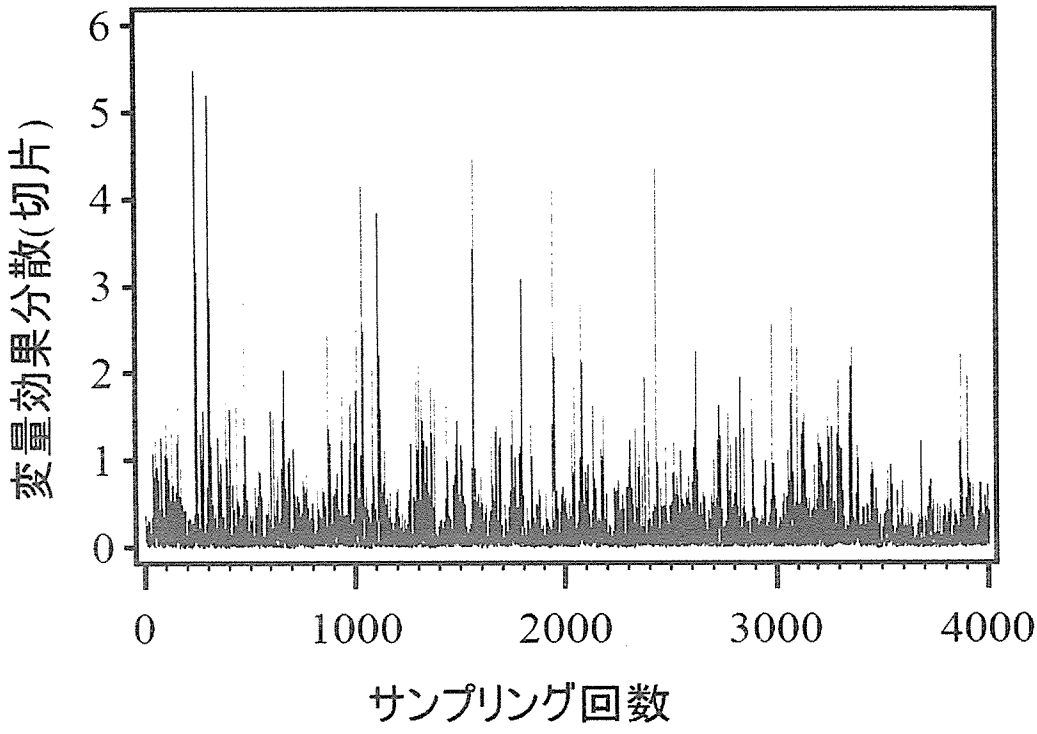

図 2 変量効果分散(切片)のサンプリングパス

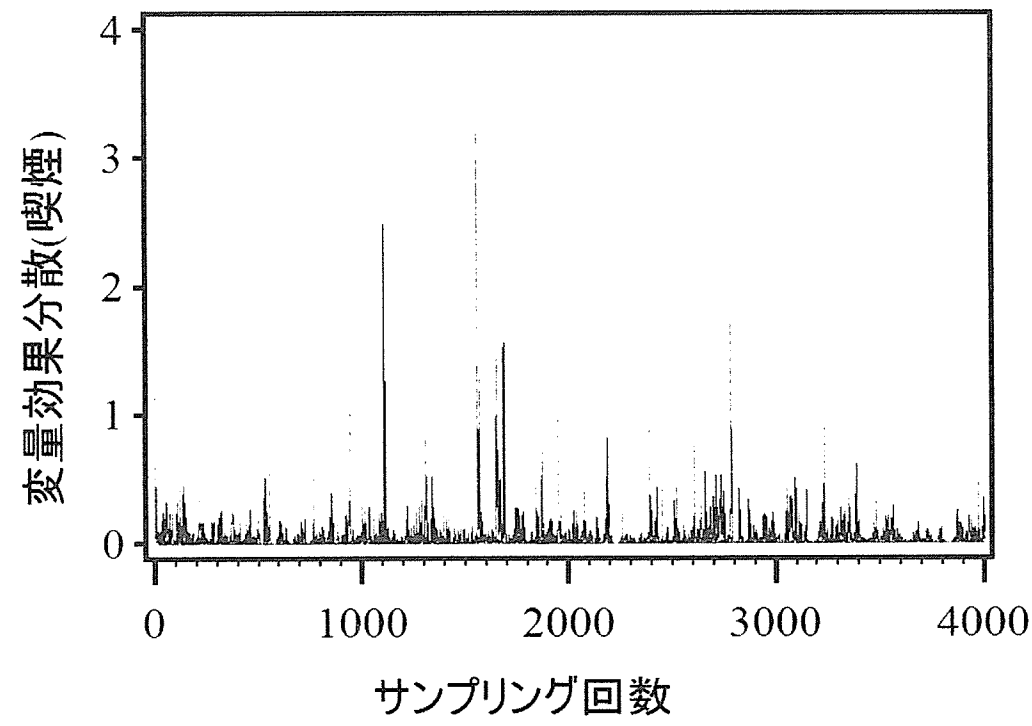

図 3 変量効果分散(喫煙)のサンプリングパス

変量効果をモデルに含まない地域を無視した通常のポアソン回帰による推定結果と(1)式のポアソン混合効果モデルを MCMC 法であてはめた結果を表 3.a、3.b に示す。MCMC 法による各パラメータの事後分布の要約は、固定効果パラメータに関しては、それぞれ 6,000 個のサンプルから求めたハザード比、その 2.5%点と 97.5%点に基づく 95%区間幅、変量効果分散に関しては中央値と標準偏差で示した。Gelman and Rubin(1992)の収束判断指標の値はいずれのパラメータもその推定値は 1 となり、2,000 回目以降のサンプルはそれぞれの周辺分布からのサンプルとみなせ、収束は十分であると判断した。

固定効果パラメータの推定結果に関しては、いずれのリスク因子においても、通常のポアソン回帰と地域差を考慮した MCMC 法による解析で、ハザード比の値が大きく異なることはなかった。脳卒中発症に対する喫煙の効果は、MCMC 法による結果では、男性でハザード比 1.56（95%区間幅：1.21, 1.99）、女性ではハザード比 1.38（95%区間幅：0.82, 2.31）となった。

表 3.a　男性の解析結果(固定効果)

	MCMC法	ポアソン回帰
パラメータ	ハザード比(95%区間幅)	ハザード比(95%信頼区間)
喫煙	1.56(1.21,1.99)	1.55(1.24,1.94)
年齢	2.80(2.22,3.50)	2.84(2.27,3.55)
SBP	2.46(1.98,3.05)	2.43(1.95,3.03)
BMI	1.03(0.81,1.31)	1.05(0.82,1.35)
飲酒	0.96(0.81,1.13)	0.96(0.76,1.21)
糖尿病	1.79(1.37,2.35)	1.82(1.36,2.44)

表 3.b　女性の解析結果(固定効果)

	MCMC法	ポアソン回帰
パラメータ	ハザード比(95%区間幅)	ハザード比(95%信頼区間)
喫煙	1.38(0.82,2.31)	1.35(0.88,2.07)
年齢	3.33(2.64,4.21)	3.45(2.79,4.28)
SBP	2.33(1.87,2.90)	2.30(1.85,2.85)
BMI	1.25(1.00,1.55)	1.33(1.07,1.64)
飲酒	0.87(0.60,1.28)	0.83(0.56,1.24)
糖尿病	1.29(0.91,1.85)	1.41(0.99,2.00)

地域間差の大きさを表す変量効果分散の推定値は、男女いずれにおいてもベースライン分散（d_{11}）のほうが喫煙効果分散（d_{22}）よりも大きな値を示しており、ベースライン、喫

煙効果どちらにおいても男性より女性のほうが大きな値を示していた。変量効果パラメータに対しては平均ゼロの正規分布を仮定しているので、脳卒中発症に対するベースライン地域間差は、ハザード比の95%区間で、男性において $\exp(\pm 1.96 \times 0.08^{0.5}) = (0.57,1.74)$、女性において $\exp(\pm 1.96 \times 0.23^{0.5}) = (0.39, 2.56)$程度のバラツキを示すことがわかる。一方、喫煙効果に関する同様の地域間差の大きさは、男性で（0.82, 1.22）、女性で（0.60, 1.68）であり、ベースライン地域間差に比べてバラツキが小さいことがわかる。

表 4.a　男性の変量効果の分散の推定

パラメータ(分散成分)	対数ハザード(SD)
d11	0.08(0.23)
d12	0.00(0.05)
d22	0.01(0.07)

表 4.b　女性の変量効果の分散の推定値

パラメータ(分散成分)	対数ハザード(SD)
d11	0.23(0.55)
d12	-0.02(0.26)
d22	0.07(0.49)

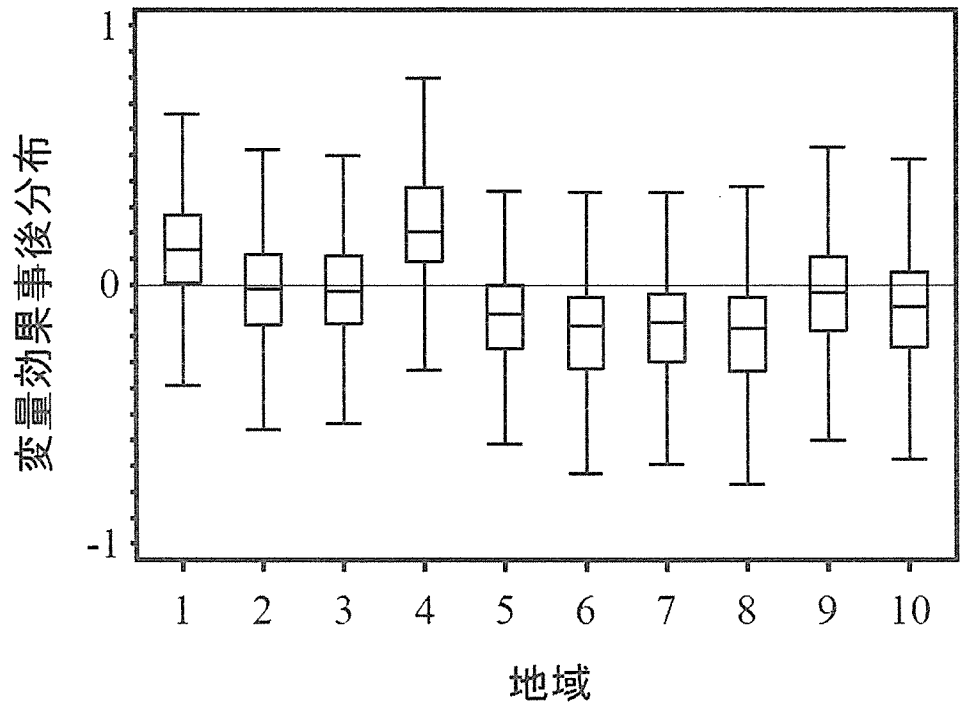

図 4.a　男性の変量効果事後分布(切片)の箱ひげ図

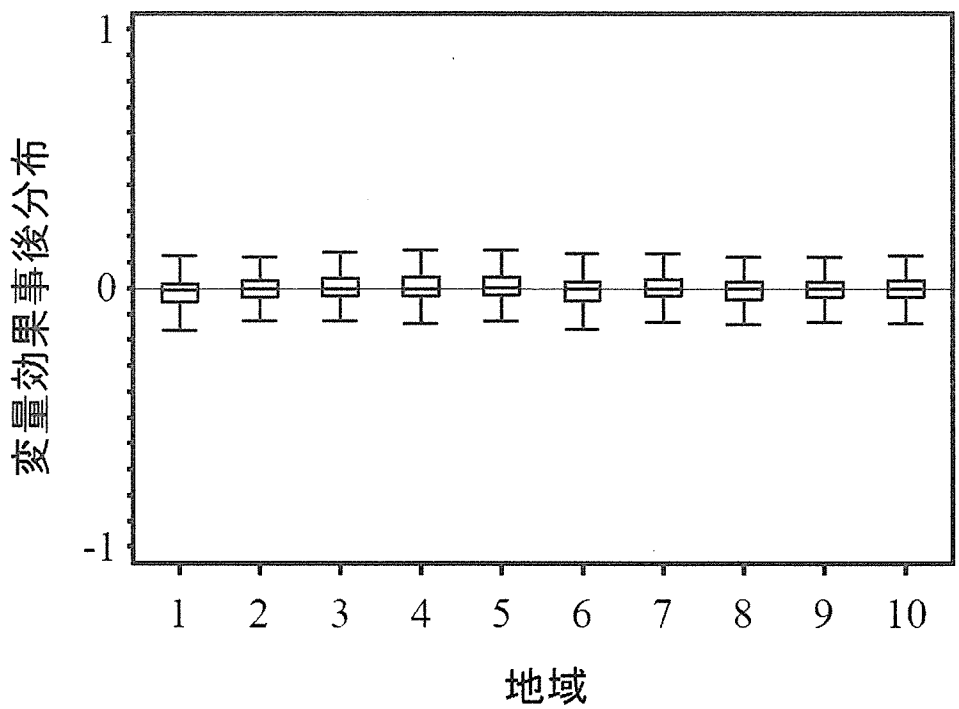

図 4.b　男性の変量効果事後分布(喫煙)の箱ひげ図

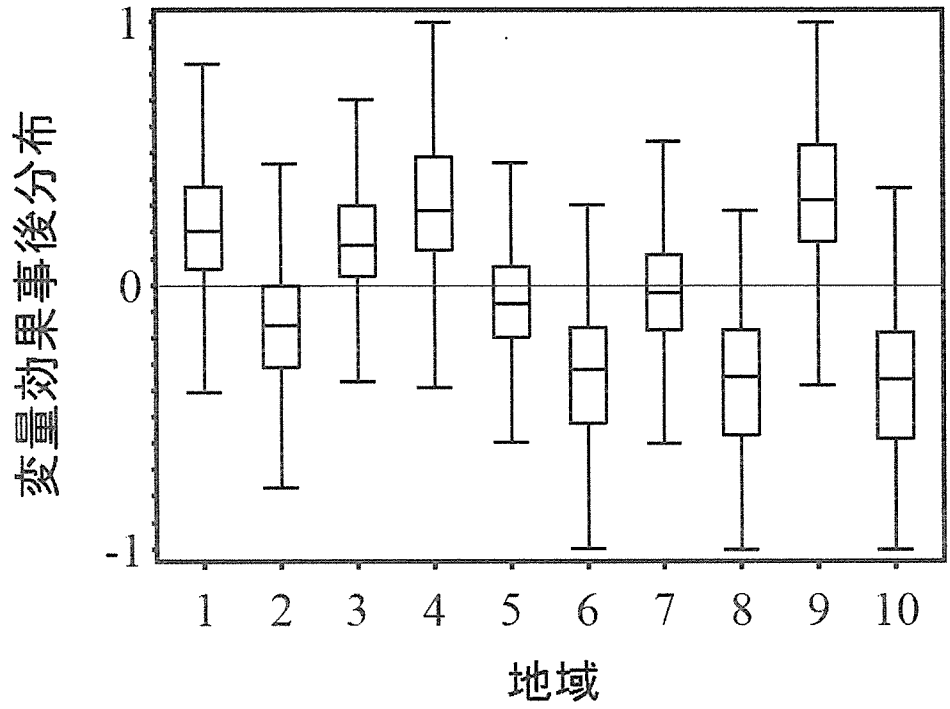

図 5.a　女性の変量効果事後分布(切片)の箱ひげ図

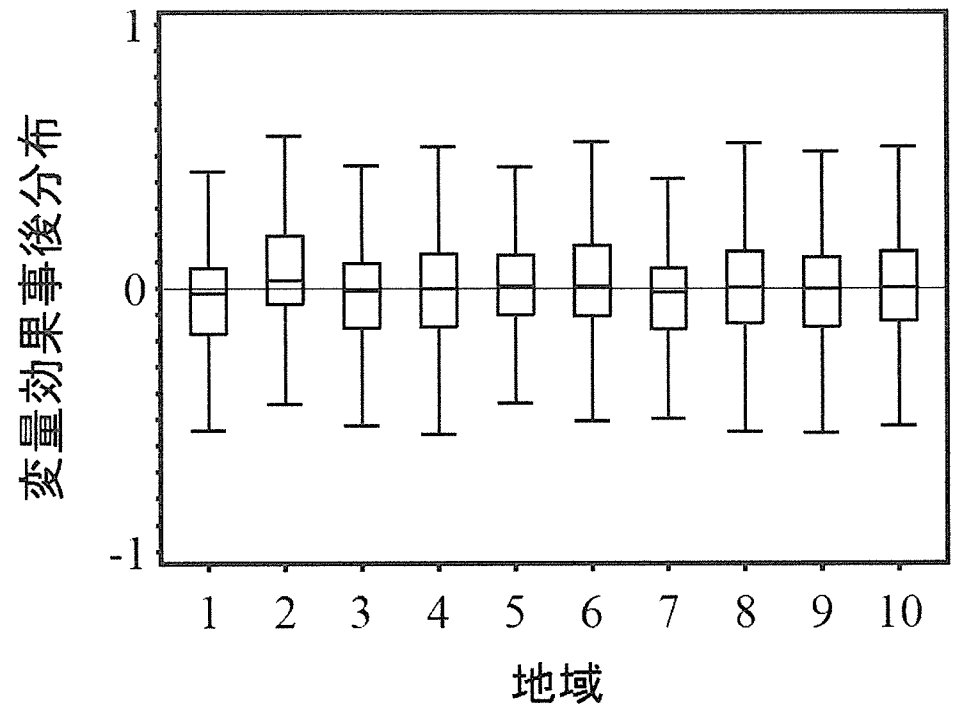

図 5.b　女性の変量効果事後分布(喫煙)の箱ひげ図

図 4.a に男性の地域毎のベースラインリスク、図 4.b に喫煙効果に関する箱ひげ図を図示する。横軸が個々の地域で 1 番から 10 番までの地域に対応し、図 4.a では縦軸がベースライン地域差（b_{0i}）の事後分布、図 4.b では喫煙効果（b_{1i}）の事後分布を表す。これらの図から、ベースラインリスクに関しては推定誤差を考慮しても、ある程度の地域間差が存在することがわかる一方、いずれの地域も喫煙効果に関するバラツキは、ベースラインリスクよりも小さく、地域間でその大きさは一様と言えることがわかる。

図 5.a、5.b に女性についての各変量効果の事後分布を示す。男性に比べパラメータの推定誤差が大きい傾向があるものの、喫煙に関する地域間差は男性と同様にベースラインリスクよりも小さく、地域間でその大きさは一様と言えることがわかる。

3.4 考察

本解析では複数のコホートデータを統合した疫学研究データにおいて、地域間差を検討するためにポアソン混合効果モデルを用い、Gibbs sampling によりそのパラメータ推定を行った。このモデルは、多施設臨床試験データ(Matsuyama et al. 1998)や経時データの解析(Zeger and Karim, 1991)においてすでに利用されているが、そのようなデータと比較して、本解析で扱った JALS0 次研究データは対象者数が非常に多い一方、イベント数が少ないという特徴を有している。そのような現実の疫学データに、ベースラインだけでなくリスク因子の効果に関する地域差も考慮したモデルを当てはめ、地域間差を検討した研究は少なくともわが国にはこれまで存在していない。

JALS データに提案したモデルを当てはめた解析の結果、脳卒中発症に関するベースラインリスクに大きな地域間差が見られた。男性においては、特に、地域 1(北海道)、4(岩手)における発症率が高く、地域 5(茨城)、6(滋賀 1)、7(大阪)、8(愛媛)における発症率は低い傾向にあった。この地域間差の原因を探索的に検討するためにメタ回帰を行なった。メタ回帰とは、もともとはメタアナリシスにおいて個々の研究における結果の食い違いの原因を検討するための方法であるが、本解析においては、各地域のベースラインに関する変量効果推定値を結果変数、各地域の特性を表す変数を説明変数とした回帰分析に相当する。今回は、地域特性として、地域ごとの解析対象者数、平均追跡年数、対象地域が北海道を含む東北地方かそれ以外か、研究開始時期が 80 年代か 90 年代かの 4 つの変数を考えた。解析は、結果変数の推定値の標準偏差の逆数を重みとした重み付き線形回帰分析を用いた。結果は割愛したが、男性において、研究開始時期が 90 年代のコホートのほうがベースラインリスクが高い傾向にあったが、その他の要因はベースラインリスクと関連していなかった。今後、地域ごとの特性を表すより適切な変数を考え、観察されたベースラインリスクに関する地域間差の原因を検討していく必要がある。例えば、本研究におけるデータでは、脳卒中発症に対する診断基準が地域間で統一されていない。このことに起因する脳卒中発見率（detection rate）の地域間での違いが、ベースライン地域間差に大きく関係していると

も考えられる。今後、統一した診断基準のもとで得られたデータに対して、本研究と同様のモデルを当てはめ、発見率の違いが結果に与える影響を検討していく必要がある。

喫煙効果に関する地域間差は、ベースラインリスクに比べて小さく、各地域の変量効果の事後分布はどの地域でも一様なものとなった。つまり、喫煙が脳卒中発症に与える影響は、対象地域によらず一定であり、その効果の大きさの地域選択に関する一般化可能性の高さが示唆されたといえる。男女いずれにおいても同様の傾向であったが、女性の方が若干バラツキが大きな結果となった。これは、女性は男性に比べ喫煙者の割合が少なく、脳卒中発症者数も少ないことから、パラメータの推定精度が男性ほど高くなかったことが原因と思われる。

今回のポアソン混合効果モデルをJALSデータに適用した結果、SAS（NLMIXEDプロシジャ）などの既存の統計解析パッケージではパラメータ推定が出来なかったのに対し、Gibbs sampling では比較的安定した結果を得ることが出来た。混合効果モデルにおけるパラメータ推定では、一般に変量効果に対する分散の推定が困難であるとされている(Diggle, 1994）。Gibbs samplingの推定結果からわかるように、JALSデータにおける分散推定値はゼロの近傍であり、これは分散に対するパラメータ空間の境界である。このことが既存の解析プログラムで採用している尤度近似アプローチによって推定が不可能であった理由と考えられる。これに対し、今回採用したGibbs sampling法によるパラメータ推定は、変量効果分散に対しては、逆ウィッシャート分布からの乱数を利用しているだけなので、分散パラメータが負の値を示すということは理論的にありえず、ゼロの近傍でも問題なくサンプリングが行なうことができる。この点で、MCMC法を用いた地域間差をモデル化したパラメータ推定は変量効果のバラツキ（地域間差）の大小にかかわらず、適用可能な柔軟性のある方法ということが出来る。

しかし、Gibbs sampling による推定方法の問題点として、近似尤度法に比べて推定結果を得るために要する計算時間が非常に多くかかるということが挙げられる。例えば本解析において、男性の解析結果を得るために、CPU : Pentium M 1.1GHz、メモリ：1.24GB、OS : Windows XP professional 環境で約8時間を要した。今後、より効率的な解析プログラムを開発していくことが望まれる。特に、変量効果パラメータに対するサンプリングステップで採用したrejection samplingは、一般に効率が高くないことが知られており、その方法を改良したサンプリング方法であるAdaptive Rejection sampling(Gilks and Wild, 1992)を適用することが考えられる。しかし、現在Adaptive Rejection samplingは変量効果の次元が1次元であるときのみ適用可能である手法なので、2次元以上の場合の拡張が今後の課題といえる。計算速度そのものの向上を目的とするならば、C言語やFortranなどよりシンプルなコンピュータ言語で実装することや、何らかの並列計算法の利用も今後の検討課題として挙げることが出来る。

今回は、脳卒中発症に対する喫煙効果の地域間差の解析に焦点を絞ったが、収縮期血圧と地域の交互作用など、喫煙以外の変数に関しても連続・離散の変数の型によらず同様の

解析が可能である。実施される研究、地域ごとに結果が大きく食い違う状況に対して、今回紹介した方法は、得られた結果の解釈をする上でも、結論の強さを議論する上でも有用な方法であり、様々なエンドポイントやリスク因子に関して同様の検討をしていくことが可能である。

3.5 結論

疫学研究における地域間差を評価するための解析モデルとして、地域を変量効果とみなし、ベースライン及びリスク因子の効果に関する2つの地域差をモデルに取り込んだポアソン混合効果モデルを仮定し、解析を行なった。このモデルをJALS0次研究データに当てはめ、Gibbs sampling を用いて推定を行い、脳卒中発症に対する喫煙効果の地域間差を検討した。その結果、男女いずれにおいても、脳卒中発症に関するベースラインリスクには地域間差が認められたものの、喫煙効果に関する地域間差は小さく、その大きさはいずれの地域においても一様であることが示された。

4. まとめ

今回は複数のコホートデータを統合に関する統計学的手法について、各地域（コホート）の効果を変量効果として考慮した混合効果モデルによる解析の方法論について紹介した。その方法を実際の大規模疫学研究であるJALSの0次研究データに適用し、結果の解釈や方法論についての考察を行なった。複数のコホートデータからなる疫学研究では地域ごとでエンドポイントに与えるリスク因子の影響が異なった場合、地域をプールした解析は結果にバイアスを含むことが予想される。そのため、今回紹介した方法を用い、地域を明示的にモデルに含めた解析で地域間差の有無を定量的に評価することは重要であると考えられる。JALS0次研究データのように、各地域を層別因子と見なした解析や固定効果と見なした解析が出来るほど十分な情報がデータから得られない場合には、地域を変量効果と見なしMCMC法に基づく推定方法を採用することが選択肢の一つとして考えられ、実際に適用されることが望ましいと言える。

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Ⅲ. 研究成果の刊行に関する一覧表・別刷

研究成果の刊行に関する一覧表・別刷

（別刷は分担研究報告書及びP295～334参照）

雑誌（英文）

発表者氏名	論文タイトル名	発表誌名	巻号	頁	出版年	本編記載頁
Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Rondo T, Watanabc Y. Koizumi A, Wada Y, Inaba Y, Tamakoshi A; JACC Study Group	Body mass index and Mortality Form Cardiovascular Disease among Japanese Men and Women: the JACC study	Stroke	36	1377-1382	2005	34
Ikeda A, Iso H, Toyoshima H, Fujino Y, Mizoue T, Yoshimura T, Inaba Y, Tamakoshi A; JACC Study Group	The relationships between interest for and participation in health screening and risk of mortality: The Japan Oollaborative Cohort Study	Prev Med	41	767-771	2005	42
Ikeda A, Iso H, Toyoshima H, Kondo T, Mizoue T, Koizumi A, Inaba Y, Tamakoshi A; JACC Study Group	Parental longevity and mortality amongst Japanese men and women the JACC Study	Journal of Internal Medicine	259	285-295	2006	48
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PAPER

Ten year recurrence after first ever stroke in a Japanese community: the Hisayama study

J Hata, Y Tanizaki, Y Kiyohara, I Kato, M Kubo, K Tanaka, K Okubo, H Nakamura, Y Oishi, S Ibayashi, M Iida

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See end of article for authors' affiliations

Correspondence to: Dr Jun Hata, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1 Higashi-ku, Fukuoka 812-8582, Japan; junhata@intmed2.med.kyushu-u.ac.jp

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Background: Very few population based cohort studies have focused on the long term recurrence of stroke.
Objective: To examine 10 year cumulative recurrence rates for stroke in a Japanese cohort according to pathological type and clinical subtype of brain infarction.
Methods: During a 32 year follow up of 1621 subjects ≥40 years of age, 410 developed first ever stroke. These were followed up prospectively for 10 years after stroke onset.
Results: During follow up, 108 (26%) experienced recurrent stroke. The cumulative recurrence rates were 35.3% at five years and 51.3% at 10 years. The 10 year recurrence rates of subarachnoid haemorrhage (SAH), brain haemorrhage, and brain infarction were 70.0%, 55.6%, and 49.7%, respectively; the difference between SAH and brain infarction was significant ($p=0.004$). Most recurrent episodes after SAH or brain haemorrhage happened within a year after the index stroke, whereas recurrence of brain infarction increased consistently throughout the observation period. Cardioembolic stroke had a higher recurrence rate (75.2%) than lacunar infarction (46.8%) ($p=0.049$). The 10 year risk of stroke recurrence increased with age after lacunar or atherothrombotic brain infarction, but not after the other types or subtypes. After atherothrombotic brain infarction, cardioembolic stroke, or SAH, the type and subtype of most recurrent strokes were the same as for the index stroke, but recurrence after lacunar infarction or brain haemorrhage showed divergent patterns.
Conclusions: Japanese people have higher recurrence rates of stroke than other populations. Recurrence rate after a first brain infarct increases consistently through the next 10 years.

Japanese people have high rates of morbidity and mortality from stroke.[1] Among stroke survivors, recurrence is common, resulting in cumulative disability and cognitive dysfunction.[2] Consequently, precise information is needed on the long term rates and determinants of recurrence after first stroke, so that clinical trials can be designed and health care policies for primary and secondary stroke prevention can be established. Most studies on stroke recurrence, reported mainly from Western countries, have been based on stroke registries[3–11] or on series of patients referred to hospitals.[12 13] A truly representative assessment of stroke recurrence in a community would require a prospective cohort of a defined population and an exhaustive follow up system. The Framingham study is the only cohort based examination of both initial and recurrent stroke, but it refers to the recurrence of thrombotic brain infarction only.[14] Stroke is divided into several pathological types. Among them, brain infarction is further classified into several clinical subtypes.[15–17] Very few studies, however, have accurately defined types and subtypes while also evaluating the long term risk of stroke recurrence.[4]

Since 1961, we have been carrying out a prospective cohort study of cardiovascular disease in the town of Hisayama, Japan.[18 19] The most outstanding features of this study are that the causes of death were verified by necropsy and that most of the stroke patients were examined morphologically at necropsy or, before death, by brain imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI). Our aim in this study was to estimate 10 year cumulative recurrence rates after first ever stroke in the community of Hisayama, using data stratified by sex, age, stroke type, and, in cases of brain infarction, the clinical subtype.

METHODS

Subjects and follow up surveys

In 1961, we carried out a screening examination among Hisayama residents and established a cohort consisting of 1621 stroke-free subjects aged ≥40 years (88.1% of the total population in this age range). These subjects were then followed up for 32 years, from 1 November 1961 to 31 October 1993. A detailed description of the study methods has been published previously.[18 19] In brief, we collected information about new cardiovascular events through a daily monitoring system established by the study team, local practitioners, and the town government. When we suspected a patient was having a new neurological symptom or a new deterioration of an already existing symptom, one of the physicians participating in the study would carefully evaluate the subject and try to obtain information by further diagnostic examinations, including lumbar puncture, cerebral angiography, or recent brain CT or MRI. During the 32 year period, all but two subjects were followed up and 1063 subjects died. Of those who died, 861 (81.0%) underwent necropsy.

The study was conducted with the approval of the human ethics review committee of Kyushu University Graduate School of Medical Sciences.

First ever stroke

Stroke, defined as the sudden onset of a non-convulsive and focal neurological deficit persisting for over 24 hours, was classified into four pathological types: brain infarction, brain haemorrhage, subarachnoid haemorrhage, and undetermined. Brain infarction was further divided into four clinical subtypes: lacunar infarction, atherothrombotic brain

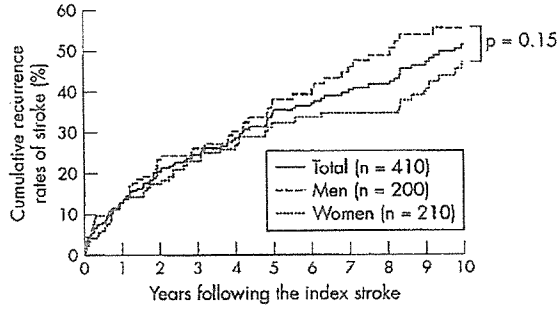

Figure 1 Kaplan–Meier estimates of cumulative recurrence rates of stroke for all subjects and for all subjects divided by sex. Deaths without stroke recurrence were censored.

infarction, cardioembolic stroke, and undetermined. These types and subtypes were defined on the basis of the *Classification of Cerebrovascular Disease III* proposed by the National Institute of Neurological Disorders and Stroke (USA).[15] The subtypes of ischaemic stroke were classified by TOAST (trial of Org 10172 in acute stroke treatment)[16] and by the Cerebral Embolism Task Force.[17] A detailed method of classifying stroke has been published previously.[12] The diagnosis and classification of stroke in our study were based on clinical history, neurological examination, all available clinical information (including brain CT or MRI), and necropsy findings.

During the 32 year follow up, we identified 410 first ever stroke events (200 men and 210 women, mean (SD) age, 73.9 (10.1) years), and divided them into 298 cases of brain infarction, 73 of brain haemorrhage, 35 of subarachnoid haemorrhage, and four undetermined. The cases of brain infarction by subtype consisted of 167 lacunar infarcts, 62 atherothrombotic brain infarcts, 56 cardioembolic strokes, and 13 undetermined.

Recurrent stroke

The definition of recurrent stroke was the same as that of index stroke, but with an additional criterion: there had to be either a new focal neurological deficit or a new deterioration of a previous deficit that was not attributed to brain oedema, haemorrhagic transformation after ischaemia, intercurrent illness, or iatrogenesis. This definition included recurrence in the early stage after the preceding stroke or recurrence in the same vascular territory as the preceding stroke.

We followed up the 410 patients with index stroke from the time of stroke onset until death or 31 August 2003. Under those conditions, all patients completed the follow up period. In the 10 years after the index stroke, 108 patients developed recurrent stroke. Of these, 88 had one recurrent stroke, 13 had two, six had three, and one had four. However, the end point of this study for each subject was the first recurrence.

Morphological evaluation

Brain imaging, including CT or MRI, was carried out in 153 (37%) of the 410 subjects with index stroke and in 43 (40%) of the 108 subjects with recurrent stroke. Necropsy findings were available in 332 (84%) of the 394 deceased stroke patients. As a result, morphological evaluation, including brain imaging or necropsy, was undertaken in 376 (92%) of the index stroke patients and 102 (94%) of the recurrent stroke patients until 31 August 2003.

Because we began collecting data on stroke subjects in 1961, imaging examinations of the brain and heart were nonexistent in the early study period. However, we compensated

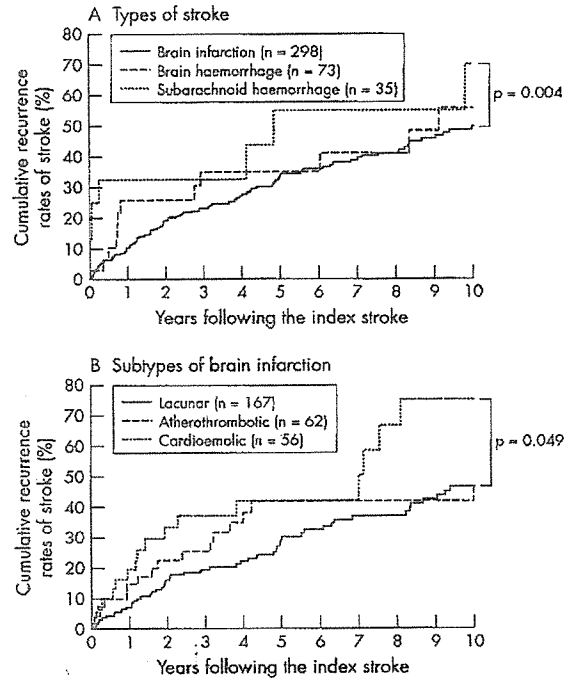

Figure 2 Kaplan–Meier estimates of cumulative recurrence rates of stroke according to stroke type (A) and, in cases of brain infarction, the subtype (B). Deaths without stroke recurrence were censored.

for this disadvantage by carrying out necropsy examinations on the vast majority of deceased patients. We reviewed the brains to evaluate the site, size, and pathological features of the stroke. We also investigated the heart and major vessels in detail—including the aorta, carotids, vertebrobasilar arteries, and the circle of Willis—in order to identify atherothrombotic stenotic lesions and embolic sources. In cases where the necropsy was carried out a long time after stroke onset, it was important to distinguish brain haemorrhage from brain infarction with haemorrhagic transformation. The latter was usually the result of a cardioembolic mechanism. When an infarcted area was surrounded by deposition of haemosiderin—with either no or mild atherosclerosis of the responsible artery, and given the presence of the embolic source—we considered the stroke lesion to be a brain infarct with haemorrhagic transformation. An old lesion that looked like a slit was considered to indicate a brain haemorrhage, especially if found in the basal ganglia or thalamus.

To classify the subtypes of brain infarction, we considered important the size and location of the infarcted area, the presence of stenosis or occlusion of a responsible cerebral artery, and the embolic source, in addition to clinical information including the disease course. Where multiple asymptomatic infarctions were present, we considered an infarct to be the lesion responsible for the stroke when it was most closely in accord with the neurological findings and disease course in the acute period of the stroke. The criteria for diagnosing brain infarction subtypes were given in full detail in our previous report.[12] When sufficient clinical and morphological information was obtained, a diagnosis of subtype was defined as "definite"; on the other hand, when either type of information was insufficient, the diagnostic level was defined as "probable." Among 298 cases of brain infarction, 272 were definite and 26 probable. In this study,

we present the data on the definite and probable cases together, as these combined data were almost identical to the data for definite cases only.

Statistical analysis

SAS software (version 6.12) was used for statistical analysis. The cumulative recurrence rates of stroke and the 95% confidence intervals (CI) were estimated by the Kaplan–Meier product limit method. The Cox proportional hazards model was used to test differences in recurrence rates as well as to estimate relative risks (RR) and 95% CIs of stroke recurrence.

RESULTS

Recurrence rates of stroke

Figure 1 shows the Kaplan–Meier estimates of cumulative recurrence rates of stroke for all subjects and for all subjects divided by sex. The recurrence rates (95% CI) at 1, 5, and 10 years were 12.8% (8.9% to 16.6%), 35.3% (29.0% to 41.5%), and 51.3% (43.8% to 58.9%), respectively, for all subjects. For men, these rates were 12.9% (7.3% to 18.5%), 38.1% (28.9% to 47.2%), and 55.6% (44.9% to 66.4%); for women the rates were 12.5% (7.3% to 17.6%), 32.3% (23.8% to 40.9%), and 47.1% (36.5% to 57.6%). The recurrence rates were slightly higher for men than for women, but the overall difference was not statistically significant ($p = 0.15$).

Figure 2, panel A, shows cumulative recurrence rates of stroke by type of index stroke. The recurrence rates at 1, 5, and 10 years were 10.0% (6.3% to 13.8%), 34.1% (27.3% to 40.9%), and 49.7% (41.4% to 57.9%) after brain infarction; 25.6% (9.0% to 42.2%), 34.9% (16.0% to 53.8%), and 55.6% (32.2% to 79.1%) after brain haemorrhage; and 32.5% (10.3% to 54.6%), 55.0% (25.6% to 84.4%), and 70.0% (39.0% to 100%) after subarachnoid haemorrhage, respectively. The 10 year recurrence rate of subarachnoid haemorrhage was significantly higher than that of brain infarction (RR = 2.89 (95% CI, 1.40 to 5.97); $p = 0.004$). Also, brain haemorrhage recurred at a slightly higher rate than brain infarction, but the difference was not statistically significant ($p = 0.52$). Annual recurrence rates after brain infarction were about 10% per year in the first two years and consistently about 4% per year afterward. On the other hand, 58.3% of recurrent episodes took place within a year after brain haemorrhage, and 66.7% within three months after subarachnoid haemorrhage.

Figure 2, panel B, shows the cumulative recurrence rates of stroke by clinical subtype of brain infarction. The recurrence rates at 1, 5, and 10 years were 7.2% (3.1% to 11.2%), 30.4% (22.1% to 38.7%), and 46.8% (36.6% to 56.9%) after lacunar infarction; 14.8% (4.5% to 25.0%), 42.0% (25.5% to 58.5%), and 46.9% (29.2% to 64.5%) after atherothrombotic brain infarction; and 19.6% (6.3% to 32.8%), 42.2% (23.8% to 60.6%), and 75.2% (52.6% to 97.8%) after cardioembolic stroke, respectively. Cardioembolic stroke had a significantly higher risk of 10 year recurrence than lacunar infarction (RR = 1.76 (95% CI, 1.00 to 3.11); $p = 0.049$). The recurrence rate of atherothrombotic brain infarction was slightly higher than that of lacunar infarction, but the difference was not statistically significant ($p = 0.59$).

Figure 3 shows the cumulative recurrence rates of stroke by age. The 10 year risk of stroke recurrence was lowest in the youngest age group (40 to 59 years) and increased with age. Table 1 shows the relative risks of stroke recurrence among age groups during 10 years for each type and subtype of index stroke. The 10 year risk of stroke recurrence after brain infarction was lowest in the youngest age group and increased with age. For brain haemorrhage or subarachnoid haemorrhage, on the other hand, there was no significant relation between age and recurrence rates. Among the subtypes of brain infarction, the 10 year risk of recurrence after lacunar and atherothrombotic brain infarction was lowest in the youngest age group and increased with age, whereas for cardioembolic stroke there was no significant relation between age and recurrence rates.

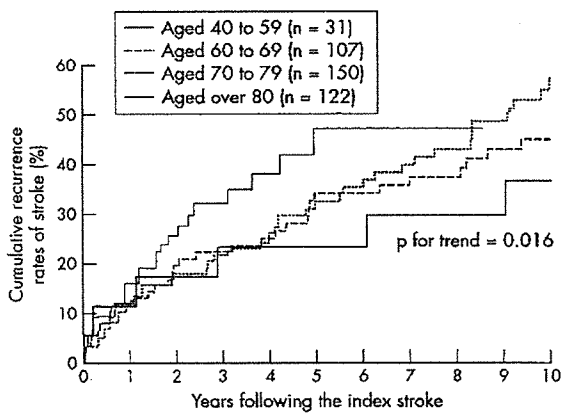

Figure 3 Kaplan–Meier estimates of cumulative recurrence rates of stroke for all subjects divided by age. Deaths without stroke recurrence were censored.

Patterns of stroke recurrence

To evaluate patterns of stroke recurrence, table 2 shows the numbers and frequencies of first recurrent stroke by pathological types and clinical subtypes according to the type of index stroke. Most recurrent strokes after atherothrombotic brain infarction, cardioembolic stroke, or subarachnoid haemorrhage were the same type or subtype as the index stroke. On the other hand, recurrence after lacunar infarction or brain haemorrhage showed divergent patterns. The 51 patients who had recurrent stroke after lacunar infarction were divided as follows: 18 cases (35%) had a second lacunar infarction, 16 (31%) had atherothrombotic brain infarction, nine (18%) had brain haemorrhage, and six (12%) had cardioembolic stroke. Among the 12 recurrent cases of brain haemorrhage, seven (58%) had a second brain haemorrhage, three (25%) had lacunar infarction, and two (17%) had atherothrombotic or cardioembolic infarction.

DISCUSSION

One of the strengths of our study is that we investigated almost all stroke events occurring in a community based prospective cohort. Our study design eliminated the selection bias encountered in stroke registries or in series of hospital inpatients. Another strength is that recurrence rates were estimated up to 10 years after a subject's first ever stroke.

Recurrence rates of stroke

Three previous reports from stroke registries in Australia[3] and Britain[4 5] have reported five year cumulative stroke recurrence rates of 16.6% to 29.5%. In comparison, our study's five year cumulative stroke recurrence rate was 35.3%. There might be several reasons for this difference. First, there was a difference in methodology. The studies of the other three stroke registries all used a single set of criteria, which excluded vascular events occurring in the first 21 days after the index stroke unless such an event was clearly in a different vascular territory.[3–5] On the other hand, our study excluded neither early recurrence (10 cases within 21 days) nor recurrence in the same vascular territory. Second, race might greatly influence stroke recurrence. In our study,

Table 1 Relative risks and 95% confidence intervals of stroke recurrence during 10 years by age in each type or subtype of index stroke

	Age group (years)				
	40 to 59	60 to 69	70 to 79	80 and over	p Value
Index stroke	RR	RR (95% CI)	RR (95% CI)	RR (95% CI)	for trend
All types of stroke	1.0	1.3 (0.5 to 3.0)	1.6 (0.7 to 3.8)	2.2 (0.9 to 5.4)	0.016
Brain infarction	1.0	2.0 (0.6 to 6.5)	2.5 (0.7 to 8.1)	3.9 (1.1 to 13.1)	0.002
Lacunar infarction	1.0	2.2 (0.5 to 9.4)	2.6 (0.6 to 11.1)	4.8 (1.0 to 22.2)	0.022
Atherothrombotic brain infarction	1.0*		1.8 (0.4 to 7.5)	4.7 (1.2 to 18.6)	0.001
Cardioembolic stroke	1.0	0.8 (0.1 to 7.3)	1.4 (0.2 to 12.3)	0.4 (0.0 to 4.1)	0.51
Brain haemorrhage	1.0	0.6 (0.0 to 6.3)	1.2 (0.2 to 10.3)	2.1 (0.2 to 24.3)	0.71
Subarachnoid haemorrhage	1.0	1.0 (0.2 to 6.0)	0.7 (0.1 to 4.4)	0.0	0.60

*Two age groups (40 to 59 and 60 to 69) were combined, as there were no recurrences after atherothrombotic brain infarction in the 40 to 59 age group.
CI, confidence interval; RR, relative risk.

haemorrhagic stroke—including brain haemorrhage and subarachnoid haemorrhage—recurred at higher rates than brain infarction, and the proportion of haemorrhagic stroke (26%) among all types was higher than those found in the three registries in Western countries (14% to 19%).[3–5] In addition, as Asians, including Japanese, have a higher stroke incidence than Europids,[1] they might also have higher rates of stroke recurrence.

In our study, most recurrent episodes occurred within a year after the index haemorrhagic stroke. This may indicate the importance of controlling risk factors and of treating the patient to prevent recurrence without delay in the first days and months after the onset of haemorrhagic stroke. On the other hand, cumulative recurrence rates after brain infarction, especially lacunar infarction, increased steadily during our 10 year study period. The Oxfordshire Community Stroke Project[6] also showed that the recurrence rate after lacunar infarction was low and almost constant throughout the follow up period. Arteriosclerosis, which is thought to progress consistently for a long period, may be related to recurrent thrombotic infarction. Thus careful observation and adequate treatment to prevent recurrence are needed for a long time after brain infarction.

Several studies have focused on the relations between brain infarction subtypes and the risks of recurrent stroke,[3 7–10 12] but their findings are equivocal. Some of those studies have claimed that the subtype of brain infarction is not a predictor of long term recurrence,[3 7 8] while others showed that the highest risk of recurrence is with atherothrombotic brain infarction.[9 10 12] In our study, cardioembolic stroke had the highest risk of recurrence among the three major subtypes of brain infarction. This is probably attributable to our inclusion of early recurrent episodes, which were often observed after cardioembolic stroke.[20 21]

In some studies,[3 11] aging was found to be a predictor of stroke recurrence. In the present study, the risk of recurrence after first ever lacunar or atherothrombotic brain infarction was lowest in the youngest age group and then increased with age. Aging would accelerate atherosclerotic changes in major cerebral arteries and arteriolosclerotic changes in penetrating arteries, thus increasing the risk of recurrent stroke.

Patterns of stroke recurrence

In the present study, the types or subtypes of most recurrent strokes after atherothrombotic brain infarction, cardioembolic stroke, or subarachnoid haemorrhage were the same as those of the index stroke. On the other hand, recurrence after lacunar infarction or brain haemorrhage showed divergent patterns. This finding was also emphasised in some previous reports.[4 11]

Several aetiological mechanisms for lacunar infarction have been proposed[22–24]: lipohyalinosis or microatheroma in a penetrating artery; branch-atheromatous disease, which is located in basilar or middle cerebral arteries and occludes the origins of one or more penetrating arteries; and microembolism from carotid or cardiac disease. These multifactorial aetiologies would support divergence in the type and subtype of recurrent stroke after lacunar infarction. Our findings denote the importance of evaluation to detect any large vessel disease or embolic source, even in patients with lacunar infarction.

Table 2 The numbers and frequencies of first recurrent stroke by pathological types and clinical subtypes according to type of index stroke

	Type or subtype of recurrent stroke								
		Subtype of BI							
Type or subtype of index stroke	All BI	LA	AT	CE	UND-BI	BH	SAH	UND	Total
Brain infarction	74 (85%)					10 (11%)	–	3 (3%)	87 (100%)
Lacunar infarction		18 (35%)	16 (31%)	6 (12%)	–	9 (18%)	–	2 (4%)	51 (100%)
Atherothrombotic brain infarction		1 (6%)	14 (82%)	–	1 (6%)	1 (6%)	–	–	17 (100%)
Cardioembolic stroke		–	–	16 (94%)	1 (6%)	–	–	–	17 (100%)
Undetermined subtype of BI (UND-BI)		–	–	–	1 (50%)	–	–	1 (50%)	2 (100%)
Brain haemorrhage	5	3 (25%)	1 (8%)	1 (8%)	–	7 (58%)	–	–	12 (100%)
Subarachnoid haemorrhage	2	1 (11%)	1 (11%)	–	–	1 (11%)	6 (67%)	–	9 (100%)
Undetermined type of stroke	–	–	–	–	–	–	–	–	0 (0%)

Percentages are the proportions of types or subtypes of recurrent stroke calculated using the numbers of total recurrent stroke as the denominators.
AT, atherothrombotic brain infarction; BH, brain haemorrhage; BI, brain infarction; CE, cardioembolic stroke; LA, lacunar infarction; SAH, subarachnoid haemorrhage; UND, undetermined.

Hypertension is a major risk factor for both lacunar infarction and brain haemorrhage, and lesions of all lacunar infarcts and most brain haemorrhages in our patients were located in brain areas that have the common feature of penetrating arteries, such as the basal ganglia, thalamus, and pons. These similarities would support the overlap between lacunar infarction and brain haemorrhage in recurrent stroke types.

Study limitations

There are several potential limitations to the findings in our study. First, we enrolled stroke cases that developed among an inception cohort during 32 years of follow up. The prevalence of cardiovascular risk factors and the risk of stroke recurrence may have changed widely during this long term observation period.[26] Secular trends in stroke recurrence should be examined, and we will do so in another study. Second, the study did not consider the effects of cardiovascular risk factors or those of medical or surgical treatment. Thus our estimates for the risk of stroke recurrence are probably quite conservative. Third, brain imaging was available in only 37% of the index stroke cases. However, we collected available clinical information on both index and recurrent strokes in minute detail and carried out necropsies on 84% of deceased stroke patients. We believe that our exhaustive and careful evaluation of the clinical information, as well as the high rate of necropsy, improved the quality and validity of the diagnosis as well as the stroke classification in our study.

Conclusions

Our findings show higher recurrence rates of stroke in a Japanese community than in Western populations. The divergent patterns of stroke recurrence after index lacunar infarction or brain haemorrhage are of interest and importance for the prevention of recurrent stroke, because the Japanese are characterised by high morbidity of lacunar infarction and brain haemorrhage. The consistent increase in cumulative recurrence rates during the long observation period and the higher recurrence rates after index brain infarction among older patients are both important for medical care. We believe that these findings will contribute to a better understanding of stroke recurrence in the Japanese, who are considered to be at greater risk of stroke than other populations.

Authors' affiliations

J Hata, Y Tanizaki, Y Kiyohara, I Kato, M Kubo, K Tanaka, K Okubo, H Nakamura, Y Oishi, S Ibayashi, M Iida, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

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