佐藤雅美, 斎藤泰紀, 渋谷潔, 中山富雄, 平野隆, 近藤丘, 馬場雅行, 池田徳彦, 佐川元保, 伊豫田明, 宝来威, 中嶋隆太郎, 平田哲士, 三宅真司, 楠洋子, 多田弘人, 古川欣也, 渡辺洋一,	日本肺癌学会･日本呼吸器内視鏡学会・日本臨床細胞学会･3 学会合同委員会報告　肺門部早期肺癌実態調査アンケート報告	肺癌	57(7)	777-786	2011
古川欣也, 楠洋子, 多田弘人, 渡辺洋一, 佐藤雅美, 斎藤泰紀, 渋谷潔, 中山富雄, 平野隆, 近藤丘, 馬場雅行, 池田徳彦, 佐川元保, 伊豫田明, 宝来威, 中嶋隆太郎, 平田哲士, 三宅真司, 日本呼吸器内視鏡学会学術企画委員会肺癌検診ワーキンググループ.	日本呼吸器内視鏡学会・日本臨床細胞学会・日本肺癌学会・3 学会合同委員会報告　肺門部早期肺癌実態調査アンケート報告	気管支学	33(6)	411-420	2011
馬場雅行、池田徳彦、佐川元保、伊豫田明、宝来威、中嶋隆太郎、平田哲士、三宅真司、佐藤雅美、斎藤泰紀、渋谷潔、中山富雄、平野隆、近藤丘、楠洋子、多田弘人、古川欣也、渡辺洋一	日本臨床細胞学会・日本呼吸器内視鏡学会・日本肺癌学会･3 学会合同委員会報告　肺門部早期肺癌実態調査アンケート報告	日本臨床細胞学会雑誌	51(1)	13-21	2012

Review Articles

総 説

利益と不利益を考慮した肺癌検診のあり方

The ideal way of lung cancer screening to consider the balance of benefit and harm

中山 富雄
大阪府立成人病センター がん予防情報センター 疫学予防課

Tomio Nakayama
Department of Cancer Epidemiology and Prevention, Center for Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Disease

Abstract

The National Lung Screening Trial (NLST) as randomized-controlled trial that evaluated the effectiveness of the lung cancer screening to compare low dose CT (LDCT) with plain chest X-ray demonstrated annual LDCT reduced 20% of lung cancer mortality than annual plain chest X-ray. This study demonstrated the mortality reduction as the benefit of annual screening with statistically significant but reported 25% of positive rate and considerable number of death within 60 days after diagnostic workup and therapy as the harm of screening. The assessment of the study result is difficult in the meaning of comparison between benefit and harm of LDCT screening. The study result caused controversy about whether LDCT screening should be spread in the point of view of comparison of benefit with harm.

Keywords: screening for lung cancer, LDCT

肺癌検診については、低線量CT検診が注目されてきた。この検診手法は、従来の手法（胸部単純X線）では指摘できない小さくかつ淡い陰影を容易に指摘できることから、従来法の数倍の発見率、8割のI期率、約8割の生存率が報告され、世界的に注目されてきた。2011年6月に、ランダム化比較試験であるNational Lung Screening Trial (NLST) が報告された[1]。

この結果は、介入群の肺癌死亡率が対照群に比べて20％減少したという意味での利益を示したが、過剰な要精検率と、精密検査に関連した死亡という不利益も、同時に報告されており、その総合的な評価は困難になっている。

ここでは、NLSTの成績を中心に利益と不利益を考慮した肺癌検診のあり方について概説する。

1. NLSTのデザイン

NLSTは、喫煙者を対象とした年1回の低線量CTの効果を明らかにするため、全米33カ所で行われた大規模ランダム化比較試験である。2002年8月から2004年4月までの間に53,454人が登録され、研究群と対照群の2群に無作為に割り付けられた。研究群には登録時と年1回の低線量CTが計3回提供され、一方対照群には登録時と年1回の胸部単純X線検査が同じく計3回提供された。CTの“陽性”の定義として4mm以上の石灰化のない結節とし、3回目で同一の所見で変化がない場合は“陰性”とした。検診相終了

表1 National Lung Screening Trialの結果の要約（文献1より作図）

群	追跡人年	肺癌死亡数	肺癌死亡率（1/10万人年）	肺癌死亡率減少（%）
CT	144,097.6	354	245.7	20.3
CXR	143,363.5	442	308.3	

受稿2011年12月7日 受理2011年12月21日

表2 National Lung Screening Trialのスクリーニング判定結果（文献1より修正して引用）
プロトコール上4mm以上の結節を"Positive"とした。精密検査のルールについては、取り決めはしなかったが、治療や診断が必須なものを臨床的問題症例率として計上している

	低線量CT検診群				単純X線検診群			
	受診者数	Positive rate（%）	臨床的問題症例率（%）*	精検不要率（%）	受診者数	Positive rate（%）	臨床的問題症例率（%）*	精検不要率（%）
初回	26,309	27.3	10.2	62.4	26,035	9.2	3.0	87.8
2回目	24,715	27.9	6.1	65.9	24,089	6.2	1.8	92.1
3回目	24,102	16.8	5.8	77.3	22,346	5.0	1.5	93.4

表3 National Lung Screening Trialの診断・治療に伴う重篤な偶発症および死亡（文献1より修正して引用）

	低線量CT検診群					単純X線検診群				
	外科的生検	気管支鏡	針生検	侵襲的診断行わず	計	外科的生検	気管支鏡	針生検	侵襲的診断行わず	計
肺癌確定例										
精検総数	509	76	33	31	649	189	46	29	15	279
重篤な偶発症	71	2	0	2	75	22	1	0	1	24
60日以内死亡	5（1.0%）	4（5.3%）	1（3.0%）	0	10（1.5%）	4（2.1%）	5（10.9%）	1（3.4%）	1（6.7%）	11（3.9%）
肺癌非確定例										
精検総数	164	227	66	16,596	17,053	45	46	24	4,559	4,674
重篤な偶発症	9	2	0	1	12	1	0	0	3	4
60日以内死亡	2（1.2%）	4（1.8）	0	5（<0.1）	11（0.1）	0	0	0	3（0.1%）	3（0.1%）

後5年間、電話と郵便で追跡された[2]。

2. NLSTの結果

表1に示すごとく研究群と対照群の死亡率の差は、63.4/10万人年であり、肺癌死亡率減少効果は20.3%と、統計学的有意に死亡率減少効果が示されている。これはNLSTのサンプルサイズ計算の際に仮定された効果の大きさ（20%）とほぼ一致しており、デザインどおりの効果が得られている。一方、検診の不利益としての要精検率の大きさについては、**表2**に示すように平均27%というとても大きな値が示されている。本研究では4mm以上を精密検査の対象と定義しておきながら、個々の症例について実際に精密検査を行うのか、診断へのステップ等については、各施設に一任されており、異常陰影が認められたうちのどれだけの割合が、実際に精密検査が行われたのかは公開されていない。また、診断治療の偶発症については（**表3**）、侵襲的診断法・治療の60日以内の死亡が報告されている。肺癌確定例で約1.5%というきわめて高い値が示されている。これらが本当に偶発症の範疇にあたるかどうかは、記載されておらず、診断治療とは無関係の死亡も含まれている可能性や、原病死の可能性もあるが、いずれにしてもきわめて高い値である。

3. 放射線被曝の影響と日本での現状

NLSTは、管電流20-30 mAsの低線量で撮影されている[2]。国内外で報告されている研究的な試みもすべて同様の低線量である[4]。この場合の被曝線量は、1.5 mSv程度の低線量であり、胃のX線検診（間接撮影）とさほど変わらない値である。一方日本人間ドック学会の調査によれば、低線量CT撮影ができている施設はわずか29.7%であり、診断レベルの通常線量撮影が多い（**図1**）[3]。あくまで検診は健常者を対象にしているものであり、診断用の線量を定期的に照射することは、リスクーベネフィットの観点から明らかに問題である。東日本大震災以降放射線被曝に対する国民の不安は極限に達しており、速やかな低線量化の普及が期待される。

4. 日本の精度管理指標の現状

日本CT検診学会の精度管理報告によれば（**図2**）、当初10.5%であった要精検率は低下し、2009年には

5.8％まで低下している。一方発見率・切除率・I期率も低下しているが、発見率の低下に比べて切除率・I期率はわずかで70-80％の範囲内で高い値を保っている。CT検診の場合、検診が開始された初期には、スリガラス状陰影（ground grass opacity: GGO）が陰影の大半を占めるpure GGOケースが積極的に外科的治療を受けていた。しかしこのようなケースは病理学的にも非浸潤がんや上皮内がんであり、過剰診断につながる可能性が高いことから、最近では経過観察のみにとどまるケースが多く、これらは病理学的診断がつかないため発見癌には含まれないので発見率の低下につながると考えられる。これはあながち精度の低下ではなく、検診の繰り返しにより適正化されてきたものと考えられる。

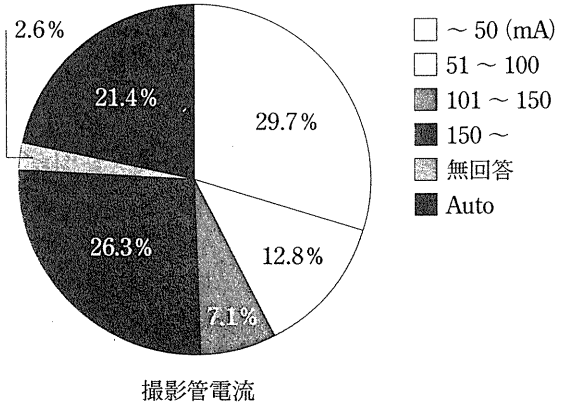

図1　国内でのCT検診実施状況
（文献3より修正して引用）撮影管電流50 mAs以下が低線量と定義されている

5. 国内での肺癌侵襲的診断法による偶発症

我が国での気管支鏡検査、経皮針生検による重篤な合併症（空気塞栓、呼吸停止、ショック、心停止）はそれぞれ0.03-0.05％、0.05-0.06％と報告され、また検査に伴う死亡率はそれぞれ0.01-0.02％、0.07％と報告されている[4]。これらは検査直後のものにおおむね限られており、NLSTの60日以内という条件とは異なるものの、あまりにもかけ離れた成績である。技術的な問題というよりも、対象者の心肺機能（COPD、間質性肺炎、動脈硬化性疾患など）等に大きな問題があったのではないかと推察される。国内の状況では偶発症という不利益は比較的小さいと考えられるものの、胃・大腸癌等に比べれば大きな値であり、対象者への十分な説明は不可欠である。

6. まとめ

NLSTの成績は、低線量CT検診の年1回の受診により喫煙者の肺癌死亡率を20％減少することができたという利益を示している一方、要精検率の高さと診断・治療関連死の多さという不利益も高いということを示しており、普及すべきかどうかの判断が困難である。日本ではすでに約20万人程度の年間CT検診受診者があり、その精度管理は適正化され、精密検査や

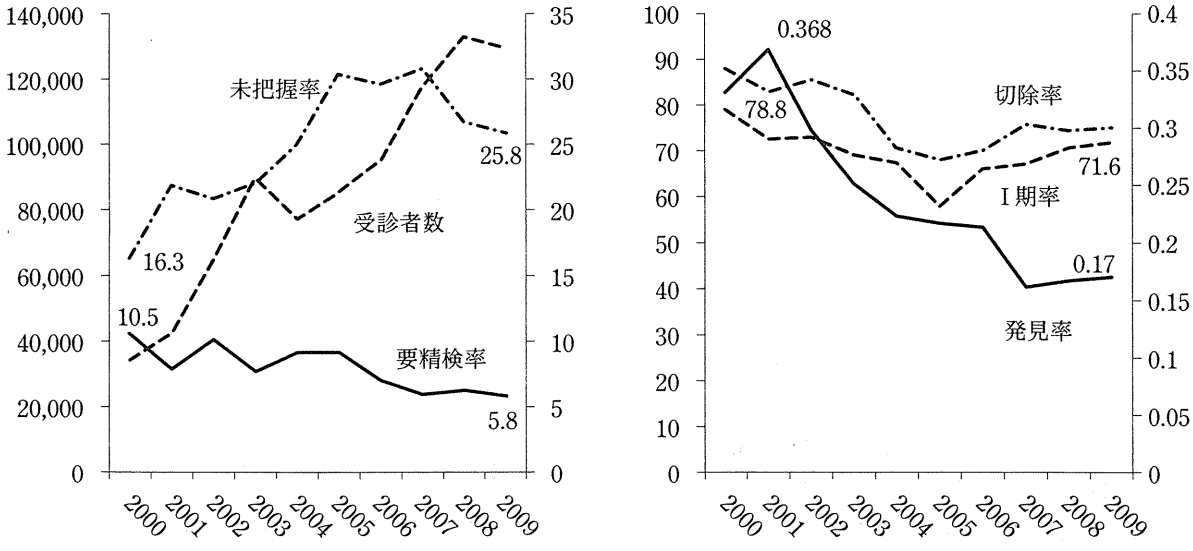

図2　CT検診の精度管理指標の推移（日本CT検診学会精度管理部会全国集計より作図）

手術による重篤な偶発症の率も米国に比べてかなり低く、安全性は担保されているように思われるが、一方で診断線量でのCT撮影を行う人間ドックも決して少なくない。人間ドック従事者に対する基本的な知識と情報の普及が十分でなく、今後の対応が期待される。

文 献

1) The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with Low-dose computed tomographic screening. NEJM 2011, 365: 395-409.
2) The National Lung Screening Trial Research Team. Lung Screening Trial: Overview and Study Design. Radiology 2011, 258(1): 243-253.
3) 瀧澤弘隆. 日本人間ドック学会会員施設における胸部CT検診に関する実態調査報告. 人間ドック 2009, 24(3): 7-14.
4) 平成18年度厚生労働省がん研究助成金「がん検診の適切な方法とその評価法の確立に関する研究」班 有効性評価に基づく肺がん検診ガイドライン. 三田村印刷所、東京、2006、62.

要旨

日本がん検診・診断学会誌 19(3) : 266-269、2012

年1回の低線量CTを用いた肺癌検診の有効性を評価したランダム化比較試験National Lung Screening Trialが、単純X線検査受診群に比べて約20%の肺癌死亡率減少効果があることを示した。この研究では、死亡率減少効果という利益を統計学的有意に示したものの、25%という高い要精検率と精密検査・治療後60日以内の死亡数が無視できないという不利益についても報告している。利益と不利益の大きさを比較し、CT検診の普及が適切かどうかを判断するには難しい研究結果であった。

わが国では年間20万人程度のCT検診受診者があり、要精検率も当初の10.5%(2001年)から5.8%(2009年)に低下していると報告されている。また肺癌診断・治療に伴う偶発症は国内では0.001%と程度と報告されている。一方で人間ドックを対象とした調査においては、低線量で撮影している施設は29.7%に過ぎないという調査結果もある。海外での研究結果を日本に外挿できるかどうかという点では、二次予防に関与するすべての医師への知識の正確な普及が鍵となる。

キーワード：肺癌検診、低線量CT

RESEARCH COMMUNICATION

Comparison of Trends in Cancer Incidence and Mortality in Osaka, Japan, Using an Age-Period-Cohort Model

Yuri Ito[1]*, Akiko Ioka[1], Tomio Nakayama[1], Hideaki Tsukuma[1], Takashi Nakamura[2]

Abstract

Background. We aimed to estimate the effects of age, period and birth cohort on trends in cancer incidence and death for all sites and selected sites of cancer in Osaka using an age-period-cohort model. Methods. Cancer incidence data during 1968-2003 were obtained from the Osaka Cancer Registry, and cancer mortality with population data in Osaka during 1968-2007 were obtained from vital statistics departments. We estimated age, period and birth cohort effects for incidence and mortality using Nakamura's Bayesian Poisson age-period-cohort model. Results. For most sites of cancer, linear ageing effects were observed, the exceptions being breast and cervix which levelled-off at around 40 years old, while period effects were small. Decreasing cohort effects were observed in stomach and liver cancer. Cohort effects peaked at the generation born in the early 1950s for colorectal, lung, breast cancers. For most sites of cancer, incidence and mortality showed similar trends, but in the late cohorts for cervical cancer, cohort effects decreased in mortality, while increasing in incidence. Conclusion. Period effects reflecting immediate effects to cancer incidence and mortality, such as development of the effective treatment and screening programme were stable in most sites of cancer. Cohort effects influenced by long-term risk factors were prominently observed for every site, decrease in stomach and liver cancer cases being related to reduction in risk factor prevalence. Cancer control activities could be evaluated through the results, indicating utility for future cancer control planning.

Keywords: Cancer incidence and mortality - time trends - age-period cohort model - joinpoint analysis - Japan

Asian Pacific J Cancer Prev, **12**, 879-888

Introduction

Monitoring trends in cancer incidence and mortality is important to plan and evaluate cancer control policy. Cancer mortality data was monitored in all prefectures from vital statistics and was used in cancer control planning. Cancer incidence data, however, are available in some prefectures where population-based cancer registries have been conducted, and then the availability for cancer control planning was limited in some local governments. The Osaka Cancer Registry has a long history since 1962 and has exploited the registry data for the local cancer control activities. We used to evaluate the trends of age-standardised incidence and mortality. Trend analysis using only age-standardised rate cannot examine how the change of the distribution of age and birth cohort and period at diagnosis or death affected the whole trends. We aimed to estimate the effects of age, period and birth cohort on trends in cancer incidence and death for all sites and selected sites of cancer in Osaka, using an age-period-cohort model. Age-period-cohort model has been used to evaluate trends in cancer incidence and mortality for a long time. Most of the previous studies evaluate only incidence or mortality. In this study, we examined the both incidence and mortality trends and evaluated the cancer control activities in Osaka, Japan.

Materials and Methods

Data sources

Cancer incidence data during 1968-2003 were obtained from the Osaka Cancer Registry, and cancer mortality data with population data in Osaka during1968-2007 were obtained from vital statistics.

Statistical analysis

Joinpoint regression model. First, we applied annual age-standardised incidence and mortality rates in 1968-2007 to joinpoint regression model to show trends using a conventional approach for all ages. This is a piecewise log linear regression model, which is able to identify the years when the trends in incidence or mortality rate statistically changed, using the established Joinpoint 3.3 package (Kim et al., 2000; US National Cancer Institute, 2008).

*[1]Department of Cancer Control and Statistics, Osaka Medical Centre for Cancer and Cardiovascular Diseases, Osaka, [2]Department of Data Science, Institute of Statistical and Mathematics, Tokyo, Japan *For correspondence : itou-yu2@mc.pref.osaka.jp*

Age-period-cohort model. The 5-year age specific incidence and mortality rate were applied to the age-period-cohort model. We estimated age, period and birth cohort effects using Nakamura's Bayesian Poisson age-period-cohort model (BAPC model)(Nakamura, 1986) as follows:

$$y_{ij} \sim Poisson(\lambda_{ij}), i = 1,...,I,\ j = 1,...,J$$

$$\log \lambda_{ij} = \log P_{ij} + \beta^G + \beta_i^A + \beta_j^P + \sum_{k=1}^{K} w_{ij,k}\beta_k^C$$

$$\sum_{i=1}^{I} \beta_i^A = \sum_{j=1}^{J} \beta_j^P = \sum_{i=1}^{I}\sum_{j=1}^{J} w_{ij,k}\beta_k^C = 0, \quad \sum_{k=1}^{K} w_{ij,k} = 1$$

where y_{ij} is the number of observed deaths or incidence in the ith age group of jth period and are assumed to have a Poisson distribution with a mean λ_{ij} and an offset P_{ij}, the size of the population at risk. The parameters β^G, β_i^A, β_j^P and β_k^C are the grand mean, age, period and cohort effect, respectively. The weight $w_{ij,k}$ (≥0) is introduced to analyse a set of data arranged in general cohort table whose range of age group is not equal to the interval between periods and determined by the extent of overlap between the cohort ranges of data cell (i,j) and the kth cohort effect parameter.

As birth cohorts are determined from period and age, the relation among age, period and cohort causes an identification problem in that the linear components of age, period and cohort effects cannot be uniquely separated. Among many researchers to entangle this problem, Nakamura's BAPC model overcomes the problem by using an assumption that the effects change gradually or minimizing the weighted sum of squares of first-order differences of the effects parameters:

$$\frac{1}{\sigma_1^2}\sum_{i}\left(\beta_{i+1}^{A} - \beta_i^{A}\right)^2 + \frac{1}{\sigma_2^2}\sum_{j}\left(\beta_{j+1}^{P} - \beta_j^{P}\right)^2 + \frac{1}{\sigma_3^2}\sum_{k}\left(\beta_{k+1}^{C} - \beta_k^{C}\right)^2$$

The hyperparameters are introduced to control the smoothness of the parameters by minimizing Akaike's Bayesian Information Criterion (ABIC, (Akaike, 1980)). This assumption enables us to estimate not only the non-linear components but also the linear component of the effects.

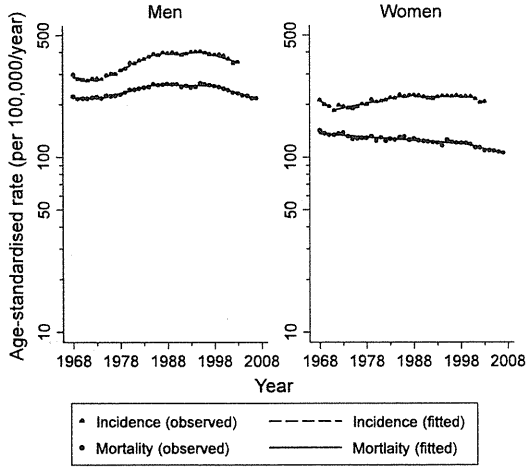

Figure 1. Trends in Age-standardised Incidence and Mortality Rates for All Sites of Cancer

Results

Joinpoint regression model

The results of joinpoint regression analysis are shown in Table 1 for trends of mortality and in Table 2 for trends of incidence. The trends in the overall cancer incidence and mortality by sex are shown in Figure 1. The trends in incidence and mortality by sex and cancer sites are shown in Figure 2.

The overall cancer mortality for men increased until 1985, and levelled-off between 1985 and 1998, then decreased by -2.0% per year since 1998. Similar trends were observed for the overall incidence. For women, the

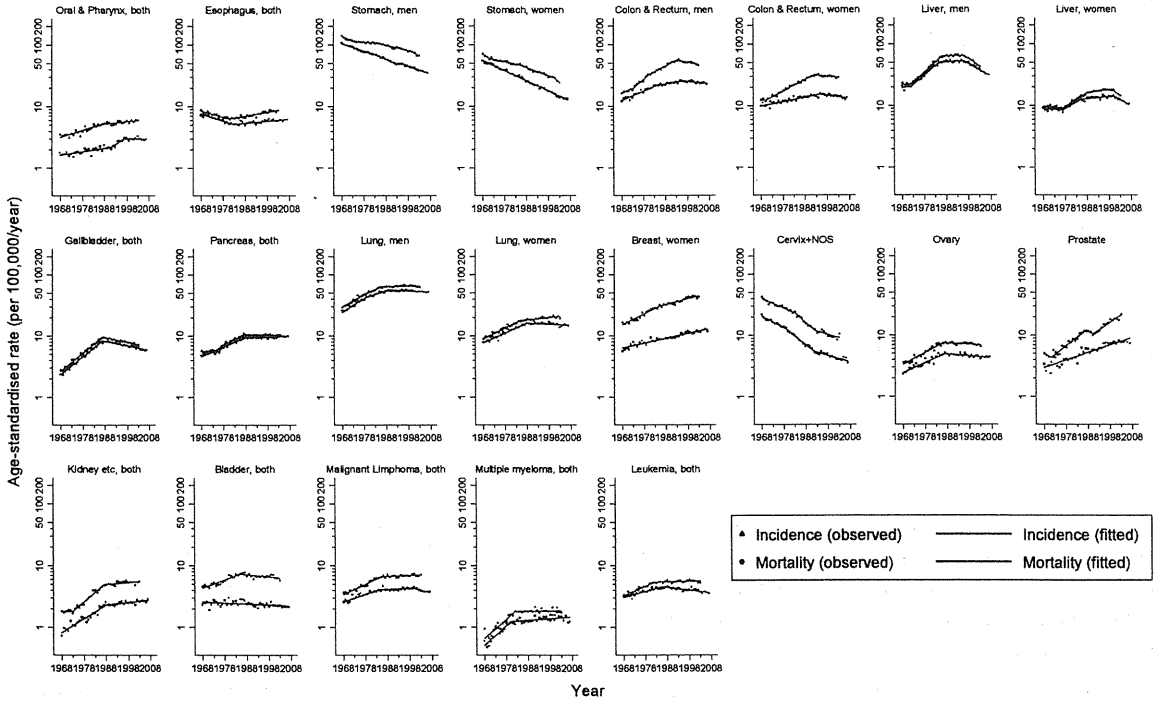

Figure 1. Trends in Age-standardised Incidence and Mortality Rates by Sex and Selected Cancer Site

trends of incidence increased by 1.3% per year between 1971 and 1985 ($P < 0.05$), then levelled-off from 1998. The overall mortality rates for women decreased gradually throughout. Both incidence and mortality for most sites of cancer decreased or levelled-off, while incidence for cancers of oral and pharynx, oesophagus, kidney renal pelvis, prostate, lung (women) and breast still increased.

Age-period-cohort model

All sites of cancer: For both incidence and mortality in both sexes, the age effect increased linearly with increasing age (Figure 3, left). The period effect was negligible (Figure 3, middle), while the cohort effect showed distinctive trends (Figure 3, right). The cohort effect in men increased for those who were born in 1900-1930s, and decreased for those born in mid-1930s to

Table 1 Trends in Age-standardised (Japanese Model Population in 1985) Mortality Rates with Joinpoint Analysis for 1975-2007 in Osaka, Japan, by Sex and Cancer Sites for All Ages

	ICD-10 code	Segment 1		Segment 2		Segment 3		Segment 4		AAPC[b]	
		Years	APC[a]	Years	APC[a]	Years	APC[a]	Years	APC[a]	1st	2nd
Both Sexes											
All sites	C00-96	1968-1976	-0.4	1976-1985	0.9*	1985-1998	-0.2	1998-2007	-1.69*	-1.7*	-1.7*
Oral and Pharynx	C00-14	1968-1991	1.3*	1991-1997	5.6*	1997-2007	-0.3			-0.3	-0.3
Esophagus	C15	1968-1983	-2.5*	1983-2007	0.7*					0.7*	0.7*
Stomach	C16	1968-1993	-3.3*	1993-2007	-2.9*					-2.9*	-2.9*
Colon	C18	1968-1993	3.7*	1993-2007	-0.7*					-0.7*	-0.7*
Rectum	C19-20	1968-1981	1.4*	1981-2007	-0.3 *					-0.3*	-0.3*
Colon & Rectum	C18-20	1968-1991	2.4*	1991-2007	-0.2					-0.2	-0.2
Liver	C22	1968-1976	2.7*	1976-1985	7.0*	1985-1997	0.5	1997-2007	-4.50*	-4.5*	-4.5*
Gallbladder	C23-24	1968-1987	7.0*	1987-2007	-1.7*					-1.7*	-1.7*
Pancreas	C25	1968-1988	3.7*	1988-2007	0.3					0.3	0.3
Larynx	C32	1968-1986	-3.9*	1986-1992	-8.2*	1992-1995	12.4	1995-2007	-4.75*	-4.7*	-4.7*
Lung	C33-34	1968-1979	4.7*	1979-1989	2.7*	1989-2007	-0.2			-0.2*	-0.2*
Kidney Renal Pelvis	C64-66, 68	1968-1988	5.3*	1988-2007	0.9*					0.9*	0.9*
Urinary Bladder	C67	1968-2007	-0.4*							-0.4*	-0.4*
Malignant Lymphoma	C81-85, 96	1968-1984	2.9*	1984-2000	0.4	2000-2007	-2.3*			-1.7*	-2.3*
Multiple Myeloma	C88-90	1968-1980	7.6*	1980-2007	0.6*					0.6*	0.6*
Leukemia	C91-95	1968-1986	2.2*	1986-2007	-1.0*					-1.0*	-1.0*
Men											
All sites	C00-96	1968-1974	-0.1	1974-1985	1.6*	1985-1998	-0.1	1998-2007	-2.0*	-2.0*	-2.0*
Esophagus	C15	1968-1971	4.3	1971-1981	-2.9*	1981-2007	0.9*			0.9*	0.9*
Stomach	C16	1968-1984	-2.7*	1984-1993	-3.5*	1993-1996	-0.4	1996-2007	-3.1*	-3.1*	-3.1*
Colon	C18	1968-1993	4.4*	1993-2007	-1.1*					-1.1*	-1.1*
Rectum	C19-20	1968-1980	2.6*	1980-2007	0.0					0	0
Colon & Rectum	C18-20	1968-1984	3.5*	1984-1996	1.5*	1996-2007	-0.8			-0.8	-0.8
Liver	C22	1968-1972	1.0	1972-1985	7.2*	1985-1996	0.5	1996-2007	-4.7*	-4.7*	-4.7
Lung	C33-34	1968-1979	5.3*	1979-1989	2.8*	1989-2007	-0.4*			-0.4*	-0.4*
Prostate	C61	1968-2007	2.9*							2.9*	2.9*
Malignant Lymphoma	C81-85, 96	1968-1984	3.4*	1984-2007	-0.4					-0.4	-0.4
Multiple Myeloma	C88-90	1968-1973	21.5*	1973-2003	1.9*	2003-2007	-10.4			-3.8	-10.4
Leukemia	C91-95	1968-1984	3.3*	1984-2007	-0.7*					-0.7*	-0.7*
Women											
All sites	C00-C96	1968-1999	-0.4*	1999-2007	-1.6*					-1.4*	-1.6*
Esophagus	C15	1968-1991	-3.5*	1991-2007	0.1					0.1	0.1
Stomach	C16	1968-2007	-3.7*							-3.7*	-3.7*
Colon	C18	1968-1995	3.0*	1995-2007	-1.2*					-1.2*	-1.2*
Rectum	C19-20	1968-2007	-0.7*							-0.7*	-0.7*
Colon & Rectum	C18-20	1968-1995	1.7*	1995-2007	-1.1*					-1.1*	-1.1*
Liver	C22	1968-1977	-0.5	1977-1985	4.9*	1985-2000	0.9*	2000-2007	-4.6*	-3.4*	-4.6*
Lung	C33-34	1968-1988	3.8*	1988-2007	-0.4					-0.4	-0.4
Breast	C50	1968-2007	1.8*							1.8*	1.8*
Cervix Uteri	C53	1968-1981	1.5	1981-2007	-0.8*					-0.8*	-0.8*
Corpus Uteri	C54	1968-2007	5.7*							5.7*	5.7*
Uterus	C53-C55	1968-1993	-4.9*	1993-2007	-1.2*					-1.2*	-1.2*
Cervix + Uterus NOS	C53, 55	1968-1979	-4.3*	1979-1992	-6.4*	1992-2007	-2.4*			-2.4*	-2.4*
Ovary	C56	1968-1987	3.8*	1987-2007	-0.7*					0.7*	-0.7*
Malignant Lymphoma	C81-85, 96	1968-1988	2.6*	1988-2007	-0.2					-0.2	-0.2
Multiple Myeloma	C88-90	1968-1983	5.8*	1983-2007	0.5					0.5	0.5
Leukemia	C91-95	1968-1988	1.3*	1988-2007	-1.5*					-1.5*	-1.5*

*Statistically significant; [a]Annual percentage change in the segment; [b]Average annual percentage change; 1st, 1998-2007; 2nd, 2003-2007

Table 2. Trends in Age-standardised (Japanese Model Population in 1985) Incidence Rates with Joinpoint Analysis for 1975-2007 in Osaka, Japan, by Sex and Cancer Sites for all Ages

	ICD-10 code	Segment 1		Segment 2		Segment 3		Segment 4		AAPC[b]	
		Years	APC[a]	Years	APC[a]	Years	APC[a]	Years	APC[a]	1st	2nd
Both Sexes											
All sites (incl. *in situ*)	C00-96[2]	1968-1971	-3.5*	1971-1986	1.9*	1986-1999	0.1	1999-2003	-2.6*	-1.1*	-2.6*
All sites	C00-96	1968-1971	-3.8*	1971-1986	2.0*	1986-1999	0.0	1999-2003	-2.6*	-1.2*	-2.6*
Oral & Pharynx	C00-14	1968-1987	2.6*	1987-2003	0.9*					0.9*	0.9*
Esophagus	C15	1968-1981	-2.2*	1981-2003	1.5*					1.5*	1.5*
Stomach	C16	1968-1971	-5.8*	1971-1985	-1.2*	1985-2001	-2.3*	2001-2003	-6.9*	-3.4*	-4.7*
Colon	C18	1968-1992	6.4*	1992-2003	-1.0*					-1.0*	-1.0*
Rectum	C19-20	1968-1972	-0.5	1972-1981	4.7*	1981-1994	1.8*	1994-2003	-1.4*	-1.4*	-1.4*
Colon & Rectum	C18-20	1968-1972	1.5	1972-1980	6.2*	1980-1993	4.3*	1993-2003	-1.3*	-1.3*	-1.3*
Liver	C22	1968-1976	2.4*	1976-1985	8.2*	1985-1996	1.0*	1996-2003	-5.0*	-3.7*	-5.0*
Gallbladder	C23-24	1968-1987	7.1*	1987-2003	-1.9*					-1.9*	-1.9*
Pancreas	C25	1968-1974	0.8	1974-1987	4.7*	1987-2003	-0.1			-0.1	-0.1
Larynx	C32	1968-2003	-1.8*							-1.8*	-1.8*
Lung	C33-34	1968-1978	5.0*	1978-1987	2.9*	1987-2003	0.4*			0.4*	0.4*
Renal + Pelvis	C64-66, 68	1968-1973	0.0	1973-1987	7.5*	1987-2003	0.7*			0.7*	0.7*
Urinary Bladder	C67	1968-1985	3.1*	1985-2003	-0.8*					-0.8*	-0.8*
Malignant Lymphoma	C81-85, 96	1968-1985	4.1*	1985-2003	0.4					0.4	0.4
Multiple Myeloma	C88-90	1968-1982	7.4*	1982-2003	0.2					0.2	0.2
Leukemia	C91-95	1968-1982	3.7*	1982-2003	0.2					0.2	0.2
Colon[1]	C18[3]	1968-1994	6.3*	1994-2003	-1.4*					-1.4*	-1.4*
Rectum[1]	C19-20[4]	1968-1972	-0.6	1972-1980	4.9*	1980-1995	2.1*	1995-2003	-1.5*	-1.1*	-1.5*
Colon & Rectum[1]	C18-20[5]	1968-1972	1.5	1972-1980	6.2*	1980-1994	4.4*	1994-2003	-1.0*	-1.0*	-1.0*
Men											
All sites (incl. in situ)	C00-96[2]	1968-1973	-1.0	1973-1985	2.9*	1985-1998	0.3	1998-2003	-2.7*	-1.4*	-2.7*
All sites	C00-96	1968-1973	-1.0	1973-1985	2.9*	1985-1996	0.3	1996-2003	-1.9 *	-1.4*	-1.9*
Esophagus	C15	1968-1980	-1.9*	1980-2003	1.7*					1.7*	1.7*
Stomach	C16	1968-1974	-3.3*	1974-1984	-0.4	1984-2000	-2.0*	2000-2003	-5.4*	-3.1*	-4.6*
Colon	C18	1968-1992	7.1*	1992-2003	-1.6*					-1.6*	-1.6*
Rectum	C19-20	1968-1971	-0.7	1971-1981	5.2*	1981-1994	2.1*	1994-2003	-1.3*	-1.3*	-1.3*
Colon & Rectum	C18-20	1968-1973	3.2*	1973-1980	7.3*	1980-1993	4.5*	1993-2003	-1.6*	-1.6*	-1.6*
Liver	C22	1968-1972	0.2	1972-1986	7.8*	1986-1996	0.2	1996-2003	-5.5*	-4.3*	-5.5*
Lung	C33-34	1968-1985	4.6*	1985-2003	0.1					0.1	0.1
Prostate	C61	1968-1971	-4.7	1971-1987	6.8*	1987-1990	-5.0	1990-2003	5.7*	5.7*	5.7*
Malignant Lymphoma	C81-85, 96	1968-1972	-1.4	1972-1983	5.3*	1983-2003	0.1			0.1	0.1
Multiple Myeloma	C88-90	1968-1982	8.1*	1982-2003	0.0					0.0	0.0
Leukemia	C91-95	1968-1982	4.3*	1982-2003	0.3					0.3	0.3
Colon[1]	C18[3]	1968-1994	7.0*	1994-2003	-2.1*					-2.1*	-2.1*
Rectum[1]	C19-20[4]	1968-1971	-0.7	1971-1981	5.2*	1981-1996	2.2 *	1996-2003	-1.9*	-1.0	-1.9*
Colon & Rectum[1]	C18-20[5]	1968-1973	3.1*	1973-1980	7.3*	1980-1995	4.5*	1995-2003	-2.0*	-1.3*	-2*
Women											
All sites (incl. in situ)	C00-96[2]	1968-1971	-3.6*	1971-1985	1.3*	1985-2000	0.0	2000-2003	-2.5	-0.8	-1.8
All sites	C00-96	1968-1971	-4.1*	1971-1985	1.3*	1985-2000	0.0	2000-2003	-2.7	-0.9	-2.0
Esophagus	C15	1968-1992	-2.4*	1992-2003	1.3					1.3	1.3
Stomach	C16	1968-1971	-5.5*	1971-1985	-1.7*	1985-2001	-3.1*	2001-2003	-7.9	-4.2*	-5.5*
Colon	C18	1968-1992	5.7*	1992-2003	-0.5					-0.5	-0.5
Rectum	C19-20	1968-1991	2.3*	1991-2003	-1.6*					-1.6*	-1.6*
Colon & Rectum	C18-20	1968-1970	-2.5	1970-1992	4.4*	1992-2003	-0.9*			-0.9*	-0.9*
Liver	C22	1968-1977	-0.6	1977-1988	5.4*	1988-1999	1.1*	1999-2003	-6.0*	-2.1*	-6.0*
Lung	C33-34	1968-1985	4.1*	1985-2003	0.9*					0.9*	0.9*
Breast	C50	1968-1985	4.2*	1985-2003	2.2*					2.2*	2.2*
Cervix Uteri	C53	1968-1981	-1.3*	1981-2000	-5.7*	2000-2003	4.2			-2.5	1.7
Corpus Uteri	C54	1968-1970	-22.1*	1970-1980	11.7*	1980-2003	1.9*			1.9*	1.9*
Uterus	C53-55	1968-1983	-2.7*	1983-1992	-5.5*	1992-2003	-1.1			-1.1	-1.1
Ovary	C56	1968-1986	4.6*	1986-2003	-0.4					-0.4	-0.4
Malignant Lymphoma	C81-85, 96	1968-1986	4.4*	1986-2003	0.7*					0.7*	0.7*
Multiple Myeloma	C88-C90	1968-1983	6.7*	1983-2003	0.1					0.1	0.1
Leukemia	C91-C95	1968-1982	3.1*	1982-2003	0.1					0.1	0.1
Colon[1]	C18[3]	1968-1994	5.6*	1994-2003	-0.8					-0.8	-0.8
Rectum[1]	C19-20[4]	1968-1992	2.3*	1992-2003	-1.4*					-1.4*	-1.4*
Colon & Rectum[1]	C18-20[5]	1968-1970	-2.5	1970-1993	4.4*	1993-2003	-0.6			-0.6	-0.6
Breast[1]	C50[6]	1968-1985	4.2*	1985-2003	2.4*					2.4*	2.4*
Cervix Uteri[1]	C53[7]	1968-1979	0.7	1979-2001	-4.5*	2001-2003	9.5			-1.6	2.3
Uterus[1]	C53-C55[7]	1968-1980	-1.4*	1980-1993	-4.3*	1993-2003	-1.1			-1.1	-1.1
Cervix + Uterus NOS[1]	C53, C55[7]	1968-1981	-2.0*	1981-1989	-6.0*	1989-2001	-3.5*	2001-2003	7.0	-1.3	1.6
Cervix + Uterus NOS	C53, C55	1968-1983	-3.5*	1983-1992	-7.1*	1992-2003	-2.5*			-2.5*	-2.5*

*Statistically significant; [a]Annual percentage change in the segment; [b]Average annual percentage change; 1st, 1998-2007; 2nd, 2003-2007; [1]including in situ; [2]D00-09; [3]D010, [5]D011-12; [5]D011-13; [6]D05; [7]D06

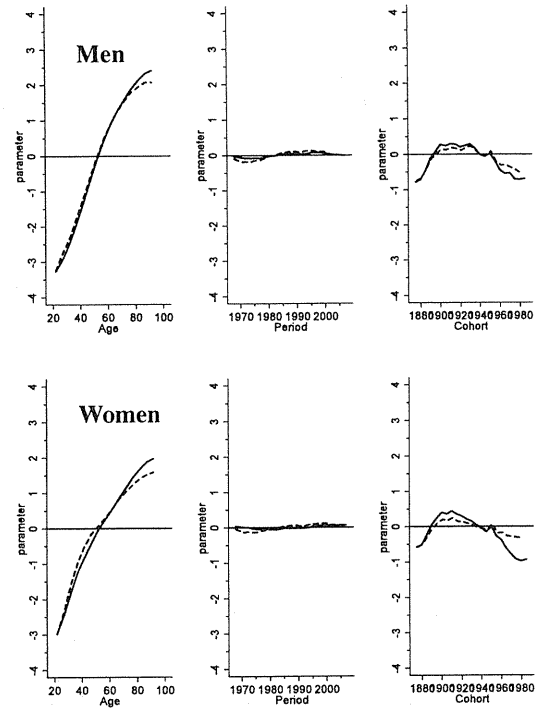

Figure 3. Age, Period and Birth Cohort Effects for all Sites of Cancer Dotted line, incidence, solid, mortality

mid-1940s. A small peak was observed at the cohort born in 1950s and then decreased. The cohort effect in women peaked at the cohort born in 1900-1910s and decreased with small re-ascending at the cohort of 1950s. The cohort effect of the latest born after 1960s has decreased; the trend was more remarkable in mortality than in incidence.

Stomach

Age effects increased as ageing. For incidence, the effects were levelled-off after age of 70. Period effects were stable. Cohort effects decreased dramatically after the 1900s birth cohort for both incidence and mortality (Figure 4).

Colon and rectum

Age effects showed linear increase for incidence and mortality in both sexes (Figure 5, left). For incidence, distinctive period effects were observed. The period effects for incidence increased until the mid-1990s, and then decreased.

For mortality, similar period effects were observed, but more moderate (Figure 5, middle). Cohort effects increased rapidly until the generation born in the 1900s, and then levelled-off/moderately increased. After peaking vwith the generation born in the 1950s, cohort effects were decreased in the latest generation (Figure 5, right).

Liver

Almost all effects showed similar trends between incidence and mortality. Increasing age effects were observed. Period effects increased until the middle of the 1980s, and decreased from the end of the 1990s. The cohort effect peaked with the birth cohort in the early 1930s and decreased immediately. Both sexes

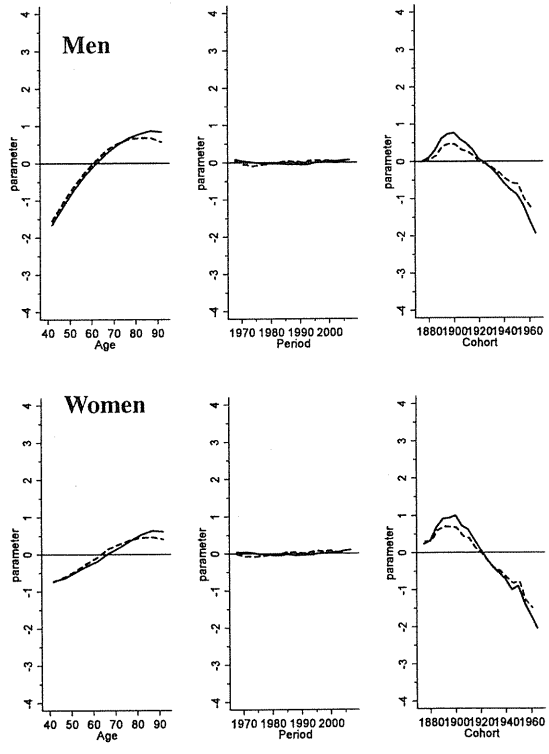

Figure 4. Age, Period and Birth Cohort Effects of Stomach Cancer in Osaka, Japan Dotted line, incidence, solid, mortality

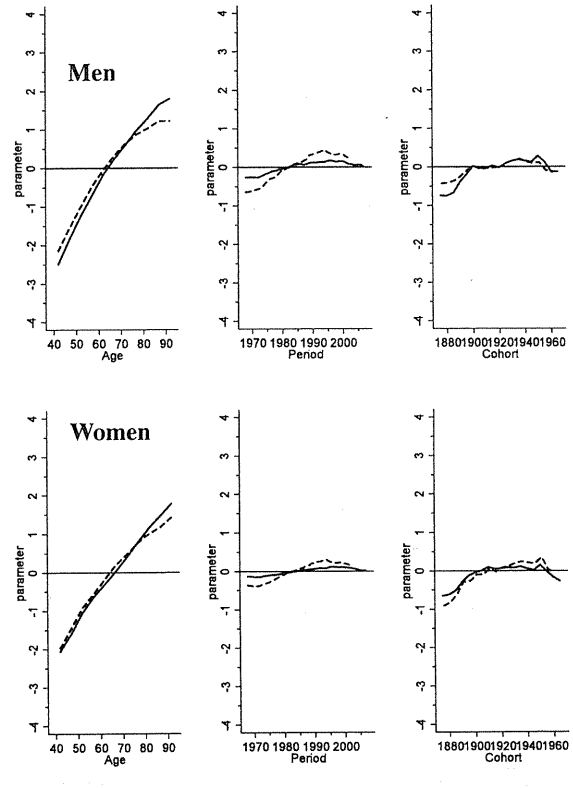

Figure 5. Age, Period and Birth Cohort Effects of Colorectal Cancer in Osaka, Japan Dotted line, incidence, solid, mortality

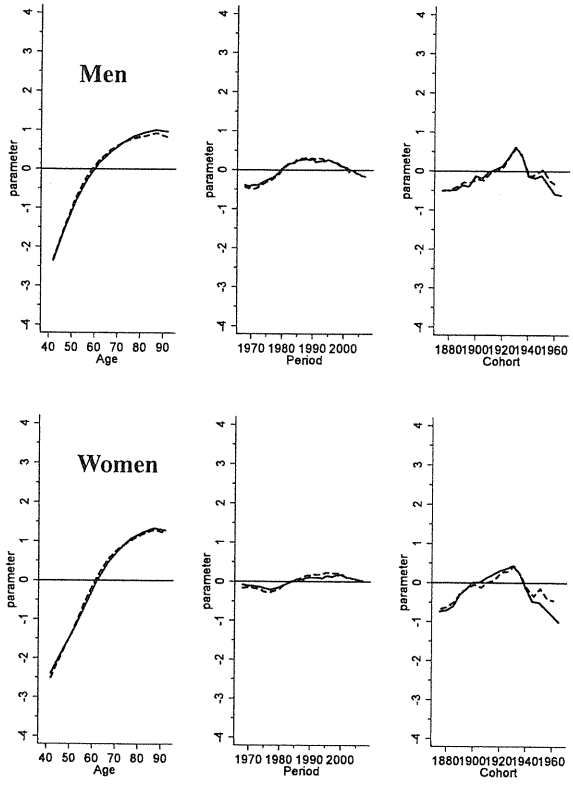

Figure 6. Age, Period and Birth Cohort Effects of Liver Cancer in Osaka, Japan

showed similar trends, but period effects in women were moderate (Figure 6).

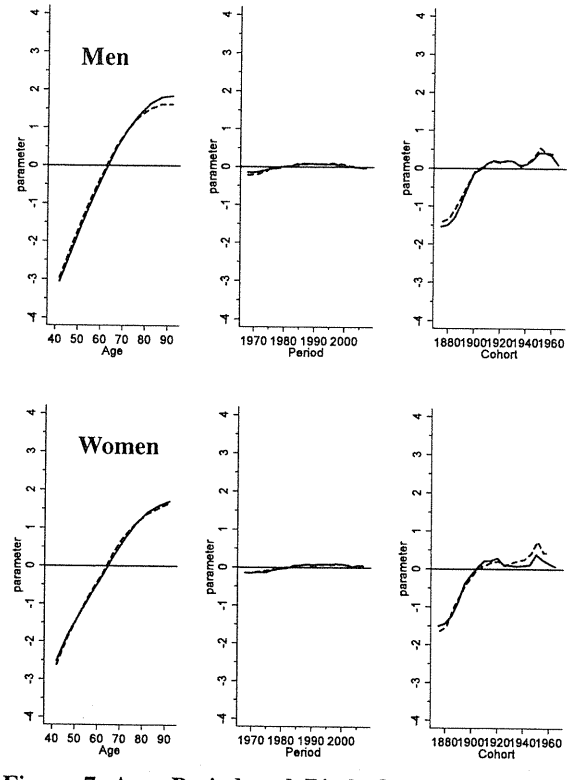

Figure 7. Age, Period and Birth Cohort Effects of Lung Cancer in Osaka, Japan

Lung

Almost all effects showed similar trends between incidence and mortality. Ageing effect was similar with other sites of cancer. Period effects were relatively small. For men, Cohort effect increased rapidly until the 1900s birth cohort and then levelled-off. Subsequently a dip in incidence in the late 1930s birth cohort was observed. The cohort effect then increased again and peaked with the 1950s cohort. The latest cohort effects (1950-60s) were still striking. For women, these effects showed similar trends in men. A small dip in the cohort born in the late 1920s was observed, and the cohort effects peaked with the1950s cohort (Figure 7).

Breast

Ageing effects showed different trends in incidence and mortality (Figure 8). For mortality, rapid increase of age effect until 50s and then moderate increase until 80s, subsequently increased rapidly again. On the other hand, age effects for incidence showed levelled-off after 40s. For mortality trends, age-cohort model was selected. This means that there was no period effect for breast cancer mortality. For incidence, small increase of period effects was observed. Cohort effects increased and peaked with the cohort born in the 1950s, and then slightly decreased.

Cervix (C53+C55)

Age and cohort effects showed different trends in incidence and mortality (see Figure 10). Ageing effect for mortality increased until the middle 50s and then levelled-off. While ageing effects for incidence peaked with the age of 40 and then decreased. Period effects were small for both incidence and mortality. Cohort effects peaked with the cohort born in the 1900s and subsequently decreased. Cohort effects for incidence

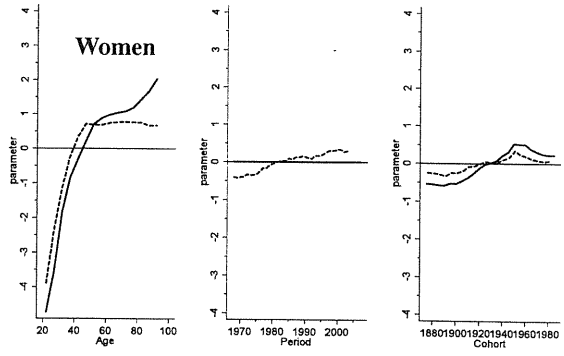

Figure 8. Age, Period and Birth Cohort Effects of Breast Cancer in Women in Osaka, Japan

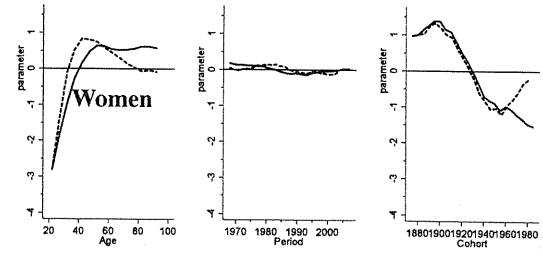

Figure 9. Age, Period and Birth Cohort Effects of Cervical Cancer (ICD 10: C53+C55) in Osaka, Japan

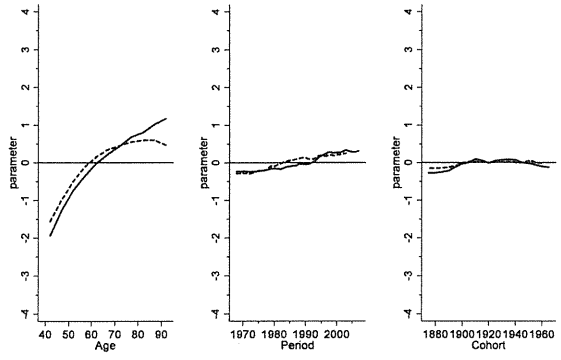

Figure 10. Age, Period and Birth Cohort Effects of Oral/ Pharynx Cancer in Both Sexes in Osaka, Japan

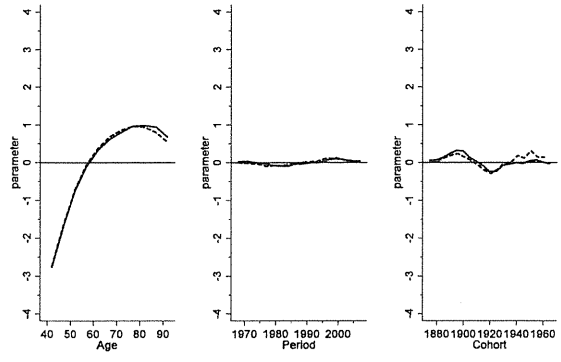

Figure 11. Age, Period and Birth Cohort Effects of Esophageal Cancer in Both Sexes in Osaka, Japan

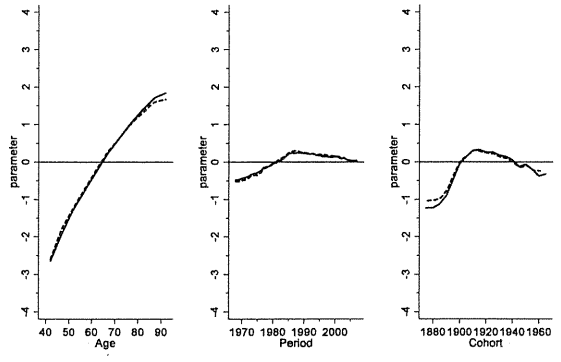

Figure 12. Age, Period and Birth Cohort Effects of Gallbladder Cancer in Both Sexes in Osaka, Japan

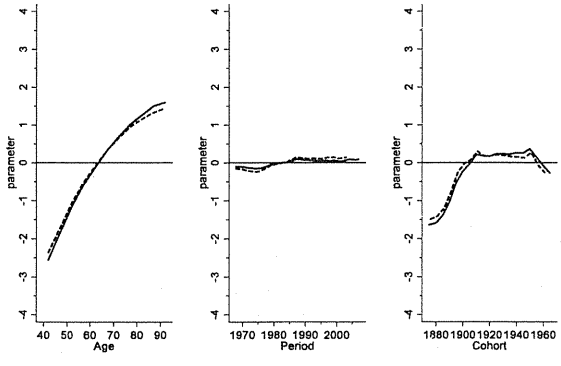

Figure 13. Age, Period and Birth Cohort Effects of Pancreas Cancer in Both Sexes in Osaka, Japan

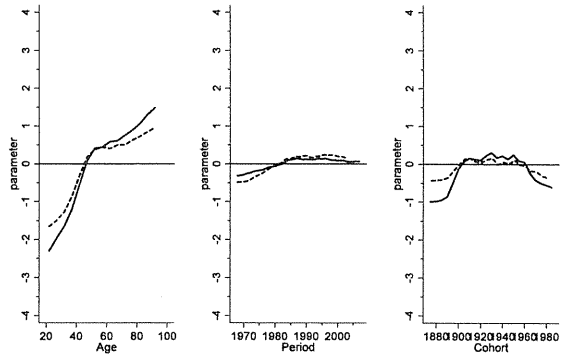

Figure 14. Age, Period and Birth Cohort Effects of Ovarian Cancer in Females in Osaka, Japan

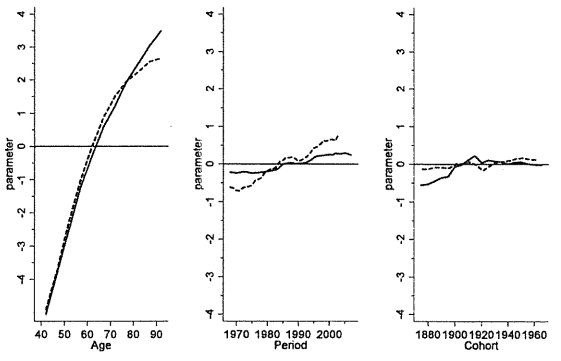

Figure 15. Age, Period and Birth Cohort Effects of Prostate Cancer in Males in Osaka, Japan

increased again after the 1950s birth cohort, while the effects for mortality still decreased. Parameters for age-cohort effects are illustrated in Figure 9.

Other sites of cancer

For oral and pharyngeal cancer in both sexes, increasing period effects were observed for both incidence and mortality (Figure 10). The cohort effects for oesophageal cancer were peaked at the cohort born in 1900s. Small dip was observed at the cohort born in the early 1920s, and then the cohort effects increased in the latest cohort (Figure 11). For gallbladder cancer, the period effects increased until the mid-1980s and then gradually decreased. The cohort effects were higher in the cohort born between 1900s and 1930s (Figure 12). For pancreas cancer, higher cohort effects were observed in the cohorts born in between 1910s and 1950s. (Figure 13)

The period effects were small for ovarian cancer. Decreased cohort effects were observed in the oldest and youngest cohorts. (Figure 14). For prostate cancer, largest aging effects were observed. Strongly increasing period effects were observed especially for incidence, while the cohort effects were small (Figure 15). Similar period effects were observed for trends in kidney cancer incidence with those in prostate cancer. The cohort effects increased until the cohort born in 1910s (Figure 16). For mortality of bladder cancer, the period effects were small. The cohort effects were peaked at the cohort

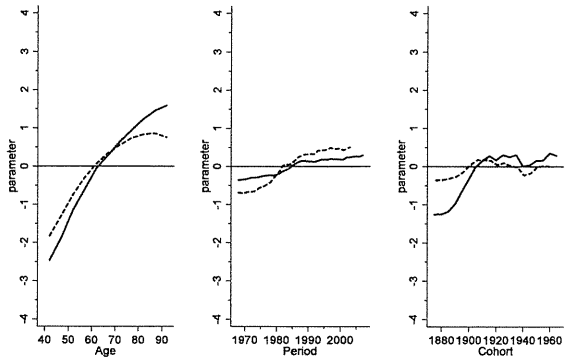

Figure 16. Age, Period and Birth Cohort Effects of Kidney Cancer in Both Sexes in Osaka, Japan

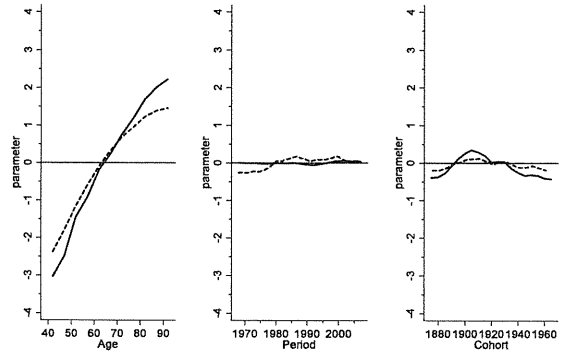

Figure 17. Age, Period and Birth Cohort Effects of Bladder Cancer in Both Sexes in Osaka, Japan

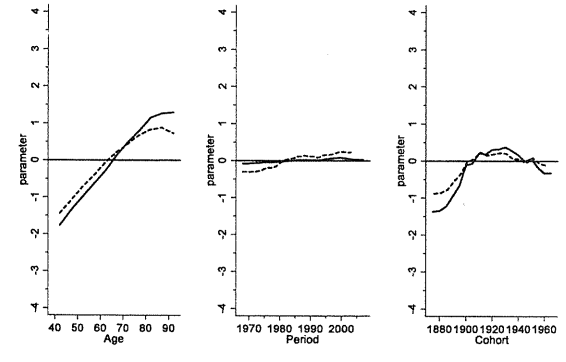

Figure 18. Age, Period and Birth Cohort Effects of Malignant Lymphoma in Both Sexes in Osaka, Japan

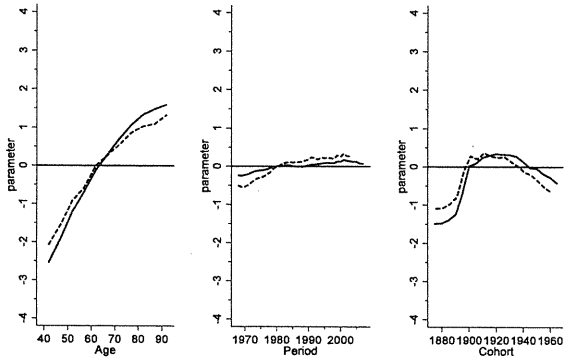

Figure 19. Age, Period and Birth Cohort Effects of Multiple Myeloma in Both Sexes in Osaka, Japan

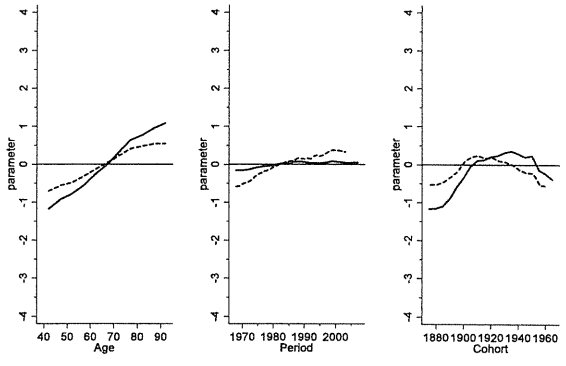

Figure 20. Age, Period and Birth Cohort Effects of Leukemia in Both Sexes in Osaka, Japan

born in 1900s, and then decreased (Figure 17).

Malignant lymphoma, multiple myeloma and leukaemia showed similar trends. Small increase in the period effects were observed for incidence trends but not for mortality. Cohort effects in the latest cohort decreased (Figure 18-20).

Discussion

Ageing effects for incidence and mortality are well-known in biological reason. For most sites of cancer, people increase the risk of growing cancer by ageing. Period effects reflect immediate effects to cancer incidence/mortality such as development of the effective treatment and screening programme. For all sites of cancer, the small period effects were observed. On the other hand, cohort effects reflect distant effects of risk factors such as smoking, dietary habits, and infectious agents. The cohort effects for all sites of cancer showed small peak at the 1950s birth cohort and decreased in the younger generation. The declining cohort effect for incidence and mortality may be mainly related with the decrease of prevalence of cancer risk factors. But the risk factors of cancer varied according to site of cancer. We need precise monitor of the trends by site, comparing with trends in the prevalence of each risk factor.

Remarkable cohort effects strongly related with decrease of the prevalence of the risk factor for stomach cancer, due to improvement of hygiene, the decrease of salt intake (Ministry of Health Labour and Walfare 1975-2007) and the prevalence of *H. pylori* infection (Haruma et al. 1997; Kobayashi et al. 2004). As a result, both age-standardised incidence and mortality rates also showed constant decrease. Small period effects indicated that there was little improvement of treatment and early detection, which should have showed immediate effect for stomach cancer.

Increasing age-standardised incidence and mortality of colorectal cancer until the mid-1990s would be explained as a result of increasing period and cohort effects. Increases of meat intake, obesity and less physical activities were risk factors of colorectal cancer. The prevalence of these risk factors is increasing in Japan, because of the change to Western lifestyle. Smoking is also one of the risk factors of colorectal

cancer. We need further investigation whether the trends of the prevalence of these risk factors corresponded with the trends in incidence and mortality. Trends of period effect indicated possibility of the immediate effect of the risk factor (Westernised lifestyle) to colorectal cancer incidence. This was confirmed at the previous study that Japanese immigrants in the US had higher incidence of colon cancer than Japanese in Japan (Haenszel and Kurihara, 1968; Shimizu et al., 1987). Improvement of diagnostic tools and treatments would be also related with the period effects.

With the liver the earlier increase in period effect could be the influence of improved diagnosis of liver cancer due to the development of diagnostic tools such as ultrasound sonography. The recent decrease was possibly caused by the effect of treatment for viral hepatitis. The influence of the prevalence of risk factors on cohort effects is clearly shown. The birth cohort born in around 1935 was suggested to show highest prevalence of HCV antibodies. The prevalence decreased in the younger generation (Tsukuma et al., 2005). As previous descriptive studies have reported, the highest cohort effect of incidence and mortality of liver cancer was observed at the cohort with the highest prevalence of HCV. The prevalence of HCV has been decreasing, so the incidence of liver cancer will continue to decrease.

Regarding the lung, the observed small period effect suggested that there was no change from immediate effects, such as development of treatment and introduction of effective screening programmes. Cohort effects reflecting change of prevalence of risk factors showed distinctive trends. The observed small dip in the middle 1930s birth cohort was consistent with the generation who had limited access to tobacco after World War II (Marugame et al., 2006). The early 1950s birth cohort peaked at the highest risk of incidence of lung cancer; they will be common age for lung cancer in the near future. Therefore the incidence will start to increase again. In some countries in Europe where tobacco control has been successful, the cohort effect of lung cancer mortality in men decreased dramatically. We need further efforts for tobacco control to decrease lung cancer in Japan (Bray and Weiderpass, 2009).

The pattern of age effect for breast cancer incidence was distinctive, which was different from the pattern in the US and western countries (Holford et al., 2006; Matsuno et al., 2007) and similar with many Asian countries(Sim et al., 2006). The pattern of age effect in mortality showed similar pattern with some other countries (Cayuela et al., 2004; Choi et al., 2006). Increasing cohort effect may be related with the recent Westernised lifestyle in Japan, in addition to dietary factor(Ministry of Health Labour and Walfare 1975-2007), reproductive factor related with the tendency to marry later and decrease of birth rate(Iwasaki et al. 2007; Ministry of Health Labour and Walfare 2010). Period effect in incidence increased in succession, while there was no effect in mortality. In some countries, decreasing period effect for mortality was observed by the improvement of treatment and effective mammography screening.(Cayuela et al., 2004; Niclis et al., 2010; Oberaigner et al., 2010).

In the cervix, decreasing cohort effect for incidence and mortality was mainly due to the improvement of the public hygiene. Since 1983, cervical cancer screening started in Japan as a nationwide public health service. But the proportion of the screening participation has been very low (about 20%). The period effect of cervical cancer incidence and mortality did not show any trend, this is because the screening programme was not successful as some countries in Europe (Quinn et al., 1999; Sasieni and Adams, 1999; Bray et al., 2005). Increase of incidence in the latest cohort possibly explained by the earlier onset of sexual activities, as the results, the prevalence of HPV also increased. Opportunistic cervical cancer screening at the gynaecological checkups also may be related with the increasing cohort effects of the younger generation in incidence.

For prostate, kidney and renal pelvis cancer, the increased period effects in incidence may be explained by the wider spread use of diagnostic tools; PSA for prostate cancer and ultrasound diagnosis for kidney cancer. These earlier detections, however, have not shown the decrease of period effect in mortality yet. For oesophageal, pancreas, kidney cancer, higher cohort effects were observed in the cohort born after 1950s. These trends suggested the possibility of increase in the incidence or mortality for these sites of cancer in future.

Although we have long-term data for both incidence and mortality in Osaka, the timeliness of incidence data is not so well at the moment. These results might not generalise to whole Japanese population, because the cancer incidence and mortality have been a little different in Osaka from other prefectures. Incidence and mortality of some sites of cancer (lung and liver) were higher than those in whole Japan.

We need to keep in mind the change in the completeness of cancer registration in Osaka when we evaluate incidence data. The percentage of under-ascertainment cases was not estimated routinely, but as an alternative index, the percentage of cases registered by death certificate only (% of DCO) was approximately 10-15% and stable in Osaka Cancer Registry during most recently two decades.(Parkin et al. 2005; Curado et al., 2007)

Among many approaches to disentangle the identification problem in the age-period-cohort model, Holford's is the most popular one in the descriptive cancer epidemiology area (Holford, 1985) and some other approaches (Yang et al., 2004; Carstensen, 2007) are still developing. Although Nakamura's method has been scarcely used in articles concerning cancer data, we adopted the method because it tackles straight on and overcome the problem in that the linear components of the three effects cannot be identified. Controlling the weighted sum of squares of first-order differences of the parameters as small as possible is a key to overcome the identification problem and Nakamura's method realizes to separate the three effects by using the framework of Bayesian approach and the minimization of the information criterion ABIC. When we compare such results, we need to pay close attention to the difference between the methods. In near future, we will need to

evaluate the difference between those methods and Nakamura's one.

In conclusion, this is the first report to show the effects of age, period and birth cohort using both incidence and mortality for various sites of cancer in Japan. Age-period-cohort model is useful approach to show these effects separately. We could evaluate cancer control activities through the results and can exploit next cancer control planning.

Acknowledgements

This work was supported by the Management Expenses Grants from the Government to the National Cancer Center 20-2, Utilization of population-based cancer registry data for cancer control and cancer epidemiology, and Health and Labour Sciences Research Grants for Clinical Cancer Research (H22-11), Demonstrative research on evaluation method of cancer control progress based on existing statistical data. We thank Dr Masahiro Tanaka for his helpful comments.

References

Akaike H (1980). Likelihood and the Bayes Procedure. Bayesian Statistics. J. Bernardo, M, et al, Eds. Valencia, University Press.

Bray F, Loos AH, McCarron P, et al (2005). Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. *Cancer Epidemiol Biomarkers Prev*, **14**, 677-86.

Bray FI, Weiderpass E (2009). Lung cancer mortality trends in 36 European countries: secular trends and birth cohort patterns by sex and region 1970-2007. *Int J Cancer*, **126**, 1454-66.

Carstensen B (2007). Age-period-cohort models for the Lexis diagram. *Stat Med*, **26**, 3018-45.

Cayuela A, Rodriguez-Dominguez S, Ruiz-Borrego M, Gili M (2004). Age-period-cohort analysis of breast cancer mortality rates in Andalucia (Spain). *Ann Oncol*, **15**, 686-8.

Choi Y, Kim Y, Park SK, et al. (2006). Age-period-cohort analysis of female breast cancer mortality in Korea. *Breast Cancer*, **13**, 266-71.

Curado MP, Edwards B, Shin HR, et al., Eds. (2007). Cancer Incidence in Five Continents, Vol. IX. IARC Scientific Publications No. 160. Lyon, IARC.

Haenszel W and Kurihara M (1968). Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. *J Natl Cancer Inst*, **40**, 43-68.

Haruma K, Okamoto S, Kawaguchi H, et al (1997). Reduced incidence of *Helicobacter pylori* infection in young Japanese persons between the 1970s and the 1990s. *J Clin Gastroenterol*, **25**, 583-6.

Holford TR (1985). An alternative approach to statistical age-period-cohort analysis. *J Chronic Dis*, **38**, 831-40.

Holford TR, Cronin KA, Mariotto AB, Feuer EJ (2006). Changing patterns in breast cancer incidence trends. *J Natl Cancer Inst Monogr*, **36**, 19-25.

Iwasaki M, Otani T, Inoue M, et al (2007). Role and impact of menstrual and reproductive factors on breast cancer risk in Japan. *Eur J Cancer Prev*, **16**, 116-23.

Kim HJ, Fay MP, Feuer EJ, Midthune DN (2000). Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med*, **19**, 335-51.

Kobayashi T, Kikuchi S, Lin Y, et al. (2004). Trends in the incidence of gastric cancer in Japan and their associations with Helicobacter pylori infection and gastric mucosal atrophy. *Gastric Cancer*, **7**, 233-9.

Marugame T, Kamo K, Sobue T, et al (2006). Trends in smoking by birth cohorts born between 1900 and 1977 in Japan. *Prev Med*, **42**, 120-7.

Matsuno RK, Anderson WF, Yamamoto S, et al (2007). Early- and late-onset breast cancer types among women in the United States and Japan. *Cancer Epidemiol Biomarkers Prev*, **16**, 1437-42.

Ministry of Health Labour and Walfare (1975-2007). The national health and nutrition survey in Japan. Retrieved 1 June, 2009, from http://www.nih.go.jp/eiken/chosa/kokumin_eiyou/index.html.

Ministry of Health Labour and Walfare (2010). Vital Statistics in Japan. Retrieved 13 Jan, 2011, from http://www.e-stat.go.jp/SG1/estat/eStatTopPortal.do.

Nakamura T (1986). Bayesian cohort models for general cohort table analyses. *Ann Inst Stat Mathematics*, **38 (2B)**, 353-370.

National Cancer Institute. (2008). Joinpoint Regression Program Ver. 3.3. 3.3. Retrieved 12 June, 2009, from http://srab.cancer.gov/joinpoint/.

Niclis C, Del Pilar Diaz M, La Vecchia C (2010). Breast cancer mortality trends and patterns in Cordoba, Argentina in the period 1986-2006. *Eur J Cancer Prev*, **19**, 94-9.

Oberaigner W, Buchberger W, Frede T, et al (2010). Breast cancer incidence and mortality in Tyrol/Austria after fifteen years of opportunistic mammography screening. *BMC Public Health*, **10**, 86.

Parkin DM, Whelan SL, Ferlay J and Storm H (2005). Cancer Incidence in Five Continents, Vol. I to VIII Lyon.

Quinn M, Babb P, Jones J and Allen E (1999). Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. BMJ, 318, 7188, 904-8.

Sasieni P and Adams J (1999). Effect of screening on cervical cancer mortality in England and Wales: analysis of trends with an age period cohort model. *BMJ*, **318**, 1244-5.

Shimizu H, Mack TM, Ross RK, Henderson BE (1987). Cancer of the gastrointestinal tract among Japanese and white immigrants in Los Angeles County. *J Natl Cancer Inst*, **78**, 223-8.

Sim X, Ali RA, Wedren S, et al (2006). Ethnic differences in the time trend of female breast cancer incidence: Singapore, 1968-2002. *BMC Cancer*, **6**, 261.

Tsukuma H, Tanaka H, Ajiki W, Oshima A (2005). Liver cancer and its prevention. *Asian Pac J Cancer Prev*, **6**, 244-50.

Yang Y, Fu WJ and Land KC (2004). A methodological comparison of age-period-cohort models: the intrinsic estimator and conventional generalized linear models. *Sociological Method*, 34, 75-110.

J Epidemiol 2011;21(2):132-143
doi:10.2188/jea.JE20100098

Original Article

An Association Between Long-Term Exposure to Ambient Air Pollution and Mortality From Lung Cancer and Respiratory Diseases in Japan

Kota Katanoda[1], Tomotaka Sobue[1], Hiroshi Satoh[2], Kazuo Tajima[3], Takaichiro Suzuki[4], Haruo Nakatsuka[5], Toshiro Takezaki[6], Tomio Nakayama[4], Hiroshi Nitta[7], Kiyoshi Tanabe[8], and Suketami Tominaga[3], for the Three-prefecture Cohort Study Group

[1]Cancer Information Services and Surveillance Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan
[2]Environmental Health Sciences, Tohoku University Graduate School of Medicine, Sendai, Japan
[3]Aichi Cancer Center Research Institute, Nagoya, Japan
[4]Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan
[5]School of Nursing, Miyagi University, Miyagi, Japan
[6]Department of International Island and Community Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan
[7]Environmental Health Sciences Division, National Institute for Environmental Studies, Tsukuba, Japan
[8]Environmental Chemistry Division, National Institute for Environmental Studies, Tsukuba, Japan

Received June 29, 2010; accepted November 30, 2010; released online February 12, 2011

ABSTRACT

Background: Evidence for a link between long-term exposure to air pollution and lung cancer is limited to Western populations. In this prospective cohort study, we examined this association in a Japanese population.

Methods: The study comprised 63 520 participants living in 6 areas in 3 Japanese prefectures who were enrolled between 1983 and 1985. Exposure to particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) was assessed using data from monitoring stations located in or nearby each area. The Cox proportional hazards model was used to calculate the hazard ratios associated with the average concentrations of these air pollutants.

Results: The 10-year average concentrations of $PM_{2.5}$, SO_2, and NO_2 before recruitment (1974–1983) were 16.8 to 41.9 μg/m^3, 2.4 to 19.0 ppb, and 1.2 to 33.7 ppb, respectively (inter-area range). During an average follow-up of 8.7 years, there were 6687 deaths, including 518 deaths from lung cancer. The hazard ratios for lung cancer mortality associated with a 10-unit increase in $PM_{2.5}$ (μg/m^3), SO_2 (ppb), and NO_2 (ppb) were 1.24 (95% confidence interval: 1.12–1.37), 1.26 (1.07–1.48), and 1.17 (1.10–1.26), respectively, after adjustment for tobacco smoking and other confounding factors. In addition, a significant increase in risk was observed for male smokers and female never smokers. Respiratory diseases, particularly pneumonia, were also significantly associated with all the air pollutants.

Conclusions: Long-term exposure to air pollution is associated with lung cancer and respiratory diseases in Japan.

Key words: air pollution; lung neoplasms; nitrogen dioxide; particulate matter; sulfur dioxide

INTRODUCTION

Many epidemiological studies of US and European populations have demonstrated an association between long-term exposure to ambient air pollution and mortality from lung cancer, cardiovascular diseases (CVDs), and respiratory diseases.[1-16] However, these findings might not apply to Asia, where both the levels and constituents of air pollutants may differ from those in the West. For example, while the annual average ambient concentration of sulfur dioxide (SO_2) in Tokyo during 2000–2005 was below 10 μg/m^3 (3.8 ppb)—which was similar to levels in the least polluted

Address for correspondence. Kota Katanoda, Cancer Information Services and Surveillance Division, Center for Cancer Control and Information Services, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan (e-mail: kkatanod@ncc.go.jp).
Three-prefecture Cohort Study Group: Miyagi prefecture: Shigeru Hisamichi, Masayuki Ikeda, Hiroyuki Shimizu, Shoko Komatsu, Akira Fukao, Ichiro Tsuji, and Yoshikazu Nishino; Aichi prefecture: Ikuko Kato, Manami Inoue, Hideo Tanaka, Akio Hiraki, Kenji Wakai, and Takeshi Suzuki; Osaka prefecture: Kenji Morinaga, Mitsuru Akao, Akira Sasaki (deceased), Isaburo Fujimoto (deceased), Hideaki Tsukuma, Akira Oshima, and Kimiko Asari; National Institute for Environmental Studies: Masatoshi Morita; National Cancer Center and other institutes: Takeo Suzuki (deceased), Tsuguyoshi Suzuki (deceased), and Dongmei Qiu.
Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; ICD, International Classification of Diseases; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter; SO_2, sulfur dioxide; SPM, suspended particulate matter.

cities of Europe, such as Copenhagen and Barcelona—the annual average ambient nitrogen dioxide (NO_2) concentration in Tokyo was 60 μg/m^3 (31.9 ppb), a value higher than those in the most polluted cities of Europe, such as Paris and Athens (unit conversion factors are based on the same citation).[17] This raises the possibility that the magnitude of the mortality association in Asian populations differs from those in the United States and Europe.

National air quality monitoring networks have been established in Japan, and data on concentrations of SO_2, NO_2, particulate matter (PM), and other substances have been available in selected areas for several decades. In the present study, we examined the long-term effect of air pollution on mortality from lung cancer and respiratory diseases, using data obtained from a large-scale population-based Japanese cohort study of individuals enrolled between 1983 and 1985.

METHODS

Study population and baseline survey

We used data collected by the prospective Three-prefecture Cohort Study, which was conducted in 8 selected areas in Miyagi (Sendai city and Wakuya/Tajiri towns), Aichi (Nagoya city and Inuyama city), and Osaka (Osaka city, Nose, Kanan, and Kumatori towns) prefectures.[18] The study areas in each prefecture were selected as a set of polluted and control areas. Specifically, the cities of Sendai, Nagoya, and Osaka were selected as the polluted areas, and the other areas were selected as the control areas. The study areas were chosen because they have national air pollution monitoring stations and well-managed cancer surveillance systems. The study population was defined as all residents in these areas aged 40 years or older. Participants were enrolled between 1983 and 1985 (February 1983 in Nose town, January-February 1984 in Sendai city and Wakuya/Tajiri towns, October-November 1984 in Osaka city, November-December 1984 in Kanan town, February-March 1985 in Kumatori town, July-August 1985 in Inuyama city, and October-November 1985 in Nagoya city). A self-administered questionnaire was distributed to 118 820 individuals identified based on residence registries in cooperation with the municipal government of each area, and responses were returned by 100 615 (84.7%). Individuals were excluded from the study if they had resided in the study areas for less than 10 years (n = 19 542) or provided incomplete answers to questions related to smoking status, pack-years (ever smokers only), smoking status of family members, frequency of vegetable and fruit consumption, or use of indoor charcoal or briquette braziers (*sumi* or *rentan* in Japanese) for heating (n = 17 553). The final analytic cohort comprised 63 520 participants (30 035 men and 33 485 women). Details of the study areas and participants are summarized in Table 1. The study was approved by the institutional review board of the National Cancer Center, Japan.

Follow-up

The follow-up period was defined as 10 years from the baseline survey in each study area (through October 1995 at the latest). Vital status and out-migration were confirmed through registries kept by the local governments. Causes of death were confirmed by vital statistics obtained with official permission, and coded according to the International Classification of Diseases, 9th revision (ICD-9). Only the underlying cause of death was used. The endpoint was defined as lung cancer death during the observation period (ICD-9: 162). Deaths from respiratory diseases (ICD-9: 460–519) were also analyzed. We did not analyze other causes of death because we lacked baseline data for potential confounding factors.

Air pollution data

Since the 1970s, there has been a network of ambient air monitoring stations in Japan operated by the Ministry of Environment (formerly the National Environment Agency) and local governments. The annual mean concentrations measured from 1974 to 1983 at an air monitoring station in or nearby each study area were used as surrogate indicators of individual exposure levels. Figure 1 shows the geographical distribution of the study areas and the air monitoring stations. All air monitoring stations were located within the study area, except those for Nose town and Kanan town in Osaka prefecture, which were located nearby. For Inuyama city, there were 2 monitoring stations, and the average values obtained from the 2 stations were used. The distance from the population center of each study area to the monitoring station was 6.5 km for Wakuya/Tajiri towns, 0.9 km for Sendai city, 1.7 km for Nagoya city, 1.4 km and 1.7 km for Inuyama city, 0.8 km for Osaka city, 15.7 km for Nose town, 10.7 km for Kanan town, and 0.4 km for Kumatori town.

The concentrations of SPM, SO_2, and NO_2 were measured by β-ray absorption, conductometry, and absorption spectrophotometry, respectively. In Japan, SPM is defined as particles with an aerodynamic diameter of ≤10 μm by the 100% cutoff point, which corresponds to approximately $PM_{7.0}$ by the 50% cutoff point. In the 2 areas of Miyagi prefecture, SPM concentrations were measured in part by gravimetry incorporated into a low-volume sampler, rather than by β-ray absorption (1974–1986 in Wakuya/Tajiri towns and 1974–1985 in Sendai city). The SPM concentrations for these periods were estimated using the concentration ratios between the 2 measurement methods calculated for the subsequent years through 1996.

Many epidemiological studies have reported the health effects of ambient PM ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$),[4,9,11,13,15,16] some of which suggested a stronger association with the fine fraction of PM than with the coarse fraction.[4,11] Because we did not have long-term concentration data for $PM_{2.5}$, we estimated $PM_{2.5}$ concentrations by converting SPM concentrations using a single ratio, as in

Table 1. Average air pollution levels and participant characteristics in the 6 study areas

	Miyagi prefecture		Aichi prefecture		Osaka prefecture	
	Wakuya/Tajiri towns (entire towns)	Sendai city (6 areas in Aoba and Miyagino wards)	Inuyama city (2 areas in the city)	Nagoya city (5 areas in Chikusa ward)	Nose/Kanan/ Kumatori towns (entire towns)	Osaka city (Higashinari ward)
Year of baseline survey	1984	1984	1985	1985	1983–1985[a]	1984
Number of participants in collected datasets	14 571	16 774	12 001	21 514	18 608	17 147
Number of participants in analytic cohorts	7813	9924	7917	13 653	10 490	13 723
Age at baseline; mean (SD)	56.8 (11.3)	57.5 (11.2)	56.2 (11.3)	57.7 (11.1)	55.9 (11.5)	57.6 (11.3)
40–49 years	30.4%	28.0%	34.0%	27.0%	35.5%	28.4%
50–59 years	33.1%	32.4%	31.1%	33.0%	30.9%	31.6%
60–69 years	20.3%	23.4%	20.3%	23.1%	18.6%	22.9%
≥70 years	16.2%	16.1%	14.6%	16.9%	15.1%	17.2%
Person-years of follow-up	71 579	80 927	70 819	114 497	94 917	117 599
% move-out during follow-up	2.9%	22.4%	8.0%	20.3%	5.5%	11.9%
Number of deaths						
Lung cancer	49	60	58	132	74	145
Respiratory diseases[b]	78	116	69	126	120	181
All causes	973	935	789	1333	1033	1624
10-year average air pollution levels						
SPM ($\mu g/m^3$) 1974–1983	24.0	44.8	46.3	49.7	36.0	59.9
1984–1993	21.9	29.0	37.4	43.7	36.2	45.0
$PM_{2.5}$ ($\mu g/m^3$)[c] 1974–1983	16.8	31.4	32.4	34.8	25.2	41.9
1984–1993	15.3	20.3	26.2	30.6	25.3	31.5
SO_2 (ppb) 1974–1983	2.4	12.0	9.5	10.4	13.5	19.0
1984–1993	2.3	5.5	6.8	7.7	6.3	10.6
NO_2 (ppb) 1974–1983	1.2	18.3	13.6	20.3	14.6	33.7
1984–1993	2.6	16.1	16.0	23.9	16.0	33.0
Results of baseline survey (1983–1985)						
Smoking status (%)						
Current smokers[e]	30.3%	29.1%	35.6%	30.1%	35.1%	33.9%
Former smokers[e]	9.0%	14.4%	15.4%	17.4%	9.9%	13.9%
Amount of smoking (pack-years)						
Current smokers; mean (SD)[f]	31.5 (17.4)	32.0 (19.6)	33.8 (19.4)	34.7 (22.3)	34.8 (19.6)	34.5 (20.8)
Former smokers; mean (SD)[f]	27.9 (20.5)	29.4 (24.5)	29.4 (28.0)	30.3 (28.2)	28.5 (23.4)	29.8 (26.5)
Passive smoking (%)						
Currently from family members[e]	62.4%	46.2%	48.4%	39.7%	54.3%	50.4%
During childhood from parents[e]	71.4%	75.1%	74.3%	75.3%	79.3%	82.6%
Daily green and yellow vegetable consumption (%)[e]	52.1%	58.0%	41.8%	48.3%	36.6%	34.4%
Daily consumption of other vegetables (%)[e]	75.5%	67.7%	63.3%	62.1%	49.3%	41.9%
Daily fruit consumption (%)[e]	64.9%	65.0%	34.8%	54.4%	49.8%	47.2%
Use of indoor charcoal or briquette braziers for heating (%)[e]	44.8%	7.1%	3.0%	1.5%	10.1%	6.3%
Occupation with potential risk (%)[d,e]	29.7%	24.7%	40.5%	27.1%	32.0%	36.3%
History of respiratory diseases (%)[e]	6.1%	6.9%	8.6%	10.4%	7.6%	6.6%
Health insurance type (%)						
National health insurance[e]	67.8%	44.2%	42.1%	42.2%	47.1%	56.2%
Government/union-managed health insurance[e]	21.1%	38.8%	48.8%	47.9%	41.9%	40.1%
Mutual aid associations health insurance[e]	9.0%	14.7%	8.2%	9.0%	10.0%	2.2%
Others	2.1%	2.3%	0.9%	0.9%	0.9%	1.5%

NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter; SO_2, sulfur dioxide; SPM, suspended particulate matter.
[a]1983 in Nose, 1984 in Kanan, and 1985 in Kumatori towns.
[b]For respiratory diseases, numbers of deaths were counted after excluding 4970 participants with a previous diagnosis of pneumonia, asthma, chronic bronchitis, emphysema, or pneumoconiosis.
[c]Estimated by multiplying the level of SPM by 0.7.
[d]Experience of occupation with potential risk of exposure to gases, fumes, or dust.
[e]Significant difference among areas (chi-square test; $P < 0.0001$).
[f]Significant difference among areas (ANOVA; $P < 0.0001$).

previous studies.[2,19] We examined the $PM_{2.5}$/SPM ratio in our study areas during a short period (2 weeks) in 1997; the ratio ranged from approximately 0.6 to 0.8. A similar range was observed in the annual average concentration data at the monitoring stations in the 3 prefectures from 2001 to 2005. The temporal correlation coefficient between the $PM_{2.5}$ and SPM concentrations calculated from the data near Osaka city in 1974–1977 was greater than 0.90. Based on these data, we

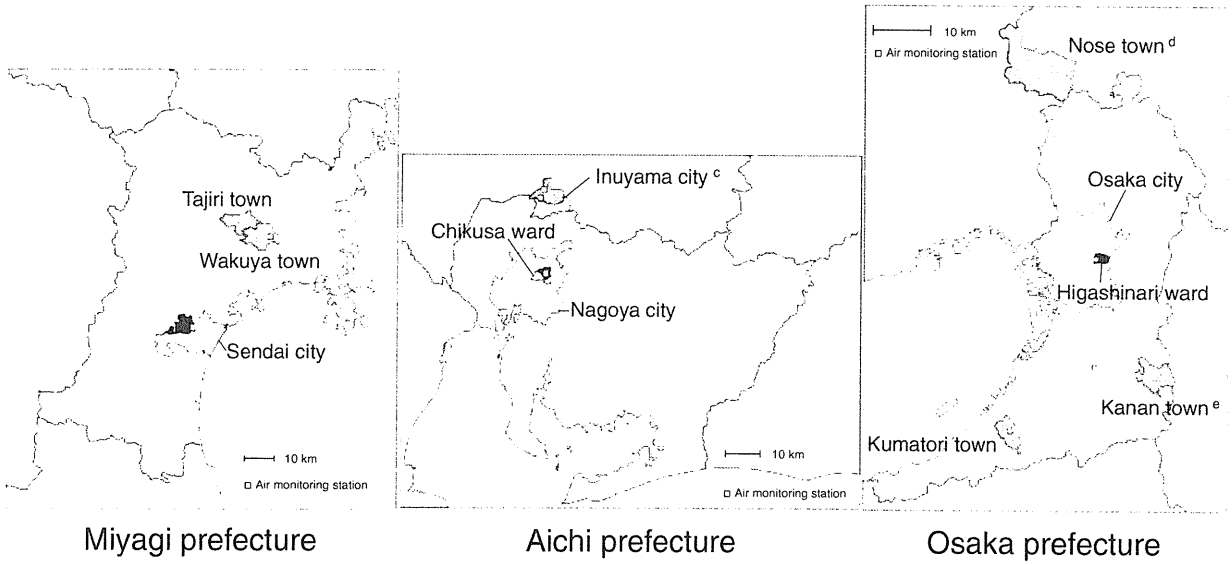

Figure 1. Geographical distribution of the study areas and air monitoring stations.[a,b] [a]Study areas are shaded in black (urban) or gray (rural). [b]The name and boundaries of each area are those at the time of the baseline survey. [c]There were 2 air monitoring stations in Inuyama city. [d]The air monitoring station for Nose town is located to the south. [e]The air monitoring station for Kanan town is located to the west.

assumed that the $PM_{2.5}$ concentration in each of the study areas was well correlated with the SPM concentration and that variations in the $PM_{2.5}$/SPM ratio would be small across the study areas. Thus, we used the $PM_{2.5}$ concentrations estimated by multiplying the SPM concentrations by a ratio of 0.7.

In the statistical analysis, the data from Nose, Kanan, and Kumatori towns were pooled and the average concentrations across those areas were used because they had similar air concentration levels (the average concentrations for the 1974–1993 period were: Nose 32.2 $\mu g/m^3$, Kanan 37.7 $\mu g/m^3$, and Kumatori 38.3 $\mu g/m^3$ for SPM; Nose 7.8 ppb, Kanan 11.9 ppb, and Kumatori 10.0 ppb for SO_2; Nose 15.4 ppb, Kanan 15.1 ppb, and Kumatori 15.5 ppb for NO_2).

Statistical analysis

Person-years of follow-up were calculated for all participants from the date of the baseline questionnaire to whichever of the following occurred first: the end of the 10-year follow-up, date of death, or date of moving out of the study area. Person-years for participants who died from causes other than those being analyzed were treated as being censored at the time of death. The Cox proportional hazards model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI). The CI was calculated using the sandwich variance estimate to adjust for correlated observation within each study area.[20]

For the analysis of deaths from lung cancer, the HRs were adjusted for sex, age (continuous), smoking status (current, former, never), pack-years (<10, 10–19, ≥20), smoking status of family members living together (current smoking/no current smoking), daily green and yellow vegetable consumption (yes/no), daily fruit consumption (yes/no), and use of indoor charcoal or briquette braziers for heating (yes/no). Green and yellow vegetable consumption and fruit consumption were added to the adjusted variables because fruit and foods containing carotenoids have been judged as "probably protective" against lung cancer by the World Cancer Research Fund and the American Institute for Cancer Research.[21] Use of indoor charcoal or briquette braziers for heating was adjusted for because household combustion of coal has been classified as carcinogenic to humans, especially with respect to lung cancer, by the International Agency for Research on Cancer.[22] In our preliminary analysis, we confirmed that the results were unchanged after adjustment for use of oil or gas heaters without a flue instead of or in addition to use of charcoal or briquette braziers. Another model was applied to additionally adjust for the smoking status of the parents during the childhood of the participants (smoking/nonsmoking), daily consumption of vegetables other than green and yellow vegetables (yes/no), occupation (experience in occupations with potential exposure to gases, fumes, or dust or not), and health insurance as an indicator of socioeconomic status (4 categories: national health insurance, government or union-managed health insurance, mutual aid associations health insurance, others). All adjusted variables were based on the baseline survey. Analyses stratified by sex and smoking status and analyses excluding participants with a history of respiratory diseases were also performed. In the analyses stratified by sex and smoking status, we examined only male current smokers, male former smokers, and female never smokers, because the numbers of participants in the other strata were small.