Declining Mortality From Subarachnoid Hemorrhage
Changes in Incidence and Case Fatality From 1985 Through 2000

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Background and Purpose—Northern Sweden has one of the highest incidence rates of subarachnoid hemorrhage (SAH) among the populations covered by the WHO MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) Project, approximately twice as high as in the other populations in Europe. In this study, trends in incidence, 28-day case fatality (CF), and mortality in SAH were followed over a 16-year period.

Methods—Since 1985, all SAHs in northern Sweden among patients 25 to 74 years old have been validated using strict MONICA criteria. From 1985 through 2000, 392 men and 592 women had SAH. During 3 years, 1997 to 1999, SAH among those aged 75 and older were also included.

Results—The total incidence among those 25 years and older was 13.3 per 100 000 in men and 24.4 per 100 000 in women. During the 16 years of observation, age standardized incidence in the group aged 25 to 74 years decreased significantly in men (P for trend <0.0001) but remained essentially unchanged in women (P for trend=0.64). The 28-day CF for all years was 36.5% in men, with no significant trend (P=0.7). In women, average CF was 35%, with a significant decline (P=0.003). The annual mortality decreased significantly in both sexes (by 3.87 [95% CI±2.75 percentage points] in men and 3.97 [95% CI±2.29] in women).

Conclusions—The decline in SAH mortality has different explanations in men (declining incidence) and in women (declining CF). (Stroke. 2004;35:2059-2063.)

Key Words: fatal outcome ■ incidence ■ stroke ■ subarachnoid hemorrhage

The incidence rates of subarachnoid hemorrhages (SAH) vary from 3 to 23 per 100 000 in different populations.1–4 In a review of population-based studies from 1960 to 1992, the case fatality (CF) in the acute phase ranged between 32% and 67%.5

The epidemiology of SAH is only partially known. One limitation is that there are conflicting results in published data about the incidence in elderly populations. Contrary to previous belief that SAH mainly affects young and middle-aged people, the results of recent studies suggest that the incidence of SAH increases with increasing age and has a maximum in the oldest age groups. However, only few population-based studies have included very old patients.6–8

Another aspect of SAH epidemiology that has been insufficiently explored is the long-time trends in SAH mortality and its determinants.4,6,8,9 If mortality is changing over time, to what extent do changes in incidence and CF contribute?

The present study was performed in northern Sweden, where incidences rates of SAH are the second highest among the 11 populations participating in the WHO MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) Project.3 The primary purpose of this study was to evaluate 16-year trends of SAH mortality, incidence, and CF in men and women aged 25 to 74 years in northern Sweden. In addition, we report the age-specific SAH incidence rates in all ages during a 3-year period (1997 to 1999).

Subjects and Methods

Study Population

In 1985, the 2 northern-most counties in Sweden joined the WHO MONICA Project. The area covered by the study is 154 000 km² (equal to the area of England and Wales together) and is sparsely populated. There are 8 acute hospitals in the region, but only 1 with neurosurgical facilities, located at the University Hospital in Umeå. The distance from the most distant community to the university hospital is 620 km. During the years 1985 to 2000, there were no systematic screening programs for unruptured aneurysms in the area. During 1985 to 2000, the total population in the 2 counties was 513 300 inhabitants, and in the group aged 25 to 74 years (the target group in this study) the population was 315 000.

In the Northern Sweden MONICA Project, all stroke events occurring among patients aged 25 to 74 years and who are permanently living in the area are recorded according to standardized MONICA protocols.10 Details on the stroke registration procedures have been published previously.11,12 The Ethics Committee of Umeå University approved the MONICA stroke registrations.

Case Ascertainment and Definitions

The main sources of case findings were hospital discharge records with International Classification of Diseases, Ninth Revision (ICD-9) code diagnoses 430 through 438 and death certificates.
Admission lists from health care centers including general practitioners were also scrutinized. From 1997, the ICD-10 was used.

The MONICA criteria for SAH included the typical symptoms and at least 1 of the following criteria:13

- Necropsy finding of recent subarachnoid hemorrhage and an aneurysm or arteriovenous malformation
- Computer tomography (CT) findings of blood in Sylvian fissure or between the frontal lobes or in the basal cistern or in the cerebral ventricles
- Cerebrospinal fluid (liquor) bloody (>2000 erythrocytes/mm³) and an aneurysm or an arteriovenous malformation found on angiography
- Cerebrospinal fluid (liquor) bloody (>2000 erythrocytes/mm³) xanthochromic and the possibility of intracerebral hemorrhage excluded by CT examination or necropsy

According to these diagnostic criteria, SAHs of all aneurysmal origins, as well as other identified and unknown causes, were included. If a new SAH occurred within the first 28 days after the initial onset, the events were considered as 1 occasion. The survival status was followed-up during the first 28 days after onset. During the 16-year period, a total of 27 of the 984 events (2.8%) had had a previous stroke (14 ischemic strokes, 13 SAHs). These events are included in the analyses.

The regular MONICA registrations concern only patients aged 25 to 74 years, but for this article we also included all SAHs for those aged 25 and older for 3 consecutive years, 1997 to 1999. The aim was to provide information on age-specific incidence, CF, and mortality over the entire age range and to estimate total SAH incidence and mortality in the adult population.

Statistical Methods
The annual incidence and mortality rates were age-standardized to the “World Standard Population” using 5-year age groups.14 The weights used were 8, 6, 6, 6, 5, 4, 3, 2, 1, 0.5, and 0.5 for the age groups 25 to 29, 30 to 34, 35 to 39, 40 to 44, 45 to 49, 50 to 54, 55 to 59, 60 to 64, 65 to 69, 70 to 74, 75 to 79, 80 to 84, and 85 and older, respectively.

To estimate the time trends of age-standardized incidence and mortality, a log-linear model log(r_t) = α + βt + ε_t, where r_t denotes the incidence, t indicates the year, and ε_t indicates the random error, was used. The annual incidence within an age group was assumed to follow a Poisson distribution and the natural logarithm of the event rate was assumed to be linear over time. In the aforementioned model, 100(β–1) is the annual percentage change in incidence; hence, when β is small, 100β estimates the annual percentage change.15 Separate analyses were performed for men and women. In the graph of mortality over time (Figure 1), the data are presented per 100 000 inhabitants, whereas the incidence and mortality in the log-linear models were estimated based on 315 000 inhabitants in the group aged 25 to 74 years.

The age-standardized CF was analyzed by a similar log-linear model, assuming that the annual CF follows a binomial distribution.

Results
During the period 1985 through 2000, a total of 984 SAHs (392 in men and 592 in women) in the group aged 25 to 74 years fulfilled the MONICA diagnostic criteria. Of all SAH patients treated in hospital, 97.2% (853/878) had undergone CT scan. Of the 106 deceased individuals not managed in hospital, all had been subjected to medico-legal autopsy. In only 5 cases (0.5%) was the diagnosis set by other procedures (lumbar puncture or angiography, alone). In 13 of the 984 events (1.3%), there was a recurrent SAH. They were included in the analyses.

Incidence Rates
Table 1 shows the age-standardized annual incidence (4-year averages) in the group aged 25 to 74 years during 1985 to 2000. The incidence was consistently higher in women than in men (Table 1). Table 2 shows the annual change in

| Table 1. Annual Age-Standardized* Incidence, Case Fatality, and Mortality Rates of Subarachnoid Hemorrhage in Men and Women 1985 Through 2000 in the Northern Sweden MONICA Study in Group Aged 25 to 74 Years |
|-----------------|-----------------|-----------------|-----------------|
|                 | Men             | Women           |
|                 | Incidence*      | Case Fatality*  | Mortality*      |
|                 | Case/Person-Years |                |                |
| 1985–1988       | 119/624 164     | 17.5            | 34.7            | 6.1 |
| 1989–1992       | 96/635 632      | 14.1            | 38.2            | 5.3 |
| 1993–1996       | 100/649 501     | 14.9            | 32.0            | 4.7 |
| 1997–2000       | 77/645 144      | 10.9            | 35.2            | 3.6 |
|                 |                |                 |                 |
|                 | 1985–1988       | 134/609 906     | 20.0            | 38.3            | 7.6 |
| 1989–1992       | 168/615 537     | 24.4            | 38.6            | 9.4 |
| 1993–1996       | 153/625 899     | 21.4            | 32.8            | 7.0 |
| 1997–2000       | 137/621 345     | 19.5            | 23.8            | 4.7 |
|                 | *Age-adjusted to the world population.14 |

| Table 2. Trends in Incidence, Case Fatality, and Mortality |
|-----------------|-----------------|-----------------|
|                 | Men             | Woman           |
|                 | 100β            | 95% CI of 100β  | P    |
|                 | Incidence       | Case Fatality   | Mortality |
| Incidence       | −3.28           | −4.89           | −1.67  | <0.0001 | −0.32           | −1.63           | 1.00   | 0.6380 |
| Case fatality   | −0.58           | −3.60           | 2.39   | 0.7044  | −3.87           | −6.42           | −1.33  | 0.0028  |
| Mortality       | −3.58           | −6.63           | −1.14  | 0.0057  | −3.97           | −6.27           | −1.69  | 0.0007  |

100β Estimates the annual percentage change with 95% confidence intervals in men and women in group aged 25–74 years in 1985–2000.
incidence, CF, and mortality. In men, the incidence decreased by $\approx 3.3\%$ per year ($P<0.0001$). In women, no significant trend was seen when the entire period between 1985 and 2000 was analyzed.

**Case Fatality**

In total, 143 of 392 (36.5%) men and 208 of 592 (35.1%) women died within the first 28 days. There was no difference in the 28-day CF between the sexes ($P=0.72$). Of those who died within the first 28 days, half (49%) of the deaths occurred within 2 days from onset in men and women. The 2-day CF was 21.4% in men and 20.5% in women ($P=0.74$).

Figure 2 and Table 2 show the trends in CF. In men, no trend in the 28-day CF was seen ($P=0.7$) over the years, whereas in women a decrease in CF was observed ($P=0.0028$).

This study covers a vast geographical area with long distances to the only neurosurgical facility in the area. When patients with $<70$ km (Umeå area) were compared with the rest of the region, there was no difference in CF (35.5% versus 36.2%; $P=0.64$). When subjects dying out of hospital were excluded, there was still no difference in CF between SAH patients living in the Umeå area or patients living far from the neurosurgical facility (data not shown).

**Level of Consciousness and Interventions**

No differences were seen in the proportion of SAH patients who had lowered level of consciousness on admission to hospital over the years 1985 to 2000 among either men or women (data not shown). Similarly, there was nothing to indicate sex differences in how patients with SAH were managed in hospital (data available only from 1995 and onward). Surgical interventions, including embolization of cerebral aneurysms using coiling, were performed in 74 of 108 (69%) men and in 139 of 192 (72%) women ($P=0.51$).

**Mortality**

As expected from the results on incidence rate and CF, the SAH mortality decreased significantly among men and women (Figure 1 and Table 2). By MONICA definitions, the change in mortality should be approximately the change in incidence combined with the change in CF.

**SAH Incidence in All Age Groups**

For the years 1997 through 1999, all SAHs in the MONICA area occurring in those aged 25 years and older were validated by the MONICA criteria. An additional 36 patients (10 men and 26 women) aged 75 years and older were identified. In 28 of the 36 patients (78%), it was a first-ever stroke. Table 3 shows the incidence rates, mortality rate, and CF (averages of all 3 years together) for 10-year age groups of men and women. The age-adjusted annual incidence among patients 25 years and older was 13.3 per 100 000 in men and 24.4 per 100 000 in women. The incidence was lowest in the youngest age group in men and women. Between ages 45 and 85 years, the incidence rates were essentially the same across ages in both sexes but consistently higher in women (Table 3).

Because of small numbers in each age group, the CF varied considerably. During 1997 to 1999, the CF was 48.2% in men and 38.9% in women in patients 25 years and older. The CF was rather constant up to 80 years. Almost all (16 of 19 patients; 84%) older than 80 years died within 28 days of their SAH, with no apparent sex difference (data not shown).

**Discussion**

In northern Sweden, mortality from SAH is declining in men and women. This is consistent with SAH mortality trends in other Western populations.4,6 Declining mortality can be
caused by decreasing incidence (fewer events occur) or decreasing CF (fewer SAHs are fatal), or both. The higher CF in men was compensated by a lower incidence, whereas in women the opposite was found. The present results show that in men, a decreasing incidence explains the downward mortality trend, whereas in women a decreasing CF, but not incidence, is involved.

In epidemiological studies, detection bias is a well-recognized problem. Improved diagnostic techniques may contribute to what is an apparent, but not a real, increase in incidence.16 The declines in SAH incidence in men in this study and other studies may possibly reflect an “inverse detection bias.” The increasing use of CT scan has made it possible to distinguish with greater accuracy between a subarachnoid hemorrhage and an intracerebral hemorrhage with rupture into the subarachnoid space.17 In the present study, however, nearly all SAH events were diagnosed by CT scan or autopsy throughout the whole study period and it is unlikely that any kind of detection bias contributed to the changes in incidence that were observed.

To monitor trends over the years, first, the number of events has to be relatively high. The present study covered a relatively large target population with one of the highest SAH incidence rates in the world (together with Finland and Japan).2,3,6 Second, the diagnostic procedures used in patients with a suspect SAH should be the same the during the study period. We strictly adhered to the MONICA criteria in the years 1985 to 2000.10 The proportion of inpatients examined by CT scan was >95%;3 and all individuals dying outside hospital from suspect SAH underwent autopsy. Thus, diagnostic procedures and MONICA criteria for SAH have been unchanged over the 16-year study period. In US hospital-based series, it has been reported that as many as 15% to 25% of SAHs are misdiagnosed at initial medical evaluation.16,19 Therefore, changes over time in the readiness to seek medical attention and the quality of clinical evaluation among referring physicians could influence incidence rates of diagnosed SAHs. To our knowledge, there are no longitudinal studies on the problem of undiagnosed SAHs, except for showing that education of doctors may increase the suspicion of SAH.20

Hypertension and smoking are the best-documented amenable risk factors for SAH.21,22 Risk factor surveys performed within the framework of the MONICA Project in northern Sweden have shown essentially unchanged blood pressure levels in the population during the years 1986 to 1999.23 During the same period, the prevalence of smoking in men decreased from 23% to 14% in the group aged 25 to 64 years.24 In women, the decline started later and it has been more modest (from 27% to 22%).24 Thus, one reason for the different trends in incidence could be the different trends in smoking habits between men and women. However, calculation of the population-attributable risk (PAR) showed that the reduction in the prevalence in smoking men during 1986 to 1999 explains only a minor part of the reduction in incidence in men. The PAR calculations showed that only 2 cases are estimated to be saved because of the lower smoking rate in 1999 as compared with 1986. Therefore, the decreasing SAH trends remain largely unexplained. The high incidence of SAH in the study area1 could indicate that there are unidentified risk factors for SAH in this population, and this would limit the generalizability of our observations. Finland also has high SAH incidence rates3 and there is a considerable Finnish genetic influence in the population of northern Sweden.25 This could be a population-specific risk factor but can hardly explain different time trends in incidence and CF between men and women.

A previous study from New Zealand showed no change in CF over time in either men or women.4 In a study from Japan, 3-month CF decreased in men and women younger than 80, from 38% to 26%, when the period 1980 to 1989 was compared with 1990 to 1999. In patients in the oldest age range, no change was seen.6 In the present study, the trends in CF were different in men and women. In men, the CF varied considerably between years and no statistically significant trends were shown, whereas in women the annual decrease was almost 4%. Although, it was recently reported that CF in patients with intracerebral hemorrhage was significantly influenced by the rate at which treating hospitals used do-not-resuscitate orders.26 Preexisting or concomitant cardiac disorders are less common in SAH patients than in patients with intracerebral hemorrhage or ischemic stroke,27 and cardiopulmonary resuscitation would therefore be less likely to be successful in patients with SAH. However, successful resuscitation is not a rare event in patients with SAH,28 and the possibility remains that differences in do not resuscitate orders over time may have influenced survivals rates of SAH patients in the present study.

Since 1995, we have monitored surgical interventions. During this period, surgical techniques have improved and new drug treatments with documented beneficial effects have been initiated. In the present study, ~70% of patients treated in hospital underwent some kind of intervention, and this proportion did not change during the 6 years of monitoring. No differences in interventions were seen between the sexes. The proportion of patients who were alert on admission to hospital was unchanged. The possibility remains that improved management may have reduced CF during the later years of observation, but the differences in CF trends between men and women remain unexplained.

When combining 3 years (1997 to 1999), we saw stable CF rates in groups aged up to 80 years in men and women. In patients older than 80 years, CF was >80%. This is in accordance with a study from Japan.6 High CF could indicate a higher proportion with a more severe SAH and also probably more fragile patients. An alternative explanation to the apparent high CF in elderly people affected by SAH may be poor clinical suspicion and detection of nonfatal cases of SAH in the elderly.

In conclusion, we observed decreasing mortality trends in men and women in northern Sweden. In men, a decreasing incidence explains the downward mortality trend, whereas in women a decreasing CF explains the downward mortality trend.

References


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