るを得ない．一方不利益としての過剰な要精検率，高いコスト，高い放射線被曝についてもいまだ解決には至っていない．これらの問題を解決しない限り，現状では低線量CT検診を推奨することはできない．

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14. 肺癌検診の問題点

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14．肺癌検診の問題点

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要　旨

胸部単純 X 線撮影と高危険群に対する喀痰細胞診を用いた，無症状者に対して肺癌のスクリーニングを目的とした肺癌検診の有効性については議論が分かれるところだが，最近の国内の知見により，有効という評価に変わりつつある。ただし精度を無視した単なる胸部単純 X 線検査については，肺癌を救命できるものではなく，精度管理のためのシステム構築に関して専門医や学会の社会的努力が必須である。

Key words：肺癌，検診，精度管理，有効性/lung cancer, screening, quality control, effectiveness

1．はじめに

わが国の癌死亡のなかで最多である肺癌対策としての肺癌検診は，昭和 52 年より老人保健事業として広く行われてきた。肺癌検診は結核検診として撮影された胸部間接 X 線撮影のフィルムを利用するという形式をふんでいたため，安価かつ処理能力が高いことから，2003 年には 780 万人という，他の癌検診に比べて抜きんでて高い受診者数を示し，4,183 人の肺癌患者が発見されている[1]。しかし，この肺癌検診の効果が満足すべきものではないことは明らかで，いくつかの議論が繰り広げられている。ここでは肺癌検診の問題点について整理し，今後の展望について議論する。

なお，ここで言及する肺癌検診とは，適正な対象者（40 歳以上の無症状者）に，肺癌取り扱い規約[2]に定義された適切な方法に基づいて肺癌のスクリーニングを目的とした定期的な検査を行うことであり，単に胸部単純 X 線検査を行うことではない。

2．胸部単純 X 線検診の有効性への疑問

胸部単純 X 線検診と喀痰細胞診を用いた定期的な肺癌検診の有効性評価に関しては，1970 年代に米国 NCI 主導で行われた 4 つのランダム化比較試験の結果が，いずれも肺癌検診の効果を示すことができなかった[3)~6)]。このことから，米国 PDQ などの諸外国のガイドラインでは，公的な資金を元に肺癌検診を行うべきではないという推奨を行っていた[7)]。しかし，その後 90 年代後半から行われた日本の 6 つの症例対照研究の結果がいずれも肺癌検診の効果を示す方向にあった[8)~13)]ことから，その評価は若干変わってきている。平成 13 年にまとめられた「新たながん検診手法の有効性の評価研究」班（主任研究者　久道茂）においては，国内の研究と国外の研究で時期が異なり，結果も異なる点に注目し，国内での肺癌検診を「検診による死亡率減少効果があるとする，相応の根拠がある」と判定されている[14)]。また US preventive service task force の第 4 版では，特に女性に関する日本の症例対照研究の効果を評価し，推奨 I（評価するに十分な資料が不十分であ

The Problems of Lung Cancer Screening

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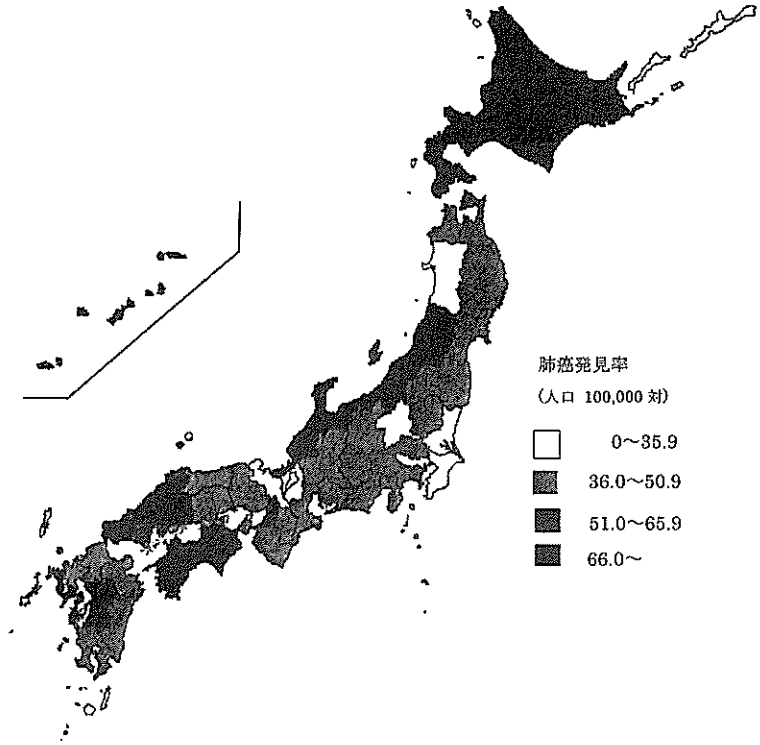

図 1　都道府県別にみた肺癌検診発見率
平成 10～14 年度の地域保健・老人保健事業報告から，各都道府県ごとに男女込みの平均肺癌発見率を求め，作図した。

る）と判定している[15]。国内では昨年結核予防法改正に伴い，職域での定期的な胸部単純 X 線検査の是非について，議論が巻き起こった。また平成 16 年度単年度で行われた「最新の科学的知見に基づいた保健事業に係る調査研究」班（主任研究者福井次矢）では，基本健康診査の各項目の一つとして，胸部単純 X 線検診の有効性について，「いかなる肺がんスクリーニングのための検査の有効性を支持する研究はなし」と判定した。しかしこれはランダム化比較試験のみを評価するという研究班の取り決め上に問題があり，国内の研究が無視された形である。また，現在まで問題視されてきた 70 年代のランダム化比較試験の方法上の問題点（割り付けの不均等性，コンタミネーション，検査精度等）については，まったく評価されておらず，論文の結果のみを集約した浅い分析である。現在，がん研究助成金「がん検診の適切な方法とその評価法の確立に関する研究」班（主任研究者祖父江友孝）では，国内外の約 1,600 の肺癌検診に関連した論文を抽出し，EBM の手法に沿った「科学的評価に基づく肺癌検診の有効性評価に関するガイドライン」を作成中である。2006 年秋には，国立がんセンターの HP 上で公開される予定であり，その結果が注目される。

3．精度は確保されているのか？

肺癌検診の問題点として，精度のバラツキという問題がある。図 1 は，各都道府県ごとに肺癌検診の肺癌発見率を示したものである。このように癌発見率にして実に 6.2 倍のバラツキがある[16]。現在乳癌検診のマンモグラフィーについては，NPO マンモグラフィー精度管理中央委員会の実施する資格試験に合格した読影医と撮影放射線技師でないと，マンモグラフィー検診には従事できない。しかし肺癌検診に関しては，すでに広まっていた結核検診で撮影されたフィルムを利用するという建前上，撮影する放射線技師や読影医に対して，何ら資格を求めなかった。これは胸部単純 X 線写真の読影は医師にとっては必修事項であるだろうという誤解の元に築かれたシステムである

が，実際胸部単純 X 線撮影で，早期肺癌を検出するには，熟練した技術を要することは医師にとっては周知のことであろう。とはいえ，今後胸部単純 X 線検診の読影認定制度を新たに構築することは甚だ困難であり，またそれを主導的に行うべき学会も存在しない。それよりも検診機関別の検診精度を国民に広く公表し，国民により検診機関の査定を行うことの方が現実的な対策であるだろう。

4．受診率対策

わが国の癌検診全般の受診率は残念ながら正確な数字がない。これは，市町村が提供する住民検診に加えて，職域検診や人間ドックなどの受診者数が把握されていないためである。また市町村の検診受診対象者という定義は，単純に 40 歳以上の全住民ということではなく，ほかに職場等で検診を受診する機会のないものと定められているために，各地での対象者の定義はバラバラである。渡邊らは，国民生活基礎調査から推定した肺癌検診受診率を 16.5％と推定している[17]が，これは諸外国の癌検診受診率に比べて極めて小さな数字である。英国を中心としたヨーロッパでは，organized screening と呼ばれる国を挙げた癌検診が行われ，対象者の実に 8〜9 割が少なくとも 2 年に 1 回は子宮頸癌検診と乳癌検診を受診している。受診率を向上させている理由は，対象者名簿に基づいた個別の受診勧奨が行われることと，一定数の対象者を検診受診へと結びつけた家庭医にインセンティブが与えられることなど，非常に実務的なシステムが構築されていることである。また同様に高い受診率を示す米国では癌患者団体を中心としたボランタリーグループによる，個別の受診干渉が行われている。主な欧米諸外国では検診の費用は無料であり，公的な費用で運営されている。日本ではこれまでの公的な費用負担により癌検診を運営してきたが，近年個人負担へと移行してきている。また個人の健康管理は個人に責任があって，自治体や職域はそれを支援するだけという体制に変わりつつある。これは諸外国とはまったく反対の動きであり，受診率上昇の障碍といわざるをえない。国民的レベルでの議論が必要である。

5．低線量 CT 検診への期待と課題

低線量 CT 検診は，1993 年に「東京から肺がんをなくす会」で世界に先駆け開始された[18]。その高い癌発見率・発見肺癌の腫瘍径の小型化・高い切除率・Ⅰ期率・生存率はすでに周知のことであろう。しかし，この検診も死亡率減少効果という検診に必須の評価指標に関してのエビデンスはまだ存在しない。また開発当初より懸念された数々の問題点についても解決されていない。被曝線量に関しては，シングル・ディテクター CT で 0.60 (25 mAs)[19]〜1.40 (50 mAs) mSv[20] とされている。この線量は胃透視検査の線量とほぼ同じであるが，胸部単純 X 線検査に比べて約 15〜20 倍である。このような大きな線量を毎年健常者に照射することを正当化するためには，よほどしっかりした効果に関するエビデンスが確立されねばならない。また要精検率の高さは，10〜25％と報告されている。新しく検診を開始した施設や，マルチディテクター CT を導入した施設から特に高い値が報告されている。過剰な要精検率は要精検者への精神的かつ費用負担を要する。また精密検査機関ではあまり小さな陰影に対しては，CT による経過観察以外に方法がなく，その費用負担やマンパワー，被曝線量は膨大なものになりうる。この分野での中心的な働きをしている日本 CT 検診学会では，「single slice helical CT による肺癌 CT 検診の判定基準と経過観察ガイドライン」が報告されている[21]。ここでは 5 mm 以上の結節のみを要精検とすることが明文化されており high resolution CT の所見により，経過観察の仕方を区分している（図 2）。このガイドラインに沿った診療の普及を期待したい。さらにいえば，現行の“CT 検診”は，CT のある医療機関ならどこでも実施可能となっている。ただしこれでは高い精度を期待できるはずがない。今後撮影や読影の認定医制度や認定施設制度が必要になることはいうまでもなく，これら諸制度の確立が必要だろう。

6．まとめ

肺癌検診は，他の癌検診と異なり，その効果が世界中で確立している訳でもなく，また精度管理

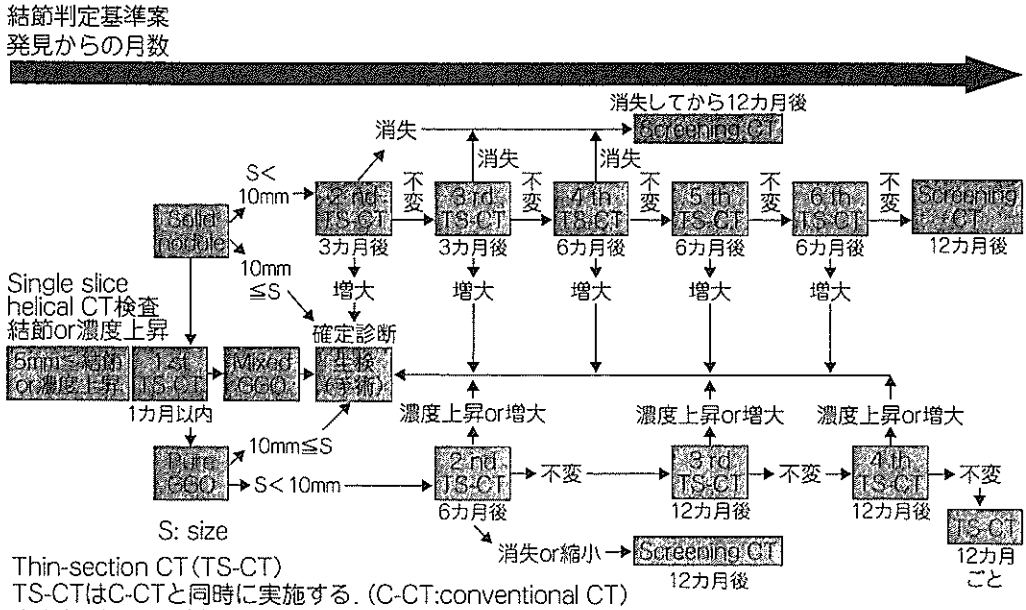

図 2　肺癌 CT 検診の判定基準と経過観察の判断樹

〔文献 21）http://www.thoracic-ct-screening.org/jpn/index.html (2006/05/19 現在) . より引用〕

が行き届いていないことから，バラツキの多いものである。これらは肺癌検診が本来もつ効果の問題というよりは，受診者の干渉，検査の精度，精密検査の受診といった検診に関わる社会的システムの不整備に基づく部分が多い。検診による恩恵は，過去 30 年間の肺癌手術例数の増加や切除例の生存率の向上などに現れていることはいうまでもなく，肺癌を扱う臨床医は単純に批判的な立場で対処することは明らかな間違いである。現在のタバコ対策の大きな動きには，関連学会の禁煙宣言等の動きが影響している。肺癌検診に関しても，関連学会等を含めた専門医の動きが社会の動きを助長するために不可欠である。

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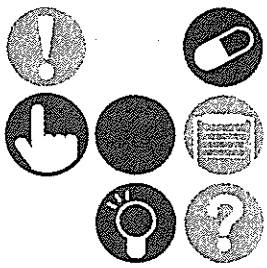

呼吸器

肺がん検診を受けると，肺がん死亡率を減らせるのか？

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呼吸器

肺がん検診を受けると，肺がん死亡率を減らせるのか？

大阪府立成人病センター調査部疫学課　中山富雄　鈴木隆一郎

はじめに

肺がん対策として，わが国では1970年代より胸部単純X線撮影を中心とした肺がん検診が老人保健法の下に広く行われてきたが，十分な成果が上がっているとはいい難い．一方米英では，70年代に行われたランダム化比較試験（RCT）において死亡率減少効果が示されなかったことから，肺がん検診の代わりに国家規模でタバコ対策が推し進められた結果，肺がん死亡率の減少が，国レベルで認められている．しかし手術で治癒しうる早期肺がんは，わが国に圧倒的に多く，その発見動機の大半は，「肺がん検診」の胸部単純X線である．本稿では，これらの矛盾に関する，現時点での考え方について概説する．

I 国外の検診の評価

表1にNational Cancer Institute（NCI）主導で，行われた4つのRCT[1~11]を示す．結果として4つの研究いずれも，研究群と対照群の間で肺がん死亡率の差は認められなかった．この成績を元に，諸外国では公的施策としての肺がん検診は行われていない．

しかしこの4つの研究の結果に関しては，30年以上たった現在においても，議論が続いておりいまだ決着はついていない．4つの研究のうち最大かつ胸部単純X線撮影の効果を評価したMayo Lung Project（MLP）に関する議論について解説する．研究デザインは45歳以上の喫煙男性9,221名を，年齢・喫煙指数・アスベスト曝露歴・COPDの有無などを層別化因子として，研究群と対照群の2群にランダムに割り付けた．研究群には4ヵ月ごと6年間の胸部単純X線撮影と喀痰細胞診を提供し，対照群には，年1回の胸部単純X線撮影と喀痰細胞診を推奨するにとどめた．その結果，研究群で206例，対照群で160例の肺がんの罹患が確認されたが，**肺がん死亡率は両群において差を認めなかった**（図1）．死亡が同数で罹患に46例の差があることに関して，**Eddyらは，過剰診断（放置しても死亡しない進行のゆるやかながん）によるものとしており**，以後肺がん検診無効論の中心となっている．一方日頃進行の速い肺がんばかりを扱う臨床家の立場から，Straussら

表1　NCI主導の肺がん検診の有効性を評価したランダム化比較試験

	開始年	検診方法		参加者数	相対危険度（95%信頼区間）
		検診群	対照群		
JHLP[1]	1973	胸部X線年1回＋喀痰4ヵ月ごと	胸部X線年1回	5,250：5,171	0.91（0.72～1.16）
MSKLP[2]	1974	胸部X線年1回＋喀痰4ヵ月ごと	胸部X線年1回	4,968：5,072	0.92（0.67～1.26）
MLP[3]	1971	X線と喀痰4ヵ月ごと	X線と喀痰年1回を推奨	4,618：4,593	1.06（0.82～1.36）
CSLP[4]	1976	X線と喀痰6ヵ月ごと	無検診	3,171：3,174	1.36（0.94～1.97）

JHLP：Hopkins Lung project，MSKLP：Memorial Sloan-Kettering Lung project，
MLP：Mayo Lung project，CSLP：Czechoslovakian Lung project

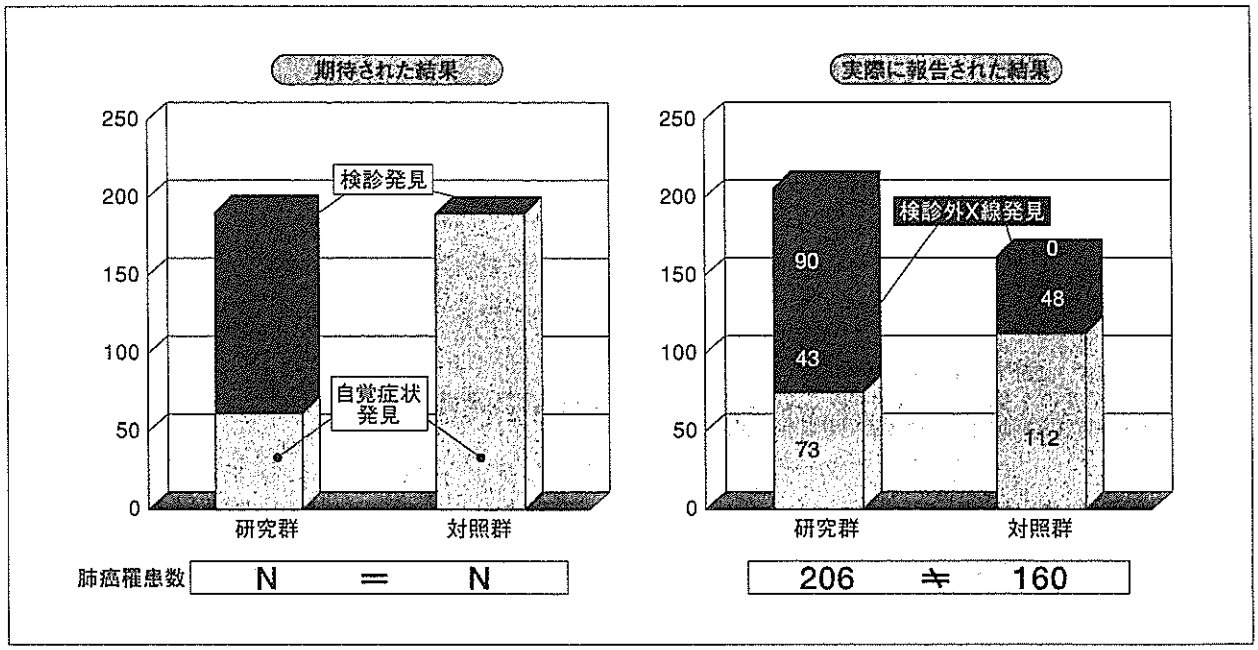

図1　Mayo Lung Projectの罹患肺癌数の期待と結果
この研究では，研究参加者は検診以外で胸部X線を撮影されることは予想されていなかったが，最後の2年間の調査では，対照群の約73%が胸部X線撮影を受診していたと報告されている．このため検診外のX線発見が両群とも予想以上に多い．

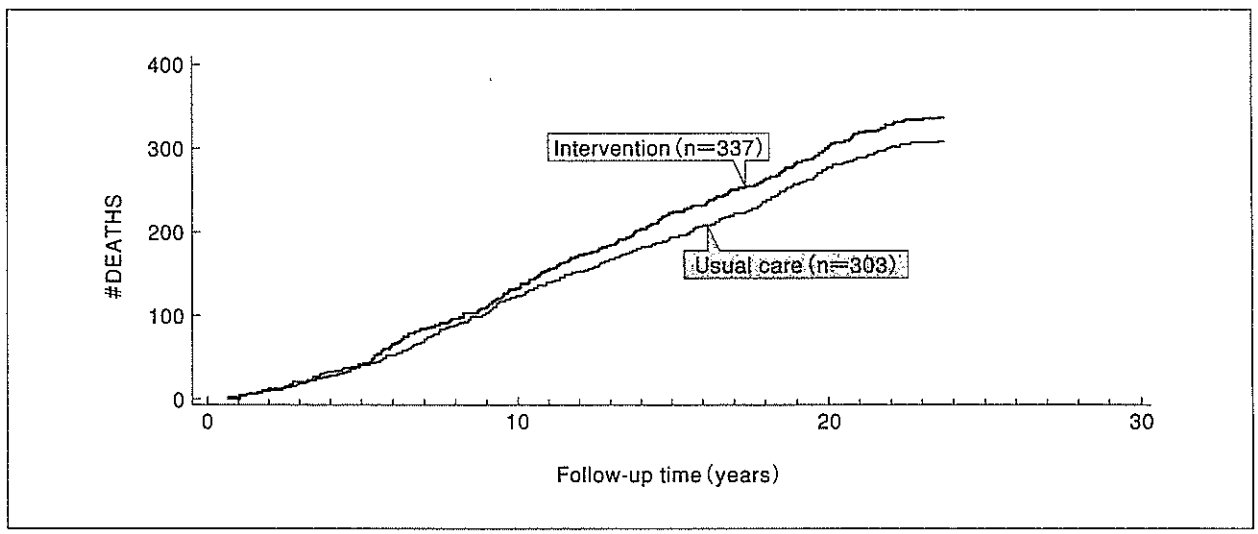

図2　Mayo Lung projectの累積肺がん死亡率　（文献5）より引用）
登録から平均20.5年の追跡期間．Interventionが研究群，Usual careが対照群を示す．

は206例（うち純粋な検診発見は90例）中46例が過剰診断という意見を容認できないとし，①追跡不十分仮説（追跡が途中で打ち切られたため，対照群の46例がまだ把握されていない），②偶然仮説（未知のリスクファクターの割付が偶然不均等になり，研究群の方が罹患率の高い集団になってしまった）などを提唱している．最近Marcusらは，MLPの対象者の20年以上にわたる死亡を把握したが肺がん死亡率に差を認めなかったとし，追跡不十分仮説を否定した[5]．しかしこの追跡研究において研究群の方が累積肺がん死亡率が高い傾向にあること（図2）などから，「偶然仮説」を否定できてはいない．このように**30年以上たった現在も"質の高い研究"であるはずの4つのRCTの**

表2　国内で行われた肺がん検診の有効性を評価した症例対照研究

	開始年	検診方法	参加者数（症例：対照）	OR (95%CI)
成毛班[9]	1977	胸部間接X線＋喀痰細胞診	273：1,269	0.72 (0.50～1.03)
金子班[9]	1985	胸部直接X線＋喀痰細胞診（個別検診）	193：579	0.53 (0.30～0.94)
藤村班 群馬[10]	1989	胸部間接X線単独	121：536	0.68 (0.44～1.05)
藤村班 宮城[11]	1990	胸部間接X線＋喀痰細胞診	328：1,886	0.54 (0.41～0.73)
藤村班 新潟[12]	1990	胸部間接X線＋喀痰細胞診	174：801	0.40 (0.27～0.59)
藤村班 岡山[13]	1991	胸部間接X線＋喀痰細胞診	412：3,490	0.59 (0.46～0.74)

下線部は，統計学的有意差を示したもの．
6つの研究のうち5つは，集団検診方式によるもので，金子班の研究は医療機関個別方式によるもの（第2読影者を呼吸器専門医とし，精度管理委員会を医師会に設けた）．

解釈は，確立していない．

II 国内の検診の評価

わが国では，結核予防法で年1回の胸部単純X線　撮影が義務づけられていたため，事前評価を行わずに，肺がん検診を行政施策として普及させた．その後症例対照研究を繰り返し行うことで，その有効性を示すことが試みられてきた．症例対照研究は，対象集団から症例（肺がん死亡者）と，ほかのリスクファクターをマッチさせた対照（生存者および非肺がん死亡者）を無作為に選択し，症例の診断前の検診受診歴を比較するものである．RCTに比べると，偏りが混入しやすいという欠点がある．表2に国内で行われた症例対照研究の成績を示す[6～11]．**6つの研究のいずれもが，年1回の肺がん検診受診により肺がん死亡リスクの減少を示しており，うち4つが統計学的に有意であった．**

III 国内外での検診の評価

国内と国外の代表的な肺がん検診の有効性評価ガイドラインを提示する．厚生労働省の久道班報告書では，国外の研究と国内の研究に分け，国内での「胸部単純X線撮影と高危険群に対する喀痰細胞診」を「検診による死亡率減少効果があるとする，相応の根拠がある」と評価し，欧米の肺がん検診を，「検診による死亡率減少効果がないとする，相応の根拠がある」と評価している[12]．

また米国で最も信頼性の高いUSpreventive service task force（USPSTF）の第4版では，日本で行われた症例対照研究も評価に加えて「無症状者に対する低線量CT，胸部単純X線撮影，喀痰細胞診あるいはこれらの組み合わせによる検診を推奨する根拠は不十分」と評価している[13]．これは従来の「肺がん検診は推奨されない」に比べると，かなり評価が検診擁護に傾いている．とくに本文においては，「30年前の研究による強いエビデンスは男性喫煙者に対してベネフィットがないことを示唆しているが，よりエビデンスの弱い研究では男女ともベネフィットがあることを示唆している．しかしどの研究にも方法論上の制限がある」と記載されている．

IV 肺がん検診は肺がん死亡率を減少させるといっていいのか？

さて，たとえ国内の複数の研究で肺がん死亡率減少効果が示されていたとしても，わが国のすべての肺がん検診の有効性が保証されている訳ではけっしてない．これらの研究は専門医が読影や精密検査に従事し，高い受診率・精検受診率などの精度管理システムが構築された地域での評価であり，あくまでefficacy（理想的な状況における有効

性）が示されただけで，effectiveness（現実の場における有効性）が示されたわけではない．胸部単純X線撮影の読影は，卓越した解剖学的知識と経験が必要とされるものの，読影専門医制度を設けずに，検診が行われてしまった．また，有症状者や，肺がん治療例の再発確認など医療でカバーされるべきものが，実際の検診の現場では多く混入する．これでは集団としてみても到底肺がん死亡率の減少は期待できない．**死亡率減少を期待するのであれば，きちんとした精度管理システムを構築する必要がある．**

結論として，「肺がん検診を受けると，肺がん死亡率は減らせるのか？」という命題に対しては，きちんとした精度管理システムの元では集団としての死亡率は減少させることが可能であると考えられる．ただし個人単位に関しては，個人の年齢・性・喫煙歴等で左右される可能性があり，今後の研究成果を待たねばならない．

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ORIGINAL INVESTIGATION

Computed Tomographic Screening for Lung Cancer

The Relationship of Disease Stage to Tumor Size

*The International Early Lung Cancer Action Program Investigators**

Background: The relationship of lung cancer stage to tumor diameter has been identified as a prognostic indicator. We report on the stage-size relationship of these asymptomatic, latent lung cancer cases diagnosed by computed tomographic screening.

Methods: Baseline and repeat screening of 28 689 people following the International Early Lung Cancer Action Program regimen of screening has resulted in 464 diagnoses of lung cancer. Each case was characterized according to tumor diameter, consistency (solid, part solid, or nonsolid), and the presence or absence of identifiable metastases (N0 M0) at the time of diagnosis, regardless of whether it was delayed.

Results: For the 436 non–small cell carcinomas, the percentages of cases with no metastases (N0 M0) were 91%, 83%, 68%, and 55% for the categories 15 mm or less, 16 to 25 mm, 26 to 35 mm, and 36 mm or greater, respectively. The gradients in the successive percentages of N0 M0 cases were significantly different (P=.02, 1-sided), except between the last 2 categories, and held for solid nodules, were suggestive for part-solid ones, but were not suggestive for nonsolid ones. For the 28 small cell carcinomas, the percentages of N0 M0 cases were 67% and 23% (P=.01, 1-sided), respectively, for those 25 mm or less compared with those greater than 25 mm.

Conclusions: Lymph node status has a strong relationship to tumor diameter for non–small cell and small cell cancers. The percentages of N0 M0 cases in screen-diagnosed lung cancers are much higher than previously reported in the Surveillance, Epidemiology, and End Results registry. These results provide direct evidence of a stage-size relationship in a screened population.

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FOR STAGE I LUNG CANCER, tumor size has been identified as a prognostic indicator. It thus was incorporated into the International System for Staging Lung Cancer[1] classification in 1986. Cases without identifiable lymph node metastases (stage I cases) were subdivided into stage IA and stage IB, according to the tumor being less or more than 30 mm in diameter. This refinement in staging has been continued,[2] but all were based on registries of cases.

Since 1986, remarkable advances have occurred in computed tomography (CT) scanners. Submillimeter slicing can now be applied to the entire chest in a single breathhold; as a result, lung cancer is being detected at a smaller size than in cases diagnosed before 1986. Further size-based subdivisions of stage I cancer have been suggested, also based on registry cases.[3-6]

The introduction of CT screening leads to consideration of the prognostic value of tumor size in the context of diagnoses of asymptomatic (thus latent) lung cancers. Until now, registry data have been used to investigate disease stage in relation to tumor size for these smaller, latent cancers.[6] Registry cases, however, do not expressly reflect the stage-size relationship of asymptomatic cases; registry cases typically come to medical attention because of symptoms, possibly metastasis induced, whereas latent cases are found in asymptomatic people.

We report the stage-size relationship of latent lung cancers diagnosed in our International Early Lung Cancer Action Program (I-ELCAP), which is dedicated to research on CT screening for lung cancer.[7] These data provide for the first time, to our knowledge, direct evidence relevant to this issue.

METHODS

Following the I-ELCAP protocol,[8] 28 689 asymptomatic men and women were enrolled and received baseline screening at 38 institutions throughout the world; among them,

*Authors: The Writing Committee members for the International Early Lung Cancer Action Program (I-ELCAP) are Claudia I. Henschke, PhD, MD; David F. Yankelevitz, MD; and Olli S. Miettinen, MD, PhD. Group Information: A complete list of the I-ELCAP investigators appears on page 325.

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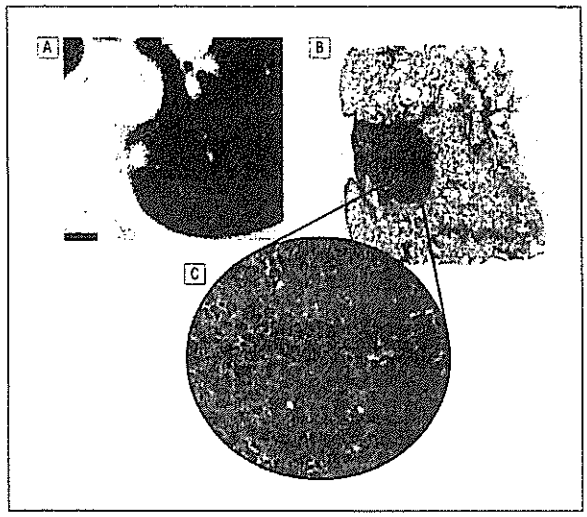

Figure 1. A computed tomographic image and biopsy specimen from a 72-year-old woman. High-resolution computed tomographic image shows a solid 7-mm left lower lobe nodule abutting the pleura (A). The diagnosis was solid adenocarcinoma with mucin, Noguchi D[6] (hematoxylin-eosin, original magnification ×2) (B). Magnified area shows that the tumor is composed of sheets of polygonal cells with enlarged vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. By definition, solid adenocarcinoma with mucin lacks acini, tubules, and papillae (as seen in this image) but contains mucin in at least 5 tumor cells in each of 2 high-power fields, confirmed by histochemical stains for mucin (not seen in this image) (hematoxylin-eosin, original magnification ×40) (C).

22 991 repeat screenings have been performed. At enrollment, the median age was 61 years, median pack-years of smoking was 30, and 58% of the study participants were men. Baseline screenings were conducted in 1993 to 2004 and repeat screenings in 1994 to 2004. All participants gave informed consent for baseline and repeat screenings under institutional review board–approved protocols.

The I-ELCAP protocol defined the initial low-dose, noncontrast CT test and its positive result at both baseline and repeat screening. It also defined the recommended diagnostic workup following a positive result. The actual workup, however, was left to the discretion of each participant and the referring physician, but it was documented in the Web-based ELCAP Management System.[7]

All screen-diagnosed cases of lung cancer are included in this report. They consist of cases in which the diagnostic workup was prompted by a positive result of the initial CT test on either the baseline or repeat screening, even if the interval to repeat screening was more than 12 months or the diagnostic workup was delayed, the latter by as much as 3 years. Thus, we excluded the interim-diagnosed cases, identified on the prompting of symptoms emerging between screenings. We focused on the first primary lung cancer that was diagnosed.

A total of 464 cases of lung cancer were screen diagnosed, 376 and 88 of the diagnoses prompted by a positive result of the initial CT test at baseline and on repeat screening, respectively. Each screen-diagnosed case of lung cancer was characterized according to tumor diameter, consistency, and the presence or absence of identifiable lymph node or distant metastases at the time of diagnosis by 1 of 3 experienced chest radiologists (C.I.H., D.F.Y., or Dorothy I. McCauley, MD) at the I-ELCAP Coordinating Center. Tumor diameter was derived as the average of its length and width measured on the pathologic specimen, if available; otherwise, it was measured on the CT images closest in time to diagnosis. Nodule consistency was classified as solid, part solid, or nonsolid on the basis of these same images.[9] It was defined as solid if the nodule obscured the entire lung parenchyma within it (**Figure 1**) or subsolid if it did not. We further subdivided subsolid nodules into part solid if it obscured part of the lung parenchyma within it (**Figure 2**) and nonsolid if it obscured none of the parenchyma within it (**Figure 3**).

Biopsy specimens were submitted to experts for independent reading: cytology specimens to an expert cytologist (Madeline Vazquez, MD) and histologic specimens to our 5-member Pathology Review Panel (Darryl Carter, MD, chair, Elizabeth Brambilla, MD, Adi Gazdar, MD, Masayuki Noguchi, MD, and William Travis, MD) for reading according to the I-ELCAP pathology protocol.[10] Histologic diagnosis superseded the cytologic one when both were available. For purposes of this report, we used the consensus diagnoses of these experts, following the 2004 World Health Organization criteria.[11] Among the 464 cases, there were 436 diagnoses of non–small cell carcinoma and 28 diagnoses of small cell carcinoma.

Lymph node status was based on the surgical findings when available; otherwise, it was based on the CT (and positron emission tomography, if done) test performed closest in time to the recommendation for biopsy, identical to the reporting in the National Cancer Institute–sponsored Surveillance, Epidemiology, and End Results (SEER) registry. Hilar and mediastinal lymph nodes were classified as metastatic if the short axis on CT was greater than 10 mm or the positron emission tomographic scan showed any uptake. It was classified as N0 (no metastases), N1 (only ipsilateral peribronchial, hilar, and/or intrapulmonary metastases), N2 (ipsilateral mediastinal and/or subcarinal metastases, no contralateral), or N3 (contralateral mediastinal and/or hilar, scalene, or supraclavicular metastases). Status of distant metastases was classified as M0 (absent) or M1 (present). Staging was based on the postsurgical findings in 368 (84%) of the 426 cases of non–small cell carcinoma and in 8 of the 28 cases of small cell carcinoma. For these 376 resected cases, the presurgical and postsurgical stages were identical for 335 (89%) of them. Of the 41 cases in which there was disagreement, 37 were presurgical N0 but postsurgical N1 to N3, and 4 were presurgical N1 to N2 but postsurgical N0.

We classified the tumors in the following categories of diameter: 15 mm or smaller, 16 to 25 mm, 26 to 35 mm, and 36 mm or greater. We focused principally on the frequency of N0 M0 status in these categories. Because it is well established that the frequency of N0 M0 decreases with increasing tumor size, we used the 1-sided test for assessing significant differences between the size categories. Statistical analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC).

RESULTS

Table 1 gives lymph node status by tumor size for 436 diagnosed cases of non–small cell lung cancer. The proportions of cases with no metastases (N0 M0) were 85% overall and 91%, 83%, 68%, and 55% for the respective size categories of 15 mm or smaller, 16 to 25 mm, 26 to 35 mm, and 36 mm or greater. The gradients in the successive percentages of N0 M0 were significantly different ($P=.02$, 1-sided), except between the last 2 categories. Of the 370 cases classified as N0 M0, 323 (87%) were based on postsurgical staging.

Table 2, like Table 1, addresses lymph node status in relation to tumor size in those 436 cases of non–small cell lung cancer, but separately according to nodule consistency. The declining trend in the frequency of N0 M0 status with increasing size of the tumor is evident for solid nodules, suggestive for part-solid ones, but not suggestive for nonsolid ones. All non–small cell patho-

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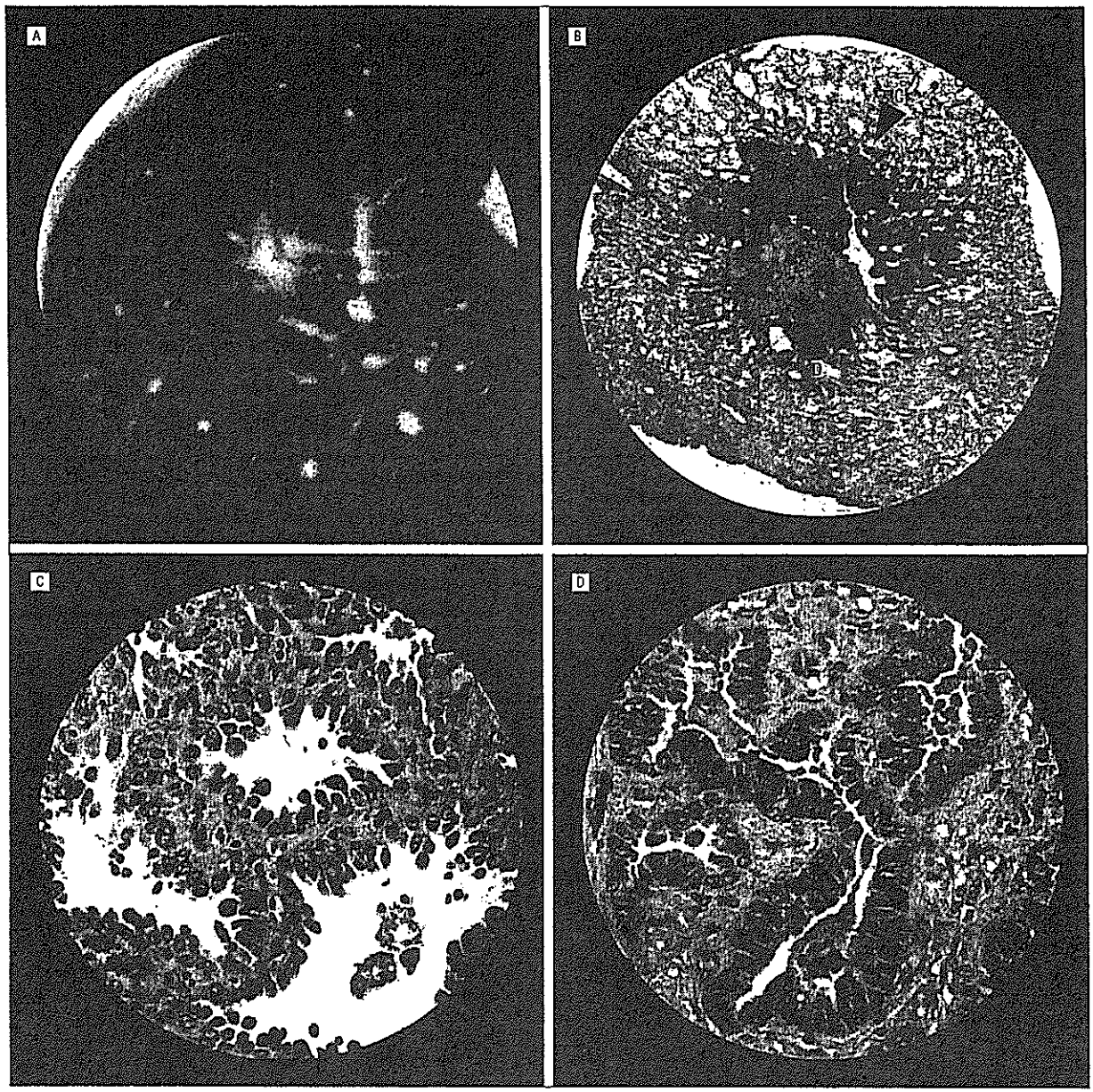

Figure 2. A computed tomographic image and biopsy specimen from a 48-year-old man. The high-resolution computed tomographic image shows a part-solid 15-mm right upper lobe pulmonary nodule; note the patent bronchus in the center of the nodule (A). The diagnosis was adenocarcinoma, mixed subtype, Noguchi C[6] (B) (hematoxylin-eosin, original magnification ×2). Arrowheads indicate magnified areas. Magnified areas show the peripheral noninvasive bronchioloalveolar subtype (C) and the central invasive acinar subtype (D) (hematoxylin-eosin, original magnification ×40).

logic classifications were represented by the cancers presenting in solid nodules, whereas only adenocarcinoma (bronchioloalveolar or mixed subtype) was found in those presenting as part-solid and nonsolid nodules. For solid nodules, the proportions of N0 M0 cases of adenocarcinoma and squamous cell carcinoma were not significantly different (81% vs 79%, respectively; $P=.69$).

For small cell lung cancers, all presenting as solid nodules, the trend in the percentage of N0 M0 status by tumor size is strongly apparent (**Table 3**). Because of the small number of cases, we pooled the data and compared only those 25 mm or less with those larger than 25 mm. The proportions of N0 M0 cases were significantly different: 67% (10/15) and 23% (3/13), respectively ($P=.01$, 1-sided).

COMMENT

Among cases of non–small cell lung cancer diagnosed in asymptomatic persons by CT screening, we find lymph node status to have a strong relationship to tumor diameter for cancers that present as solid nodules. Among the few cases of small cell lung cancer, all presenting as solid nodules, a relationship between lymph node status and tumor diameter was also seen.

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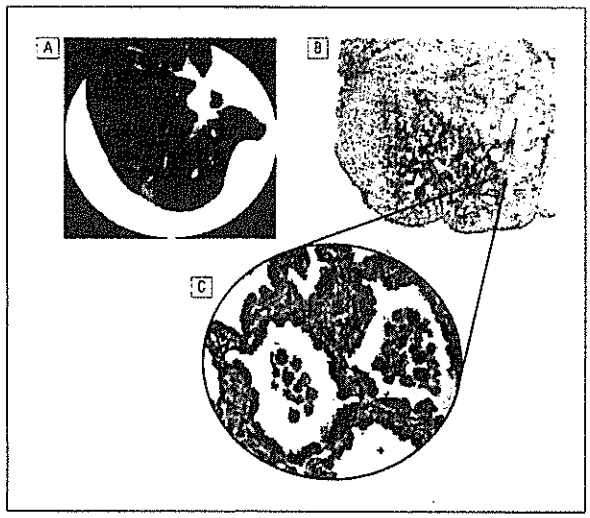

Figure 3. A computed tomographic image and biopsy specimen from a 66-year-old woman. High-resolution computed tomographic image shows a nonsolid 5-mm right lower lobe nodule abutting the pleura (A). The diagnosis was adenocarcinoma, nonmucinous bronchioloalveolar subtype, Noguchi A[6] (hematoxylin-eosin, original magnification ×2) (B). Magnified area shows a classic lepidic growth pattern lining the alveolar septa (hematoxylin-eosin, original magnification ×40) (C).

Table 1. Lymph Node Status of 436 Cases of Non–Small Cell Lung Cancer at Diagnosis by Tumor Diameter*

	Tumor Diameter, mm				
Lymph Node†	≤15	16-25	26-35	≥36	Any
N0 M0	234	98	27	11	370
N1 M0	5	9	5	4	23
N2 M0	19	10	8	4	41
N3 M0/M1	0	1	0	1	2
Total (% of N0 M0)	**258 (91)**	**118 (83)**	**40 (68)**	**20 (55)**	**436 (85)**

*For tumor diameter ≤15 vs 16-25, $P = .02$; for 16-25 vs 26-36, $P = .02$; and for 26-35 vs ≥36, $P = .17$.

†Cancer stages are as follows: N0 M0, absence of identifiable metastases; N1 M0, peribronchial or hilar lymph nodes, no other metastases; N2 M0, ipsilateral mediastinal lymph nodes, no other metastases; N3, M0/M1, contralateral mediastinal lymph nodes, without or with other metastases.

The relationship of lymph node status to tumor size was not apparent for cancers that presented as nonsolid nodules, whereas it was suggestive for those that presented as part-solid nodules. Cancers that present as nonsolid nodules are noninvasive adenocarcinomas or adenocarcinoma–mixed subtype with a small invasive component and thus have not yet spread to the lymph nodes, as demonstrated by Noguchi et al.[12]

The percentages of N0 M0 cases specific to categories of tumor diameter for non–small cell lung cancer in this report are much higher than those reported from the SEER registry data, which were 54%, 46%, 34%, and 18%, respectively (**Figure 4**).[6] The trend, however, was evident in the SEER data as well. It was not apparent in the analysis of a much smaller registry[13] for reasons explained in subsequent publications.[14,15] Nevertheless, results from that same registry were used as part of the justification for performing a large randomized controlled trial.[16] We have now demonstrated the prognostic significance of tumor size directly.

Table 2. Lymph Node Status of 436 Cases of Non–Small Cell Lung Cancer at Diagnosis by Tumor Diameter and Separately According to Nodule Consistency

	Tumor Diameter, mm				
Nodule Consistency and Lymph Node Status	≤15	16-25	26-35	≥36	All
Solid					
N0 M0*	146	65	18	6	235
Other	23	18	12	9	62
Total (% of N0 M0)	**169 (86)**	**83 (78)**	**30 (60)**	**15 (40)**	**297 (79)**
Part solid					
N0 M0*	48	22	5	2	77
Other	1	2	1	0	4
Total (% of N0 M0)	**49 (98)**	**24 (92)**	**6 (83)**	**2 (100)**	**81 (95)**
Nonsolid					
N0 M0*	40	11	4	3	58
Other	0	0	0	0	0
Total (% of N0 M0)	**40 (100)**	**11 (100)**	**4 (100)**	**3 (100)**	**58 (100)**

*Absence of identifiable metastases.

Table 3. Lymph Node Status of 28 Cases of Small Cell Lung Cancer at Diagnosis by Tumor Diameter (All With Solid Consistency)

	Tumor Diameter, mm				
Lymph Node	≤15	16-25	26-35	≥36	Any
N0 M0*	6	4	2	1	13
Other	3	2	3	7	15
Total (% of N0 M0)	**9 (67)**	**6 (67)**	**5 (40)**	**8 (13)**	**28 (46)**

*Absence of identifiable metastases.

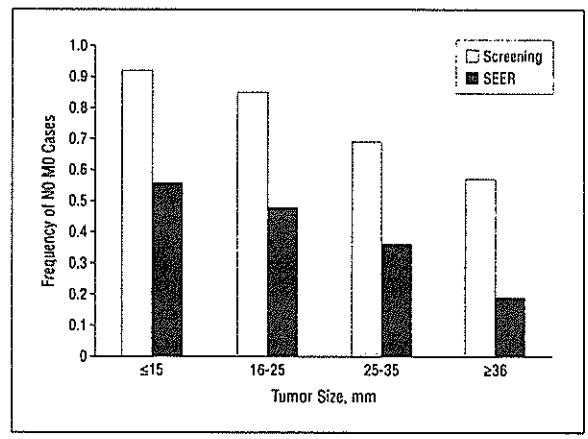

Figure 4. Frequency distribution of cases with absence of identifiable metastases (N0 M0) specific to categories of tumor diameter (≤15 mm, 16-25 mm, 26-35 mm, and ≥36 mm) for non–small cell lung cancer diagnosed as a result of screening and compared with the Surveillance, Epidemiology, and End Results (SEER) registry data.

The pattern confirmed herein suggests the usefulness of finding latent cancers at small sizes. Most lung cancers without evidence of lymph node metastases are curable, with the curability rate being higher at smaller sizes.[5,6] This suggests that tumor diameter also serves as a prognostic indicator for curability, perhaps even for micrometastases not detectable by our current techniques.

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Women's Susceptibility to Tobacco Carcinogens and Survival After Diagnosis of Lung Cancer

International Early Lung Cancer Action Program Investigators*

Context It has been hypothesized that women are more susceptible to tobacco carcinogens than men, but after diagnosis of lung cancer, they have better survival rates than men.

Objective To add to the evidence on the lung cancer risk of women who smoke and their survival after diagnosis of lung cancer, conditional on other prognostic indicators and compared with men of the same age who smoke.

Design, Setting, and Participants Nonexperimental, etiologic study with prospective collection of data based on baseline computed tomographic screening for lung cancer and follow-up of diagnosed cases of lung cancer in North America in 1993-2005. A total of 7498 women and 9427 men were screened, all of whom were asymptomatic, aged at least 40 years, and had a history of cigarette smoking.

Main Outcome Measures Comparing women with men, the prevalence odds ratio (OR) for screen-detectable lung cancer (conditional on age and smoking history) and the hazard ratio of fatal outcome of lung cancer (conditional on smoking history, disease stage, tumor cell type, and resection).

Results Lung cancer was diagnosed in 156 women and 113 men (rates of 2.1% and 1.2%, respectively).The prevalence OR comparing women with men was 1.9 (95% confidence interval [CI], 1.5-2.5). The hazard ratio of fatal outcome of lung cancer comparing women with men was 0.48 (95% CI, 0.25-0.89).

Conclusion Women appear to have increased susceptibility to tobacco carcinogens but have a lower rate of fatal outcome of lung cancer compared with men.

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In 2006 in the United States, it is estimated that lung cancer will cause 73 020 deaths in women, proportionately only slightly fewer than the estimated 90 470 deaths in men.[1] Lung cancer now accounts for more deaths in women than any other cancer, more even than the second and third cancer killers (breast and colon cancer) combined.

Research to quantify the benefit of computed tomographic (CT) screening for lung cancer in preventing deaths is ongoing. We previously reported on the Early Lung Cancer Action Project (ELCAP) baseline screening study of 2490 high-risk persons, which indicated that women have a higher absolute risk for lung cancer than do men of the same age with the same history of smoking.[2] There have been other studies indicating that women have a higher relative risk of getting lung cancer than men[3-9]; other studies disagree,[10-12] the issue being the smoker vs nonsmoker risk ratio.

Sex differences in rates of survival following diagnosis of lung cancer have also been reported. Women have been reported to have higher survival rates regardless of the stage of the disease at diagnosis,[9,12-21] the most recent evidence in the United States derived from the national Surveillance, Epidemiology, and End Results (SEER) database[9] and a large cohort at the Mayo Clinic.[21]

Since our previous report, screening has continued at the original ELCAP institutions and has markedly expanded the amount of poolable data by institutions collaborating worldwide in the International Early Lung Cancer Action Project (I-ELCAP).[22] In this article, we again address the lung cancer risk of women compared with men, accounting for age and history of smoking, but herein we also compare the rate of fatal outcomes between sexes.

For editorial comment see p 218.

METHODS

In our previous report, we addressed the risk for lung cancer in 1202 women and 1288 men using New York City data undergoing baseline screening at Joan and Sanford I. Weill Medical College of Cornell University in 1993-1999 (series 1).[2] This report is based on a new

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series of 14 435 persons (6296 women and 8139 men) undergoing baseline CT screening for lung cancer in North America in 1999-2005 (series 2), and also on both series combined (7498 women and 9427 men). The comparison of women with men as to fatal outcome of cancer is based on cases from both screening series combined.

All of the screenees were asymptomatic volunteers with no history of cancer (other than nonmelanotic skin cancer) and fit to undergo thoracic surgery, were at least 40 years of age, and were past or current cigarette smokers. All of the participants gave informed consent for baseline and repeat screenings under institutional review board–approved protocols. The cohorts' distributions by age and history of smoking are shown in TABLE 1.

Table 1. Distribution of the 2 Series of Baseline Screenings by Age and History of Smoking

Characteristic	Series 1 (n = 2490)		Series 2 (n = 14 435)		Combined (N = 16 925)	
	Women	Men	Women	Men	Women	Men
Age, y						
Median	63	64	63	64	63	64
Mean	63	63	63	64	63	64
Pack-years of smoking, No.						
Median	36	42	40	40	39	40
Mean	40	47	42	44	42	45
Age at start of smoking, y						
Median	17	17	17	17	17	17
Mean	18	17	18	17	18	17

Information about smoking history was recorded at the time of the initial CT baseline screening. Participants were asked about the following by an interviewer: the age at which habitual smoking began and whether the habit had continued to the last month; if smoking had continued, the daily number of cigarettes smoked in that month; and if smoking had not continued, the typical number of cigarettes smoked per day and the duration of the smoking history. Pack-years of smoking was calculated as the product of the number of cigarettes smoked per day divided by 20 and the number of years of smoking.

The protocol specified a diagnostic workup following a positive result of the initial low-dose CT, ie, the identification of a specified pattern of noncalcified nodules. Although updated since our prior report, this workup has remained essentially unchanged in its indications for biopsy: demonstration of tumor growth on the CT scan, positive positron emission tomographic scan result, or CT 1 month after the initial scan not showing resolution after antibiotic treatment[23]; for nodules 15 mm or more in diameter, immediate biopsy was an option. A nodule's diameter was calculated as the average of its length and width in the image showing its largest cross-section in the CT scan closest to the time of diagnosis.

The consensus diagnoses by a panel of 5 experts on lung pathology, following the I-ELCAP pathology protocol[24,25] based on the 2004 World Health Organization criteria,[26] are used in this article. For patients undergoing resection, diagnoses were based on the histology of the surgical specimens; for other patients, diagnoses were based on the cytology of the biopsy specimens.

The women vs men incidence density ratio for lung cancer was the ratio of the corresponding prevalence odds ratio (OR) (cancer present vs cancer absent),[27] conditional on age and history of smoking. In logistic regression analysis (unconditional), with the dependent variate an indicator of cancer diagnosed (Y = 1 if diagnosed, 0 otherwise), we controlled for possible confounding by age by means of a single quantitative term, there being no apparent actual confounding (Table 1); we also used a single quantitative term for pack-years of smoking, which indicated a slight confounding (Table 1).

All cases of lung cancer diagnosed in the combined series have been followed up. In cases of known death, the date and cause of death were obtained from the patient's physician and/or family members. If the patient died as a result of the lung cancer treatment, it was also considered to be a lung cancer death. Follow-up time from diagnosis onward—to death from lung cancer, last contact, or March 15, 2006, whichever came first—was calculated for each case; it ranged from 1 to 117 months (median, 46 months).

The women vs men incidence density (hazard) ratio of fatal outcome of lung cancer in the combined cohort was addressed as the ratio of the respective risks, conditional on pack-years of smoking, disease stage, tumor cell type, and resection. This was performed using multivariate Cox proportional hazards regression analysis to test the independent effect of patient sex after accounting for pack-years of smoking at time of diagnosis, clinical stage of the disease (I, II+), cell type (adenocarcinoma, other non–small cell, small/large cell), and resection (yes, no).

All statistical analyses were performed using the SAS version 8.2 (SAS Institute Inc, Cary, NC) statistical package.

RESULTS

In the new series of 14 435 baseline screenings, lung cancer was diagnosed in 111 of 6296 women and 93 of 8139 men. Thus, for the crude women vs men prevalence OR, the point estimate was 1.6 (111/[6296 - 111]/[93/(8139 - 93)]; $P = .001$, 1-sided). TABLE 2 shows the corresponding result from the logistic regression discrimination between the case (N = 204) and the noncase (N = 14231 [14 435 - 204]) series, and also the result when controlling for age and pack-years of cigarette smoking. The OR for age and smoking was 1.7 (95% confidence interval [CI], 1.3-2.3). Combining the 2 series of baseline screenings, lung cancer was diagnosed in 269 cases

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Table 2. Logistic Regression Analysis of 14 435 Baseline Screenings for Lung Cancer, Prevalence Odds Ratio, Women vs Men by Controlled Covariates

Covariates	Coefficient (SE)*	Odds Ratio (95% CI) Estimate	*P* Value†
None	0.44 (0.14)	1.6 (1.2-2.0)	.002
Age and smoking	0.54 (0.14)	1.7 (1.3-2.3)	<.001

Abbreviation: CI, confidence interval.
*Coefficient of sex indicator: 1 if female, 0 otherwise.
†Two-sided.

Table 3. Distributions of Women and Men With Baseline Diagnosis of Lung Cancer According to Age, History of Smoking at Time of Diagnosis, Clinical Stage I of the Disease, and Resection*

Characteristic	Women (n = 156)	Men (n = 113)
Age, median (range), y	67 (47-84)	68 (49-83)
Pack-years of smoking, median (range), No.	47 (2-125)	64 (9-130)
Stage I disease	139 (89)	90 (80)
Underwent resection	125 (90)	79 (88)

*Data are reported as No. (%) of participants unless otherwise noted.

Table 4. Distributions of Cases of Baseline Diagnosis of Lung Cancer by Tumor Diameter

Tumor Diameter, mm	No. (%) Women (n = 156)	Men (n = 113)
<10	17 (11)	10 (9)
10-20	103 (66)	69 (61)
>20	36 (23)	34 (30)

(156/7498 women and 113/9427 men). The combined women vs men prevalence OR estimate, when controlling for age and pack-years of cigarette smoking, was 1.9 (95% CI, 1.5-2.5).

TABLE 3 shows that women diagnosed as having lung cancer were of a similar age as the men (67 vs 68 years) but had smoked considerably less (47 vs 64 pack-years, respectively). Also, the women were more frequently diagnosed as having clinical stage I disease (89% vs 80%), but when diagnosed as clinical stage I, women underwent resection only slightly more often than men (90% vs 88%). TABLE 4 shows the sex-specific frequency distribution of the diagnosed cases of lung cancer by tumor diameter to be quite similar. TABLE 5 provides the cell type distribution of the diagnosed cases. The proportions of adenocarcinoma among the women and men were 73% (114/156) and 59% (67/113), respectively ($P=.01$, 1-sided).

The incidence density (hazard) ratio of fatal outcome of lung cancer, women vs men, was 0.48 (95% CI, 0.25-0.89) (TABLE 6) when controlling for pack-years of smoking, disease stage, tumor cell type, and resection.

COMMENT

Following up on our previous study,[2] the findings reported herein again indicate that the risk of lung cancer is higher in women who smoke than in men of the same age who smoke the same amount.

The diagnoses were initially derived in the institutions in which the screenees were cared for, but in 222 of the 269 cases, the pathology specimens were independently reviewed by an expert panel of pulmonary pathologists. This panel confirmed all of the 222 cases as representing lung cancer, changing only the cell-type particulars in some of them. The low proportions of squamous and small cell carcinomas among the diagnosed cases were to be expected, as baseline screening less commonly leads to the detection of relatively fast-growing types, and also because there has been a shift to adenocarcinoma in cancer registry data in the United States and elsewhere.[9,13-15,28-31]

The results of our analysis do involve some residual confounding by age and/or smoking, despite the data in Table 1, but this confounding is negative, resulting in a diluted association (Table 2). As for potential confounding by other airborne carcinogens, the exposures presumably are more common and more pronounced among men, with the consequent bias again diluting rather than accentuating the apparent role of sex.

Our results also raise other questions. First, could the pursuit of malignancy diagnosis have been more vigorous with women screenees? We see no reason to presume this: not only was the diagnostic protocol the same for the 2 sexes, but its recommendations were followed equally. Had the reading of the images been biased in favor of more common nodule detection in the women, this would have accentuated the frequency of relatively small tumors among the diagnosed cases in the women (being that relatively small nodules are less readily detectable), but the proportions of tumors under 10 mm in diameter were quite similar for women and men (0.11 [17/156] vs 0.09 [10/113], respectively).

Second, could women more commonly have presented themselves for screening on the prompting not merely of risk, but also the presence of cancer-suggestive symptoms? Again, we see no reason to presume this. Nevertheless, if this was the case, the largest tumors would have been relatively more common in the cases diagnosed in the women (as larger cancers are more likely to be symptomatic). But the proportion of tumors more than 20 mm in diameter was actually lower in the women than in the men (0.23 [36/156] vs 0.30 [34/113], respectively). Thus, insofar as some of the diagnosed cases actually were symptomatic and differentially so between the sexes, this again more likely diluted rather than accentuated the apparent role of patient sex.

Third, could the higher prevalence of detected cancer in women have resulted from a generally lesser aggressiveness—lower rate of growth—of the women's cancers compared with those of the men? Referring to Table 5, we note that for the slowest-growing malignancies, typical carcinoids and adenocarcinomas of the bronchioloalveolar subtype, the proportions in women's and men's cases were 6% (9/156) and 4% (5/113), respectively. Also, for the fastest-growing type, small cell carci-

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