Cancer Epidemiology 34 (2010) 40–46

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Micronutrient intake and risk of colon and rectal cancer in a Danish cohort

Nina Roswall [a,*], Anja Olsen [a], Jane Christensen [a], Lars O. Dragsted [b], Kim Overvad [c], Anne Tjønneland [a]

[a] Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark
[b] Faculty of Life Sciences, Department of Human Nutrition, University of Copenhagen, Copenhagen, Denmark
[c] Department of Clinical Epidemiology, Aarhus University Hospital, Aalborg, Denmark

ARTICLE INFO

Article history:
Accepted 10 December 2009

Keywords:
Dietary supplements
Micronutrients
Prospective cohort study
Colonic neoplasms
Rectal neoplasms
Colorectal neoplasms

ABSTRACT

Background: Micronutrients may protect against colorectal cancer. Especially folate has been considered potentially preventive. However, studies on folate and colorectal cancer have found contradicting results; dietary folate seems preventive, whereas folic acid in supplements and fortification may increase the risk. *Objective*: To evaluate the association between intake of vitamins C, E, folate and beta-carotene and colorectal cancer risk, focusing on possibly different effects of dietary, supplemental and total intake, and on potential effect modification by lifestyle factors. *Design*: In a prospective cohort study of 56,332 participants aged 50–64 years, information on diet, supplements and lifestyle was collected through questionnaires. 465 Colon and 283 rectal cancer cases were identified during follow-up. Incidence rate ratios of colon and rectal cancers related to micronutrient intake were calculated using Cox proportional hazard analyses. *Results*: The present study found a protective effect of dietary but not supplemental folate on colon cancer. No association with any other micronutrient was found. Rectal cancer did not seem associated with any micronutrient. For both colon and rectal cancer, we found an interaction between dietary folate and alcohol intake, with a significant, preventive effect among those consuming above 10 g alcohol/day only. *Conclusions*: This study adds further weight to the evidence that dietary folate protects against colon cancer, and specifies that there is a source-specific effect, with no preventive effect of supplemental folic acid. Further studies should thus take source into account. Vitamins C, E and beta-carotene showed no relation with colorectal cancer.

1. Introduction

A wide range of studies has been conducted on the potential effects of micronutrient intake in colorectal cancer prevention. It has been speculated that vitamins C, E and beta-carotene have preventive properties due to their antioxidative effects, protecting the epithelial cells in the intestinal tract against free radicals [1]. Results from epidemiological studies on these micronutrients have, however, been inconsistent [1,2]. More promising results have been shown for folate, where a range of observational studies of dietary folate found a protective effect [3]. A meta-analysis of cohort studies found a protective effect of dietary but not total folate [4]. It has however been suggested, that components co-existing with folate in the diet are what is causing the true beneficial effect [3].

The lack of firm conclusions from existing studies of micronutrients and colorectal cancer may be explained by the difficulty in untangling the effect of different lifestyle factors affecting the colorectal cancer risk, as these are often closely linked. Smoking and alcohol have been shown to affect both the level of oxidative stress in the body as well as the bioavailability of micronutrients [5,6], and existing studies have found an effect modification between folate and smoking [7] and beta-carotene and alcohol [8] in relation to colon cancer.

Recent studies have lead to renewed debate regarding folate's role in colorectal carcinogenesis: in an intervention study among persons with a history of colorectal adenomas, supplemental folic acid showed increased risk of more and further advanced colorectal adenomas in the intervention group [9]. This harmful effect may be ascribed the high dose of folic acid [10]. Studies of colorectal cancer incidence in populations where folate fortifications is used, have also shown increased incidence after fortification was initiated [11,12].

It thus seems, that the relationship between micronutrients and colorectal cancer is more complex than initially expected, and further research is needed to examine interaction with lifestyle factors and consider the micronutrient source as the exposure, since the increased risk found in some studies may be explained by the high doses of folate reached through fortification and supplementation compared to intake from the diet. Dietary and supplemental folates also have different biological properties, which may render differing effects [13,14].

* Corresponding author at: Institute of Epidemiology, The Danish Cancer Society, Strandboulevarden 49, DK-2100 Copenhagen Ø, Denmark. Tel.: +45 35 25 77 14.
E-mail address: roswall@cancer.dk (N. Roswall).

1877-7821/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.canep.2009.12.012

The aim of the present study was to evaluate the association between intake of the micronutrients vitamins C, E, folate and beta-carotene and colorectal cancer risk, focusing on possible source-specific effects of dietary, supplemental and total intake, and on the potential effect modification by smoking, alcohol and red meat consumption.

2. Subjects and methods

2.1. Study population

The prospective Diet, Cancer and Health study invited 160,725 Danes to participate from 1993 to 1997. Inclusion criteria were 50–64 years of age, residence in the greater Copenhagen or Aarhus area and no previous cancer diagnosis in the Danish Cancer Registry; 57,053 participants accepted the invitation [15].

The study was approved by the regional ethical committees of human studies in Copenhagen and Aarhus and by the Danish Data Protection Agency.

2.2. Data collection

Baseline diet was assessed through a 192-item food frequency questionnaire mailed to each participant, which considered food intake during the past 12 months (16). Supplement use was assessed through open-ended questions on brands and doses and categorical questions on consumption frequency. Information on micronutrient content in each supplement brand was obtained from producers or distributors. For each participant, average daily micronutrient intake was calculated by the software programme Food Calc (http://www.ibt.ku.dk/jesper/foodcalc) as total, dietary and supplemental intake.

Furthermore, each participant visited the study clinic and filled in a lifestyle questionnaire, including information on factors relevant for colorectal cancer. The questionnaire was processed by optical scanning and checked for missing information during the visit, so that unclear information could be checked with the participant, preferably before leaving the study centre. A few missing questions were accepted in the lifestyle questionnaire but not the food frequency questionnaire in order to be included in the cohort.

Participants were excluded if they had a cancer diagnosis before baseline ($n = 571$) and if information on one or more confounders or exposure variables ($n = 160$) was lacking, leaving 56,332 participants for the analyses.

2.3. Case ascertainment

Information on vital status and emigration of participants was obtained from the Central Population Registry. Follow-up was initiated on the day of visit to the study centre and continued until date of diagnosis of any cancer (except non-melanoma skin cancer), date of death, date of emigration or December 31, 2006, whichever came first.

Colorectal cancer cases during follow-up were identified by linkage to the Danish Cancer Registry [17], which contains data on all cancer diagnoses in Denmark. The ICD-10 codes C18 and C19 were used to define colon cancer cases and the ICD-10 code C20 to define rectal cancer cases [18].

2.4. Statistical analysis

The analyses of relations between colorectal cancer incidence and exposure variables was based on Cox proportional hazards models with age as the underlying time scale to ensure that the estimation procedure was based on comparison of individuals of the same age. Time under study was included as a time-dependent variable and modelled as a linear spline with a boundary at one, two and three years after entry into the study-cohort. All analyses were conducted for both sexes together, after having tested that these could be combined.

The four micronutrients were examined for possible association with colorectal cancer in source-specific analyses. The association was examined for total, dietary and supplemental intake of each micronutrient.

Estimates were calculated as crude estimates, as estimates adjusted for intake of the three other micronutrients as well as mutual adjustment for dietary intake of supplemental intake and vice versa, and as estimates further adjusted for body mass index (kg/m^2, *continuous*), education (<7 years, 7–10 years, >10 years), alcohol consumption (g/day, *continuous)*, red and processed meat consumption (g/day, *continuous)*, smoking status (never/former/current), leisure time physical activity (yes/no) and HRT status (never/former/current) (among women only). Further control for energy intake, calcium intake and use of non-steroid anti-inflammatory drugs did not significantly change the results. These were thus not included in the final analyses.

Separate analyses were conducted stratified by alcohol (≤10 g/day; >10 g/day), smoking (never/former; current), and red meat intake (≤500 g/week; >500 g/week), to explore potential effect modification.

Quantitative variables were included linearly in the Cox model, because this increases the power of the analysis [19]. Linearity was evaluated graphically using linear spline models with boundaries at the three quartiles among cases [20]. We found no significant deviation from linearity, and all quantitative variables were therefore entered linearly into the model.

Incidence rate ratios (IRRs) of the association with linear micronutrient variables were presented as IRRs associated with a 100 mg/day higher consumption for vitamin C, 10 mg/day for vitamin E, 100 μg/day for folate and 5000 μg/day for beta-carotene. These units were based on evaluations of the inter-quartile range of the different linear micronutrient variables among cases. In addition, categorical analyses, where micronutrient variables were categorised into quartiles based on the exposure distribution in cases, were conducted.

All tests were based on the likelihood ratio test statistic. Two-sided 95% confidence intervals were calculated based on Wald's test of the Cox regression parameter, i.e., on the log ratio scale. The SAS procedure PHREG in SAS 8.2 on the TextPad platform was used for statistical analyses.

3. Results

A total of 465 incident colon cancer cases and 283 incident rectal cancer cases were diagnosed during a median follow-up time of 10.6 years (5–95% percentile: 4.6–12.1). The median age of entry into the study-cohort was 56.2 years (5–95% percentile: 50.7–64.2 years). As expected, a higher number of cases were smokers, fewer cases participated in leisure time physical activity and they had a higher intake of red and processed meats and alcohol (Table 1).

Table 2 shows the relationship between micronutrient intake and colon cancer. The only micronutrient exhibiting a different effect by source was folate ($p = 0.04$). Dietary folate was significantly associated with a protective effect: IRR 0.85 (95% confidence interval (CI): 0.73–0.99) per 100 μg/day. A similar association was not found for supplemental folic acid: IRR 1.01 (95% CI: 0.96–1.06) per 100 μg/day. No other micronutrient showed an association with colon cancer.

No association was found between any micronutrient and rectal cancer, and neither any difference with source (Table 3).