouraud Dextrose agar and blood agar as culture media. Flow rate of sampling pump was 28.3 L/min. Pretest experiments showed that the appropriate sampling time was about 6 min. Bacterial and fungal genera and species were identified by an expert microbiologist and an experienced mycologist. Air temperature, pressure and humidity were also measured during air sampling by a dry bulb

Table 1 Demographic characteristics, smoking habits, and exposure levels of the studied subjects

Variables	Exposed workers (n = 51)	Unexposed subjects (n = 51)
Age (yr)[1]	40.7 ± 11.5[4]	40.2 ± 12.1
Height (cm)[1]	169 ± 4.8[4]	170.3 ± 4.8
Weight (kg)[1]	70.1 ± 9.7[4]	73.5 ± 12.1
Duration of exposure or employment (yr)[1]	10.7 ± 7.8[4]	9.5 ± 5.2
Marital status[2]		
Single	5 (10%)[4]	9 (18%)
Married	46 (90%)[4]	42 (82%)
Smoking[2]		
Yes	31 (61%)[4]	28 (55%)
No	20 (39%)[4]	23 (45%)
Light[3]	21 (41%)[4]	19 (37%)
Heavy	10 (20%)[4]	9 (18%)
Cotton exposure (mg/m^3)		
Ginning section	35.2 ± 11.6	NA
Fed section	14.9 ± 6.2	NA
Seed separator area	18.5 ± 10.1	NA
Outdoor	6.8 ± 4.2	NA

[1]Independent sample T test; [2]χ^2 or Fisher's exact test; [3]Light: < 5 cigarettes per day, heavy: ⩾ 5 cigarettes per day; [4]No significant differences exist between the exposed and unexposed subjects (P > 0.05). NA: Not available.

thermometer, a digital barometer and a whirling hygrometer, respectively.

Statistical analysis

Data were statistically analyzed using t; and χ^2; or Fisher's exact test, where applicable (with a preset probability of P < 0.05). Additionally, using multiple linear regression analysis, the simultaneous effects of confounding variables on the prevalence of respiratory symptoms and changes in the parameters of pulmonary function were evaluated. Mean concentrations of total dust and bioaerosols in different parts of the mill were compared using ANOVA test. The statistical methods of this study were reviewed by a biostatistician and a clinical epidemiologist.

RESULTS

The averages (mean ± SD) of age (year), weight (kg), height (cm), duration of exposure (length of employment for the referent subjects), marital status and smoking habits of the studied population are presented in Table 1. As shown, there were no significant differences between both groups as far as demographic variables and smoking habits were concerned. None of the exposed subjects had a past medical or family history of respiratory illness or any other chest operations or injuries. Likewise, none of the referent subjects had been exposed to cotton dust or other chemicals known to cause respiratory symptoms or ventilatory disorders during the course of their employment or prior to it. The mean concentrations of cotton dust from 17 area air samples collected from different parts of the plant including ginning, seed separator and feed areas were calculated to be 35.2 ± 11.6, 14.9 ± 6.2, and 18.5 ± 10.1 mg/m^3, respectively. The mean outdoor concentration of cotton dust (17 air samples) was 6.8 ± 4.2 mg/m^3. The mean temperature and relative humidity in different parts of the plant were recorded to be as follows: 22.8 ℃ and 40.8%, 21.5 ℃ and 34.7%, 21 ℃ and 34.7%, and 20.7 ℃ and 33.7% for ginning section, seed separator area, feed section and outdoor air, respectively.

Table 2 Frequency (%) of respiratory symptoms in the exposed and unexposed subjects[1] n (%)

Symptoms	Exposed (n = 51)	Unexposed (n = 51)
Cough	19 (37)[b]	2 (4%)
Phlegm	19 (37)[b]	4 (8%)
Productive cough	4 (8)	0
Wheezing during a cold	21 (41)[b]	5 (10%)
Wheezing apart from colds	14 (27)[b]	3 (6%)
Wheezing accompanied by Shortness of breath	7 (14)[d]	0
Shortness of breath	8 (16)[d]	1 (2%)
Byssinosis grade 1/2	9 (17.6)[b]	0
Byssinosis grade Ⅰ	3 (6)	0
Byssinosis grade Ⅱ	2 (4)	0

[1]χ^2 or Fisher's exact test; [b]P < 0.001; [d]P < 0.01.

Isolated bacteria were gram negatives including *Enterobacter agglomerans*, *Pseudomonas spp.*, *Citrobacter freundii*, and *Enterobacter aerogenes*. *Enterobacter agglomerans* and *Pseudomonas spp.* were the dominant species and genera, respectively. Additionally, isolated fungi included *Penicillium*, *Mucor*, *Rhizopus*, *Aspergillus niger*, and *Aspergillus fumigatus* from which *Mucor*, *Rhizopus* and *Aspergillus niger* were the dominant genera and species. Bacterial count indicated that the atmospheric concentrations of bacteria in ginning section, seed separator area, feed section and outdoor were 30045 ± 8117, 6495 ± 1594, 3103 ± 883, and 464 ± 288 CFU/m^3 respectively. Additionally, the concentrations of fungi in the ginning section, seed separator area, feed section, and outdoor were 587 ± 210, 58 ± 21, 393 ± 94 and 33 ± 16 CFU/m^3, respectively. Statistically significant differences were noted among the mean concentrations of bacteria and fungi in different parts of the plant and at the outdoor environment (P < 0.05). There were positive correlations between dust concentration and number of bacterial (r = 0.786) and fungal (r = 0.718) colonies in the work place (P ⩽ 0.0005).

Table 2 shows the frequency of abnormal respiratory findings. As shown, the prevalence of most respiratory symptoms (cough, phlegm, wheezing, shortness of breath, wheezing accompanied by shortness of breath and grade 1/2 byssinosis) in the exposed subjects was significantly higher than those of the referent subjects (P < 0.05). Table 3 exhibits the results of pulmonary function tests (PFTs) before the start of the work season

Table 3 Changes in pulmonary function test parameters of the exposed and unexposed subjects

Parameters	Exposed workers (n = 51)					Referent group (n = 51)
	Preshift[1]	Postshift[1]	End of season[2]	End of shift end of workweek[3]	After 48 h of exposure free period[4]	
VC	78.9 ± 16.3[b]	76.6 ± 17[d]	73.2 ± 16.6[f]	78.8 ± 16.3[h]	76.1 ± 16.3	85.5 ± 13.5
FVC	84.8 ± 12.6[b]	85.2 ± 12.9	86.2 ± 16.5	85.5 ± 12.8	84.8 ± 12.6	81 ± 4.4
FEV1	79.7 ± 13.7[b]	78.3 ± 12.4[d]	74.6 ± 13.1[f]	76.7 ± 11.7[h]	79.1 ± 13.7	90.1 ± 10.5
FEV1/FVC	94.1 ± 14.5[b]	89.3 ± 20.2	89.3 ± 20.2	90.6 ± 12[h]	94.1 ± 14.5	107.6 ± 14.5

[1]At the beginning of work season (prior to and end of first shift of workweek); [2]At end of the work season; [3]At end of shift at end of workweek; [4]48 h after exposure ceased; [b]$P < 0.05$ *vs* the referent group; [d]$P < 0.05$ *vs* preshift; [f]$P < 0.05$ *vs* preshift; [h]$P < 0.05$ *vs* after 48 h of exposure free period. VC: Vital capacity; FVC: Forced vital capacity; FEV: Forced expiratory volume.

Table 4 Association between exposure to cotton dust and duration of exposure with changes in the pulmonary function test parameters[1] (n = 51)

Period of time	Parameters	Independent variable	Adjusted R^2	β
At the beginning of work season	VC[b]	Duration of exposure	0.23	-0.5
	FVC[b]		0.4	-0.65
	FEV_1[b]		0.21	-0.48
	FEV_1/FVC[d]		0.16	0.42
During the work shift	FVC[a]	Duration of exposure	0.06	-0.28
During the work shift	FEV_1[d]	Dust concentration	0.14	0.4
During the work season	VC[d]	Dust concentration	0.1	0.4
	FVC[d]		0.1	0.32
	FEV_1[a]		0.06	0.28

[1]Multiple linear regression analysis; [b]$P < 0.001$; [d]$P < 0.01$; [a]$P < 0.05$. VC: Vital capacity; FVC: Forced vital capacity; FEV: Forced expiratory volume.

Table 5 Comparison of the subjects with normal spirogram, possibly restrictive, obstructive or mixed pattern for both groups[1]

Period of time		Spirogram pattern n (%)			
		Normal	Restrictive	Obstructive	Mixed
Before exposure, at the start of the work season	Exposed	40 (87.4)	6 (11.8)	5 (9.8)	0
	Unexposed	45 (88.2)	4 (7.8)	2 (3.9)	0
After exposure, at the start of the work season	Exposed	39 (76.5)	4 (7.8)	8 (15.7)	0
	Unexposed	45 (88.2)	4 (7.8)	2 (3.9)	0
At the end of the work season[2]	Exposed	27 (53)	6 (11.8)	18 (35.3)	0
	Unexposed	45 (88.2)	4 (7.8)	2 (3.9)	0

[1]χ^2 or Fisher's exact test; [2]significant difference exists between the exposed and unexposed groups ($P < 0.001$).

(following an eight-month exposure-free period), cross shift and seasonal changes as well as changes in PFTs after a temporary short time (48 h) exposure free period. As shown, base line values of PFTs of the exposed subjects were significantly lower than those of the referent subjects. Additionally, further significant cross shift and seasonal decrements observed after exposure to cotton dust. However, a relative and partial recovery was also noted after a brief, 48 h, exposure free period. Similarly, cross shift changes showed that a significant number of the workers (51%) experienced 5% or more decline in FEV1 value. Stratification for smoking yielded similar results (for the sake of clarity data were not shown).

Association between cotton dust concentration and duration of exposure with the changes in the parameters of pulmonary function is displayed in Table 4. Multiple linear regression analysis including variables of age, weight, height, smoking habits, and marital status in the model showed that after adjusting for these important confounders, there were statistically significant associations between exposure to cotton dust and duration of exposure with lung function parameters at the beginning of the season, during the work shift and during the work season. Table 5 shows the proportion of the subjects with normal and impaired spirometry results. As shown, at the end of the work season, a significantly higher proportion of the exposed subjects had abnormal spirometry results.

DISCUSSION

This study was conducted to ascertain whether seasonal intermittent exposure to cotton dust and its bioaerosol contaminants for a couple of months per year, followed by several months of exposure free period, is associated with any symptoms of respiratory disease and/or any acute and /or chronic ventilatory disorders, over years.

Additionally, it aimed to assess the extent to which employees were exposed to cotton dust and bioaerosols and identify and characterize the predominant germs.

Given the data provided, it was evident that seasonal exposure to high concentrations of cotton dust increases the prevalence rates of respiratory symptoms and grade 1/2 byssinosis when compared with the corresponding values of the unexposed referent group (Table 2). Similarly, the base line values of all parameters of pulmonary function of the exposed employees (values at the beginning of work season prior to exposure) were shown to be significantly lower than those of the referent subjects (Table 3) indicating that, under the exposure scenario explained in this study, even seasonal exposure to cotton dust, over years, may induce chronic irreversible ventilatory disorders. Moreover, additional significant cross shift and end of season decrements were noted in most parameters of pulmonary function of the exposed employees. However, a relative, but significant, recovery was also evident in the spirograms of the exposed employees following a short (48 h) exposure-free period (Table 3), indicating that exposure to cotton dust is also associated with acute partially reversible changes in the parameters of pulmonary function. Similar findings have been reported by other investigators where acute airway obstruction has been shown as a result of short-term exposure to cotton dust[32,33].

For employees who are covered by OSHA's Cotton Standard (29 CFR 1910.1043), the exposure limits are as follows: 200 $\mu g/m^3$ of cotton dust for yarn manufacturing; 500 $\mu g/m^3$ for textile waste houses; 750 $\mu g/m^3$ for slashing and weaving operations; and 1000 $\mu g/m^3$ for waste recycling and garneting. Operations such as cotton gins and non-textile processing are covered by a different standard (29 CFR 1910.1000). In this standard the PEL is 1 mg/m^3 measured over an eight-hour workday[34]. Dust concentrations in different parts of this plant were much higher than those of similar studies such as those of Jiang *et al*[11], Zuskin *et al*[15], Glindmeyer *et al*[16], Alemu *et al*[25], Fox *et al*[35], Molyneux *et al*[36], and Fishwick *et al*[37].

No significant differences existed between both groups as far as major confounding variables of weight, height, length of employment, number of smokers, and severity of smoking were concerned. Additionally, the subjects were free from past medical or family history of respiratory illnesses or any other chest operations or injuries. Therefore, the findings of the study could not be attributed to these confounding variables, and particularly, to that of the most important potential confounder, smoking. This conclusion is further supported by the results of multiple linear regression analysis where after adjusting for the effects of potential confounders significant associations were present between exposure to cotton dust and changes in lung function parameters (Table 4).

In this study, prevalence of byssinosis was found to be high (27%); this is consistent with the findings of Alemu *et al*[25] (43%), Molyneux *et al*[36] (39%), El Batawi *et al*[26] (52.6%), Awad el Karim *et al*[38] (46%), Woldeyohannes *et al*[39] (43%), Memon *et al*[40] (35.6%), and Nafees *et al*[41] (10.5%). Similarly, the prevalence of respiratory symptoms such as cough (37%), phlegm (37%), productive cough (9%), wheezing (27%), shortness of breath (16%) and wheezing associated with shortness of breath (14%) was quantitatively similar to those reported by others[20,25,42]. Likewise, significant declines in FEV_1values noted in this study were in accord with the observations of Wang *et al*[20], Jiang *et al*[11], Zuskin *et al*[15], Fox *et al*[35], Kamat *et al*[42], and Christiani *et al*[43].

The rate of FEV_1decrement has been proposed as an appropriate parameter to evaluate the effects of exposure to cotton dust. For clinicians, it is essential to determine the association between exposure to cotton dust and decline in FEV_1 and FVC values. The bronchospasm (which is typically reversible at early stages), seen with byssinosis, can be demonstrated by spirometry performed prior to the start of a working shift and again 5 to 6 h later to determine if there has been any diminution in FEV1 value. A 10% decline in FEV_1 is generally considered to be sufficient evidence that a worker is significantly reactive to cotton dust. It is important to note that OSHA considers FEV_1 declines of as little as 5% to be clinically significant. In these cases, OSHA requires that such individuals be placed on a program of increased surveillance[10]. In the present study, a significant number of the workers (51%) experienced 5% or more decline in FEV1.

More than one third (35.3%) of the employees, at the end of the work season, had a spirometric pattern consistent with that of obstructive ventilatory disorders (Table 5) because in obstructive ventilatory disorders FVC is either normal or increased, but the hallmark is a decreased FEV_1. Therefore, the ratio of FEV_1/FVC is characteristically decreased[44]. This is consistent with the mechanism of respiratory effects of exposure to cotton dust[11,20,43]. Given the reversible nature of byssinosis and other respiratory disorders and symptoms at the early stages, susceptible individuals should be identified and placed under increased surveillance and their exposure to cotton dust should be eliminated or significantly reduced. Moreover, the high prevalence of respiratory symptoms and disorders noted in this study deserve serious attention.

Different genera and species of gram negative bacteria (*Enterobacter agglomerans*, *Pseudomonas spp.*, *Citrobacter freundii*, and *Enterobacter aerogenes*) and fungi (*Penicillium*, *Mucor*, *Rhizopus*, *Aspergillus niger* and *Aspergillus fumigatus*) were isolated and identified. While some investigators have suggested that similar organisms are harbored on lint from cotton grown and harvested from different parts of United States, and other countries[45], others[46] believe that these may vary from one sample to another, and a large number of samples would be required to establish a valid generalization regarding the types of

bacteria commonly present. Rylander and Lundholm[47] examined the bacterial contamination of various parts of the cotton plant as well as the baled cotton in several textile mills. They found that the predominant bacterial species were *Enterobacter agglomerans*, *Pseudomonas syringae* and *Agrobacterium spp.* which were found in about 60% of the cotton samples. They reported that waste cotton from carding machines contained up to 10^8 bacteria/g and that occasionally up to 50% of them were gram positive. They also examined raw cotton plant parts and cotton from blending machines and isolated gram-negative microorganisms such as *Enterobacter agglomerans*, *Pseudomonas syringae*, *Agrobacterium*, and occasionally klebsiella, *Enterobacter cloacae*, *Acinetabacter*, *Flavobacterium*, and other *Pseudomonas*. Furthermore, the most widely isolated fungi were several species of *Aspergillus*[47]. Air borne respirable fungal species of cotton mills were listed by Fischer[48]. Aspergillus species including niger, glaucus, and versicolor, *Penicillium*, *Hormodendrum*, *Fusarium*, *Alternaria*, and occasionally *Rhizopus* were the most isolated germs.

Our findings are qualitatively compatible with those of other studies in which most contaminants of cotton dust were reported to be gram negative bacteria[2,3,47]. However, quantitatively, airborne concentrations of bacteria and fungi in this study were lower than those of Cinkotai *et al*[49], Lacey *et al*[50], and Tuffnell *et al*[51]. This is presumably due to unfavorable climate conditions for rapid growth of bacteria and fungi (lower ambient temperatures and relative humidity in our studied plant over the course of study in the winter). Additionally, fungal and bacterial contaminants of the cotton dust at species level were not necessarily similar to those reported from elsewhere of the world.

Inherent limitations of cross sectional studies such as the present study do not allow a cause and effect relationship to be established. Therefore, it may be argued that significant increases in the prevalence of respiratory symptoms and decrements in the lungs' functional capacities could not necessarily be linked with exposure to cotton dust. While true, it should none the less be noted that a few lines of circumstantial evidence indicate that these are very likely to be the direct consequence of exposure to cotton dust and its biological contaminants. First, none of the exposed employees had any history of respiratory disorders or preexisting medical conditions at the beginning of their employment in the plant or prior to it. Second, the exposed individuals, apart from cotton dust, did not have any exposure to chemical agents known to be pulmonotoxic during the course of their employment in the plant or prior to it. Third, the prevalence of respiratory symptoms was significantly higher in the exposed workers than in the unexposed population. Fourth, although the exposed subjects performed better in their pre-shift spirometry test (the test was conducted after a 48 h exposure free period), the difference between the exposed and unexposed groups remained statistically significant. Fifth, after adjusting for potential confounders significant associations were noted between exposure and reduced lungs' functional capacities and increased prevalence of respiratory symptoms. Sixth, base line, end of shift and end of season values of PFTs of the exposed subjects were both significantly lower than those of referent individuals.

In conclusion, the findings of the present study collectively indicate that unprotected long term intermittent seasonal occupational exposure to high concentrations of cotton dust and its contaminating bioaerosols, even for a couple of months per year, can be a risk factor for byssinosis manifested by acute, partially reversible, and chronic irreversible significant decrements in the lungs' functional capacities and increased prevalence of respiratory symptoms. Additionally, while cotton dust was contaminated with gram negative bacteria and fungi, they were not exactly similar to those reported from elsewhere in the world, *Enterobactaer*, *Alternaria tenuis*, *Aspergillus niger* and *Fusarium Solani*[1]. Thus, engineering control measures (replacing of old machines by new ones, work rotation, and installation of local exhaust ventilation systems), administrative measures (work rotation and changing the job of susceptible and reactive individuals), and the use of appropriate respirators are recommended to eliminate or reduce the workers' exposure to this organic dust. Additionally, the exposed workers should be instructed to quit smoking. Active rather than common periodic examinations are recommended to identify reactive workers to cotton dust prior to developing permanent irreversible respiratory disorders. Further, longitudinal, follow up cohort studies with larger sample sizes are required to further substantiate our findings and provide corroborative evidence in favor of the notion that long-term seasonal exposure to high concentrations of cotton dust in ginning industry is associated with byssinosis, similar to continuous exposure to this organic dust in textile industries.

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COMMENTS

Background

Some studies in the textile industry have shown that the prevalence rates of byssinosis and respiratory symptoms in workers who are continuously exposed to cotton dust are very high. Similarly, significant associations between exposure to cotton dust and reduced lung functional capacities have been demonstrated. However, it is not known whether the same is true for intermittent, seasonal exposure to cotton dust. Ginning process is a seasonal activity which takes place for a few months per year followed by several months of exposure free period. Whether this long-term intermittent seasonal exposure to cotton dust is associated with any acute and/or chronic changes in the parameters of pulmonary function and increased prevalence of respiratory symptoms, is not known. Additionally, it is not clear whether bioaerosols

contaminating the cotton are similar in different parts of the world. This study was undertaken to further address these issues.

Innovations and breakthroughs

Interestingly, the findings of our study demonstrate that even seasonal exposure to cotton dust, over years, may induce chronic irreversible ventilatory disorders. Moreover, additional significant cross shift and end of season decrements were noted in most parameters of pulmonary function of the exposed employees. However, a relative, but significant, recovery was also evident in the spirograms of the exposed employees following a short (48 h) exposure-free period, indicating that exposure to cotton dust is also associated with acute partially reversible changes in the parameters of pulmonary function.

Applications

Similar to textile industries, in ginning industries also active rather than common periodic examinations are recommended to identify reactive workers to cotton dust prior to developing permanent irreversible respiratory disorders.

Peer-review

The manuscript is well written. The aims are well spelt out and the methodology is sound. The results are also well tabulated and described followed by adequate interpretations of the findings in the Discussion.

REFERENCES

1 **Baxter PJ,** Aw T-C, Cockcroft A, Durrington P, Harrington JM. Hunter's diseases of occupations: CRC Press, 2010
2 **DeLucca AJ**, Palmgren MS. Mesophilic microorganisms and endotoxin levels on developing cotton plants. *Am Ind Hyg Assoc J* 1986; **47**: 437-442 [PMID: 3751893]
3 **Heintz CE,** Fisher JJ, Brashears A, editors. Viable counts of bacteria on cotton grown in Lubbock, Texas in 1986. Cotton dust: proceedings of the Twelfth Cotton Dust Research Conference, beltwide cotton research conferences, New Orleans, LA, January 6-7, 1988/proc of Endotoxin Inhalation Workshop, Clearwater, FL, Sept 28-30, 1987; 1988
4 **Jahangiri M**, Neghab M, Nasiri G, Aghabeigi M, Khademian V, Rostami R, Kargar V, Rasooli J. Respiratory disorders associated with occupational inhalational exposure to bioaerosols among wastewater treatment workers of petrochemical complexes. *Int J Occup Environ Med* 2015; **6**: 41-49 [PMID: 25588225]
5 **Lavoie J,** Dunkerley CJ. Assessing waste collectors' exposure to bioaerosols. *Aerobiologia* 2002; **18:** 277-285 [DOI: 10.1023/A: 1021381826042]
6 **Eduard W**, Heederik D, Duchaine C, Green BJ. Bioaerosol exposure assessment in the workplace: the past, present and recent advances. *J Environ Monit* 2012; **14**: 334-339 [PMID: 22267210 DOI: 10.1039/C2EM10717A]
7 **Drummond DG**, Hamlin M. Airborne bacteria in cotton mills. I. Survey of counts of viable bacteria. *Br J Ind Med* 1952; **9**: 309-311 [PMID: 12987585]
8 **Rom WN,** Markowitz SB. Environmental and occupational medicine: Lippincott Williams & Wilkins, 2007
9 **Kleinerman J,** Bardana E, Battigelli M, Fornes R, Hershl S, Hitchcock M, Kilburn KH, McCormick JP, Marey PR, Pratt PC, Weill H, Willoughby WF. Byssinosis: clinical and research issues. National Academy Press, Washington, DC, 1982
10 **Greenberg MI.** Occupational, industrial, and environmental toxicology: Elsevier Health Sciences, 2003
11 **Jiang CQ**, Lam TH, Kong C, Cui CA, Huang HK, Chen DC, He JM, Xian PZ, Chen YH. Byssinosis in Guangzhou, China. *Occup Environ Med* 1995; **52**: 268-272 [PMID: 7795743 DOI: 10.1136/oem.52.4.268]
12 **Schilling RS**, Hughes JP, Dingwall-Fordyce I, Gilson JC. An epidemiological study of byssinosis among Lancashire cotton workers. *Br J Ind Med* 1955; **12**: 217-227 [PMID: 13240025 DOI: 10.1136/oem.12.3.217]
13 **Baratawidjaja K**. Byssinosis study among 250 textile mill workers in Jakarta. *Am J Ind Med* 1990; **17**: 71-72 [PMID: 2305795 DOI: 10.1002/ajim.4700170117]
14 **Dube KJ**, Ingale LT, Ingle ST. Respiratory impairment in cotton-ginning workers exposed to cotton dust. *Int J Occup Saf Ergon* 2013; **19**: 551-560 [PMID: 24321634]
15 **Zuskin E**, Ivankovic D, Schachter EN, Witek TJ. A ten-year follow-up study of cotton textile workers. *Am Rev Respir Dis* 1991; **143**: 301-305 [PMID: 1990943 DOI: 10.1164/ajrccm/143.2.30]
16 **Glindmeyer HW**, Lefante JJ, Jones RN, Rando RJ, Abdel Kader HM, Weill H. Exposure-related declines in the lung function of cotton textile workers. Relationship to current workplace standards. *Am Rev Respir Dis* 1991; **144**: 675-683 [PMID: 1892310 DOI: 10.1164/ajrccm/144.3_Pt_1.675]
17 **McL Niven R**, Pickering CA. Byssinosis: a review. *Thorax* 1996; **51**: 632-637 [PMID: 8693449]
18 **Altin R**, Ozkurt S, Fisekçi F, Cimrin AH, Zencir M, Sevinc C. Prevalence of byssinosis and respiratory symptoms among cotton mill workers. *Respiration* 2002; **69**: 52-56 [PMID: 11844963 DOI: 10.1159/000049370]
19 **Su YM**, Su JR, Sheu JY, Loh CH, Liou SH. Additive effect of smoking and cotton dust exposure on respiratory symptoms and pulmonary function of cotton textile workers. *Ind Health* 2003; **41**: 109-115 [PMID: 12725471 DOI: 10.2486/indhealth.41.109]
20 **Wang XR**, Eisen EA, Zhang HX, Sun BX, Dai HL, Pan LD, Wegman DH, Olenchock SA, Christiani DC. Respiratory symptoms and cotton dust exposure; results of a 15 year follow up observation. *Occup Environ Med* 2003; **60**: 935-941 [PMID: 14634185 DOI: 10.1136/oem.60.12.935]
21 **Christiani DC**, Wang XR, Pan LD, Zhang HX, Sun BX, Dai H, Eisen EA, Wegman DH, Olenchock SA. Longitudinal changes in pulmonary function and respiratory symptoms in cotton textile workers. A 15-yr follow-up study. *Am J Respir Crit Care Med* 2001; **163**: 847-853 [PMID: 11282755 DOI: 10.1164/ajrccm.163.4.2006063]
22 **Schachter EN**, Zuskin E, Buck M, Witek TJ, Godbold J, Roy N, Castranova V, Whitmer M, Siegel PD, Bluhm EC. Airway responses to the inhalation of cotton dust and cotton bract extracts. *Respiration* 2006; **73**: 41-47 [PMID: 16179819 DOI: 10.1159/000088354]
23 **Bouhuys A,** Lindell S-E. Release of histamine by cotton dust extracts from human lung tissuein vitro. *Experientia* 1961; **17:** 211-212 [DOI: 10.1007/BF02160619]
24 **Jannet J,** Jeyanthi G. Pulmonary health status of ginning factory women laborers in Tirupur, India. *Indian J Occup EnvironMed* 2006; **10:** 116-120 [DOI: 10.4103/0019-5278.29571]
25 **Alemu K,** Kumie A, Davey G. Byssinosis and other respiratory symptoms among factory workers in Akaki textile factory, Ethiopia. *Ethiop J Health Dev* 2010; **24:** 133-193 [DOI: 10.4314/ejhd.v24i2.62962]
26 **EL Batawi MA**. Byssinosis in the cotton industry of Egypt. *Br J Ind Med* 1962; **19**: 126-130 [PMID: 13875361 DOI: 10.1136/oem.19.2.126]
27 **Wang XR**, Zhang HX, Sun BX, Dai HL, Hang JQ, Eisen EA, Wegman DH, Olenchock SA, Christiani DC. A 20-year follow-up study on chronic respiratory effects of exposure to cotton dust. *Eur Respir J* 2005; **26**: 881-886 [PMID: 16264050 DOI: 10.1183/09031936.05.00125604]
28 **Paudyal P,** Semple S, Ayres J. Respiratory symptoms and lung function in relation to cotton dust and endotoxin exposure in textile workers in Nepal. *Occup and Environ Med* 2011; **68** Suppl 1: A65-A [DOI: 10.1136/oemed-2011-100382.208]
29 **Ferris BG**. Epidemiology Standardization Project (American Thoracic Society). *Am Rev Respir Dis* 1978; **118**: 1-120 [PMID: 742764]
30 **American Thoracic Society.** Standardization of spirometry. *Am J Respir Crit Care Med* 1995; **152:** 1107-1136 [DOI: 10.1164/ajrccm.152.3.7663792]
31 **Neghab M**, Mohraz MH, Hassanzadeh J. Symptoms of respiratory disease and lung functional impairment associated with occupational inhalation exposure to carbon black dust. *J Occup Health* 2011; **53**: 432-438 [PMID: 21996929 DOI: 10.1539/joh.11-0083-OA]

32 **Merchant JA**, Halprin GM, Hudson AR, Kilburn KH, McKenzie WM, Bermanzohn P, Hurst DJ, Hamilton JD, Germino VH. Evaluation before and after exposure--the pattern of physiological response to cotton dust. *Ann N Y Acad Sci* 1974; **221**: 38-43 [PMID: 4522561 DOI: 10.1111/j.1749-6632.1974.tb28196.x]

33 **Rylander R**, Haglind P, Lundholm M. Endotoxin in cotton dust and respiratory function decrement among cotton workers in an experimental cardroom. *Am Rev Respir Dis* 1985; **131**: 209-213 [PMID: 3970452]

34 **Safety O,** Administration H. OSHA safety and health standards. 29 CFR 1910.1000. Occupational Safety and Health Administration, revised 1983; **1**: 444

35 **Fox AJ**, Tombleson JB, Watt A, Wilkie AG. A survey of respiratory disease in cotton operatives. I. Symptoms and ventilation test results. *Br J Ind Med* 1973; **30**: 42-47 [PMID: 4685299 DOI: 10.1136/oem.30.1.42]

36 **Molyneux MK**, Tombleson JB. An epidemiological study of respiratory symptoms in Lancashire mills, 1963-66. *Br J Ind Med* 1970; **27**: 225-234 [PMID: 5448120 DOI: 10.1136/oem.27.3.225]

37 **Fishwick D**, Fletcher AM, Pickering CA, McL Niven R, Faragher EB. Lung function in Lancashire cotton and man made fibre spinning mill operatives. *Occup Environ Med* 1996; **53**: 46-50 [PMID: 8563857 DOI: 10.1136/oem.53.1.46]

38 **Awad el Karim MA**, Osman Y, el Haimi YA. Byssinosis: environmental and respiratory symptoms among textile workers in Sudan. *Int Arch Occup Environ Health* 1986; **57**: 101-108 [PMID: 3949393 DOI: 10.1007/BF00381377]

39 **Woldeyohannes M**, Bergevin Y, Mgeni AY, Theriault G. Respiratory problems among cotton textile mill workers in Ethiopia. *Br J Ind Med* 1991; **48**: 110-115 [PMID: 1998605 DOI: 10.1136/oem.48.2.110]

40 **Memon I**, Panhwar A, Rohra DK, Azam SI, Khan N. Prevalence of byssinosis in spinning and textile workers of Karachi, Pakistan. *Arch Environ Occup Health* 2008; **63**: 137-142 [PMID: 18980877 DOI: 10.3200/AEOH.63.3.137-142]

41 **Nafees AA**, Fatmi Z, Kadir MM, Sathiakumar N. Pattern and predictors for respiratory illnesses and symptoms and lung function among textile workers in Karachi, Pakistan. *Occup Environ Med* 2013; **70**: 99-107 [PMID: 23155188 DOI: 10.1136/oemed-2011-100561]

42 **Kamat SR**, Kamat GR, Salpekar VY, Lobo E. Distinguishing byssinosis from chronic obstructive pulmonary disease. Results of a prospective five-year study of cotton mill workers in India. *Am Rev Respir Dis* 1981; **124**: 31-40 [PMID: 7258817]

43 **Christiani DC**, Ye TT, Wegman DH, Eisen EA, Dai HL, Lu PL. Cotton dust exposure, across-shift drop in FEV1, and five-year change in lung function. *Am J Respir Crit Care Med* 1994; **150**: 1250-1255 [PMID: 7952548 DOI: 10.1164/ajrccm.150.5.7952548]

44 **Kumar V,** Cotran RS, Robbins SL.Basic pathology. 5th ed. Philadelphia: WBSaunders Company, 1997

45 **Fischer J,** Klyberg K, editors. Microbial flora associated with cotton plant parts and the air of cotton mills. Proceedings Beltwide Cotton Production Research Conferences, 1983

46 **Simpson M,** Choper E, Prickett I, editors. Report on the identification of gram-negative bacteria on cotton fiber from two US field locations. Cotton dust: proceedings of the 12th Cotton Dust Research Conference, beltwide cotton research conferences, New Orleans, LA, January 6-7, 1988/proc of Endotoxin Inhalation Workshop, Clearwater, FL, Sept 28-30, 1987, 1988

47 **Rylander R**, Lundholm M. Bacterial contamination of cotton and cotton dust and effects on the lung. *Br J Ind Med* 1978; **35**: 204-207 [PMID: 698133]

48 **Fischer JJ,** editor The microbial composition of cotton dusts, raw cotton lint samples and the air of carding areas in mills. Proceedings of the 3rd Cotton Dust Research Conference National Cotton Council, Memphis, Tenn, 1979

49 **Cinkotai FF**, Whitaker CJ. Airborne bacteria and the prevalence of byssinotic symptoms in 21 cotton spinning mills in Lancashire. *Ann Occup Hyg* 1978; **21**: 239-250 [PMID: 751550 DOI: 10.1093/annhyg/21.3.239]

50 **Lacey J.** The microflora of grain dusts. In: Dosman, J. A., Cotton, D. J. eds., Occupational pulmonary disease: Focus on grain dust and health. Academic, London, 1980: 189-200

51 **Tuffnell P**. The relationship of byssinosis to the bacteria and fungi in the air of textile mills. *Br J Ind Med* 1960; **17**: 304-306 [PMID: 13778564 DOI: 10.1136/oem.17.4.304]

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ORIGINAL ARTICLE

Retrospective Study

Interactions between traffic air pollution and glutathione S-transferase genes on childhood asthma

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Abstract

AIM: To evaluate the role of glutathione S-transferase P1 (*GSTP1*) genetic polymorphisms potentially modifying the association between NO_2 and asthma/wheeze in Taiwanese children.

METHODS: We investigated 3714 schoolchildren in Taiwan Children Health Study from 14 communities. Children's information was measured from questionnaire by parents. The traffic air pollutant was available from Environmental Protection Administration monitoring stations.

RESULTS: A two-stage hierarchical model and a multiple logistic regression model were fitted to estimate the effects of NO_2 exposures and GSTs polymorphisms on the prevalence of asthma and wheeze. Among children with *GSTP1* Ile/Val or Val/Val genotypes, those residing in high-NO_2 communities had significantly increased risks of asthma (OR = 1.76, 95%CI: 1.15-2.70), late-onset asthma (OR = 2.59, 95%CI: 1.24-5.41), active asthma (OR = 1.93, 95%CI: 1.05-3.57), asthma under medication (OR = 2.95, 95%CI: 1.37-6.32) and wheeze (OR = 1.54, 95%CI: 1.09-2.18) when compared with children in low-NO_2 communities. Significant interactions were noted between ambient NO_2 and *GSTP1* on asthma, late-onset asthma, asthma under medication and wheeze (*P* for interaction < 0.05). However, we did

not find any association with polymorphisms in *GSTM1* and *GSTT1*.

CONCLUSION: Children under high traffic air pollution exposure are more susceptible to asthma, especially among those with *GSTP1* Val allele.

Key words: Nitrogen dioxide; *GSTP1*; Asthma; Wheeze; Children

Core tip: Children under high traffic air pollution exposure are more susceptible to asthma, especially among those with glutathione S-transferase P1 (*GSTP1*) Val allele. This relatively common genetic polymorphism thus may play an important role in asthma pathogenesis among children depending on airway oxidative stress generation.

Tsai CH, Su MW, Lee YL. Interactions between traffic air pollution and glutathione S-transferase genes on childhood asthma. *World J Respirol* 2016; 6(1): 33-41 Available from: URL: http://www.wjgnet.com/2218-6255/full/v6/i1/33.htm DOI: http://dx.doi.org/10.5320/wjr.v6.i1.33

INTRODUCTION

The prevalence of childhood asthma/wheeze has been increasing around the world[1-4], potentially leading to increased medical costs and social burden[5]. Asthma is a complex, multifactorial disease that includes a number of environmental and genetic components[6,7]. Although gene-environment interactions are likely to be important in both the etiology and aggravation of asthma in children, few studies have examined the interactive associations between childhood exposure to common air pollutants, such as ambient NO_2, and common genetic polymorphisms that might be involved in asthma susceptibility.

Traffic-related air pollution, such as ambient nitrogen dioxide (NO_2), has been demonstrated to increase risks for childhood asthma[8-10] and bronchitic symptoms[11,12] and results in diminished pulmonary function development[13,14]. NO_2 is a key component of automobile emissions and is frequently used as an indicator of exposure to traffic-related air pollution[9,15]. NO_2 has relatively strong oxidation potential and can lead to pulmonary epithelial cells injury[16,17]. Polymorphisms in antioxidative genes are likely to play important roles in mediating oxidative stress and thus could influence inflammatory response. Members of glutathione S-transferases (GSTs) have been extensively studied for gene-environment interactions, because of their ability to conjugate hazardous reactive oxygen species (ROS) with glutathione, and the high prevalence of variant alleles[18-21].

The Taiwan Children Health Study (TCHS) is a population-based study representing a wide range of environmental factors and genetic susceptibility. TCHS offers an opportunity to investigate the potential contributions of gene-environment interactions to respiratory health. In the present study, we evaluated the role of GSTs genetic polymorphisms as potential modifiers of the association between ambient NO_2 and asthma/wheeze in children.

MATERIALS AND METHODS

Study population

We conducted a population-based survey for children's health in 2007; the study protocol has been described in detail previously[11,22]. The parents or guardians of each participating student provided written informed consent at study entry. Briefly, the TCHS recruited 5082 7th and 8th-grade schoolchildren from 14 diverse communities that were selected with the aim of maximizing the variability and minimizing the correlations of exposures to outdoor pollutants based on historic routine air monitoring data in Taiwan. We excluded 37 subjects with active smoking habits in risk factor determination, due to sample size limitation for stratification analyses. In this analysis, we randomly selected 3714 seventh-grade children to provide buccal cells as the DNA resource for genotyping. The study protocol was approved by the institutional review board (National Taiwan University Hospital Research Ethics Committee).

Questionnaire of asthma phenotypes

The standard questionnaire for childhood exposures and health status was taken home by students and answered by parents or guardians. Children were considered to have asthma if there was a positive answer to the question "Has a doctor ever diagnosed this child as having asthma?" Wheeze was defined as any occurrence of the child's chest sounding wheezy or whistling. Early-onset asthma was defined as age of onset for asthma before 5 years of age. Late-onset asthma was onset after 5 years of age. Active asthma was defined as physician-diagnosed asthma with any asthma-related symptoms or illness in the previous 12 mo. Asthma under medication was defined as use of any inhaled, oral, or intravenous medication in the past 12 mo.

Traffic air pollution and other covariates

The monitoring data of traffic air pollutant, NO_2, are available from 14 Environmental Protection Administration monitoring stations in Taiwan. Concentrations of NO_2 were measured continuously by chemiluminescence and reported hourly. The yearly averaged concentration was calculated from the daily (24-h) NO_2 in each community. We used the annual average of ambient NO_2 levels from 2005 through 2007 to response the

Table 1 Primer and probe sequences for *GSTP1*, *GSTM1* and *GSTT1* genes variants

Gene	Sequence
GSTP1 (Ile105Val)	
Forward primer	5′-CCTGGTGGACATGGTGAATG-3′
Reverse primer	5′-TGCTCACATAGTTGGTGTAGATGA-3′
Prob for Ile allele	5′-(VIC)CTGCAAATACGTCTCC-3′
Prob for Val allele	5′-(6FAM)TGCAAATACATCTCCCT-3′
GSTM1	
Forward primer	5′-GGAAACAAGGTAAAGGAGGAGTGAT-3′
Reverse primer	5′-CAAGAATATGTGGGCTGGAACCT-3′
Prob	5′-ACGTGAAGCAAAACAG-3′
GSTT1	
Forward primer	5′-GTGGTCCCCAAATCAGATGCT-3′
Reverse primer	5′-GCACCCACGGGCTGT-3′
Prob	5′-CCCTGCCCTCACAACC-3′

long-term exposure to traffic air pollution. Community-level NO_2 was classified into low and high groups using a median cutoff. The means of high- and low-NO_2 communities were 22.13-ppb and 13.96-ppb respectively.

Basic demographic data and possible confounding exposures were also collected, including sex, age, grade, community, dampness at home, *in utero* exposures to maternal smoking and environmental tobacco smoke (ETS) at home. Dampness at home was determined as any one of the following: Visible mould or perceived mould odor or perceived wet stamps because of moisture in the ceilings, floors or walls in the house.

DNA collection and genotyping

Genomic DNA was isolated from buccal cells collected on cotton swabs containing oral mucosa using phenol/chloroform extraction method. The glutathione S-transferase P1 (*GSTP1*) Ile105Val, *GSTM1 null* and *GSTT1 null* polymorphisms were detected by real-time polymerase chain reaction using the TaqMan Allelic Discrimination assay on an ABI PRISMTM 7900 Sequence Detector (Applied Biosystems, Foster City, CA). The details of primer and probe sequences are presented in Table 1.

Statistical analysis

We used a mixed model approach to estimate the individual effect of NO_2 for community as a random effect variable. Unconditional multiple logistic regression models were fitted to estimate the individual effects of *GSTP1*, *GSTM1* and *GSTT1* on asthma phenotypes. When considering the effects of the variant *GSTP1* allele, we used dominant, co-dominant and additive models. On the basis of *a priori* consideration, we included age, sex, family income and parental education in all models. If estimates of GSTP1 effects on asthma changed by at least 10% when a covariate was included in the base models, then the covariate was included in the final models. The interaction between ambient NO_2 level and genotype was assessed by adding an interactive term in the logistic regression model, and a likelihood ratio test was used to test its significance.

Two-stage methods were used to correct for between-community variances. In the first step, a logistic regression model was used to estimate the adjusted logit of disease frequency in each of the 14 communities, controlling for individual-level confounders. In the second step, these estimated logits were regressed against the community-specific NO_2 measurements using weights that were inversely proportional to the sum of the between-community variance and the within-community variance of the adjusted logits. The association between levels of traffic-related air pollution and prevalence of asthma phenotypes were graphically presented by plotting NO_2 levels on the X-axis and community-specific adjusted prevalence on the Y-axis. The regression curves were drawn through the community-specific prevalence derived from exponential regression models. All analyses were conducted using SAS software version 9.1 (SAS Institute, Cary, NC, United States).

RESULTS

A total of 3714 children with genotyping data were enrolled in this study, after excluding children with active smoking. The mean age of participants was 12.8 years and all participants were of Han Chinese ethnic origin (Table 2). More than half subjects reported presence of dampness at home, 43.2% had ETS exposure at home, and only 3.8% had maternal smoking exposure during pregnancy. The prevalence rates were 7.8%, 2.6% and 12.0% for lifetime asthma, asthma under medication and wheeze, respectively. The *GSTP1* alleles were in Hardy-Weinberg equilibrium, with 65.5% having the Ile/Ile genotype and 4.0% the Val/Val genotype.

Table 3 showed the main effects for exposure to NO_2, *GSTP1*, *GSTM1* and *GSTT1* genotypes, respectively. After adjustment for potential confounders, ambient NO_2 level tended toward positive associations with all asthma phenotypes, although none of the associations were statistically significant. There were no observed significant genetic effects for any GST polymorphism.

To assess the role of the *GSTP1* gene on the effects of the NO_2 exposure on asthma (Table 4), we fitted models stratifying subjects by their *GSTP1* Ile105Val genotypes. In Ile/Val or Val/Val genotypes, compared with children exposed in low-NO_2 communities, those exposed in high-NO_2 communities had significantly increased risks of asthma (OR = 1.76, 95%CI: 1.15-2.70), late-onset asthma (OR = 2.59, 95%CI: 1.24-5.41), active asthma (OR = 1.93, 95%CI: 1.05-3.57), asthma under medication (OR = 2.95, 95%CI: 1.37-6.32) and wheeze (OR = 1.54, 95%CI: 1.09-2.18). However, there were no significantly associations between NO_2 levels on asthma phenotypes in *GSTP1* Ile/Ile genotypes. We also found significantly interactive effects on asthma, late-onset

Table 2 Selected characteristics for participants in Taiwan children health study *n* (%)

	With genotyping (*n* = 3714)	All eligible participants (*n* = 5045)
Demographic information		
Sex		
Boys	1820 (49.0)	2436 (48.3)
Girls	1894 (51.0)	2609 (51.7)
Age, yr (mean ± SD)	12.8 ± 0.4	12.9 ± 0.6
Parental education, yr[1]		
≤ 12	2301 (62.0)	3176 (63.5)
13-15	734 (19.8)	956 (19.1)
≥ 16	674 (18.2)	873 (17.4)
Gestational age[1]		
Full term	3318 (90.9)	4461 (90.7)
< 4 wk early	236 (6.5)	316 (6.4)
≥ 4 wk early	98 (2.7)	142 (2.9)
Parental history of atopy[1]		
Yes	952 (26.5)	1257 (25.9)
No	2645 (73.5)	3590 (74.1)
Family income[1,2]		
≤ 400000	1233 (35.7)	1751 (37.5)
410000-800000	1402 (40.6)	1844 (39.5)
≥ 810000	822 (23.8)	1072 (23.0)
Number of siblings[1]		
0	346 (9.3)	458 (9.1)
1	1748 (46.9)	2265 (45.0)
2	1229 (33.0)	1697 (33.7)
≥ 3	406 (10.9)	613 (12.2)
Home exposures[1]		
Dampness at home	1915 (51.6)	2610 (51.7)
In utero exposure maternal smoking	141 (3.8)	193 (3.8)
ETS at home	1597 (43.2)	2246 (44.8)
Respiratory outcomes[1]		
Asthma	289 (7.8)	372 (7.4)
Asthma under medication	95 (2.6)	122 (2.4)
Wheeze	443 (12.0)	583 (11.6)
Early-onset asthma	186 (5.2)	239 (4.9)
Late-onset asthma	95 (2.7)	121 (2.5)
Active asthma	136 (3.7)	168 (3.4)
Genetic markers[1]		
GSTP1		
Ile/Ile	2433 (65.5)	
Ile/Val	1132 (30.5)	
Val/Val	149 (4.0)	
GSTM1		
Present	1596 (43.0)	
Null	2118 (57.0)	
GSTT1		
Present	1923 (51.8)	
Null	1791 (48.2)	

[1]Number of subjects do not add up to total N because of missing data; [2]New Taiwan dollars per year ($1 US = $ 33 New Taiwan). ETS: Environmental tobacco smoke.

asthma, asthma under medication and wheeze (*P* for interaction < 0.05). However, there were no significant relationships between NO_2 level and *GSTM1* and *GSTT1* genotypes on asthma and wheeze (Tables 5 and 6).

We also calculated the adjusted community-specific prevalence of asthma and wheeze, stratified by *GSTP1* genotypes (Figure 1). Children with *GSTP1* Val allele had a higher prevalence of asthma if they lived in communities with higher NO_2.

DISCUSSION

In this study, we found that, overall, children exposed to ambient NO_2 level tended toward increased risks on asthma phenotypes. None of the main effects of the various GST genotypes were significant, and neither the *GSTM1* nor *GSTT1 null* polymorphisms showed any significant modifying effect of ambient NO_2 on childhood asthma. However, in children with *GSTP1* Val alleles, those resided in high-NO_2 communities had significantly increased risks of asthma-related diseases.

Although the genetic main effects of GSTs were not significant, *GSTP1* was noted to modify the effects of ambient NO_2 on childhood asthma. In children with *GSTP1* Val alleles, those resided in high-NO_2 communities had significantly increased risks of asthma, late-onset asthma, active asthma, asthma under medication and wheeze.

Age, sex, parental education and family income have been suggested as personal and social confounders for contributing to asthma and wheeze in childhood. Exposure to other residential factors, such as number of siblings, parental atopic history, *in utero* exposures to maternal smoking, ETS exposure at home, dampness at home, gestational age, history of any pets and air cleaner use were also considered in our survey. However, some covariates were not includes in the final model because of less than 10% change in point estimates in the statistical procedures. One strength of this study is that we minimized interference from these confounders by recruiting lifelong non-smokers of similar age at study entry, and adjusting these potential confounders by regression models. An additional strength of the study is that all of the schools were chosen in the vicinity of monitoring stations. Almost all children attending their schools generally lived within walking distance, because the density of middle schools is very high in Taiwan. Children usually spend at least 8 h in schools and there are few air-conditions in classrooms. Outdoor air-pollutants generated by nearby traffic have been reported to readily penetrate indoors[23]. A potential weakness of this study is that we did not have individual exposure measurements for traffic-related air pollutants, but rather relied on air pollution monitoring data to represent both school and home exposure. However, two-stage regressions were used to consider the community-level and individual-level exposure to reduce potential ecological bias.

Although not statistically significant as a main effect, our data suggested that increased exposure to ambient NO_2 was positive related to asthma phenotypes (Table 3). This is consistent with previous studies, where NO_2 levels measured from monitoring stations were reported to be associated with an increased incidence of asthma in a Japan cohort[24] and with wheeze prevalence in United States[25]. Gauderman and coworkers also suggested that residential distance to a freeway and model-based estimates of freeway traffic-

Table 3 Association of ambient NO_2 and glutathione S-transferases genotypes with asthma phenotypes

	Asthma		Early-onset asthma		Late-onset asthma		Active asthma		Asthma under medication		Wheeze	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
NO_2	1.03	(0.80, 1.32)	1.03	(0.76, 1.39)	1.1	(0.72, 1.66)	1.16	(0.82, 1.65)	1.33	(0.87, 2.03)	1.08	(0.88, 1.32)
GSTP1												
Co-dominant model												
Ile/Ile	1		1		1		1		1		1	
Ile/Val	0.98	(0.75, 1.28)	0.99	(0.71, 1.38)	1.01	(0.64, 1.61)	1.01	(0.69, 1.49)	0.94	(0.59, 1.49)	1.03	(0.82, 1.28)
Val/Val	0.80	(0.41, 1.57)	0.50	(0.18, 1.39)	1.47	(0.62, 3.51)	1.07	(0.45, 2.54)	1.30	(0.50, 3.34)	0.99	(0.59, 1.66)
Dominant model												
Ile/Ile	1		1		1		1		1		1	
Ile/Val or Val/Val	0.96	(0.74, 1.24)	0.93	(0.68, 1.29)	1.07	(0.69, 1.66)	1.02	(0.70, 1.48)	0.98	(0.63, 1.52)	1.02	(0.82, 1.27)
Additive model												
Val allele	0.95	(0.76, 1.18)	0.89	(0.67, 1.17)	1.11	(0.78, 1.58)	1.02	(0.75, 1.39)	1.02	(0.71, 1.48)	1.01	(0.85, 1.21)
GSTM1												
Null	0.89	(0.69, 1.13)	0.83	(0.62, 1.13)	0.94	(0.62, 1.43)	0.88	(0.62, 1.26)	0.81	(0.54, 1.23)	0.99	(0.81, 1.22)
GSTT1												
Null	1.18	(0.92, 1.51)	1.29	(0.95, 1.75)	1.04	(0.69, 1.58)	1.43	(1.00, 2.03)	1.47	(0.96, 2.23)	1.16	(0.95, 1.42)

Models are adjusted for age, sex, family income, parental education, parental history of atopy, number of siblings, *in utero* exposures to maternal smoking, environmental tobacco smoke at home, gestational age and dampness at home.

Table 4 Association of ambient NO_2 level with asthma phenotypes, stratified by *GSTP1* genotypes

	GSTP1				*P* for interaction
	Ile/Ile		Ile/Val or Val/Val		
	OR	95%CI	OR	95%CI	
Asthma					
Low NO_2	1		1		0.003
High NO_2	0.78	(0.57, 1.06)	1.76	(1.15, 2.70)	
Early-onset asthma					
Low NO_2	1		1		0.10
High NO_2	0.88	(0.60, 1.29)	1.45	(0.86, 2.47)	
Late-onset asthma					
Low NO_2	1		1		0.01
High NO_2	0.63	(0.37, 1.07)	2.59	(1.24, 5.41)	
Active asthma					
Low NO_2	1		1		0.06
High NO_2	0.89	(0.57, 1.39)	1.93	(1.05, 3.57)	
Asthma under medication					
Low NO_2	1		1		0.02
High NO_2	0.88	(0.52, 1.49)	2.95	(1.37, 6.32)	
Wheeze					
Low NO_2	1		1		0.01
High NO_2	0.90	(0.69, 1.16)	1.54	(1.09, 2.18)	

Models are adjusted for age, sex, family income, parental education, parental history of atopy, number of siblings, *in utero* exposures to maternal smoking, environmental tobacco smoke at home, gestational age and dampness at home.

emission exposure at homes were both associated with the prevalence of childhood asthma[15]. In that study each of the traffic metrics was also correlated with measured concentrations of NO_2, and measured NO_2 was associated with asthma. Other studies with direct residential measurement or with exposure assessment models of ambient NO_2 have generally shown associations with asthma and asthma-related outcomes among children[26,27]. In Taiwan, we have previously reported that the risk of childhood asthma was positively associated with NOx[28] and an increase of 8.79 ppb of ambient NO_2 exposure would result in 80% increase in the prevalence of bronchial symptoms[11]. *In vitro* and experimental human studies have also demonstrated that high concentrations of NO_2 exposure can result in cell damage accompanied by release of cytokines[29] and may lead to an increase in early and late asthmatic response after challenge with house dust mite allergen compared with ordinary air[30]. Although low ambient concentration of NO_2 exposure was usual,

Table 5 Association of ambient NO_2 level with asthma phenotypes, stratified by *GSTM1* genotypes

	GSTM1				*P* for interaction
	Present		Null		
	OR	95%CI	OR	95%CI	
Asthma					
Low NO_2	1		1		0.87
High NO_2	1.11	(0.76, 1.60)	0.98	(0.70, 1.38)	
Early-onset asthma					
Low NO_2	1		1		0.79
High NO_2	1.02	(0.65, 1.59)	1.01	(0.66, 1.54)	
Late-onset asthma					
Low NO_2	1		1		0.68
High NO_2	1.33	(0.71, 2.50)	1.02	(0.58, 1.78)	
Active asthma					
Low NO_2	1		1		0.97
High NO_2	1.18	(0.69, 2.01)	1.16	(0.72, 1.87)	
Asthma under medication					
Low NO_2	1		1		0.61
High NO_2	1.16	(0.62, 2.16)	1.50	(0.84, 2.69)	
Wheeze					
Low NO_2	1		1		0.75
High NO_2	1.05	(0.76, 1.44)	1.10	(0.84, 1.44)	

Models are adjusted for age, sex, family income, parental education, parental history of atopy, number of siblings, *in utero* exposures to maternal smoking, environmental tobacco smoke at home, gestational age and dampness at home.

Table 6 Association of ambient NO_2 level with asthma phenotypes, stratified by *GSTT1* genotypes

	GSTT1				*P* for interaction
	Present		Null		
	OR	95%CI	OR	95%CI	
Asthma					
Low NO_2	1		1		0.96
High NO_2	1.09	(0.76, 1.57)	0.99	(0.70, 1.39)	
Early-onset asthma					
Low NO_2	1		1		0.39
High NO_2	1.29	(0.82, 2.05)	0.87	(0.58, 1.32)	
Late-onset asthma					
Low NO_2	1		1		0.39
High NO_2	0.96	(0.52, 1.75)	1.24	(0.69, 2.24)	
Active asthma					
Low NO_2	1		1		0.66
High NO_2	1.31	(0.76, 2.28)	1.07	(0.67, 1.71)	
Asthma under medication					
Low NO_2	1		1		0.23
High NO_2	1.96	(1.00, 3.84)	1.03	(0.59, 1.79)	
Wheeze					
Low NO_2	1		1		0.33
High NO_2	1.23	(0.91, 1.66)	0.96	(0.73, 1.28)	

Models are adjusted for age, sex, family income, parental education, parental history of atopy, number of siblings, *in utero* exposures to maternal smoking, environmental tobacco smoke at home, gestational age and dampness at home.

the adverse effects of NO_2 on respiratory outcomes were still important in epidemiologic studies[8,9,31]. As a whole, these results indicated that exposure to outdoor NO_2 or other freeway-related pollutants was a significant risk factor for childhood asthma.

In the present study, we identified a statistically

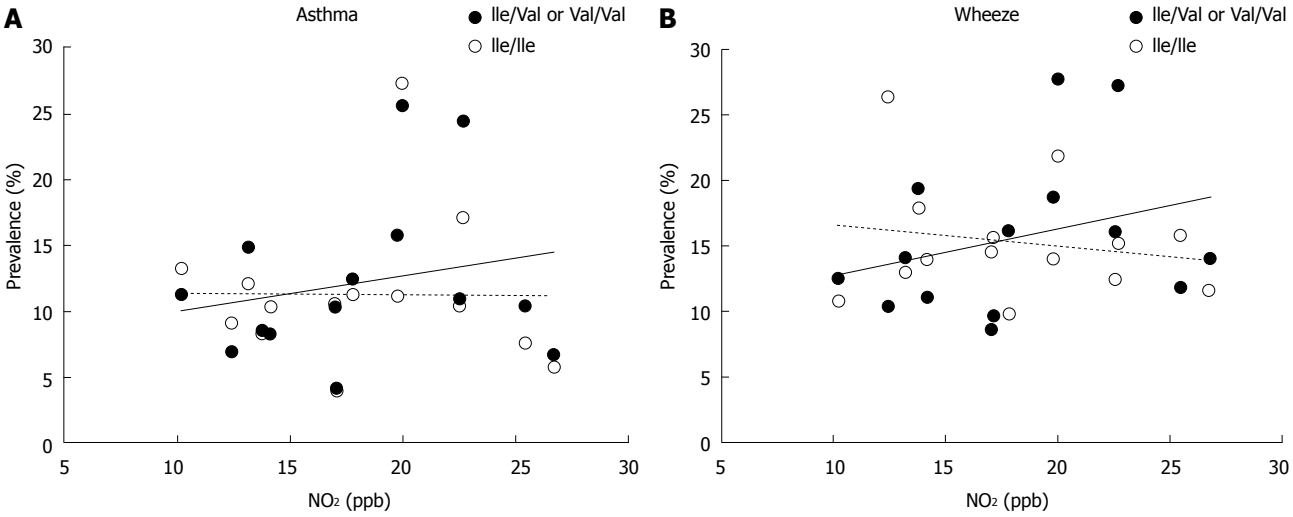

Figure 1 Community-specific prevalence of asthma phenotypes across ambient NO_2 levels, stratified by *GSTP1* genotypes. A: Asthma; B: Wheeze. Solid circles and the solid trend line indicate children with Ile/Val or Val/Val genotypes and hollow circles with the dashed trend line indicate children with Ile/Ile genotype.

significant interactive effect between the *GSTP1* Val allele polymorphism and increased effects of NO_2 on childhood asthma (Table 4). NO_2, a component of ambient air pollution, is an oxidant gas and could lead to pulmonary epithelial cell injury that contributes to a variety of diseases, including asthma[16,17]. The GSTP1-1 enzyme is a phase Ⅱ enzyme that participates in the eliminate ROS by conjugation with glutathione and thus may be an important tissue defense mechanism against oxidative stress[18]. GSTP1 is the most common form of GST found in the respiratory tract lining fluid, representing over 90% of total GST-derived enzyme activity in the lung[19,32]. Our results suggested that children carrying *GSTP1* Val allele and who have exposure to high NO_2 levels may be at increased risks of asthma, because the low GST enzyme activity and high NO_2 levels would increase the oxidant stress in airways (Figure 1).

Thus, our study suggests a gene-environment interaction between the *GSTP1* and NO_2 exposure with individual susceptibility to asthma/wheeze in children. Melen and colleagues also reported that children with *GSTP1* Ile/Val or Val/Val genotypes had an increased risk of sensitization to any allergen when exposed to elevated levels of traffic NOx during the first year of life[33]. In a large birth cohort, children carrying *GSTP1* minor alleles may constitute a susceptible population at increased risk of asthma associated with NO_2 exposure[21]. Previous studies reported that *GSTP1* Val/Val genotype and microsomal epoxide hydroxylase (EPHX1) high activity genotype might contribute to the occurrence of childhood asthma, especially among those who lived near major roads or in high-NO_2 communities[34,35]. Castro-Giner *et al*[36] explored the associations between multiple antioxidant-related genetic polymorphisms, NO_2 and asthma. They only found an association with *NQO1* [NAD(P)H: Quinine oxidoreductase], traffic-related air pollution and asthma in adults, but *GSTs* genetic polymorphisms were not significant. The inconsistent results might be the different ethnic populations and differential age groups.

GSTM1 and *GSTT1* genes are two common deletion polymorphisms and they have been related to asthma in children[19,37,38]. Some studies reported that certain subgroups of children with *GSTM1* null genotype were more susceptible to ozone than others[39,40]. However, we did not identify any other studies that have reported significantly interactive effects between *GSTM1*, *GSTT1* and ambient NO_2 among childhood asthma[36], consistent with our findings in this report (Tables 5 and 6).

In conclusion, our data showed that the high prevalence of childhood asthma was associated with high concentrations of ambient NO_2. Among children with *GSTP1* Val alleles, those with high-NO_2 exposure had significantly increased risks of asthma, late-onset asthma, active asthma, asthma under medication and wheeze. This relatively common genetic polymorphism thus may play an important role in asthma pathogenesis among children depending on airway oxidative stress generation.

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COMMENTS

Background

Ambient traffic-related air pollutants, such as nitrogen dioxide (NO_2), have shown adverse respiratory effects in children. Members of glutathione S-transferases (GSTs) have been extensively studied for gene-environment interactions, because of their ability to conjugate hazardous reactive oxygen

species with glutathione. In this study, the authors evaluated the role of *GST* genetic polymorphisms potentially modifying the association between NO_2 and asthma/wheeze in Taiwanese children.

Research frontiers

Few studies have explored the interactive associations between traffic-related air pollution and genetic polymorphisms on childhood asthma. In this study, the authors identified a statistically significant interactive effect between the glutathione S-transferase P1 (*GSTP1*) Val allele polymorphism and increased effects of NO_2 on childhood asthma in Han Chinese population.

Innovations and breakthroughs

The authors found that the high prevalence of childhood asthma was associated with high concentrations of ambient NO_2. Among children with *GSTP1* Val alleles, those with high-NO_2 exposure had significantly increased risks of asthma, late-onset asthma, active asthma, asthma under medication and wheeze. This relatively common genetic polymorphism thus may play an important role in asthma pathogenesis among children depending on airway oxidative stress generation.

Applications

This study suggests that children should avoid ambient NO_2 exposure to decrease risks of asthma phenotypes, specifically those with *GSTP1* Val alleles.

Peer-review

The article clearly demonstrates the interaction between genetics (genetic polymorphism) and the environment (level of NO_2) in the development of asthma.

REFERENCES

1 **Lee YL**, Lin YC, Hwang BF, Guo YL. Changing prevalence of asthma in Taiwanese adolescents: two surveys 6 years apart. *Pediatr Allergy Immunol* 2005; **16**: 157-164 [PMID: 15787874 DOI: 10.1111/j.1399-3038.2005.00211.x]

2 **Maziak W**, Behrens T, Brasky TM, Duhme H, Rzehak P, Weiland SK, Keil U. Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Münster, Germany. *Allergy* 2003; **58**: 572-579 [PMID: 12823113 DOI: 10.1034/j.1398-9995.2003.00161.x]

3 **Yeh KW**, Ou LS, Yao TC, Chen LC, Lee WI, Huang JL. Prevalence and risk factors for early presentation of asthma among preschool children in Taiwan. *Asian Pac J Allergy Immunol* 2011; **29**: 120-126 [PMID: 21980826]

4 **Sears MR**. Trends in the prevalence of asthma. *Chest* 2014; **145**: 219-225 [PMID: 24493506 DOI: 10.1378/chest.13-2059]

5 **Masoli M,** Fabian D, Holt S, Beasley R. Global burden of asthma. Global Initiative for Asthma (GINA) 2004. [accessed 2015 Nov 17]. Available from: URL: http://www.ginasthma.org/local/uploads/files/GINABurdenReport_1.pdf

6 **Romieu I**, Moreno-Macias H, London SJ. Gene by environment interaction and ambient air pollution. *Proc Am Thorac Soc* 2010; **7**: 116-122 [PMID: 20427582 DOI: 10.1513/pats.200909-097RM]

7 **Su MW**, Tung KY, Liang PH, Tsai CH, Kuo NW, Lee YL. Gene-gene and gene-environmental interactions of childhood asthma: a multifactor dimension reduction approach. *PLoS One* 2012; **7**: e30694 [PMID: 22355322 DOI: 10.1371/journal.pone.0030694]

8 **McConnell R**, Islam T, Shankardass K, Jerrett M, Lurmann F, Gilliland F, Gauderman J, Avol E, Künzli N, Yao L, Peters J, Berhane K. Childhood incident asthma and traffic-related air pollution at home and school. *Environ Health Perspect* 2010; **118**: 1021-1026 [PMID: 20371422 DOI: 10.1289/ehp.0901232]

9 **Jerrett M**, Shankardass K, Berhane K, Gauderman WJ, Künzli N, Avol E, Gilliland F, Lurmann F, Molitor JN, Molitor JT, Thomas DC, Peters J, McConnell R. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. *Environ Health Perspect* 2008; **116**: 1433-1438 [PMID: 18941591 DOI: 10.1289/ehp.10968]

10 **Nishimura KK**, Galanter JM, Roth LA, Oh SS, Thakur N, Nguyen EA, Thyne S, Farber HJ, Serebrisky D, Kumar R, Brigino-Buenaventura E, Davis A, LeNoir MA, Meade K, Rodriguez-Cintron W, Avila PC, Borrell LN, Bibbins-Domingo K, Rodriguez-Santana JR, Sen Ś, Lurmann F, Balmes JR, Burchard EG. Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies. *Am J Respir Crit Care Med* 2013; **188**: 309-318 [PMID: 23750510 DOI: 10.1164/rccm.201302-0264OC]

11 **Hwang BF**, Lee YL. Air pollution and prevalence of bronchitic symptoms among children in Taiwan. *Chest* 2010; **138**: 956-964 [PMID: 20299625 DOI: 10.1378/chest.09-2600]

12 **Kim JJ**, Smorodinsky S, Lipsett M, Singer BC, Hodgson AT, Ostro B. Traffic-related air pollution near busy roads: the East Bay Children's Respiratory Health Study. *Am J Respir Crit Care Med* 2004; **170**: 520-526 [PMID: 15184208 DOI: 10.1164/rccm.200403-281OC]

13 **Gauderman WJ**, Vora H, McConnell R, Berhane K, Gilliland F, Thomas D, Lurmann F, Avol E, Kunzli N, Jerrett M, Peters J. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet* 2007; **369**: 571-577 [PMID: 17307103 DOI: 10.1016/S0140-6736(07)60037-3]

14 **Lee YL**, Wang WH, Lu CW, Lin YH, Hwang BF. Effects of ambient air pollution on pulmonary function among schoolchildren. *Int J Hyg Environ Health* 2011; **214**: 369-375 [PMID: 21680243 DOI: 10.1016/j.ijheh.2011.05.004]

15 **Gauderman WJ**, Avol E, Lurmann F, Kuenzli N, Gilliland F, Peters J, McConnell R. Childhood asthma and exposure to traffic and nitrogen dioxide. *Epidemiology* 2005; **16**: 737-743 [PMID: 16222162 DOI: 10.1097/01.ede.0000181308.51440.75]

16 **Persinger RL**, Poynter ME, Ckless K, Janssen-Heininger YM. Molecular mechanisms of nitrogen dioxide induced epithelial injury in the lung. *Mol Cell Biochem* 2002; **234-235**: 71-80 [PMID: 12162462 DOI: 10.1023/A: 1015973530559]

17 **Shima M**, Adachi M. Effect of outdoor and indoor nitrogen dioxide on respiratory symptoms in schoolchildren. *Int J Epidemiol* 2000; **29**: 862-870 [PMID: 11034970 DOI: 10.1093/ije/29.5.862]

18 **McCunney RJ**. Asthma, genes, and air pollution. *J Occup Environ Med* 2005; **47**: 1285-1291 [PMID: 16340710 DOI: 10.1097/01.jom.0000188561.75578.bf]

19 **Lee YL**, Hsiue TR, Lee YC, Lin YC, Guo YL. The association between glutathione S-transferase P1, M1 polymorphisms and asthma in Taiwanese schoolchildren. *Chest* 2005; **128**: 1156-1162 [PMID: 16162701 DOI: 10.1378/chest.128.3.1156]

20 **Su MW**, Tsai CH, Tung KY, Hwang BF, Liang PH, Chiang BL, Yang YH, Lee YL. GSTP1 is a hub gene for gene-air pollution interactions on childhood asthma. *Allergy* 2013; **68**: 1614-1617 [PMID: 24117884 DOI: 10.1111/all.12298]

21 **MacIntyre EA**, Brauer M, Melén E, Bauer CP, Bauer M, Berdel D, Bergström A, Brunekreef B, Chan-Yeung M, Klümper C, Fuertes E, Gehring U, Gref A, Heinrich J, Herbarth O, Kerkhof M, Koppelman GH, Kozyrskyj AL, Pershagen G, Postma DS, Thiering E, Tiesler CM, Carlsten C. GSTP1 and TNF Gene variants and associations between air pollution and incident childhood asthma: the traffic, asthma and genetics (TAG) study. *Environ Health Perspect* 2014; **122**: 418-424 [PMID: 24465030 DOI: 10.1289/ehp.1307459]

22 **Tsai CH**, Huang JH, Hwang BF, Lee YL. Household environmental tobacco smoke and risks of asthma, wheeze and bronchitic symptoms among children in Taiwan. *Respir Res* 2010; **11**: 11 [PMID: 20113468 DOI: 10.1186/1465-9921-11-11]

23 **Partti-Pellinen K**, Marttila O, Ahonen A, Suominen O, Haahtela T. Penetration of nitrogen oxides and particles from outdoor into indoor air and removal of the pollutants through filtration of incoming air. *Indoor Air* 2000; **10**: 126-132 [PMID: 11980102 DOI: 10.1034/j.1600-0668.2000.010002126.x]

24 **Shima M**, Nitta Y, Ando M, Adachi M. Effects of air pollution on the prevalence and incidence of asthma in children. *Arch Environ Health* 2002; **57**: 529-535 [PMID: 12696649 DOI: 10.1080/00039890209602084]

25 **Peters JM**, Avol E, Navidi W, London SJ, Gauderman WJ, Lurmann F, Linn WS, Margolis H, Rappaport E, Gong H,

Thomas DC. A study of twelve Southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity. *Am J Respir Crit Care Med* 1999; **159**: 760-767 [PMID: 10051248 DOI: 10.1164/ajrccm.159.3.9804143]

26 **Nicolai T**, Carr D, Weiland SK, Duhme H, von Ehrenstein O, Wagner C, von Mutius E. Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children. *Eur Respir J* 2003; **21**: 956-963 [PMID: 12797488 DOI: 10.1183/09031936.03.00041103a]

27 **Brauer M**, Hoek G, Van Vliet P, Meliefste K, Fischer PH, Wijga A, Koopman LP, Neijens HJ, Gerritsen J, Kerkhof M, Heinrich J, Bellander T, Brunekreef B. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. *Am J Respir Crit Care Med* 2002; **166**: 1092-1098 [PMID: 12379553 DOI: 10.1164/rccm.200108-007OC]

28 **Hwang BF**, Lee YL, Lin YC, Jaakkola JJ, Guo YL. Traffic related air pollution as a determinant of asthma among Taiwanese school children. *Thorax* 2005; **60**: 467-473 [PMID: 15923246 DOI: 10.1136/thx.2004.033977]

29 **Devalia JL**, Campbell AM, Sapsford RJ, Rusznak C, Quint D, Godard P, Bousquet J, Davies RJ. Effect of nitrogen dioxide on synthesis of inflammatory cytokines expressed by human bronchial epithelial cells in vitro. *Am J Respir Cell Mol Biol* 1993; **9**: 271-278 [PMID: 8398164 DOI: 10.1165/ajrcmb/9.3.271]

30 **Tunnicliffe WS**, Burge PS, Ayres JG. Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. *Lancet* 1994; **344**: 1733-1736 [PMID: 7997002 DOI: 10.1016/S0140-6736(94)92886-X]

31 **Clark NA**, Demers PA, Karr CJ, Koehoorn M, Lencar C, Tamburic L, Brauer M. Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect* 2010; **118**: 284-290 [PMID: 20123607 DOI: 10.1289/ehp.0900916]

32 **Minelli C**, Wei I, Sagoo G, Jarvis D, Shaheen S, Burney P. Interactive effects of antioxidant genes and air pollution on respiratory function and airway disease: a HuGE review. *Am J Epidemiol* 2011; **173**: 603-620 [PMID: 21343247 DOI: 10.1093/aje/kwq403]

33 **Melén E**, Nyberg F, Lindgren CM, Berglind N, Zucchelli M, Nordling E, Hallberg J, Svartengren M, Morgenstern R, Kere J, Bellander T, Wickman M, Pershagen G. Interactions between glutathione S-transferase P1, tumor necrosis factor, and traffic-related air pollution for development of childhood allergic disease. *Environ Health Perspect* 2008; **116**: 1077-1084 [PMID: 18709160 DOI: 10.1289/ehp.11117]

34 **Salam MT**, Lin PC, Avol EL, Gauderman WJ, Gilliland FD. Microsomal epoxide hydrolase, glutathione S-transferase P1, traffic and childhood asthma. *Thorax* 2007; **62**: 1050-1057 [PMID: 17711870 DOI: 10.1136/thx.2007.080127]

35 **Tung KY**, Tsai CH, Lee YL. Microsomal epoxide hydroxylase genotypes/diplotypes, traffic air pollution, and childhood asthma. *Chest* 2011; **139**: 839-848 [PMID: 21183608 DOI: 10.1378/chest.10-2479]

36 **Castro-Giner F**, Künzli N, Jacquemin B, Forsberg B, de Cid R, Sunyer J, Jarvis D, Briggs D, Vienneau D, Norback D, González JR, Guerra S, Janson C, Antó JM, Wjst M, Heinrich J, Estivill X, Kogevinas M. Traffic-related air pollution, oxidative stress genes, and asthma (ECHRS). *Environ Health Perspect* 2009; **117**: 1919-1924 [PMID: 20049212 DOI: 10.1289/ehp.0900589]

37 **Gilliland FD**, Li YF, Saxon A, Diaz-Sanchez D. Effect of glutathione-S-transferase M1 and P1 genotypes on xenobiotic enhancement of allergic responses: randomised, placebo-controlled crossover study. *Lancet* 2004; **363**: 119-125 [PMID: 14726165 DOI: 10.1016/S0140-6736(03)15262-2]

38 **Wang IJ**, Tsai CH, Chen CH, Tung KY, Lee YL. Glutathione S-transferase, incense burning and asthma in children. *Eur Respir J* 2011; **37**: 1371-1377 [PMID: 21109554 DOI: 10.1183/09031936.00137210]

39 **Li YF**, Gauderman WJ, Avol E, Dubeau L, Gilliland FD. Associations of tumor necrosis factor G-308A with childhood asthma and wheezing. *Am J Respir Crit Care Med* 2006; **173**: 970-976 [PMID: 16456144 DOI: 10.1164/rccm.200508-1256OC]

40 **Romieu I**, Ramirez-Aguilar M, Sienra-Monge JJ, Moreno-Macías H, del Rio-Navarro BE, David G, Marzec J, Hernández-Avila M, London S. GSTM1 and GSTP1 and respiratory health in asthmatic children exposed to ozone. *Eur Respir J* 2006; **28**: 953-959 [PMID: 16870661 DOI: 10.1183/09031936.06.00114905]

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ORIGINAL ARTICLE

Observational Study

Multicenter cooperative observational study of idiopathic pulmonary fibrosis with non-small cell lung cancer

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Data sharing statement: Technical appendix. The data analyzed in this study will be shared. It is stored as a Stata dataset readable by Stata 11 or later version. Stata is statistical analysis software developed by Stata Corporation at Texas, United States. The codes and labels of the variables were embedded in the dataset. The dataset was stored with a name of "a_b_back_ipf.dta".

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Abstract

AIM: To research the natural course of idiopathic pulmonary fibrosis (IPF) with advanced non-small cell lung cancer (NSCLC) and the association between acute

exacerbation (AE) of IPF and chemotherapy (CT).

METHODS: From May 2007 through April 2011, 17 CT naive patients with IPF and advanced NSCLC were enrolled. Patients were classified into best supportive care (BSC) group or CT group based on the patient's preference. Patients in the CT group received carboplatin (CBDCA) (AUC 5-6) plus paclitaxel (PTX) (175-200 mg/m^2) on day 1 of each 21-d cycle as first-line therapy.

RESULTS: All patients but one chose the CT group. In the CT group, the objective response rate was 38%. The most frequent toxicity ⩾ grade 3 was neutropenia (88%). Two patients (12.5%) developed AE-IPF. The median progression-free survival, the median survival time and the 1-year survival rate were 4.1 mo, 8.7 mo and 35%, respectively. Second-line CT-related AE and CT-unrelated AE occurred in 2 and 3 patients (1: BSC group; 2: CT group), respectively. Seven (41%) of all patients developed AE-IPF throughout the clinical course, and 6 of 7 patients with AE-IPF died within one month.

CONCLUSION: The incidence of AE-IPF was higher among IPF patients with advanced NSCLC than among those without NSCLC. CBDCA plus PTX regimen was tolerable and effective. However, AE-IPF has a fatal toxicity with or without CT in IPF patients with advanced NSCLC.

Key words: Non-small cell lung cancer; Chemotherapy; Idiopathic pulmonary fibrosis; Acute exacerbation; Best supportive care

Core tip: Acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) has been generally recognized. Little is known, however, about the natural history of IPF and the frequency of AE-IPF with advanced non-small cell lung cancer (NSCLC). We conducted a prospective observational study of IPF with advanced NSCLC for each group of patients receiving chemotherapy or the best supportive care according to the patient's preference for the purpose of excluding a potential selection bias by the treating physicians.

Ebi N, Tokunaga S, Itoh K, Okamoto I, Edakuni N, Fujii S, Watanabe K, Hayashi S, Maeyama T, Nakanishi Y. Multicenter cooperative observational study of idiopathic pulmonary fibrosis with non-small cell lung cancer. *World J Respirol* 2016; 6(1): 42-48 Available from: URL: http://www.wjgnet.com/2218-6255/full/v6/i1/42.htm DOI: http://dx.doi.org/10.5320/wjr.v6.i1.42

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause by progressive worsening of dyspnea and lung function and is associated with a poor prognosis[1]. The association of IPF and lung cancer is well recognized and IPF patients have a higher incidence of lung cancer than the general population, with relative risks of 7 to 14 being reported[2,3]. According to recent observations, acute exacerbation (AE) of IPF has increased in some patients with IPF and occurs in approximately 5%-15% of patients with IPF annually[4-6]. AE-IPF often results in respiratory failure and has a fatal toxicity. The etiology of AE-IPF is unknown, however, chemotherapy (CT) agents are considered to be one of various factors associated with it. There have been only a few retrospective reports demonstrating that patients with lung cancer and IPF have a high risk of developing AE after CT. However, it is unknown how often AE-IPF happens throughout the natural course of IPF with advanced NSCLC and how much the frequency of AE-IPF increases due to CT. Therefore, we conducted a prospective observational study to research the clinical course of IPF with advanced NSCLC and the association between AE-IPF and CT.

MATERIALS AND METHODS

Patient population

Patients with histologically and/or cytologically confirmed NSCLC and histologically or clinically diagnosed IPF were eligible for participation in the study. Each patient had to meet the following criteria: Inoperable clinical stage Ⅲ or Ⅳ, no prior CT, and/or radiotherapy for the primary site, age 20-74 years, Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, estimated life expectancy > 3 mo, adequate organ functions and partial pressure of arterial oxygen (PaO_2) > 60 mmHg. Main exclusion criteria included active concomitant malignancy, symptomatic brain metastasis, heart failure, uncontrolled diabetes mellitus, active infection, and a past history of drug allergy including hypersensitivity for polysorbate 80. The diagnosis of IPF was based on the histologic appearance of usual interstitial pneumonia (UIP) on surgical lung biopsy[1]. In the absence of surgical biopsy, the diagnosis of IPF was made according to the radiologic pattern on high-resolution computed tomography (HRCT) such as predominantly peripheral, subpleural, bibasal reticular abnormalities with honeycomb cysts and other clinical data. Patients with unstable IPF, oxygen inhalation or immunosuppressive drugs such as steroids were excluded. Patients who did not meet a % vital capacity (VC) < 60% of the predicted value, % diffusing capacity for carbon monoxide (DLCO) < 40% of the predicted value or desaturation < 88% during the 6-min walk test (6MWT) as poor prognostic factors[7-9] of patients with IPF were included. The diagnostic criteria for AE-IPF were as follows[10,11]: (1) exacerbation of dyspnea within 1 mo; (2) newly developed diffuse pulmonary opacities on chest CT and/or a chest X-ray; (3) a decrease in PaO_2

Table 1 Patient characteristics

No. of patients	17
Age (yr)	
Median	65
Range	43-74
Sex	
Male	16
Female	1
Performance status	
0	6
1	11
Stage at enrollment	
ⅢA	2
ⅢB	5
Ⅳ	10
Histology	
Adenocarcinoma	11
Squamous cell carcinoma	5
Non-small cell carcinoma	1
Smoking status	
Smoker	16
Non-smoker	1

of more than 10 mmHg under similar conditions; and (4) the absence of heart failure or infectious lung diseases. For the purpose of making the diagnosis of AE-IPF fairly certain, we excluded bacterial pneumonia, pulmonary embolism, and heart failure by physical examination, laboratory and culture findings, or echocardiography as necessary. When the diagnosis of AE-IPF was made, steroid pulse therapy and/or sivelestat sodium were actively administered. In this study, AE related to CT was defined as AE which occurred within three months after final CT. The diagnosis of IPF and AE-IPF in this study was confirmed centrally by three independent respirologists.

This study was performed in accordance with the principles of the Declaration of Helsinki and the good clinical practice guidelines. Written informed consent was obtained from all patients before study entry. This study was approved by our institutional review board and trial document approval was obtained from each participating institution. This study was registered with the UMIN Clinical Trials Registry (ID: UMIN000015929).

Treatment plan

Patients were classified into best supportive care (BSC) group or CT group based on the patient's preference. Patients in the CT group received carboplatin (CBDCA) (AUC 5-6) plus paclitaxel (PTX) (175-200 mg/m^2) every 3 wk up to 6 cycles as first-line therapy unless there was a progression of the disease, an appearance of intolerable toxicity, or a withdrawal of consent. Diphenhydramine, a histamine H2 receptor antagonist and dexamethasone were administered to patients in the CT group as premedication for prophylaxis of hypersensitivity reactions to PTX. No prophylaxis with granulocyte colony-stimulating factors (G-CSF) was designed.

The incidence of AE-IPF as the clinical course of IPF with advanced NSCLC was examined in each group. Regarding first-line CT (CBDCA plus PTX) defined by the protocol, the objective response rate (ORR) were evaluated using the Response Evaluation Criteria in Solid Tumors guidelines[12] and the toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria Version 3.0. Second-line or later CT was not defined by the protocol, however, the incidence of AE-IPF for each CT was recorded. To evaluate AE-IPF, a HRCT scan was performed at least every 2 mo. The relationship between AE-IPF and the parameters, including inflammatory markers and lung function, was compared according to the presence or absence of AE-IPF. An evaluation of the inflammatory markers and the lung function test was conducted every 3 mo.

Statistical analysis

We assessed the incidence of AE-IPF as the clinical course of IPF with advanced NSCLC according to the presence or absence of CT. The associations between AE-IPF and pre-enrollment parameters, including CRP, LDH, KL-6, SP-D, PaO_2, %VC, %DLCO, and desaturation during 6MWT were examined using the Wilcoxon rank-sum test. The progression-free survival (PFS) was defined as the period from the start of CT to an identifiable time for progression. The overall survival (OS) was defined as the period from the entry of this study until death by all causes. Survival curves for the PFS and OS were estimated using the Kaplan-Meier method. The log-rank test was used for the comparison of the survival times. The confidence interval for the response rate was estimated by exact binomial method. All tests were two-tailed and *P* values less than 0.05 were considered to be statistically significant. All statistical analyses were performed using the Stata 11 software program (Stata Corporation, Texas, United States). The statistical analyses were performed by one of the authors (Shoji Tokunaga), an expert biomedical statistician, assuring the standard of biostatistics required for a clinical research.

RESULTS

Patients' characteristics

From May 2007 through April 2011, 17 CT naive patients with IPF and advanced NSCLC were enrolled in this study. All patients but one chose the CT group. Their characteristics are shown in Table 1. All patients were diagnosed with IPF according to the radiologic pattern on HRCT and other clinical data. All patients were eligible and assessed the incidence of AE-IPF and survival. The median age at the time of diagnosis of lung cancer was 65 years; 16 patients were current or former smokers and all of the patients were male. There were 10 patients with stage Ⅳ disease. The most common histologic NSCLC subtype was adenocarcinoma.

Treatment safety and efficacy

All of 16 patients in the CT group were assessable for

Table 2 Main toxicities of chemotherapy

	Grade				Grade
	1	2	3	4	3-4 (%)
Leukopenia	3	8	2	1	19
Neutropenia[1]	0	1	8	6	88
Febrile neutropenia	0	0	1	0	6
Anemia[2]	5	2	3	0	19
Thrombocytopenia	8	3	0	0	0
Neuropathy	8	6	0	0	0
Myalgia	2	0	0	0	0
Anorexia	2	3	0	0	0
AST/ALT elevation	3	3	0	0	0

[1]Seven patients received granulocyte colony-stimulating factors (75 or 100 μg); [2]One patient with grade 3 anemia required a bloo d transfusion.

Table 3 First-line chemotherapy

Tumor response	CT group (n = 16)
Complete response	0
Partial response	6
Stable disease	5
Progressive disease	5
Response rate	38%
(95%CI)	(15%-65%)

CT: Chemotherapy.

toxicity and tumor response. The toxicities of treatment, with the exception of AE-IPF, are summarized in Table 2. Among the hematological toxicities, the most common toxicity was neutropenia. The grade 3 and 4 neutropenia were observed in 8 patients and 6 patients, respectively, although only one patient developed febrile neutropenia. Seven patients received G-CSF (75 or 100 μg). One patient with grade 3 anemia required a blood transfusion. Among the non-hematologic toxicities, the most common toxicity was grade 2 or less peripheral neuropathy. The tumor responses of CBDCA plus PTX are summarized in Table 3. Six patients had partial responses, 5 had stable diseases and 5 had progressive diseases. The ORR was 38% (95%CI: 15%-65%). The median number of treatment cycles administered was 4 (range, 2 to 6) and the average dose administration of CBDCA plus PTX on the first cycle and the total cycles were AUC 5.5/190 mg/m^2 and AUC 5.3/179 mg/m^2, respectively. The reasons for protocol discontinuation, with the exception of AE-IPF, were disease progression (n = 6), second dose reduction (n = 1) and suspected drug-induced pneumonitis (n = 1). The median PFS, the median survival time (MST) and the 1-year survival rate were 4.1 mo, 8.7 mo and 35%, respectively.

Incidence of AE-IPF

Table 4 summarizes the incidence of AE-IPF, which was observed in 7 (41%) of all patients through the clinical course. All patients but one chose the CT group. AE-IPF was observed in one patient in the BSC group and 6 in the CT group. One patient in the BSC group developed AE-IPF 4 mo after the registry and died 2 mo from AE-IPF. Patients in the CT group received CBDCA plus PTX. In cases 1 and 2, AE-IPF developed within 2 mo of receiving final CT. In cases 3 and 4, AE-IPF developed beyond 3 mo of receiving final CT. In cases 5 and 6, AE-IPF developed within one month of receiving second-line CT. AE-IPF occurred in 2 (12.5%) of 16 patients who received first-line CT (CBDCA plus PTX). AE related to second-line CT was observed in 2 patients (1: pemetrexed; 1: docetaxel). In addition, AE unrelated to CT was observed in 3 patients, 1 in the BSC group and 2 in the CT group. Six of 7 patients who developed AE-IPF died of respiratory failure within 1 mo. The MST according to the absence or presence of AE-IPF was 9.0 and 4.2 mo, respectively (Figure 1).

Table 5 shows the relationship between AE-IPF and each pre-enrollment parameter, including CRP, LDH, KL-6, SP-D, PaO_2, %VC, %DLCO, and desaturation during 6MWT. However, none of these factors were associated with the incidence of AE-IPF.

Table 4 Cases of acute exacerbation of idiopathic pulmonary fibrosis

	Period (d)	
	From registry (last chemotherapy) to AE-IPF	From AE-IPF to death
A group (n =1)	136	66
B group (n =16)		
Case 1 CBDCA/PTX 2 cycles	56 (27)	20
Case 2 CBDCA/PTX 2 cycles	77 (47)	16
Case 3 CBDCA/PTX 3 cycles	124 (101)	6
Case 4 CBDCA/PTX 3 cycles	317 (249)	24
Case 5 CBDCA/PTX 3 cycles → 2nd line PEM 1 cycle	83 (12)	18
Case 6 CBDCA/PTX 3 cycles → 2nd line PEM 4 cycles	583 (14)	8

AE: Acute exacerbation; IPF: Idiopathic pulmonary fibrosis; CBDCA: Carboplatin; PTX: Plus paclitaxel; PEM: Pemetrexed; DOC: Docetaxel.

Table 5 Pretreatment parameters based on the presence or absence of an acute exacerbation of idiopathic pulmonary fibrosis

	AE-IPF		
	+ (n = 7)	- (n = 10)	P[1]
CRP (mg/dL)	0.51 (0.14-15.0)	3.43 (0.15-11.1)	0.77
LDH (IU/L)	191 (132-399)	205 (163-969)	0.73
KL-6 (U/mL)	603 (285-1373)	683 (381-2340)	0.56
SP-D (ng/dL)	88.3 (69.1-457)	101 (58.9-139)	1.00
PaO_2 (mmHg)	77.1 (75.0-85.3)	76.8 (69.0-91.7)	0.78
%VC (%)	100.1 (83.7-131.1)	83.6 (68.0-115.7)	0.07
%DLCO (%)	58.9 (49.5-78.3)	65.3 (58.3-92.2)	0.25
6MWT: Minimum SpO_2 (%)	93 (90-98)	93 (90-95)	0.77

Values are expressed as the median (range). [1]Wilcoxon rank-sum test. AE-IPF: Acute exacerbation of idiopathic pulmonary fibrosis; 6MWT: 6-min walk test.

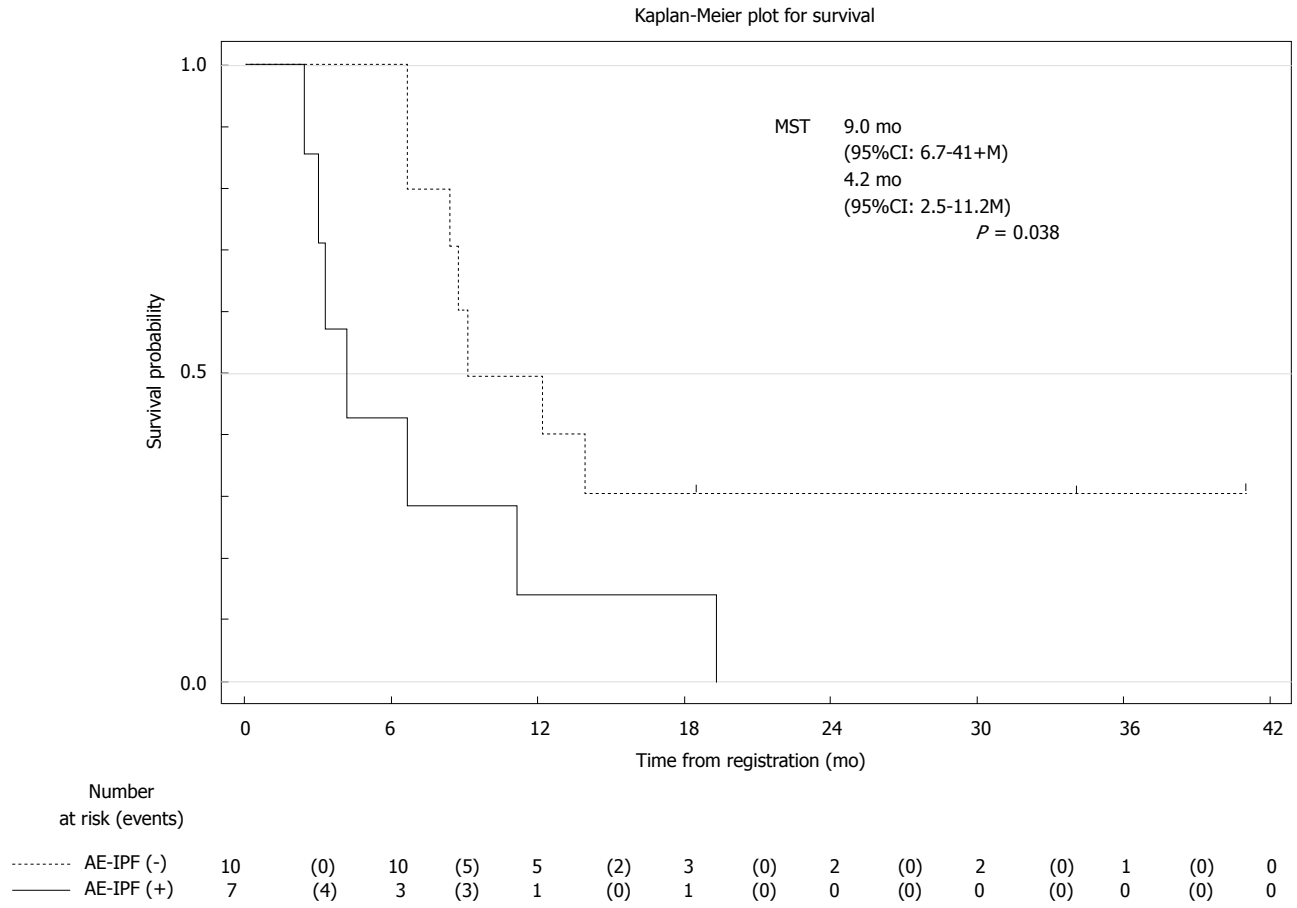

Figure 1 Survival time based on the absence or presence of acute exacerbation of idiopathic pulmonary fibrosis. The median survival time in these subgroups was 9.0 and 4.2 mo, respectively. AE: Acute exacerbation; IPF: Idiopathic pulmonary fibrosis; MST: Median survival time.

DISCUSSION

To the best of our knowledge, this is the first report to prospectively observe the clinical course of IPF with advanced NSCLC. In our study, AE-IPF was observed in 7 (41%) of all patients during the median 18 mo of follow-up. AE-IPF has been recognized as a well-known phenomenon that develops during the natural course of IPF. Recent placebo-controlled studies reported that the incidence of AE during the natural course of IPF was approximately 5%-15% of patients with IPF annually[4,13-15]. There have been few reports concerning AE-IPF following CT. Therefore, we conducted a prospective observational study of IPF with advanced NSCLC for each group of patients receiving CT or the BSC according to the patient's preference for the purpose of excluding a potential selection bias by the treating physicians; we found it difficult to ethically conduct a randomized controlled trial to research the clinical course of IPF with advanced NSCLC and the association between AE-IPF and CT. In fact, all patients but one chose the CT group, despite the explanation of the potential fatal toxicity due to AE-IPF. AE related to CT was defined as AE which occurred within three months after final CT and CT-unrelated AE beyond three months. AE-IPF occurred in 2 (12.5%) of 16 patients who received first-line CT (CBDCA plus PTX). AE related to second-line CT was observed in 2 patients (1: pemetrexed; 1: docetaxel). In addition, AE unrelated to CT was observed in 3 patients, 1 in the BSC group and 2 in the CT group.

Kenmotsu *et al*[16] reported that the incidence of AE related to CT was higher among the patients with a UIP pattern than among those with a non-UIP pattern (30% *vs* 8%), taken from evidence gleaned from the HRCT scans for the diagnosis of IPF; nevertheless, AE related to CT was defined as AE which occurred within four weeks after final CT[16]. A recent prospective study for idiopathic interstitial pneumonias with advanced NSCLC (6 IPF and 12 NSIP patients) showed that the incidences of AE related to first-line (CBDCA plus PTX) and second-line CT were 5.6% and 18%, respectively, and 2 of 6 IPF patients developed AE[17]. The incidence of AE-IPF was higher among IPF patients with advanced NSCLC than among those without NSCLC.

In a Japanese case-controlled study, preexisting ILD was reported to be an independent risk factor for developing AE[18]. The incidence of AE related to treatment is considered to be more than AE unrelated to treatment. Minegishi retrospectively demonstrated that the incidence of AE for patients receiving CT or the BSC was 20.0% and 31.3%, respectively, and the

higher incidence of AE in the BSC group appeared to be dependent on selection bias based on a poor PS[19].

The etiology of AE-IPF is unknown. In this study, the associations between AE-IPF and pre-enrollment parameters, including CRP, LDH, KL-6, SP-D, PaO_2, %VC, %DLCO, and desaturation during 6MWT, which were considered to be markers of IPF progression, were investigated, however no significant differences between patients who did and those who did not develop AE-IPF were observed among these factors. Inflammatory cytokines induced by CT agents, which are considered to be one of the causes of AE, worsen inflammation in the lung tissue[20]. Without CT, lung cancer has been reported to produce inflammatory cytokines[21], thus lung cancer itself may be a risk factor of AE, which might explain the higher incidence of IPF patients with advanced NSCLC.

CBDCA plus PTX is most widely used as a standard regimen for advanced NSCLC. A randomized phase Ⅲ study in Japanese patients without IPF reported that the ORR, median PFS, OS and 1-year survival rate in CBDCA plus PTX, were 32.4%, 4.5 mo, 12.3 mo and 51.0%, respectively[22]. The ORR (38%) and median PFS (4.1 mo) in this study were comparable to Japanese phase Ⅲ study. However, the MST (8.7 mo) and 1-year survival (35%) would be regarded as unsatisfactory for patients without IPF. The results of this study were comparable to the prospective study by Minegishi[17], which demonstrated that the ORR, median PFS, MST and 1-year survival rate were 61%, 5.3 mo, 10.6 mo, and 22%, respectively. The incidence of neutropenia (grade > 3) in our study was higher than the data reported by Minegishi and is likely due to the PTX administration schedule of the PTX plus CBDCA regimen, in which PTX was administered every 3 wk, not weekly. Febrile neutropenia was observed in one patient. Seven patients received G-CSF, which could lead to pulmonary toxicities[23], however, no patients developed AE related to G-CSF. Regarding patients treated with second-line CT, AE occurred in 2 patients (1: pemetrexed; 1: docetaxel) comparable to the report by Kenmotsu *et al*[16]. In this study, 6 of 7 patients who developed AE-IPF died of respiratory failure within one month. AE-IPF has a fatal toxicity with a poor prognosis, as observed in previous reports[5,6].

One major limitation associated with this study was that all patients were diagnosed with IPF and AE-IPF according to evidence from the HRCT scans of the chest and other clinical features. The diagnosis of IPF and AE-IPF in this study was confirmed centrally by three independent respirologists. HRCT findings were consistent with the UIP pattern defined by the international evidence-based guideline on the diagnosis and management of IPF[24]. Another major limitation of this study was the small sample size and that only one patient chose to receive BSC. This study was terminated early due to poor accrual. The association of IPF and lung cancer is well recognized and IPF patients have a higher incidence of lung cancer than the general population. However, a good PS in IPF patients with advanced NSCLC is limited. In the entry criteria of this study, %VC, %DLCO, or desaturation during the 6MWT as poor prognostic factors of patients with IPF were added to PaO_2 as normal pulmonary function to prevent AE-IPF, which might be less easily enrolled. This study was not a randomized controlled trial, thus all patients but one chose CT, despite the explanation of potential fatal toxicity due to AE-IPF. IPF patients with advanced NSCLC and almost good PS did not wish to receive BSC, which we considered to reflect the clinical practice, and thus it was difficult to ethically conduct a randomized controlled trial to compare CT with BSC.

In conclusion, we showed that the incidence of AE-IPF was higher among IPF patients with advanced NSCLC than among those without NSCLC. CBDCA plus PTX regimen was tolerable and effective even for IPF patients. However, AE-IPF has a fatal toxicity with or without regimen in IPF patients with advanced NSCLC. Our understanding of AE-IPF with advanced NSCLC is poor. Further studies are required to establish an optimal treatment plan that is safe and effective for IPF patients with advanced NSCLC.

COMMENTS

Background

Acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) has been generally recognized. Little is known, however, about the natural history of IPF and the frequency of AE-IPF with advanced non-small cell lung cancer (NSCLC).

Research frontiers

The authors aimed to investigate the natural history of IPF with advanced NSCLC and the relationship between AE-IPF and chemotherapy (CT).

Innovations and breakthroughs

This is the first report to prospectively observe the clinical course of IPF with advanced NSCLC.

Applications

IPF patients with advanced NSCLC had a higher AE incidence than those without NSCLC.

Terminology

IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause by progressive worsening of dyspnea and lung function and is associated with a poor prognosis. AE-IPF often results in respiratory failure and has a fatal toxicity. The etiology of AE-IPF is unknown, however, CT agents are considered to be one of various factors associated with it.

Peer-review

This is a well performed study on a relevant subject. The presentation is good, the quality of written English as well.

REFERENCES

1 **American Thoracic Society**. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med* 2000; **161**: 646-664 [PMID: 10673212]

2 **Turner-Warwick M**, Lebowitz M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis and lung cancer. *Thorax* 1980; **35**: 496-499 [PMID: 7434310]

3 **Hubbard R**, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. *Am J Respir Crit Care Med* 2000; **161**: 5-8 [PMID: 10619790]

4 **Azuma A**, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, Taguchi Y, Nagai S, Itoh H, Ohi M, Sato A, Kudoh S. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2005; **171**: 1040-1047 [PMID: 15665326]

5 **Kim DS**, Park JH, Park BK, Lee JS, Nicholson AG, Colby T. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. *Eur Respir J* 2006; **27**: 143-150 [PMID: 16387947]

6 **Collard HR**, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE, Lasky JA, Loyd JE, Noth I, Olman MA, Raghu G, Roman J, Ryu JH, Zisman DA, Hunninghake GW, Colby TV, Egan JJ, Hansell DM, Johkoh T, Kaminski N, Kim DS, Kondoh Y, Lynch DA, Müller-Quernheim J, Myers JL, Nicholson AG, Selman M, Toews GB, Wells AU, Martinez FJ. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007; **176**: 636-643 [PMID: 17585107]

7 **Jezek V**, Fucik J, Michaljanic A, Jezkova L. The prognostic significance of functional tests in cryptogenic fibrosing alveolitis. *Bull Eur Physiopathol Respir* 1980; **16**: 711-720 [PMID: 7448462]

8 **Lama VN**, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, Murray S, Kazerooni EA, Gross BH, Lynch JP, Martinez FJ. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003; **168**: 1084-1090 [PMID: 12917227]

9 **Egan JJ**, Martinez FJ, Wells AU, Williams T. Lung function estimates in idiopathic pulmonary fibrosis: the potential for a simple classification. *Thorax* 2005; **60**: 270-273 [PMID: 15790978]

10 **Kondoh Y**, Taniguchi H, Kawabata Y, Yokoi T, Suzuki K, Takagi K. Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases. *Chest* 1993; **103**: 1808-1812 [PMID: 8404104]

11 **Akira M**, Hamada H, Sakatani M, Kobayashi C, Nishioka M, Yamamoto S. CT findings during phase of accelerated deterioration in patients with idiopathic pulmonary fibrosis. *AJR Am J Roentgenol* 1997; **168**: 79-83 [PMID: 8976924]

12 **Therasse P**, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205-216 [PMID: 10655437]

13 **King TE**, Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, Stähler G, Leconte I, Roux S, Raghu G. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008; **177**: 75-81 [PMID: 17901413]

14 **Taniguchi H**, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, Taguchi Y, Takahashi H, Nakata K, Sato A, Takeuchi M, Raghu G, Kudoh S, Nukiwa T. Pirfenidone in idiopathic pulmonary fibrosis. *Eur Respir J* 2010; **35**: 821-829 [PMID: 19996196 DOI: 10.1183/09031936.00005209]

15 **Richeldi L**, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, Flaherty KR, Noble PW, Raghu G, Brun M, Gupta A, Juhel N, Klüglich M, du Bois RM. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011; **365**: 1079-1087 [PMID: 21992121 DOI: 10.1056/NEJMoa1103690]

16 **Kenmotsu H**, Naito T, Kimura M, Ono A, Shukuya T, Nakamura Y, Tsuya A, Kaira K, Murakami H, Takahashi T, Endo M, Yamamoto N. The risk of cytotoxic chemotherapy-related exacerbation of interstitial lung disease with lung cancer. *J Thorac Oncol* 2011; **6**: 1242-1246 [PMID: 21623239 DOI: 10.1097/JTO.0b013e318216ee6b]

17 **Minegishi Y**, Sudoh J, Kuribayasi H, Mizutani H, Seike M, Azuma A, Yoshimura A, Kudoh S, Gemma A. The safety and efficacy of weekly paclitaxel in combination with carboplatin for advanced non-small cell lung cancer with idiopathic interstitial pneumonias. *Lung Cancer* 2011; **71**: 70-74 [PMID: 20493578 DOI: 10.1016/j.lungcan.2010.04.014]

18 **Kudoh S**, Kato H, Nishiwaki Y, Fukuoka M, Nakata K, Ichinose Y, Tsuboi M, Yokota S, Nakagawa K, Suga M, Jiang H, Itoh Y, Armour A, Watkins C, Higenbottam T, Nyberg F. Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study. *Am J Respir Crit Care Med* 2008; **177**: 1348-1357 [PMID: 18337594 DOI: 10.1164/rccm.200710-1501OC]

19 **Minegishi Y**, Takenaka K, Mizutani H, Sudoh J, Noro R, Okano T, Azuma A, Yoshimura A, Ando M, Tsuboi E, Kudoh S, Gemma A. Exacerbation of idiopathic interstitial pneumonias associated with lung cancer therapy. *Intern Med* 2009; **48**: 665-672 [PMID: 19420811]

20 **Sheppard MN**, Harrison NK. New perspectives on basic mechanisms in lung disease. 1. Lung injury, inflammatory mediators, and fibroblast activation in fibrosing alveolitis. *Thorax* 1992; **47**: 1064-1074 [PMID: 1494772]

21 **Collard HR**, Calfee CS, Wolters PJ, Song JW, Hong SB, Brady S, Ishizaka A, Jones KD, King TE, Matthay MA, Kim DS. Plasma biomarker profiles in acute exacerbation of idiopathic pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol* 2010; **299**: L3-L7 [PMID: 20418386 DOI: 10.1152/ajplung.90637]

22 **Ohe Y**, Ohashi Y, Kubota K, Tamura T, Nakagawa K, Negoro S, Nishiwaki Y, Saijo N, Ariyoshi Y, Fukuoka M. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007; **18**: 317-323 [PMID: 17079694]

23 **Adach K**, Suzuki M, Sugimoto T, Suzuki S, Niki R, Oyama A, Uetsuka K, Nakamaya H, Doi K. Granulocyte colony-stimulating factor exacerbates the acute lung injury and pulmonary fibrosis induced by intratracheal administration of bleomycin in rats. *Exp Toxicol Pathol* 2002; **53**: 501-510 [PMID: 11926293]

24 **Raghu G**, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schünemann HJ. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; **183**: 788-824 [PMID: 21471066 DOI: 10.1164/rccm.2009-040GL]

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