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Tobacco smoking and aortic aneurysm: Two population-based studies ☆

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ABSTRACT

Background: We determined the predictive power of tobacco smoking on aortic aneurysm as opposed to other risk factors in the general population.
Methods: We recorded tobacco smoking and other risk factors at baseline, and assessed hospitalization and death from aortic aneurysm in 15,072 individuals from the Copenhagen City Heart Study followed for up to 34 years and in 56,211 individuals from the Copenhagen General Population Study followed for up to 7 years.
Results: During follow-up, 335 and 169 individuals developed aortic aneurysm outcomes in the Copenhagen City Heart Study and Copenhagen General Population Study, respectively. According to the magnitude of the hazard ratios, tobacco consumption was the most important risk factor for hospitalization and death from aortic aneurysm, followed by male sex and hypertension in both cohorts. The population attributable risk of aortic aneurysm outcomes due to tobacco consumption was 64% and 47% in the Copenhagen City Heart Study and Copenhagen General Population Study, respectively, and ranked highest among population attributable risks of aortic aneurysm in both cohorts. The absolute 10-year risk for hospitalization or death from aortic aneurysm in males and females consuming above 20 g tobacco daily was 3.5% and 1.3%, among those >60 years with plasma cholesterol >5 mmol/L and a systolic blood pressure >140 mm Hg.
Conclusions: Tobacco smoking is the most important predictor of future aortic aneurysm outcomes in the general population, with population attributable risks at or above 47%.

1. Introduction

An aortic aneurysm is defined as a 50% increase in diameter compared with the normal adjacent aorta, though a 3 cm cut-off is more commonly used [1,2]. The prevalence of aortic aneurysm in the general population is 1–2%. Most cases of aortic aneurysm in the general population go undetected until a rupture occurs, and mortality after an aortic aneurysm rupture is up to 65–90% [1,2]. Thus, early detection of individuals at high risk of aortic aneurysm is important to improve the chances of preventing the disease and acute ruptures.

Preventive efforts against aortic aneurysm include among others a screening of individuals who have or are currently smoking tobacco [1,2]. This is because tobacco smoking clearly associates with risk of having the disease [3,4], and with some of the pathophysiological processes underlying weakening of the aortic wall and subsequent aneurysm development [4–6]. However, even though tobacco smoking is likely causally related to aortic aneurysm, its predictive power in the general population on future events as opposed to other risk factors is unclear.

The aim of this study was to determine the predictive power of tobacco smoking on aortic aneurysm as opposed to other risk factors in the general population. For this purpose we recorded tobacco smoking at baseline and assessed future hospitalization and death from aortic aneurysm in 15,072 individuals from the Copenhagen City Heart Study followed for up to 34 years and in 56,211 individuals from the Copenhagen General Population Study followed for up to 7 years. Finally, for potential use in clinical practise, we calculated 10-year absolute risks of aortic aneurysm hospitalization and death as a function of smoking and other risk factors.

2. Materials and methods

2.1. Study cohorts

The study participants were randomly selected white individuals of Danish descent from two similar, but independent cohorts recruited from the adult Danish

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general population: the Copenhagen City Heart Study (n = 15,072) and the Copenhagen General Population Study (n = 56,211). In both studies, individuals were selected based on the Central Population Register Code to reflect the general population aged 20 to 80+ years [7–9]. The Copenhagen City Heart Study was initiated in 1976–1978 (n = 13,357) with follow-up examinations in 1981–1983 (additional individuals; n = 243), 1991–1994 (additional individuals; n = 1265) and in 2001–2003 (additional individuals; n = 207). The Copenhagen General Population Study is an ongoing study initiated in 2003 and roughly receiving 10,000 individuals yearly [10]. All subjects answered similar questionnaires, and objective clinical parameters were measured by similar methods. Participants in the two studies were recruited from different parts of Copenhagen and there was no overlap of individuals between the two studies. The studies were approved by Herlev Hospital and Danish ethical committees (Nos. KF-100.2039/91 and H-KF-01-421/94), and were conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.2. Aortic aneurysm as endpoint

In both studies information on discharge diagnoses and causes of death diagnoses for aortic aneurysm (World Health Organization International Classification of Diseases, 8th and 10th editions; ICD8: 441; ICD10: I71) was obtained from the national Danish Patient Registry and the national Danish Causes of Death Registry, using the unique Danish Central Person Register number from 1976 until August 8th, 2010. Patient completeness between the national Danish Patient Registry and the Danish Vascular Registry, collecting data from all Vascular Departments in Denmark, was 99.0% for patients with abdominal aortic aneurysm, carotid thromboendarterectomy, and infrainguinal bypass 2001–2010 [11]. The median and maximal follow-up was 23 and 34 years for the Copenhagen City Heart Study and 4 and 7 years for the Copenhagen General Population Study. Follow-up was 100% complete.

2.3. Tobacco consumption and other risk factors

All subjects indicated at study entry whether they were never smokers, ex-smokers, or current smokers. We also divided subjects into the following three groups according to the average amount of tobacco consumed daily at study entry: 0 g daily, 1–20 g daily, and >20 g daily. Participants were also divided into two groups according to the average amount of alcohol consumed weekly. Cut-off was 168 g weekly for women and 252 g weekly for men in accordance with the recommended maximum level of weekly alcohol consumption given by the Danish National Board of Health. Plasma levels of cholesterol was measured using standard hospital assays (Boehringer Mannheim or Konelab). Blood pressure was measured once per subject by trained technicians on the left arm, after 5 min of rest, and with the subject in the sitting position. In the Copenhagen City Herat Study we used a London School of Hygiene sphygmomanometer with a cuff measuring 12 × 26 cm; if the circumference of the upper arm was >46 cm, we used a 15 × 38-cm cuff. In the Copenhagen General Population Study we used an automatic Digital Blood Pressure Monitor (Kivex) with a cuff measuring 22 × 32 cm; if the circumference of the upper arm was >46 cm, we used a 32 × 45-cm cuff. Diabetes mellitus was self-reported disease, use of anti-diabetic medication, non-fasting plasma glucose >11.0 mmol/l, and/or a diagnosis of diabetes mellitus collected from registers (World Health Organization International Classification of Diseases-8th edition: codes 249–250; 10th edition: E10–E11, E13–E14). Information on co-variates was 98.4% complete for the Copenhagen City Heart Study and 99.7% complete for the Copenhagen General Population Study.

2.4. Statistical analysis

Statistical analyses were performed using STATA 11.0. P-values below 0.05 on two-sided tests were considered statistically significant. We assessed the association between smoking and aortic aneurysm outcomes using Kaplan–Meier curves, log-rank tests, trend tests, and Cox regression models with age as the time scale, which implies that age is automatically adjusted for [8,10,12]. Models were left truncated (at study entry) with delayed entry, and individuals were censored at aortic aneurysm event, death, or end of follow-up, August 8th, 2010. For trend tests, never, ex- and current smokers were coded 0, 1, and 2; this was also the case for tobacco use of 0, 1–20, and >20 g daily. Multivariate models adjusted for age (continuous), sex, alcohol consumption (continuous), systolic blood pressure (continuous), cholesterol levels (continuous), lipid lowering medication, and antihypertensive medication. Ranking of dichotomized risk factors was by magnitude of significant hazard ratios from Cox regression models with age as underlying time scale and by population attributable risk. For ranking of risk factors, baseline risk factors of cardiovascular disease were dichotomized: smoking was never versus ever smoker, hypercholesterolemia was no hypercholesterolemia versus hypercholesterolemia (plasma cholesterol above 5 mmol/L and/or use of lipid lowering medication), hypertension was no hypertension versus hypertension (systolic bloodpressure above 140 mm Hg, diastolic blood pressure above 90 mm Hg, and/or use of anti-hypertensive medication), diabetes mellitus was no diabetes mellitus versus diabetes mellitus (self-reported disease, use of anti-diabetic medication, non-fasting plasma glucose >11 mmol/L, and/or a diagnosis of diabetes mellitus collected from registers (World Health Organization International Classification of Diseases-8th edition: codes 249–250; 10th edition: E10–E11, E13–E14), overweight was body mass index below and equal to 25 kg/m^2 versus above 25 kg/m^2, and alcohol consumption was equal to or below 168 g weekly for women and 252 g weekly for men versus above (following recommendations from the National Danish Board of Health). Because age is adjusted for automatically in the Cox regression model, this risk factor was not included in the ranking analysis. Ranking analyses were performed using a step-up model.

Population attributable risk was calculated as $[f(HR-1)]/[1+f(HR-1)]$, where f is the frequency of the risk factor in the population at baseline and HR is the hazard ratio for hospitalization or death from aortic aneurysm; only significant hazard ratios were used. Poisson regression was used for calculating 10-year absolute risk according to tobacco smoking, age, sex, systolic blood pressure, and cholesterol levels.

3. Results

We studied two independent general population cohort studies, the Copenhagen City Heart Study (n = 15,072) and the Copenhagen General Population Study (n = 56,211); none of these individuals had previously been diagnosed with aortic aneurysm in the national Danish Patient Registry. During follow-up from 1976 to 2010 304 individuals were hospitalized due to aortic aneurysm and 31 died of aortic aneurysm in the Copenhagen City Heart Study, whereas 165 individuals were hospitalized due to aortic aneurysm and 4 died of aortic aneurysm in the Copenhagen General Population Study (Table 1). Of those who developed an aortic aneurysm outcome 194 individuals had abdominal aneurysm, 75 were unspecified, 34 had thoracic aneurysm, and 12 had thoraco-abdominal aneurysm in the Copenhagen City Heart Study, whereas 114 individuals had abdominal aneurysm, 22 were unspecified, 11 had thoracic aneurysm, and 8 had thoraco-abdominal aneurysm in the Copenhagen General Population Study.

Individuals who subsequently developed an aortic aneurysm outcome in the Copenhagen City Heart Study were more likely males and smokers, were older, had higher systolic blood pressure and plasma cholesterol levels, and consumed more alcohol at baseline (Table 1). Individuals who subsequently developed an aortic aneurysm

Table 1
Baseline characteristics of individuals who were subsequently hospitalized due to aortic aneurysm or died of aortic aneurysm in the Copenhagen City Heart Study and Copenhagen General Population Study.

	Copenhagen City Heart Study		Copenhagen General Population Study	
	No event	Aortic aneurysm	No event	Aortic aneurysm
Women/Men	7887/6850	109/226	31,410/24,632	52/117
Men, %	46	67	44	69
Age, years	51 (41–59)	54 (48–60)	57 (47–66)	70 (64–77)
Ever smokers, %	85	94	59	84
Systolic blood pressure, mm Hg	132 (120–147)	139 (128–154)	140 (125–154)	148 (133–164)
P-Cholesterol, mmol/L	5.9 (5.1–6.7)	6.4 (5.8–7.3)	5.6 (4.9–6.3)	5.6 (4.8–6.3)
Alcohol consumption, grams/day	8.6 (1.7–21)	10 (1.7–26)	14 (5.1–26)	15 (5.1–31)
Lipid lowering medication, %	0.05	0.3	10	20
Anti-hypertensive medication, %	5	8	19	40
Diabetes Mellitus, %	4	3	5	9

Values are numbers, median (interquartile range), or percent. Values were obtained at study entry. Aortic aneurysm = hospitalization or death from aortic aneurysm (ICD8: 441; ICD10: I71).