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ORIGINAL PAPER

Intake of whole-grain products and risk of prostate cancer among men in the Danish Diet, Cancer and Health cohort study

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Abstract
Objective High intake of whole-grain products may protect against prostate cancer, but overall evidence is limited and inconclusive. The aim of the present study was to investigate the relationship between the intake of whole-grain products and risk of prostate cancer in a large prospective cohort.
Methods A total of 26,691 men aged 50–64 years participated in the Diet, Cancer and Health cohort study and provided information about diet and potential prostate cancer risk factors. During a median follow-up of 12.4 years, we identified 1,081 prostate cancer cases. Associations between whole-grain product intake and prostate cancer incidence were analyzed using Cox's regression model.
Results Overall, there was no association between total intake of whole-grain products and prostate cancer risk (adjusted incidence rate ratio per 50 g day^{-1}: 1.00 (95% confidence interval: 0.96, 1.05)) as well as between intake of the specific whole-grain products: whole-grain rye bread, whole-grain bread, and oatmeal, and risk of prostate cancer. No risk estimates did differ according to either stage or grade of disease.
Conclusions Results from this prospective study suggest that higher intakes of total or specific whole-grain products are not associated with risk of prostate cancer in a population of Danish middle-aged men.

Keywords Whole-grain products · Prostate cancer · Prospective study

Introduction

Prostate cancer is the most common cancer in men and the second most common cause of cancer death in men living in the Western world [1]. The only generally accepted risk factors of prostate cancer are age, ethnicity, and family history of prostate cancer [2]. The considerable variation in the incidence of prostate cancer observed internationally [3], and the adapted high risk observed in men migrating from low- to high-incidence areas [4] indicates that environmental factors, including diet, may be involved in the etiology of prostate cancer. Despite that several dietary factors have been investigated in relation to prostate cancer risk, findings have been inconsistent, highlighting the challenges in understanding prostate cancer etiology.

Whole-grain products have been shown protective of several cancer types, including colorectal cancer [5, 6], upper aerodigestive cancers [7], and endometrial cancer [8]. This beneficial effect of whole-grain products may be extended to prostate cancer as well, and there are a number of biologically plausible reasons for this. In comparison with their refined counterparts, whole-grain products are rich in several components, including dietary fibers,

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vitamins (especially high in B vitamins and E vitamins), trace minerals (e.g., magnesium and selenium), phytooestrogens (lignans), and several other phenolic compounds that may have antioxidative or other beneficial properties. These substances may all be involved in the prevention of prostate cancer through several and perhaps overlapping biological mechanisms [9]. For example, lignan phytooestrogens may be implicated in the prevention of hormone-dependent cancers, including prostate cancer, through effects on steroid metabolism and activity, proliferation, angiogenesis, or antioxidant pathways [10]. Dietary fibers have been shown positively correlated with levels of sex hormone–binding globulin in men [11]. Sex hormone–binding globulin affects the bioavailability of androgens and estradiol, and higher serum concentrations have been related to modestly lower prostate cancer risk [12].

The hypothesis that whole-grain products may protect against the development of prostate cancer has only been examined in a few epidemiological studies. Results from case–control studies have been inconclusive showing either statistically nonsignificantly, inverse associations [13], or no associations [14, 15]. Moreover, in one case–control study on individual whole-grain foods, high whole-grain breakfast cereal consumption was unexpectedly associated with a significant higher risk of prostate cancer [15]. In a recent prospective investigation, whole-grain intake was found significantly positively associated with total prostate cancer, but this finding was largely attenuated when the analysis was restricted to men who had undergone prostate-specific antigen (PSA) screening [16].

So far, all of the published epidemiological studies on the role of whole-grain products in prostate cancer prevention have been conducted in Western populations, namely Italy [13, 14], Canada [15], and USA [16], where whole-grain products only account for a minor part of the diet in general. In contrast to many other Western countries, whole-grain products have long been traditional and characteristic food items of the existing food cultures in the Nordic countries, including Denmark [17]. Therefore, the conduction of epidemiological studies based on data from Nordic populations would be highly valuable in the further elucidation of the role of whole-grain products in relation to prostate cancer risk. In addition, no prospective study so far has investigated the association between different types of whole-grain products in relation to prostate cancer.

The objective of this prospective cohort study was to investigate the association between whole-grain product intake and risk of prostate cancer in Danish men participating in the Diet, Cancer and Health cohort study. Analysis was focused on total whole-grain product consumption and individual whole-grain products (whole-grain rye bread, whole-grain bread, and oatmeal). We also evaluate these associations by stage and grade of disease.

Materials and methods

Study population

Diet, Cancer and Health is an ongoing cohort study that was initiated in 1993–1997. In brief, 160,725 Danish men and women were invited to participate in the study. The inclusion criteria were age 50–64 years, living in the greater Copenhagen and Aarhus, born in Denmark, and not registered with a previous cancer diagnosis in the Danish Cancer Registry [18]. Subjects were identified by the unique, 10-digit identification number, which is allocated to every Danish citizen by the Danish Central Population Registry. Among the invited men, 27,178 accepted participation. A more detailed description of the cohort is given elsewhere [19].

The Diet, Cancer and Health cohort study and the present study were approved by the Regional Ethical Committees on human studies in Copenhagen and Aarhus and by the Danish Data Protection Agency.

Data collection

Before examination at one of two established study centers, participants completed a 192-item food frequency questionnaire, which they had received by mail. A full description of the development of the food frequency questionnaire has been published previously [20, 21]. In brief, the participants were asked to report their average intake of specific foods and beverages over the past 12 months within 12 categories of predefined responses, ranging from "never" to "eight times or more per day." Daily intakes of foods and nutrients were calculated for each participant by means of the software program FoodCalc (www.ibt.ku.dk/jesper/foodcalc/) using population-specific standardized recipes and portion sizes. Information about whole-grain product intake was summed up and measured in grams per day from two general categories of cereal groups: breads and breakfast cereals. From the bread group, whole-grain rye bread and whole-grain bread were both identified as whole-grain products, and from the breakfast cereal group, oatmeal was identified as a whole-grain product. The FFQ was validated against two times seven days of weighed diet records [22]. The energy-adjusted correlation coefficient for dietary fiber, the most relevant dietary component for whole-grain products, was 0.39 among men [22]. On entry to the study clinic, participants were further asked to complete a lifestyle questionnaire, which included questions covering social factors,

health status, and lifestyle habits. From this questionnaire, we obtained information about years of school education and smoking status. During the visit to the study clinic, the two self-administered questionnaires were processed by optical scanning and checked for missing or unclear information. This allowed correct information to be obtained from the participants while still at the study clinic. A few missing questions were accepted in the lifestyle questionnaire but not in the food frequency questionnaire. Additional anthropometrical measurements (weight and height) were obtained by trained professionals.

Exclusions

A total of 263 men were later reported in the Danish Cancer Registry with a diagnosis of cancer before entry into the study or did not respond to the lifestyle questionnaire and were excluded. Finally, 224 men were excluded because of missing information on intake of whole-grain products or missing information on one or more of the potential confounders. A total of 26,691 men were included in this study.

Case ascertainment and follow-up

All 26,691 participants were linked to the Central Population Registry for information on vital status and emigration. Each cohort member was followed up for prostate cancer from date of entry, i.e., date of visit to the study center until the date of diagnosis of any cancer (except nonmelanoma skin cancer), date of death, date of emigration or December 31, 2008. Information on cancer incidence was obtained by linkage to the Danish Cancer Registry using the personal identification number of each participant. All individuals in Denmark who are diagnosed with cancer are registered herein by means of the Central Population Registry system [18]. Definition of prostate cancer was based on the 10th Revision of the International Classification of Diseases, and prostate cancer was defined as code C61. Information on tumor, node, metastasis (TNM) stage and Gleason grade was collected for each prostate cancer case when possible. Data on TNM stage were available from the Danish Cancer Registry. Using the TNM staging score, tumors were categorized as: localized (T0 or T1 or T2 and N0 or NX and M0) or advanced (T3 or T4 and/or N1+ and/or M1). Hospital records of prostate cancer cases registered in the Danish Cancer Registry up until December 31, 2003, were retrieved from hospitals for information on Gleason score. If cases had Gleason scores determined from more than one hospitalization or sample, the higher score was recorded. Prostate tumors were classified as either low-grade (Gleason sum <7) or high-grade (Gleason sum ≥ 7) prostate cancer.

Statistical analysis

The analyses of the relation between whole-grain product variables and prostate cancer rates were based on the Cox proportional hazard model using age as the time scale to ensure that the estimation procedure was based on comparisons of individuals at the same age, which allowed for age adjustments to prevent confounding by age. Time-under-study was included as a time-dependent variable and was modeled by a linear spline with a boundary at one, two, and three years after entry into the cohort study to allow the rate to change with time [23].

All models were adjusted for baseline values of potential prostate cancer risk factors: height (cm; *continuous*), weight (kg; *continuous*), school education (low ($\leq$7 years), medium (8–10 years), and high ($\geq$11 years)), intake of red meat (g/day; *continuous*), intake of processed meat (g/day; *continuous*), intake of dairy products (g/day; *continuous*), and smoking status (never, past, and current). Additional adjustment for sports activities (entered as two variables: a dummy variable (nonactive/active) and a linear variable (number of hours doing sport per week)), alcohol intake (g/day; *continuous*), total energy intake (kJ/day; *continuous*), and a more detailed adjustment for smoking (smoking duration, current tobacco consumption, and time since smoking cessation) in the analyses did not change the associations materially and were therefore not included in the final confounder package. All analyses of specific whole-grain products (whole-grain rye bread, whole-grain bread, and oatmeal) were mutually adjusted.

All quantitative variables were entered linearly in the Cox model because this is biologically more reasonable than the step functions corresponding to categorization and, furthermore, increases the power of the analyses [24]. The linearity of the associations was evaluated graphically by linear splines with three boundaries placed at the quartiles among cases. We found no significant departures from linearity; therefore, all quantitative variables could be entered linearly in the model [23].

In the analyses, whole-grain product variables included intakes (g/day) of total whole-grain products and specific whole-grain products (rye bread, oatmeal, and whole-grain bread). The incidence rate ratios (IRR) of the associations of linear whole-grain product variables were presented as the IRRs associated with a higher intake of 25 or 50 g per day based on an evaluation of the interquartile range among cases. The continuous analyses were further supplemented with categorical analyses. In these categorical analyses, the whole-grain product variables were categorized into quartiles based on the distribution among cases.

A possible interaction between age at recruitment (using 56 years (median age at recruitment) and 60 years as cut-points) and whole-grain product consumption on risk of

prostate cancer was investigated to examine whether older men may particularly benefit from whole-grain product consumption. We tested for interaction of age with whole-grain product intake by testing whether the slopes for the intake of whole-grain products differed significantly in the two age categories. This means that the model included the main effect of the indicator variables for the two age categories and the two variables representing the whole-grain product intake in the two age categories. This model was compared with a model (including the main effect of the indicator variable for the two age categories) estimating a single common slope for the intake of whole-grain products using the likelihood ratio test.

Stage (localized and advanced), grade (high grade and low grade) of disease, and onset of disease (age at diagnosis <65 or ≥65 years) were analyzed using a competing risk model in which the different subgroups of prostate cancer were treated as competing causes of failure, that is, in separate analyses in which prostate cancers of the opposite type were censored at the age at the cancer diagnosis.

Two-sided 95% confidence intervals (CI) for the IRR were calculated based on Wald's test of the Cox regression parameter, i.e., on the log rate ratio scale. The procedure PHREG in SAS (release 9.0; SAS Institute, Cary, NC) on a TextPad platform was used for the statistical analyses.

Results

The study includes 1,081 cases of prostate cancer that was diagnosed during a median follow-up (5th–95th percentile) of 12.4 (4.3–14.1) years. Differences between cases and the total cohort were minor, although cases had a lower intake of red and processed meat, had a higher intake of dairy products, and were less likely to be current smokers than the total cohort (Table 1). For cases, the median age at diagnosis was 67 years (range: 52–80). The stage of disease at diagnosis was known for 980 cases (91%); of these, 631 (58%) were localized and 349 (32%) were advanced. Tumor grade of disease at diagnosis was available for 192 cases (18%); of these, 78 (7%) were low grade (Gleason sum <7) and 114 (11%) were high grade (Gleason sum ≥7) (Table 1).

Table 2 shows the relationship between intake of whole-grain products and prostate cancer IRRs and their corresponding 95% CIs. Overall, there were no associations between intake of total or specific whole-grain products and risk of prostate cancer. The adjusted IRRs for the linear analyses were 1.00 (95% CI: 0.96, 1.05) for total whole-grain products (per 50 g day^{-1}); 0.99 (95% CI: 0.96, 1.03) for whole-grain rye bread (per 25 g day^{-1}); 1.01 (95% CI: 0.98, 1.04) for whole-grain bread (per 25 g day^{-1}), and 0.96 (95% CI: 0.88, 1.06) for oatmeal (per 25 g day^{-1}) (Table 2).

Table 1 Baseline characteristics of 1,081 prostate cancer cases and 26,691 men in the Danish Diet, Cancer and Health study

	Cases (n = 1,081)	Total cohort (n = 26,691)
Age at baseline (years)[a]	58 (51–64)	56 (50–64)
Height (cm)[a]	177 (168–188)	177 (166–188)
Weight (kg)[a]	82 (67–104)	82 (65–105)
School education [n (%)]		
Low	369 (34)	9,265 (35)
Medium	448 (41)	11,107 (42)
High	264 (24)	6,319 (24)
Smoking status [n (%)]		
Current smoker	374 (35)	10,602 (40)
Past smoker	401 (37)	9,243 (35)
Never smoker	306 (28)	6,846 (26)
Red meat (g day^{-1})[a]	97 (46–179)	100 (46–190)
Processed meat (g day^{-1})[a]	34 (9–84)	35 (9–90)
Dairy products (g day^{-1})[a]	305 (55–993)	294 (53–1,018)
Total whole-grain products (g day^{-1})[a]	134 (42–284)	130 (42–267)
Whole-grain rye bread (g day^{-1})[a]	63 (20–163)	63 (20–163)
Oatmeal (g day^{-1})[a]	21 (1–50)	21 (1–50)
Whole-grain bread (g day^{-1})[a]	40 (1–180)	31 (1–100)
Cases only		
Age at diagnosis (years)[a]	67 (59–74)	–
Stage[b] [n (%)]		
Localized	631 (58)	–
Advanced	349 (32)	–
Unknown	101 (9)	–
Grade[c] [n (%)]		
Low grade	78 (7)	–
High grade	114 (11)	–
Unknown	889 (82)	–

[a] Values are medians (and 5th–95th percentiles in parentheses)

[b] Tumor, node, metastasis (TNM) staging score of T0 or T1 or T2 and N0 or NX and M0 (localized); TNM staging score of T3 or T4 and/or N1+ and/or M1 (advanced)

[c] Gleason sum <7 (low grade) and Gleason sum ≥7 (high grade)

We observed no significant interactions between age at recruitment and total whole-grain product consumption (cut-point 56 years: $p_{\text{interaction}} = 0.31$ and cut-point 60 years: $p_{\text{interaction}} = 0.66$) or between age at recruitment and specific whole-grain products (data not shown).

When we examined the associations between intakes of whole-grain products and cancer risk subdivided by stage (localized or advanced) and grade of disease (Gleason sum low or high), we found no significant associations (Table 3). Also, there were no associations between total or specific whole-grain products with prostate cancer risk

Table 2 Incidence rate ratios (IRR) and 95% confidence intervals (CI) for prostate cancer in men according to intake of whole-grain products, the Danish Diet, Cancer and Health study

Food	No. of cases	Crude[a] IRR (95% CI)	Adjusted[b,c] IRR (95% CI)
Total whole-grain products			
50-g increment day^{-1}	1,081	1.02 (0.98–1.06)	1.00 (0.96–1.05)
In groups:			
≤103 g day^{-1}	299	1.00	1.00
103 to ≤134 g day^{-1}	245	1.11 (0.94–1.31)	1.11 (0.93–1.31)
134 to ≤200 g day^{-1}	267	1.03 (0.87–1.21)	1.01 (0.85–1.19)
> 200 g day^{-1}	270	1.10 (0.94–1.30)	1.06 (0.89–1.26)
Whole-grain rye bread			
25-g increment day^{-1}	1,081	0.99 (0.96–1.02)	0.99 (0.96–1.03)
In groups:			
≤63 g day^{-1}	543	1.00	1.00
63 to ≤113 g day^{-1}	397	1.08 (0.95–1.23)	1.08 (0.94–1.23)
>113 g day^{-1}	141	0.89 (0.74–1.08)	0.89 (0.73–1.08)
Whole-grain bread			
25-g increment day^{-1}	1,081	1.01 (0.98–1.05)	1.01 (0.98–1.04)
In groups:			
≤17 g day^{-1}	366	1.00	1.00
17 to ≤40 g day^{-1}	408	1.06 (0.90–1.25)	1.04 (0.88–1.22)
>40 g day^{-1}	307	1.12 (0.94–1.33)	1.07 (0.90–1.28)
Oatmeal			
25-g increment day^{-1}	1,081	0.98 (0.90–1.07)	0.96 (0.88–1.06)
In groups:			
≤4 g day^{-1}	624	1.00	1.00
4 to ≤ 39 g day^{-1}	210	0.97 (0.79–1.20)	0.95 (0.77–1.18)
>39 g day^{-1}	247	0.93 (0.76–1.14)	0.90 (0.73–1.11)

IRR incidence rate ratio and *CI* confidence interval

[a] Unadjusted analysis

[b] Analysis adjusted for height, weight, school education, intake of red meat, processed meat and dairy products, and smoking status

[c] Specific whole-grain products (whole-grain rye bread, whole-grain bread, and oatmeal) are mutual adjusted

Table 3 Incidence rate ratios (IRR) and 95% confidence intervals (CI) for prostate cancer subtypes in men according to intake of whole-grain products, the Danish Diet, Cancer and Health study

Food	Increment (g day$^{-1)}$	Stage of disease		Grade of disease	
		Localized (n = 631)	Advanced (n = 349)	Low grade (n = 78)	High grade (n = 114)
Total whole-grain products					
Crude IRR (95% CI)[a]	50	1.00 (0.94–1.05)	1.05 (0.98–1.12)	0.94 (0.81–1.11)	1.01 (0.89–1.15)
Adjusted IRR (95% CI)[b]	50	0.97 (0.92–1.03)	1.05 (0.98–1.13)	0.92 (0.78–1.08)	0.98 (0.86–1.12)
Whole-grain rye bread					
Crude IRR (95% CI)[a]	25	0.99 (0.95–1.03)	1.00 (0.94–1.05)	0.95 (0.84–1.07)	0.97 (0.88–1.08)
Adjusted IRR (95% CI)[b, c]	25	0.99 (0.94–1.03)	1.00 (0.94–1.06)	0.96 (0.84–1.09)	0.97 (0.87–1.07)
Whole-grain bread					
Crude IRR (95% CI)[a]	25	0.99 (0.95–1.03)	1.04 (0.99–1.10)	1.03 (0.92–1.16)	1.01 (0.91–1.11)
Adjusted IRR (95% CI)[b, c]	25	0.98 (0.94–1.02)	1.04 (0.99–1.10)	1.01 (0.90–1.14)	0.99 (0.90–1.10)
Oatmeal					
Crude IRR (95% CI)[a]	25	0.98 (0.87–1.10)	0.98 (0.83–1.15)	1.10 (0.75–1.61)	1.08 (0.82–1.43)
Adjusted IRR (95% CI)[b, c]	25	0.95 (0.84–1.07)	0.98 (0.84–1.16)	1.04 (0.71–1.53)	1.03 (0.78–1.36)

IRR incidence rate ratio and *CI* confidence interval

[a] Unadjusted analysis

[b] Analysis adjusted for height, weight, school education, intake of red meat, processed meat and dairy products, and smoking status

[c] Specific whole-grain products (whole-grain rye bread, whole-grain bread, and oatmeal) are mutual adjusted

diagnosed in younger (age at diagnosis <65 y) or older (age at diagnosis ≥65 y) men (data not shown).

Discussion

To our knowledge, this is the first prospective study on the association between intake of whole-grain products and prostate cancer incidence using data from a Nordic population. Overall, we did not observe any associations between consumption of total or specific whole-grain products and prostate cancer risk. Furthermore, the associations did not differ significantly according to stage or grade of disease.

There at several notable strengths of our study including its prospective design; large number of prostate cases ($n = 1{,}081$); the complete and valid identification of prostate cancer cases through the Danish Cancer Registry; and its nearly complete follow-up (99.1%). Furthermore, variation in intake of total whole-grain products was considered sufficiently large among the study participants (a more than sixfold difference in the 5th and 95th intake percentiles, Table 1), thereby enhancing the ability to detect an association between whole-grain product intake and prostate cancer risk, if one truly exists. Finally, we had comprehensive information available on potential prostate cancer confounders.

Limitations include our use of a self-reported questionnaire for whole-grain consumption estimations that are subject to random measurement errors. Thus, we cannot rule out that our results have been affected by potential misclassification of the exposure that subsequent has biased findings toward unity. There is a possibility that men with more health-conscious behaviors, including eating more whole-grain products, are exposed to a higher degree of diagnostic intensity, such as PSA testing for prostate cancer [25]. As a consequence, this could lead to (over)-diagnosis of subclinical prostate cancer (diagnostic bias) and potential attenuation of a beneficial association between whole-grain product consumption and incidence of prostate cancer. The PSA test is relatively easily administered, thus despite expert warning [26], opportunistic PSA screening in Denmark is highly probable. However, the exact extent of PSA use in Danish men is unknown, but in other European countries, figures around 6–16% have been published [27–29]. We controlled for several potential prostate cancer risk factors in the analyses, but this did not change the estimates and residual confounding from unknown confounding remains possible.

The consumption of whole-grain products in Denmark is high, reflecting their basic position in the Danish food culture. Indeed, intakes of this food group in the Diet, Cancer and Health cohort (median 130 g/day) is substantially higher than those found in, e.g., populations from the United States (typically less than one serving per day ≈, e.g., 1 slice of bread or ½ cup of cooked rice or cereal) [30]. However, the results from this present study suggest that whole-grain products do not prevent prostate cancer in a population of men with high consumption of whole-grain products. It is likely that our inability to detect an association could be placed at the possibility that a potential preventive effect of whole grain on prostate cancer is to be found at very low intakes (e.g., intakes lower than our 5th intake percentile). Our findings are, however, in agreement with most earlier case–control studies of whole-grain food intake and prostate cancer risk [13, 14]. In contrast, a recent prospective cohort study among US men found a significant higher risk of prostate cancer with increasing whole-grain intake, although the association was attenuated when analysis was restricted to PSA-screened men [16].

Whole-grain rye and rye-based products have in particular been in focus when considering prostate cancer, showing beneficial effects on prostate cancer progression in animal models, including retarding of cancer growth and increase tumor cell apoptosis [31, 32]. In men diagnosed with prostate cancer, increased prostate cancer cell apoptosis has been shown following consumption of rye bran bread in one intervention study [33], and in a more recent intervention study, consumption of whole-grain and bran rye products resulted in lower plasma PSA levels compared with a diet rich in refined wheat products in patients with prostate cancer [34]. Taken together, these findings suggest that whole-grain rye may have prostate cancer chemopreventive properties. However, our study provided no evidence in support of a protective effect of whole-grain rye bread on prostate cancer incidence. Whether this is a true finding needs to be confirmed by other future observational studies on prostate cancer incidence also the relationship between rye and prostate cancer prognosis may be a potential interest in future studies.

The aggressiveness of prostate cancer is commonly measured using the two indicators: prostate cancer stage and the grade of the prostate tumor (degree of differentiation). Due to the increasing awareness that localized and low-grade prostate cancer tumors may have different etiologies compared with advanced and high-grade tumors, prostate cancer stage and grade have been of interest in previous studies on diet and prostate cancer risk [2]. In our study, we found no evidence for a difference in the relationship between intake of whole-grain products and prostate cancer risk by either stage or grade of the disease. However, the conclusions of these subgroup analyses are limited by the small numbers in each group. Of particular concern is the limited number of cases that we currently have collected Gleason values for (18% of all cases).

In conclusion, results from this prospective study suggest that higher intakes of total or specific whole-grain products are not associated with risk of prostate cancer in a population of Danish middle-aged men.

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Conflict of interest The authors declare no conflicts of interest.

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