一般演題13

胸部CT検診発見肺癌の生存率ー従来型検診との比較ー

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住民検診として行われた胸部CT検診発見肺癌の生存率を従来型胸部単純X線検診発見肺癌の予後と比較した。発見肺癌43例の5年生存率は70.2%であった。男女別に見ると、男性では62.7%、女性は92.3%（4年生存率）であった。喫煙状況別に見ると、非喫煙者では、100%（4年）、喫煙指数600未満では80.4%、600以上では49.4%であった。従来型検診に比べると、非喫煙者では生存率の改善は、精検にCTを用いた場合20%、精検にCTを用いない場合50%と大きかったが、喫煙指数600以上では、生存率は10-15%の改善にすぎなかった。生存率による解析のため、overdiagnosis bias 等の偏りが混入している可能性はあるが、喫煙の曝露とCT検診による効果は逆相関する可能性がある。検診の対象者を決定するにあたっては、死亡率の検討も加えた慎重な判断が必要である。

キーワード：ヘリカルCT、検診、肺癌、生存率
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1. はじめに

胸部CTを用いた肺癌検診が、胸部単純X線撮影を用いた従来型検診に比べて、がん発見率や切除率などの即時的指標が極めて高いということはすでに確立されている[1-3]。しかし、発見肺癌の予後を示す生存率については、いまだ祖父江らが報告した東京から肺癌をなくす会（以下ALCA）の成績[4]しかない。この報告によると、発見肺癌の5年生存率は71%と非常に良好であるとされている。しかしALCAは、重喫煙者に特化した年2回の会員制検診であり、精検受診率もほぼ100%という理想的な状況で行われた検診である。この成績単独では、CT検診発見肺癌の予後が確立されたとは言い難い。そこで今回住民検診として行われた大阪の肺癌CT検診の生存率を、従来型検診と比較して検討した。

2. 方法

大阪府立成人病センター調査部疫学課では、昭和56年以降大阪府下7市町で行われた肺癌検診の読影・精密検査・治療・追跡に関与してきた。これら地区では、胸部単純間接X線撮影が、現在も全受診者に行われており、喀痰細胞診も喫煙指数400以上あるいは6ヶ月以内に血痰を有するものに、行われている。従来これらのスクリーニングで、精検が必要とされた場合、府立成人病センターもしくは府立羽曳野病院の呼吸器内科医師が、保健所や、市民病院で出張精検を行い、更なる精密検査や治療が必要なものを、成

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人病センターもしくは羽曳野病院で行ってきた。平成７年度までは、出張精検の際に、胸部単純直接Ｘ線撮影あるいは断層撮影を行なっていたが、平成８年度からは、CT検診車による全肺野CT撮影を精密検査受診者全員に行った。また平成10年度以降重喫煙者を中心にリクルートを行い、CTによる肺癌検診も同一市町で行っている。

昭和56年以降、これらの市町での40才以上の肺がん住民検診の受診者を以下の３つの群に分類した。

Ａ群：平成10～14年度のCT肺癌スクリーニングの受診者

Ｂ群：平成８～14年度までの従来型肺癌検診の受診者(間接Ｘ線と高危険群に対する喀痰細胞診をスクリーニングで行い、精検受診者に全員全肺野ＣＴを行った)

Ｃ群：昭和56～ 平成７年度までの従来型肺癌検診の受診者(精検受診者に直接撮影や断層撮影を行った)

検診で要精検とされても、翌年度まで確定診断がつかずに、再び検診を受診し肺癌と診断される場合がある。この場合、病巣が最初に検診で指摘された受診の群に振り分けた。

生存期間の始点は、発見につながる検診受診日とし、2004年５月15日まで追跡した。原死因死亡をエンドポイントとし、Kaplan-Mayer 法で生存率を測定した。生存率は、１）発見肺癌全体、２）男女別、３）喫煙指数別（非喫煙者、喫煙指数600未満、600以上）の三通りで測定した。

表１．各群のべ受診者の性・年齢・喫煙指数の分布

	A群		B群		C群	
年齢		(%)		(%)		(%)
男						
40-49	816	14.9	4,848	13.6	9,988	19.2
50-59	1,363	24.9	6,539	18.4	10,894	21.0
60-69	2,370	43.3	14,854,	41.8	19,221	37.0
70-79	866	15.8	7,857	22.1	9,860	19.0
80-	55	1.0	1,437	4.0	1,939	3.8
女						
40-49	594	18.0	16,245	20.7	35,116	31.0
50-59	1,373	41.7	25,884	33.0	35,326	31.2
60-69	1,070	32.5	25,278	32.2	29,993	26.5
70-79	239	7.3	9,613	7.3	11,069	9.8
80-	16	0.5	1,502	0.5	1,770	1.6
喫煙指数		(%)		(%)		(%)
男						
0	378	6.9	7,419	20.9	9,559	18.4
1-599	1,389	25.4	11,236	31.6	15,105	29.1
600-	3,703	67.7	16,880	47.5	27,238	52.5
女						
0	2,416	73.4	70,758	90.1	101,227	89.4
1-599	592	18.0	6,195	8.3	10,335	9.1
600-	284	8.6	1,269	1.6	1,722	1.5

3. 結果

＜即時的指標の比較＞

表１に受診者の性・年齢構成を示した。A群は男性5,470人、女性3,292人と男性が多く、年齢も80歳以上の高齢者はごくわずかであり、喫煙指数600以上の占める率が男性の67.7%、女性の8.6%を占める肺癌罹患率が高い集団であった。一方B群は男性35,535人、女性78,522人、C群も男性51,902人、女性113,284人といずれも男女比が１：２を超える女性の多い集団であった。これは一般にわが国で行われている肺癌住民検診の受診者構成とほぼ一致する。また喫煙指数で見ても、B群・C群とも喫煙指数600以上の占める率が男性で50%前後、女性で1.5%前後であり、A群に比べれば喫煙の曝露の低い集団であった。

表２に各群の検診成績を示した。A群は肺癌発見率(対10万人比)が男性548.4、女性394.9と極めて高い値を示した。一方B群とC群を比較すると男性における発見率はいずれも170前後で大差を示さないものの、女性でB群62.4、C群38.0と、女性の発見率が約２倍に向上していることが示された。

発見肺癌のstage分布を見ると、A群ではＩ期の占める割合が男性で73.3%、女性で92.3%と高率を示した。一方B群とC群に関しては、男性では両者40%前後で大差を示さなかったが、女性ではB群79.6%とC群の51.2%にくらべて飛躍的に向上した。すなわち胸部単純X線をスクリーニングとして行った従来型検診では、精検にCTを加えることで、男性

表２．検診成績の比較

	A群		B群		C群	
受診者数	5,470	3,292	35,535	78,522	51,902	113,274
発見肺癌数	30	13	59	49	98	43
発見率*	548.4	394.9	166.0	62.4	188.8	38.0
Stage						
I	22(73.3)	12(92.3)	23(39.0)	39(79.6)	44(44.9)	22(51.2)
II	2(6.7)	0(・)	17(28.8)	4(8.2)	6(6.1)	1(2.3)
III	3(10.0)	0(・)	5(8.5)	1(2.0)	28(28.6)	15(34.9)
IV	3(10.0)	1(7.7)	11(18.6)	5(10.2	20(20.4)	5(11.6)
組織型						
AD	22(73.7)	11(84.6)	28(47.5)	45(91.8)	29(29.6)	36(83.7)
SQ	4(13.3)	1(7.7)	24(40.7)	2(4.1)	48(49.0)	3(7.0)
SM	2(6.7)	0(・)	4(6.8)	1(2.0)	16(16.3)	3(7.0)
LA	2(6.7)	1(7.7)	1(1.7)	1(2.0)	5(5.1)	1(2.3)
OTH			2(3.4)			

*：対10万人比、

AD; adenocarcinoma, SQ; Squamous cell ca. SM; small cell ca. LA; Large cell ca.

OTH; Large cell neuroendcrine ca.、adenosquamous cell ca.

では発見率・stage に変化を示さなかったが、女性では、発見率・stage の大幅な改善が認められた。

＜生存率の比較＞

図1-a）に、各群の発見肺癌の生存率を示した。各群の5年生存率はA群70.2%、B群64.4%、C群42.8%で、ALCA の成績とほぼ同じ値であった。

次に男女別に分けて各群の発見肺癌の生存率を求めた（図1-b）,c))。男性の5年生存率はA群62.7%、B群51.3%、C群42.7%であった。一方女性の生存率はA群92.3%（4年）、B群79.0%（5年）、C群44.4%(5年)であった。男性が9割を占めるALCA の成績と比較すれば、大阪の男性の CT 検診発見肺癌の生存率は約8%低い値を示した。

また、発見肺癌の生存率を喫煙指数別に分けて生存率を求めた（図1-d),e),f))。非喫煙者においては、各群の生存率はそれぞれA群100%(4年)、B群80.4%、C群49.4%であった。一方喫煙指数600以上では、A群58.1%、B群48.6%、C群43.7%であった。従来型検診に比べて10-15%の生存率の改善に過ぎなかった。

4. 考察

CT 肺癌検診がわが国で行われてからすでに相当の年数が過ぎており、発見率や臨床病期などの即時的な指標に関する評価の段階から、予後を評価する段階に来ている。今回、住民検診として大阪で行われた CT 肺癌検診発見肺癌の生存率を従来法検診発見肺癌と比較検討した。その結果、CT 検診発見肺癌の5年生存率は70.2%と、ALCA の成績71%とほぼ同じ値を示した。しかし受診者集団の背景因子を比較すると、喫煙男性に特化したALCA に比べれば今回検討した集団は女性の占める割合が多い集団であった。このため、男女別に比較すると、男性では62.7%と ALCA に比べて8%程度低い値を示していた。この原因としては、臨床病期の偏りが考えられる。ALCA の成績では、IA 期の占める率は発見肺癌36例中28例（77.8%）であったが、大阪の男性では30例中18例（60%）にすぎなかった。また発見時すでにⅣ期はALCA では36例中1例（2.8%）であったが、大阪では30例中3例（10%）であった。実際の死亡例を表3に示すが、ＣＴ検診からの発見肺癌7例中6例はⅢ期とⅣ期であった。7例中5例は初回受診者であったが、従来型検診も含めて数年ぶりの受診というものが多かった。また他の人間ドックで要精検となり、精検目的で CT 検診を受診しているものも一例含まれていた。住民検診の場合、多大な私費を投じて会員制検診や人間ドックよりも、健康意識や医療・疾病に対する知識が低いものが多く含まれると考えられる。これらのことが、住民検診の成績を悪化させる因子になるのではないかと考えられる。

一方 ALCA では例数が少なく評価できなかった女性のＣＴ検診発見肺癌の予後に関しては、大阪の検討では92.3%と極めて高い値を示していた。唯一の死亡例は、重喫煙者で、ＣＴ検診の初回受診時にすでに強い体重減少とリンパ節腫脹を示していた。

喫煙指数別の解析では、男女別の解析よりも各群の生存率の差が明瞭に示された。非喫煙者では、CT 検診発見例は死亡

表3. A群（CT検診群）の死亡例

症例	年齢 / 性別	検診回数	組織型	臨床病期
1	59 / M	1	AD	IIIA
2	79 / M	1	AD	IIIB
3	62 / M	1	AD	IIIA
4	67 / M	1	AD	IV
5*	75 / M	2	SQ	IA
6**	64 / M	2	AD	IV
7	63 / F	1	LA	IV

*; 術後短期間に縦隔リンパ節再発した。
** ; 高CEA血症で精査とされ、診断目的で検診を受診。肺胞上皮癌による多発肺内転移を認めた。

例がなく、スクリーニングを従来型としたB群、C群との生存率の差は大きかった。一方喫煙指数600以上の重喫煙者については、各群の差は小さく、精検で全肺野CTを撮影する群との5年生存率の差はわずか10%であった。現状のCT検診はマンパワーやコストという経済的問題が解決されていない。この状況で、効率的な検診の運営策として、検診の対象者を男性に限定するとか、喫煙者に限定する等の議論がなされている。今回の成績からは、小さな効果しか期待できないものの罹患率・死亡率の高い喫煙者に限定するのか、あるいは大きな効果が期待されるが罹患率・死亡率の低い非喫煙者を対象にするのかという議論も起こりうる。しかし生存率単独での評価の場合、lead-time biasやoverdiagnosis biasなどの種々の偏りが混入することは明らかであり、対象者の決定には、やはり死亡率の検討が不可欠であるといわざるを得ない。

今回の検討も、ALCAの検討も、40例前後の比較的少数例かつ短期間の予後調査である。本来もっと多数かつ長期間の追跡が正確な情報を提供することは言うまでもない。今後多施設共同の生存率調査を期待したい。

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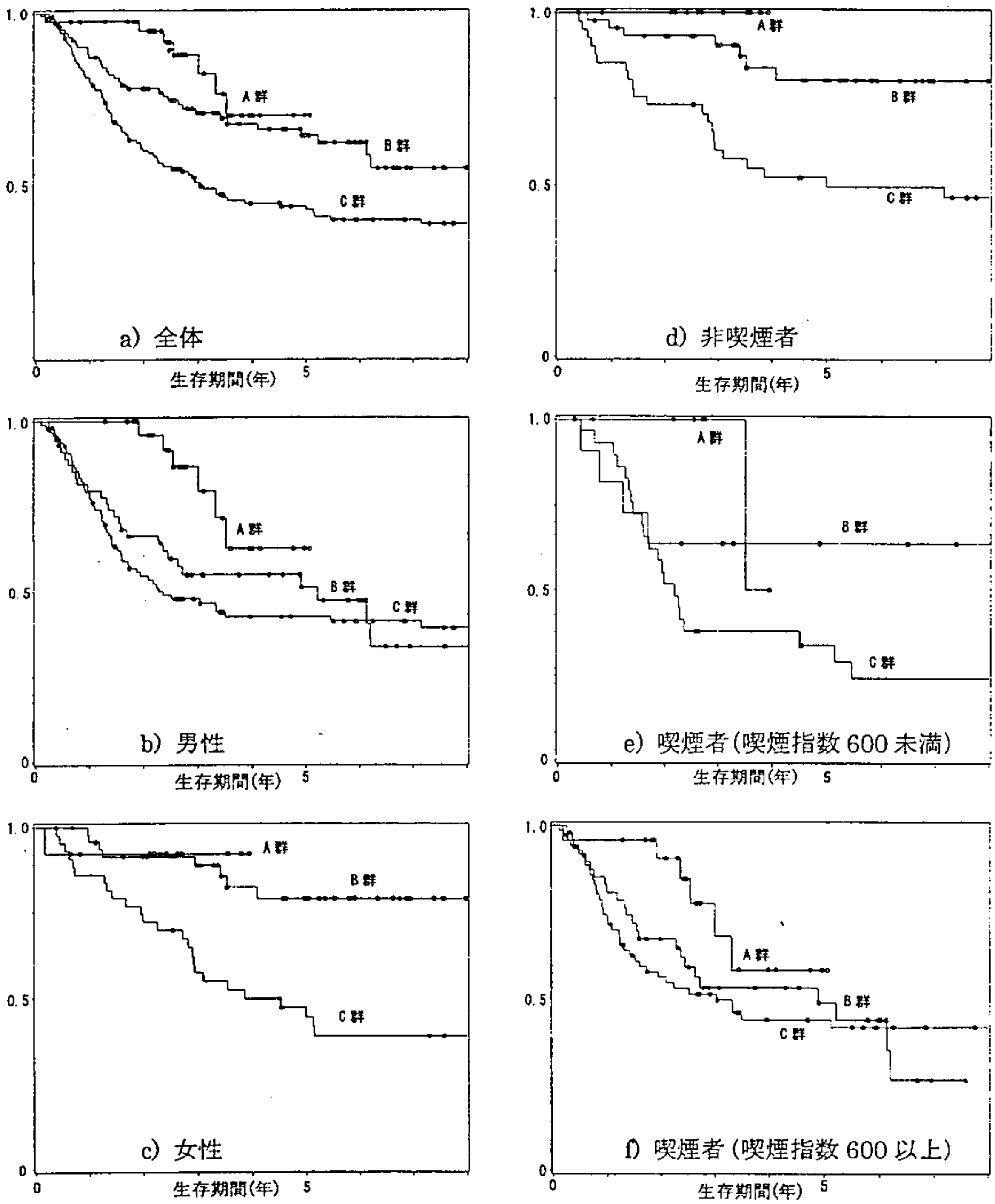

図 1．検診手法別発見肺癌の男女別・喫煙指数別生存率曲線

A 群：CT 検診発見群、B 群：従来型検診をスクリーニング法とし、精検として CT を行った群、C 群：従来型検診をスクリーニング法とし、精検として直接単純撮影や断層撮影を行った群

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Filter cigarette smoking and lung cancer risk; a hospital-based case–control study in Japan

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Epidemiology

Recent changes in the histology of lung cancer, namely a relative increase of adenocarcinoma compared to squamous cell carcinoma, might be due to a temporal shift from nonfilter to filter cigarettes. To investigate the association between type of cigarette and lung cancer by histological type, we conducted a case–control study in Japan, comprising 356 histologically confirmed lung cancer cases and 162 controls of male current smokers, who provided complete smoking histories. Overall, logistic regression analysis after controlling for age and prefecture revealed decreased risk, as shown by adjusted odds ratios, for both squamous cell carcinoma and adenocarcinoma among lifelong filter-exclusive smokers as compared to nonfilter or mixed smokers. This decrease was greater for squamous cell carcinoma than for adenocarcinoma. Among men under 54 years, filter-exclusive smokers displayed increased risk of adenocarcinoma, but decreased risk of squamous cell carcinoma. The recent shift in histology from squamous cell carcinoma to adenocarcinoma, particularly among younger smokers, might be due to changes in cigarette type. However, among subjects aged 65 years or more, no differences in histological type appeared related to type of cigarette smoked, implying that other factors are associated with increases in adenocarcinoma among older Japanese population.
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Keywords: lung cancer; histological type; filter and nonfilter cigarettes; hospital-based case–control study; Japan

Recently, the overall incidence of lung cancer has increased in Japan. However, incidence by histological type has shown a changing pattern. A relative increase in incidence of adenocarcinoma (AC), as compared to squamous cell carcinoma (SCC), has been observed, particularly for the younger age group (Tanaka *et al*, 1988; Yoshimi *et al*, 2003). While the same trends have been demonstrated in Western countries (Levi *et al*, 1997; Russo *et al*, 1997; Skuladottir *et al*, 2000; Janssen-Heijnen *et al*, 2001), AC accounts for a larger proportion of all lung cancer in Japan (Parkin *et al*, 1992). These relative increases in AC do not appear attributable to changes in pathological diagnosis alone (Charloux *et al*, 1997).

Changes in the composition of cigarettes, such as content of tar and nicotine, might influence lung cancer trends. The market share held by high-tar nonfilter cigarettes was almost completely taken over by low-tar filter cigarettes in the 1960s in both Japan and Western countries (Wynder *et al*, 1991). The links between changes in histology of lung cancer and type of cigarettes have led to the hypothesis that the type of cigarette, that is, filter or nonfilter, is associated with changing histological patterns of lung cancer. Several epidemiological studies have found that the effect of low-tar filter cigarettes on lung cancer risk differs according to histological type of tumour (Wynder and Kabat, 1988; Stellman *et al*, 1997). However, to date, no studies have examined possible relationships between type of cigarette and lung cancer risk by histological type in Asian populations. The present study explored the relationship between type of cigarettes smoked and lung cancer histology in Japan, focusing on differences between SCC and AC, by means of a multicentre, hospital-based case-control study.

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MATERIALS AND METHODS

A multicentre, hospital-based case-control study was conducted in 17 hospitals that participated in the Osaka Anti-Lung Cancer Association in Osaka prefecture, two hospitals in Okinawa prefecture, and one hospital in Nagano prefecture in Japan. In participating hospitals, patients were recruited from all lung cancer wards, in addition to one or more wards for other diseases. Study subjects comprised patients who were newly admitted to the participating hospitals from January 1996 to December 1998. A total of 1324 patients (945 men and 379 women) were admitted with newly diagnosed lung cancer. All lung cancer cases were confirmed microscopically. Controls comprised 3600 patients (2169 men and 1431 women) who were admitted to the same hospitals during the same period with diseases other than lung cancer. Of the 3600 controls, 2348 patients with diseases related to smoking were excluded, that is, no patients with respiratory tuberculosis (ICD-10: A15, 16, 19, B90), respiratory infection (A31), neoplasm (C00-D48), inguinal hernia (K40), ischaemic heart disease (I20-I25), subarachnoid haemorrhage (I60), arterial disease (I70-I73), respiratory disease (J00-J99), peptic ulcer (K25-K27), or respiratory symptoms (R04, R06, R09) were included in the study. After further exclusion of subjects ⩽39 or ⩾80 years (65 cases and 286 controls) and subjects who did not provide complete information on current smoking habits (104 cases and 86 controls), 1115 lung cancer cases and 880 controls remained for analysis.

Among the 880 controls, distribution of diagnoses was as follows: 19% ear and mastoid (H60-H95); 16% digestive system (K00-K93); 12% nervous system (G00-G99); 9% circulatory system (I00-I99); 9% endocrine, nutritional and metabolic (E50-90); 8% symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified (R00-R99); 5% infectious and parasitic (A00-B99); 5% musculoskeletal system and connective tissue (M00-M99); 4% genitourinary system (N00-N99); 4% injury, poisoning, and certain other consequences of external causes (S00-T98); 3% blood and blood-forming organs and certain disorders involving the immune mechanisms (D50-D89); 3% skin and subcutaneous tissue (L00-L99), 3% congenital malformations, deformations, and chromosomal abnormalities (Q00-Q99) and less than 2% for other categories.

Information on smoking history and other lifestyle factors was obtained by means of a self-administered questionnaire completed during admission. Current smoking status was confirmed using a closed question. Detailed smoking histories were then obtained from current and former smokers by means of open questions regarding ages at which smoking habits changed substantially; information on number of cigarettes smoked per day and type of cigarettes (filter, nonfilter, or others) was requested for each period.

To investigate associations between type of cigarette (filter/nonfilter) and histological type of lung cancer, we further examined male current smokers (356 cases and 162 controls) for whom complete smoking histories regarding filter/nonfilter cigarettes were available. Owing to the small number of female current smokers with complete smoking histories, this analysis was restricted to male current smokers. Duration of nonfilter or filter use was calculated separately, based on the history of smoking. Current smokers were categorised into two groups: 'filter-exclusive smokers' comprised men who were lifetime smokers of filter cigarettes; 'mixed or nonfilter smokers' were men who had smoked nonfilter cigarettes at some point. Any history of cigarette use before 1957, when filter cigarettes first became commercially available in Japan, was regarded as nonfilter cigarette use. The mean number of cigarettes per day was defined as the weighted mean of each average number of filter and nonfilter cigarettes smoked per day. Total duration was defined as the sum of durations of filter and nonfilter smoking. Subjects who reported smoking other types of cigarettes were excluded from the analysis.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression analysis in order to estimate the risk of lung cancer by histological type. Statistical adjustment was made for age (continuous variable) and prefecture (three categories). Adjusted ORs in relation to type of cigarettes were presented with and without adjustment for mean number of cigarettes smoked per day (continuous variable). All statistical computations were performed using PC-SAS (SAS Institute Inc., Cary, NC, USA).

RESULTS

Prevalences of SCC, AC, small cell carcinoma, large cell carcinoma, and unknown histology were 34.3, 44.0, 11.3, 3.9 and 6.4% for men and 8.9, 75.6, 7.6, 2.8, and 5.1% for women, respectively.

Current cigarette smoking was associated with increased risk of overall lung cancer, SCC and AC; adjusted ORs of current smokers as compared to nonsmokers were 4.56 (95% CI: 3.00-6.94) for all lung cancers, 24.5 (95% CI: 7.39-80.9) for SCC, and 2.56 (95% CI: 1.61-4.07) for AC, respectively, for men, and 2.29 (95% CI: 1.44-3.64) for all lung cancers, 10.9 (95% CI: 3.99-30.0) for SCC, and 1.48 (95% CI: 0.87-2.51) for AC, respectively, for women.

Adjusted ORs for lung cancer in relation to duration of smoking and number of cigarettes per day are presented by sex in Tables 1 and 2. For men, adjusted ORs among current smokers as compared to lifelong nonsmokers increased with longer duration of smoking and increasing number of cigarettes per day, irrespective of histological type of lung cancer (Table 1). The adjusted OR for SCC was much higher than that for AC. Male former smokers displayed an approximately 14-fold increase in risk of SCC, whereas elevation in the adjusted OR for AC was two-fold.

Similarly, in women, increasing risk regardless of lung cancer histology (as indicated by adjusted OR) with increasing intensity of smoking was observed among current smokers (Table 2). Adjusted ORs for SCC were much greater than those for AC. Female former smokers were only at significant elevated risk for SCC.

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Table 1 Adjusted odds ratios (ORs) for lung cancer associated with cigarette smoking by histological type among men

		Cases					
	Controls	Squamous cell carcinoma		Adenocarcinoma		All lung cancers	
Smoking status	No.	No.	Adjusted[a] OR (95% CI)	No.	Adjusted[a] OR (95% CI)	No.	Adjusted[a] OR (95% CI)
Nonsmoker	90	3	1.00 (reference)	30	1.00 (reference)	40	1.00 (reference)
Past smoker	161	87	13.9 (3.16-61.0)	120	1.95 (1.09-3.50)	246	2.46 (1.47-4.12)
Current smoker							
Duration of smoking in years							
1-20	13	2	5.65 (0.80-39.9)	6	1.56 (0.53-4.62)	9	1.85 (0.71-4.85)
21-39	137	52	17.4 (5.08-59.9)	94	2.38 (1.42-3.99)	189	3.74 (2.37-5.90)
40+	90	144	29.8 (8.96-89.4)	119	2.89 (1.70-4.90)	355	6.02 (3.76-9.62)
Number of cigarettes per day[b]							
1-20	104	69	3.00 (1.61-5.59)	84	1.67 (1.05-2.65)	197	1.94 (1.31-2.87)
21-39	88	73	7.11 (3.74-13.5)	80	2.23 (1.39-3.59)	210	3.38 (2.67-5.05)
40+	37	43	12.5 (5.88-26.6)	43	3.01 (1.69-5.37)	110	4.61 (2.80-7.57)

[a]Adjusted for age and prefecture. [b]In total, 36 cases and 11 controls for current smokers were not included because of incomplete data. CI = confidence interval.

Table 2 Adjusted odds ratios (ORs) for lung cancer associated with cigarette smoking by histological type among women

Smoking status	Controls No.	Cases: Squamous cell carcinoma No.	Squamous cell carcinoma Adjusted[a] OR (95% CI)	Adenocarcinoma No.	Adenocarcinoma Adjusted[a] OR (95% CI)	All lung cancers No.	All lung cancers Adjusted[a] OR (95% CI)
Nonsmoker	320	10	1.00 (reference)	195	1.00 (reference)	231	1.00 (reference)
Past smoker	28	8	9.56 (2.73–33.4)	14	0.54 (0.23–1.26)	29	0.93 (0.47–1.81)
Current Smoker							
Duration of smoking in years							
1–20	16	1	2.48 (0.28–21.8)	4	0.48 (0.15–1.50)	6	0.63 (0.23–1.68)
21–39	23	6	12.5 (3.77–41.5)	19	1.85 (0.95–3.63)	32	2.61 (1.44–4.74)
40+	2	3	40.2 (5.71–282.7)	7	4.26 (0.87–20.9)	18	9.34 (2.13–41.1)
Number of cigarettes per day[b]							
1–20	33	9	12.3 (4.34–35.0)	22	1.31 (0.72–2.37)	40	1.98 (1.18–3.32)
21+	6	1	7.54 (0.75–75.8)	7	3.09 (0.97–9.86)	13	4.37 (1.57–12.2)

[a]Adjusted for age and prefecture. [b]In total, three case and two controls for current smokers were not included because of incomplete data. CI = confidence interval.

Table 3 Mean age and smoking status by histological type and filter/nonfilter cigarette consumption among male current smokers

	Type of smoking	Cases: Squamous cell carcinoma	Adenocarcinoma	All lung cancers	Controls
Number (%)	Mixed	114 (83.2)	84 (61.3)	259 (72.8)	80 (49.4)
	Filter	23 (16.8)	53 (38.7)	97 (27.2)	82 (50.6)
Mean age	Mixed	67.2	65.5	66.6	63.6
	Filter	56.3	52.3	53.2	51.6
Mean number of cigarettes per day	Mixed	28.3	26.4	27.3	23.9
	Filter	34.5	32.1	32.6	28.6
Mean total duration	Mixed	47.0	45.3	46.5	43.7
	Filter	34.1	30.4	32.0	28.5
Mean duration of filtered cigarettes	Mixed	29.4	29.2	29.5	26.6
	Filter	34.1	30.4	32.0	28.5
Mean duration of nonfiltered cigarettes	Mixed	17.6	16.1	17.0	17.2
	Filter	—	—	—	—

Mixed = nonfilter-exclusive smoker or filter/nonfilter-mixed smoker; Filter = filter-exclusive smoker.

Table 3 shows mean age and smoking status in terms of filter/nonfilter cigarette consumption among current male smokers by histological type. Lifelong nonfilter-exclusive smokers comprised 7.5% (39 of 518 men). Filter-exclusive smokers were much younger and consumed more cigarettes per day. Total duration of smoking among nonfilter or mixed cigarette smokers was substantially longer than that of filter smokers; this difference was largely due to the duration of nonfilter cigarette smoking among nonfilter or mixed smokers. Although duration of filter cigarette smoking showed less variation, smoking duration was slightly longer among filter-exclusive smokers. Men with SCC were older, had smoked for a longer duration and consumed more cigarettes per day than men with AC, for both filter and nonfilter users.

Table 4 shows adjusted ORs for lung cancer according to filter/nonfilter use among male current smokers by histological type. Overall, after adjustment for age and prefecture, OR for all lung cancers tended to be decreased by 30% (not significant) among filter-exclusive smokers as compared to mixed or nonfilter smokers. A nonsignificant tendency towards a reduction in adjusted OR was found for SCC, but not for AC. When we further examined the association between type of cigarettes and lung cancer histology according to age, by dividing participants into age groups of ⩽54-, 55–64-, and ⩾65-year old, ORs were shown to vary according to age and histology. Adjusted ORs in filter-exclusive smokers compared to mixed or nonfilter smokers decreased with increasing age group, regardless of histology. For men ⩽54-year old, a nonsignificant two-fold increase in risk in prefecture-adjusted OR of AC was observed among filter-exclusive smokers, whereas the adjusted OR indicated a nonsignificant 60% reduction in the risk of SCC. For men 55–64-year -old, a reduction in adjusted ORs in filter-exclusive smokers as compared to mixed or nonfilter smokers was observed for SCC, but not for AC. For the oldest group (⩾65-years), filter-exclusive smoking was associated with decreased risk irrespective of histological type. The reduction in adjusted ORs related to SCC and AC in filter-exclusive smokers was similar. Odds ratios after further controlling for mean number of cigarettes smoked per day were not substantially different, generally displaying a slight decline in adjusted ORs.

DISCUSSION

The present study supports existing evidence of increased risks of both SCC and AC with higher numbers of cigarettes smoked and longer duration of smoking. In current smokers, risks indicated by adjusted ORs were higher for SCC than for AC. Furthermore,

Table 4 Adjusted odds ratios (ORs) for lung cancer by histological type according to filter/nonfilter cigarette consumption and age

	Controls	Cases								
		Squamous cell carcinoma			Adenocarcinoma			All lung cancers		
	No.	No.	OR1[a] (95% CI)	OR2[b] (95% CI)	No.	OR1[a] (95% CI)	OR2[b] (95% CI)	No.	OR1[a](95% CI)	OR2[b] (95% CI)
All subjects										
Mixed	80	114	1.00 (ref.)	1.00 (ref.)	84	1.00 (ref.)	1.00 (ref.)	259	1.00 (ref.)	1.00 (ref.)
Filter	82	23	0.52 (0.27–1.03)	0.55 (0.27–1.15)	53	0.88 (0.47–1.63)	0.83 (0.44–1.59)	97	0.70 (0.40–1.15)	0.70 (0.41–1.21)
Age ≤54										
Mixed	12	5	1.00 (ref.)	1.00 (ref.)	4	1.00 (ref.)	1.00 (ref.)	13	1.00 (ref.)	1.00 (ref.)
Filter	53	8	0.38 (0.10–1.42)	0.38 (0.10–1.45)	33	2.01 (0.60–6.81)	2.54 (0.66–9.79)	54	1.00 (0.42–2.40)	1.05 (0.43–2.56)
55 ≤age ≤64										
Mixed	34	33	1.00 (ref.)	1.00 (ref.)	24	1.00 (ref.)	1.00 (ref.)	72	1.00 (ref.)	1.00 (ref.)
Filter	25	13	0.38 (0.10–1.42)	0.49 (0.18–1.35)	18	1.05 (0.46–2.43)	0.83 (0.33–2.11)	37	0.68 (0.34–1.36)	0.62 (0.29–1.35)
Age ≥65										
Mixed	34	76	1.00 (ref.)	1.00 (ref.)	56	1.00 (ref.)	1.00 (ref.)	174	1.00 (ref.)	1.00 (ref.)
Filter	4	2	0.36 (0.05–2.24)	0.30 (0.05–1.97)	2	0.30 (0.05–1.74)	0.28 (0.05–1.71)	6	0.31 (0.08–1.21)	0.31 (0.08–1.20)

Mixed = nonfilter-exclusive smoker or filter/nonfilter-mixed smoker; Filter = filter-exclusive smoker. [a]Adjusted ORs were presented after controlling for age and prefecture for all subjects, and for prefecture for each age-specific stratum. [b]Additional control for number of cigarettes smoked per day.

overall, although filter cigarette smokers were at lower risk compared to nonfilter smokers regardless of histology, a greater reduction in adjusted OR was observed for SCC than for AC.

Lower risk of all lung cancers has been observed among filter cigarette smokers compared to nonfilter cigarette smokers in some case–control studies of men (Wynder and Stellman, 1979; Lubin *et al*, 1984; Benhamou *et al*, 1989; Benhamou *et al*, 1994; Armadans *et al*, 1999) and women (Wynder and Stellman, 1979; Lubin *et al*, 1984; Agudo *et al*, 2000). However, the reduction in risk of all lung cancers among filter cigarette smokers compared to nonfilter cigarette smokers has been obscured. This results from the fact that the total incidence of lung cancer has increased in recent years, despite the widespread predominance of filter cigarettes. It is possible that, since this move towards filter cigarettes, insufficient time has elapsed to reflect a reduction in lung cancer incidence. Furthermore, overall lung cancer mortality rates had been increasing, although they have tended to level off in the last 5 years (Yoshimi *et al*, 2003). Separate analysis of an association between type of cigarette and lung cancer should therefore be performed by histological type of lung cancer.

One US case–control study has shown that the effect of filter cigarettes varies depending on the histological type of lung cancer, and revealed that reduced risk of SCC, but not AC, was apparent among filter cigarette smokers compared to nonfilter smokers (Stellman *et al*, 1997). These results are consistent with those of the present study. Another case–control study demonstrated a reduction in risk of Kreyberg I lung cancer, but not of Kreyberg II, among filter smokers (Wynder and Kabat, 1988). Trends towards a relative increase in AC compared to SCC might be partially attributable to a greater reduction in SCC among filter cigarette smokers compared to nonfilter cigarette smokers.

However, we cannot assume that the relative increase in AC observed in Japan is attributable to the same mechanisms seen in Western countries, since smoking has a lower impact on lung cancer risk among Asian populations and overall lung cancer death rates are lower in Japan than in Western countries (Sobue *et al*, 2002). This implies that factors other than smoking, such as lifestyle and diet, particularly the traditional Japanese diet, play important roles in lung cancer development (Wynder and Hoffmann, 1994). Furthermore, the association between certain dietary factors and lung cancer may be histological type specific (De Stefani *et al*, 1997; Kubik *et al*, 2001). The traditional Japanese diet, incorporating elements such as fish and soybean products, was found to be associated with a reduced risk of AC (Takezaki *et al*, 2001), and one study found the protective effects of tofu (a soybean product) appeared more significant for SCC (Wakai *et al*, 1999). In contrast, high levels of fat consumption increase the risk of lung cancer, particularly for AC (Ozasa *et al*, 2001). The Japanese diet has recently undergone substantial Westernisation, and such dietary alterations might represent an alternate explanation for the observed changes in histological types of lung cancer.

It should be noted that the effects of filter cigarettes on lung cancer by histological type varied according to age. Among men aged ≤54 years, elevation in the adjusted OR for filter cigarettes compared to nonfilter cigarettes was found for AC, but not SCC. For men aged 55–64 years, use of filter cigarettes was associated with a reduction in adjusted ORs for SCC, but not for AC, whereas the magnitude of reduction was similar for SCC and AC in men ≥65 years. No clear explanation for the age-related effects of filter cigarettes was apparent. Among young smokers, the tendency of filter smokers to inhale deeply to compensate for the low-tar delivery of filter cigarettes (Wynder and Muscat, 1995) might sufficiently affect the more peripheral regions of the lung, where most AC appear, even among short-term filter cigarette smokers. However, for older smokers, and considering long-term smoking, the cumulative exposure to tar contained in smoke might be substantially reduced among filter-exclusive cigarette smokers than among nonfilter or mixed cigarette smokers. The total protective effects for both SCC and AC might therefore be more apparent among older smokers. Indeed, trends in SCC and AC incidence from 1974 to 1997 among Japanese men differed according to age group, and the relative increase of AC compared to SCC was intensified in younger age groups (Yoshimi *et al*, 2003). Any elevation in risk of AC (or a smaller reduction in AC compared to SCC) attributable to filter cigarette use among younger smokers might represent an important issue, as the younger the age group, the more the smokers consume filter cigarettes in preference to nonfilter cigarettes. However, since no studies have addressed age-specific or duration-dependent protective effects of filter cigarettes, further confirmation is needed for other populations.

Reasons other than deep inhalation have been proposed as being responsible for filter cigarettes not providing relative protection against AC. These include reduced tar and nicotine delivery in filter cigarettes. Filter cigarettes remove the larger carcinogenic particles, meaning that smaller particles in the smoke from filter

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cigarettes reach the peripheral regions of the lung. Although tar delivery from filter cigarettes is reduced, concentrations of nitrosamines such as NNK (4-(methylnitrosamino)-1-3(pyridil)-1-butanone), which is known to induce the formation of AC, are not decreased in filter smoke (Agudo *et al*, 2000).

When we analysed the association between filter and nonfilter smoking, the most likely confounding factors were age and total duration of smoking. Duration of smoking was strongly associated with both SCC and AC in a dose-dependent manner. As age and total duration of smoking were also well correlated (correlation coefficient = 0.80 ($P < 0.0001$)), we avoided simultaneous inclusion of these variables in the logistic regression model. However, residual confounding related to cumulative smoking exposure might be partially responsible for the protective effects of filter cigarettes observed. In our subjects, mean number of cigarettes smoked per day was associated with risk of overall lung cancers and was higher among filter cigarette smokers than among nonfilter or mixed smokers. Comparison of filter/nonfilter cigarette smokers might thus be confounded by daily cigarette consumption. In this regard, the relationship between type of cigarette and lung cancer with adjustment for mean number of cigarettes is interesting. However, controlling for the amount of smoking, as a measure of exposure to lung carcinogens, requires caution when comparing the risks of different types of cigarettes. As low-nicotine low-tar filter cigarette smokers tend to smoke more cigarettes in order to maintain nicotine intake, adjustment by number of cigarettes may not be appropriate in case comparison between low-tar filter smokers and nonfilter or mixed cigarette smokers. These result in a spurious reduction in risk for filter cigarette smokers as compared to nonfilter or mixed cigarette smokers. Indeed, after adjustment for mean number of cigarettes per day, most adjusted ORs for overall lung cancers, SCC, and AC for filter cigarette smokers as compared to nonfilter or mixed cigarette smokers were slightly decreased. However, the increased risk of AC among men ⩽54-year and no reduction in the risk of AC among men aged 55–64 years were not changed even after controlling for this variable.

As controls were patients admitted to hospital, and controls with conditions known to be related to cigarette smoking were excluded, the possibility of underestimating lung cancer risks in smokers due to over-representation of smokers among hospital patients was minimised. However, one limitation of the present study should be considered. Smoking histories were obtained using self-reported questionnaires, and the number of subjects recording complete smoking histories was low; among current smokers, only 65% of the original subjects eligible as cases or controls were used for further analysis of associations between type of cigarette and lung cancer. The present study might therefore lack the power to detect slight to moderate increases (or decreases) in ORs. Finally, we did not obtain data on brand names of cigarettes smoked, which might have led to misclassification of cigarette types.

In conclusion, this study of a Japanese population revealed a type-specific association of filter cigarettes as compared to nonfilter cigarettes, that is, a protective effect against SCC, but no such effect (or, at least, a relatively reduced effect) against AC, particularly among younger smokers. Further confirmation is required to ascertain possible differences in risks of filter cigarettes for lung cancer. However, almost all smokers have now changed to filter cigarettes. The more prevalent smoking of filter cigarettes becomes, the more limited the opportunities for further investigations comparing filter and nonfilter cigarettes.

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Lung cancer death rates by smoking status: Comparison of the Three-Prefecture Cohort study in Japan to the Cancer Prevention Study II in the USA

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Cigarette smoking is an established risk factor for lung cancer. However, the magnitude of the relative risk (RR) on lung cancer mortality in relation to cigarette smoking is reported to be lower in Japan than in Western countries. We investigated whether this discrepancy could be explained by differences in the exposure to cigarettes smoked, by differences in sensitivity to smoking, or by differences in lung cancer mortality among non-smokers. We examined the 10-year follow-up data on 88 153 participants in a Japanese population-based prospective study conducted in three prefectures. Data used as a Western counterpart was retrieved from a published report of the US Cancer Prevention Study (CPS)-II. Although there was a significant increased risk of lung cancer death among current smokers compared with non-smokers, the observed RR in the Three-Prefecture Study were much lower than RR reported in the CPS-II. Lung cancer mortality of our Japanese sample was lower among current smokers and higher among non-smokers regardless of age and sex. Current smokers in our sample had initiated smoking at an older age and smoked fewer cigarettes per day for shorter durations than those in the CPS-II sample. The Poisson regression model (controlling for age, number of cigarettes smoked per day and duration of smoking) showed that male current smokers in our sample had a lower risk of lung cancer compared with those in the CPS-II sample (rate ratio 0.34 [95%CI 0.27–0.43]). These findings might explain why Japanese risks of lung cancer are lower than those observed in Western countries. (*Cancer Sci* 2005; 96: 120–126)

Numerous epidemiological studies have consistently reported smoking as a risk factor for lung cancer. Three prospective studies[1–3] and several case-control studies[4–6] in Japan have shown that the magnitude of the relative risk (RR) associated with cigarette smoking is lower than those in Western countries.[2] For example, in the Six-Prefecture Study[3] and the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC),[1] the RR of lung cancer death among smokers compared to non-smokers was estimated at 4.5 for men, whereas the RR for men ranged from 11.6 to 23.2 in prospective studies conducted in the USA[7–9] and the UK.[10] For women, the RR were 2.3 in the Six-Prefecture Study[3] and 3.6 in the JACC study,[1] while corresponding RR ranged from 2.7 to 12.8 in the USA.[7,9] The first aim of this study was to verify these figures by evaluating lung cancer death and smoking habits with a new large-scale, population-based prospective survey (The Three-Prefecture Cohort Study), conducted in three prefectures in Japan.

The RR expresses a single summary estimate of the effects of smoking on lung cancer. However, the RR is computed by simply dividing the death rate among smokers by that among non-smokers. For a better understanding of the reasons for the lower RR of lung cancer among the Japanese, it would be more accurate to compare the death rates by smoking status. Furthermore, exposure levels to smoking might account for differences in the risk of lung cancer between Japanese and Western current smokers. It is well known that lung cancer risk depends on the amount, duration, and initiation age of smoking. Thus, to determine the reason for the lower RR associated with smoking in Japanese subjects, it is also important to compare the exposure levels to smoking as well as the lung cancer death rates between Japanese and Western subjects.

The second aim of this study was to compare death rates by smoking status and smoking exposure levels with published data from a large American prospective sample, the Cancer Prevention Study II (CPS-II),[9] which began at nearly the same time as the Three-Prefecture Cohort Study (1982). Finally, we examined whether any discrepancy in the RR of lung cancer between the studies could be explained by the difference in death rates due to smoking status (i.e. non-smokers vs smokers) and smoking exposure level between the Japanese and the US samples.

Materials and Methods

Study population. The Three-Prefecture Cohort Study collected data from February 1, 1983 to November 1, 1985, in selected areas of three prefectures in Japan: Miyagi, Aichi, and Osaka. The study areas of each prefecture included six areas of a city and two towns in Miyagi Prefecture, five elementary school districts in one area of a city and two areas of a city in Aichi Prefecture, and three towns in Osaka Prefecture. An additional study cohort was sampled in December 1, 1990, in one city in the Osaka Prefecture. The study population included all persons aged 40 years or older, who resided in the study areas according to each town's residential registry. A self-administered questionnaire was distributed to 130 839 persons, and 108 774 (50 544 men and 58 230 women) of them responded (83.1%). We then excluded individuals under 40 years (one man and one woman) and over 80 years of age (1 427 men and 2 465 women), any who

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moved out before the start of the follow up (five men and three women), and any whose information on smoking status at enrollment was incomplete (4 660 men and 12 059 women). After exclusion of these individuals, 44 451 men and 43 702 women remained in the analysis. This study was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

Follow up. Information on whether each subject was still alive and living in the same location was obtained from residential registries. If the subject had died, we then searched the population-based cancer registry in each prefecture and ascertained whether they had died from lung cancer. Sites of any cancers were coded using the International Classification of Disease and Injuries–ninth revision (ICD-9), except for one city in Osaka where the ICD 10th revision was used. Study subjects were followed for 10 years in each area. Therefore, the end of the study period varied from January 31, 1993 to October 31, 1995 (and February 28, 2000 for the one city in the Osaka Prefecture) according to the dates of enrollment. During the follow up, 8 836 (15.6%) individuals moved out of the study areas.

Smoking Information. At enrollment, study participants completed a self-administered questionnaire, including demographic information such as sex, date of birth, and smoking habits. The smoking habits questions were the same in each study area, except for one town in the Osaka Prefecture. All participants were asked: 'Do you smoke?' Response categories included: (1) yes; (2) smoked but quit; and (3) never smoked. We defined participants who chose response (1) as current smokers; those who chose response (2) as former smokers; and those who chose response (3) as non-smokers. For one city in the Osaka Prefecture, the response categories were: (1) yes (smoking every day); (2) yes, but occasionally; (3) smoked, but quit; and (4) never smoked. We defined participants who chose response (1) and (2) as current smokers, those who chose response (3) as former smokers, and those who chose response (4) as non-smokers.

The ages at initiation of smoking and the average number of cigarettes smoked per day for current and former smokers were obtained. The number of years of smoking that current smokers had smoked prior to enrollment was calculated by subtracting the age at initiation of smoking from the age at enrollment. Pack-years were defined as the number of years of smoking multiplied by the number of packs of cigarettes per day.

Cancer Prevention Study II. The CPS-II[9] is a prospective cohort study, conducted by the American Cancer Society (ACS). It was selected as the Western counterpart to our Japanese prospective cohort study because it contained detailed data on lung cancer mortality by sex, age group and smoking status, as well as data on smoking patterns of current smokers by sex and age group. The CPS-II data for the comparison were retrieved from the Smoking and Tobacco Control Monograph no. 8. Study participants were friends, neighbors, and acquaintances of ACS volunteers. Approximately 1.2 million men and women were enrolled in 1982. Enrollment included all household members 30 years of age or older if at least one family member was 45 years of age or older. Study participants completed an initial questionnaire including smoking habits and other lifestyle factors. The vital status of study participants was determined through personal inquiry by the volunteers. The underlying cause of death was obtained through death certificates. During the 6-year follow up of 711 363 current cigarette smokers and lifelong non-smokers, 3 229 died of lung cancer.

Statistical Analysis. Person years during the follow-up were counted from the date of enrollment into the study until the date of death, migration from the study areas, or the end of the study period, whichever came first. The RR was estimated with a Cox proportional hazards model with adjustments for age (continuous variable) and prefecture. Non-smokers were used as a reference category. A dose–response relationship among current smokers was examined in terms of the number of pack-years.

Using data from the CPS-II, we compared the baseline data on smoking patterns among current smokers and the follow-up data on lung cancer deaths among non-smokers and current smokers. Follow-up data were restricted to the first 6 years, the duration of the CPS-II. The mean number of cigarettes smoked per day and the mean number of years of smoking were calculated within the 5-year age groups fixed at the baseline. The age-adjusted number of cigarettes smoked per day and the age-adjusted number of years of smoking was obtained by directly standardizing to the combined distribution of age groups of the Japanese and US cohorts. Because the mean age at initiation of smoking among the CPS-II subjects was provided as 10-year birth cohorts, we calculated mean age of initiation in the Japanese study in the same way.

Sex- and age-specific death rates of lung cancer (per 100 000) were computed for non-smokers and current smokers. Calculation of the number of person years at risk was based on attained age. To compare the death rates of the Japanese and US cohorts, cumulative death rates between 40 and 84 years were presented. Rate ratios of the Japanese cohort to US cohort were calculated by using a Poisson regression model.

Lung cancer death rates were computed for male current smokers, stratified by the duration of smoking and the number of cigarettes smoked per day. Because of limited CPS-II data, only subjects who smoked 20 or 40 cigarettes per day were analyzed. To compare the lung cancer risks among male current smokers in Japan to those in the USA, adjusted rate ratios were obtained by Poisson regression analysis. The model included the natural logarithm of the number of lung cancer deaths as a response variable and the natural logarithm of person-years as an offset. Indicator variables for age group, number of cigarettes per day, and duration of smoking were used as covariates. Statistical computations were carried out using the SAS statistical package (version 8.02; SAS Institute, Cary, NC, USA).

Results

Current and former smokers in the Three-Prefecture Cohort Study showed a significantly increased risk of lung cancer death for both men and women compared with non-smokers (Table 1). A statistically significant dose–response trend of RR was observed for men and women current smokers (Table 2).

In the first 6 years of follow up, the Three-Prefecture Cohort Study had 341 deaths due to lung cancer (260 men and 81 women). Adjusted RR for current smokers versus non-smokers were 3.16 (95%CI 1.29–3.64) for men and 2.68 (95%CI 1.58–4.53) for women. Corresponding reported RR in the CPS-II study were 23.2 (95%CI 19.3–27.9) for men and 12.8 (95%CI 11.3–14.7) for women.

Death rates among current smokers and non-smokers were calculated, based on attained age (Fig. 1). Compared with the CPS-II, death rates among Japanese current smokers were lower in all age groups, with the exception of the youngest and oldest female age groups. In contrast, death rates among Japanese non-smokers were higher than those in the USA, for both men and women regardless of age. Cumulative death rates between 40 and 84 years and rate ratios are presented in Table 3. Compared with US non-smokers, Japanese non-smokers had a higher cumulative mortality of lung cancer with an approximately threefold increased risk for men and a twofold increased risk for women. However, Japanese current smokers were at a significantly 60% lower risk of lung cancer compared to those in the USA.

The mean number of cigarettes smoked per day (Fig. 2a) decreased with age for men and women in both Japan and the USA. However, current smokers in Japan had a lower daily

Table 1. Relative risk of lung cancer death associated with cigarette smoking, Three-Prefecture Cohort Study, Japan

Smoking status	No. subjects	Person-years	No. lung cancer deaths	Crude mortality rates	Relative risk† (95%CI)
Men					
Non-smokers	7 590	64 645	23	35.6	1.00
Former smokers	11 164	91 792	102	110.9	2.60 (1.65–4.10)
Current smokers	25 697	215 139	341	158.5	5.10 (3.34–7.79)
Women					
Non-smokers	36 884	321 170	79	24.6	1.00
Former smokers	1 630	13 258	13	98.1	2.94 (1.63–5.31)
Current smokers	5 188	42 931	40	93.2	3.66 (2.50–5.35)

†Adjusted for age and prefecture.

Table 2. Relative risk of lung cancer death by pack-years among current smokers, Three-Prefecture Cohort Study, Japan

Pack-years of smoking	No. subjects	Person-years	No. lung cancer deaths	Crude death rate	Relative risk† (95%CI)
Men‡					
<20	3 982	33 592	19	56.6	1.16 (0.72–1.88)
20–39	12 066	101 910	113	110.9	2.10 (1.62–2.71)
40–59	6 574	54 374	129	237.2	2.86 (2.23–3.65)
60 +	2 765	22 770	78	342.6	4.44 (3.34–5.89)
P for trend					<0.0001
Women§					
<20	3 136	26 212	12	45.8	1.75 (0.96–3.19)
20–39	1 545	12 642	15	118.7	3.92 (2.27–6.76)
40 +	397	3 157	10	316.8	7.22 (3.75–13.9)
P for trend					<0.0001

†Adjusted for age and prefecture. Reference category was non-smokers. ‡310 men were excluded because of missing data. §110 women were excluded because of missing data.

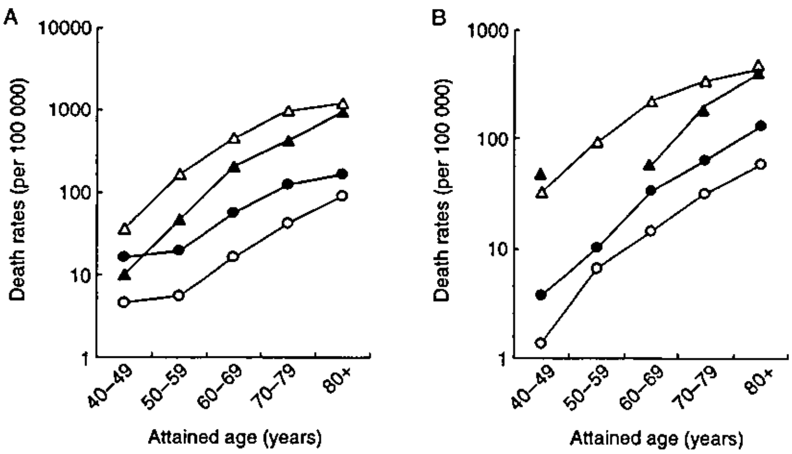

Fig. 1. Age-specific death rates due to lung cancer by attained age among current smokers and non-smokers in the Three-Prefecture cohort in Japan and Cancer Prevention Study II (CPS-II) in the USA. (a), Death rates of men; (b), death rates of women. (▲), Three-Prefecture cohort current smokers; (●), Three-Prefecture cohort nonsmokers; (△), CPS-II current smokers; (○), CPS-II non-smokers.

cigarette consumption for all age groups and for both men and women than current smokers in the USA. The differences ranged from 0.8 (aged 40–44 years) to 4.4 (aged 55–59 years) for men. Daily consumption of cigarettes in the youngest male age group showed the least difference. Japanese women constantly used approximately five fewer cigarettes per day in all age groups. The age-adjusted number of cigarettes per day for the Japanese and US cohorts were 21.5 and 24.8 for men, respectively, and 14.1 and 19.4 for women, respectively.

The mean number of years of smoking was slightly lower among Japanese men in all age groups than those in the USA (range 0.8–2.1) (Fig. 2b). Except for the youngest and oldest age groups, Japanese women had smoked for a much shorter time than comparable women in the USA. The range of differences was from 1.7 (aged 75–79 years) to 8.9 (aged 55–59 years). The age-adjusted years of smoking for the Japanese and US smokers were 37.1 and 38.6 years for men, respectively, and 26.8 and 34.2 years for women, respectively.

Japanese smokers in all age groups started smoking later than their counterparts in the USA, and this was especially true for women (Fig. 2c). While the age at initiation of smoking for Japanese women gradually became younger in recent birth

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Table 3. Cumulative mortality and rate ratios for lung cancer among non-smokers and current smokers, Three-Prefecture Cohort Study in Japan compared to Cancer Prevention Study II in the USA

	Non-smokers		Current smokers	
	Three-Prefecture	CPS-II	Three-Prefecture	CPS-II
Men				
Cumulative mortality rate (%)†	3.0	1.1	11.6	27.5
Rate ratio‡ (95%CI)	2.95 (1.79–4.87)	1.00	0.38 (0.32–0.41)	1.00
Women				
Cumulative mortality rate (%)†	1.9	0.8	5.3	11.6
Rate ratio‡ (95%CI)	2.10 (1.56–2.82)	1.00	0.42 (0.27–0.67)	1.00

Analysis restricted to first 6 years of follow-up to enhance comparability to Cancer Prevention Study II (CPS-II) data. †Cumulative mortality rates between 40 and 84 years. ‡Estimated based on Poisson regression model.

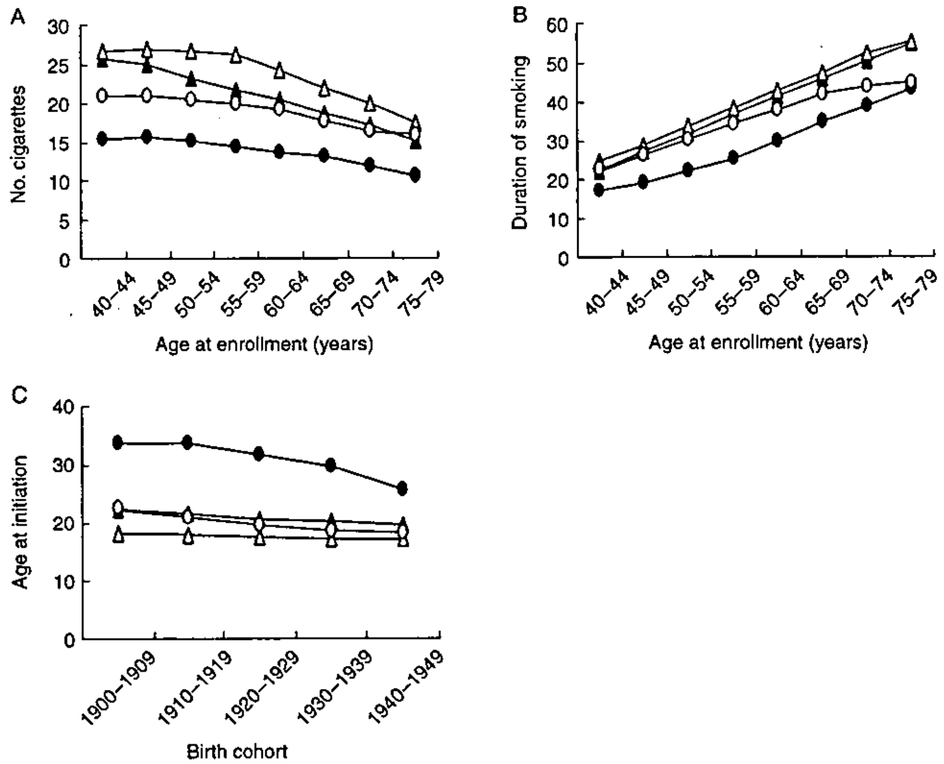

Fig. 2. Comparison of smoking patterns of current smokers at baseline between Three-Prefecture study in Japan and Cancer Prevention Study II (CPS-II) in the US. (a), Mean number of cigarettes smoked per day by age at enrolment; (b), mean duration of smoking by age at enrolment; (C), mean age of initiation of smoking by birth cohort. (▲), Three-Prefecture cohort men; (●), Three-Prefecture cohort women; (△), CPS-II men; (O), CPS-II women.

cohorts, they still began smoking much later than US women. The mean age at initiation of smoking among Japanese men in all birth cohorts was slightly older than those in the USA.

Finally, we calculated lung cancer death rates by years of smoking among current male smokers who had consumed 20 cigarettes per day (Table 4). Similar calculations for men who had smoked 40 cigarettes per day are not presented because there were too few of these men. We were unable to calculate lung cancer death rates in strata where no deaths occurred. For strata where calculations could be made, death rates of current Japanese smokers were lower than those in the USA. Rate ratios in all strata were less than 0.6. After controlling for age, duration of smoking and number of cigarettes smoked per day by the Poisson regression analysis, rate ratios of male Japanese current smokers relative to those in the USA was 0.34 (95%CI 0.27–0.43).

Discussion

The present large-scale, population-based prospective study confirmed an increased lung cancer risk among smokers, as compared with non-smokers, in Japan. The RR observed for Japanese smokers was lower than that observed in the USA. This finding is consistent with other studies conducted in Japan.[1–6] Comparison of death rates and exposure levels of current smokers in the two samples revealed one reason for the lower RR in Japan, namely, higher death rates among non-smokers

Table 4. Death rates by duration of smoking among current male smokers of 20 cigarettes per day, Three-Prefecture Study in Japan compared to the Cancer Prevention Study II in the USA

Attained age (years)	Three-Prefecture Duration*			CPS-II Duration†			Rate ratio Duration†		
	30–39	40–49	50 +	30–39	40–49	50 +	30–39	40–49	50 +
50–59	42.0	—	—	143.1	267.3	483.1	0.29	—	—
60–69	119.0	170.1	—	215.7	452.3	848.5	0.55	0.38	—
70–79	180.5	142.1	590.6	455.9	702.1	1149.0	0.40	0.20	0.51

†Duration of smoking was fixed at enrollment. —, no lung cancer deaths observed (Three-Prefecture cohort study), or no data available because of five or fewer deaths observed (Cancer Prevention Study II).

combined with lower death rates among smokers. A lower exposure level to smoking was responsible for the lower death rates among current smokers. However, even after adjustment for age, duration of smoking and daily cigarette consumption, male Japanese current smokers had a lower risk of lung cancer compared to those in the USA.

Death rates for non-smokers in all Japanese age groups were higher than those for non-smokers in the USA. The CPS-II used more detailed questions regarding smoking habits. For example, the CPS-II questionnaire clearly asked whether or not participants had smoked at least one cigarette per day for 1 year.[9] However, the questionnaire in our study did not specify the number of cigarettes or the duration of smoking. Therefore, the definition of non-smokers in the CPS-II was more strictly limited in terms of lifelong non-smokers, while non-smokers in our study might have included former smokers who had quit and not smoked for a long time. Such a difference in classification of non-smokers might have led to overestimation of death rates among Japanese non-smokers. Second-hand smoking might also have contributed to the difference. The prevalence of current smokers among Japanese subjects was higher than in the CPS-II. Among Japanese men, the prevalence was 58% for current smokers and 83% for ever smokers (ever smokers = current + former smokers); somewhat higher than the prevalence reported in the CPS-II (24% for white, male current smokers, 75% for white, male ever smokers, 36% for black, male current smokers, and 73% for black, male ever smokers).[9] Therefore, Japanese non-smokers might have had more opportunity to be exposed to environmental tobacco smoke (ETS). Furthermore, it was only in 2003 that Japanese law promoted the separation of smoking and non-smoking areas at the workplace and in public places. As well, since Japanese residences are small, Japanese non-smokers who had lived with parents or a spouse who smoked would have been exposed to concentrated tobacco carcinogens. Some, but not all, Japanese studies showed higher RR associated with spousal ETS,[11] and a pooled RR calculated from Japanese studies (1.41) was higher than the pooled RR calculated from US studies (1.19).[11] Therefore, until recently, Japanese non-smokers would have had a much higher cumulative exposure to ETS at home and in the workplace than their US counterparts.

Other risk factors, such as air pollution, radon and asbestos, do not offer a clear explanation for the observed differences. Several observational studies have shown an association between air pollution levels and lung cancer.[12,13] Even if a difference in air pollution levels exists between the two countries, it is unlikely that this small difference could account for the large difference in the risk of lung cancer among non-smokers given the only moderate association between air pollution and lung cancer.[14] The level of indoor radon in Japan, a known risk factor for lung cancer in Western countries[15] is much lower than in the USA.[16] Although asbestos consumption per capita was higher in Japan than in the USA during the mid-1970s,[17] it remains unknown whether low environmental exposure to asbestos (in contrast to heavy occupational exposure) causes lung cancer.[18]

In contrast to non-smokers, death rates among current smokers in our sample were lower than those observed in the CPS-II sample, regardless of age and sex. Because lung cancer risk and exposure level to smoking are clearly dose-related, the discrepancy in exposure levels among current smokers is probably a major factor explaining the difference in death rates among current smokers. However, considering lower exposure as a reason for the lower death rates among current smokers assumes that individuals with similar exposure levels have the same risk of lung cancer. However, the risk of lung cancer among male Japanese current smokers was lower than those in the USA, even after adjustment for age, duration of smoking and number of cigarettes smoked per day.

Although the difference in smoking patterns between the Japanese and US samples was greater among women than among men, the rate ratio for the current smokers was not very different between men and women. We have no clear explanation for this. However, the unit change in the lung cancer risk between Japanese female smokers and US female smokers with low levels of smoking exposure might not have the same magnitude as the unit change seen between Japanese male smokers and US male smokers with high levels of smoking exposure. Furthermore, Japanese women might under-report their smoking history. A single inquiry about smoking at baseline might not reflect the whole smoking history of individuals in either the Japanese or US samples.

Caution is advised when exposure levels to smoking are assessed, based on self-reported smoking history collected from a single questionnaire at the point of enrollment. Cigarette consumption per capita was much lower in Japan than in the USA from 1920 to 1970,[19] when the participants in these two cohorts were in adolescence to young adulthood. Furthermore, Japanese smokers experienced an extreme tobacco shortage during and immediately after World War II. It was not until the late 1970s that Japanese cigarette consumption per capita caught up with US consumption levels. Japanese participants classified in the same strata by smoking exposure undoubtedly experienced periods of cigarette shortage, and this bias toward overestimation of exposure may have produced spurious lower lung cancer death rates in our sample. Similarly, possible bias in the CPS-II sample may have included smokers who underreported usage of cigarettes due to strong social prohibitions to smoking in the USA.

Changes in tar content and the prevalence of filter-tipped cigarettes were also influential. The sales-weighted average yields of tar in the 1980s, and the reduction in tar levels during the 1960s and 1970s were similar in Japan and the USA.[20,21] Filter-tipped cigarettes were first marketed in the 1950s and their market share grew to more than 80% in the 1970s, reaching over 90% in both countries. However, as Stellmen *et al.* have noted, American manufactured cigarettes contain higher tobacco-specific nitrosamines than Japanese cigarettes.[22] Furthermore,

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charcoal filters, which remove certain compounds that inhibit lung clearance, are more widely used in Japanese cigarettes than American cigarettes.

Causes of death, other than lung cancer, might be influential in the estimation of lung cancer death rates among current smokers. Coronary heart disease (CHD) was the second leading cause of death among CPS-II smokers.[9] Premature death from CHD among CPS-II smokers might have led to somewhat lower lung cancer death rates in the USA. An increase in the discrepancy of lung cancer death rates among current smokers might have occurred, because death rates from CHD in Japan are not as high as in the USA.[23]

Other confounding factors, such as lifestyle or genetic factors, might also lower lung cancer death rates among Japanese smokers. The traditional Japanese diet, which is low in fat and high in several phytochemicals, might help decrease the risk of death due to lung cancer.[24–27] Deletion-type polymorphism CYP2A6, the principal enzyme in the metabolic activation of tobacco-specific nitrosamines, was found to be inversely associated with lung cancer among Japanese male smokers.[28] It has been demonstrated that the frequency of occurrence of this variant is higher amongst Japanese than among Caucasians.[29] However, caution is required, because diet and the odds of having CYP2A6 can be assumed to be constants (i.e. would be equally likely to affect non-smokers) and non-smokers presented the opposite pattern to current smokers.

Another potential explanation is different histological distribution of lung cancer between American and Japanese populations.[30] Adenocarcinoma, which is less strongly related to smoking than squamous cell carcinoma,[2] contributes to a larger proportion of Japanese lung cancer than US lung cancers. The relatively lower incidence of squamous cell carcinoma among Japanese smokers would reduce the overall Japanese lung cancer incidence for the same level of exposure to smoking as in the US cohort.

Generally, in Western countries non-smokers have a higher socioeconomic status than smokers. People with a high socioeconomic status tend to have more health conscious lifestyles, such as a higher intake of fruits and vegetables, as well as lower occupational exposures to other factors, such as asbestos. In the USA, the socioeconomic gap between smokers and non-smokers is much larger due to a strong societal antismoking campaign. This larger disparity of background risk factors resulted in a larger difference of lung cancer mortality between US non-smokers and smokers, as compared with Japanese non-smokers and smokers.

Finally, the comparability of the Japanese and US samples should be considered. A potential advantage was that both studies were conducted using a prospective design during approximately the same time period. Dates of birth of participants covered approximately the same years. Because cigarette types, such as non-filtered versus filtered cigarettes changed similarly in both the USA and Japan from the 1950s to the 1970s,[31] different study periods or birth cohorts might have weakened the comparability, especially in terms of exposure. In addition, lung cancer deaths were basically diagnosed by the same ICD-9 codes. Lung cancer deaths were determined based on death certificates for the US sample, and the Japanese sample lung cancer deaths were determined using the cancer registry, which was based on death certificate data. Death certificates were usually considered complete both in the US and Japan. As well, the cause of death was also considered to have been identified with reasonable accuracy. In 1988, the percentage of deaths with no classifiable diagnosis, including unknown cause of morbidity and mortality (ICD-9: 780–799) was 3.9% for Japan and 1.4% for USA. Therefore, both studies appeared to be equal in their precision of determining lung cancer deaths. Finally, follow-up periods were restricted to 6 years in both studies. However, over this relatively short time interval, there were too few deaths among the Japanese cohort to produce stable and informative estimates of death rates, especially at high exposure levels. To solve this problem, further investigation with samples as large as the CPS-II sample, or the pooling of several studies, are needed.

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シンポジウム

CT 検診で発見された肺結核

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1996年4月～2003年3月の期間のCT一次精検およびCT検診受診者を対象に、発見された肺結核の病態やCT所見等を検討した。受診者のべ16,811人のうち、肺結核が27例（0.14%）、AM症が7例（0.04%）であった。確定診断は、喀痰および胃液からの菌陽性が29%、気管支鏡的検査や経皮的針生検によるものが60%、手術を含む診断的治療が結核のうちの44%であった。
CT画像では、結節影がTBの59%, NTMの57%に見られ、TBの結節影では、娘病巣や散布影を伴わないのがその半数以上を占めた。空洞はTBで48%、NTMで86%とNTMに多く見られた。陰影の多彩性はNTMに著明であった。TSCT所見において、NTMではTB に比べ気管支拡張像や気管支壁の肥厚が多く認められ、肺がんとの鑑別にも役立ったが、検診モードのCT所見では特に気管支壁の肥厚まで判定するのは容易ではない。TB腫瘤影のnotchingや小葉間隔壁の肥厚は肺がんのindentationなどとの鑑別が不可能であった。結核の初期像と思われる小型腫瘤陰影は肺がんとの鑑別が困難であり、積極的な確定診断法を採る必要がある。検診モード上でも判断可能な所見を検討して、CT検診読影に寄与できるようにする必要がある。
キーワード： CT検診、抗酸菌症、肺結核、非結核性抗酸菌症、CT所見
J Thorac CT Screen

【はじめに】

本邦の肺結核罹患率はそれまで下降線を辿っていたが、1997年から再び増加傾向を示し始め、1999年に厚生労働省より「結核緊急事態宣言」がだされたほどである。その後2000年以降は再び減少傾向を示している。この様に結核は対策を強化すれば減少するが、少し手を緩めるとすぐに抵抗を始める疾患である[1]。その意味では方策は執りやすい対象疾患といえる。減少傾向を示しているとはいえ、年間の新規登録者は30,000人を越えている。世界的に見ても年間800万人の結核患者が発生し、年間200万人の死亡者が推測されている。本邦は結核に関しては中進国と称されている。大阪市での2001年の肺結核罹患率は10万人に対し80と、2位の名古屋市の2倍を示した[2]。
肺がん検診は老健法が開始された時には結核検診のシステムを利用して行われたが、いまCT肺がん検診が普及し始めて反対に肺結核も多く指摘されるようになった。さらには肺がんとの鑑別が困難な微小陰影も多く経験するようになった。
今回CT検診で発見された結核を含む抗酸菌症について、その病態やCT所見を検討した。

【対象症例】

抗酸菌症の分類は、結核菌症（tuberculosis: TB）、と非結核性抗酸菌症（nontuberculosis mycobacteria 症: NTM）、及びライ病に分けられる。Mycobacterium avium complex (MAC) はNTMのうちの70%を占めるといわれている。

今回1996年4月～2003年3月までにCT一次精検およびCT検診を受診した中で抗酸菌症（結核症および非結核性抗酸菌症）と診断された人を対象とした。CT検診受診者ののべ16,811人中、TBは27例 (0.14%) 発見され、男性：女性は 12：15 人、年齢中央値は 62 (28-78) 才であった。NTMは7例 (0.04%) で、男女比は4：3、年齢中央値は 59 (43-70) 才であった。これらは同時期の検診発見肺がん症例の年齢 66 (47-82) 才より若年であった。