Diet and Risk of Rheumatoid Arthritis in a Prospective Cohort

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ABSTRACT. ***Objective.*** To assess the association between dietary factors and risk of rheumatoid arthritis (RA) in a large prospective cohort.

Methods. Information about dietary intake was obtained from a detailed self-administered food frequency questionnaire completed by 57,053 individuals who participated in a prospective cohort. Linking the cohort to the Danish National Patient Registry we identified patients who developed RA. A rheumatologist scrutinized original medical records for these individuals in order to confirm the diagnosis of RA. Cox proportional hazards regression analyses were performed for dietary and lifestyle factors.

Results. The average time of followup in the cohort was 5.3 years (range < 1 mo to 7.7 yrs). Sixty-nine individuals were identified with confirmed incident RA. In multivariate models each increase in intake of 30 g fat fish (≥ 8 g fat/100 g fish) per day was associated with 49% reduction in the risk of RA (p = 0.06), whereas medium fat fish (3-7 g fat/100 g fish) was associated with significantly increased risk of RA. Intake of fruit and coffee was not associated with risk of RA. Furthermore, no associations were found between risk of RA and intake of a range of other dietary factors including long chain fatty acids, olive oil, vitamins A, E, C, D, zinc, selenium, iron, and meat.

Conclusion. The limited number of patients who developed RA during followup of our large cohort prevented us from concluding that dietary factors are unimportant as risk factors for RA. It appears, however, that if dietary factors are important modifiers of RA risk, they must play a role more than a few years before clinical diagnosis. (J Rheumatol 2005;32:1249–52)

Key Indexing Terms:
RHEUMATOID ARTHRITIS EPIDEMIOLOGY
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Rheumatoid arthritis (RA) is a chronic inflammatory joint disease with a prevalence around 0.5-1% and an annual incidence rate between 25 and 50 per 100,000 individuals[1]. Both inherited and environmental factors have been suggested as causal factors in RA. Several studies have suggested that diet may influence clinical disease progression in patients with RA, and high intake of fish oil in particular has been associated with alleviation of symptoms[2]. However, only a few studies have examined the role of different dietary factors in the etiology of RA. These studies have suggested that high intake of certain antioxidants, particularly ß-cryptoxanthin and supplemental zinc[3] and high levels of serum selenium and α-tocopherol[4] may be associated with decreased risk of RA. Furthermore, it has been suggested that diets high in fruit[3], fish[5,6], and olive oil[6] may be protective against development of RA. Prospective cohort studies found no effect of coffee consumption on risk of RA[7]. Two recent studies found that low level of vitamin C intake[8] and high intake of red meat[9] were associated with increased risk of inflammatory polyarthritis.

Our objective was to undertake a broad assessment of the association between dietary factors, including intake of fish and long chain fatty acids, fruits, vegetables, meat, coffee, antioxidant vitamins, and trace elements, and the risk of RA in a large prospective cohort with the possibility of adjusting for potential confounding factors.

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MATERIALS AND METHODS

Subjects. A total of 57,053 individuals, identified by the Civil Registration System in Denmark, were included in the Diet, Cancer, and Health cohort between 1993 and 1997[10]. All individuals resided in Copenhagen or Aarhus and were between 50 and 64 years of age at entry and had no history of cancer.

Patients with RA were identified by linking the cohort to the Danish National Patient Registry (NPR), which includes nationwide information on somatic inpatient hospital discharges in Denmark since 1977 and on all outpatient discharges since 1995[11]. A rheumatologist (MK) scrutinized original medical records for individuals who had a first RA diagnosis recorded in the NPR after inclusion in the cohort to confirm RA diagnoses and assess time of diagnoses. A case was defined as a patient for whom RA could be clinically confirmed by the rheumatologist scrutinizing all available medical records, meaning that RA diagnosis was stated in the medical record and judged reasonable, based on either the mention of fulfilment of the American College of Rheumatology (ACR) 1987 classification criteria for RA[12] or a clinical description otherwise judged to be clearly indicative of RA. Onset of RA was defined as the day of diagnosis stated in the medical record. Only cases with onset of RA after inclusion in the cohort were included.

Exposures and outcomes. Information about dietary intake was obtained from a detailed self-administered food frequency questionnaire administered to all participants in the Diet, Cancer, and Health cohort. Respondents were asked how often, on average, over the past year they had consumed each item. Answers to questions on intake of different foods and dishes were given in 12 different categories, ranging from 'never' to '8 or more times per day'. For foods that come in natural units, such as slices of bread, cups or glasses, and pieces of fruit, participants were asked to average their daily intake of the relevant unit. For other foods a gender-specific portion size was calculated. A mean daily intake of foods and nutrients was calculated by multiplying the frequencies of intake by the portion size. Intake of fish was divided into 3 groups: lean fish [0-2 g fat/100 g fish: plaice, codfish, coalfish, and flounder (fresh); shrimps (frozen); tuna (processed)], medium fat fish [3-7 g fat/100 g fish: trout and garfish (fresh); cod roe and lumpsucker roe (processed)], and fat fish [≥ 8 g fat/100 g fish: salmon, mackerel, herring (fresh); mackerel, herring, and sardine (processed)]. Furthermore, information about lifestyle factors including education, smoking status and duration, alcohol intake, reproductive factors, intake of sex hormones, and physical activity was obtained in a separate self-administered questionnaire. Descriptions of the validity of the questionnaire have been published[13,14].

Analyses. Cox proportional hazards regression analyses adjusted for age and gender were performed for dietary and lifestyle factors (Model 1, Table 1). All dietary variables were analyzed as continuous variables. Incidence rate ratios (IRR) and 95% confidence intervals (CI) for associations were estimated for females and males separately; if there was no significant interaction with gender ($\alpha = 0.05$), information for females and males was combined. Dietary factors with a p trend < 0.2 were analyzed in multivariate Cox proportional hazards models including, in addition to age and gender, tobacco smoking (never, former, current) and post-school education (not educated, educated), as detailed below (Model 2, Table 1). Multivariate models were analyzed both with and without adjusting for total energy intake.

This study was approved by the Scientific Ethical Committees for Copenhagen and Frederiksberg (J.no. KF 01-345/93 and J.no. KF 11-091/01) and the Danish Data Protection Agency (2001-41-0576).

RESULTS

Of the 57,053 cohort members, representing 35% of 160,725 initially invited individuals, we excluded 320 persons because NPR information and scrutiny of medical records revealed that they had been diagnosed with RA before inclusion in the cohort. Furthermore, we excluded 42 cohort members without date of inclusion in the cohort. The remaining 56,691 individuals (29,626 women and 27,065 men) without a history of RA were included in the study. Among the 56,691 individuals in the cohort, 69 patients (47 women and 22 men) with first RA diagnosis recorded in the NPR after inclusion in the cohort were confirmed by scrutiny of medical records by a rheumatologist. Average time of followup from inclusion in the cohort to diagnosis of RA, death, emigration, or end of followup in August 2001 was 5.3 years (range < 1 mo to 7.7 yrs). Among patients 42/69 (61%) were rheumatoid factor positive and 16/69 (23%) had joint erosions.

No significant interaction with gender was found for any dietary variables, so data for men and women were combined. Adjusted for age and gender, tobacco smoking was positively ($p < 0.05$) associated with risk of RA: never smoker, IRR = 1 (reference); former smoker, IRR = 1.63, 95% CI 0.81-3.29; current smoker, IRR = 2.7, 95% CI 1.48-4.96. Information about post-school education was obtained in 4 categories (none, short, medium length, and long). The group without any post-school education had an increased risk of RA compared to the 3 groups with some post-school education; the groups with some post-school education did not differ from each other. We therefore divided the variable post-school education into 2 groups (no post-school education and some post-school education). Risk of RA was marginally associated with status as non-educated versus edu-

Table 1. Incidence rate ratios (IRR) of RA associated with selected dietary factors. Model 1 was adjusted for age and gender; Model 2 was adjusted for age, gender, tobacco smoking (never, former, current smoker), and education (not educated, educated). Medium fat fish intake was adjusted for intake of fat fish and vice versa, and intake included both fresh and processed fish.

Dietary Factor	Model 1 IRR	Model 1 95% CI	Model 1 p	Model 2 IRR	Model 2 95% CI	Model 2 p
Fish, medium fat, per 30 g/day	2.06	0.99–4.30	0.05	2.74	1.39–5.42	0.004
Fish, fat, per 30 g/day	0.62	0.32–1.22	0.17	0.51	0.25–1.03	0.06
All fruits and fruit juices per 100 g/day	0.89	0.75–1.05	0.17	0.93	0.79–1.09	0.37
Coffee, per 200 g/day	1.10	0.99–1.21	0.07	1.04	0.94–1.15	0.47

CI: confidence interval; medium fat: 3-7 g fat/100 g fish; fat: ≥ 8 g fat/100 g fish; 200 g/day coffee: 1 cup.

cated ($p < 0.06$): non-educated, IRR = 1 (reference); educated, IRR = 0.59, 95% CI 0.34-1.02. In addition to age and gender we therefore adjusted for tobacco smoking and education in the multivariate models.

In gender and age adjusted analyses (Model 1) no associations were found (all p values for trend > 0.2) between risk of RA and intake of the following dietary factors: fish [all types and lean (0-2 g fat/100 g fish)], long chain fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)], α-linolenic acid (ALA), olive oil, oleic acid, citrus fruit, all vegetables (including juices), retinol, beta carotene, vitamins A, E, C, and D, zinc, selenium, iron, meat (including red meat, fish, poultry, processed meat), and red meat. Weak gender and age adjusted associations (Model 1, all p values for trend < 0.2) were found between risk of RA and intake of the following dietary factors: medium fat fish (3-7 g fat/100 g fish) was associated with increased risk; fat fish (≥ 8 g fat/100 g fish) was associated with decreased risk; fruit (including juice) was associated with decreased risk; and coffee was associated with increased risk (Table 2).

Multivariate associations of RA risk with medium fat fish, fat fish, all fruit, or coffee intake, adjusted for tobacco smoking and education (Model 2) are shown in Table 1. These models did not confirm an association between intake of fruit and coffee and risk of RA. Adjusting for total energy intake did not influence estimates.

Table 2. Incidence rate ratios (IRR) of RA associated with dietary factors. IRR were adjusted for age and gender. Fish intake included both fresh and processed products.

Dietary Factor	IRR	95% CI	p
Fish (all types), per 30 g/day	0.91	0.68–1.23	0.55
Fish, lean, per 30 g/day	0.83	0.47–1.46	0.52
Fish, medium fat, per 30 g/day	2.06	0.99–4.30	0.05
Fish, fat, per 30 g/day	0.62	0.32–1.22	0.17
Olive oil, g/day	1.00	0.92–1.08	0.92
All fruits and fruit juices, per 100 g/day	0.89	0.75–1.05	0.17
Citrus fruits, per 100 g/day	1.02	0.64–1.64	0.93
All vegetables and vegetable juices, per 100 g/day	0.95	0.75–1.19	0.64
All vegetables, and fruits and juices, per 100 g/day	0.95	0.85–1.05	0.31
Retinol, µg/day	1.00	1.00–1.00	0.66
Beta carotene, µg/day	1.00	1.00–1.00	0.49
Vitamin			
A, µg/day	1.00	1.00–1.00	0.79
E, mg/day	0.99	0.92–1.06	0.72
C, mg/day	1.00	1.00–1.00	0.83
D, µg/day	1.01	0.91–1.11	0.90
Zinc, mg/day	0.99	0.93–1.05	0.66
Selenium, µg/day	1.00	0.98–1.01	0.51
Iron, mg/day	0.99	0.93–1.06	0.86
Red meat, fish, poultry, processed meat, per 100 g/day	1.16	0.83–1.62	0.39
Red meat, per 100 g/day	1.36	0.75–2.47	0.31
Coffee, per 200 g/day	1.10	0.99–1.21	0.07

CI: confidence interval; lean: 0–2 g fat/100 g fish; medium fat: 3–7 g fat/100 g fish; fat: ≥ 8 g fat/100 g fish; 200 g/day coffee: 1 cup. p for trend.

DISCUSSION

Previous studies suggested that high intake of fish protects against development of RA[5,6]. These results supported the hypothesis that n-3 fatty acids may protect against RA[15]. Negative associations between intake of fat fish or long chain fatty acids (EPA and DHA) and risk of RA were therefore *a priori* hypotheses. In agreement with these hypotheses, our results show that each additional intake of 30 g fat fish per day was associated with 49% reduction in the risk of RA in the multivariate model ($p = 0.06$). However in the same model, intake of medium fat fish was associated with significantly increased risk of RA. Dividing data for both medium fat fish and fat fish into tertiles suggested that the lowest tertile was responsible for the positive and negative association with RA, respectively. We can provide no intuitive explanation for increased risk associated with intake of medium fat fish. Despite statistical significance, it may be a chance finding, considering the many food items we studied. We found no associations between risk of RA and intake of a wide range of dietary factors including citrus fruit, vegetables, retinol, beta carotene, vitamins A, E, C, and D, zinc, selenium, iron, and meat. Furthermore, the suggested protective effect of olive oil could not be confirmed by our results. Although we found high intake of fruit was associated with decreased risk of RA, this effect was weak and not significant in contrast to findings by others[3]. Finally, we found no association between intake of coffee and risk of RA in the multivariate model, which is in accordance with previous results[7,16], although one study suggested that decaffeinated coffee might be associated with increased risk of RA[16].

The nature of the dietary survey method used, relying on self-reported recalled intake over the previous 12 months, is likely to be subject to misclassification, which would be anticipated to be random in relation to the hypotheses under test. This random misclassification, if of sufficient magnitude, could well be responsible for negative findings for some of the nutrients. However, information about fish intake was previously found to correlate with biomarkers of fish intake[14]. Furthermore, our study confirms reported non-null associations with tobacco smoking[17], another exposure subject to misclassification. We therefore believe that strong associations between dietary intake and risk of RA are unlikely to have been missed due to misclassification of dietary intake.

This was a prospective population-based cohort study in which exposure information (diet) was collected entirely independent of outcome (RA). The risk of systematic bias is therefore minimal. Ascertainment of incident patients in the cohort is incomplete because those cohort members diagnosed with RA before 1995 and treated in outpatient settings

were not identified through our record linkage with hospitalization data in the Danish National Patient Registry. It is, however, unlikely that the identified RA patients would differ systematically in dietary habits from those who were not ascertained in a manner that would have biased our results. A more relevant limitation, however, is that the followup period in our study was relatively short, with a mean time from inclusion to RA of only 2.8 yrs (range 50 days to 5.5 yrs) among our 69 patients with RA. Autoantibodies have been found several years before diagnosis of RA[18], and the period before RA onset when dietary and other potential risk factors should be studied could well be considerably longer.

In conclusion, the limited number of patients who developed RA during followup of our large cohort prevents us from concluding that dietary factors are unimportant as risk factors for RA. It appears, however, that if dietary factors are important modifiers of RA risk, they must play a role more than a few years before clinical diagnosis.

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