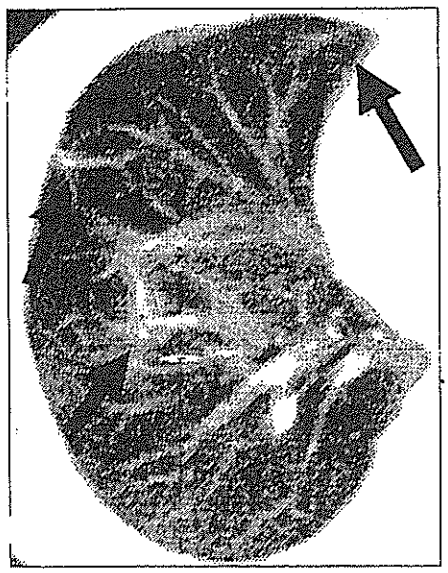
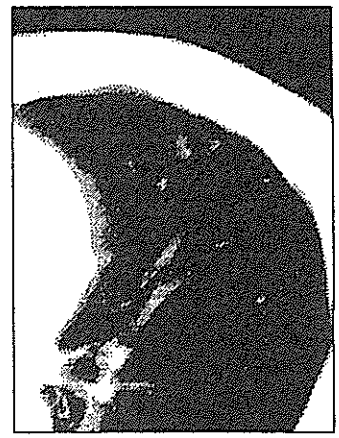
Fig.8 炎症性瘢痕



一方、solid nodule が、炎症性瘢痕と非常に紛らわしいことがある。症例 9[fig.9 a-c]は中分化腺がんの症例である。初回受診時に索状結節を指摘されたが炎症性病変を疑われ放置可とされ、その後の検診画像で縮小したように見えたためやはり炎症性瘢痕と判断された。しかし、翌年の検診で充実成分の増大が認められ、肺がん疑いとして医療機関に紹介され、手術施行され中分化腺がんの確定診断が得られた。1 度縮小した様に見えた原因は定かではないが、可能性としてはＸ線ビームが腫瘍の中心部分に合わなかったために partial volume effect の影響を受け縮小したように見えたものか、あるいは腫瘍に生じた二次性の炎症性変化が実際に消退したために小さく写ったのかなどが考えられる。Part solid nodule の形状を呈するものはがんの可能性が高いことを先に述べたが、こういった場合でも重要な情報は喫煙歴である。現喫煙者の場合では、更にがんの可能性が高まるため積極的な精密検査を考慮すべきである。

Fig.9 中分化腺がん



a;'98/9/1 検診画像

b;'00/1/15 検診画像

c;'01/9/10 検診画像

間質性変化・荷重効果とそこに生じるがん

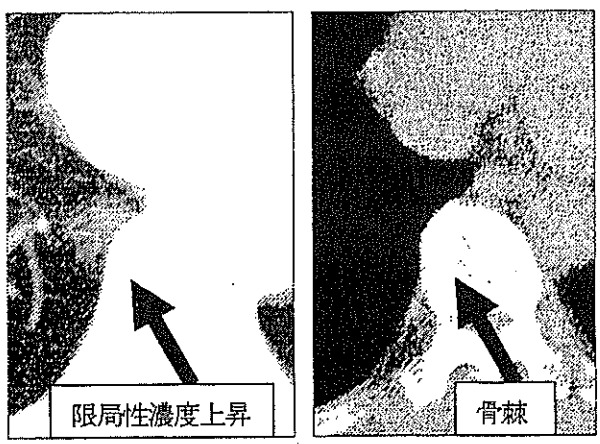
症例 10[fig.10]は荷重効果による、濃度上昇である。仰臥位での撮影では、下肺野背側に重力効果に伴う非特異的な濃度上昇が生じることがある。伏臥位撮影で消失すること

により重力効果と確認されるが通常不要であり、胸膜に沿った境界のぼやけた帯状のほぼ均一の濃度上昇で内部に線維構造が認められないようなものはほとんどこういった非特異的な所見と考えられる。[5]

Fig.10 荷重効果による濃度上昇

また、症例 11[fig.11 a, b]のように椎体右縁に限局性の淡い濃度上昇が見られることがしばしばあり、腫瘍性病変と紛らわしいことがあるが、縦隔条件や骨条件の Window 設定で観察すると、椎体に生じた骨棘が二次的に肺野を圧排し生じた陰影であることが認められる。[6]

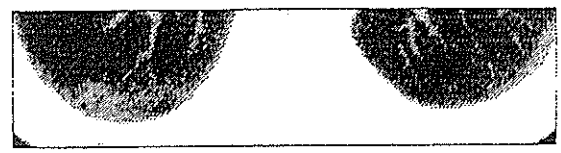
Fig.11 骨棘に関連した限局性濃度上昇



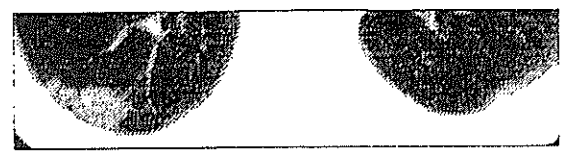
a;肺野条件　b;縦隔条件

一方、繊維性の網目構造が見られる場合は間質性肺炎の疑いがあり、内部の濃度にムラがあるような場合には腫瘍性病変の除外診断が必要となり、注意せねばならない。症例症例 11[fig.12 a-d]は、下肺野背側の間質性肺炎に生じた中分化腺がんと MALT Lymphoma (MALToma)の症例である。間質性肺炎は高率に肺がんを発生し、注意深い観察を必要とする。

Fig.12 中分化腺がんと MALToma



a;'98/8/5 検診画像



b;'01/6/19 検診画像

c;'02/1/21 精検画像右下葉の中分化腺がん

d;'02/7/22 精検画像左下葉の MALToma

【撮影・読影・事後措置での留意点】

胸部CT検診を行うためには、機器の選定や撮影条件、読影方法、診断基準、事後措置、広報、事務手続き、会計などの多く部分で考慮すべき点がある。ここでは撮影・読影・事後措置など運用に関係するような項目[Table 2]についての留意点を簡単に述べる。

Table 2　胸部CT検診の運用上の留意点

項目	留意点
機器	対象に応じた機器選定
	Single or Multidetector-row
撮影	効果的な追加撮影
	習熟した診療放射線技師
観察	上下関係に留意し隈なく観察
	Cine や Paging
読影	先入観なく画像所見を判断
	既知の知見を元に忠実に読影
照合	臨床情報や検査所見と照合
	危険因子や疫学データ
追跡	経時変化を観察
	再検査や次年度検診の勧奨
紹介	連携の取れた医療機関に紹介
	胸部CT検診に習熟した医師
解析	集計・統計データを出す
	データベース管理

機器の選定

近年はMDCT(multidetector-row CT)が胸部CT検診の場にも用いられるようになり、検診時の撮影でこれまでの精密検査に近いような画像を得ることが可能になってきた。しかし、MDCTは未だ高価であるために機器の新規購入や更新の際にMDCTを導入するだけのメリットがあるか否かを十分に判断して導入の是非を考えなくてはならない。

・どのような特性（潜在的にどの程度の肺がんが存在していると推定されているのかなど）をもった、何人の集団（全体で何人、1日あたり何人か）に胸部CT検診を計画しているのか？

・管球の耐久性やその他の検査の流れなどを考慮した上でのスループットは、どの程度なのか？

・その中でどれだけの効果；その優れた画像により発見率の向上や不要な精検の低減がなされるのか？　個人や集団に対してどの程度の被曝低減が期待されるのか？

・膨大なデータを管理するためにPACSの導入も顧慮する必要があるが、それによる読影効率の向上、また過去画像との比較が容易になることやフィルムレスになることのメリットがどの程度期待できるのか？　等を十分吟味する必要がある。

特に当施設のようにこれまで数年に渡りシングルスライスの胸部CT検診を実施している場合では、検査対象者に一通りのscreeningが施行されており、新規に胸部CT検診を受診する人数が見込まれないことや、シングルスライスCTで発見できなかったようなきわめて微小な結節を診断することが可能なのか、といった問題がある。

MDCTはきわめて精密な画像を短時間かつ低被曝で行うことができる。また、三次元表示などの新たな手法により新たな画像診断の可能性や、肺がん以外の冠動脈の石灰化や肺気腫などの診断にも素晴らしい効果を期待できる。現在でも多くの施設がMDCTを導入し様々な報告がなされているが、今後更に多くの知見の蓄積により胸部CT検診におけるMDCTの有効性が明らかになってゆくものと思われる。

追加撮影の重要性

当センタにおいては、シングルスライスの低線量らせんCTを行っており、病院で行われるようなCT検査の画像に比して画質は劣ってしまうことは否めない。存在診断は出来ても質的診断に迫れないため、後日改めてHRCTの再検査が必要になり、受診者さまへの心理的・経済的・時間的負担を強いることになる。この問題を解決するために重要なのは、撮影する診療放射線技師の追加撮影である。撮影時点で何かしら存在が疑われた場合にその場でHRCTを追加することで、問題の陰影がartifactなのか真の結節なのか、がんの特徴を有する結節なのかといったMDCTにも劣らない画像診断が可能となる。

そのためには、胸部CT検診に習熟した診療放射線技師を育成する修練プログラムが必要になってくるであろう。当センタにおいては、毎週1回　精密検査の症例や検診での興味深い症例についての検討会を行っている。これには全読影医と担当の診療放射線技師が参加し、所見の整理や事後措置の決定や医療機関での結果報告を行っている。日々の事例をフィードバックすることは、読影医および診療放射線技師にとって大きな教育効果をもたらすことが期待でき、非常に有効な修練プログラムの一つになるだろう。また、マンモグラフィ検診制度管理中央委員会[4]は、検診マンモグラフィ　読影医師および撮影診療放射線技師・医師認定を行うために、試験を実施しており、こういった仕組みも質の高い胸部CT検診を普及させるために参考になると思われる。[7]

観察方法

大量の画像が発生する検診の場においては、効率よく処理することが重要になり、モニタ診断が有用である。中でも“Cine”や“Paging”と呼ばれる動画のような条件で読影することで、視点の動きが効率よくなるとともに、上下のスライスとの関連がわかりやすくなり、負荷が少なく精度の高い読影が可能となる。

読影に先入観を入れない

読影は非常に複雑な知的業務であり、様々な情報を元に判断の修正を行って、正確な診断にたどり着かねならない。そのためには、以下に示すような手順で読影を進めることが望ましいかと考える。既に胸部CT検診を始めておられる諸兄姉には述べるまでもないが、これから胸部CT検診を始められる方にとって少しでも参考になれば幸いである。

画像の読影をする際の最初の情報は、氏名やID番号（加えて、性別や年齢）など最小限のものにとどめて、1度読影することが望ましいと考える。異常な陰影があった場合には、まず画像から正確に所見を読み取って、それが画像診断として存在するのか、どういう疾患が考えられるのか、どの程度の可能性をもってがんが疑われるのかを判断する。更に、過去画像と比較して経時的変化がないかを注意深く読影してある程度、その症例の診断を想定する。その後、喫煙歴や職歴、既往歴、家族歴、自覚症状、他の検査項目の結果などを参照して、想定した診断にその他の条件が矛盾しないのかを判断をする。

もし、先に臨床情報や他の検査結果を得てしまうと最初から良悪性の目星をつけて読影してしまい、中立的な画像判断が出来なくなってしまうおそれがある。もちろん、がんの普遍的・最新の知見や疫学データなどを把握し、教科書やteaching filmや自施設・学会での検討会などで実際の症例について学習することの必要性はいうまでもない。

なお、女性では初回受診時の肺がん発見率が高くが逐年受診では低下することと、喫煙者男性では経年受診時でも一定のがんの発見率が見られることは多くの施設から報告されており、着目すべき情報である。

事後措置

検診で有意な結節を発見したら、それを後日HRCTにて精検したり、医療機関に紹介したりすることになる。確実に精検率や受診率を上げ　確実に精検結果を把握することは、質の高い胸部CT検診を行ってゆくために重要な事項である。

まず、検診結果を分かりやすく不安を少なく説明し精検や紹介の必要性を十分に伝えて受診の勧奨と確認を行ってゆく。紹介する医療機関としては、胸部CT検診に造詣の深い呼吸器内科医や胸部外科医が望ましいが、診察の結果を確実把握できるように、医療機関と連携結んでゆくことが何よりも重要な事柄だろう。

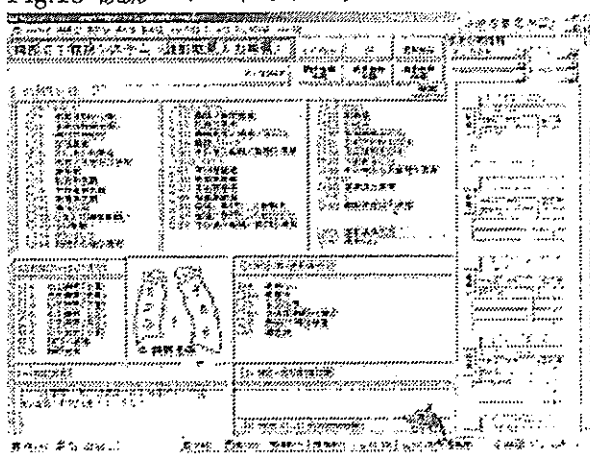
このように、受診者と紹介医療機関と我々胸部CT検診スタッフの繋がりを確固たるものにすることは、医師や受診者のみならず検診業務全体を把握しmanagementする事務系担当者の果たす役目が非常に大きなものと考える。

データ管理

検診で扱う情報は多岐にわたり、それを管理するには、データベースの構築が不可欠である。以下に当センタで使用しているフォーマット[fig.13]を例としてあげる。特徴としては、特別なワークステーションがなくても市販のWINDOWSのコンピュータで作動するように ACSESS　Microsoft で作成されている。効率記録ができるように、個人属性情報は既に自動あるいは事務担当者によって組み込まれた状態になっており、読影結果は基本的にチェックボタンで記録される。詳細な情報を記録するためにフリーコメント欄も用意されている。これにより、1 度入力された読影結果は、次年度での参照が簡便になり読影の際に非常に有用である。このようにデータベースを構築すると、他の検査データなどのデータベースとの関連づけを簡単に行うことが出来、様々な集計や解析が簡便に行えるといった大きなメリットがある。

またデータベース管理するうえでは、データ漏洩を防止する手段を講じることと、バックアップファイルを作成することと、データ改竄が出来ない仕組みを構築するなどに留意しなくてはならない。

Fig.13 読影レポートのシステム



【最後に】

今後も多くの施設が継続的な研究をし、それらを有機的に結び付けることで、胸部 CT 検診の有効性実証の成果をあげることができると確信する。更には、肺がんの発生や COPD・循環器疾患などに対して、喫煙などのリスクファクターがどの程度影響しているのかを明らかにし、そもそも病気を作らないような対策を講じてゆくことも本研究会に科せられる大きな課題である。

文　献

[1] Fraser RS, Pare JAP, Fraser RG, et al: Chapter 1. The normal chest; synopsis of diseases of the chest. 2nd ed, Saunders, Philadelphia, p.1-116, 1994.

[2] 原眞咲, 小田京太, 白木法雄, 他：特集 小さい肺癌をどう診断するか-小さい肺癌と鑑別を要する疾患. 画像診断 vol.21 No.7 2001.

[3] Remy－JardinM, Beuscart R, Sault MC, et al: Subpleural micronodules in diffuse infiltrative lung diseases: evaluation with thin-section CT scans. Radiology 177: 133-139, 1990

[4] 高橋雅士, 九嶋亮治, 井上修平, 他：特集 肺肉芽腫症の画像診断-リンパ腫様肉芽腫症、偽リンパ腫、炎症性偽腫瘍. 画像診断 vol.18 No.8 1998.

[5] 南部敦史：特集　よく見る偽病変／正常変異. 画像診断 vol.24 No.6 2004

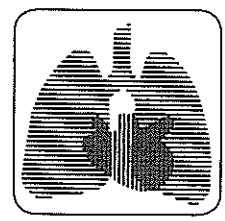
[6] Otake S, Takahashi M, Ishigaki T: Focal pulmonary interstitial opacities adjacent to thoracic spine osteophytes. AJR 179: 893-896, 2002.

[7] 特定非営利活動法人　マンモグラフィ検診制度管理中央委員会：http://www.mammography.jp/

The Natural History of Radiographically Occult Bronchogenic Squamous Cell Carcinoma*

A Retrospective Study of Overdiagnosis Bias

Masami Sato, MD, FCCP; Yasuki Saito, MD; Chiaki Endo, MD; Akira Sakurada, MD; David Feller-Kopman, MD; Armin Ernst, MD, FCCP; and Takashi Kondo, MD



Vol. 126, p. 108-113
July 2004 Issue

Reprinted from CHEST

The Natural History of Radiographically Occult Bronchogenic Squamous Cell Carcinoma*

A Retrospective Study of Overdiagnosis Bias

Masami Sato, MD, FCCP; Yasuki Saito, MD; Chiaki Endo, MD; Akira Sakurada, MD; David Feller-Kopman, MD; Armin Ernst, MD, FCCP; and Takashi Kondo, MD

Objective: **An *overdiagnosis bias* occurs with the diagnosis of a disease that does not produce signs or symptoms before the patient dies from other causes. We sought to determine whether overdiagnosis bias is a factor when screening for squamous cell carcinoma of the lung.**
Design: **Retrospective study of the Miyagi Population-Based Lung Cancer Screening Registry for high-risk patients who were seen between January 1, 1982 (when sputum cytology tests were added for men with long smoking histories), and December 31, 1996.**
Setting: **Miyagi Prefecture, Japan.**
Patients: **A total of 251 patients (all men) who had sputum cytology test results that were positive for squamous cell carcinoma but had normal radiograph findings, 44 of whom declined cancer treatment (mean age, 70 years) and 207 of whom were treated with resection within 12 weeks of diagnosis (mean age, 65.5 year).**
End Points: **Five-year and 10-year survival rates from primary lung cancer in both groups as of August 15, 2001.**
Results: **Among the 44 untreated patients, 15 (34%) remained asymptomatic. The survival rate due to primary lung cancer death in the untreated group was 53.2% at 5 years and 33.5% at 10 years. The survival rate among treated patients was 96.7% at 5 years and 94.9% at 10 years. Of the 125 treated patients who died, 14 (11.2%) died from primary lung cancer.**
Conclusion: **Given that the two thirds of the untreated patients with squamous cell carcinoma of the bronchus died from lung cancer within 10 years, overdiagnosis bias does not appear to be a factor in screening for this disease. Thus, we recommend that patients with radiographically occult squamous cell carcinoma of the bronchus undergo tumor treatment after localization.**
(CHEST 2004; 126:108–113)

Key words: early detection; lead-time bias; lung cancer; mass screening; overdiagnosis bias; sputum cytology; squamous cell carcinoma; tumor localization

Abbreviation: CI = confidence interval

The concept of overdiagnosis, as formulated after the Mayo Lung Project,[1–6] is based on the fact that many patients with slow-growing cancers will likely die of other causes before the cancer produces clinical signs and symptoms. In such cancers, screening programs for the early diagnosis of cancer will produce an *overdiagnosis bias* by diagnosing patients with a cancer that may not need to be treated.

Screening for lung cancer has been thought to be

*From the Department of Thoracic Surgery (Drs. Sato, Endo, Sakurada, and Kondo), Institute of Development, Aging, and Cancer, Tohoku University, Sendai, Japan; the Department of Thoracic Surgery (Dr. Saito), National Sendai Hospital, Sendai, Japan; and the Division of Interventional Pulmonology (Drs. Feller-Kopman and Ernst), Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.
The results of this study were presented at the 10th World Conference on Lung Cancer, Vancouver, BC, Canada, August 14, 2003.
This study was partly supported by grants-in-aid from the Ministry of Education, Science, Sports, and Culture of the Japanese Government.

Manuscript received March 24, 2003; revision accepted January 22, 2004.

Correspondence to: Masami Sato, MD, Department of Thoracic Surgery, Institute of Development, Aging, and Cancer, Tohoku University, 4–1 Seiryo-machi, Aoba-Ku, Sendai 980-8575, Japan; e-mail: m-sato@idac.tohoku.ac.jp

ineffective, and overdiagnosis bias has been used to explain the disappointing results of mass screening programs.[7–14] However, in the late 1990s, the Mayo Lung Project was reevaluated,[9,10,13–17] and some authors have suggested[15,16] the possible usefulness of chest radiography for lung cancer screening.

Knowing the natural course of a disease in untreated patients can be helpful in determining the presence of overdiagnosis bias. Sobue et al[18] reported the course of nonsurgically treated, clinical stage I lung cancer detected by radiography. Including their report, most studies[19,20] have dealt with adenocarcinoma diagnosed from an abnormal shadow on a radiograph. To our knowledge, however, the natural course of radiographically negative squamous cell carcinoma of the lung has not been described. Patients who have cytologic evidence of lung cancer but have normal chest radiographs are thought to be in the early stages of cancer. The introduction of autofluorescence bronchoscopy has made it easy to detect many intraepithelial lesions.[21,22] However, it is not known whether these lesions should be treated or not. Clarifying the natural history of this type of lung cancer could help to determine whether a latent or nonprogressive form of squamous cell carcinoma exists and, in turn, whether this cancer is subject to overdiagnosis bias.

In the United States, lung cancer screening tests are generally administered only to persons with good cardiopulmonary function who can undergo surgical treatment. Japan, however, has a 50-year history of screening for tuberculosis with chest radiography. Everyone is screened because some people remain worried about tuberculosis. As a result, some people with poor cardiopulmonary function in whom cancer is detected may decline cancer treatment. Others may mistake sputum cytology, which became part of the screening program in 1982, as a screening test for tuberculosis and thus may also decline treatment for lung cancer if it is diagnosed. We took advantage of this unique situation, in which patients with cytologic evidence of squamous cell carcinoma and normal chest radiograph findings remain untreated, to study the natural history of squamous cell carcinoma. We herein report the results of a retrospective study of a cancer screening registry in which we compared the survival of cancer patients with cytologic evidence of squamous cell carcinoma and normal chest radiograph findings, who did and did not undergo tumor resection.

Patients and Methods

We reviewed the registry of the Miyagi Population-Based Lung Cancer Screening Program, which is a database of people from Miyagi Prefecture who were screened with radiography, originally for tuberculosis and later for lung cancer. In 1982, the registry added sputum cytology as a new screening method for the early detection of lung cancer.[23] Men with a Brinkman index[24] of ≥ 600 were candidates for screening.

All patients with abnormal sputum cytology test results were examined at the Department of Thoracic Surgery, Tohoku University Hospital, where they underwent CT scans of the chest and bronchoscopy. When patients had abnormal radiographic findings, they were referred to other hospitals.

Records dated between January 1, 1982, and December 31, 1996, were studied to identify patients in whom sputum cytology test results were positive for squamous cell carcinoma of the lung and in whom the findings of miniature (*ie*, 100 mm × 100 mm) posteroanterior chest radiographs were normal. These patients constituted two groups, namely, those who chose not to receive treatment for cancer and those who underwent tumor resection (Table 1). Patients receiving radiotherapy or photodynamic therapy were excluded.

Willing patients in the untreated group underwent a chest radiograph and sputum cytology test every 4 months, chest CT scans every 6 months, and bronchoscopic examinations every 12 months. The cause of death for patients who died before August 15, 2001, also was obtained from the registry. Death from primary lung cancer was defined as a tumor in the lung that was accompanied by clinical complications, such as obstructive pneumonia, hemoptysis, or brain metastasis. When the registry did not list the patient's cause of death, we used the cause of death identified by the patient's personal physician. The end points of this study were the 5-year and 10-year survival rates from primary lung cancer in both groups.

Statistical Analysis

Kaplan-Meier curves were plotted for both treated patients (*ie*, those who underwent resection) and untreated patients using a statistical software package (StatView; SAS Institute; Cary, NC).

Results

We identified 251 patients (all men) with positive sputum cytology test results and normal radiograph findings (Table 1). Of these patients, 44 did not receive treatment for cancer (*ie*, *untreated patients*). The mean (± SD) age was 70 ± 8.2 years (age range,

Table 1—*Background of Patients*

Variables	Natural Course Cases (n = 44)	Resected Cases (n = 207)*
Gender	All male	All male
Age		
Mean/SD	70/8.2	65.5/6.5
Minimum–maximum	53–86	51–81
Brinkman index†		
Mean/SD	1,065/381	1,053/442
Minimum–maximum	500–2,400‡	400–3,420

*Two patients who died within 30 days after operation were excluded.

†Brinkman index[24]: (No. of cigarettes per day) × (No. of years subject has smoked).

‡In 10 patients, we could not obtain information about the smoking history.

53 to 86 years). In this group, 27 patients had tumors that were localized by bronchoscopic examination, but they nevertheless declined treatment, 13 patients declined bronchoscopic examinations, and 4 patients had disease that could not be localized, even after intensive examinations,[21,23,25,26] including bronchoscopy, CT scans of the chest, and inspections by otorhinolaryngologists. These last 17 patients were eventually confirmed as having lung cancer at a mean of 49 months after the initial examination (range, 4.6 to 160 months).

Although the smoking histories of 10 untreated patients were not available, the 34 remaining patients each had a history of smoking. The mean Brinkman index[24] (*ie*, the number of cigarettes smoked per day times the number of years of smoking) was 1,065 (range, 500 to 2,400).

We also identified 207 patients who underwent pulmonary resection shortly after learning the results of the sputum cytology test (*ie, treated patients*). The mean age was 65.5 years (SD, 6.5 years) [age range, 51 to 81 years]. The mean Brinkman index was 1,053 (range, 400 to 3,420).

The overall survival rates of the 44 untreated patients were 53.2% at 5 years and 33.5% at 10 years (Fig 1). Among the 44 untreated patients, 15 (34%) remained asymptomatic. Nine of the 15, however, died due to the following conditions: cardiovascular disease (4 patients); extrapulmonary malignancy (2 patients); emphysema (1 patient); and unknown causes (2 patients).

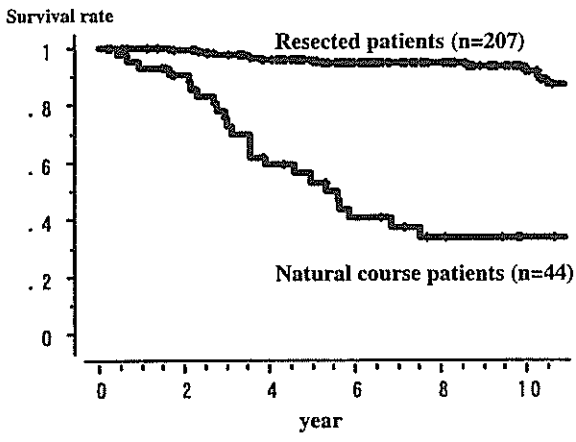


FIGURE 1. Survival curves of natural course patients and of patients who underwent resection. The lower curve represents the survival curve of 44 patients with sputum cytology results that were positive for squamous cell carcinoma of the bronchus but with normal chest radiograph findings, who chose not to be treated for cancer. The upper curve represents 207 patients with sputum cytology positive for squamous cell carcinoma of the bronchus but with normal chest radiograph findings, who underwent tumor resection.

The survival rates based on death from primary lung cancer in the 207 treated patients were 96.7% at 5 years and 94.9% at 10 years (Fig 1). None of these patients had abnormal radiographic findings at the time of treatment.

Of the 207 surgically treated patients, 125 (60%) died within 10 years (from primary lung cancer, 14 [11%]; from metachronous secondary lung cancer, 28 [22%]) [Table 2]. Thus, among treated patients who died, the rate of lung cancer death, including the first primary and metachronous second primary lung cancer, was 33.6% (42 of 125 patients).

We also analyzed data from 19 additional patients with radiographically occult lung cancer, identified as described, who initially declined treatment but who eventually sought treatment for cancer. When cancer cells were present in the sputum anytime during the follow-up period, or when chest radiographs showed abnormalities, we recommended bronchoscopic examination to the patients. At the time of treatment, all 19 patients had lung cancer, as diagnosed bronchoscopically, but chest radiograph findings were still normal in 10 patients and abnormal in 9 patients.

In the 10 patients with normal radiograph findings, there were no lung cancer deaths. However, patients who had abnormal shadows at the time of treatment had worse prognoses (Fig 2).

Discussion

Overdiagnosis bias is often discussed in the field of mass cancer screening. The concept is easily understood, and many authors have used it when discussing their data. However, this bias is difficult to evaluate. One common approach is to analyze autopsy data to determine retrospectively the incidence of undiagnosed cancer. However, this method yields only the prevalence of cancer at the time of autopsy and does not include much information concerning the development of the disease. Drlicek and

Table 2—*Causes of Death in Patients With Roentgenographically Occult Squamous Cell Carcinoma Who Underwent Resection (n = 125)*

Cause of Death	Patients (n = 125) No.	%
Primary lung cancer	14	11.2
Second primary lung cancer	28	22.4
Extrapulmonary malignancy	23	18.4
Others	59	47.2
Unknown	1	0.8

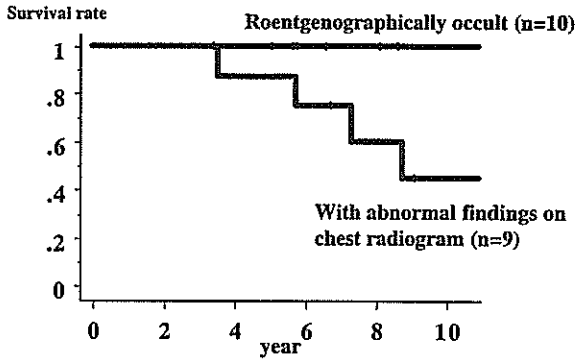


FIGURE 2. Survival curves of patients who received treatment later and radiographic findings at the time of therapy.

Bodenteich[27] examined a large number of autopsy reports from three hospitals and reported an overall incidence of undiagnosed lung cancer of 7.8% (67 of 859 patients). He also reported the incidence of clinically undiagnosed lung cancer for each of the three hospitals. The incidence of undiagnosed cancer in the hospital having a pulmonary department was 3.4%, which was the lowest among the three hospitals.

Another way of evaluating overdiagnosis bias is to observe patients who have received a diagnosis of cancer but who have not received treatment. Ethical issues do not allow a prospective study of such patients. Since 1982, we have been conducting lung cancer screening tests with both miniature chest radiographs and sputum cytology among high-risk individuals whose Brinkman index is ≥ 600.[23] Between 1982 and 1996, we detected 282 cases of bronchogenic squamous cell carcinoma with sputum cytology tests in patients with normal chest radiograph findings, 251 of whom had undergone resection or had declined treatment. (The latter 251 patients were included in the present analysis. The remaining 31 excluded patients consisted of 15 patients who received radiotherapy and 16 patients who were treated with photodynamic therapy.) Although almost all the patients were asymptomatic, most chose to undergo treatment. Among them, however, were 44 patients reported here who declined further examination or treatment and 19 patients who eventually sought treatment when the diagnosis was confirmed. We analyzed the natural course of the disease in these patients because we could observe, retrospectively, the biological behavior of the cancer.

We also analyzed the survival curves of the occult lung cancer patients who underwent complete resection. A few of these patients died from a recurrence of resected cancer, although their resected tumors were small. This result indicates that some of these patients had an extremely high malignant potential, despite the cancer being at an early stage at the time of surgery. It also suggests that overdiagnosis bias is not applicable in all cases of radiographically occult, bronchogenic squamous cell carcinoma.

All the untreated patients had cancer cells in their sputum, but all had normal chest radiograph findings. Two thirds of the patients died from lung cancer within 10 years. This finding indicates that overdiagnosis bias is not a major factor in such patients. We speculate that a long lead-time bias is a key factor in understanding the natural course as well as the clinical course in this group. In cases in which tumors could not be localized but showed positive cytology results, some tumors in the otorhinolaryngeal region were detected during the follow-up period. In this study, however, we focused on the natural course of radiographically occult bronchogenic squamous cell carcinoma. Thus, the data of patients with tumors in the otorhinolaryngeal region are not included in this report. Similarly, regarding the treatment group, we chose patients who had undergone pulmonary resection from among those who received various kinds of treatment, because pulmonary resection is believed to be the most curative.

To our knowledge, no one has described the natural course of patients with radiographically occult, bronchogenic squamous cell carcinoma. Sobue et al[18] described the course of stage I lung cancer. The 5-year survival rate was 14.3% for the screening-detected group and 3.7% for the symptom-detected group.[18] Because the patients of Sobue et al[18] had abnormal shadows on their radiographs, the difference between the 5-year survival rate of their patients and ours is also understandable in terms of lead-time bias. Nou,[19] reporting on the natural course of bronchial carcinoma, found a 5-year survival rate of 7.5% in cases of squamous cell carcinoma detected by radiography. He did not document cancer stage distributions, however.

Motohiro et al[20] examined the prognosis of nonsurgically treated clinical stage I lung cancer patients and reported a 5-year survival rate of about 20%. Interestingly, he also found that the survival rate continued to decrease after 5 years. Although his cases were detected by radiography, we believe they support our results. In an early report of the Mayo Lung Project, Woolner et al[4] described a case in which positive sputum findings preceded the development of a radiographic abnormality.

In addition to the Mayo Lung Project, two other famous randomized trials, the Johns Hopkins Study[28,29] and the Memorial Sloan-Kettering study,[30,31] also have addressed this issue. Based on the

results of the Sloan-Kettering study, Melamed et al[32] concluded that the squamous cell carcinomas detected by cytologic examination alone are very slow growing and tend to remain localized until detected by radiography. This conclusion may be based on the fact that survival and mortality rates in their study were the same between the screened and control groups. Thus, we tried to observe the treatment results of the patients who received treatment later. The 9 patients who had abnormal radiographic shadows at the time of their delayed treatment had a worse prognosis than did the 10 patients with normal radiograph findings.

Finally, three randomized controlled trials in the United States in the late 1970s and early 1980s reported that screening with sputum cytology did not reduce deaths from lung cancer. The Johns Hopkins Study[28,29] and the Memorial Sloan-Kettering study[30,31] examined the effectiveness of sputum cytology screening in combination with radiographic screening compared with that of radiographic screening alone. There were 2.7 lung cancer deaths per person-year in both the screened and the control group in the Memorial Sloan-Kettering study,[30,31] and 3.4 per person-year in the screened group and 3.8 per person-year in the control group in the Johns Hopkins Study.[28,29]

Sagawa et al,[33] however, reported on the efficacy of lung cancer screening conducted in the 1990s. He reported four case-control studies in Japan, three of which revealed statistically significant reductions in lung cancer deaths among screened patients. The odds ratios in each study were 0.54 (95% confidence interval [CI], 0.41 to 0.73) in Miyagi Prefecture, 0.40 (95% CI, 0.27 to 0.59) in Niigata Prefecture, 0.59 (95% CI, 0.46 to 0.74) in Okayama Prefecture, and 0.68 (95% CI, 0.44 to 1.05) in Gunma Prefecture. In the three studies showing significant reductions, high-risk persons (*ie*, smokers) were screened with annual chest radiographs and sputum cytology tests, and nonsmokers were screened with an annual chest radiograph. In the one prefecture in which screening did not yield a significant reduction in lung cancer deaths, only annual radiographs were used.

Limitations of the Study

Our study was retrospective and nonrandomized, so the groups were not necessarily equivalent at baseline. For example, the age distributions were slightly different between the two groups. Patients who underwent resection likely had a will to survive and a strong interest in their health, whereas those who declined treatment may not have. Our study cannot exclude such biases. Our study nevertheless offers some important information on the natural course of radiographically occult squamous cell carcinoma of the bronchus.

Conclusion

In conclusion, although some investigators believe that cancer patients with normal radiograph findings have slow-growing tumors, two thirds of the patients with such tumors in our study died from primary lung cancer within 10 years. This result suggests that overdiagnosis bias is not a factor in the course of squamous cell carcinoma of the bronchus in patients with normal chest radiograph findings. We recommend that these patients be treated after the tumor is localized.

ACKNOWLEDGMENT: We thank Drs. Yoshitaka Tsubono, Ichiro Tsuji, and Zen'ichi Nishino, and the Miyagi Cancer Registry for their help.

References

1 Woolner LB, Fontana RS, Cortese DA, et al. Roentgenographically occult lung cancer: pathologic findings and frequency of multicentricity during a 10-year period. Mayo Clin Proc 1984; 59:453–466
2 Fontana RS, Sanderson DR, Taylor WF, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic Study. Am Rev Respir Dis 1984; 130:561–565
3 Fontana RS. The Mayo Lung Project: a perspective. Cancer 2000; 89:2352–2355
4 Woolner LB, Fontana RS, Sanderson DR, et al. Mayo Lung Project: evaluation of lung cancer screening through December 1979. Mayo Clin Proc 1981; 56:544–555
5 Sanderson D, Fontana R. Results of the Mayo Lung Project: an interim report. Recent Results Cancer Res 1982; 82:179–186
6 Fontana RS, Sanderson DR, Woolner LB, et al. Screening for lung cancer: a critique of the Mayo Lung Project. Cancer 1991; 67:1155–1164
7 Dammas S, Patz EF, Goodman PC. Identification of small lung nodules at autopsy: implications for lung cancer screening and overdiagnosis bias. Lung Cancer 2001; 33:11–16
8 Hakama M, Holli K, Visakorpi T, et al. Low biological aggressiveness of screen-detected lung cancers may indicate over-diagnosis. Int J Cancer 1996; 66:6–10
9 Sugarbaker DJ, Strauss GM. Extent of surgery and survival in early lung carcinoma: implications for overdiagnosis in stage IA non-small cell lung cancer. Cancer 2000; 89(suppl):2432–2437
10 Strauss GM, Gleason RE, Sugarbaker DJ. Screening for lung cancer re-examined: a reinterpretation of the Mayo Lung Project randomized trial on lung cancer screening. Chest 1993; 103(suppl):337S–341S
11 Eddy D. Screening for lung cancer. Ann Intern Med 1989; 111:232–237
12 Fontana RS. Screening for lung cancer: recent experience in the United States. In: Hansen HH, ed. Lung cancer: basic and clinical aspects. Boston, MA: Martinus Nijhoff, 1989; 91–111

13 Straus GM, Gleason RE, Sugarbaker DJ. Screening for lung cancer: another look, a different view. Chest 1997; 111:754–768
14 Marcus PM, Bergstralh EJ, Fagerstrom RM, et al. Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. J Natl Cancer Inst 2000; 92:1308–1316
15 Flehinger BJ, Kimmel M, Polyak T, et al. Screening for lung cancer: the Mayo Lung Project revisited. Cancer 1993; 72:1573–1580
16 Strauss GM, Gleason RE, Sugarbaker DJ. Chest x-ray screening improves outcome in lung cancer, a reappraisal of randomized trials on lung cancer screening. Chest 1995; 107: 270S–279S
17 Marcus PM, Prorok P. Reanalysis of the Mayo Lung Project data: the impact of confounding and effect modification. J Med Screen 1999; 6:47–49
18 Sobue T, Suzuki T, Matuda M, et al. Survival for clinical stage I lung cancer not surgically treated. Cancer 1992; 69:685–692
19 Nou E. The natural five-year course in bronchial carcinoma: epidemiologic results. Cancer 1984; 53:2211–2216
20 Motohiro A, Ueda H, Komatsu H, et al. Prognosis of non-surgically treated, clinical stage I lung cancer patients in Japan. Lung Cancer 2002; 36:65–69
21 Sato M, Saito Y, Nagamoto N, et al. Diagnostic value of differential brushing of all branches of the bronchi in patients with sputum positive or suspected positive for lung cancer. Acta Cytol 1993; 37:879–883
22 Lam S, MacAulay C, Hung J, et al. Detection of dysplasia and carcinoma *in situ* with a lung imaging fluorescence endoscope devise. J Thorac Cardiovasc Surg 1993; 105:1035–1040
23 Nakada T, Sato M, Saito Y, et al. Detection of early lung cancer: results of radiologic and cytologic screening in the Miyagi Program. Tohoku J Exp Med 1987; 152: 173–185
24 Brinkman GL, Coates EB. The effect of bronchitis, smoking, and occupation on ventilation. Am Rev Respir Dis 1963; 87:684–693
25 Sato M, Sakurada A, Sagawa M, et al. Diagnostic results before and after introduction of autofluorescence bronchoscopy in patients suspected of having lung cancer detected by sputum cytology in lung cancer mass screening. Lung Cancer 2001; 32:247–253
26 Sato M, Saito Y, Usuda K, et al. Occult lung cancer beyond bronchoscopic visibility in sputum-cytology positive patients. Lung Cancer 1998; 20:17–24
27 Drlicek M, Bodenteich A. Identification of lung cancer by autopsy: an indicator for clinical underdiagnosis. Lung Cancer 2002; 35:217
28 Tockman MS. Survival and mortality from lung cancer in a screened population: the Johns Hopkins Study. Chest 1989; 96(suppl):324–325
29 Johns Hopkins Medical Institutions. Final report: lung cancer control, detection and therapy, phase II, NCI-PHS; contract No. N01-CN-4537, December 31,1984. Bethesda, MD: National Cancer Institute, 1984
30 Flehinger BJ, Melamed MR, Zaman MB, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Memorial Sloan-Kettering study. Am Rev Respir Dis 1984; 130:555–560
31 National Lung Program, Memorial Sloan-Kettering Cancer Center. Final report and data summary, December 31, 1984. Bethesda, MD: National Cancer Institute, 1984
32 Melamed MR, Flehinger BJ, Zaman MB, et al. Screening for early lung cancer: results of the Memorial Sloan-Kettering study in New York. Chest, 1983; 86:44–53
33 Sagawa M, Nakayama T, Tsukada H, et al. The efficacy of lung cancer screening conducted in 1990s: four case-control studies in Japan. Lung Cancer 2003; 41:29–36

喫煙が予後に及ぼす影響の性差

—原発性肺癌2220切除症例における検討—

山中澄隆[1]・佐藤雅美[1]・桜田　晃[1]・
遠藤千顕[1]・半田政志[2]・近藤　丘[1]

[1]東北大学加齢医学研究所呼吸器再建研究分野；
[2]仙台厚生病院外科

Japanese Journal of Lung Cancer

肺　癌　第44巻 第2号 2004年4月

喫煙が予後に及ぼす影響の性差
—原発性肺癌2220切除症例における検討—

山中澄隆[1]・佐藤雅美[1]・桜田　晃[1]・
遠藤千顕[1]・半田政志[2]・近藤　丘[1]

要旨 —— 目的．東北大学呼吸器外科および仙台厚生病院にて切除された2220症例の肺癌患者を対象に，臨床像ならびに喫煙が予後に及ぼす影響における男女差の検討を行なった．方法．1952年から2000年において，当施設にて切除された原発性肺癌手術症例のうち喫煙指数が把握できた2220例（男性1617例，女性603例）を対象とした．結果．女性では男性に比し，腺癌の比率が高く，男性は扁平上皮癌と大細胞癌の比率が高かった．男女とも非喫煙者の5年生存率は喫煙者より有意に良好であった．男女とも喫煙指数の増加によって腺癌の比率の減少が認められた．癌死の割合が最も少なく，非癌死の影響を観察するのに適切であると考えられる病理病期IA期症例にて検討したところ，男性では全死因にて喫煙者の予後が有意に不良であったが，肺癌死のみで生存曲線を比較すると非喫煙者と同等の予後であった．結論．喫煙と関連してI期腺癌男性患者にて非癌死が増加することが示された．I期腺癌女性患者において喫煙の影響は明らかとはならなかったが，喫煙者の全死因での生存率は不良であり，肺癌切除後の予後改善という観点からも両性での禁煙指導の重要性が示された．（肺癌．2004;44:83-89）

索引用語 —— 肺癌，喫煙，ブリンクマン指数，I期腺癌

Sex Differentiation of Smoking Effect for Prognosis of Lung Cancer
—Study of 2220 Cases of Primary Lung Cancer Undergone Pulmonary Resection—

Sumitaka Yamanaka[1]; *Masami Sato*[1]; *Akira Sakurada*[1];
Chiaki Endo[1]; *Masashi Handa*[2]; *Takashi Kondo*[1]

ABSTRACT —— ***Objective.*** The objective of this study was to examine the clinical characteristics and the differences between the sexes as to the effects of smoking on the survival rate in lung cancer patients who had undergone lung resection in the Department of Thoracic Surgery of Tohoku University Hospital. ***Methods.*** The clinical records and Brinkman index values (number of cigarettes for day × years smoked) of 2220 patients, 1617 men and 603 women, who had undergone pulmonary resection from 1952 to 2000 at Tohoku University Hospital were reviewed. ***Results.*** The ratio of adenocarcinoma patients was higher in women than men, while men had a higher ratio of squamous cell carcinoma and large cell carcinoma. In both sexes, the 5-year survival rates of non-smokers were significantly better than those of smokers. The larger the Brinkman index value was, the lower was the incidence of adenocarcinoma. There was no significant impact of the Brinkman index on stage progression. To clarify the effect of smoking on the survival rate, we reviewed the records of patients with pathological stage IA adenocarcinoma, since most of these patients are ex-

[1]東北大学加齢医学研究所呼吸器再建研究分野；[2]仙台厚生病院外科．

別刷請求先：山中澄隆，東北大学加齢医学研究所呼吸器再建研究分野，〒980-8575　宮城県仙台市青葉区星陵町4-1．

[1]Department of Thoracic Surgery, Institute of Development, Aging and Cancer, Tohoku University, Japan; [2]Department of Surgery, Sendai Kousei Hospital, Japan.

Reprints: Sumitaka Yamanaka, Department of Thoracic Surgery, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-cho, Aoba-ku, Sendai-shi, Miyagi 980-8575, Japan.

Received November 27, 2003; accepted February 16, 2004.

pected to die from non-cancerous causes. As a result, the outcome in male smokers in terms of overall survival was significantly worse than that in non-smokers. There was no significant difference, however, in survival between smokers and non-smokers, based on death due to lung cancer. ***Conclusion.*** It is suggested that smoking-related deaths resulting from causes other than cancer were not negligible in male surgically treated lung cancer patients. Although the impact of the effect of smoking on the survival of female patients with stage Ia adenocarcinoma was not clear, the overall survival of lung cancer patients with a history of smoking was worse than that of non-smokers in both sexes. As described above, smoking cessation is still an important issue in Japan. (*JJLC.* 2004;44:83-89)

KEY WORDS —— Lung cancer, Smoking, Brinkman index, Stage I adenocarcinoma

はじめに

肺癌死亡が悪性疾患死亡の第1位となる一方，治療技術に breakthrough が見出せない現状において予防医学の重要性が増している．喫煙と肺癌発生の強い相関から禁煙活動が肺癌予防に重要と考えられるが，[1-3] 本邦での喫煙率は，欧米と比較すると未だ高率である．更に，今後20～30年後，肺癌好発年齢に達すると予想される若年女性喫煙者の増加傾向が指摘されている（JT 全国喫煙者調査）．このような背景を踏まえ，肺癌治療後生存率に対する喫煙の影響を両性にて比較検討することは有用であると考えられる．今回，東北大学加齢医学研究所呼吸器再建研究分野および仙台厚生病院にて切除された2220症例の肺癌患者について検討を行なった．

対象および方法

1952年9月から2000年12月において，東北大学加齢医学研究所呼吸器再建研究分野および仙台厚生病院にて切除された3530例の原発性肺癌手術症例のうち喫煙指数（Brinkman index，以下 BI）が病歴から把握できた2220例（男性1617例，女性603例）を対象とした．腫瘍の組織型，病理病期分類は肺癌取扱い規約第5版[4]に準拠した．

男女別に BI により 0，1～399，400～799，800以上の4群に分け，各組織型，病理病期の割合を算出し，患者構成の差異について検討した．統計学的検討では，2群の比較には Fisher's exact test を，男女間での BI の比較では unpaired *t* test を用い $p<0.05$ を有意とした．生存曲線は Kaplan-Meier 法で算出し，log-rank test で検定し $p<0.05$ を有意とした．

結　果

1．喫煙と性差

対象症例2220例の手術時平均年齢は63.9歳，男性

Table 1. Patient characteristics (1952-2000)

	Men (%)	Women (%)	p value
Number	1617	603	
Age (mean)	64.5	62.4	NS
Smokers	1497 (92.6)	81 (13.4)	$p < 0.001$
Mean BI among smokers	1004	458	$p < 0.001$
Detected by mass screening	725 (44.8)	325 (53.9)	$p < 0.001$
Histology *			
Squamous cell carcinoma	732 (45.3)	25 (4.1)	$p < 0.001$
Adenocarcinoma	567 (35.1)	510 (84.6)	$p < 0.001$
Small cell carcinoma	53 (3.3)	9 (1.5)	$p = 0.02$
Large cell carcinoma	193 (11.9)	16 (2.7)	$p < 0.001$
Pathological stage †			
I	860 (53.2)	367 (60.9)	$p = 0.001$
II	282 (17.4)	67 (11.1)	$p < 0.001$
III	412 (25.5)	147 (24.4)	NS
IV	30 (1.9)	15 (2.5)	NS

NS: not significant.
* Excluding other histologic types.
† Excluding cases of unknown stage.

Table 2. Histology classified by Brinkman index

	BI	all cases	Ad	Sq	Sm	La	Total
Men							
	0	120	84 (70%)	20 (17%)	2 (2%)	4 (3%)	110 (100%)
	1-399	92	61 (66%)	14 (15%)	5 (5%)	7 (8%)	87 (100%)
	400-799	412	147 (36%)	184 (45%)	16 (4%)	53 (13%)	400 (100%)
	800-	993	275 (29%)	514 (54%)	30 (3%)	129 (14%)	948 (100%)
Women							
	0	522	475 (91%)	10 (2%)	2 (0.4%)	8 (2%)	495 (100%)
	1-399	42	21 (50%)	4 (38%)	1 (2%)	3 (7%)	29 (100%)
	400-799	24	11 (46%)	6 (25%)	3 (13%)	2 (8%)	22 (100%)
	800-	15	3 (21%)	5 (36%)	3 (21%)	3 (21%)	11 (100%)

Ad: adenocarcinoma, Sm: small cell carcinoma, La: large cell carcinoma, Sq: squamous cell carcinoma.

Table 3. Pathological stage classified by Brinkman index

	BI	all cases	stage Ⅰ	stage Ⅱ	stage Ⅲ	stage Ⅳ	Total
Men							
	0	120	68 (57%)	10 (8%)	36 (30%)	3 (3%)	117 (100%)
	1-399	92	48 (52%)	11 (12%)	30 (33%)	2 (2%)	91 (100%)
	400-799	412	216 (52%)	73 (18%)	107 (26%)	8 (2%)	404 (100%)
	800-	993	528 (54%)	188 (19%)	239 (25%)	17 (2%)	972 (100%)
Women							
	0	522	281 (54%)	53 (10%)	122 (23%)	13 (2%)	469 (100%)
	1-399	42	17 (40%)	8 (19%)	13 (31%)	2 (5%)	40 (100%)
	400-799	24	13 (54%)	3 (13%)	7 (29%)	0	23 (100%)
	800-	15	7 (47%)	3 (20%)	5 (33%)	0	15 (100%)

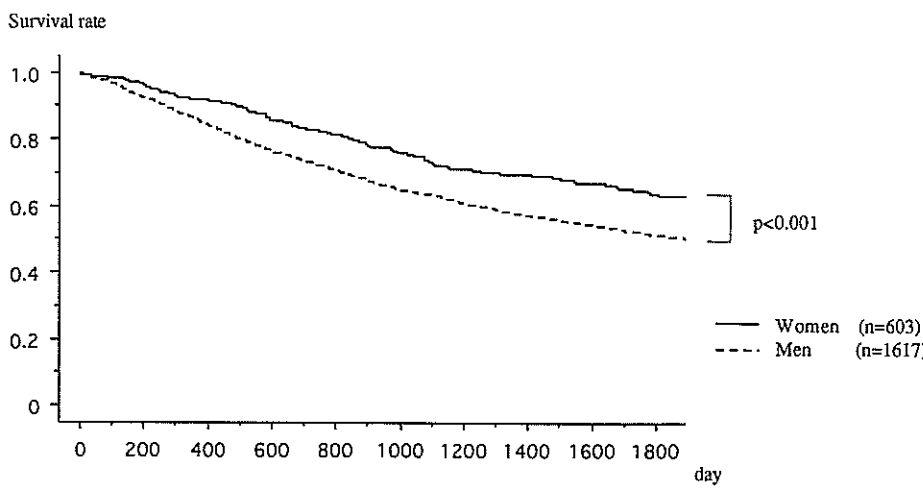


Figure 1. Overall survival curves classified by sex.

(1617 例) で 64.5 歳，女性 (603 例) では 62.4 歳であった．喫煙率は男性 92.6%，女性 13.2% で，男性で有意に高かった．また，喫煙者における BI の平均±標準偏差は，男性 1004.0±514.5，女性 458.5±383.4 と男性で有意に高値であった ($p<0.001$) (Table1)．

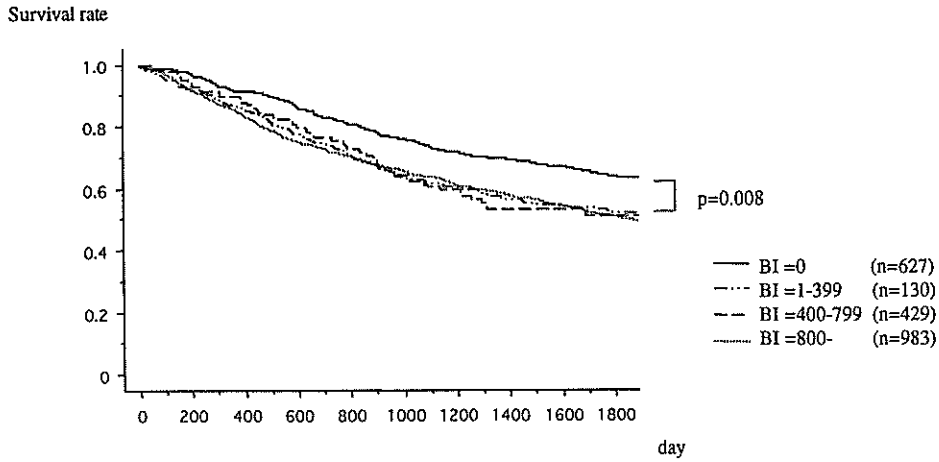


Figure 2. Overall survival curves classified by Brinkman index.

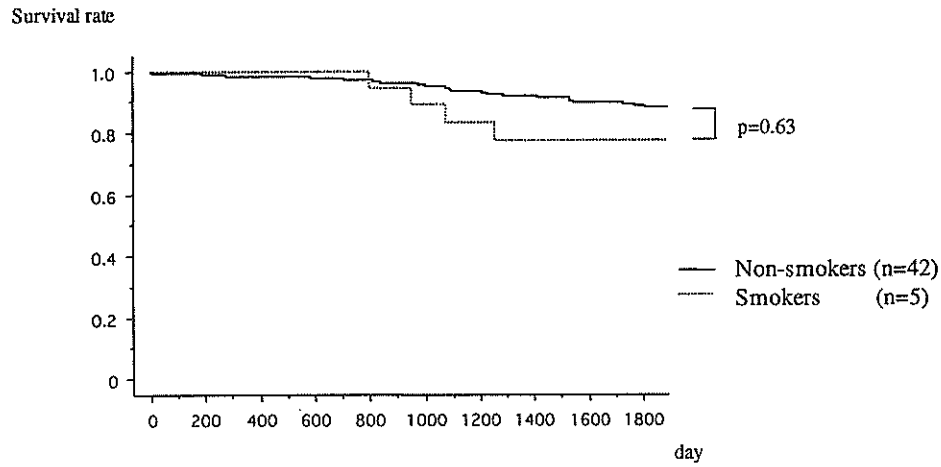


Figure 3. Overall survival curves for women with stage IA adenocarcinoma classified as smokers or non-smokers.

2. 喫煙と組織型

組織型に関して，女性では男性に比し腺癌が多く（$p<0.001$），反対に男性は扁平上皮癌（$p<0.001$）が多く，大細胞癌（$p<0.001$），小細胞癌（$p=0.02$）も男性に多かった（Table 1）.

BI別の組織型の比較では，男女ともBIの増加によって腺癌の比率の減少が認められ，男性では扁平上皮癌の比率の上昇が認められた（Table 2）.

3. 喫煙と病期

病期の分布は性別によって差異があり，女性ではI期肺癌の全体に占める比率が多かった（$p=0.001$）．かつ女性では検診発見例が多かった（$p<0.001$）(Table 1).

BI別の病理病期の比較では，男女ともBIによる病理病期の比率の相違は明瞭ではなかった（Table 3）.

4. 喫煙と予後

対象症例の全死因における5年生存率を男女で比較すると，男性51.7%，女性63.2%と有意に女性が良好であった（$p<0.01$）(Figure 1).

BI別の全死因で見た全症例の5年生存率の比較では，非喫煙者の予後が有意に良好であり（$p=0.008$）(Figure 2)，喫煙者間においてBI別では予後に差がなかった (Figure 2).

次に腺癌に着目し，中でも他病期より手術による根治度が高く，肺癌死以外の死亡の影響を，より反映することが予想される病理病期IA期腺癌の群にて全死因での5年生存率の比較を行なった．女性では喫煙，非喫煙にて

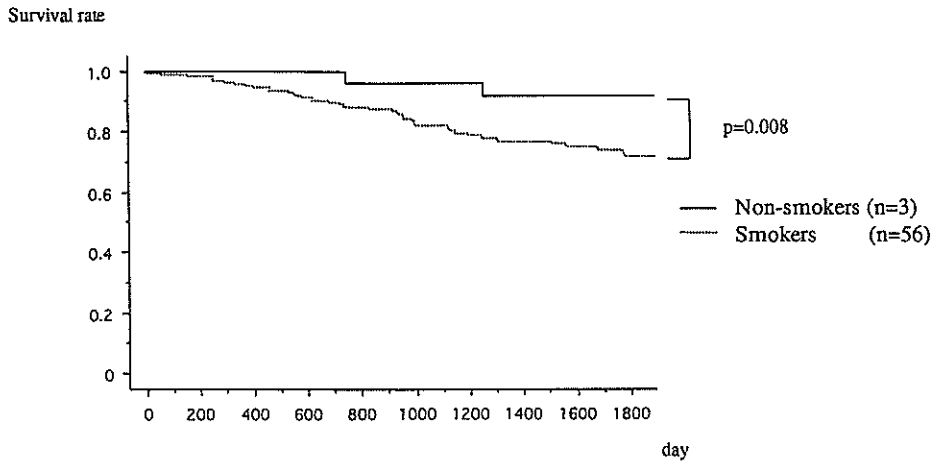


Figure 4. Overall survival curves for men with stage IA adenocarcinoma classified as smokers or non-smokers.

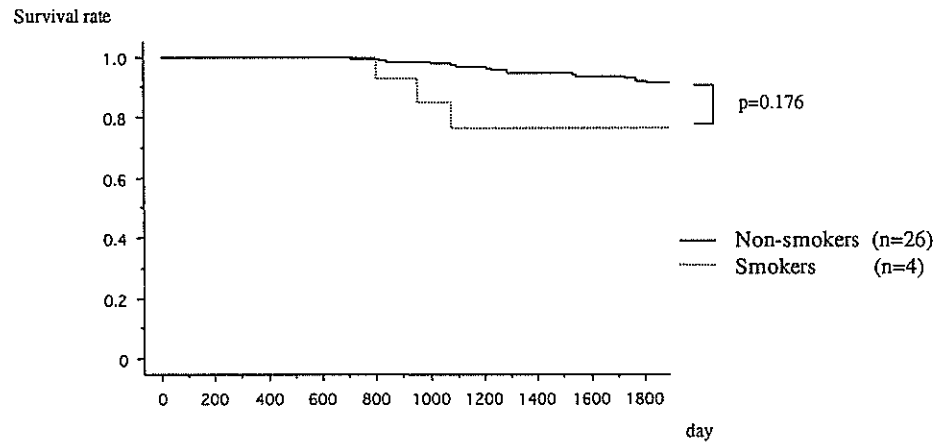


Figure 5. Lung cancer survival curves for women, classified as smokers or non-smokers, with stage IA adenocarcinoma.

予後に有意差は認めなかったが (Figure 3)，男性では喫煙者の予後が有意に不良であった (p = 0.008) (Figure 4)．肺癌死の 5 年生存率を検討すると，男女とも有意差を認めなかった (Figure 5，6)．

考　察

今回の検討対象は肺癌手術症例であり，手術患者というセレクションバイアスがあることは否めないものの，本邦における原発性肺癌症例の予後に関する特徴の一端を示唆していると考える．また，一般に重喫煙者は BI 600 以上を指すが，今回の検討では男女の平均 BI から考慮して便宜的に BI を 0，1～399，400～799，800 以上と 4 群に分類した．

喫煙と性差に関しては，全国的に男性の喫煙率の減少が見られ (JT 全国喫煙者調査)，自施設でも喫煙率の男女比は近年ほぼ平衡状態にある．しかし，やはり男性の喫煙率，BI は有意に女性より高いことが本検討にて示された．

近年，腺癌の増加が指摘されているが，[5-9] 自施設の切除例でも女性腺癌の全症例に占める割合は高い結果となった．喫煙指数の増加に伴い男女とも扁平上皮癌，大細胞癌の比率が上昇した．発癌機構に対する性差の検討として，芳香族炭化水素-DNA　付加体量，[10] ニコチンの血漿クリアランス，[11] 腫瘍細胞におけるエストロゲン受容体の発現，[12] 等が報告されており興味深いが，まだ一定の見解は得られておらず更なる解明が望まれる．年齢

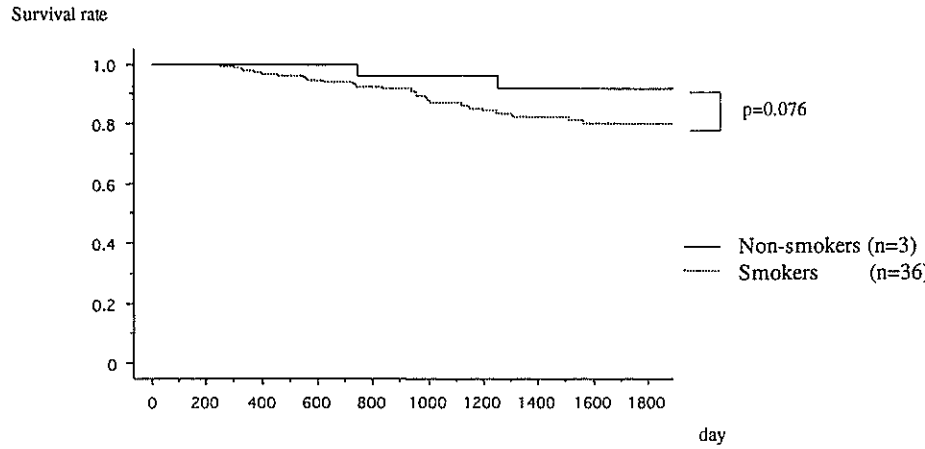


Figure 6. Lung cancer survival curves for men, classified as smokers or non-smokers, with stage IA adenocarcinoma.

と予後については，関連の有無が議論されているが，[1,13,14] 一定の見解に達していない．

喫煙と病期の関連の検討では，喫煙を加味せずに全体で見ると，女性にI期肺癌が多く（Table 1），女性が男性に比して5年生存率が良好である原因が示唆された．なお，今回の検討では1950年代からの症例も含まれるが，病期については病理病期を用いており，年代における差違は考慮しなくてもよいと思われる．一方，手術手技，術後管理に関しては，著しい進歩が見られているのは周知の通りである．しかし全症例に占める50年代の症例は1.5%（60年代4.6%，70年代11.7%，80年代31.8%，90年代50.5%）と僅少であり，全体に与える影響は少ないと考えられた．

男女各々の群にて，BI別に病理病期I期，II期，III期，IV期の全体に占める比率を検討すると，性別にて喫煙による病期分布の違いは認められなかった．喫煙の肺癌進行に対する影響は明らかとはならなかった（Table 3）．

喫煙の予後に及ぼす影響の検討では，喫煙指数が有意に高い男性は，女性より全死因において5年生存率が低いことを示したが（Figure 1），喫煙が男女の予後の差違にもたらす影響として，1）癌の悪性度に対する影響，2）肺癌死以外の合併症死に対する影響が考えられる．そのため，男女にて十分に罹患数があり，癌死が最も少なく，非癌死の影響を観察するのに適切である病理病期IA期症例において喫煙，非喫煙群にて予後を調査した．その結果，全死因における5年生存率では女性は喫煙，非喫煙にて予後に差が見られなかったが（$p=0.63$），男性では喫煙者は有意に予後不良であった（$p=0.008$）．一方，肺癌死5年生存率では女性（$p=0.176$），男性（$p=0.08$）ともに喫煙，非喫煙にて予後に差が見られなかった．従って男性では，喫煙が癌死による比較では認められない有意差を，非癌死を含めた全死因において発生させたと考えられた．このことから，男性喫煙者では非癌死が多いという結果が示唆された．その原因の一つとして，術後早期死亡が多い男性重喫煙者の存在が指摘されている．[15] 女性では喫煙，非喫煙による術後合併症死の差は明らかにならなかったが，禁煙は喫煙者の扁平上皮癌のみならず腺癌の罹患率をも減少することが報告されており，[16] また喫煙は女性腺癌の進行に関与するとの報告もあり，[17] 女性にても禁煙の重要性は男性と同様である．

以上のことから，禁煙は肺癌罹患率の減少のみならず，肺癌外科治療後の予後の改善にも深く結びつくことが示され，男女双方において禁煙活動を推進することは以前にもまして重要であると考えられた．

結　語

全症例で見ると女性ではI期肺癌が多く，男性より予後良好であった．非喫煙群の全死因5年生存率は有意に喫煙群より良好であった．

癌死の割合が最も少なく，非癌死の影響を観察するのに適切であると考えられる病理病期IA期症例にて検討した結果，男性では喫煙者の予後が有意に不良であるが，女性では喫煙者の予後に有意差は認めず，喫煙の非癌死に及ぼす影響に男女差を認めた．

禁煙は肺癌罹患率減少のみならず，肺癌外科治療後の予後の改善にも関連することが示され，両性において禁煙は重要であると考えられた．

REFERENCES

1. Sobue T, Yamamoto S, Hara M, et al. Cigarette smoking and subsequent risk of lung cancer by histologic type in middle-aged Japanese men and women. *Int J Cancer*. 2002;99:245-251.
2. Khuder SA, Mutgi AB. Effect of smoking cessation on major histologic type of lung cancer. *Chest*. 2002;120:1577-1583.
3. Kubik A, Zatloukal P, Tomasek L, et al. Diet and the risk of lung cancer among women. *Neoplasma*. 2001;48:262-266.
4. 日本肺癌学会，編集．肺癌取扱い規約．第5版．東京：医学書院；1999.
5. Sobue T, Ajiki W, Tsukuma H, et al. Trends of lung cancer incidence by histologic type. *Jpn J Cancer Res*. 1999; 90:6-15.
6. Harley HRS. Cancer of the lung in women. *Thorax*. 1976; 31:254-264.
7. Osann EK, Culver AH, Kurosaki T, et al. Sex differences in lung cancer risk associated with cigarette smoking. *Int J Cancer*. 1993;54:44-48.
8. Baldini HE, Strauss MG. Women and lung cancer. *Chest*. 1997;112:229s-234s.
9. Charloux A, Quoix E, Wolkove N, et al. The increasing of lung adenocarcinoma: reality or artefact? A review of the epidemmiology of lung adenocarcinoma. *Int J Epidemiology*. 1997;26;14-23.
10. Ryberg D, Hewer A, Phillips DH, et al. Different susceptibility to smoking-induced DNA damage among male and female lung cancer. *Cancer Res*. 1994;5801-5803.
11. Benowits NL, Jacob PI. Daily intake of nicotine during cigarette smoking. *Clin Pharmacol Ther*. 1984;35:499-504.
12. Fasco MJ, Hurteau GJ, Spivack SD. Gender-dependent expression of alpha and beta estrogen receptors in human nontumor and tumor lung tissue. *Mol Cell Endocrinol*. 2002;188:125-140.
13. de Perrot M, Licker M, Bouchardy C, et al. Sex differences in presentation, management, and prognosis of patients with non-small cell carcinoma. *J Thorac Cardiovasc Surg*. 2000;119;21-26.
14. Tominaga K, Mori K, Yokoi K, et al. Lung cancer in patients under 50 years. *Jpn J Cancer Res*. 1999;90;490-495.
15. Myrdal G, Gustafsson G, Lamble M, et al. Outcome after lung cancer surgery. Factors predicting early mortality and major morbidity. *Euro J Cardiothorac Surg*. 2001;20; 694-699.
16. Soda H, Oka M, Nakatomi K, et al. Birth cohort effects in incedence of lung cancers: a population-based study in Nagasaki, Japan. *Jpn J Cancer Res*. 2000;91;960-965.
17. Sekine I, Nagai K, Tsugane S, et al. Association between smoking and tumor progression in Japanese women with adenocarcinoma of the lung. *Jpn J Cancer Res*. 1999;90: 129-135.