Epidemiology and Health Policy Research Based on the National Health Insurance Reimbursement Database

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Outlines of my presentation

- **Pharmacoepidemiology: β-blocker and ischemic stroke (***J Hypertens* 2009; 27:174-180**)**
- **Chinese herbal products and urinary tract cancer: case-control study** (*J Natl Cancer Inst 2009; revised and under review*)
- **Monitoring of drug usage: Treatment of uncomplicated hypertension (ARB vs. diurectics** *BMC Health Serv Res* 2008;8:133**)**
- **Cost-effectiveness analysis: Different treatment of liver cancer** (*J Hepatol 2009; submitted*)

Differential risks of stroke in pharmacotherapy on uncomplicated hypertensive patients?

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Objective To determine the risk of stroke associated with various antihypertensive drugs among previously uncomplicated hypertensive patients.

Methods A retrospective cohort study was undertaken, covering the period from 1997 to 2004, of a 1 000 000-person random sample obtained from Taiwan's National Health Insurance reimbursement database. Between January 1999 and December 2004, 29 759 patients aged 30 years or older were identified as newly diagnosed uncomplicated hypertensive cases. They were followed up until the end of 2004. A time-dependent Cox's proportional hazards model was specified to analyze the risk of stroke development.

Results From the 29 759 uncomplicated hypertensive patients, 1078 new cases of stroke were identified and followed up for at least 1 month during the study period, including 654 ischemic stroke cases. After adjustment for various risk factors, the hazard ratio of developing stroke was significantly higher for poor medication compliance (hazard ratio 1.5–1.9), old age, male sex, and comorbid diabetes mellitus and/or other heart diseases. Different categories of antihypertensive medications were not associated with differential effects on stroke development. In the subsequent analysis, we found that patients receiving pharmacotherapy with beta-blockers were 1.3 (95% confidence interval 1.0–1.6) times more likely to develop ischemic stroke than those who had been treated with other types of antihypertensive medication.

Conclusion Poor medication compliance is a key determinant of developing stroke among hypertensive patients. This study suggests that there has been no differential effect of antihypertensive medication on overall risk of stroke, whereas beta-blockers might be associated with more ischemic stroke. Further studies are needed to corroborate this hypothesis. *J Hypertens* 27:174–180

Journal of Hypertension 2009, 27:174–180

Keywords: antihypertensive therapy, cerebrovascular disorders, compliance, National Health Insurance Research Database

Abbreviations: ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; BP, Blood pressure; CCB, Calcium channel blocker; CT, Computerized tomography; ICD-9-CM, the International Classification of Disease, 9th Revision, Clinical Modification; NHI, National Health Insurance

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Received 24 December 2007 Revised 19 August 2008
Accepted 15 September 2008

Objectives

- To assess the risk of stroke development amongst the newly-diagnosed uncomplicated hypertensive patients treated with different antihypertensive drugs in Taiwan
- To determine whether different antihypertensive agents possess differential risks of developing stroke among these patients

Antihypertensive Drugs

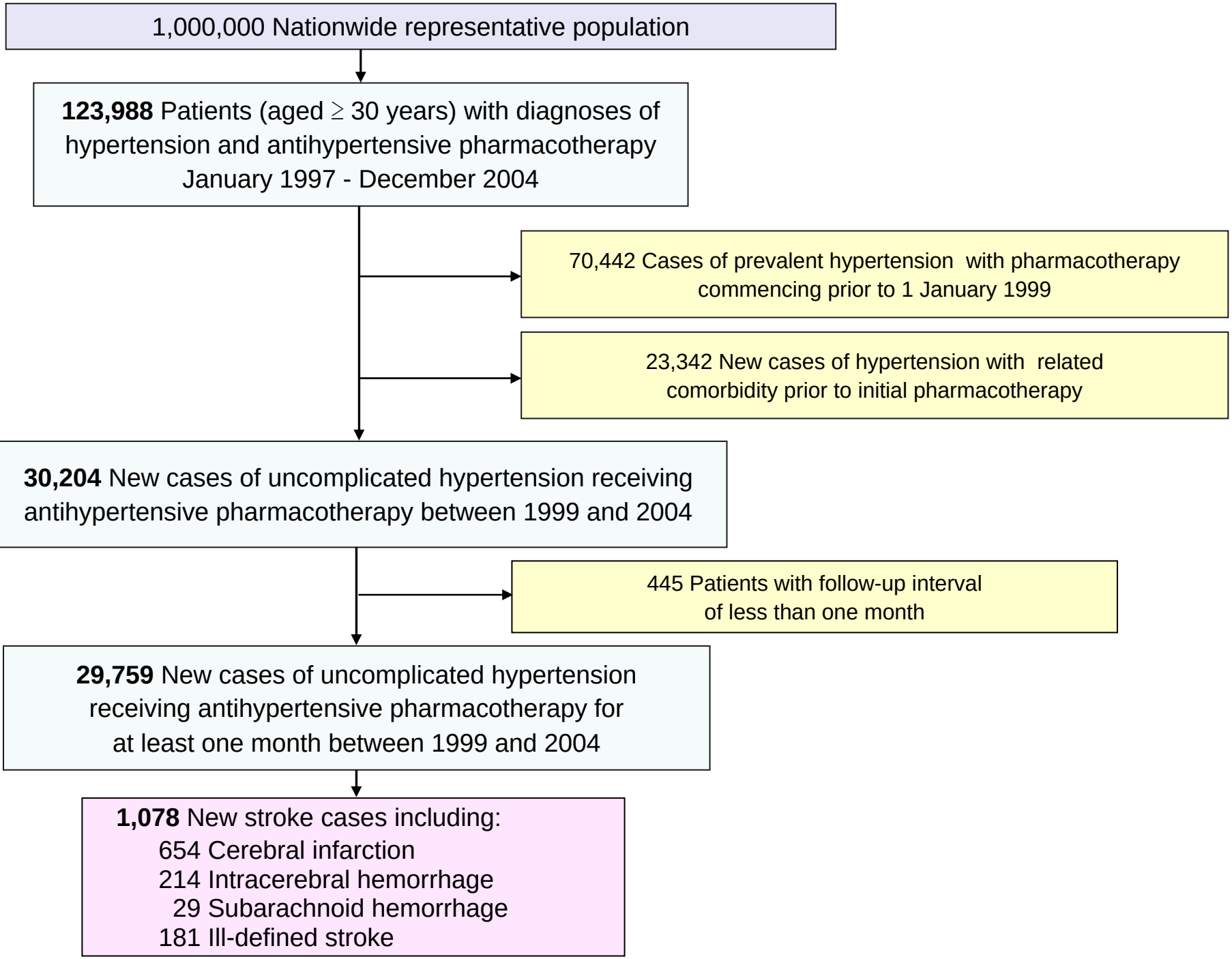
- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin-receptor blockers (ARBs)
- β-Blockers
- Calcium channel blockers (CCBs)
- Diuretics
- Others (including α-blockers).

Study Designs

- A retrospective cohort study using Taiwan's **National Health Insurance Reimbursement Database (1,000,000 persons)** during January 1997 to December 2004
- **53,546 patients – ≧30 years old**, newly diagnosed as hypertension and were prescribed with antihypertensive drugs, were identified after December 31, 1998.

Study Designs

- Excluding those who had had other related **comorbidities** (DM, ischemic heart diseases and other forms of heart disease, cerebrovascular diseases, and renal disorders) before initial treatments for essential hypertension
- **29,759** uncomplicated hypertensive patients, $\geqq$30 years old, during January 1999 to December 2004


1,000,000 Nationwide representative population
123,988 Patients (aged ≥ 30 years) with diagnoses of hypertension and antihypertensive pharmacotherapy January 1997 - December 2004
70,442 Cases of prevalent hypertension with pharmacotherapy commencing prior to 1 January 1999
23,342 New cases of hypertension with related comorbidity prior to initial pharmacotherapy
30,204 New cases of uncomplicated hypertension receiving antihypertensive pharmacotherapy between 1999 and 2004
445 Patients with follow-up interval of less than one month
29,759 New cases of uncomplicated hypertension receiving antihypertensive pharmacotherapy for at least one month between 1999 and 2004
1,078 New stroke cases including:
654 Cerebral infarction
214 Intracerebral hemorrhage
29 Subarachnoid hemorrhage
181 Ill-defined stroke

Inclusion Criteria

- Diagnoses of hypertension (ICD-9-CM: 401-5, A-Code: A260, A269) for **at least thrice**
- Ever prescribed with antihypertensive drugs
- Age of initial diagnosis $\geqq$ 30 years old
- Initial diagnosis & treatment during 1999-2004
- Follow-up time or onset interval of stroke from first antihypertensive therapy $\geqq$ 30 days
- Prescriptions from ambulatory care claims & prescriptions dispensed at contracted pharmacies

Defining the cases of stroke

- Diagnosed after initiation of anti-hypertensive therapy for uncomplicated hypertension → new case
- Transient ischemic attacks were not included in this study.
  - **Subarachnoid hemorrhage,**
  - **Intracerebral hemorrhage,**
  - **Occlusion of precerebral or cerebral arteries**
  - **Acute, but ill-defined, cerebrovascular disease**

[ICD-9-CM codes: 430-434, 436; or A codes: A290-A293]

Defining the cases of stroke

- To further secure the validity of diagnosis, only those patients diagnosed as stroke after imaging examination by **CT or MRI** in one of the following conditions were considered to be new cases of stroke:
  - **at least once inpatient diagnosis of stroke;**
  - **at least once diagnosis of stroke from emergency room**;
  - **at least thrice outpatient** diagnosis of stroke

Time-dependent variables

- We analyzed the time-dependent variables divided as multiple periods of months, i.e. every 30 days.
- Being designated as ever using that drug in that month for prescription $\geqq$ 7 days, and vice versa
- Time-Dependent Medical Compliance Rate =

$$\frac{\text{(the cumulated months with antihypertensive prescriptions)}}{\text{(the total months beginning with the first antihypertensive prescriptions)}}$$

Statistical analysis

- SAS version 9.1 for Windows
- Time-dependent proportional hazards (Cox) regression model
- The final model was selected by the stepwise method setting the inclusion and exclusion criteria with both *p*'s = 0.10.

Results

- **29,759** newly diagnosed uncomplicated hypertensive patients remained for the final analysis
- **1078 new stroke** cases were identified (**654 ischemic stroke** patients)
- The hazard ratio (HR) was higher for older patients, for male patients and in those with poor medical compliance.

Variable	All types of stroke		Ischemic stroke	
	Case No.	HR* (95% CI)	Case No.	HR† (95% CI)
Age (years)				
30-44	101	1.00 –	43	1.00 –
45-54	196	1.49 (1.17-1.90)	118	2.12 (1.50-3.01)
55-64	270	2.60 (2.07-3.27)	165	3.77 (2.70-5.28)
≥ 65	511	4.75 (3.83-5.88)	328	7.26 (5.28-9.99)
Gender				
Women	388	1.00 –	232	1.00 –
Men	690	1.82 (1.61-2.07)	422	1.90 (1.61-2.23)
Mean number of antihypertensive drugs‡¶				
<1.5 drugs	690	1.00 –	432	1.00 –
≥1.5 drugs	388	1.25 (1.10-1.42)	222	1.09 (0.92-1.29)

Drug compliance rate‡						
≥ 70%	185	1.00	–	126	1.00	–
40-69%	215	1.51	(1.22-1.86)	132	1.37	(1.05-1.78)
20-39%	248	1.79	(1.46-2.20)	156	1.66	(1.28-2.16)
< 20%	430	1.92	(1.58-2.34)	240	1.62	(1.25-2.09)
Comorbidity‡						
DM	98	1.64	(1.33-2.03)	62	1.65	(1.26-2.16)
Other heart diseases	122	1.51	(1.24-1.84)	76	1.48	(1.15-1.89)
Renal diseases	33	1.11	(0.78-1.57)	27	1.47	(0.99-2.17)
Antihypertensive drugs‡						
ACE inhibitors or ARBs	133	0.95	(0.78-1.16)	90	1.05	(0.83-1.33)
Beta-blockers	138	1.04	(0.86-1.27)	98	1.27	(1.00-1.60)
CCBs	188	1.01	(0.85-1.21)	128	1.13	(0.91-1.40)
Diuretics	64	0.96	(0.74-1.25)	39	0.96	(0.68-1.34)
Others	41	0.84	(0.61-1.15)	35	1.11	(0.78-1.58)

Results

- No definite category of antihypertensive drugs was associated with a statistically significant hazard ratio (HR).
- After adjustment for potential confounders, the estimated HR of developing ischemic stroke was **1.3 (95% CI: 1.0-1.6; *P* = 0.046)** for those patients receiving beta-blockers as compared to those without prescriptions of beta-blockers in the previous month.

Antihypertensive drug	Ischemic stroke (case No.)	Prescription (person-months)	Crude event rate (1000 years^{-1})	Adjusted HR*
ACE inhibitors or ARBs	90	157,424	6.9	1.05
Beta-blockers	98	175,109	6.7	1.27†
CCBs	128	210,892	7.3	1.13
Diuretics	39	66,990	7.0	0.96
Others	35	41,072	10.2	1.11

Results

- Among the **98 ischemic stroke** cases with antihypertensive pharmacotherapy containing a beta-blocker, **40 patients (40.8%) were receiving mono-therapy** while the others were using combination therapy with other antihypertensive drugs.

  Such a proportion seemed similar to that of all patients receiving beta-blockers, or 35.4%.

- The HR of ischemic stroke was significantly greater for **atenolol (1.4; 95% CI: 1.1-1.9)** according to the fitted time-dependent Cox's proportional hazards model.

Drug	Ischemic stroke (No. of cases)	Prescription (person-months)	Crude event rate (1000 years^{-1})
Atenolol	56	90,427	7.4
Bisoprolol	9	25,586	4.2
Propranolol	15	23,191	7.8
Carvedilol	9	11,053	9.8
Betaxolol	4	7,188	6.7
Acebutolol	0	7,163	0
Metoprolol	0	4,225	0
Labetalol	2	3,518	6.8
Carteolol	2	1,103	21.8
Other	1	1,655	7.3
Total	98	175,109	6.7

Discussion

- The hazard ratios of developing stroke were significantly higher for **older** and **male** hypertensive patients and among those with comorbidities of **diabetes** and **heart disease**.
- **Poor compliance** with antihypertensive pharmacotherapy was an important risk factor in stroke development, for both ischemic and hemorrhagic types.

Discussion

- We found **no** evidence of a differential effect of antihypertensive pharmacotherapy on stroke risk when all stroke subtypes were included in the multivariate analysis.
- In the subsequent analysis restricted to **ischemic stroke**, we observed an excess risk of ischemic stroke associated with **beta-blocker** therapy.

Conclusions

- The control of hypertension played a major role in determining the risk of stroke among the previously uncomplicated hypertensive patients.
- After controlling other major potential confounding factors, we found no differential risks of stroke related to any type of antihypertensive medication, while some unintended association between the pharmacotherapy with beta-blockers and a higher risk of ischemic stroke was observed in the subgroup analysis.

Increased risks of urinary tract cancer associated with Chinese herbal products containing aristolochic acid: A population based case-control study

Introduction

- Aristolochic acid nephropathy (AAN) was first reported in a group of young patients with end-stage renal disease in Belgium in 1993, because they took herbal medicinal remedies containing aristolochic acid (AA).
- AA has also been found to be an urothelial carcinogen in studies of clinical cases around the world, animal models, and the detection of AA-DNA adducts in kidney and ureteral tissues.

Purpose of the study

- Using the reimbursement database of NHI, we conducted this case-control study to determine the risk and potential dose-response relationship of UTC associated with prescribed Chinese herbal products containing AA in Taiwan.

Methods:

- A retrospective case-control study
- Potential risk factors:
  - Age
  - Gender
  - Residence in the endemic townships of blackfoot disease (arsenic exposure)
  - Chronic urinary tract infection
  - Cumulative prescribed doses of Chinese herbs containing AA up to one year before diagnosis of UTC
  - Consumption of more than a total of 500 pills of NSAIDs and acetaminophen,
- multiple logistic regression models

Cases

From 20,777 prevalent cases of urinary tract cancer during 1997-2002 in Taiwan, we identified 5,995 new cases developed after 2001

Excluding 1401 subjects with high analgesics users (over 500 pills of acetaminophen and NSAIDs)

Cases (n= 4,594), including
upper urinary tract cancer (n=1985) and
bladder cancer (n=2609)

Controls

Simple random sampling of all insured people, 1997-2002 in Taiwan(n= 200,000)

Excluding 152 subjects with incomplete data on age or sex, 145 with urinary tract cancer, and 25,002 with high analgesics users (over 500 pills of acetaminophen and NSAIDs)

Controls (n=174,701)

Exposure assessment for traditional Chinese medicines

1. Genus Aristolochiae

- 細辛 Asarum heterotoppoides
- 關木通Aristolochia manshuriensis
- 廣防己Aristolochia fungchi

2. Adulteration of Aristolochiae herbs

- 木通 (Akebia species) ➔關木通
- 防己 Stephania species ➔廣防己

徐雅慧 藥物食品檢驗局調查研究年報 1997；15：136-142。
莊美淑 藥物食品檢驗局調查研究年報 2002；20：104-119。

Potential Risks

- 4 townships (endemic areas of blackfoot disease)
  - Pu-Tai and Yi-Chu of Chiayi County
  - Hsueh-Chia and Pei-Men of Tainan County
- Chronic UTI: having UTI diagnosis for at least 12 times prior to one year before the diagnosis of UTC

Estimated AA dose

- According to the studies of the national survey in Taiwan
- Estimated AA total does (mg) =

  2.59 mg/g * Mu Tong (g) +

  2.04 mg/g * Fangchi (g) +

  0.042 mg/g * Xi Xin (g)

Table 1. Frequency distributions, Crude OR (odds ratio) and ORA (adjusted odds ratio) with 95% CI (confidence interval) of various risk factors for new occurrence of urinary tract cancer based on construction of multiple logistic regression models

Risk factors	Cases N= 4,594	Controls N= 174,701	Crude OR	Model 1 OR_A (95% CI) ‡
Gender				
Female	1566	83671	1.0	1.0
Male	3028	91030	1.8*	1.7* (1.6-1.8)
Age				
< 40 years	199	115789	1.0	1.0
40 to 59 years	1194	42260	16.4*	16.2* (14.0-18.9)
60 to 74 years	1932	11308	99.3*	96.3* (83.1-112)
75 to 99 years	1269	5344	138.1*	135* (116-158)
Townships endemic for blackfoot disease				
No	4506	174151	1.0	1.0
Yes (4 townships)	88	550	6.2*	4.4* (3.4-5.8)
Chronic UTI				
No	4511	174091	1.0	1.0
Yes	83	610	5.3*	1.6* (1.3-2.1)

Mu-Tong					
0 g	**3987**	**149464**	**1.0**	**1.0**	
1 to 60 g	**489**	**18805**	**0.8**		**1.0 (0.9-1.2)**
61 to 100 g	**50**	**3549**	**1.3***		**1.6* (1.3-2.1)**
101 to 200 g	**46**	**1485**	**1.7***		**2.0* (1.4-2.7)**
> 200 g	**22**	**1003**	**2.1***		**2.1* (1.3-3.4)**
† Each 30 g increase			**1.1***		**1.1† (1.06-1.15)**
Fangchi					
0 g	**3927**	**150456**	**1.0**	**1.0**	
1 to 60 g	**623**	**23456**	**1.0**		**0.9 (0.8-1.0)**
61 to 100 g	**15**	**427**	**1.3**		**0.7 (0.4-1.2)**
> 100 g	**29**	**362**	**3.1***		**1.3 (0.9-2.0)**
Xi-Xin					
0 g	**3680**	**139385**	**1.0**	**1.0**	
1 to 100 g	**839**	**33072**	**1.0**		**1.1* (1.0-1.2)**
101 to 300 g	**54**	**1917**	**1.1**		**0.7 (0.4-1.2)**
> 300 g	**21**	**327**	**2.4***		**1.3 (0.9-2.0)**

UTI; urinary tract infection; * significant at $p < 0.05$; † Estimation of ORA based on continouous variable for every increment of 30 grams of Mu Tong or 100 mg of AA, and both *p* values were less than 0.001; ‡ ORA, adjusted for age, gender, 4 townships and UTI.

Risk factors	Cases N= 4,594	Controls N= 174,701	Crude OR	Model 2 OR_A (95% CI) ‡
Gender				
Female	1566	83671	1.0	1.0
Male	3028	91030	1.8*	1.7* (1.6-1.8)
Age				
< 40 years	199	115789	1.0	1.0
40 to 59 years	1194	42260	16.4*	16.1* (13.9-18.8)
60 to 74 years	1932	11308	99.3*	95.5* (82.4-111)
75 to 99 years	1269	5344	138.1*	135* (116-157)
Townships endemic for blackfoot disease				
No	4506	174151	1.0	1.0
Yes (4 townships)	88	550	6.2*	4.4* (3.4-5.8)
Chronic UTI				
No	4511	174091	1.0	1.0
Yes	83	610	5.3*	1.6* (1.3-2.1)
Aristolochic acid				
0 mg	3274	121820	1.0	
1 to 150 mg	1151	48869	0.9*	1.0 (0.96-1.1)
151 to 250 mg	69	2032	1.3*	1.4* (1.1-1.8)
251 to 500 mg	64	1403	1.7*	1.6* (1.2-2.1)
> 500 mg	36	577	2.3*	2.0* (1.4-2.9)
† Each 100 mg increase			1.1†	1.1† (1.06-1.13)

Table 2. Adjusted odds ratio (ORA) for the development of upper urinary tract cancer (UTC) and bladder cancer

Variables	Upper UTC	OR_A (95% CI)	Bladder cancer	OR_A (95% CI)
No. of subjects	1,985		2,609	
Townships endemic for blackfoot disease				
No	1953	1.0	2553	1.0
Yes (4 townships)	32	3.8* (2.6-5.6)	56	5.0* (3.6-6.9)
Chronic UTI				
No	1965	1.0	2546	1.0
Yes	20	0.9 (0.6-1.4)	63	2.3* (1.7-3.0)

Mu-Tong				
0 g	**1698**	**1.0**	**2289**	**1.0**
1 to 60 g	**239**	**1.1 (0.9 - 1.3)**	**250**	**1.0 (0.8 - 1.2)**
61 to 100 g	**22**	**1.5 (0.9 – 2.3)**	**28**	**1.7* (1.1 – 2.6)**
101 to 200 g	**19**	**1.8* (1.1 - 2.9)**	**27**	**2.2* (1.4 - 3.4)**
> 200 g	**7**	**1.3 (0.6 – 3.0)**	**15**	**2.8* (1.6 – 5.1)**
Fangchi				
0 g	**1684**	**1.0**	**2243**	**1.0**
1 to 60 g	**282**	**0.9 (0.8 – 1.0)**	**341**	**1.0 (0.8-1.1)**
61 to 100 g	**6**	**0.6 (0.3-1.4)**	**9**	**0.7 (0.4-1.5)**
> 100 g	**13**	**1.3 (0.7 – 2.4)**	**16**	**1.3 (0.8-2.3)**
Xi-Xin				
0 g	**1556**	**1.0**	**2124**	**1.0**
1 to 100 g	**391**	**1.1 (1.0 – 1.3)**	**448**	**1.1 (0.96-1.2)**
101 to 300 g	**27**	**1.0 (0.6-1.5)**	**27**	**0.7 (0.5-1.1)**
> 300 g	**11**	**1.8 (0.9 – 3.5)**	**10**	**0.9 (0.4 – 1.8)**

Table 3. Clinical features of patients with urinary tract cancer consuming more than 60 g of Mu Tong or living in the endemic area of blackfoot disease

	Upper UTC			Bladder Cancer		
	Mu Tong > 60 g (n = 48)	Blackfoot disease area (n = 32)	*p* value	Mu Tong > 60 g (n = 70)	Blackfoot disease area (n = 56)	*p* value
Age (years old) (mean, SD)	60.6, 12.3	66.2, 10.3	0.303	63.4, 11.9	69.5, 9.5	0.098
Gender ratio (Male/Female)	1.1	0.8	0.430	1.5	1.4	0.889
ESRD before UTC occurrence (%)	6.3	0	0.213	17.1	0	0.001
Blackfoot disease endemic area (%)	2.1	100	--	1.4	100	--
More than 60 g of Mu Tong (%)	100	3.1	--	100	1.8	--

SD, standard deviation. ESRD, end-stage renal disease. UTC, urinary tract cancer ; *p* values were calculated by Chi square test or t test.

Conclusions

- Consumption of AA-associated Chinese herbal products is associated with an increased risk of cancer of urinary tract in a dose-response relationship, which is independent of arsenic exposure.

BMC Health Services Research

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Antihypertensive medication prescription patterns and time trends for newly-diagnosed uncomplicated hypertension patients in Taiwan

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Published: 18 June 2008

BMC Health Services Research 2008, 8:133 doi:10.1186/1472-6963-8-133

Received: 25 July 2007
Accepted: 18 June 2008

This article is available from: http://www.biomedcentral.com/1472-6963/8/133

Abstract

Background: Knowledge of existing prescription patterns in the treatment of newly-diagnosed hypertension can provide useful information for improving clinical practice in this field. The aims of this study are to determine the prescription patterns and time trends for antihypertensive medication in newly-diagnosed cases of uncomplicated hypertension in Taiwan and to compare these with current clinical guidelines.

Methods: A total of 6,536 newly-diagnosed patients with uncomplicated hypertension, aged ≥30 years, were identified from the representative 200,000-person sample in the computerized reimbursement database of the National Health Insurance in Taiwan. These patients were followed from 1998 to 2004 with all diagnoses, prescription data and medication charges being retrieved for subsequent analysis.

Hypertension Treatment in Taiwan

- In 2003, the medical expenditure for outpatients of hypertension – 23.9 billion NT dollars (11.6% of all outpatient clinics expenditure)
- The pharmaceutical cost for outpatients of hypertension – 10.6 billion NT dollars (27.3% of all outpatient pharmaceutical expenditure)
- The most frequently prescribed drug is calcium channel blockers (CCBs)

Recent Major Guidelines for Hypertension

	Initial drug choice (uncomplicated HTN)
WHO	Low dose. All available drug classes are suitable for initial therapy.
JNC-7	Low dose thiazide diuretics either alone or in combination with 1 of the other classes
ESH	Low dose of a single agent or low dose combination of 2 agents
NICE('04)	Low dose thiazide diuretic
NICE('06)	A Calcium channel blocker or a thiazide-type diuretic for patients aged 55 or older

Goal

- To promote a cost-effective clinical guideline to improve clinical care for hypertension in Taiwan
- Why is cost-effectiveness analysis necessary?
- Knowledge of existing prescription patterns in the treatment of newly-diagnosed hypertension can provide useful information for improving clinical practice in this field.

Hypothesis

- In patients with uncomplicated hypertension, diuretic has no different clinical outcomes compared with other classes of antihypertensive drugs
  - For patients without a compelling indication for a particular drug class, on the basis of comparative trial data, availability, and cost, a low dose of diuretic should be considered for initiation of therapy.

[*J Hypertens.* 2003;21(11):1983-92]

Table 4 Compelling indications for specific antihypertensive drugs

Compelling indications	Preferred drug	Reference for evidence	Primary endpoint
Elderly with isolated systolic hypertension	Diuretic	71	Stroke
	DHPCCB	72	Stroke
Renal disease			
Diabetic nephropathy type 1	ACEI	73	Progression of renal failure
Diabetic nephropathy type 2	ARB	30–32	Progression of renal failure
Non-diabetic nephropathy	ACEI	70	Progression of renal failure
Cardiac disease			
Post-MI	ACEI	26,74	Mortality
	β-blocker	75	Mortality
Left ventricular dysfunction	ACEI	76	Heart failure
	ACEI	76,77	Mortality
CHF (diuretics almost always included)	β-blocker	78	Mortality
	Spironolactone	79	Mortality
Left ventricular hypertrophy	ARB	64,65	CV morbidity and mortality
Cerebrovascular disease	ACEI + diuretic	27	Recurrent stroke
	Diuretic	28	Recurrent stroke

DHPCCB, dihydropyridine calcium channel-blocker; ACEI, angiotensin-converting inhibitor; ARB, angiotensin receptor blocker; MI, myocardial infarction; CHF, congestive heart failure; CV, cardiovascular.

[*J Hypertens* 2003;21:1983-1992]

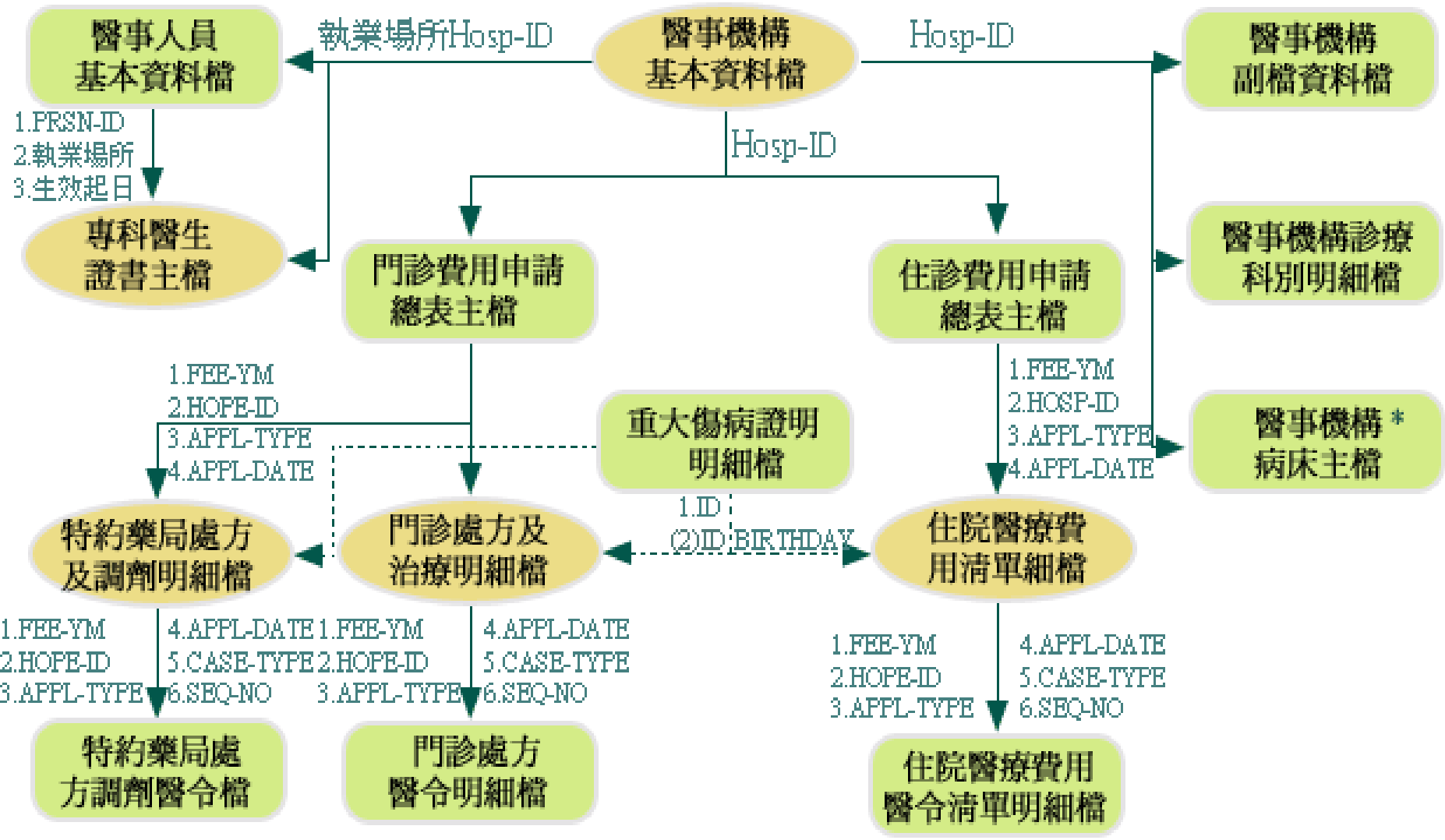
Study Designs

- A retrospective cohort study using Taiwan's National Health Insurance Research Database (**200,000** persons) between Jan. 1997 and Dec. 2004
- **15,835** patients – $\geqq$30 years old, newly diagnosed as essential hypertension and were prescribed with antihypertensive drugs, were identified after December 1997

Study Designs

- Excluding those who had had other related comorbidities (DM, ischemic heart diseases and other forms of heart disease, cerebro-vascular diseases, and renal disorders) before initial treatments for essential hypertension
- 6,536 uncomplicated hypertension patients, $\geqq$30 years old, between January 1998 and December 2004

各檔案間串檔變項說明



註:*須注意生效起訖日期

(2)可由ID+BIRTHDAY串檔

→ 各檔案間由所註明變項串檔可獲得對應資訊

→ 各檔案間可由所註明變項串檔,但未必獲得對應資料

Results

- 6,536 patients / 178,754 prescriptions
- 3,268 women (50.0%)
- Mean age: 55.9 ± 12.3 (SD)
- The mean follow-up duration: 42.8 ± 27.2 months
  The average number of overall prescriptions was 27.3 ± 26.0
- Each prescription included 1.64 ± 0.84 antihypertensive drugs prescribed for an average period of 22.3 ± 10.5 days.

Table 1. Prescription patterns of antihypertensive therapies for the 6,536 newly-diagnosed uncomplicated hypertension patients, 1998–2004

Regimen	Men (%)	Women (%)	< 55 Years (%)	≧ 55 Years (%)
Monotherapy	44,738 (51.36)	50,059 (54.62)	40,357 (50.67)	54,440 (54.93)
Two-drug combination	31,494 (36.16)	31,927 (34.84)	29,784 (37.39)	33,637 (33.94)
Three-drug combination	6,815 (7.82)	6,024 (6.57)	6,130 (7.70)	6,709 (6.77)
Four-drug or more combination	4,058 (4.66)	3,639 (3.97)	3,380 (4.24)	4,317 (4.36)
Total prescriptions	87,105	91,649	79,651	99,103

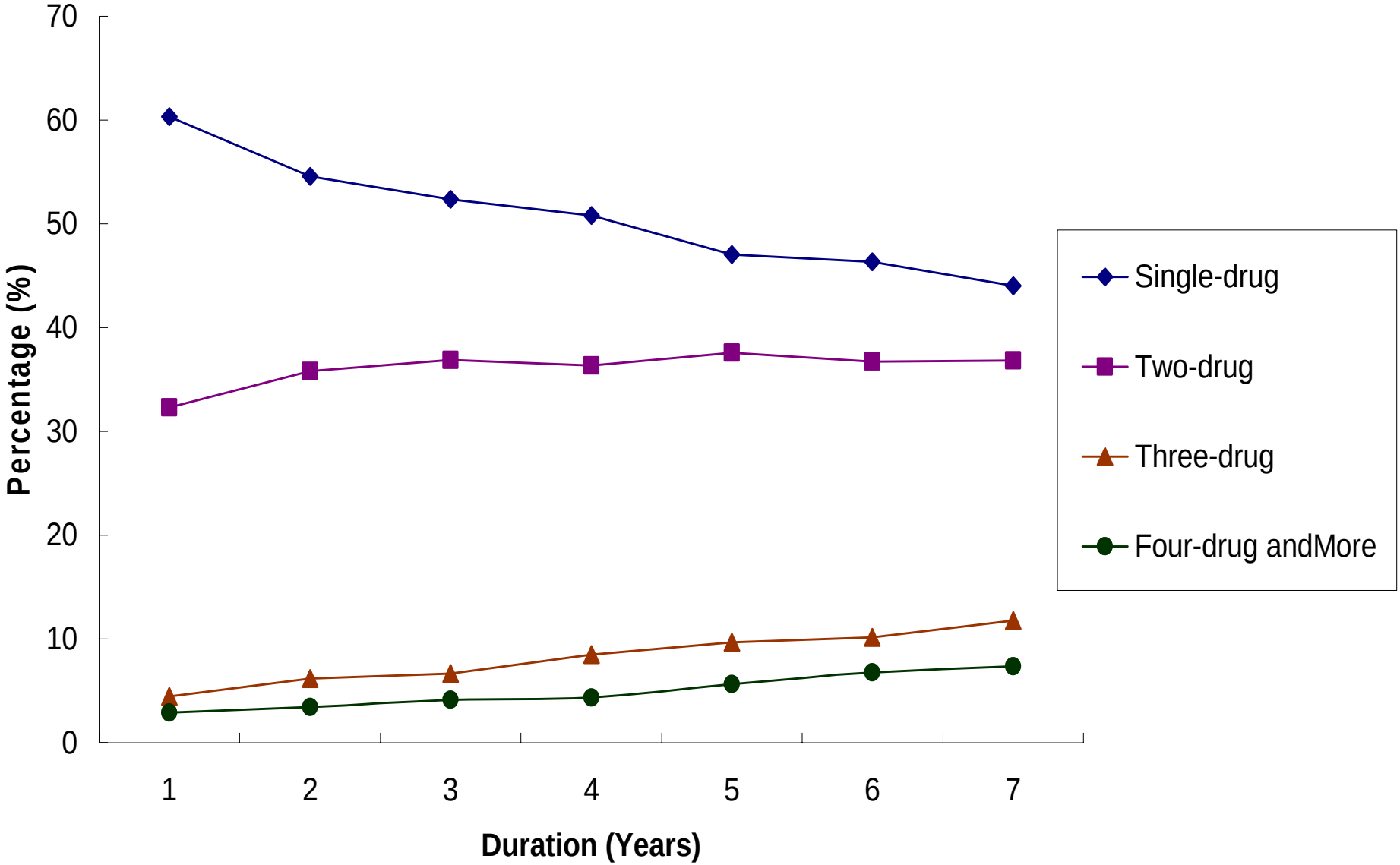


Fig 3.1 (Page 53)

健保20萬人抽樣歸人檔1998-2004年單純高血壓新個案各類降壓藥處方率分佈情形 (6,536人)

降壓藥物類型	男性 (%)	女性 (%)	< 55 Years (%)	≧55 Years (%)	Overall (%)
Diuretics 利尿劑	**15,525** (17.82)*	**19,981** (21.80)	**13,556** (17.02)*	**21,950** (22.15)	**35,506** (19.86)
Beta-blockers 乙型阻斷劑	**34,703** (39.84)*	**40,941** (44.67)	**39,445** (49.52)*	**36,199** (36.53)	**75,644** (42.32)
CCBs 鈣離子阻斷劑	**46,468** (53.35)*	**46,106** (50.31)	**40,270** (50.56)*	**52,304** (52.78)	**92,574** (51.79)
ACE inhibitors 升壓素轉化酶抑制劑	**22,825** (26.20)*	**21,306** (23.25)	**21,282** (26.72)*	**22,849** (23.06)	**44,131** (24.69)
ARBs 升壓素受器阻斷劑	**10,635** (12.21)*	**10,339** (11.28)	**10,421** (13.08)*	**10,553** (10.65)	**20,974** (11.73)
Others 其他	**15,212** (17.46)*	**8,826** (9.63)	**7,578** (9.51)*	**16,460** (16.61)	**24,038** (13.45)
所有降壓藥物	**87,105**	**91,649**	**79,651**	**99,103**	**178,754**

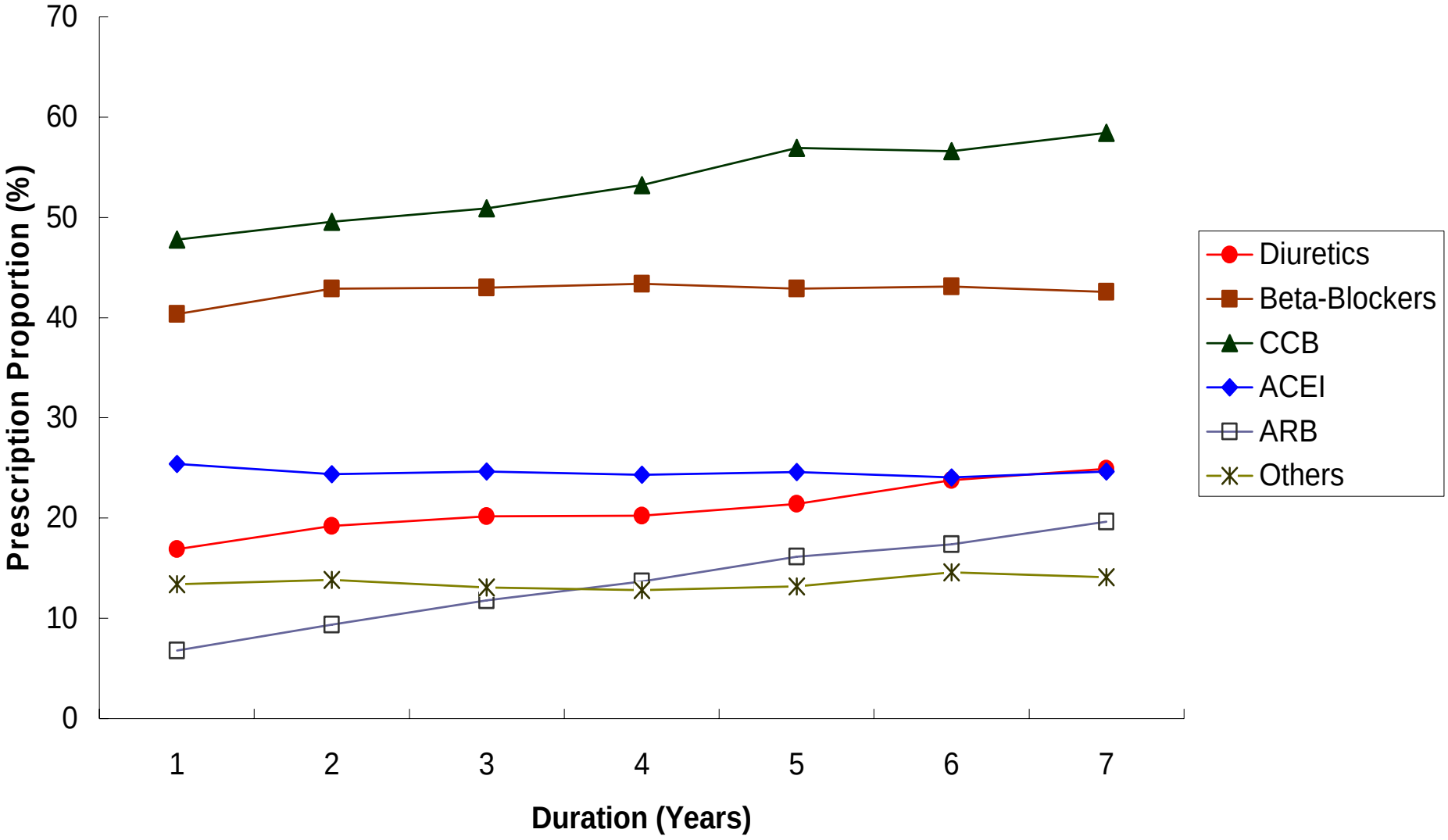


Fig 3.2 單純高血壓病患自開始藥物治療後之各類降壓藥物分佈隨時間變化情形

健保20萬人抽樣歸人檔1998-2004年單純高血壓新個案單一降壓藥物治療各類降壓藥處方率分佈情形

降壓藥物類型	男性 (%)	女性 (%)	< 55 Years (%)	≧ 55 Years (%)	醫學中心 (%)	區域醫院 (%)	地區醫院 (%)	基層診所 (%)	Overall (%)
Diuretics 利尿劑	2,974	4,849	2,366	5,457	1,067	1,026	1,363	4,367	7,823
	(6.65) *	(9.69)	(5.86) *	(10.02)	(6.38) †	(6.93) †	(7.47) †	(9.71)	(8.25)
Beta-blockers 乙型阻斷劑	11,602	14,233	13,627	12,208	4,474	4,144	4,171	13,043	25,835
	(25.93) *	(28.43)	(33.77) *	(22.42)	(26.76) †	(27.98) ‡	(22.84) †	(28.99)	(27.25)
CCBs 鈣離子阻斷劑	14,881	16,830	12,083	19,628	5,841	5,690	8,186	11,991	31,711
	(33.26)	(33.62)	(29.94) *	(36.05)	(34.93) †	(38.42) †	(44.84) †	(26.65)	(33.45)
ACE inhibitors 升壓素轉化酶抑制劑	7,004	7,619	7,134	7,489	2,255	1,710	1,728	8,927	14,623
	(15.66)	(15.22)	(17.68) *	(13.76)	(13.49) †	(11.55) †	(9.46) †	(19.84)	(15.43)
ARBs 升壓素受器阻斷劑	2,561	2,822	2,677	2,706	2,099	1,272	920	1,089	5,383
	(5.72)	(5.64)	(6.63) *	(4.97)	(12.55) †	(8.59) †	(5.04) †	(2.42)	(5.68)
Others 其他	5,716	3,706	2,470	6,952	985	967	1,890	5,580	9,422
	(12.78) *	(7.40)	(6.12) *	(12.77)	(5.89) †	(6.53) †	(10.35) †	(12.40)	(9.94)
所有降壓藥物處方	44,738	50,059	40,357	54,440	16,721 [a]	14,809 [a]	18,258 [a]	44,997 [a]	94,797

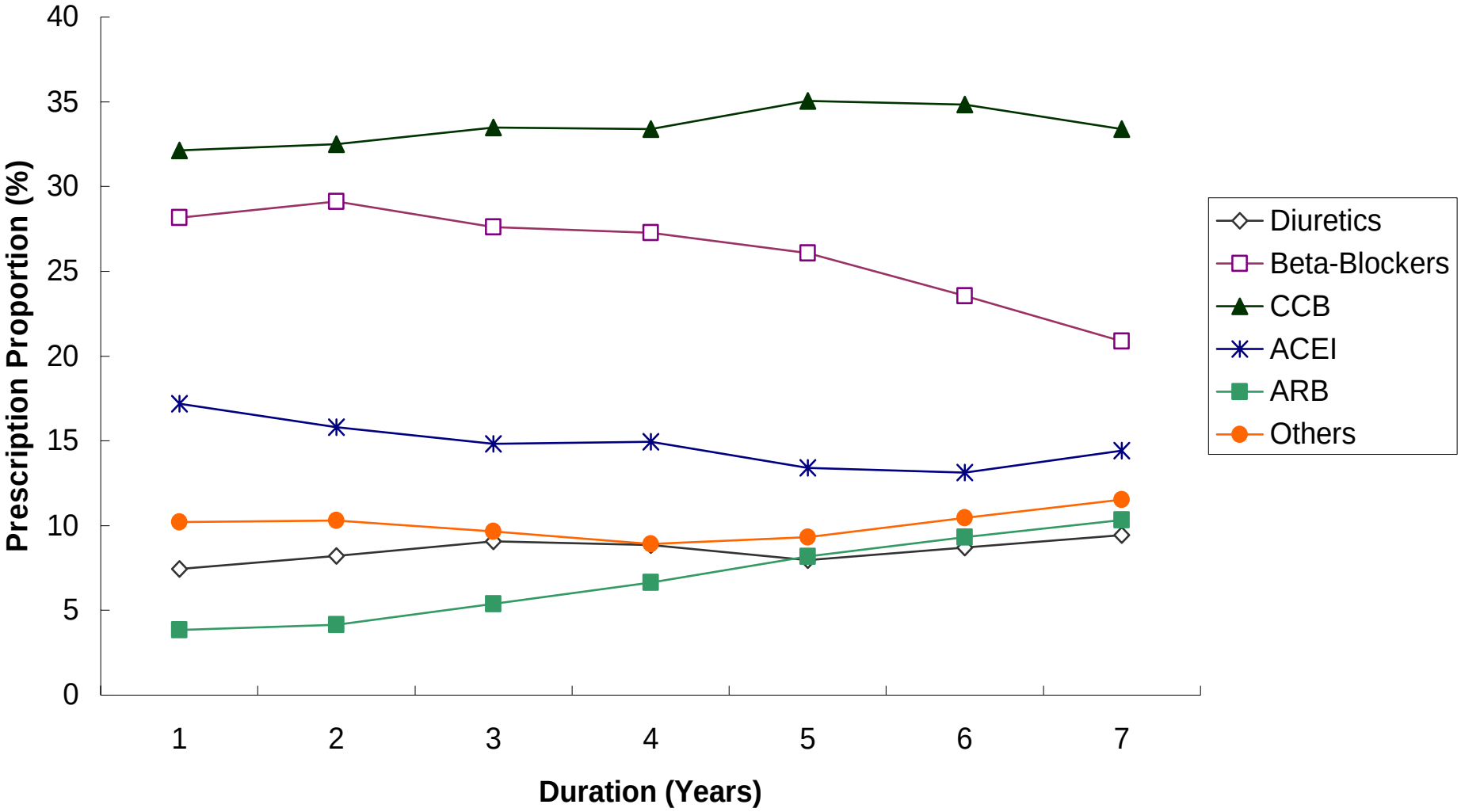


Fig 3.3 單純高血壓自開始藥物治療後之各類單一降壓藥物治療分佈變化情形

單純高血壓病患使用單一降壓藥物治療，各類藥物平均每日藥費

降壓藥物類型	男性	女性	< 55 歲	≧ 55 歲	全部
Diuretics 利尿劑	**5.48** (0.09)	**5.47** (0.08)	**6.39** (0.12)	**5.15** (0.07)	**5.47** (0.06)
β-blockers 乙型阻斷劑	**9.52** (0.06)	**8.22** (0.05)	**8.49** (0.05)	**9.23** (0.06)	**8.83** (0.04)
CCBs 鈣離子阻斷劑	**18.99** (0.05)	**18.18** (0.04)	**18.65** (0.05)	**18.50** (0.04)	**18.56** (0.03)
ACE inhibitors 升壓素轉化酶抑制劑	**18.64** (0.09)	**18.31** (0.08)	**18.52** (0.08)	**18.41** (0.08)	**18.47** (0.06)
ARBs 升壓素受器阻斷劑	**28.21** (0.14)	**27.64** (0.13)	**27.69** (0.13)	**28.13** (0.14)	**27.91** (0.10)
Others 其他	**11.66** (0.11)	**4.63** (0.07)	**8.27** (0.17)	**9.56** (0.10)	**9.26** (0.09)

影響降壓藥物使用之各項因子–多變數羅吉斯迴歸分析

	ARB (升壓素受器阻斷劑)		ACEI (升壓素轉化酶抑制劑)	
Variables	OR	(95% CI)	OR	(95% CI)
病患年紀				
30-54 Years	1.00	(reference)	1.00	(reference)
≧ 55 Years	0.74	(0.70-0.78)	0.75	(0.72-0.78)
性別				
女性	1.00	(reference)	1.00	(reference)
男性	0.99	(0.94-1.05)	1.07	(1.03-1.11)
區域分布				
北台灣	1.00	(reference)	1.00	(reference)
中台灣	0.74	(0.68-0.80)	0.98	(0.93-1.02)
南台灣	0.67	(0.62-0.72)	0.86	(0.82-0.90)
東部	1.34	(1.19-1.52)	1.39	(1.29-1.49)
離島	2.78	(2.21-3.49)	0.45	(0.35-0.57)
醫院層級				
基層診所	1.00	(reference)	1.00	(reference)
地區醫院	2.17	(1.98-2.38)	0.43	(0.41-0.45)
區域醫院	3.55	(3.26-3.87)	0.52	(0.49-0.55)
醫學中心	5.77	(5.32-6.25)	0.63	(0.60-0.66)

影響降壓藥物使用之各項因子–多變數羅吉斯迴歸分析 (續)

	ARB (升壓素受器阻斷劑)		ACEI (升壓素轉化酶抑制劑)	
Variables	OR	(95% CI)	OR	(95% CI)
自起始時間				
1年內	1.00	(reference)	1.00	(reference)
2 - 3 年	1.00	(0.92-1.09)	0.93	(0.89-0.97)
4 - 7 年	1.12	(1.03-1.21)	0.95	(0.90-1.00)
高血壓後發生之併發症				
糖尿病	1.55	(1.42-1.68)	1.36	(1.28-1.44)
缺血性心臟病	1.10	(1.02-1.19)	0.78	(0.73-0.82)
中風	1.02	(0.93-1.11)	0.98	(0.91-1.05)
慢性腎臟病	1.07	(0.94-1.22)	0.92	(0.83-1.02)
處方年度				
1998-2000	1.00	(reference)	1.00	(reference)
2001-2002	2.35	(2.12-2.62)	0.87	(0.83-0.91)
2003-2004	4.45	(4.01-4.94)	0.79	(0.75-0.83)

Discussion

- The prescription patterns of initial antihypertensive therapies for uncomplicated hypertension in Taiwan seemed inconsistent with international clinical guidelines.
- **Diuretics were the least expensive class of antihypertensive drugs, however, they were used as a second or third choice medication with a notably low prescription rate.**
- Diuretics have been found to be the mainly prescribed class of antihypertensive drugs in the United Kingdom, Denmark and the USA.

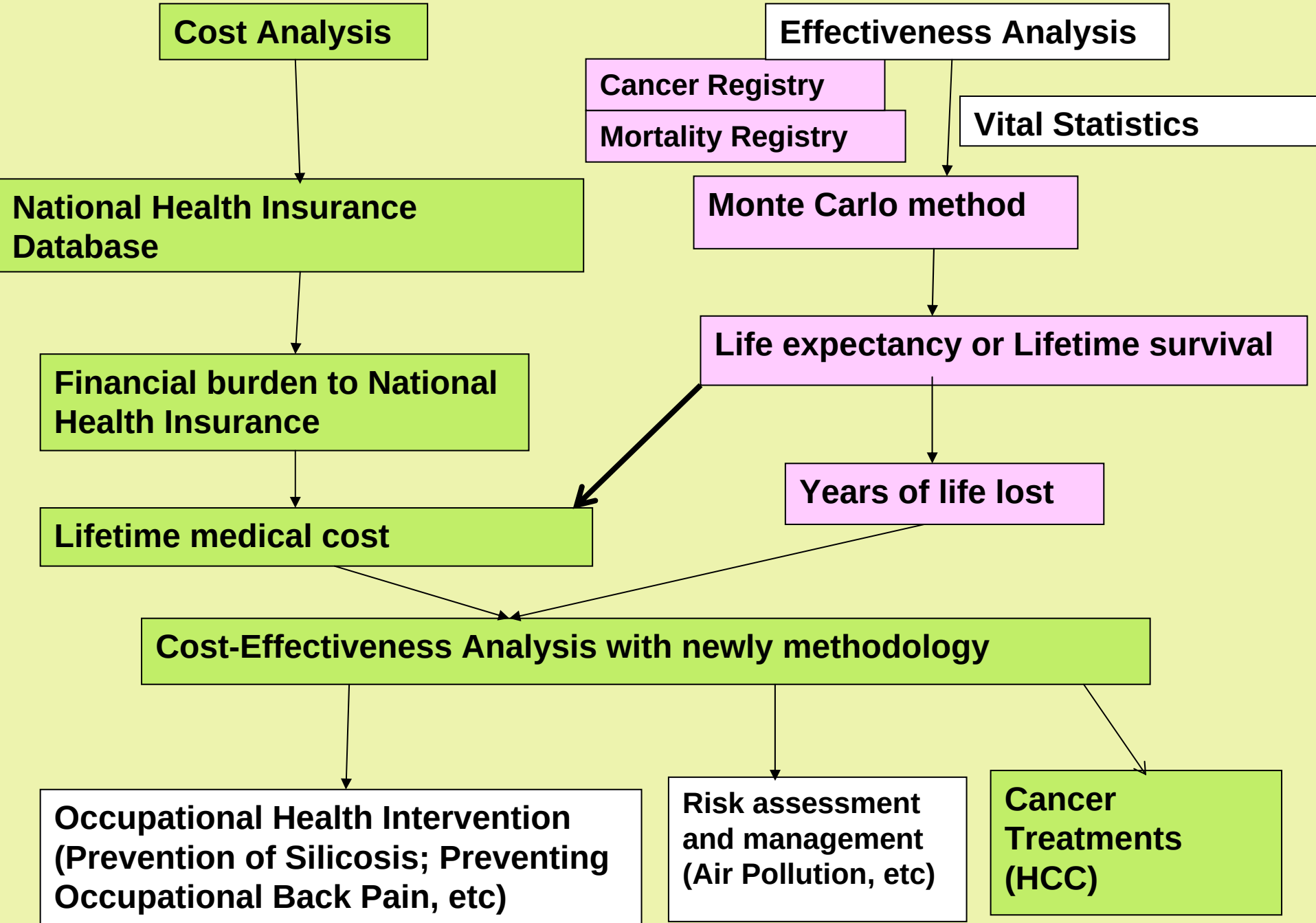
Discussion

- Rapid growing use of **ARBs** as initial therapies for uncomplicated hypertension, particularly in medical centers and regional hospitals
- Differences in cost consciousness
- Physicians in **large medical facility** are more frequently exposed to new drugs and tending to readily accept the latest, or most up-to-date, medications.
- Some studies suggest that promotional activities of pharmaceutical industry have a major impact on physicians' prescribing patterns.

Study Purposes

- **Which treatments on hepatocellular carcinoma are more cost-effective in Taiwan?**

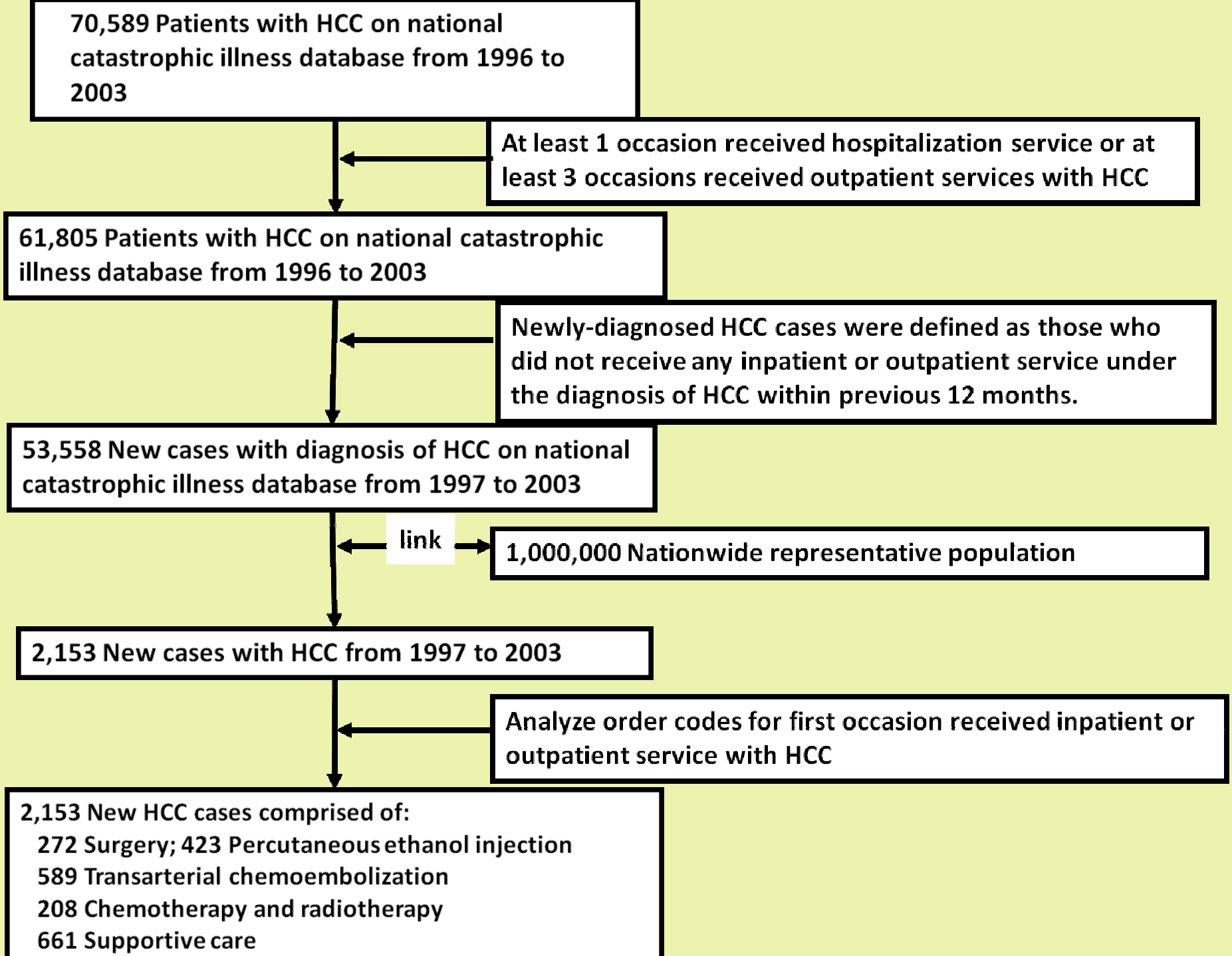
(A combination of studies based on NHIRD, National Cancer Registry and National Mortality Registry)


Cost Analysis
Effectiveness Analysis
Cancer Registry
Mortality Registry
Vital Statistics
National Health Insurance Database
Monte Carlo method
Life expectancy or Lifetime survival
Financial burden to National Health Insurance
Years of life lost
Lifetime medical cost
Cost-Effectiveness Analysis with newly methodology
Occupational Health Intervention (Prevention of Silicosis; Preventing Occupational Back Pain, etc)
Risk assessment and management (Air Pollution, etc)
Cancer Treatments (HCC)

Cost-Effectiveness of Different Treatments in Patients with Hepatocellular Carcinoma:

A Retrospective Population-based study in Taiwan

Have submitted to J Hepatology


70,589 Patients with HCC on national catastrophic illness database from 1996 to 2003
At least 1 occasion received hospitalization service or at least 3 occasions received outpatient services with HCC
61,805 Patients with HCC on national catastrophic illness database from 1996 to 2003
Newly-diagnosed HCC cases were defined as those who did not receive any inpatient or outpatient service under the diagnosis of HCC within previous 12 months.
53,558 New cases with diagnosis of HCC on national catastrophic illness database from 1997 to 2003
link
1,000,000 Nationwide representative population
2,153 New cases with HCC from 1997 to 2003
Analyze order codes for first occasion received inpatient or outpatient service with HCC
2,153 New HCC cases comprised of:
272 Surgery; 423 Percutaneous ethanol injection
589 Transarterial chemoembolization
208 Chemotherapy and radiotherapy
661 Supportive care

Methods

- An cost-effectiveness analysis was carried out to compare different treatments of HCC, using the longitudinal claim data from the NHI reimbursement database
- Real costs of national resource utilization to identify treatment-related costs for HCC
- Effectiveness was estimated in terms of life expectancy or lifetime survival (up to 50 years of follow-up)

Methods

- **Cost-effectiveness ratios:**
  - **Net cost of specific treatment groups divided by the increased number of life years relative to the supportive care or baseline group**

$$\frac{\left[\text{Cost}_{\text{groups of specific treatments}}\,(\$)\right] - \left[\text{Cost}_{\text{baseline group}}\,(\$)\right]}{\text{Life expectancy}_{\text{groups of specific treatments}}\,(\text{t}) - \text{Life expectancy}_{\text{baseline group}}\,(\text{t})}$$

Determination of the Costs

- **Direct medical costs included:**
  - **Inpatient hospitalization**
  - **Outpatient clinic visits**
  - **Diagnostic tests**
  - **Therapeutic procedures**
  - **Medications**
  - **Physicians' fees**

Extrapolation of expected long-term direct medical cost for a disease x_i, which x_i is HCC:

$$\text{Expected long-term medical cost} = \int_{t_0}^{\infty} E[Cost(t|x_i)]S(t \mid x_i)dt$$

Cost ($t \mid x_i$)

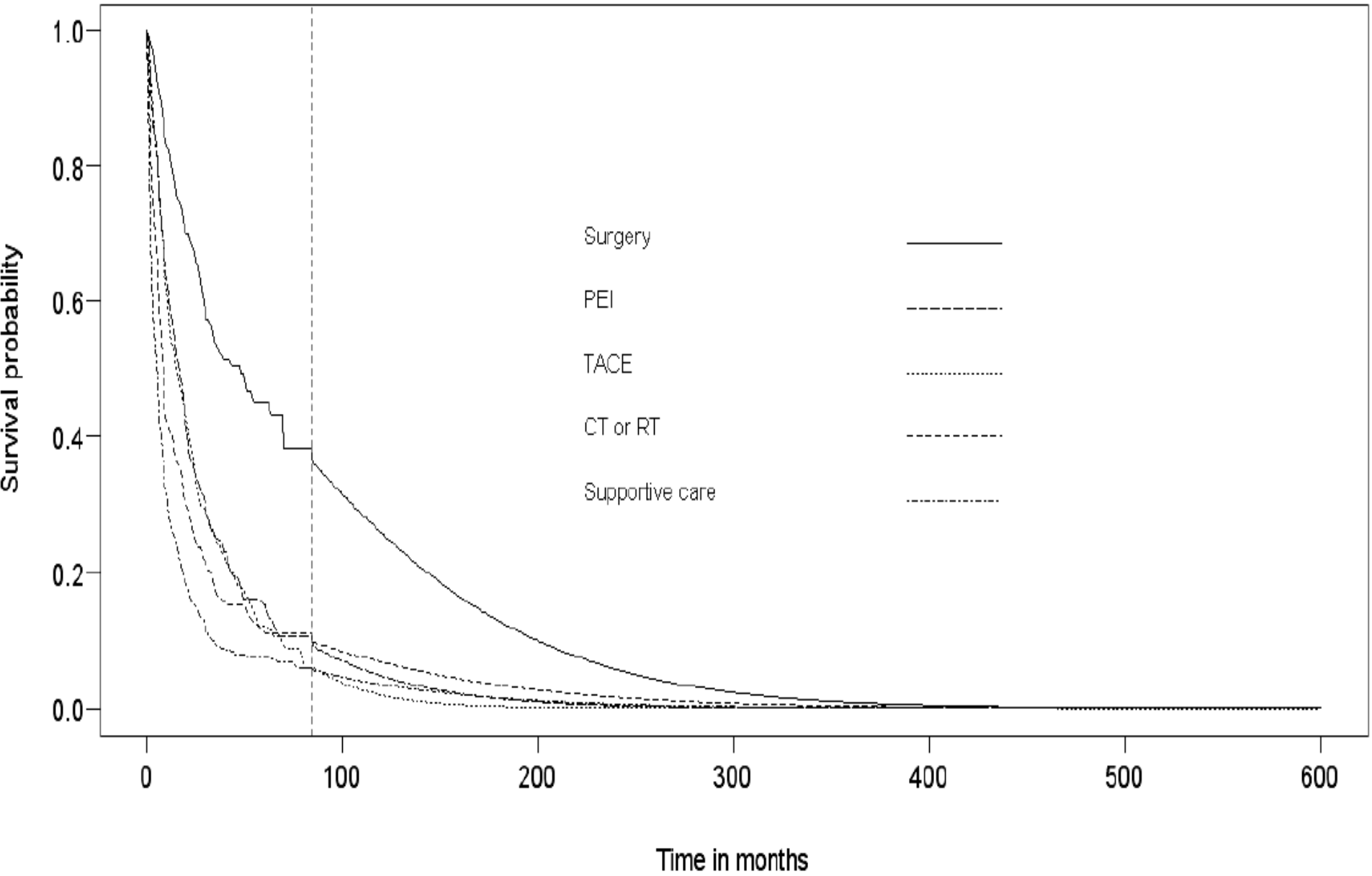
- **Before the follow-up limit of this study:**
  - **Calculate for the mean costs per month, t, after diagnosis of HCC**

- **After the follow-up limit:**
  - **Calculate for the mean costs for the last six months of follow-up period, which assumed that the constant value of direct medical costs after the period of 7-year follow-up**

Frequency distributions and survival estimates for different types of treatments on HCC after 7 years of follow-up and extrapolation to lifetime

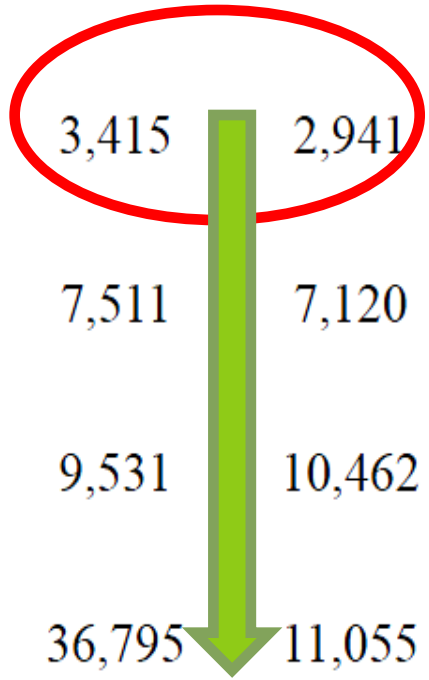
Treatment type	Overall (n=2,153)	Surgery (n=272)	PEI (n=423)	TACE (n=589)	CT or RT (n=208)	Supportive care (n=661)
Mean age at diagnosis (SD) (years)	60.69(13.27)	56.13(14.07	60.02(12.68)	61.14(12.21)	60.73(13.76)	62.59(13.60)
Male (%) 70+ %	73.39	77.94	73.52	70.12	75.00	73.83
Censored rate (%)	28.19	61.40	30.97	29.37	26.44	12.25
7-year survival based on Kaplan-Meier method (months)	11.5	47.4	16.3	15.0	7.8	4.8
Lifetime survival based on Monte Carlo method (months)	28.8	79.6	30.3	26.4	28.5	17.3
EYLL based on Monte Carlo method (years)	18.1	17.0	18.5	18.0	18.0	17.8
Average expected life span (years)	63.1	62.8	62.5	63.3	63.1	64.0

Lifetime survival curves of HCC for different types of treatments



Cost-effectiveness ratios for different types of treatment of HCC after 7 years of follow-up and extrapolation to lifetime

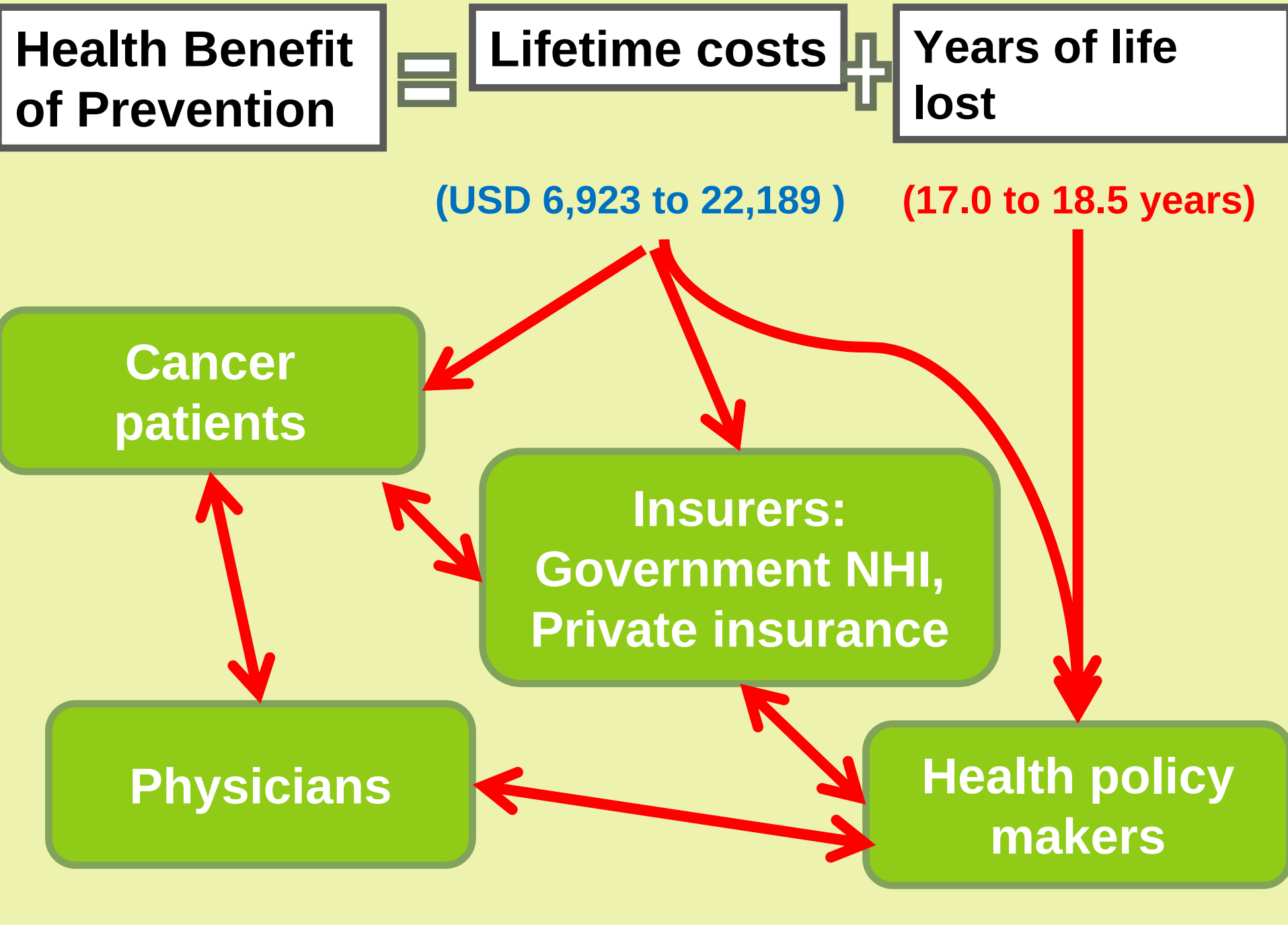
Items	Total cost (USD)		Total effectiveness (life expectancy in year)		Estimated cost per years of life saved (USD)	
Follow-up	**7-year**	**lifetime**	**7-year**	**lifetime**	**7-year**	**lifetime**
Baseline: Supportive care	6,641	6,923	0.40	1.44		
Surgery	18,759	22,189	3.95	6.63	3,415	2,941
PEI	13,838	14,642	1.36	2.53	7,511	7,120
TACE	14,756	14,883	1.25	2.20	9,531	10,462
CT or RT	15,808	17,204	0.65	2.37	36,795	11,055



How to quantify “Health benefit” of successful preventing a case of HCC

- **Lifetime cost savings for successful prevention of a case of HCC: range from USD 6,923 to 22,189, depending on the treatment type**

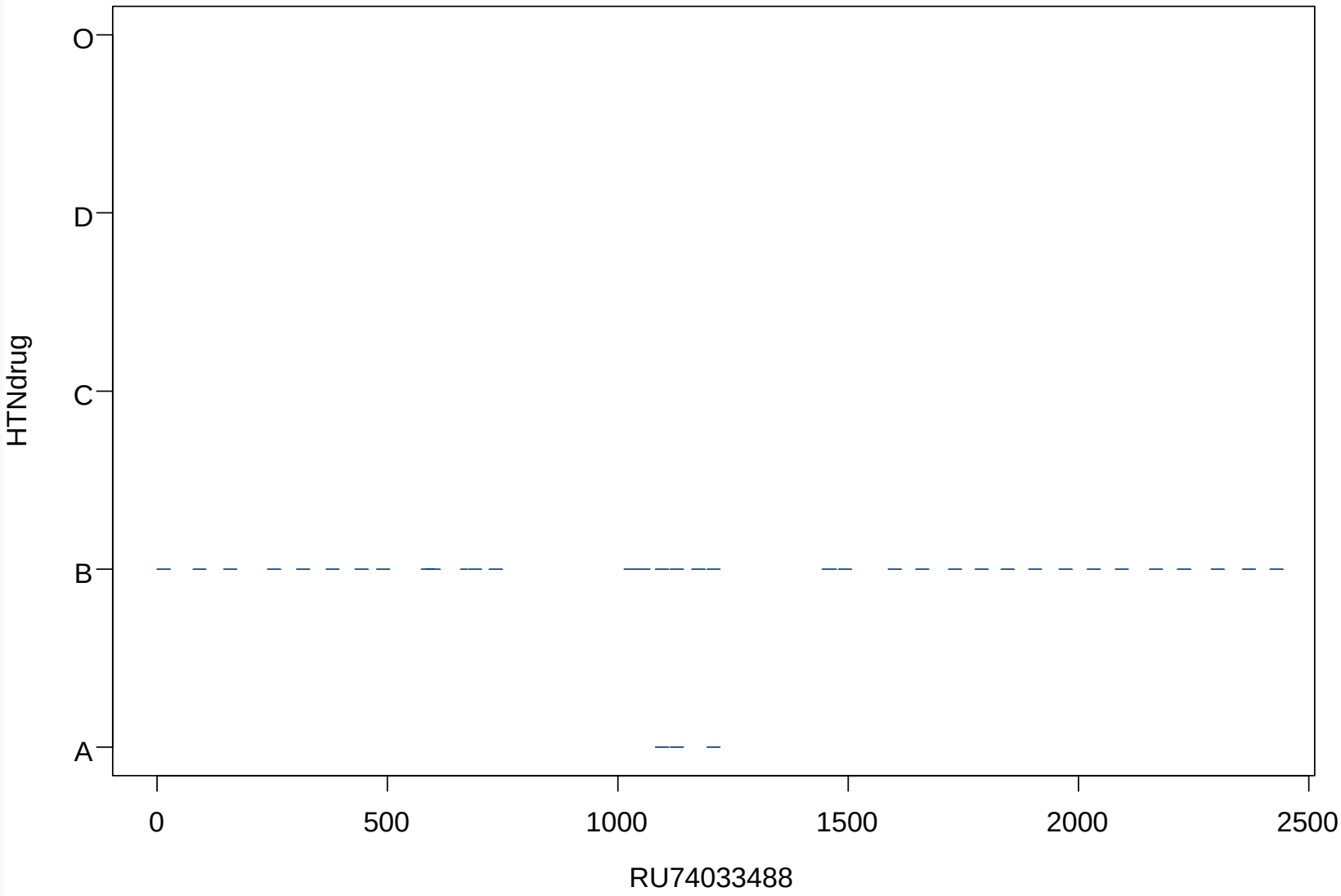
- **Years of life gain for successful prevention of a case of HCC: range from 17.0 to 18.5 years, depending on the treatment type**


Health Benefit of Prevention
=
Lifetime costs
+
Years of life lost
(USD 6,923 to 22,189)
(17.0 to 18.5 years)
Cancer patients
Insurers: Government NHI, Private insurance
Physicians
Health policy makers

Thank you for your attention

Why should a time-dependent Cox model?

- However, constant ratio is unrealistic because the effect of certain covariates on survival time may vary over time.
- For examples, the effects of pharmaceutical variables such as drug compliance, use of certain antihypertensive drug or not on incidence of stroke may fluctuate with time.
- Accordingly, a time-dependent proportional hazards regression model is needed.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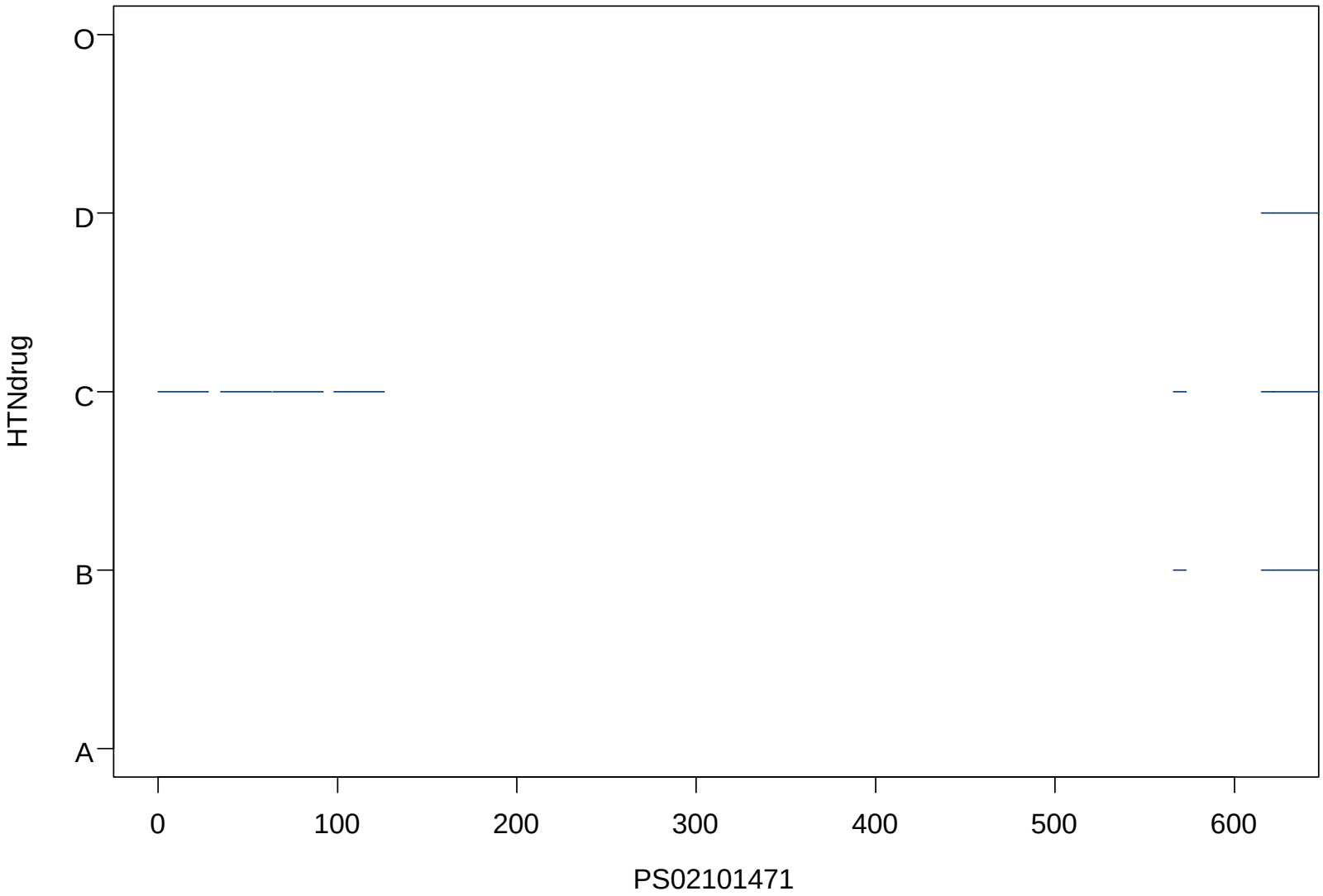
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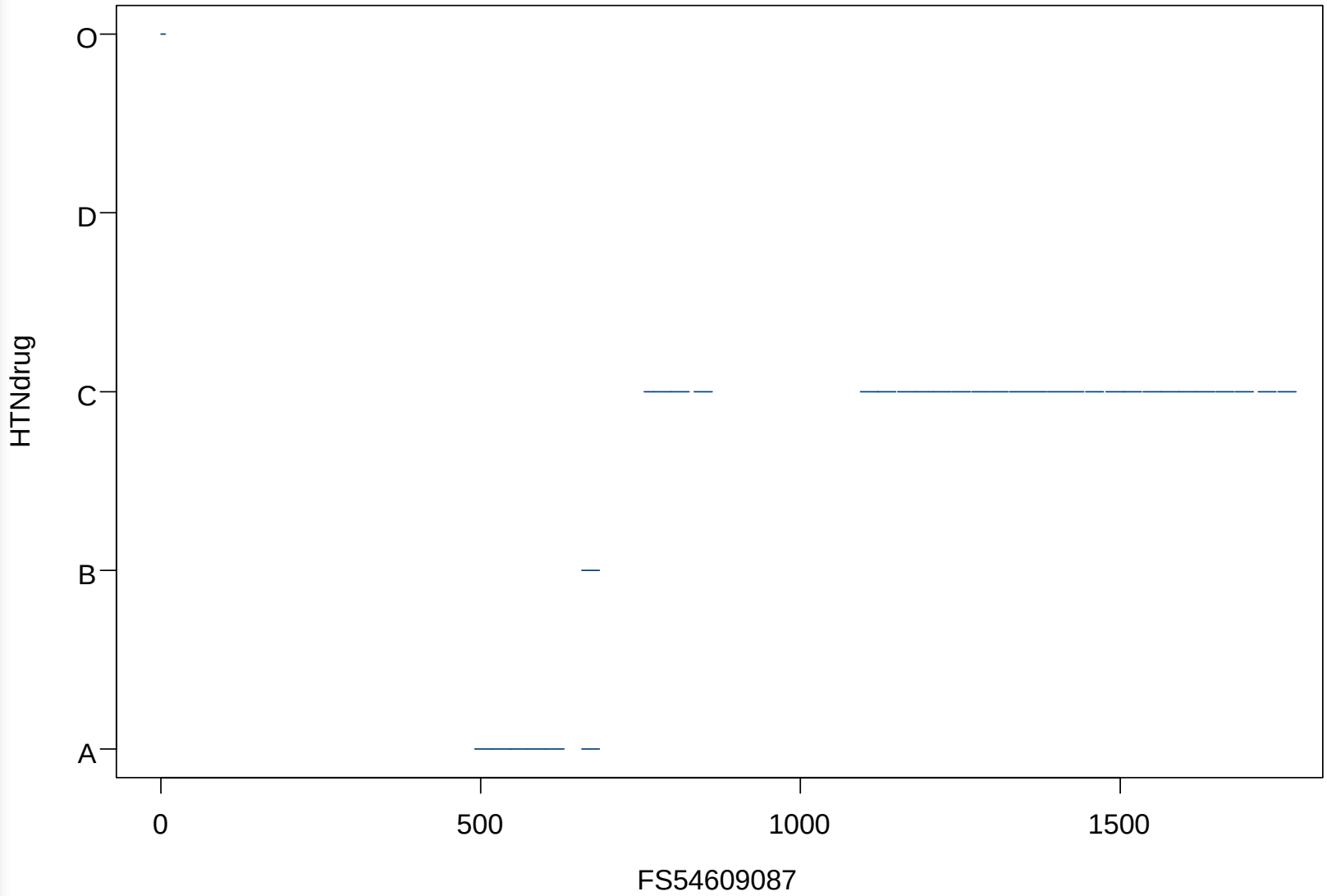
HTNdrug
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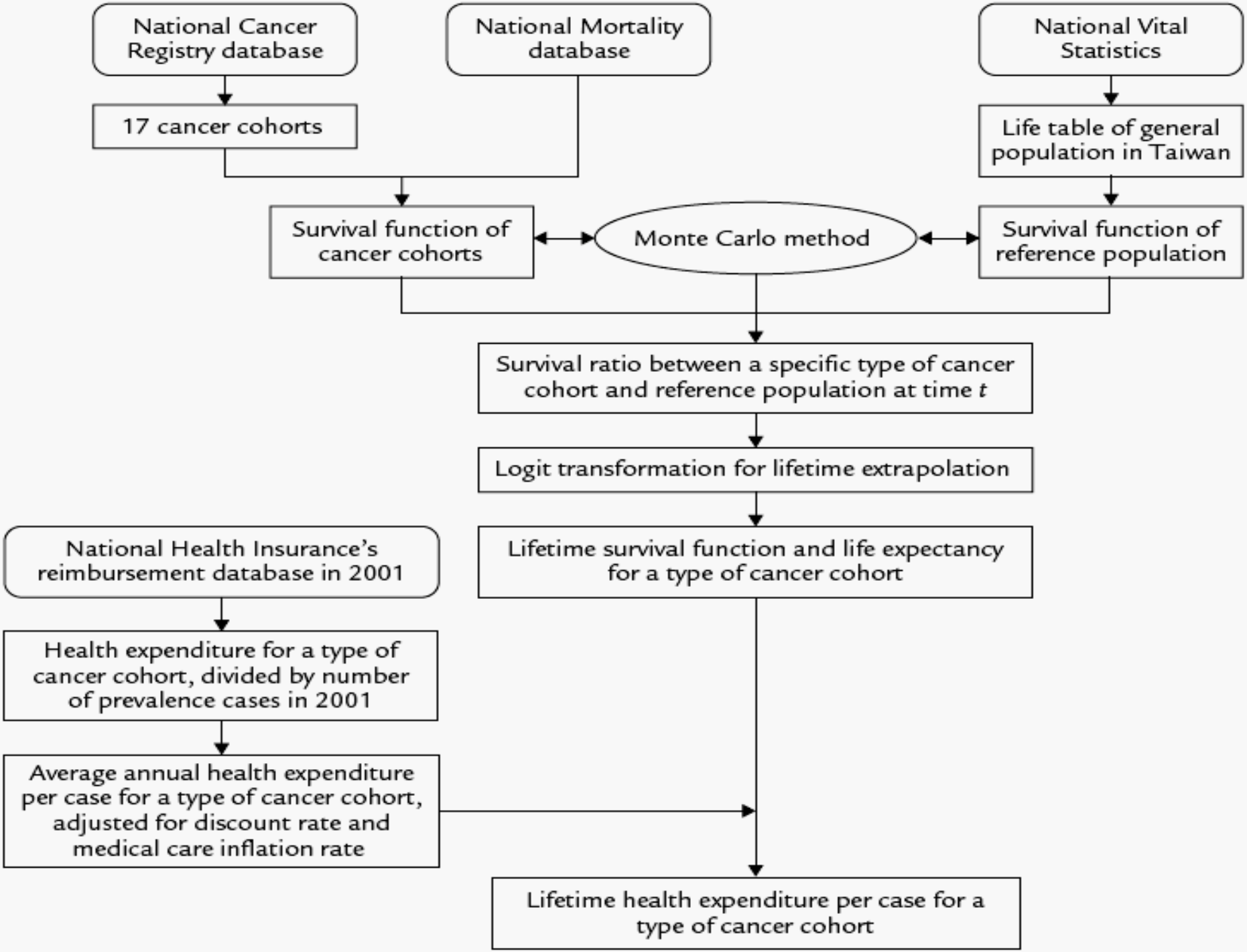
Mechanism?

- We suspected that the progression of atherosclerosis, aggravated by the **slowing down of the circulatory system**, as a direct result of the use of beta-blockers, might be responsible for the increased risk of ischemic stroke development.


National Cancer Registry database
National Mortality database
National Vital Statistics
17 cancer cohorts
Life table of general population in Taiwan
Survival function of cancer cohorts
Monte Carlo method
Survival function of reference population
Survival ratio between a specific type of cancer cohort and reference population at time t
Logit transformation for lifetime extrapolation
National Health Insurance's reimbursement database in 2001
Lifetime survival function and life expectancy for a type of cancer cohort
Health expenditure for a type of cancer cohort, divided by number of prevalence cases in 2001
Average annual health expenditure per case for a type of cancer cohort, adjusted for discount rate and medical care inflation rate
Lifetime health expenditure per case for a type of cancer cohort

Methods

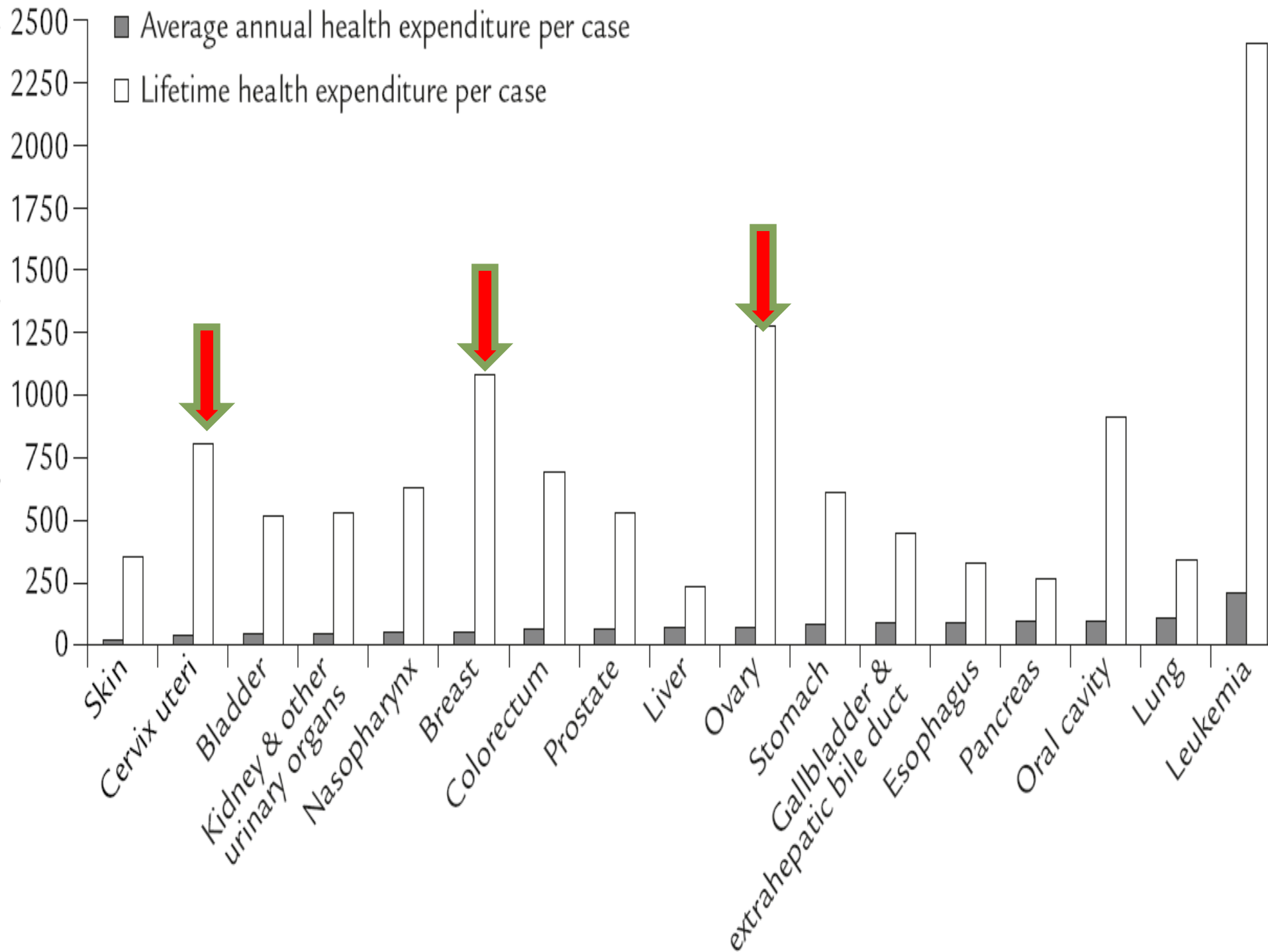
- **A total of 425,294 patients , registered in Taiwan from 1990 to 2001 for 17 major cancers**
- **The survival status: followed until the end of 2004**
- **Monte Carlo simulation was used to extrapolate survival for up to 600 months to derive the life expectancy or lifetime survival function after**

Methods

- **The average annual health expenditure per case for each cancer was calculated by using data from the NHI's reimbursement database**
- **The lifetime health expenditure per case was estimated by multiplying the monthly survival probability by the average monthly health expenditure (in 2001), adjusting for the annual discount rate and the medical care inflation rate**
- **By incorporating the number of annual incidence cases, the total lifetime health expenditure can also be estimated**

Results

Cancer site	Censoring rate (%)	Life expectancy, yr (SE)	Annual number of incidence cases	Annual number of prevalence cases	Average annual health expenditure per case ($\times 10^3$ TWD)	Lifetime health expenditure per case ($\times 10^3$ TWD)		Total lifetime health expenditure ($\times 10^6$ TWD)	
						Medical care inflation rate (3%)		Medical care inflation rate (3%)	
						Discount rates		Discount rates	
						3%	5%	3%	5%
Oral cavity	35.94	9.58 (0.61)	3549	15,677	95	910	725	3230	2574
Nasopharynx	43.06	12.59 (0.74)	1371	13,908	53	632	496	867	680
Esophagus	11.28	3.54 (0.20)	1229	6055	93	330	273	405	335
Stomach	26.80	7.51 (0.14)	3501	13,310	81	609	487	2133	1704
Colorectum	41.94	10.86 (0.11)	7215	40,902	64	692	555	4995	4002
Liver	13.28	3.45 (0.08)	8541	31,368	69	238	203	2030	1731
Gallbladder & extrahepatic bile duct	17.72	4.98 (0.20)	609	2359	90	446	365	272	223
Pancreas	8.28	2.81 (0.17)	992	3231	94	263	211	261	209
Lung	9.97	3.09 (0.07)	6752	22,304	111	342	286	2313	1932
Leukemia	28.49	11.61 (0.94)	962	5236	207	2404	1706	2312	1641
Skin	62.18	16.16 (0.22)	1806	4368	22	354	276	640	499
Breast	66.94	20.01 (0.80)	4667	35,082	54	1081	817	5046	3812
Cervix uteri	63.92	19.77 (0.30)	2423	22,225	41	808	608	1958	1474
Ovary	52.59	17.71 (0.80)	737	5366	72	1277	939	941	692
Prostate	44.65	8.17 (0.13)	1991	10,348	65	527	463	1050	922
Bladder	46.93	10.99 (0.20)	1756	9748	47	519	426	911	748
Kidney & other urinary organs	43.68	10.97 (0.85)	1502	7353	48	528	423	794	635


Average annual health expenditure per case
Lifetime health expenditure per case
2500
2250
2000
1750
1500
1250
1000
750
500
250
0
Skin
Cervix uteri
Bladder
Kidney & other urinary organs
Nasopharynx
Breast
Colorectum
Prostate
Liver
Ovary
Stomach
Gallbladder & extrahepatic bile duct
Esophagus
Pancreas
Oral cavity
Lung
Leukemia

Estimation of Life Expectancy and the Expected Years of Life Lost in Patients with Major Cancers: Extrapolation of Survival Curves under High- Censored Rates

Value in Health
11:1102-09, 2008

Methods

- **Study cohort:**
  - **Patients diagnosed with 17 different types of major cancer**
  - **Registered in Cancer Registry between 1990 and 2001**
  - **Their survivals were followed through the end of 2004**

- **The survival function for an age- and sex-matched reference population was generated using the Monte Carlo method from the life table of the general population**

Methods

- **Lifetime survival of the cancer patients:**
  - **Using linear extrapolation of a logit-transformed curve of the survival ratio between the cancer and reference populations**

Survival ratio between the survival functions of two populations:

$$W(t) = S(t|\text{patient population}) / S(t|\text{reference population})$$

Logit transformation of W(t)

⬇

If the cancer-associated excess hazard remains constant over time, the curve of logit of W(t) will converge to a straight line

⬇

Fitted a simple linear regression for the logit of W(t)

⬇

Given the least squares estimates

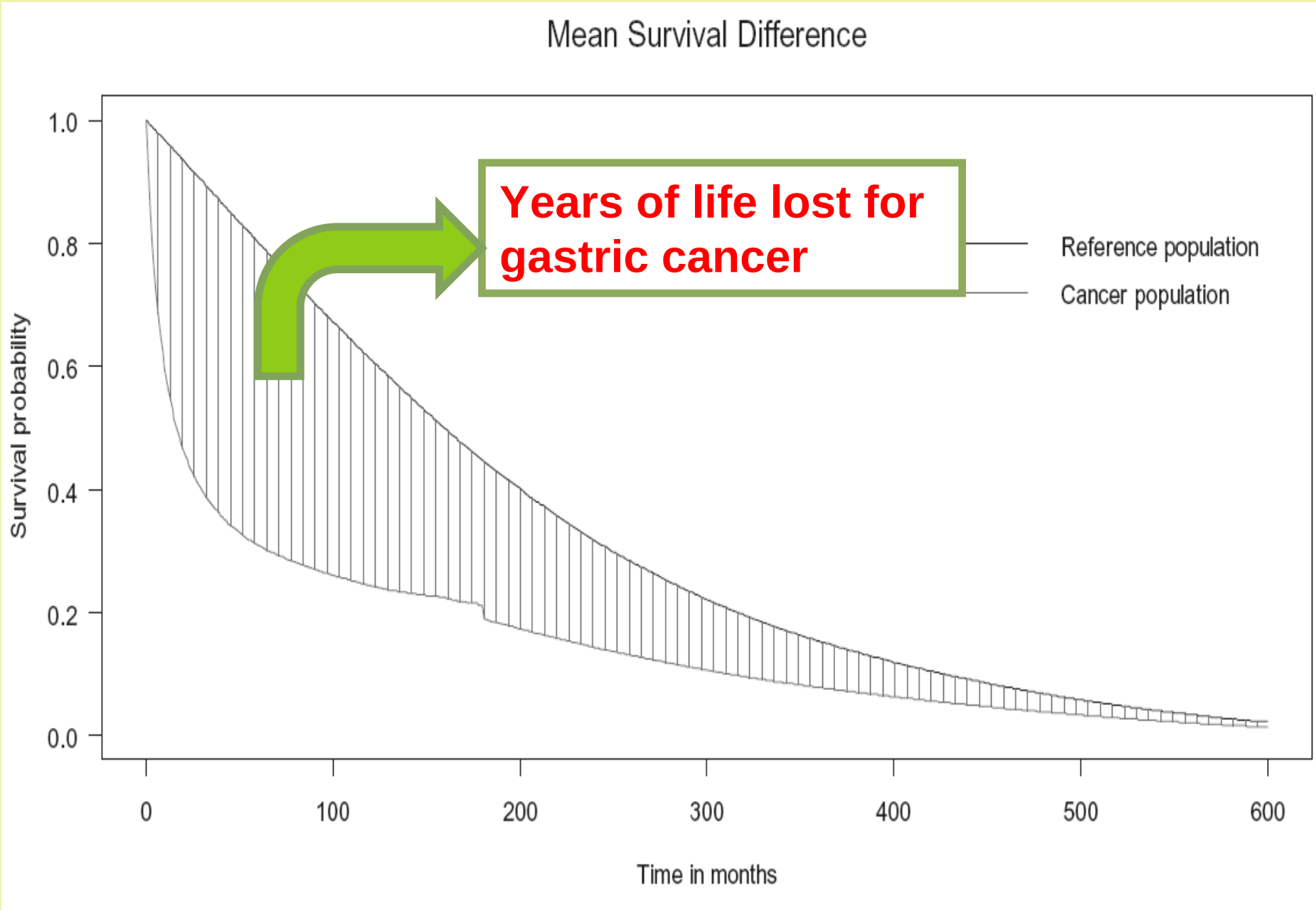
⬇

Long-term survival curve of the patient population beyond the follow-up limits as:

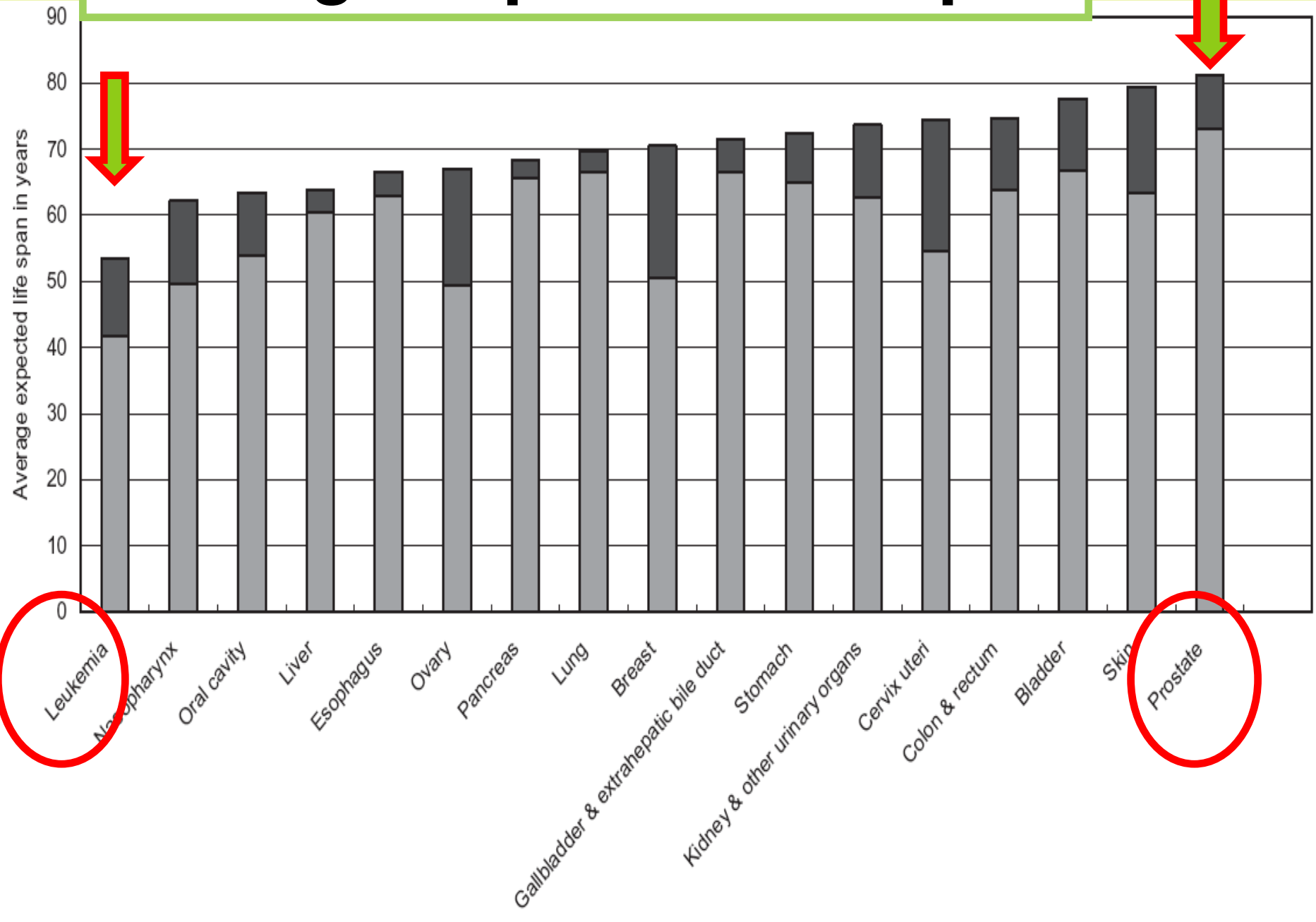
$$\hat{S}(t|\,\text{patient population}) = \hat{S}(t|\,\text{reference population})\frac{\exp(\hat{\alpha}+\hat{\beta}t)}{1+\exp(\hat{\alpha}+\hat{\beta}t)}.$$

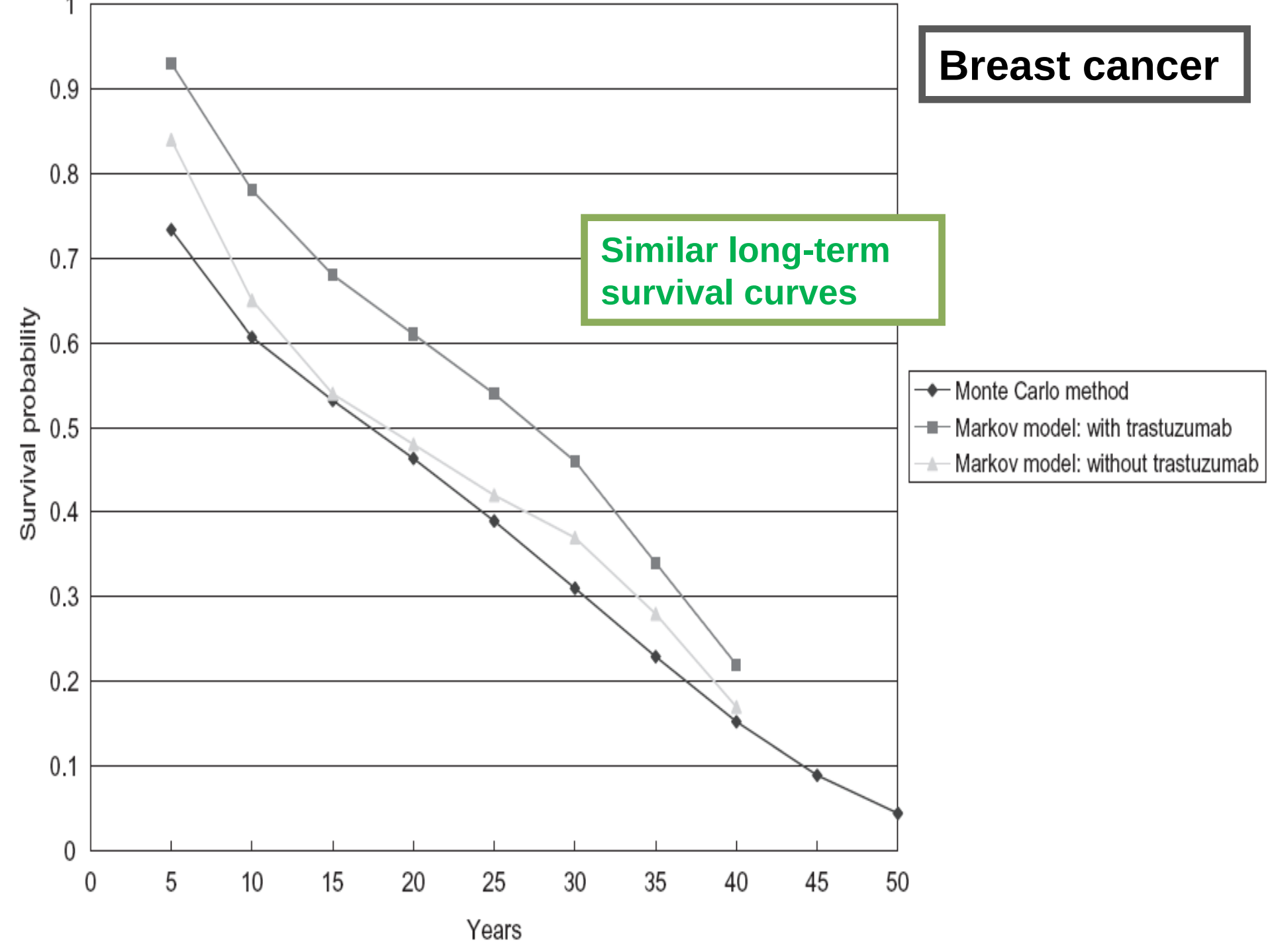
Results

Cancer site	Cohort size	Mean age at diagnosis (SD)	Censoring rate (%)	15-year survival based on K–M estimate	Lifetime survival based on MC method (SE)	Average EYLL based on MC method (SE)	Subtotal of EYLL based on MC method
Pancreas	7,931	65.6 (12.7)	8.28	1.75 (0.05)	2.81 (0.17)	12.87	12,769
Lung	58,773	66.6 (11.7)	9.97	2.20 (0.02)	3.09 (0.07)	11.79	79,584
Liver	68,585	60.4 (13.5)	13.28	2.63 (0.02)	3.45 (0.08)	15.61	133,282
Esophagus	9,710	63.0 (12.1)	11.28	2.42 (0.04)	3.54 (0.20)	13.25	16,279
Gallbladder and extrahepatic bile duct	5,097	66.5 (12.0)	17.72	3.37 (0.07)	4.98 (0.20)	10.36	6,312
Stomach	35,477	64.9 (13.6)	26.80	4.78 (0.03)	7.51 (0.14)	8.80	30,794
Prostate	14,288	73.1 (8.0)	44.65	7.05 (0.06)	8.17 (0.13)	1.72	3,433
Oral cavity	26,681	53.8 (12.9)	35.94	5.96 (0.04)	9.58 (0.61)	14.00	49,671
Colon and rectum	60,789	63.8 (13.7)	41.94	7.00 (0.03)	10.86 (0.11)	6.36	45,905
Kidney and other urinary organs	11,671	62.7 (15.1)	43.68	7.07 (0.07)	10.97 (0.85)	6.74	10,120
Bladder	15,092	66.7 (12.6)	46.93	7.71 (0.05)	10.99 (0.20)	3.83	6,727
Leukemia	9,224	41.8 (25.5)	28.49	4.97 (0.08)	11.61 (0.94)	19.34	18,602
Nasopharynx	15,231	49.6 (13.4)	43.06	7.42 (0.05)	12.59 (0.74)	14.79	20,271
Skin	14,005	63.3 (16.9)	62.18	9.71 (0.05)	16.16 (0.22)	1.59	2,873
Ovary	6,436	49.3 (17.0)	52.59	8.46 (0.11)	17.71 (0.80)	11.91	8,775
Cervix uteri	29,636	54.7 (13.8)	63.92	10.21 (0.03)	19.77 (0.30)	6.18	14,978
Breast	36,668	50.5 (12.5)	66.94	10.41 (0.03)	20.01 (0.80)	9.35	43,633


Mean Survival Difference
Years of life lost for gastric cancer
Reference population
Cancer population
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
Time in months

Average expected life span




Breast cancer
Similar long-term survival curves
Survival probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Years
Monte Carlo method
Markov model: with trastuzumab
Markov model: without trastuzumab