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Lindbohm, Joni V.

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Survival bias explains improved survival in smokers and hypertensive individuals after aSAH

Joni V. Lindbohm, MD, PhD;¹ Jaakko Kaprio, MD, PhD;^{1,2} Miikka Korja, MD, PhD;³

¹Clinicum, Department of Public Health, University of Helsinki, P.O. Box 41, FI-00014 Helsinki, Finland

²Institute for Molecular Medicine FIMM, University of Helsinki, P.O. Box 20, FI-00014 Helsinki, Finland

³Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, P.O. Box 266, FI-00029 Helsinki, Finland

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Correspondence to Joni Lindbohm, Department of Public Health, University of Helsinki, P.O. Box 41, FI-00014 Helsinki, Finland; E-mail address: joni.lindbohm@helsinki.fi; Telephone: +358 9 1911 Fax: +358 9 191 27 600

Co-authors: jaakko.kaprio@helsinki.fi, miikka.korja@hus.fi

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Dr. Korja reports no disclosures.

Abstract

Objectives

Two recent hospital-based studies have reported that both smoking and hypertension – the two most important risk factors for aneurysmal subarachnoid hemorrhage (aSAH) – may improve survival after aSAH. We tested the hypothesis that a higher case fatality among smokers and hypertensive individuals after aSAH contributes to these paradoxical findings.

Methods

We followed 65 521 population-based FINRISK participants during 1.52 million person-years and identified 445 first-ever hospitalized aSAHs and 98 sudden-death aSAHs occurring between 1974 and 2014. We measured risk factors prior to disease onset in the cohort surveys, and confirmed, among all sudden-death aSAHs, 80% by extensive (including the brain) forensic autopsy; the remaining 20% were based on clinical examination (computer tomography of the head, spinal tap, or both). The Cox proportional hazards model estimated survival curves.

Results

Analyses repeating the protocol of the two recent hospital-based studies again showed improved survival among smokers and those with hypertension. Conversely, in analyses including more accurate risk factor measurements and including sudden-death aSAH patients who never reached a hospital, these paradoxical results were reversed. Smokers had reduced survival compared to that of never-smokers ($p=0.04$), and those with high systolic blood pressure ($SBP \geq 160$ mmHg) had reduced survival when compared to survival of those with $SBP < 160$ mmHg ($p=0.05$).

Conclusions

After aSAH, smoking and hypertension were associated with worse survival. The earlier and opposite findings are likely explained by inadequate risk factor measurement and by survival bias

inherent to hospital-based risk factor studies lacking information on out-of-hospital deaths confirmed by autopsy.

Introduction

Two recent hospital-based studies reported that smokers and those with history of hypertension have better survival after aneurysmal subarachnoid hemorrhage (aSAH),^{2,3} even though these two factors are considered the main risk factors for aSAH.¹ It is important to recognize that these studies included only hospital-admitted early aSAH survivors and excluded the sudden-death aSAH individuals that, among all aSAH cases, account for approximately 25%.⁴ The exclusion of those aSAH individuals who never reach hospitals may have caused survival bias, particularly because the suddenly dying aSAH patients have worse risk factor profiles than those of early-aSAH survivors.⁵ We aimed to study whether this survival bias explains the reported^{2,3} paradoxically improved survival after aSAH among smokers and patients with history of hypertension.

Methods

Study base and outcome. Our earlier studies describe the study protocol in detail.^{5,6} In brief, during 1.52 million person-years of follow-up of the population-based FINRISK cohorts, including 65 521 adult men and women, we identified 445 first-ever hospitalized aSAHs and 98 sudden-death aSAHs between 1974 and 2014. Sudden deaths from aSAH we defined as those occurring away from a hospital, in an ambulance, or in an emergency room. Of all sudden-death aSAH diagnoses, 80% were confirmed by extensive (including the brain) forensic autopsy, with the remaining 20% based on clinical examinations (computer tomography of the head, spinal tap, or both). Sudden-death aSAHs occurring soon after arrival at an emergency department were not recorded in the hospital discharge register, and therefore the clinical examination includes these cases. Hospitalized aSAHs we defined as aSAH patients admitted to hospital wards or intensive care units.

Measurement of risk factors and covariates occurred prior to disease onset in the cohort surveys

between 1972 and 2012,⁵ and of SBP, twice, after a 5-minute rest, with analyses using the average value.⁷ Validation of smoking status was by serum cotinine measurement.⁷

Data analysis and statistics. We used complete case analysis, because only 2% had data missing on smoking or SBP. We first did analyses similar to those of the two earlier hospital-based studies^{2,3} reporting paradoxically better survival after aSAH among smokers and those with a history of hypertension. These analyses included covariates (such as hypertension instead of SBP) similar to those of the two earlier studies, and included only hospitalized aSAH patients. We then repeated the same analyses and included a wider range of covariates as well as more accurate risk factor measurements (SBP instead of hypertension history/diagnosis). Moreover, these analyses included aSAH individuals who died suddenly and never reached hospitals. In these analyses, the Cox proportional hazards model estimated survival curves with all analyses adjusted for age, sex, SBP, smoking status, total cholesterol, BMI, hypertension medication, degree of education, year of admission, number of comorbidities mentioned in the death certificate, and survey study year and area.

Data Availability Statement. Data for this submission are available on request to the FINRISK Management Group, according to the given ethical guidelines and to Finnish legislation.

Ethics Statement. Ethical approval came from the corresponding ethics committee according to the commonly required research procedures and Finnish legislation for each survey, and the study was conducted according to the World Medical Association's Declaration of Helsinki on ethical principles for medical research. From 2002 onward, each participant has provided written informed consent.

Results

Cohort characteristics. Those who suffered sudden-death aSAH were slightly older and seemed to more often be smokers and be hypertensive than were hospitalized aSAH patients. (Table 1).

Analyses with hospital-admitted aSAH patients only. Our analyses following the protocol of the two earlier studies^{2,3} showed similar, paradoxically better survival among smokers and those with hypertension (Figures 1 A and B) in line with findings of those two studies.

Analyses including also sudden-death aSAHs. When our analyses included potential confounders and the sudden-death aSAH patients who never reached hospitals, the results were reversed (Figures 1 C and D). With the higher case fatality among smokers taken into account by inclusion of the sudden-death aSAHs, smokers had worse survival than did never-smokers. Similarly, with the higher case fatality among those with higher blood pressure taken into account, those with SBP ≥ 160 mmHg had worse survival after aSAH than did aSAH patients with SBP < 160 mmHg. Figure 2 demonstrates a hypothetical situation in which the direction of risk ratio can change because of the higher case fatality in smokers.

Discussion

Contrary to earlier findings,^{2,3} we found that, after aSAH, both smoking and high SBP associated with worse survival. This seems logical because the strongest risk factors for aSAHs are smoking and hypertension.¹ Importantly, the mean age in the two earlier studies^{2,3} was only five years lower than in our cohort, and proportions of smokers and hypertensive individuals were similar. This

means that differences between cohorts are unlikely to explain these contradictory associations.

Compared to the two earlier studies,^{2,3} however, our study has two main differences.

First, our cohort included aSAH individuals who die suddenly before reaching hospital wards. Such individuals account for about 25% of all aSAHs,⁴ smoke more, and have higher blood pressure values than do the remaining three-quarters.⁵ Our analyses that first excluded and then included the sudden deaths revealed the pivotal role that these individuals play in survival analyses after aSAH. The analyses showed evidence of survival bias, meaning that those smokers and hypertensive aSAH patients who survive the initial bleed and reach hospital wards are selected patients with a prognosis better than average. If studies include only early aSAH survivors who end up in hospital wards and exclude heavy smokers and highly hypertensive individuals with higher sudden-death aSAH rates, smoking and hypertension may paradoxically associate with improved survival after aSAH.

Second, we used the gold-standard protocols to identify hypertensive individuals (*i.e.* SBP measured after a 5-minute rest, and the average of two measurements) and smoking status (*i.e.* validated with cotinine measurements) to identify true smokers.⁷ In contrast, the two earlier studies had to rely on register-based ICD codes and on admission questionnaires. These sources recognize only about 60% of all smokers and hypertensive individuals,⁸⁻¹⁰ suggesting that one in three smokers and hypertensive individuals may have been missed. Such misclassification could have further contributed to the paradoxical survival benefit.

The main limitation of this study is that our aSAHs may include a small fraction of non-aneurysmal SAHs. This is, however, unlikely to make any major contribution to our results, because non-aneurysmal SAHs have no documented robust association with smoking or with SBP.

Conclusions

In conclusion, our results suggest that both smoking and hypertension lead to worse survival after aSAH. The explanation of the earlier opposite findings is likely their inaccurate risk factor measurements and a survival bias that is inherent to hospital-based risk factor studies omitting information on out-of-hospital deaths confirmed by autopsy. This emphasizes the importance of pre-aSAH risk factor measurement and inclusion of the sudden-death individuals when studying risk factors for aSAH and survival after aSAH.

Appendix 1

Name	Location	Role	Contribution
Joni V. Lindbohm, MD, PhD	University of Helsinki	Author	Designed and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Jaakko Kaprio, MD, PhD	University of Helsinki	Author	Designed and conceptualized study; drafted the manuscript for intellectual content
Miikka Korja, MD, PhD	University of Helsinki and Helsinki University Hospital	Author	Designed and conceptualized study; drafted the manuscript for intellectual content

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Table 1. Characteristics of hospitalized and sudden-death aSAH individuals of the FINRISK cohorts.

	FINRISK	FINRISK hospitalized	FINRISK sudden-death
aSAHs (n)	543	445	98
Age (SD)	61.4 (12.7)	60.9 (12.7)	63.3 (12.5)
Women (%)	53.8	53.9	53.1
Current smoking (%)	40.6	34.4	46.2
Hypertension (%)	63.6	62.7	67.7
Year of diagnosis (%)			
1972-1980	7.1	7.2	7.1
1980-1990	21.7	20.7	26.5
1990-2000	23.6	24.7	18.4
2000-2010	29.8	29.7	30.6
2010-2014	17.7	17.8	17.4
Outcome		Death	
Follow-up after aSAH		6.6 years (mean)	
Participants		Population-based cohorts	

Figure 1. Survival change after aSAH with sudden-death aSAHs included versus excluded.

Panels A and B: Adjusted survival after aSAH by smoking status and by hypertension status for only the hospitalized patients from FINRISK studies.

C and D: The same analysis with baseline risk factors more comprehensively adjusted, with both hospitalized and sudden-death aSAH patients included; and based on systolic blood pressure measurement instead of on hypertension status.

Figure 2. How survival bias can change risk ratios (RR).