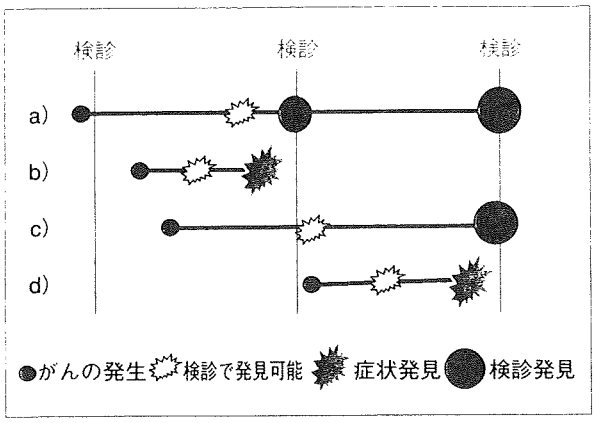

図1　Length bias

定期的な検診を行った場合，進行速度の遅いもの（a，c）は，何回かの受診機会のどこかで発見される可能性があるが，進行速度の速いもの（b，d）は，検診の受診機会が来る前に，症状が出て検診外で発見されてしまう．このことにより検診発見例だけに着目すると進行速度の遅いもの（＝予後のよいもの）に偏ってしまい，進行速度の速いもの（＝予後の悪いもの）は見逃されてしまう．

場合は，受診者個人に換算するとメリットは小さく，デメリットと近接してくるため，その是非については，より厳密な評価が要求される．

検診の場合，発見率や生存率などの発見がんに限った指標は，バイアス（偏り）が混入しやすく，検診の効果を過大評価することにつながるといわれている．**図1**に示すように，定期的な検診により，進行速度の緩やかながんが発見されやすく，進行速度の速いがんは発見されにくいという傾向がある（レングス・バイアス）．CT検診の場合は，このバイアスの影響を強く受けている．一方，進行速度の速いがんは，検診と検診との間に症状を伴って発見されることが多い．検診の評価とすれば，“発見できたがん”のみならず，“発見できなかった”がんの割合およびその予後を併せて評価することが不可欠である．このため受診者集団全体の当該がん死亡率こそが，がん検診の有効性を示すもっとも重要な指標と国際的に位置づけられている．

がん検診の死亡率減少効果を評価する研究デザインとしては，ランダム化比較試験，コホート研究，症例対照研究などがあり，もっとも偏りが混入しにくいといわれているのは，ランダム化比較試験である．治療の評価と異なり，がん検診の評価の場合，がん死亡自体が稀なため，サンプルサイズは1万人規模，追跡期間も10年程度となり，国際的に見ても容易には実施し得ない状況にある．

□ 肺がんCT検診の現状

CT検診に関しては，2008年3月の時点で感度・特異度を報告した論文はない．あくまで単純X線で見えないものをCTで発見できたという意味でのものしかなく，がん登録との照合などの標準的な方法を用いた報告はない．また受診者集団の死亡率を報告した論文も，現状ではSwensenらの報告のみに留まる[4]．この報告はMayo Clinicの4年間のCT検診受診者の肺がん死亡率を，70年代に行われたMayo Lung Projectの肺がん死亡率と比較し，差を認めなかったというものであり，30年前のhistorical controlとの比較という点と，追跡期間が登録後4年と短い点で十分な評価とはいえない．Henschkeらが設立した，I-ELCAPという国際的CT検診の共同研究がもっとも有名ではあるが[5]，生存率の報告しかなされていない．この研究はCT検診受診群のみで，対照群が設けられておらず，検診の評価研究としては，はなはだ不十分といわざるをえない．

CT検診受診者の死亡率を評価指標とする進行中の研究がいくつかある．国内では厚生労働省第3次対がん総合戦略研究事業に基づき筆者が主任研究者をしているJapan Lung Screening Studyが進行中である．本研究は，CT肺がん検診を一度でも受診したことのあるもの約4万人と単純X線による肺がん検診を受診しCT検診を受診していない8万人を登録し追跡したコホート研究である．本研究は登録後約6年弱の追跡結果を現在解析している最中であり，現時点で結果の公開には至らないが，少なくとも一度のみのCT肺がん検診の受診では大幅な死亡率減少効果は期待できないようである．

また国外においては，二つのランダム化比較試験が進行中である（**表2**）．National Lung Screening Trial（NLST）は，米国で進行中の53500人を対象とした研究であり，研究群は年1回計3回の

表2　国内外における低線量肺がんCT検診の有効性評価を目的とした現在進行中の研究

	Japan Lung Screening Study (JLSS)	National Lung Screening Trial (NLST)	NELSON study
国　名	日本	米国	オランダ-ベルギー
開始年	2001 (1997～2002年まで登録)	2002 (2004年に登録終了)	2003
対象者	40歳以上男女 CT検診受診者46700人 通常検診受診者84000人	55～74歳　重喫煙者 53500人	50～75歳　男性喫煙者 28000人
肺がん死亡率減少の想定		20% reduction	25% reduction (検出力80%)
方　法	コホート研究 CT検診群 　少なくとも一度受診 通常検診群 　CT検診の受診歴なし	ランダム化比較試験 研究群 　CT検診1，2，3年目 対照群 　単純X線検診	ランダム化比較試験 研究群 　CT検診1，2，4年目 対照群 　無検診
追跡年数	平均7年	4.5年	10年
最終解析予定	2008年	2009年	記載なし

低線量CT検診を，対照群は単純X線検診をそれぞれ提供されるデザインである．ただしこの研究は追跡期間がわずか5年であり，国内で経験されるような高分化な小型腺がんの発見および救命を評価することはできないと危惧されている．一方，オランダ・ベルギーで行われているNELSON trialは28000人規模の研究であり，対照群には検診を一切提供しないデザインである．こちらは追跡期間を10年と予定しており，NLSTに比べると成果は期待できるデザインではある．

まとめ

低線量CT検診は，従来の単純X線検査では発見不可能であった肺野の小型腺がんを高頻度に発見し得ることで世界的に注目されたものの，その代名詞であった充実性部分を有さないすりガラス状陰影を呈する肺がんを切除する意義自体に疑問が投げかけられている[6]．検診として実施する場合には受診者集団の死亡率減少効果が証明される必要があるが，いまだその結果は公表されていない．したがって現時点では公的資金が用いられる地域住民を対象とした対策型検診での利用は正当化されない．人間ドックにおいての任意型検診においては，効果が確認されていないことや過剰診断などの不利益が存在することを，受診者に説明し同意が得られたうえで，実施されることが必要であろう[7]．

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肺　　癌

—基礎・臨床研究のアップデート—

臨床研究　II. 検　　診

胸部単純X線と喀痰細胞診を用いた肺癌検診の評価

中山富雄

胸部単純X線と喀痰細胞診を用いた肺癌検診の評価

Evaluation of the effectiveness lung cancer screening used by plain chest X-ray and sputum cytology

中山富雄

Key words：肺癌検診，ランダム化比較試験，症例対照研究，過剰診断

はじめに

肺癌の早期発見法としては，肺野末梢に発生する肺癌を標的とした画像診断と，中枢気管支に発生する肺癌(主に扁平上皮癌)を標的とした喀痰細胞診が，広く用いられてきた．近年画像診断法として低線量CTを肺癌検診に導入することが期待されているが，従来の胸部単純X線も，いまだ広く用いられている．この胸部単純X線と喀痰細胞診を用いた肺癌検診の有効性については，古くから世界的に議論が行われてきたが，いまだ解決をみていない．

本稿では，まずがん検診に関する評価方法を概説し，肺癌検診の評価に関する国内外の研究と，現状での評価について解説する．

1. がん検診の評価指標

がん検診の評価指標としては，発見率や発見がんの切除率・I期率・腫瘍径の小型化などがよく用いられている．しかし，これらの発見がんに限った指標は，バイアス(偏り)が混入しやすく，検診の効果を過大評価することにつながる．図1に示すように，定期的な検診により，進行速度の緩やかながんが発見されやすく，進行速度の速いがんは発見されにくいという傾向がある(レングス・バイアス)．したがって進行速度の速いがんは，検診と検診との間に症状を伴って検診とは別に医療機関を受診し発見される(中間期がん)ことが多い．中間期がんの把握は容易ではないが，これらの割合およびその予後を発見がんの指標と併せて評価しないと，がん検診の正しい評価にはならない．したがって，

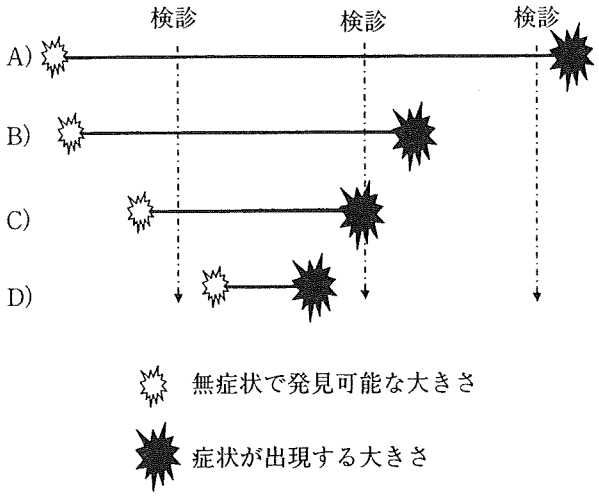

図1　レングス・バイアス

定期的検診が行われた場合，A)では3回の検診の機会いずれでも早期で発見可能，B)では2回の検診の機会で早期発見可能，C)では早期発見可能なのは1回のみ，D)では定期検診による発見自体困難で中間期がんとして診断される．このように進行速度の遅いがん(＝予後の良いがん)が検診では発見されやすい．

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0047-1852/08/¥40/頁/JCLS

表1 70年代に行われた胸部X線と喀痰細胞診を用いた肺癌検診の有効性評価のためのランダム化比較試験

	文献	開始年	検診方法		参加者数	RR (95%CI)
			検診群	対照群		
Johns-Hopkins Lung Project	1	1973	胸部X線年1回＋喀痰4カ月ごと	胸部X線年1回	5,250: 5,171	0.91 (0.72-1.16)
Memorial Sloan-Kettering Lung Project	2	1,974	胸部X線年1回＋喀痰4カ月ごと	胸部X線年1回	4,968: 5,072	0.92 (0.67-1.26)
Mayo Lung Project	4	1971	X線と喀痰4カ月ごと	X線と喀痰年1回を推奨	4,618: 4,593	1.06 (0.82-1.36)
Czechoslovakian Lung Project	5	1976	X線と喀痰6カ月ごと	無検診	3,171: 3,174	1.36 (0.94-1.97)

発見がんという限られた集団ではなく，検診受診者全体の予後の指標であるがん死亡率が，がん検診の有効性を示す最も重要な指標となる．

がん検診の死亡率減少効果を評価する研究デザインとしては，ランダム化比較試験，コホート研究，症例対照研究などがあり，最も偏りが混入しにくいといわれているのは，ランダム化比較試験である．近年がん患者に対する抗がん剤の臨床試験などでは，ランダム化比較試験が広く普及したものの，健常者に対するがん検診の評価の場合は，がん死亡というイベント自体がまれなため，サンプルサイズは1万人規模，追跡期間も10年程度となるため，容易には実施しえない．肺癌については1970年代に米国を中心に4つのランダム化比較試験が行われ，90年代以降我が国で6つの症例対照研究が行われた．

2. 70年代に行われた肺癌検診を評価するランダム化比較試験

1970年代には，胸部単純X線撮影は，肺癌の早期発見に欠かせないものとして，世界的に認識されていた．一方，喀痰細胞診を用いることで，単純X線で指摘不可能な肺門部早期扁平上皮癌を発見可能であること，その診断に当時我が国で開発された気管支ファイバースコピーが必要であることが，世界的トピックスであった．このため，主に喀痰細胞診の評価を行うことを目的として，4つのランダム化比較試験が米国を中心に行われた(**表1**)．

Johns-HopkinsおよびSloan-Ketteringで行われた研究は，いずれも胸部X線写真に喀痰細胞診を上乗せする効果を評価した研究である[1,2]．この2つの研究は，いずれも喀痰細胞診の上乗せ効果を証明することはできなかったが，最近の佐藤らの報告によれば，日本の検診の成績と比べて，精度が不良であったことが報告されている[3]．

Mayoの研究とチェコの研究は，胸部単純X線撮影と喀痰細胞診の併用法を評価した研究である[4,5]．チェコの研究は，腺癌(大細胞癌を含めて)の割合が全体の18%しかなく，また術後30日以内の死亡率が11%と際立って高いという当時の東ヨーロッパの貧困な医療状況を示す結果であり，現在の日本の医療と比較することは無理といわざるを得ない．したがって，肺癌検診の評価として参考にすべきは，規模が最も大きいMayo Clinicの研究が中心となる．

Mayo Lung Projectは，そのユニークなデザインと，得られた結果の矛盾点について，いまだに論争の絶えない研究である．**図2**に示すように，この研究は45歳以上の重喫煙男性10,933人をリクルートし，まず胸部単純X線と喀痰細胞診でスクリーニングし，発見された肺癌例(prevalence case)および全身状態不良例1,722人を研究から除外した．これは初回検診の受診者の中に

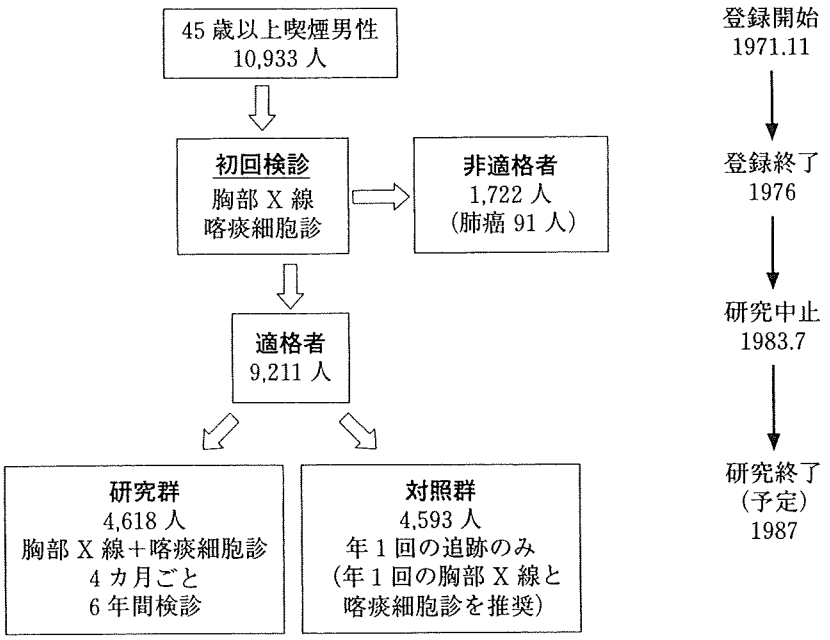

図2 Mayo Lung Projectの構造

研究群には4カ月ごと6年間検診が提供され，対照群には年1回の検診受診が推奨されるだけにとどまった．しかし研究群のコンプライアンスは75％と低く，対照群のコンタミネーションは73％(最後の2年間のうち1回以上検査を受診した割合)と高かった．

は，進行がんの占める割合が高いことから，これを除外して，その後の検診の効果を評価することに専念したためである．適格者9,211人を2群に割り付け，研究群は4カ月に1度の検診が提供されたが，対照群には，年に1度検診を受けるようにアドバイスがなされた．これは当時のMayo Clinicの外来に，'喫煙者は年に1回検診を受診するように！'というポスターが掲示されていたように，検診を年1回受診することの妥当性には問題ないと考えられていた事情を反映している．1971年から開始された研究は，研究群と対照群の間で肺癌死亡率に差がないという83年の中間報告をきっかけに，研究は中止に追い込まれた．

当時は疑いもされていなかった肺癌検診の効果を否定する結果は，大きな衝撃を与えたが，更にランダム化比較試験でありながら両群中の肺癌罹患数に明らかな差があったことが，その後の議論の焦点となった(**表2**)．すなわち，対照群で把握された肺癌(当然すべて検診外発見)は160例であったが，研究群で把握された肺癌(検診発見に検診外発見を加えたもの)は206例であり，46例も研究群の罹患数が多かったのである．Eddyは，この差を過剰診断(本来放置しても死に至らないがんを検診で発見していた)と解釈し，本研究の結果の解釈の中心となっている[6]．一方Straussらは，追跡が不十分であった，あるいは割り付けが不適切であったと

表2 Mayo Lung Projectの肺癌罹患の状況(文献[4]より引用)

	研究群	対照群
検診発見	**90**	
胸部X線	66	
喀痰細胞診	18	
双方発見	6	
検診外発見	**116**	**160**
胸部X線*	43	48
症状	73	112
計	**206**	**160**

*検診以外で撮影された胸部X線を示す．研究群においても年3回の研究の枠内の検査以外に，更に胸部X線を受診しているものが少なくなかったことを示している．

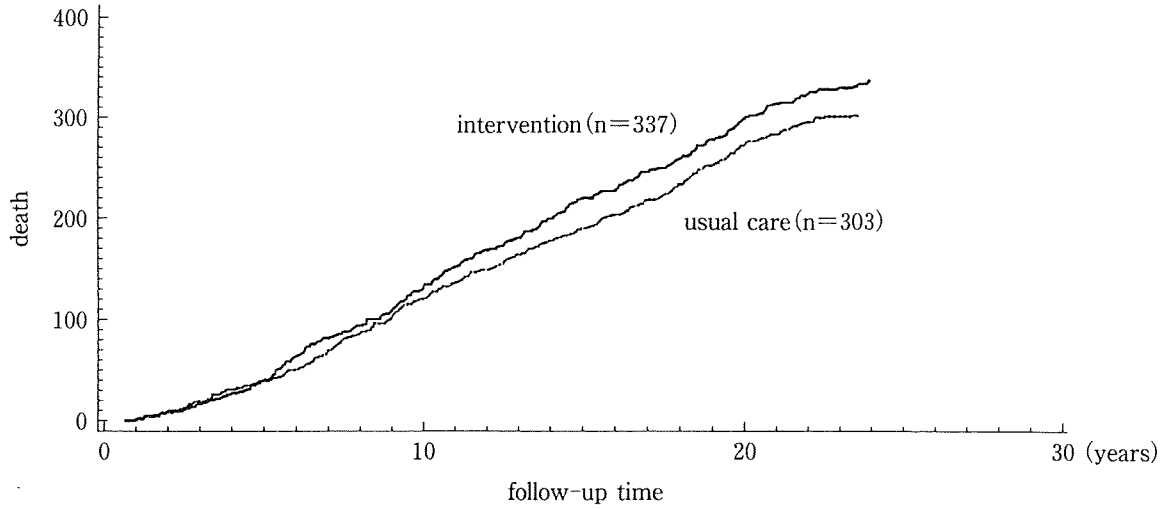

図3 Mayo Lung Projectの長期追跡研究における累積肺癌死亡数の推移
intervention：研究群，usual care：対照群．
（文献[8]より引用）

表3 Mayo Lung Projectの長期追跡研究での組織型別死亡数・生存率（文献[8]より引用）

	扁平上皮癌		腺癌		大細胞癌		小細胞癌	
	研究群	対照群	研究群	対照群	研究群	対照群	研究群	対照群
発見肺癌数	68	51	59	38	29	24	48	45
肺癌死亡	35	33	39	25	19	20	40	40
全死因死亡	61	49	55	37	37	26	47	44
5年生存率								
（肺癌死）	55	26	30	33	35	9	6	6
（全死亡）	40	14	21	21	29	6	4	2

いう解釈を提案している[7]．

最近Marcusらは，研究対象者の20年にわたる長期追跡結果を明らかにしたが，研究開始後20年を経過しても肺癌死亡率に差はなかったと報告しており，追跡不十分説や割り付け不均等説を否定し，過剰診断のみで説明可能としている[8]．しかしMarcusらの論文においても，2つの問題がある．まずこの論文で示されている肺癌累積死亡率の図（**図3**）をみると，統計学的有意差はないものの，研究群の方の肺癌死亡率が高いことが示されている．また組織型別死亡率・生存率の表（**表3**）によると，腺癌では研究群も対照群も5年生存率に差はなく，扁平上皮癌で研究群の方が有意に対照群よりも高い成績が示されている．Marcusらの説のとおり，46例の差が過剰診断によるとすれば，その大半は進行速度の遅い腺癌によるものと考えられ，腺癌の生存率が研究群で上昇しているはずであるが，そうではなかった．もし扁平上皮癌で過剰診断が起こるとすれば，喀痰細胞診発見による肺門部扁平上皮癌のはずであるが，Mayoの扁平上皮癌の7割が胸部X線発見であったと報告されている[4]．

このように，いまだに疑問が残った結果であり，ランダム化比較試験とはいえ，偏りを制御できなかった可能性が残る．

3. 国内で行われた肺癌検診を評価する症例対照研究

国内でも1980年代に肺癌検診に関するランダム化比較試験を行うべきであるという議論が行われたようであるが，当時は結核予防法によ

表4 我が国で行われた肺癌検診の有効性評価のための症例対照研究

	文献	対象期間	症例数	対照数	オッズ比	95%信頼区間
成毛班の研究	9	1977-88	273	1,269	0.76	0.58-1.03
金子班の研究	10	1985-93	145	435	0.65	0.52-0.82
藤村班						
宮城の研究	11	1990-94	328	1,886	0.54	0.41-0.73
新潟の研究	12	1990-96	149	687	0.40	0.27-0.59
岡山の研究	13	1991-97	412	3,506	0.59	0.46-0.74
群馬の研究	14	1992-96	109	493	0.68	0.44-1.05

り年1回の胸部X線検査が義務づけられていたこともあり，実行には移されなかった．このため，既に行われた検診を後ろ向きに評価する6つの症例対照研究が行われている[9-14]．**表4**に，この6つの症例対照研究をまとめた．6つの症例対照研究はいずれも年1回の肺癌検診受診により肺癌死亡率減少を示す傾向を示しており，うち4つは統計学的有意差を示している．観察的研究ではあるが，再現性という面から信頼性が高いと考えられる．

症例対照研究はバイアスの混入しやすい研究だとされているが，これらの症例対照研究では，バイアスを軽減する様々な試みがなされている．宮城の研究では，セルフ・セレクション・バイアスを軽減するため平成元年の検診受診者名簿から症例と対照を選択し，その後の検診受診歴を比較している[11]．新潟の研究では，検診以外の胸部X線受診歴を調整因子に含めている[12]．また，群馬の研究では血痰などの症状受診を除外し，検診の真の対象者である無症状受診者のみに限った解析を行っている[14]．このようなバイアスを軽減する試みがなされているが，いずれの研究においても，検診受診による死亡率減少効果には大きな変動は認められない．

4. 肺癌検診についての現状のコンセンサス

厚生労働省がん研究助成金祖父江班は，各種がん検診の有効性を，EBMの手法を用いて評価する研究班である．平成18年に'有効性評価に基づく肺がん検診ガイドライン'を発表した[15]．このガイドラインにおいては，'非高危険群に対する胸部X線検査，及び高危険群に対する胸部X線検査と喀痰細胞診併用法は，肺がん検診として死亡率減少効果を示す相応な証拠があるので，対策型及び任意型検診として実施することを勧める'と記載されている．これは70年代に行われたランダム化比較試験よりも90年代に行われた国内の症例対照研究の結果を重んじた結果で，診断方法と治療成績の向上をその理由にしている．

おわりに

胸部X線と喀痰細胞診を用いた肺癌検診の評価に関しては，長く議論が続いてきた．その原因はエビデンスとなる研究が70年代という研究方法・臨床技術とも未熟な段階で行われたためである．現在，米国では10万人規模で行われたPLCO研究の追跡相にある．この研究の成果を期待したい．

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Trends in Lung Cancer Incidence by Histological Type in Osaka, Japan

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Background: In Japan, an increase in age-adjusted incidence rates of lung adenocarcinoma (ADC) and a decrease in lung squamous cell carcinoma (SQCC) have been reported.
Methods: The number of lung cancer incidence, age-adjusted rates, and age-specific rates by birth-cohort according to histological type were examined using the data from Osaka Cancer Registry.
Results: The numbers of lung cancer incidence among men and women have increased, particularly in ADC. The age-adjusted incidence rates of ADC among men and women have continuously increased, while those of SQCC and small cell carcinoma (SMCC) turned to decrease since 1990s. A trough of lung cancer incidence rates was observed among men in 1935–39 birth-cohorts. The declining trend appeared in 1955–59 birth-cohorts. Lung cancer incidence rates among women have increased since 1895–99 birth-cohorts, but those rates leveled off or decreased in 1950s birth-cohorts. Trends of ADC by birth-cohort were almost the same as those of all histological types. The SQCC among men peaked in 1915–19 birth-cohorts, and decreased in the subsequent birth-cohorts. The SMCC among men peaked in 1920s birth-cohorts, and decreased or leveled off in the subsequent birth-cohorts.
Conclusions: Lung cancer incidence rates by birth-cohorts were almost parallel to the smoking prevalence. However, those for ADC among young women in 1950s birth-cohorts were not parallel to the smoking prevalence, which requires careful monitoring to confirm such findings.

Key words: lung cancer – incidence – histological type – birth-cohort

BACKGROUND

Lung cancer is the leading cause of cancer deaths in Japan, with 45 927 men and 17 307 women dying from lung cancer in 2006. To date, increase in the incidence rates of lung adenocarcinoma (ADC) and decrease in the incidence rates of squamous cell carcinoma (SQCC) and small cell carcinoma (SMCC) have been reported in Japan (1,2). The same trend has been reported in Western countries also (3–5). Some previous studies reported that there was a trough of lung cancer incidence or mortality in Japanese male 1935–39 birth-cohorts because of the limited cigarette supply just after World War II (6–10). Soda et al. (7) reported the birth-cohort analysis by histological type using Nagasaki Cancer Registry in 2000. However, this study was based on the small number of registered lung cancer cases and excluded the cases without histological diagnoses.

In the present study, we updated the recent trends in lung cancer incidence by histological type and tried to clarify their characteristics by birth-cohort, using the data from Osaka Cancer Registry (OCR) with the large number of lung cancer incidence.

MATERIALS AND METHODS

OCR, which started in 1962, is the population-based cancer registry covering Osaka prefecture (population: 8.8 million, 2005 census). Using OCR data on lung cancer incidence

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(International Classification of Diseases 10th revision C33–C34) diagnosed between 1975 and 2003, we calculated the number of lung cancer incidence per year, age-adjusted rates and age-specific rates by birth-cohort according to histological type.

Histological types were categorized into three major types: ADC (ICD-O: 8140, 8141, 8200, 8211, 8250, 8251, 8260, 8310, 8323, 8440, 8470, 8480, 8481 and 8490), SQCC (ICD-O: 8050, 8052 and 8070–8076), SMCC (ICD-O: 8041–8045) and the others.

Incident years are divided into 5-year periods: 1975–78, 1979–83, 1989–93, 1994–98 and 1999–2003. Birth years were also divided into 5-year periods. The population data by age group in Osaka prefecture were obtained from the data of Population Census. For age-standardization, the Japanese model population in 1985 was used.

The data from OCR included the cases without specific histological diagnosis: a maximum of 60.4% in 1975–78 and a minimum of 31.4% in 1994–98. Based on the assumption that distributions of histological types in the same sex and age group were the same between those with and without a specific histological type, we compensated for the proportion of cases without a specific histological type. The detailed procedure was followed to the previous study (1); first, the sex-, age (5-year)- and incident year (or birth-cohort)-specific numbers of incidence were calculated for all histological types including the cases without histological diagnosis. Second, the sex-, age (10-year)- and incident year (or birth-cohort)-specific proportion of each histological type among the cases with histological diagnosis were calculated for three major histological types. Finally, the sex-, age (5-year)-, incident year (or birth-cohort)-specific number of incidence were multiplied by the corresponding sex-, age- and incident year (or birth-cohort)-specific proportion to approximate the number of incidence by histological type.

RESULTS

Table 1 shows the trends in the number of lung cancer incidence per year according to histological type. Lung cancer incidence per year for all histological types among men and women increased consistently; from 1086 in 1975–78 to 3487 in 1999–2003 among men and from 395 in 1975–78 to 1482 in 1999–2003 among women. As for histological type, the number of ADC incidence has increased remarkably among men and women. The shift in main histological type among men occurred in the 1990s.

Table 2 shows the trends in the age-adjusted rates according to the histological type. The age-adjusted rates for all histological types peaked in 1994–98 and recently leveled off among men, while those consistently increased among women. The rates for ADC consistently increased among men and women. In contrast, the rates for SQCC and SMCC peaked in 1989–93 among men, and decreased subsequently. Those rates for SQCC and SMCC peaked in 1984–88 and 1989–93, respectively, among women, and decreased subsequently.

Fig. 1 shows the trends in the age-specific lung cancer incidence rates with 95% confidence interval by birth-cohort for all histological types. Among men, there was a trough in rates for all age groups in 1935–39 birth-cohorts, which was consistent with the previous findings (7,10). In the subsequent birth-cohorts, the rates increased for all age groups, but the declining tendency appeared in 1955–59 birth-cohorts. Among women, the trough in rates in 1935–39 birth-cohorts was not confirmed. The rates for aged ≥ 50 years increased gradually, while it seemed that the rates for aged <50 years turned to decrease or level off after 1950–54 birth-cohorts: however, these trends were unstable because of the wide confidence intervals due to the small number of incidence.

Table 1. Trends in the number of lung cancer incidence per year according to histological type

Histological type	Incident year					
	1975–78	1979–83	1984–88	1989–93	1994–98	1999–2003
Men						
Adenocarcinoma (%)	372 (34.2)	510 (35.7)	696 (35.5)	853 (35.8)	1191 (40.2)	1497 (42.9)
Squamous cell carcinoma (%)	474 (43.6)	582 (40.8)	760 (38.8)	921 (38.6)	1086 (36.6)	1208 (34.7)
Small cell carcinoma (%)	142 (13.0)	203 (14.2)	315 (16.1)	410 (17.2)	483 (16.3)	543 (15.6)
Others (%)	99 (9.1)	132 (9.3)	189 (9.7)	200 (8.4)	204 (6.9)	239 (6.8)
All histological types (%)	1086 (100)	1428 (100)	1961 (100)	2383 (100)	2964 (100)	3487 (100)
Women						
Adenocarcinoma (%)	242 (61.2)	328 (60.2)	453 (58.7)	579 (60.3)	792 (64.8)	996 (67.2)
Squamous cell carcinoma (%)	86 (21.9)	106 (19.5)	163 (21.2)	184 (19.2)	218 (17.9)	241 (16.3)
Small cell carcinoma (%)	32 (8.0)	73 (13.3)	97 (12.5)	132 (13.7)	152 (12.5)	178 (12.0)
Others (%)	35 (8.9)	38 (6.9)	59 (7.6)	65 (6.8)	60 (4.9)	66 (4.4)
All histological types (%)	395 (100)	545 (100)	772 (100)	961 (100)	1223 (100)	1482 (100)

Table 2. Trends in age-adjusted lung cancer incidence rates per 100 000 person-years according to histological type

Histological type	Incident year					
	1975–78	1979–83	1984–88	1989–93	1994–98	1999–2003
Men						
Adenocarcinoma	15.5	18.9	21.7	22.3	26.0	27.2
Squamous cell carcinoma	20.4	22.2	25.0	25.6	24.8	22.3
Small cell carcinoma	6.0	7.6	10.1	11.1	10.8	10.0
All histological types	46.2	53.7	62.9	64.7	66.5	64.3
Women						
Adenocarcinoma	7.9	9.2	10.5	11.3	13.1	13.8
Squamous cell carcinoma	2.8	3.0	3.8	3.5	3.4	3.1
Small cell carcinoma	1.0	2.0	2.3	2.5	2.4	2.3
All histological types	12.9	15.2	17.9	18.6	19.9	20.2

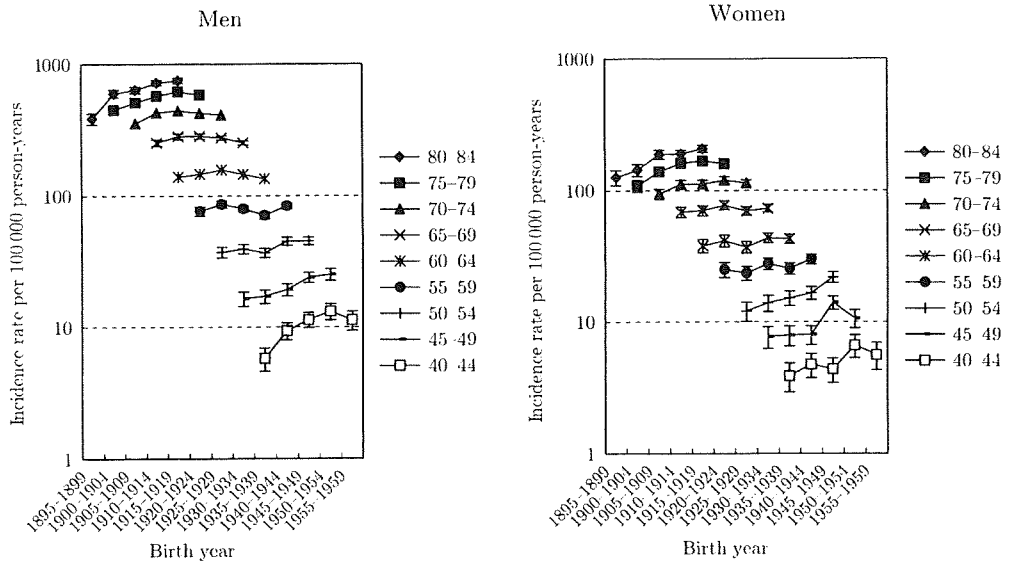

Figure 1. Trends in age-group-specific lung cancer incidence rates with 95% confidence interval by birth-cohort for all histological types.

Figs 2–4 show the trends in the age-specific incidence rates with 95% confidence interval by birth-cohort for ADC, SQCC and SMCC, respectively. The rates for ADC among men increased gradually for all age groups, but the declining tendency appeared in 1955–59 birth-cohorts. Furthermore, it seemed that there was a slight trough in rates in 1935–39 birth-cohorts, as well as findings in all histological types. The trends in ADC among women were almost similar with those in all histological types. The rates for SQCC among men peaked in 1910–14 birth-cohorts and decreased in the subsequent birth-cohorts. The trough in rates during 1935–39 birth-cohorts was not clear for SQCC among men. Trends in the rates for SQCC among women aged ≥65 years were similar with those among men. The trends in aged <65 years were, however, unclear because of the wide confidence interval. The rates for SMCC among men peaked around 1920s birth-cohorts and turned to slightly decrease or level off in the subsequent birth-cohorts. The rates for SMCC among women were unclear because of the wide confidence interval.

DISCUSSION

In the present study, we reported the population-based trends in lung cancer incidence including birth-cohort analyses according to histological type using OCR. The number of lung cancer incidence per year increased continuously because of the population aging. The main histological type of lung cancer switched from SQCC to ADC among men in

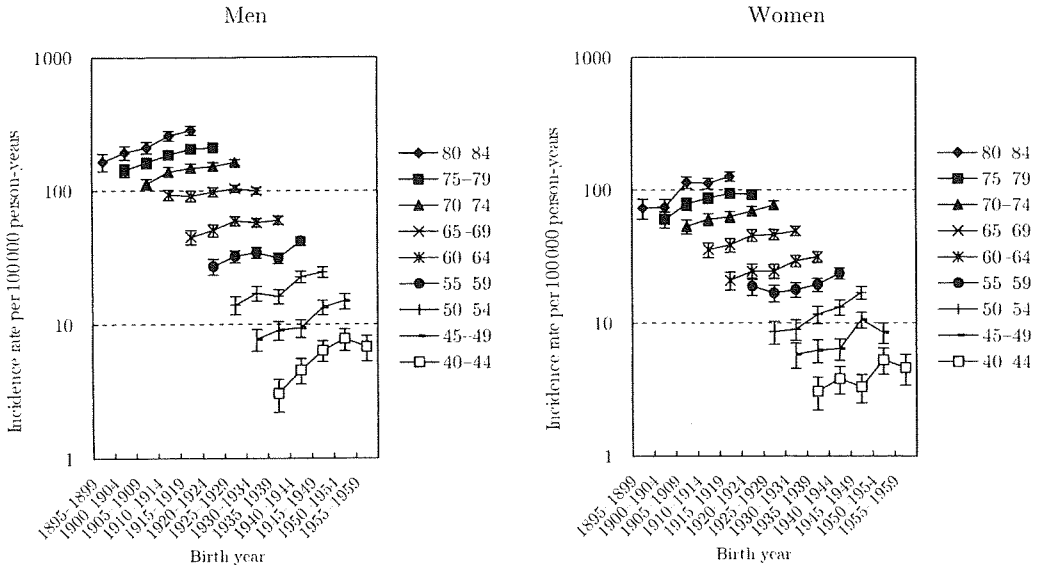

Figure 2. Trends in age-group-specific incidence rates with 95% confidence interval by birth-cohort for adenocarcinoma.

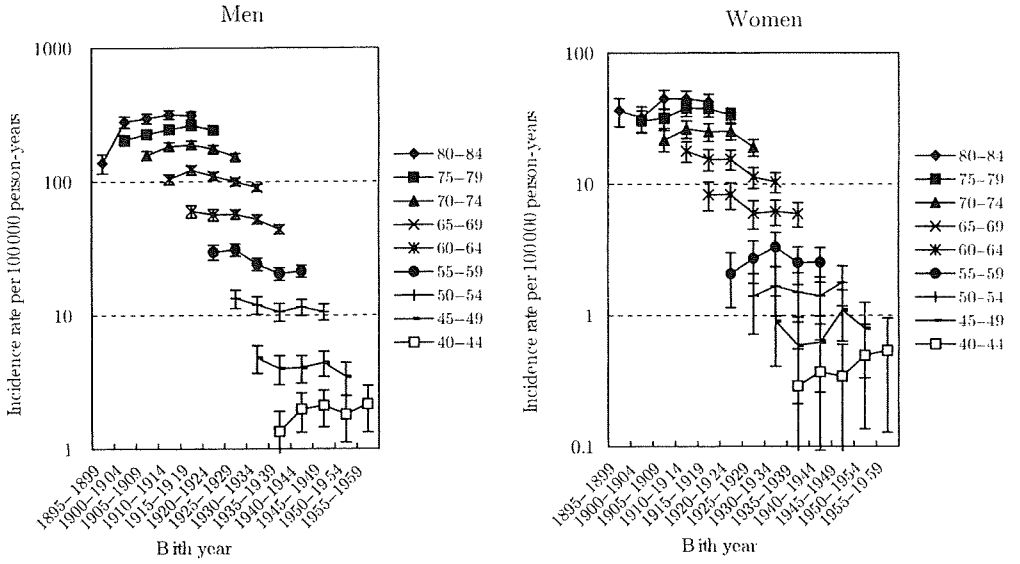

Figure 3. Trends in age-group-specific incidence rates with 95% confidence interval by birth-cohort for squamous cell carcinoma.

1990s. The declining trends for SQCC and SMCC continued in the updated present study.

Smoking prevalence by birth-cohort among Japanese men was reported to have two peaks: around the 1925 birth-cohort and around the 1950 birth-cohort (11). In addition, there was a trough of smoking prevalence in 1930–40 birth-cohorts because of the limited cigarette supply just after World War II (11). In general, the trends in lung cancer incidence or mortality by birth-cohort were parallel to the trends in the smoking prevalence. Our results were consistent with the findings from previous studies, showing that lung cancer mortality and incidence rates among men in 1935–39 birth-cohorts were lower than the subsequent birth-cohorts (6–10). Since the smoking prevalence among Japanese men was declining after 1950s birth-cohorts, the appearance of declining trends of lung cancer incidence among men in 1955–59 birth-cohorts was an expected result.

Classically, smoking behavior was considered to be more strongly associated with SQCC than with ADC. However, SQCC incidence rates by birth-cohort among men were not

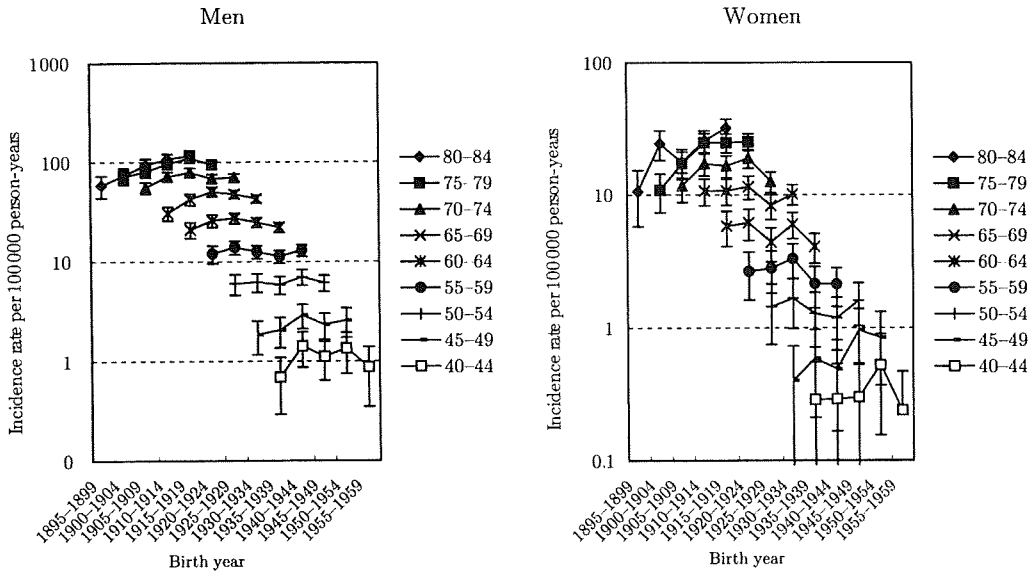

Figure 4. Trends in age-group-specific incidence rates with 95% confidence interval by birth-cohort for small cell carcinoma.

parallel to the smoking prevalence by birth-cohort. SQCC incidence rates among men after 1940–44 birth-cohorts leveled off, whereas the smoking prevalence among men after 1940–44 birth-cohorts increased. One reason would be the switching from non-filtered cigarettes to filtered cigarettes. Filtered cigarettes were considered to be associated with peripheral ADC because of the deep inhalation (3,12,13). According to the information from Japan Tobacco Inc., the switching from non-filtered cigarettes to filtered cigarettes occurred in the 1960s in Japan (14). The shift from SQCC to ADC among men in 1990s observed in the present study might have been the result of this shift in cigarette types.

The smoking prevalence by birth-cohort among women is continuously increasing after 1930s birth-cohorts (11). However, lung cancer incidence among women in 1950s birth-cohorts, particularly for ADC, seemed to be leveling off or decreasing. Marugame et al. (15) also reported the trends in lung cancer mortality by birth-cohort using the National Vital Statistics. In that study, lung cancer mortality trends appeared to be decreasing for female birth-cohorts born after 1960. Although our results were unstable because of the wide confidence intervals, those were not contradictory to this previous study. There is no clear explanation for these findings among younger Japanese women. There would be some factors other than active smoking for lung cancer incidence among them.

The present study has some limitations. First, there may be some missing cases in the OCR. The proportion of death certificate only for lung cancer in OCR was 19.3% in 1998–2002 (16). Therefore, lung cancer incidence may be under-estimated as a whole. Secondly, the trends by histological type among young women were unstable because of the small number of incidence; the number of lung cancer incidence among women aged <50 years per year was ~ 80 cases in 2003. Finally, the data from OCR included many lung cancer cases without specific histological diagnoses. We had to use assumption in order to calculate the number of incidence according to histological type. The proportions of lung cancer cases without histological diagnoses for aged <80 years decreased between 1975–78 and 1999–2003; from 49.7 to 16.4% among aged 40–49 years, from 47.4 to 17.6% among aged 50–59 years, from 55.9 to 22.7% among aged 60–69 years and from 70.8 to 31.6% among aged 70–79 years, respectively. However, those for aged ≥ 80 years were still high: from 78.9 to 64.1%. Therefore, we require carefulness to interpret the findings, particularly for elderly.

In conclusion, we reported recent trends in lung cancer incidence according to histological type. The increase in ADC incidence and the decrease in SQCC and SMCC incidence were confirmed. The trends in lung cancer incidence among young women in 1950s birth-cohorts, particularly for ADC, were not parallel to the smoking prevalence. We need careful monitoring of the trends in lung cancer incidence, particularly for ADC among young women.

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Conflict of interest statement

None declared.

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Clinical Studies

Sensitivity and specificity of lung cancer screening using chest low-dose computed tomography

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Lung cancer screening programmes using chest X-ray and sputum cytology are routinely performed in Japan; however, the efficacy is insufficient. Screening using low-dose computed tomography (CT) is a more effective approach and has the potential to detect the disease more accurately. A total of 7183 low-dose CT screening tests for 4689 participants and 36 085 chest X-ray screening tests for 13 381 participants were conducted between August 1998 and May 2002. Sensitivity and specificity of lung cancer screening were calculated by both the detection method and the incidence method by linkage of the screening database and the Cancer Registry database. The preclinical detectable phase was assumed to be 1 year. Sensitivity and specificity by the detection method were 88.9 and 92.6% for low-dose CT and 78.3 and 97.0% for chest X-ray, respectively. Sensitivity of low-dose CT by the incidence method was 79.5%, whereas that of chest X-ray was 86.5%. Lung cancer screening using low-dose CT resulted in higher sensitivity and lower specificity than traditional screening according to the detection method. However, sensitivity by the incidence method was not as high as this. These findings demonstrate the potential for overdiagnosis in CT screening-detected cases.
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Lung cancer is the leading cause of cancer death in Japan, with 45 927 men and 17 307 women dying from lung cancer in 2006. Since 1987, lung cancer screening programme using chest X-ray and sputum cytology for all residents aged 40 years of age and older regardless of smoking status has been conducted by the Ministry of Health and Welfare. Unfortunately, the efficacy of lung cancer screening using chest X-ray and sputum cytology is insufficient (Fontana *et al*, 1986; Marcus *et al*, 2000a, 2006b; Sagawa *et al*, 2003a). Therefore, a more effective approach is required to decrease lung cancer deaths.

Annual lung cancer screening using low-dose computed tomography (CT) has been performed as an opportunistic screening method since the early 1990s in Japan. Several study groups introduced low-dose CT for population-based screening in clinical trials. These previous studies reported a high detection rate, an ability to detect small tumours and a high survival rate in detected cases (Henschke *et al*, 2001, 2006; Sone *et al*, 2001; Nawa *et al*, 2002; Sobue *et al*, 2002a; Swensen *et al*, 2002; Diederich *et al*, 2004; Jett, 2005; Libby *et al*, 2006). Some studies referred to interval cancer cases of lung cancer screening using low-dose CT, and one study referred to the sensitivity of screening (Sone *et al*, 2001; Diederich *et al*, 2004). However, screening databases are yet to be linked to a cancer registry, which is essential for accurate evaluation of screening, including the confirmation of all interval cancer cases. To date, no study has been conducted on sensitivity and specificity of annual lung cancer screening using low-dose CT and cancer registry data. Therefore, the present study was conducted to evaluate sensitivity and specificity of annual lung cancer screening using low-dose CT and data from screening and local cancer registry databases.

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MATERIALS AND METHODS

Study setting

Since 1998, annual population-based lung cancer screening using low-dose CT has been conducted at five municipalities in Osaka prefecture: A (city), B (city), C (town), D (town) and E (town). All residents aged 40 years of age and older were recruited by mail using a letter from the public health division of each municipality regardless of smoking status. Subjects recruited to the lung cancer screening programme underwent either miniature chest X-ray or low-dose chest CT.

As a principle, heavy smokers were recommended to undergo low-dose CT screening. In addition, the persons who want to undergo low-dose CT screening also underwent low-dose CT screening. Others underwent chest X-ray screening.

A high-risk group for lung cancer, smokers with over a 20 pack index or who had haemosputum, was examined by 3-day pooled sputum cytology.

Low-dose CT or chest X-ray images were reviewed and classified by two trained physicians to determine the need for further clinical examination. Sputum cytology was also performed by a certified cytopathologist to determine the need for further clinical examination.

Those diagnosed with the need for further clinical examination were regarded as screen-positive. These individuals were asked to undergo further diagnostic evaluation at Osaka Medical Center for Cancer and Cardiovascular Disease. All individuals with positive chest X-ray screening were asked to undergo chest CT as a further examination.

Data collection

All subjects were individuals who had undergone either low-dose CT or chest X-ray screening tests between August 1998 and May 2002. The following participants were excluded from the analyses: (1) participants who had a past history of lung cancer, (2) participants who were suspected of having lung cancer by a previous screening or other medical examination and had received medical treatment and (3) participants who were suspected of having lung cancer at the previous screening or by other medical examination, but had refused further examinations.

Participants were divided into two groups: (a) low-dose CT group and (b) chest X-ray group. The low-dose CT group consisted of persons who had undergone low-dose CT at least one time during the study period, whereas the chest X-ray group consisted of persons who had undergone only chest X-ray. The low-dose CT group included those who had undergone both CT screening and chest X-ray screening within the study period. For these cases, screenings using chest X-ray were ignored to evaluate low-dose CT screening.

All data were entered into the screening database that was linked to the Osaka Cancer Registry (OCR) database with data reflecting incidence cases through December 2003. The indices used to collate the two databases were name, sex, address and date of birth. Information about lung cancer cases was extracted from hospital medical records or the OCR file.

We assumed that the preclinical detectable phase was 1 year for interval cancer cases. For death certificate-only cases, the date of 3 months before death was regarded as the date of diagnosis. Using these parameters, all lung cancer cases diagnosed within 1 year after a negative screen were regarded as interval lung cancers. Screen-detected cases were considered as true-positive cases regardless of the time between the date of screening and the date of diagnosis.

Statistical analyses

The sensitivity of screening was calculated by both the detection method and the incidence method. Although the detection method is simple and widely used, sensitivity estimated by detection method is affected by length and overdiagnosis biases (Day, 1985). The incidence method is not affected by length or overdiagnosis bias and is often used for breast cancer screening or colorectal cancer screening (Fletcher *et al*, 1993; Zappa *et al*, 2001).

Detection method

Sensitivity and specificity were calculated by the detection method using the following formulae.

		True disease state	
		+	−
Screening test	+	a	b
	−	c	d

Sensitivity $= a/(a+c)$

Specificity $= d/(b+d)$

Sensitivity and specificity calculated by the detection method were stratified by smoking status, histological type and screening rank. The screening rank was classified as the initial and repeated screenings, regardless of the number of years since the initial screening.

Incidence method

In addition, we calculated sensitivity by the incidence method using the following approximate formula (Day, 1985; Zappa *et al*, 2001):

$$\text{Sensitivity} = 1 - [I(t)/I]$$

Where $I(t)$ = the observed number of interval cancer cases during time t and I = the expected number of cases in the absence of screening.

We calculated the number of expected lung cancer cases in the absence of screening based on the following data. Age-specific lung cancer incidence rates provided from the OCR in 2001 were 16.3, 61.6, 180.9, 477.3 and 770.2 (per 100 000 person-years) for men, and 6.3, 25.9, 53.4, 116.7 and 241.3 for women, for age groups 40–49, 50–59, 60–69, 70–79 and ⩾80, respectively. Lung cancer incidence rates in the OCR were weighted by smoking status. According to the previous large-scale cohort study in Japan, the lung cancer incidence rates among ex-smokers and current smokers were assumed to be 2.2 times and 4.5 times of that of nonsmokers, respectively, among men, and 3.7 times and 4.2 times, respectively, among women (Sobue *et al*, 2002b). According to an official report from Osaka prefecture in 2003, the proportions of current smokers, ex-smokers and nonsmokers were 40, 30 and 30% among men, and 11, 7 and 82% among women, respectively (Department of public health, Osaka Prefecuture, 2006).

We assumed that smoking status proportions were the same across all age groups, so the expected incidence rate according to sex and smoking status was modified using the following formulae:

Expected incidence rate among male nonsmokers
$= \text{Incidence rate in OCR}/(4.5\times0.40 + 2.2\times0.30 + 1\times0.30)$

Expected incidence rate among female nonsmokers
$= \text{Incidence rate in OCR}/(4.2\times0.11 + 3.7\times0.07 + 1\times0.82)$

The expected incidence rates for ex-smokers and current smokers were assumed to be 2.2 times and 4.5 times of that of nonsmokers, respectively, among men, and 3.7 times and 4.2 times, respectively, among women.

The differences in sensitivity and specificity among the stratified variables were tested by χ^2 test. All statistical analyses were performed using SAS software, version 8.01 (SAS Institute Inc., Cary, NC, USA).

Ethical approval

The protocol for the present study was approved by the Ethics Committee of Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan. Informed consent for participation in the clinical trial, including CT screening, was obtained from all individuals.

RESULTS

From August 1998 to May 2002, a total of 7190 low-dose CT screening tests and a total of 36 085 chest X-ray screening tests were performed. Seven screening participants were excluded from analysis because they did not meet the eligibility criteria. Participants were ineligible for the following reasons: two participants were under follow-up care, one was suspected of having lung cancer but refused further examination and four had a history of lung cancer. A total of 7183 low-dose CT screening tests for 4689 participants (2765 men and 1924 women) and 36 085 chest

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X-ray screening tests for 13381 participants (4180 men and 9201 women) enrolled in the study.

Table 1 shows the number of screening tests by sex, age group, smoking status and rank of screening tests. Most of the participants who underwent low-dose CT screening were male current smokers or ex-smokers. Sputum cytology was additionally performed for 3539 screening tests for the low-dose CT group and 5417 screening tests for the chest X-ray group.

Table 1 Number of screening tests performed by age group, smoking status and rank; (a) low-dose CT group and (b) chest X-ray group: Osaka, 1998–2002

	Male	Female	Total
(a) Low-dose CT group			
Age (years)			
40–49	700	490	1190
50–59	1147	1132	2279
60–69	1885	886	2771
70–79	690	194	884
80–	43	16	59
Smoking status			
Nonsmoker	362	2048	2410
Ex-smoker	1012	113	1125
Current smoker	3091	557	3648
Rank			
Initial	2765	1924	4689
Repeated	1700	794	2494
Total	4465	2718	7183
(b) Chest X-ray group			
Age (years)			
40–49	1258	4862	6120
50–59	1679	8632	10311
60–69	4163	7910	12073
70–79	2695	3670	6365
80–	573	643	1216
Smoking status			
Nonsmoker	2807	23790	26597
Ex-smoker	4328	740	5068
Current smoker	3233	1187	4420
Rank			
Initial	4180	9201	13381
Repeated	6188	16516	22704
Total	10368	25717	36085

CT = computed tomography.

Forty cases in the low-dose CT group and 29 cases in the chest X-ray group were detected by the screening. Five interval cases in the low-dose CT group and eight interval cases in the chest X-ray group were confirmed by linkage to OCR (Table 2). All of the interval cancer cases for both the low-dose CT group and the chest X-ray group were smokers. As for the low-dose CT group, all of them were nonadenocarcinoma. Two cases, one in the low-dose CT group and one in the chest X-ray group, were detected by sputum cytology on negative radiological screen.

Table 3 shows sensitivity and specificity by the detection method according to histological type, smoking status and rank of screening. As a result, sensitivity and specificity (95% confidence interval) of screening were 88.9% (79.7–98.1%) and 92.6% (92.0–93.2%) for the low-dose CT group, and 78.3% (65.1–91.6%) and 97.0% (96.9–97.2%) for the chest X-ray group, respectively. Specificity of chest X-ray screening was significantly higher than that of low-dose CT screening ($P<0.001$). The difference in sensitivity by the detection method was not significant.

As for histological type, sensitivity for adenocarcinoma was significantly higher than that for nonadenocarcinoma (low-dose CT: 100 *vs* 61.5%; $P<0.001$, and chest X-ray: 95.8 and 50.0%; $P<0.001$); however, the histological type of three interval cases in the chest X-ray group was unknown. As for screening rank, specificity for the repeated screenings was significantly higher than that for the initial screenings (low-dose CT: 95.7 *vs* 91.0%; $P<0.001$, and chest X-ray: 97.7 *vs* 95.9%; $P<0.001$). As for sex, specificity for men was significantly lower than that for women (low-dose CT: 92.1 *vs* 93.5%; $P<0.05$, and chest X-ray: 95.7 *vs* 97.6%; $P<0.001$). Sensitivity of chest X-ray screening for women was significantly higher than that for men (100 *vs* 68.2%; $P<0.05$). As for smoking status, sensitivity of both low-dose CT and chest X-ray for nonsmokers was 100%.

Table 4 shows sensitivity estimated by the incidence method. Until the end of December 2003, a total of 14434 person-years (total for men: 9173 person-years; total for women: 5512 person-years) for the low-dose CT group and a total of 59725 person-years (total for men: 17962 person-years; total for women: 41763 person-years) for the chest X-ray group had been followed up for. The mean follow-up terms were 3.1 person-years and 4.5 person-years, respectively. The number of expected lung cancer cases was calculated to be 24.4 persons for the low-dose CT group and 59.3 persons for the chest X-ray group. As a result, sensitivity

Table 2 Interval cancer cases of screening; (a) low-dose CT group and (b) chest X-ray group

	Sex	Age (years)	Pack index	Smoking status	Histological type	Location	Rank	Clinical stage
(a) Low-dose CT group								
1	F	71	48	Current	Squamous	Unknown	Initial	III
2	M	60	43	Current	Large cell	Peripheral	Initial	III
3	M	72	48	Current	Small cell	Unknown	Repeated	IV
4	M	72	45	Current	Squamous	Unknown	Repeated	I
5[a]	F	59	29	Ex	Squamous	Central	Initial	I
(b) Chest X-ray group								
1	M	68	48	Current	Squamous	Unknown	Repeated	III
2	M	83	61	Current	Small cell	Unknown	Repeated	Unknown
3	M	72	21	Ex	Adeno	Unknown	Repeated	I
4	M	69	25	Current	Undifferentiated	Unknown	Initial	III
5	M	60	50	Current	Unknown	Unknown	Initial	Unknown
6[a]	M	63	68	Ex	Squamous	Central	Repeated	I
7	M	59	80	Current	Unknown	Unknown	Repeated	Unknown
8	M	85	15	Ex	Unknown	Unknown	Repeated	Unknown

CT = computed tomography. [a]Detected by sputum cytology.

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Table 3 Sensitivity and specificity by the detection method according to histological type, smoking status and rank of screening; (a) low-dose CT group and (b) chest X-ray group

	No. of screenings	Screen-detected cases	Interval cases	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
(a) Low-dose CT group					
Sex					
Men	4465	29	3	90.6 (80.5–100)	92.1 (91.3–92.9)
Women	2718	11	2	84.6 (65.0–100)	93.5 (92.6–94.4)
Smoking status					
Nonsmoker	2410	13	0	100	93.5 (92.5–94.4)
Ex-smoker	1125	6	1	85.7 (59.8–100)	91.5 (89.9–93.1)
Current smoker	3648	21	4	84.0 (69.6–98.4)	92.4 (91.6–93.3)
Histological type					
Adenocarcinoma	—	32	0	100	—
Nonadenocarcinoma	—	8	5	61.5 (35.1–88.0)	—
Rank					
Initial	4688	32	3	91.4 (82.2–100)	91.0 (90.2–91.8)
Repeated	2494	8	2	80.0 (55.2–100)	95.7 (94.9–96.5)
Total	7183	40	5	88.9 (79.7–98.1)	92.6 (92.0–93.2)
(b) Chest X-ray group					
Sex					
Men	10368	15	8	65.2 (45.8–84.7)	95.7 (95.3–96.1)
Women	25717	14	0	100	97.6 (97.3–97.8)
Smoking status					
Nonsmoker	26597	13	0	100	97.4 (97.3–97.7)
Ex-smoker	5068	4	3	57.1 (20.5–93.8)	95.9 (95.3–96.4)
Current smoker	4420	12	5	70.6 (48.9–92.2)	95.7 (95.1–96.3)
Histological type					
Adenocarcinoma	—	23	1	95.8 (87.8–100)	—
Nonadenocarcinoma	—	6	4	50.0 (21.7–78.3)	—
Unknown	—	0	3	—	—
Rank					
Initial	13381	13	2	86.7 (69.5–100)	95.9 (95.5–96.2)
Repeated	22704	16	6	76.2 (58.0–94.4)	97.7 (97.5–97.9)
Total	36085	29	8	78.3 (65.1–91.6)	97.0 (96.9–97.2)

CI = confidence interval; CT = computed tomography.

(95% confidence interval) estimated by the incidence method was 79.5% (63.5–95.5%) and 86.5% (77.8–95.2%), respectively. The difference in sensitivity by the incidence method was not statistically significant.

Discussion

The present study is the first report on sensitivity and specificity of annual lung cancer screening using low-dose CT and data from a local Cancer Registry. Sensitivity and specificity of low-dose CT screening according to the detection method were 88.9 and 92.6%. The sensitivity estimated by the incidence method resulted in a value of 79.5%. On the other hand, sensitivity and specificity of chest X-ray in the same time frame by the detection method were 78.3 and 97.0%, respectively. Furthermore, sensitivity of chest X-ray screening by the incidence method was 86.5%.

In previous studies conducted in the1980s, sensitivity and specificity of annual lung cancer screening using chest X-ray and sputum cytology were also evaluated by the detection method. In those studies, sensitivity and specificity for usual screening were 63.6–88.0% and 94.7–99.6%, respectively (Sobue *et al*, 1991c; Soda *et al*, 1993; Sagawa *et al*, 1994b; Tsukada *et al*, 2002). The use of low-dose CT screening resulted in a higher sensitivity and lower specificity than usual screening. The reported high sensitivity in participants undergoing low-dose CT screening is the result of improvement in the detection of small tumours. The lower specificity value indicates the difficulty of diagnosing nodules detected by screening.

Several points must be considered when the present study results are compared with previous results. Since 1980s, lung cancer incidence by histological type has undergone a change over time. With a large decline in the smoking rate among men, the proportion of squamous cell carcinoma or small cell carcinoma has decreased, whereas the proportion of adenocarcinoma has increased (Yoshimi *et al*, 2003). The current environment may be more advantageous for lung cancer screening because adenocarcinoma occurring in the peripheral lung has a longer doubling time than squamous cell carcinoma (Arai *et al*, 1994). In addition, as most low-dose CT screening-detected lung cancer lesions are too small to detect by chest X-ray and have a longer preclinical phase, simple comparison of low-dose CT screening with chest X-ray screening is difficult.

We used the detection method and stratified analyses by screening rank and histological type. As for screening rank, specificity of both low-dose CT and chest X-ray for the repeated

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