A register-based SAH study in Japan: high incidence rate and recent decline trend based on lifestyle

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OBJECTIVE Japan has been reported to have the highest (and increasing) incidence of subarachnoid hemorrhage (SAH) in the world. However, there has never been a report on the nationwide incidence rate and recent trends for SAH in Japan. In this register-based study, the authors aimed to clarify the estimated nationwide SAH incidence rate and the recent trend in SAH incidence in Japan and the reasons for any changes in this trend.

METHODS The authors compiled data from the Japanese Ministry of Health, Labour and Welfare and from the records of the Japan Neurosurgical Society. They reviewed the age-standardized nationwide SAH mortality rate, the estimated age-standardized SAH incidence rate according to the age-standardized SAH mortality rate, and the estimated crude SAH incidence rate, including the 95% confidence intervals, from 2003 to 2015. The trends in the number of treatments for unruptured and ruptured cerebral aneurysms, as well as the prevalence of hypertension, current smoking status, and use of cholesterol-lowering drugs, were assessed. The estimated treatment rate for unruptured cerebral aneurysms (UCAs) was also calculated along with the 95% confidence interval.

RESULTS The estimated age-standardized nationwide SAH incidence rate significantly declined from 31.34 cases (95% CI 31.32–31.34) to 27.63 (95% CI 27.59–27.63; decrease by 11.8%) per 100,000 person-years. This decline was based on the 2010 population as the reference from 2003 through 2015 and a case-fatality rate of SAH that was assumed to decrease by 1% annually from 44% in 2003 to 32% in 2015. According to sensitivity analysis, the change rate of the estimated age-standardized SAH incidence rate ranged from –56.69% to 23.27%, with a mean of –30.91% (SD 20.52%), and there were decline trends in 92% of all trends. The estimated nationwide crude SAH incidence rate also showed a significant decline from 23.79 (95% CI 23.78–23.79) to 20.25 (95% CI 20.24–20.25; decrease by 14.9%) per 100,000 person-years. The trend in treatment numbers for UCAs increased significantly ($p < 0.0001$) from 2003 through 2015; however, the estimated treatment rate for UCAs was only 0.19 (95% CI 0.19–0.20) to 0.51 (95% CI 0.50–0.51) among all UCA patients. The prevalence of hypertension (males, $p = 0.0003$; females, $p < 0.0001$) and current smoking

ABBREVIATIONS JNS = Japan Neurosurgical Society; MHLW = Ministry of Health, Labour and Welfare; NHNS = National Health and Nutrition Survey; RCA = ruptured cerebral aneurysm; SAH = subarachnoid hemorrhage; UCA = unruptured cerebral aneurysm.

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status (males, $p < 0.0001$; females, $p = 0.0002$) declined significantly from 2003 through 2015, while the use of cholesterol-lowering drugs increased significantly (males, $p < 0.0001$; females, $p = 0.0005$) during the same period.

CONCLUSIONS The estimated nationwide SAH incidence rate in Japan was higher than rates in other countries, although it has declined recently. An improving lifestyle may have contributed to the declining rate of SAH incidence in Japan.

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KEYWORDS subarachnoid hemorrhage; epidemiology; incidence; trends; registry; vascular disorders

FINLAND¹ and Japan² have been reported to have the highest incidences of subarachnoid hemorrhage (SAH) in the world. However, recently available evidence does not support a high incidence in Finland³ because the evidence was based on regional studies without standardization of reference populations^{4–6} and because, according to other data, the incidence rate decreased by 24% between 1998 and 2012 along with a simultaneous decrease in smoking prevalence.⁷ According to a recent meta-analysis,⁸ the crude global incidence of SAH has declined from 10.2 per 100,000 person-years in 1980 to 6.1 in 2010 (decline by 40.2%), paralleling a global decrease in mean blood pressure and smoking prevalence. On the other hand, the regional incidence rate of SAH in Japan was reported as 13.7 per 100,000 person-years in 1977⁹ and 27.9 per 100,000 person-years in 2006,¹⁰ and according to the aforementioned meta-analysis,⁸ there was a significant increase in the crude SAH incidence and sex-adjusted SAH incidence (by 59.1%) over the past 3 decades. However, the Japanese data used in this study were from up to 2008 and all studies were regional rather than nationwide. Based on data to date from the Ministry of Health, Labour and Welfare (MHLW) in Japan, the recent crude SAH mortality has declined after a peak in 2005, even though the peak in the population occurred in 2008.¹¹

In contrast, the number of treatments for unruptured cerebral aneurysms (UCAs) has been increasing in Japan because UCAs are frequently discovered at screening checkups.¹² Furthermore, the high rates of total UCA treatments (45.5%) and small UCA (< 5 mm in diameter) treatments (37.1%)^{13,14} are attributable to a 2.8 times higher rupture rate of UCAs in Japan than in Western countries.¹⁵ However, there is no evidence that the increasing trend in the number of treatments for UCAs or changing lifestyle habits would contribute to reducing the incidence of SAH in Japan. Therefore, in this register-based study, we aimed to clarify the estimated nationwide SAH incidence rate and the recent trend in SAH incidence in Japan, as well as to investigate the effects of the increasing number of treatments for UCAs and changes in the prevalence of hypertension, current smoking, and use of cholesterol-lowering drugs on this trend.

Methods

Protocol Approval, Patient Consent, Role of the Funding Source, and Data Availability

This study was approved by the Institutional Review Board of Hiroshima University and the Japan Neurosurgical Society (JNS; clinical trial registration no.: UMIN000034241, <http://www.umin.ac.jp/icdr/index.html>).

Because of the anonymous nature of the data, the requirement for informed consent by patients was waived, and an opt-out method was used as the informed consent for this study.

The anonymized data for this study will be shared by the request of any qualified investigator to the corresponding author. Investigators may access the data in the MHLW through the Statistics link on the website of the Japan MHLW. Primary data from the JNS will be made available upon reasonable request in accordance with the review board of the JNS.

Funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author has full access to all data in the study and has final responsibility for the decision to submit for publication.

Data Extraction

We extracted data from records in a database at the MHLW in Japan. Since 1970, the MHLW has conducted surveys every 5 years, the same years as the general population census.¹⁶ Every survey period lasted for the 12 months of the fiscal year (April 1 of the survey year to March 31 of the next year). The MHLW approved the secondary use of the data, which included the total population and the crude number of deaths caused by SAH every 5 years in males and females.¹⁷ Using these data and a direct method, we calculated the standardized nationwide SAH mortality rate per 100,000 person-years by age and sex using the years 2005 and 2010 as representative samples¹⁶ between 2003 and 2015. From the database of the MHLW, we extracted annual trends in the age-standardized percentage of subjects with high systolic blood pressure (> 140 mm Hg), current smoking status, and use of cholesterol-lowering drugs between 2003 and 2015.¹⁸ Additionally, we reviewed data from the JNS for 2003–2015. The JNS requires a certain number of operations to certify training programs and receives reports from each facility annually to meet this requirement. These reports include the number of UCAs and ruptured cerebral aneurysms (RCAs) treated with surgical clipping or endovascular coiling (radical treatment). We extracted these annual data for each procedure from 2003 to 2015 with the approval of the JNS.

Accuracy of Register-Based Diagnosis of SAH, Mortality, and MHLW Data

As required by law, all causes of death were reported to the government office. Emergent or autopsy CT imaging was conducted for almost all sudden-death patients in

Japan. The Organisation for Economic Co-operation and Development data show that Japan has the most acute care beds per 1000 population and the largest number of CT units per million population under a universal healthcare system.¹⁹ Additionally, the MHLW conducted a National Health and Nutrition Survey (NHNS) to determine levels of health and nutrition in Japan.^{20,21} The NHNS is a national nutrition survey conducted annually since 1945 by public health centers under the supervision of the MHLW in accordance with the Health Promotion Law. The NHNS has been detailed elsewhere.^{18,20} Briefly, based on the population census, 475 of the approximately 1 million census units were randomly sampled as survey areas. All noninstitutionalized Japanese persons aged 1 year or older and living in survey areas were asked to participate, excluding individuals holding foreign citizenship, those whose diet was not self-selected, and those using a special diet (mainly due to disease). By using the NHNS, the trends in hypertension, current smoking status, and use of cholesterol-lowering drugs from 2003 to 2015 were researched. Unfortunately, data on the use of cholesterol-lowering drugs started in 2005; therefore, the data from 2003 to 2004 were not available.

The accuracy of register-based diagnoses of SAH in the JNS is the responsibility of the director of each institute and is regularly verified by the JNS. All definitive diagnoses and medical records are linked to the universal medical insurance system and regularly checked by the MHLW. The JNS data include all major facilities listed in the Appendix and certified facilities belonging to the major facilities in Japan and all cases of aneurysm treatment in these facilities.

Calculation of SAH Mortality Rate and Incidence Rate

The SAH mortality rate and incidence rate are expressed as cases per 100,000 person-years. First, from the statistics of the MHLW, we collected the crude number of deaths caused by SAH every 5 years for males and females.¹⁷ Additionally, we retrieved the 5-year age group numbers from census populations in 2005 and 2010.¹⁶ Therefore, the SAH mortality rate could be standardized for age and sex by using the 2005 and 2010 populations as the standard.¹⁶ The age-standardized SAH mortality rate and 95% confidence interval could be calculated using the age-specific SAH mortality rates for each 5-year age group, dividing the number of deaths by the respective population and then multiplying the result by 100,000 person-years. The estimated age-standardized SAH incidence rate per 100,000 person-years could be estimated according to the age-standardized SAH mortality rate. The case-fatality rate of SAH has been reported to be from 32% to 45%—improving but higher in the elderly.^{22–26} Therefore, the case-fatality rate of SAH was assumed to decrease by 1% annually from 44% in 2003 to 32% in 2015 (Table 1). Additionally, we conducted a sensitivity analysis by changing both the case-fatality rate of SAH and the annual change in the case-fatality rate of SAH based on a range of assumed mortality rates and the annual change rate. The case-fatality rate of SAH was changed from 25% to 45% at 5% intervals, and the annual change in the case-fatality rate of SAH changed from –1% to 1% at 0.5% intervals

TABLE 1. Crude SAH mortality rates, age-standardized nationwide SAH mortality, and incidence rates, 2003–2015

Year	Crude SAH Mortality Rate			Age-Standardized SAH Mortality Rate (95% CI)						Estimated Age-Standardized SAH Incidence Rate (95% CI)*	
				By 2005			By 2010			Total by 2005	Total by 2010
	Total	M	F	Total	M	F	Total	M	F		
2003	11.8	9.2	14.4	12.35 (12.34–12.36)	9.47 (9.46–9.48)	15.06 (15.05–15.07)	13.79 (13.78–13.79)	10.27 (10.26–10.28)	16.98 (16.97–16.99)	28.07 (28.05–28.09)	31.34 (31.32–31.34)
2004	11.7	9.0	14.2	11.89 (11.88–11.89)	9.12 (9.11–9.12)	14.51 (14.50–14.52)	13.29 (13.29–13.30)	9.91 (9.90–9.92)	16.37 (16.36–16.38)	27.65 (27.63–27.65)	30.91 (30.91–30.93)
2005	11.8	9.2	14.2	11.64 (11.64–11.65)	9.12 (9.11–9.13)	14.06 (14.05–14.07)	13.03 (13.02–13.04)	9.96 (9.95–9.96)	15.85 (15.84–15.86)	27.71 (27.71–27.74)	31.02 (31.00–31.05)
2006	11.5	8.9	14.0	11.07 (11.06–11.07)	8.62 (8.61–8.63)	13.42 (13.41–13.42)	12.37 (12.36–12.38)	9.37 (9.36–9.38)	15.15 (15.14–15.15)	27.00 (26.98–27.00)	30.17 (30.15–30.20)
2007	11.3	8.7	13.8	10.64 (10.64–10.65)	8.30 (8.30–8.31)	12.90 (12.89–12.91)	11.88 (11.88–11.89)	9.02 (9.01–9.03)	14.56 (14.55–14.57)	26.60 (26.60–26.63)	29.70 (29.70–29.73)
2008	11.2	8.7	13.6	10.28 (10.28–10.29)	8.12 (8.11–8.13)	12.38 (12.37–12.39)	11.47 (11.48–11.49)	8.83 (8.82–8.83)	11.75 (11.74–11.75)	26.36 (26.36–26.38)	29.41 (29.44–29.46)
2009	11.1	8.5	13.5	9.95 (9.95–9.96)	7.87 (7.86–7.88)	12.01 (12.00–12.01)	11.12 (11.11–11.12)	8.54 (8.54–8.55)	13.56 (13.55–13.56)	26.18 (26.18–26.21)	29.26 (29.24–29.26)
2010	10.8	8.5	12.9	9.48 (9.48–9.49)	7.75 (7.74–7.75)	11.18 (11.17–11.18)	10.61 (10.60–10.61)	8.44 (8.43–8.45)	12.66 (12.65–12.66)	25.62 (25.62–25.65)	28.68 (28.65–28.68)
2011	10.7	8.1	13.1	9.18 (9.18–9.19)	7.20 (7.20–7.21)	11.13 (11.12–11.14)	10.30 (10.29–10.30)	7.87 (7.87–7.88)	12.60 (12.59–12.61)	25.50 (25.50–25.53)	28.61 (28.58–28.61)
2012	10.3	8.0	12.5	8.70 (8.69–8.70)	7.04 (7.03–7.04)	10.35 (10.34–10.35)	9.75 (9.74–9.75)	7.66 (7.66–7.67)	11.75 (11.74–11.75)	24.86 (24.83–24.86)	27.86 (27.83–27.86)
2013	9.9	7.7	12.0	8.20 (8.20–8.21)	6.68 (6.67–6.68)	9.73 (9.73–9.74)	9.17 (9.16–9.18)	7.26 (7.25–7.26)	11.02 (11.01–11.03)	24.12 (24.12–24.15)	26.97 (26.94–27.00)
2014	10.1	7.7	12.3	8.13 (8.13–8.14)	6.53 (6.53–6.54)	9.75 (9.74–9.75)	9.12 (9.12–9.13)	7.13 (7.12–7.14)	11.07 (11.06–11.08)	24.64 (24.64–24.67)	27.64 (27.64–27.67)
2015	10.0	7.6	12.2	7.90 (7.90–7.91)	6.39 (6.39–6.40)	9.43 (9.42–9.44)	8.84 (8.83–8.84)	6.93 (6.92–6.93)	10.71 (10.70–10.72)	24.69 (24.69–24.72)	27.63 (27.59–27.63)

Values in the table represent no. of cases per 100,000 person-years. Used as standard years: 2005 and 2010.

* The case-fatality rate of SAH was assumed to decrease by 1% annually from 44% in 2003 to 32% in 2015.

TABLE 2. Sensitivity analysis by the case-fatality rate of SAH and the annual change, 2003–2015

Case-Fatality Rate of SAH	Annual Change in Case-Fatality Rate of SAH from 2003 to 2015				
	1%	0.5%	0	–0.5%	–1%
45%					
2003	30.64 (30.62–30.64)	30.64 (30.62–30.64)	30.64 (30.62–30.64)	30.64 (30.62–30.64)	30.64 (30.62–30.64)
2015	15.51 (15.49–15.51)	17.33 (17.31–17.33)	19.64 (19.62–19.64)	22.67 (22.64–22.67)	26.79 (26.76–26.79)
Change rate from 2003 to 2015 (%)	–49.38	–43.44	–35.9	–26.01	–12.57
40%					
2003	34.48 (34.45–34.48)	34.48 (34.45–34.48)	34.48 (34.45–34.48)	34.48 (34.45–34.48)	34.48 (34.45–34.48)
2015	17.00 (16.98–17.00)	19.22 (19.20–19.22)	22.10 (22.08–22.10)	26.00 (25.97–26.00)	31.57 (31.54–31.57)
Change rate from 2003 to 2015 (%)	–50.70	–44.26	–35.90	–24.59	–8.44
35%					
2003	39.40 (39.37–39.40)	39.40 (39.37–39.40)	39.40 (39.37–39.40)	39.40 (39.37–39.40)	39.40 (39.37–39.40)
2015	18.81 (18.79–18.81)	21.56 (21.54–21.56)	25.26 (25.23–25.26)	30.48 (30.45–30.48)	38.43 (38.39–38.43)
Change rate from 2003 to 2015 (%)	–52.26	–45.28	–35.89	–22.64	–2.46
30%					
2003	45.97 (45.93–45.97)	45.97 (45.93–45.97)	45.97 (45.93–45.97)	45.97 (45.93–45.97)	45.97 (45.93–45.97)
2015	21.05 (21.02–21.05)	24.56 (24.53–24.56)	29.47 (29.43–29.47)	36.83 (36.79–36.83)	49.11 (49.06–49.11)
Change rate from 2003 to 2015 (%)	–54.21	–46.57	–35.89	–19.88	6.83
25%					
2003	55.16 (55.12–55.16)	55.16 (55.12–55.16)	55.16 (55.12–55.16)	55.16 (55.12–55.16)	55.16 (55.12–55.16)
2015	23.89 (23.86–23.89)	28.52 (28.48–28.52)	35.36 (35.32–35.36)	46.53 (46.47–46.53)	68.00 (67.92–68.00)
Change rate from 2003 to 2015 (%)	–56.69	–48.30	–35.90	–15.65	23.27

Values in the table body represent the estimated age-standardized SAH incidence rate per 100,000 person-years in total and the change rate (%) from 2003 to 2015.

(Table 2). The formula for the estimated age-standardized SAH incidence rate was the age-standardized SAH mortality rate/case-fatality rate of SAH/100).

Second, the estimated crude SAH incidence rate was calculated using the number of radical treatments of RCAs from the JNS registered data and the crude number of deaths caused by SAH from the MHLW. The total number of SAHs per year was calculated with the following formula: number of deaths caused by SAH + number of RCA survivors after radical treatment + number of conservative treatment survivors after SAH. The number of RCA survivors after radical treatment was calculated with the following formula: number of radical treatments for RCA $\times$ (1 – [10%–20%]/100). We used this formula because the case-fatality rate after radical treatment in Japan has been reported to range from 10% to 20%,^{27,28} with the assumption of no change in the case-fatality rate after radical treatment during the study period. The number of conservative treatment survivors after SAH (α) and the SAH incidence rate of conservative treatment survivors (β) were assessed. The estimated crude SAH incidence rate was (total number of SAHs in a year/population in the same year) $\times$ 100,000. Finally, total number of SAHs – α = number of deaths caused by SAH + (number of radical treatments for RCA) $\times$ (1 – [10%–20%]/100), and crude

SAH incidence rate – β per 100,000 person-years = (total number of SAHs – α)/population in the same year. Therefore, we can estimate the crude SAH incidence rate – β per 100,000 person-years including the 95% confidence interval (Table 3).

Estimation of Treatment Rate for UCAs

To estimate the treatment rate for UCAs, we used a range from approximately 3% to 5% for the prevalence rate of UCAs in patients 50 years of age.²⁹ The estimated number of patients with UCAs and the estimated treatment rate for UCAs per year could be calculated based on the following formula. The estimated number of patients with UCAs per year was the number of people over 15 years of age $\times$ [(3%–5%)/100] because the incidence of de novo UCAs was 0.6% per patient-year and negligible.³⁰ The estimated treatment rate for UCAs per year including the 95% confidence interval was (number of treatments of UCAs/estimated number of patients with UCAs) $\times$ 100 (Table 4). In this formula, we assumed that multiple UCAs were treated simultaneously and all de novo aneurysms were included among UCAs.

Statistical Analysis

We used Stata statistical software (version 13.1, Stata

TABLE 3. Estimation of the nationwide crude SAH incidence rate from 2003 to 2015

Year	No. of Deaths Caused by SAH	No. of Radical Tx for RCAs	No. of RCA Survivors After Radical Tx		α After SAH	Estimated Total No. of SAHs – α		Population ($\times 1000$)	Estimated Crude SAH Incidence Rate – $\beta/100,000$ Person-Yrs (95% CI)	
			10% CFR	20% CFR		10% CFR	20% CFR		10% CFR	20% CFR
2003	14,929	19,305	17,375	15,444	α_1	30,373	32,304	127,694	25.30 (25.29–25.31)	23.79 (23.78–23.79)
2004	14,737	19,366	17,429	15,493	α_2	30,230	32,166	127,787	25.17 (25.16–25.18)	23.66 (23.65–23.66)
2005	14,883	18,942	17,048	15,154	α_3	30,037	31,931	127,768	24.99 (24.98–25.00)	23.51 (23.50–23.52)
2006	14,466	19,097	17,187	15,278	α_4	29,744	31,653	127,901	24.75 (24.74–24.76)	23.26 (23.25–23.26)
2007	14,243	19,085	17,177	15,268	α_5	29,511	31,420	128,033	24.54 (24.53–24.55)	23.05 (23.04–23.06)
2008	14,075	18,815	16,934	15,052	α_6	29,127	31,009	128,084	24.21 (24.20–24.22)	22.74 (22.73–22.75)
2009	13,923	18,758	16,882	15,006	α_7	28,929	30,805	128,032	24.06 (24.05–24.07)	22.60 (22.59–22.60)
2010	13,591	18,047	16,242	14,438	α_8	28,029	29,833	128,057	23.30 (23.29–23.30)	21.89 (21.88–21.90)
2011	13,460	17,616	15,854	14,093	α_9	27,553	29,314	127,799	22.94 (22.93–22.95)	21.56 (21.55–21.57)
2012	13,004	17,618	15,856	14,094	α_{10}	27,098	28,860	127,515	22.63 (22.62–22.64)	21.25 (21.24–21.26)
2013	12,479	17,040	15,336	13,632	α_{11}	26,111	27,815	127,298	21.85 (21.84–21.86)	20.51 (20.50–20.52)
2014	12,662	16,751	15,076	13,401	α_{12}	26,063	27,738	127,083	21.83 (21.82–21.83)	20.51 (20.50–20.52)
2015	12,476	16,571	14,914	13,257	α_{13}	25,733	27,390	127,095	21.55 (21.54–21.56)	20.25 (20.24–20.25)

α = number of conservative treatment survivors; β = incidence rate of conservative treatment survivors per 100,000 person-years; CFR = case-fatality rate after radical treatment; Tx = treatment.

Corp) for analyses. By using the linear regression model to compute the slope, we examined several trends from 2003 to 2015: trends in the nationwide age-standardized SAH mortality rate, crude SAH incidence rate, treatment numbers for UCAs and RCAs, and number of deaths caused by SAH, as well as annual trends in the age-standardized percentage of subjects with systolic blood pressure over 140 mm Hg, current smokers, and patients taking cholesterol-lowering drugs.

Results

Table 1 shows the crude SAH mortality rates, age-standardized nationwide SAH mortality rates, and inci-

dence rates per 100,000 person-years from 2003 to 2015 using 2005 and 2010 as standard years. The crude SAH mortality rate significantly declined from 11.8 to 10.0 (by 15.3%) per 100,000 person-years during this period ($p < 0.001$). The age-standardized SAH mortality rates from 2003 to 2015 also significantly declined from 12.35 (95% CI 12.34–12.36) to 7.90 (95% CI 7.90–7.91; decrease by 37.0%, $p < 0.001$) per 100,000 person-years using the 2005 Japanese population as standard and from 13.79 (95% CI 13.78–13.79) to 8.84 (95% CI 8.83–8.84; decrease by 35.9%, $p < 0.001$) per 100,000 person-years using the 2010 Japanese population as standard. The estimated age-standardized nationwide SAH incidence rate also declined from 28.07 (95% CI 28.05–28.09) to 24.69

TABLE 4. Estimation of treatment rate for UCAs from 2003 to 2015

Year	No. of Population Over 15 Yrs ($\times 1000$)	Estimated No. of UCA Patients $\times 1000$		Tx No. for UCAs	Estimated Tx Rate for UCAs per Yr Expressed as % (95% CI)	
		3% Prevalence of UCAs	5% Prevalence of UCAs		3% Prevalence of UCAs	5% Prevalence of UCAs
2003	109,715	3,291	5,486	10,666	0.32 (0.32–0.33)	0.19 (0.19–0.20)
2004	109,953	3,299	5,498	10,607	0.32 (0.32–0.33)	0.19 (0.19–0.20)
2005	110,183	3,305	5,509	11,132	0.34 (0.33–0.34)	0.20 (0.20–0.21)
2006	110,326	3,310	5,516	11,892	0.36 (0.35–0.37)	0.22 (0.21–0.22)
2007	110,456	3,314	5,523	13,165	0.40 (0.39–0.40)	0.24 (0.23–0.24)
2008	110,545	3,316	5,527	14,025	0.42 (0.42–0.43)	0.25 (0.25–0.26)
2009	110,631	3,319	5,532	14,135	0.43 (0.42–0.43)	0.26 (0.25–0.26)
2010	111,254	3,338	5,563	16,008	0.48 (0.47–0.49)	0.29 (0.28–0.29)
2011	111,094	3,333	5,555	15,830	0.47 (0.47–0.48)	0.28 (0.28–0.29)
2012	110,968	3,329	5,548	16,198	0.49 (0.48–0.49)	0.29 (0.29–0.30)
2013	110,908	3,327	5,545	16,840	0.51 (0.50–0.51)	0.30 (0.30–0.31)
2014	110,850	3,326	5,543	16,416	0.49 (0.49–0.50)	0.30 (0.29–0.30)
2015	111,208	3,336	5,560	16,291	0.49 (0.48–0.50)	0.29 (0.29–0.30)

FIG. 1. Trends in treatment numbers for UCAs and RCAs and number of deaths caused by SAH in Japan, from 2003 through 2015. * $p < 0.0001$. Figure is available in color online only.

(95% CI 24.69–24.72; decrease by 12.0%, $p < 0.001$) per 100,000 person-years using the 2005 population as standard and from 31.34 (95% CI 31.32–31.34) to 27.63 (95% CI 27.59–27.63; decrease by 11.8%, $p < 0.001$) per 100,000 person-years using the 2010 population as standard, assuming that the case-fatality rate of SAH decreased by 1% annually from 44% in 2003 to 32% in 2015. Table 2 shows that the change rate of the estimated age-standardized SAH incidence rate per 100,000 person-years in total SAH from 2003 to 2015 ranged from –56.69% to 23.27%, with a mean of –30.91% (SD 20.52%), and there were decline trends in 92% of all trends.

Table 3 reveals the number of deaths caused by SAH, the number of radical treatments for RCAs, the number of RCA survivors after radical treatment, the number of conservative treatment survivors after SAH (α), the estimated total number of SAHs excluding the conservative treatment survivors after SAH (α), the population, and the estimated crude SAH incidence rate excluding the incidence rate of conservative treatment survivors after SAH (β) per 100,000 person-years from 2003 to 2015. The estimated crude SAH incidence rate excluding the incidence rate of conservative treatment survivors after SAH (β) per 100,000 person-years significantly declined from 25.30 (95% CI 25.29–25.31) to 21.55 (95% CI 21.54–21.56; decrease by 14.8%, $p < 0.001$) per 100,000 population and from 23.79 (95% CI 23.78–23.79) to 20.25 (95% CI 20.24–20.25; decrease by 14.9%, $p < 0.001$) per 100,000 person-years, if the case-fatality rate after radical treatment of SAH was 10% or 20%, respectively.

Figure 1 shows the trends in radical treatment numbers for UCAs and RCAs and number of deaths caused by SAH, from 2003 through 2015. The radical treatment numbers for UCAs significantly increased ($p < 0.0001$), whereas radical treatment numbers for RCAs and number of deaths caused by SAH significantly declined ($p < 0.0001$) during this period. Table 4 shows the trends in the population number over 15 years of age, the estimated number of UCA patients, the treatment number for UCAs, and the estimated treatment rate for UCAs, from 2003 to

FIG. 2. Annual trends in the age-standardized percentage of subjects with systolic blood pressure over 140 mm Hg. †Male ($p = 0.0003$); *female ($p < 0.0001$). Figure is available in color online only.

2015. The estimated treatment rate for UCAs ranged from 0.32% (95% CI 0.32%–0.33%) to 0.51% (0.50%–0.51%) and 0.19% (0.19%–0.20%) to 0.30% (0.30%–0.31%), if the prevalence of UCAs was 3% or 5%, respectively. Figures 2–4 show annual trends from 2003 through 2015 in the age-standardized percentage of subjects with high systolic blood pressure (over 140 mm Hg; Fig. 2), current smoking status (Fig. 3), and patients taking cholesterol-lowering drugs (Fig. 4). The trend in the percentage of males ($p = 0.0003$) and females ($p < 0.0001$) with high systolic blood pressure and males ($p < 0.0001$) and females ($p = 0.0002$) currently smoking significantly declined from 2003 through 2015. The trend in the percentage of males ($p < 0.0001$) and females ($p = 0.0005$) taking cholesterol-lowering drugs significantly increased from 2005 through 2015. (Data on the use of cholesterol-lowering drugs for 2003–2004 were not available.)

Discussion

Nationwide SAH Incidence Rate and Recent Trend in Japan

To our knowledge, this is the first register-based study to report the nationwide SAH incidence rate and the recent trend in SAH in Japan. We analyzed the estimated nationwide SAH incidence rate in Japan by using two different methods, namely the estimated age-standardized SAH incidence rate per 100,000 person-years according to MHLW data and the estimated crude SAH incidence rate excluding the incidence rate of conservative treatment survivors after SAH per 100,000 person-years according to JNS register-based data. The estimated age-standardized SAH incidence rate was higher than the estimated crude SAH incidence rate excluding the incidence rate of conservative treatment survivors after SAH. The treatment method, emergency transport rate, and emergent imaging rate for SAH have never changed rapidly; however, aging has accelerated during the study period in Japan. This rapid aging could be the reason for the difference between the

FIG. 3. Annual trends in the age-standardized percentage of subjects with current smoking status. *Male ($p < 0.0001$); †female ($p = 0.0002$). Figure is available in color online only.

two estimated nationwide SAH incidence rates. We found a higher decline in the SAH mortality rate after age standardization than in the crude data (Table 1). Additionally, there was no longer a significant increase in the SAH incidence rate after age standardization by meta-analysis.⁸ We selected the maximum conceivable reduction rate of the case fatality of SAH as 1% annually, from 44% in 2003 to 32% in 2015. According to our sensitivity analysis (Table 2), there were significant decline trends in 92% of all trends. The change rate of the estimated age-standardized SAH incidence rate increased in only two assumptions from 30% and 25% with an annual 1% decline trend in the case-fatality rate of SAH. However, these two assumptions were far from real clinical evidence. Therefore, we could conclude that there was at least a significant decline in the SAH incidence rate between 2003 and 2015 in Japan and a higher SAH incidence rate in Japan compared to that of other countries.⁸

Reasons for a Decline in the Incidence of SAH

We tried to verify whether the rapidly increasing trend in the treatment number for UCAs contributed to the decline in the incidence of SAH. The estimated treatment rate for UCAs from 2003 to 2015 ranged from only 0.19% to 0.51% (Table 4). The number needed to treat was 204 to 548 UCAs for 1 SAH reduction if the annual rupture rate was 0.96% per year.¹⁴ From this fact, we could conclude that the decline in the incidence of SAH according to the increase in treating UCAs was too low.

Hypertension and smoking have been strong risk factors for SAH,^{31,32} and the use of statin drugs has been an inverse risk for SAH.³³ In Japan, statins are used as the cholesterol-lowering drug in more than 80% of patients. Therefore, we investigated the trends in these lifestyle diseases and the use of cholesterol-lowering drugs. The prevalence of hypertension and smoking has declined significantly from 2003 through 2015, and the use of cholesterol-lowering drugs has increased significantly from 2005

FIG. 4. Annual trends in the age-standardized percentage of subjects taking cholesterol-lowering drugs. *Male ($p < 0.0001$); †female ($p = 0.0005$). Figure is available in color online only.

through 2015. Accordingly, the decline in the incidence of SAH could relate to improvements in the general risk factors for SAH, such as hypertension and smoking, as was noted in a recent meta-analysis.⁸ While it is difficult to measure the direct impact of these health factors on the decline of SAH, we speculate that the significant decrease in SAH incidence may strongly relate to improved risk factor control. The present study revealed that we could not reduce the incidence of SAH through the radical treatment of individual UCAs because of the excessive numbers of UCAs. Reducing lifestyle diseases and the use of some drugs^{33,34} are possible solutions leading to the decline of SAH in Japan.

Study Limitations

To our knowledge, this is the first study to report the estimated nationwide SAH incidence rate and recent trends in SAH in Japan, but it does have several limitations. First, because of their retrospective register-based nature, the statistical data from the MHLW could not be precisely controlled. A population-based study or prospective observation study could be ideal for the SAH incidence rate, but it seemed impossible given the high cost. A register-based study can have coding errors or possibly inaccurate case-finding methods; however, it can also have a large number of cases. Therefore, we used a register-based study realistically. Second, the estimated nationwide age-standardized SAH incidence rate could not be directly searched because there has never been data on the nationwide SAH incidence in Japan. Therefore, deaths caused by SAH, as well as the population in the census, were used to estimate the nationwide age-standardized SAH incidence rate. Third, no reports have previously defined the formulas to estimate the SAH incidence rate or the estimated treatment rate of UCAs, and we could not know the change in SAH case-fatality rate and case-fatality rate after radical treatment of SAH during the research period; however, we assumed these rates according to previous studies. Fourth, because the Japanese population is rapidly aging, the age-

standardized incidence rate also changes according to the year selected as the standard.

Conclusions

The nationwide SAH incidence rate in Japan is higher than in other countries. However, a recent decline trend in SAH was shown in this study. An improving lifestyle may have contributed to reducing the incidence of SAH in Japan. Further prospective studies are necessary to validate the reasons for this decline in SAH.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Ikawa, Morita, Nakayama, Sakai, Iihara, Shiokawa, Date, Nozaki, Kinouchi, Houkin, Saito, Tominaga, Suzuki, Miyamoto, Kurisu, Arai. Acquisition of data: Ikawa, Morita, Nakayama, Sakai, Iihara, Shiokawa, Date, Nozaki, Kinouchi, Houkin, Saito, Tominaga, Suzuki, Miyamoto, Kurisu, Arai. Analysis and interpretation of data: Ikawa, Goto. Drafting the article: Ikawa, Goto, Sakai, Iihara, Shiokawa, Date,

Kinouchi. Critically revising the article: Ikawa, Morita, Nozaki. Reviewed submitted version of manuscript: Ikawa, Morita, Shiokawa, Nozaki, Tominaga. Approved the final version of the manuscript on behalf of all authors: Ikawa. Statistical analysis: Ikawa, Nakayama, Goto. Administrative/technical/material support: Nozaki, Kinouchi, Houkin, Saito, Tominaga, Arai. Study supervision: Morita, Nakayama, Shiokawa, Date, Nozaki, Kinouchi, Saito, Tominaga, Suzuki, Miyamoto, Kurisu, Arai.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Appendix. <https://thejns.org/doi/suppl/10.3171/2020.1.JNS192848>.

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