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Fish intake and venous thromboembolism: A Danish follow-up study

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ABSTRACT

Introduction: Data on the association between fish intake and venous thromboembolism (VTE) is sparse and inconsistent.
Objective: To investigate whether intake of total, lean or fatty fish is associated with development of incident VTE.
Material and methods: This study is based on the Danish follow-up study Diet, Cancer and Health including 27,178 men and 29,876 women aged 50–64 with no history of cancer. Participants were included between 1993 and 1997 and followed through 2006. Information on fish intake and potential confounders was obtained from baseline questionnaires. The outcome was incident VTE (all) and idiopathic VTE. We used Cox proportional hazard models with age as time axis. Separate analyses were performed for men and women. Adjustment was made for BMI, smoking, physical activity, energy intake and women's use of hormone replacement therapy.
Results: During follow-up, 641 incident VTE events were verified. We found no association between total fish intake and VTE, but moderate intake of fatty fish was associated with a statistically non-significant 20-40% lower risk of idiopathic VTE compared with consumption of a low intake (less than 8 g) of fatty fish per day.
Conclusions: Intake of neither total nor fatty fish was statistically significantly associated with the incidence rate of VTE. However, intake of fatty fish may be associated with a reduction of the risk of idiopathic VTE.

Introduction

Venous thromboembolism (VTE), i.e. deep vein thrombosis (DVT) and pulmonary emboli (PE), is a multifactorial disease that shares several risk factors with coronary heart disease (CHD) such as age, obesity, and smoking [1–4].

Fish intake may lower the risk of CHD [5,6], while a possible effect on VTE by marine n-3 polyunsaturated fatty acids (PUFA) is largely unknown - data on fish consumption and VTE are sparse and inconsistent [7–10]. Although n-3 PUFA probably have no clinically relevant effect on coagulation [11,12] these fatty acids do reduce platelet reactivity and have anti-inflammatory effects [5] that potentially may be of benefit in relation to VTE [5,12,13]. Diets rich in n-3 PUFA may, therefore, reduce the risk of VTE.

Few studies have examined the association between VTE and fish intake. Rosenzweig reported a remarkably low frequency of post-operative deep vein thrombosis in Alaska natives, with diets based on marine mammals and fish [14]. Three previous cohort studies have evaluated the association between fish intake and VTE; two showing no association [7,9] and the third one showing a beneficial association between fish intake and the risk of VTE [8].

We hypothesized that the intake of fish rich in marine n-3 PUFA may reduce the risk of VTE. Therefore, we assessed the association between VTE and intake of total, lean and fatty fish in the large Danish Diet, Cancer and Health Study in which very detailed information on diet and life style of the participants has been registered.

Materials and Methods

Study population

From December 1993 to May 1997, 27,178 men and 29,876 women were enrolled into the Danish prospective study Diet, Cancer and Health. The study has been described in detail elsewhere [15,16]. Eligible cohort members were born in Denmark, were living in the urban areas of Copenhagen and Aarhus, and were not, at the time of invitation to join the study, registered with a previous diagnosis of cancer in the Danish Cancer Registry. Participants were identified from computerized records of the Civil Registration System in Denmark, which has included all

Abbreviations: DVT, deep venous thrombosis; CHD, coronary heart disease; HR, hazard ratio; PE, pulmonary embolism; PUFA, polyunsaturated fatty acids; PY, person years at risk; VTE, venous thromboembolism.

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Danish inhabitants since 1968. The information includes a unique personal identification number in addition to name, address, and vital status [17]. For the present study, we included only participants with no prior VTE, leaving 56,014 participants for the follow-up study on fish intake and risk of VTE. This substudy was approved by the regional ethics committees in Copenhagen and Aarhus and by the Danish Data Protection Agency.

Outcomes and follow-up

The outcomes of the study were objectively verified VTE and the verification and classification of VTE events have been described previously [18]. In brief, we linked the Diet, Cancer and Health cohort with the Danish National Patient Registry using the civil registration number of the participants. The Danish National Patient Registry has collected data on hospital admissions nationwide since 1977 and on discharges from emergency departments and out-patient clinics since 1995 [19]. Based on the available hospital discharge history of each participant, we identified those who were registered with a discharge diagnosis of VTE (ICD-8: 450.99, 451.00, 451.08, 451.09, 451.99 and ICD-10: I26, I80.1-I80.9). We reviewed all hospital records from participants with a first-time VTE diagnosis from the time of enrolment into Diet, Cancer and Health until June 30th, 2006. The localization of VTE (DVT or PE) was registered and events were classified as idiopathic or secondary to another condition according to information in the medical records. An event was regarded as secondary when any of the following criteria was registered in the medical record: a cancer diagnosis prior to or within three months after admission with VTE, surgery, trauma, travel (at least five hours), acute medical disease with bed rest of at least three days (stroke, acute myocardial infarction, exacerbation of chronic lung disease, infection, activity in collagenous disease), immobilization, central vein catheter, or other provoking factors three months or less before the VTE. An event was regarded as idiopathic when the physician concluded that no provoking factors could be identified or when the health of the patient was described as good without information indicating secondary VTE. The event was registered as "unclassified" when information in medical records was sparse (18). Furthermore, we included participants who died of VTE by linkage with the Danish National Death Registry (until 2003), and by review of death certificates from participants who died between 2003 and 2006. Only participants with autopsy verified VTE were identified as VTE deaths [2].

Data on fish intake and other lifestyle factors

Participants completed a 192-item semi-quantitative food frequency questionnaire at the time of enrolment into the Diet, Cancer, and Health study. They were asked to estimate their daily intake of foods that come in natural units, such as slices of bread, pieces of fruit, and cups and glasses of different beverages. For other foods, such as mixed dishes, a sex-specific portion size was calculated based on the results from a calibration study. By multiplying the frequencies of intake by portion size, an individual average intake in grams/day of all foods and nutrients was calculated. A detailed description of the questionnaire and its validation has been published previously [20–22]. A total of 24 foods and recipes in the food frequency questionnaires were related to intakes of fresh and processed fish. The different species of fish were categorized as either lean or fatty fish according to the content of n-3 PUFA below or above 1 g per 100 g fish based on data from the Danish Food Composition Databank. Furthermore, the participants completed a detailed questionnaire regarding lifestyle factors including smoking habits, sports activities, education, work, and medication (for example the use of HRT in women). The questionnaires were optically scanned into a computer, and in subsequent interviews performed by trained lab technicians, information was amended as necessary. In addition, physical examinations were performed.

Statistical analysis

We assessed the association between VTE and intake of fish using Cox regression analyses. Age was used as time axis to adjust for age in all analyses, with entry time defined as the subject's age at recruitment, and age at VTE or censoring because of death, emigration, or 30 June 2006, as exit time, whichever came first. Time in the study was included as time-varying binary covariate, allowing the hazard ratio (HR) to change after one year in the study. For model control, we used a log-rank test in addition to graphical inspection of smoothed scaled Schoenfeld residuals. Separate analyses were performed for the two sexes. Participants for whom information on fish intake or potential confounding factors was missing were excluded from the analyses. Participants with a reported energy intake below basic requirements were excluded from the analysis. We computed incidence rates and HR of VTE in quintiles of: total fish intake (g/day), intake of lean fish (g/day), and intake of fatty fish (g/day) according to the exposure distribution among cases [23]. The incidence rates of VTE were computed using the number of VTE events as the numerator and the sum of individual person time risk as the denominator. The HRs of VTE were computed using the lowest quintiles as reference group. We assessed the crude HR and adjusted HR with adjustment at two levels. Adjustment 1 included total energy intake, smoking categories (non-smokers, former smokers, smoking <15 g/day, smoking 15-25 g/day, smoking >25 g/day), BMI (continuous variables), women's use of HRT (user, non-user), and stratification for use of fish oil capsules (yes, no). Adjustment 2 further included total dietary intake of fruits and vegetables (g/day). We examined the HR for VTE, idiopathic VTE, provoked VTE, and PE. Stata version 11 (Stata Corporation, College Station, Texas, US) was used for the statistical analyses.

Results

Study population and case ascertainment

Baseline characteristics of the 56,014 participants in this follow-up study on VTE are presented in Table 1. The median follow-up time was 10.2 years (interquartile range 9.6 to 10.8 years) with a total of 641 confirmed VTE events that were identified among participants during follow-up (24 of those were identified by review of death reports).

Analyses

Table 2 shows the incidence rate of VTE per 100,000 person years at risk and the crude and adjusted hazard ratio with 95% confidence interval for VTE and idiopathic VTE in quintiles according to intake of total fish, lean fish, and fatty fish in men. We found no statistically significant association between intake of various types of fish and VTE, but the adjusted hazard ratios in the four highest quintiles of fatty fish intake were below one in all the analyses. We found a negative association, although also statistically non-significant, between intake of more than 7 g of fatty fish and idiopathic VTE compared with intake of 0–7 g fatty fish. The association tended to be U-shaped. Thus, the risk of idiopathic VTE was 38% lower in men with an average daily intake of 14–19 g of fatty fish compared with men with an intake below 8 g.

Table 3 shows the incidence rate of VTE per 100,000 person years at risk and the crude and adjusted hazard ratio with 95% confidence interval for VTE and idiopathic VTE in quintiles of average intake of total fish, lean fish, and fatty fish in women. For total VTE and the various fish groups the results were statistically non-significant but all associations were u-shaped. This picture was more pronounced when the associations between idiopathic VTE and the various fish groups were examined.

If we dichotomized the intake of total fish, lean and fatty fish or separated into tertiles we did not get a clearer picture of the associations to the risk of VTE, i.e. we neither found any significant associations in these calculations.