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Rye Bread Consumption in Early Life and Reduced Risk of Advanced Prostate Cancer

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Abstract

Objective—To determine whether consumption of whole-grain; rye bread, oatmeal, and whole-wheat bread, during different periods of life, is associated with risk of prostate cancer (PCa).

Methods—In 2002 to 2006, 2,268 men, aged 67-96 years, reported their dietary habits in the AGES-Reykjavik cohort study. Dietary habits were assessed for early-, mid- , and current life using a validated food frequency questionnaire (FFQ). Through linkage to cancer- and mortality registers, we retrieved information on PCa diagnosis and mortality through 2009. We used regression models to estimate odds ratios (ORs) and hazard ratios (HRs) for PCa according to whole grain consumption, adjusted for possible confounding factors including fish-, fish liver oil-, meat-, and milk intake.

Results—Of the 2,268 men, 347 had or were diagnosed with PCa during follow-up, 63 with advanced disease (stage 3+ or died of PCa). Daily rye bread consumption in adolescence (vs. less than daily) was associated with a decreased risk of PCa diagnosis (OR = 0.76, 95% Confidence interval (CI): 0.59-0.98), and of advanced PCa (OR = 0.47, 95% CI: 0.27-0.84). High intake of oatmeal in adolescence (≥5 vs. ≤4 times/ week) was not significantly associated with risk of PCa diagnosis (OR = 0.99, 95% CI: 0.77-1.27) nor advanced PCa (OR = 0.67, 95% CI: 0.37-1.20). Mid-, and late life consumption of rye bread, oatmeal, or whole-wheat bread was not associated with PCa risk.

Conclusion—Our results suggest that rye bread consumption in adolescence may be associated with reduced risk of PCa, particularly advanced disease.

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Keywords

adolescent; diet; epidemiology; rye bread; prostatic neoplasms; whole-grain; AGES Reykjavik study

INTRODUCTION

Several lines of evidence support a role of dietary factors in prostate cancer incidence and mortality. Firstly, prostate cancer is the malignancy with the largest variation in incidence and mortality across countries, a finding that cannot be completely accounted for by screening patterns [1]. Moreover, the rapid change in prostate cancer incidence and mortality among second generation immigrants to Western countries compared with host countries suggests a role of modifiable risk factors in early life, such as dietary habits [2]. The identification of dietary factors that lower risk of prostate cancer incidence and progression could have a major public health impact.

Whole-grain has been linked to reduced cancer risk. Although mechanisms behind it are as yet unclear, many components of the whole grain could play a role such as fiber, starch, fatty acids, antioxidants, minerals, vitamins, phytoestrogens (lignans) and phenolic compounds [3]. Beneficial effects of whole-grain consumption for hormonal-dependent cancer such as prostate cancer could for example be due to lignans that affect the steroid metabolism [4]. In addition, dietary fiber increases butyrate production in the colon, and butyrate has been shown to inhibit cell growth, and promote cell differentiation and apoptosis in prostate cancer cells [5]. Rye, a rich source of lignans, minerals and vitamins [4], has also been suggested to have positive effects on long-term insulin secretion [6,7], which could be important since prostate cancer has been associated with insulin resistance [8-10]

Few epidemiological studies have specifically studied intake of whole-grain and prostate cancer risk, but two studies have reported increased risk [11,12] and three studies found no association [13-15]. These studies did not present data on advanced and localized prostate cancer separately. However, one recent prospective study on whole-grain rye-, and oatmeal consumption, among Danish men in their fifties and sixties at baseline, found no association between whole grain consumption and either localized or advanced prostate cancer [16]. Yet, animal models indicate that rye bran may have protective properties against prostate cancer [17-19] and pilot intervention studies among prostate cancer patients have shown promising effects of high rye intake on markers of prostate cancer progression [20,21]. No published study to date has addressed rye intake in early life or other types of whole grain and prostate cancer risk. Early life diet may be important in the pathogenesis of prostate cancer, because the prostate undergoes considerable growth and maturation during pubertal development. We have previously found that frequent milk intake in adolescence as well as rural residency in early life, representing high milk intake, was associated with increased risk of advanced prostate cancer [22], which suggests a role of modifiable risk factors in early life.

In Iceland, rye and oatmeal were the main types of whole-grain in the diet during the first half of the 20th century. In particular, rye consumption was 152 kilograms per year on average for an adult male in 1930 [23]. However there was considerable residency-based variability in dietary habits, including rye bread consumption, which was most common in rural areas and substantially lower in other areas during this time period [24].

In this study we investigated whether whole-grain consumption in different periods of life is associated with risk of prostate cancer in adult life in a prospective cohort study.

METHODS

Study population

The Reykjavík Study, established in 1967, is a population-based cohort of men aged 33 to 79 years, residing in the Reykjavik capital area at enrolment (1967-1987). A subgroup of 2,424 men was later enrolled in the AGES-Reykjavik study, initiated in 2002 [25].

Dietary habits in early-, mid-, and late-life

In total 2,268 men participated in AGES-Reykjavik, including men with prevalent prostate cancer (n = 214) and provided information on dietary habits in early life (between the ages of 14 to 19), midlife (between the ages of 40-50) and at the present time using a short, validated food frequency questionnaire (FFQ) [26]. The FFQ provides information on frequency of intake of eleven common foods and food groups, including rye bread and flatbread made of rye (hereafter referred to as rye bread) and oatmeal. The question on oatmeal consumption in the midlife and current period also included muesli. For these items, along with nine other food groups, participants reported frequency of consumption in each time period, using the following response categories; 1) never, 2) less than once a week, 3) 1-2/ week, 4) 3-4/ week, 5) 5-6/ week, 6) daily, and 7) more than once a day. These other food groups were: meat, fish (including salted or smoked fish), blood sausage or liver sausage, potatoes, fruits, vegetables, milk and milk products, whole wheat bread (only in midlife and at present time), and fish liver oil. The current analysis is based on those men responding to questions on early life rye bread consumption (n = 2,258), midlife rye bread consumption (n = 2,260), early life oatmeal consumption (n = 2,255), midlife oatmeal consumption (n = 2,259) and midlife whole wheat bread consumption (n =2,255). Analysis on current intake were based on participants, who were free of prostate cancer where 1,978 men answered question on rye bread, 1,983 on oatmeal and 1,980 on whole-wheat bread.

Covariate Assessment

Information on potential confounders in midlife was retrieved from the questionnaire or health check-ups at entry to the Reykjavik Study. We collected information on birth year, age at entry to the study, family history of prostate disease (yes/no), early life residency (rural, city, seaside village) [22], whether participants went regularly to a physician for a health check-up (at least every 3rd year) and education (elementary school, secondary school, college education, and university education). Information on nutritional factors such as fish-, salted or smoked fish, fish liver oil-, meat- and milk intake for all time periods were obtained from the FFQ in the AGES-Reykjavik study as well as recall information about physical activity in the past [27].

Body Mass Index (BMI, kg/m^2) was calculated from weight and height measured at the clinical exam at enrollment, categorized by obesity status (≥ 30 or <30 kg/m^2). Participants were considered to have type 2 diabetes if they had a self-reported history or if they had fasting blood glucose of ≥126 mg/dL at enrolment [28].

Ascertainment of outcome

We ascertained prostate cancer diagnoses through linkage with the nationwide Icelandic Cancer Registry, which captures 99% of cancers diagnosed in Iceland [29-31]. All men with prevalent prostate cancer at entry to the cohort (n=214) or diagnosed at follow-up, through Dec 31 2009 (n = 133) were included in the analysis. Information on cause of death was obtained from Statistics Iceland. Classification of stage at diagnosis was based on medical

records and classified as stage I (incidental finding) included T1a, NX/0, and MX/0. Stage II (tumor confined to prostate gland) included T1b/1c/1/2, NX/0, and MX/0. Stage III (tumor extending through prostatic capsule) included T3, NX/0, and MX/0. Stage IV (locally advanced or metastatic disease) included T4, NX/0, MX/0; or any T, N1 and/or M1.We had information on stage at diagnosis for approximately 75% of cases. Information on Gleason grade was not available for this study. Since 1990 there has been a rapid increase in prostate cancer incidence rates in Iceland, but at the same time the mortality rates have stayed similar, suggesting increased detection of nonlethal tumors [32].

Men who died from prostate cancer or had stage III or IV at diagnosis were classified as having advanced prostate cancer. We retrieved information on cancer diagnosis (including cancers that were prevalent in AGES) and mortality through December 31, 2009 (first diagnosis was made in 1981). Because of computerized national roster that includes a unique identification number for each person, follow-up is virtually complete [33].

Statistical Analyses

We used logistic regression models to calculate odds ratios (ORs) and 95% confidence intervals (CIs) of advanced, localized and total prostate cancer. We compared men who were high (daily or more) and low (less than daily) consumers of rye bread in early life and midlife. We created the cut-point based on extreme intake of rye bread in early life, while retaining proportions sufficient for meaningful analysis. Low intake groups in early life (less than daily) represented 53.7% of the participants (only 1.1% men never consumed rye bread) while the high intake group (daily or more) represented 46.3% of the participants (only 2.7% men consumed rye bread more than once a day). We also divided rye intake into three groups and explored the association with advanced prostate cancer risk: two times per week or less (reference group, 15.3% of participants), 3-6 times per week (38.4% of participants) and daily or more (46.3%). We then employed a trend analysis using these three groups as a continuous variable.

We considered potential confounders and adjusted in multivariate models for birth year (continuous), age at study entry in midlife (continuous), as well as: height (continuous), BMI (≥30, <30 kg/m^2), type 2 diabetes in midlife, education (three categories: elementary or secondary school; college education; university education), family history of prostate disease, and seeing a physician regularly (model two). In a third model, we further adjusted for total fish consumption (in three categories: 2.0 portions or less per week, 2.1 – 4.0 portions per week, and 4.1 portions or more per week), salted or smoked fish (once per week or more vs. 3 times per month or less) fish oil consumption (never vs. once a week or more); meat consumption (up to 4 times per week vs. 5 times per week or more), and milk intake (daily or more vs. less than daily). Fruit and vegetable intake as well as physical activity were excluded from the models since they did not affect the estimates for any of the whole-grain examined.

Similarly, in the analysis for oatmeal consumption we contrasted cancer odds among frequent consumers (5 per week) compared with less frequent (≤4 per week) in early life and midlife. Low intake groups (≤4 per week) included 61.5% of the participants (with 13.3% who never consumed oatmeal) while the high intake group (5+ per week) represented 38.5% of the participants (only 0.5% men consumed oatmeal more than once a day). Models were adjusted as was done in the rye bread analysis, however based on our findings for rye bread we also adjusted for rye bread intake (daily or more vs. less than daily) in the third model. Finally, we also analysed the intake of whole-wheat bread in midlife and contrasted cancer odds among high (daily or more) and low (less than daily) intake. The high intake group represented 48% of the participants. We used the same covariates in the multivariate analysis as was done for the oatmeal in the third model.

For current intake of whole-grain we used proportional hazard regression models to calculate hazard ratios (HRs) for advanced and total prostate cancer, since prevalent cases were excluded.

Lastly, the rye bread consumption in midlife and adolescence was pooled in one variable with four categories to assess potential effects of longitudinal rye bread consumption on prostate cancer risk. Adjustments were made for same factors as described in the third model.

In a sensitivity analysis we used logistic regression models to calculate ORs and 95% CIs of prostate cancer for rye- and oatmeal consumption in early life for incident cases only, adjusting for the same covariates as was done in the third model. Furthermore, for the estimates that were statistically significant in the models we also provided confidence intervals for odds ratios derived by bootstrapping using 200 samples.[34]

For all statistical analyses we used PASW software, version 18.0 (SPSS Inc., 2009, IBM Chicago, IL, www.spss.com) and STATA version 11 (StataCorp. 2009. *Stata Statistical Software: Release 11.* College Station, TX: StataCorp LP). The study protocol was approved by the Icelandic Ethical Review Board (VSNb2007120014/03-7) and the Icelandic Data Protection Authority.

RESULTS

The mean age (SD) was 46.8 years (6.9) when the participants entered the Reykjavik Study and 76.6 years (5.3) when they entered the AGES-Reykjavik component and provided the dietary information. The mean follow-up time (SD) for our participants was 34.3 years (6.4).

Table 1 shows characteristics, mostly collected in midlife in the Reykjavik Study, of the men who reported their dietary habits in the study (n = 2,268) by categories of rye bread- and oatmeal consumption in early- and midlife. Compared with those who did not consume rye bread on a daily basis, the high rye bread group was more likely to have lived in a rural area in early life (33% vs. 21%, respectively). Similarly, high vs. low oatmeal consumption was correlated with rural residency in early life (37% vs. 21%, respectively). High oatmeal consumption both in early life and midlife was associated with lower obesity. Otherwise the groups were similar.

Among the 347 prostate cancer cases who reported their dietary habits, 214 were diagnosed before and 133 after completing the FFQ. Information on stage at diagnosis was available for 259 (75%) individuals, and 63 had advanced prostate cancer defined as locally advanced or metastatic at diagnosis or prostate cancer death. The mean age (SD) at cancer diagnosis was 74.9 years (6.5).

Whole-grain intake

Men who consumed rye bread daily in adolescence were at decreased risk of prostate cancer overall (OR = 0.76, 95% CI: 0.59-0.98), and more pronounced decrease for advanced cancer (OR = 0.47, 95% CI: 0.27-0.84) compared with those consuming rye bread less than daily (Table 2). When milk intake in adolescence was not included in the model the association between early life rye bread consumption and advanced prostate cancer was marginally significant (OR = 0.57, 95% CI: 0.32-1.00). We examined further the association between rye bread consumption in early life and advanced prostate cancer within the high milk group, which yielded an odds ratio of 0.50 (95% CI: 0.28-0.91).

When adding early life residency to the multivariate model, the risk estimate for rye bread consumption remained the same for advanced prostate cancer (OR = 0.48, 95% CI: 0.26-0.88). We further divided rye intake into three groups and explored the association with advanced prostate cancer risk. We found a significant trend with risk estimates of 3-6 times per week (OR = 0.77, 95% CI: 0.35-1.66), and daily or more (OR = 0.39, 95% CI: 0.17-0.87) compared with two times per week or less (P_{trend} = 0.009). In contrast to early life intake, we found no association between daily consumption of rye bread in midlife with risk of prostate cancer overall nor for advanced prostate cancer. With prevalent prostate cancer cases excluded, we further explored the association between current daily rye bread intake and prostate cancer incidence yielding no statistically significant associations; HR = 0.69 (95% CI: 0.45-1.06) for total prostate cancer (n = 133) and HR = 0.64 (95% CI: 0.25-1.61) for advanced prostate cancer (n = 27).

Table 3 presents ORs and 95% CIs of advanced, localized and total prostate cancer by oatmeal consumption in adolescence and midlife. High intake of oatmeal in adolescence (≥5 vs. ≤4 times/ week) was not associated with risk of prostate cancer diagnosis (OR = 0.99, 95% CI: 0.77-1.27), nor statistically significant with advanced prostate cancer (OR = 0.67, 95% CI: 0.37-1.20). High intake of oatmeal in midlife was not associated with prostate cancer risk and neither was current intake for either total prostate cancer (HR = 1.06, 95% CI: 0.74-1.52) nor advanced disease (HR = 0.99, 95% CI: 0.44-2.23). Similarly, we found no association between intake of whole-wheat bread in midlife, which was only reported for midlife and current time, and risk of total prostate cancer (OR = 0.92, 95% CI: 0.71-1.18) nor with advanced prostate cancer (OR = 0.74, 95% CI 0.42-1.30). Similar results were obtained for current daily intake of whole-wheat bread for total prostate cancer (HR = 1.07, 95% CI: 0.75-1.53) and advanced disease (HR = 0.96, 95% CI: 0.43-2.14).

Table 4 presents ORs and 95% CIs of total prostate cancer and advanced prostate cancer by consumption of rye bread both in adolescence and midlife. Compared to low rye bread intake in both life periods, the risk estimates were very similar for high intake in adolescence, irrespective of consumption pattern in midlife, which suggests that the reduction of prostate cancer risk is mainly driven by early life consumption.

Sensitivity analysis

To address potential recall bias or differential survival, we performed a sensitivity analysis limited to men who reported early life whole-grain consumption. Number of incident prostate cancer in that group was132 and only 27 were diagnosed with advanced disease. Compared with men consuming rye bread less than once per day, the OR in the multivariate model for total prostate cancer was 0.82 (95% CI: 0.56-1.20) and 0.73 (95% CI: 0.32-1.68) for advanced disease among men with high rye bread consumption in adolescence. Men consuming oatmeal more than five times per week, had an OR of 0.80 (95% CI: 0.54-1.19) for total prostate cancer and 0.93 (95% CI: 0.40-2.19) for advanced disease compared with men with low oatmeal consumption (≤4 times/ week) in adolescence. We also performed sensitivity analysis using a bootstrap approach which largely confirmed our main findings (table 2).

DISCUSSION

In this population-based cohort of Icelandic men, we found that frequent rye bread consumption during adolescence was associated with a decreased risk of prostate cancer and particularly prostate specific mortality or being diagnosed with late stage prostate cancer. In contrast, frequent oatmeal consumption in adolescence was not associated with prostate cancer risk nor was mid- or late life consumption for either rye bread or oatmeal. These findings highlight the potential role of early life diet for prostate cancer risk and are in

accordance with our previous findings showing that high milk intake in early life, but not in midlife, is a risk factor for advanced prostate cancer [22]. In fact, early life residency in rural area, representing high milk and rye bread consumption, was associated with prostate cancer risk, indicating confounding effect by milk consumption. The association between early life rye consumption and prostate cancer risk was thus more evident after adjusting for early life milk consumption and the estimates did not change when we additionally adjusted for early life residency. Our findings on the importance of early life environment also agree with evidence from migrant studies showing that it takes at least one generation to gain prostate cancer risk of the host country [35,2]. A study from Sweden found that immigrants entering the country in their twenties retain prostate cancer incidence rates similar to those in their native country [36]. Our findings on midlife consumption are in line with result from a Danish study on whole-grain intake showing no significant association [16].

Studying early life exposures is a challenge but also imperative for understanding many chronic diseases that may originate in early life. An important strength of this study is the extensive background data allowing control for several potential confounding factors. Further, record linkage to the cancer- and mortality registers permitted complete follow-up for prostate cancer diagnosis and deaths. However, we cannot exclude the possibility that unmeasured confounders obscure our observations or that our findings are due to chance. Moreover, our study is particularly vulnerable to recall bias. Men with prevalent prostate cancer may evaluate their past dietary consumption differently from men without prostate cancer. However, our findings indicate that only rye bread in early life, not midlife, is associated with advanced prostate cancer (not localized prostate cancer) which argues against differential recall of past rye intake between men with and without prostate cancer. Furthermore, the hypothesis that rye might be beneficial for health is not well known in the general Icelandic population. Finally, our sensitivity analysis limited to incident cases, although with less statistical power, also suggests lower risk of prostate cancer by high rye bread consumption in early life and our bootstrap analysis suggests similar results.

Non-differential misclassification could also be of concern here; participants have to recall their dietary habits many decades back in time. Indeed a previous validation study of the AGES FFQ midlife dietary habits, the retrospective assessment of midlife rye bread consumption did not correlate with dietary data gathered from the same individuals 18-19 years previously (n = 174) [27]. We have no data on the validity of adolescence dietary assessment. This would however typically lead to underestimation of the observed associations and even failure to observe true associations, for example a potential association between oatmeal consumption in early life as well as midlife rye bread consumption and advance prostate cancer. Nevertheless, a previous US-based study indicated that food related memory from childhood over four decades later can be as accurate as from current diet, especially for food items eaten rarely or daily [37]. Yet, another limitation to our study is the lack of information about total energy intake and fat intake; however we adjusted for body mass index measured in midlife, which correlates with fat- and total energy intake. In conclusion, we still remain cautious when interpreting the observed association between rye bread consumption in early life and risk of advanced prostate cancer. The association between consumption of whole grain products at different stages of life and prostate cancer risk should be further studied in cohorts with more advanced prostate cancer cases as some of the estimates suggest a decreased risk.

Potential mechanisms that could mediate the effect of rye bread consumption on reduced prostate cancer risk have not been sufficiently explored. In animal models, rye bran has especially protective properties against prostate cancer [17-19], most likely because of its high lignans content compared with oatmeal and wheat [4]. Since there are few human studies available on rye consumption and prostate cancer risk our attention has been drawn

to studies on lignans consumption or serum level of enterolactone, a metabolite of lignans. A small case-control study (83 cases vs. 103 controls) did not find an association between consumption of lignan precursors (such as flaxseed, dark bread, broccoli, coffee and tea) and prostate cancer risk [38]. However a case-control study (433 cases vs. 538 controls) in the United States found an inverse association between high intake of lignans and prostate cancer [39]. Both studies assessed the diet 1-2 years prior to diagnosis and they did not distinguish between localized and advanced disease. One case-control study has found high serum levels of enterolactone to decrease prostate cancer risk [40]. While two nested case-control studies and one prospective study have not observed an association between enterolactone and prostate cancer [41-43].

While a prospective study on whole grain rye consumption among men in their fifties did not observe association with prostate cancer risk [16], some evidence indicates late effect of rye bran on prostate cancer progression. A pilot intervention study found a reduced plasma prostate-specific antigen (PSA) among patients with prostate cancer consuming rye whole grain and bran compared with patients consuming refined wheat products [20] and another pilot study suggests that rye bran bread can increase apoptosis in prostate tumors [21].

To date no study has addressed early life effect of rye intake on prostate cancer risk. Prostate tissue contains both estrogen α and β receptors (ERα and ERβ) [44] and the steroid hormone 17β-estradiol mediates cell growth, proliferation, and differentiation through these two intracellular receptors [45]. Enterolactone binds to ERα and also somewhat to ERβ, and can potentially disrupt the effect of 17β-estradiol to some extent and thereby prevent or reduce estrogen-dependent tumor growth [46]. Conversely, because rye is also a source of fiber the mechanism of butyrate production may be involved. Butyrate production in the gut increases with high consumption of fiber from cereals due to fermentation [47], and butyrate has been shown to inhibit cell growth, and promote cell differentiation and apoptosis in prostate cancer cells [5]. Furthermore, fiber may reduce reabsorption of estrogen in the bowel [48]. Alternatively, rye has been suggested to have positive effects on long-term insulin secretion [6,7], which could be important since prostate cancer has been associated with insulin resistance [8-10]. Insulin is indeed a growth factor for many tumors and hyperinsulinemia results in increased availability of insulin-like growth factor-1 (IGF-1) [49], a potential risk factor for prostate cancer [50]. Thus intake of rye may affect several pathways relevant for carcinogenesis in the prostate. The fact that we did not get the same results for oatmeal consumption possibly strengthens the hypothesis between lignans and prostate cancer, because oatmeal contains only half the amount of total lignans compared with rye, and contains also different types of lignans [4]. Possibly a combination of lignans and fiber from rye affects different mechanisms and should be studied further, especially for early life period.

In summary, our data suggest that rye bread consumption in adolescence is associated with decreased risk of advanced prostate cancer later in life. Our findings call for further studies on potential mechanisms for the early life-dependent impact of rye and other food items on the risk of advanced prostate cancer.

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Table 1

Characteristics of male participants by their rye bread- and oatmeal consumption

	All	Rye bread intake in adolescence		Oatmeal intake in adolescence		Rye bread intake in midlife		Oatmeal intake in midlife	
	N= 2,268	High[a], n= 1,046	Low[b], n= 1,212	High[c], n= 869	Low[d], n= 1,386	High[a], n= 678	Low[b], n= 1,582	High[c], n= 572	Low[d], n= 1,687
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age at entry to the AGES-Reykjavik									
-mean age (SD)	76.6 (5.3)	77.9 (5.5)	75.4 (4.9)	77.6 (5.5)	75.9 (5.1)	78.2 (5.7)	75.8 (5.0)	78.2 (5.8)	76.2 (5.2)
Education									
-Primary and Secondary	1663 (73.3)	763 (72.9)	896 (73.9)	623 (71.7)	1032 (74.5)	504 (74.3)	1155 (73.0)	400 (69.9)	1260 (74.7)
-College	314 (13.8)	146 (14.0)	165 (13.6)	125 (14.4)	185 (13.3)	90 (13.3)	222 (14.0)	84 (14.7)	226 (13.4)
-University	291 (12.8)	137 (13.1)	151 (12.5)	121 (13.9)	169 (12.2)	84 (12.4)	205 (13.0)	88 (15.4)	201 (11.9)
Prostate disease in the family	224 (9.9)	113 (10.8)	111 (9.2)	99 (11.4)	123 (8.9)	68 (10.0)	156 (9.9)	59 (10.3)	164 (9.7)
Regular health check-up	421 (18.6)	189 (18.1)	229 (18.9)	154 (17.7)	263 (19.0)	120 (17.7)	297 (18.8)	113 (19.8)	301 (17.8)
Diabetes type 2 in midlife	38 (1.7)	18 (1.7)	20 (1.7)	17 (2.0)	21 (1.5)	13 (1.9)	25 (1.6)	10 (1.7)	28 (1.7)
Smoking status in midlife									
-Never	575 (25.4)	276 (26.4)	295 (24.3)	251 (28.9)	323 (23.3)	181 (26.7)	390 (24.7)	172 (30.1)	401 (23.8)
-Previously	529 (23.3)	274 (26.2)	253 (20.9)	202 (23.2)	321 (23.2)	165 (24.3)	363 (22.9)	154 (26.9)	374 (22.2)
-Current	1164 (51.3)	496 (47.4)	664 (54.8)	416 (47.9)	742 (53.5)	332 (49.0)	829 (52.4)	246 (43.0)	912 (54.1)
Early life residency [e]									
-Reykjavik	816 (36.9)	336 (32.9)	477 (40.4)	214 (25.6)	594 (43.6)	221(33.5)	592 (38.3)	179 (32.3)	633 (38.4)
-Sea village	724 (32.7)	309 (30.2)	414 (35.1)	281 (33.6)	443 (32.5)	210 (31.9)	514 (33.2)	177 (31.9)	547 (33.2)
-Rural area	599 (27.1)	341 (33.4)	253 (21.4)	310 (37.0)	286 (21.0)	203 (30.8)	392 (25.4)	184 (33.2)	411 (24.9)
-Combination of rural area / sea village	74 (3.3)	37 (3.6)	36 (3.1)	32 (3.8)	40 (2.9)	25 (3.8)	48 (3.1)	14 (2.5)	59 (3.6)
BMI ≥ 30 in midlife	163 (7.2)	84 (8.0)	79 (6.5)	44 (5.1)	172 (9.1)	47 (7.0)	116 (7.3)	28 (4.9)	135 (8.0)
Mean BMI (m/kg^2) in midlife (SD)	25.5 (3.1)	25.6 (3.1)	25.4 (3.1)	25.3 (3.0)	25.6 (3.2)	25.6 (3.1)	25.4 (3.1)	25.2 (3.0)	25.6 (3.2)
Mean height (cm) in midlife (SD)	177.9 (6.0)	177.7 (6.0)	178.1 (6.0)	177.5 (5.9)	178.2 (6.1)	177.7 (6.1)	178.0 (6.0)	177.8 (6.1)	178.0 (6.0)
High intake of other food groups [f]									
-Milk and milk products (*daily or more*)	1804 (79.5)	935 (89.4)	863 (71.2)	760 (87.5)	1031 (74.5)	512 (75.5)	909 (57.8)	431 (75.6)	991 (58.8)
-Fish (> *4 portions per week*)	868 (38.3)	460 (44.0)	404 (33.4)	407 (46.9)	457 (33.0)	256 (37.8)	423 (26.8)	240 (42.0)	440 (26.1)
-Fish liver oil (≥ *1 per week*)	1461 (64.4)	657 (63.0)	797 (66.0)	599 (69.2)	857 (62.0)	502 (74.3)	1168 (74.1)	468 (82.1)	1202 (71.4)
-Meat (≥ *5 per week*)	114 (5.0)	58 (5.6)	55 (4.5)	42 (4.9)	70 (5.1)	84 (12.4)	144 (9.1)	72 (12.6)	156 (9.3)
- Fruits (*daily or more*)	21 (0.9)	16 (1.5)	5 (0.4)	6 (0.7)	15 (1.1)	35 (5.2)	67 (4.2)	42 (7.5)	60 (3.6)
- Vegetables (*daily or more*)	35 (1.5)	27 (2.6)	7 (0.7)	20 (2.3)	15 (1.1)	55 (8.1)	59 (3.7)	52 (9.1)	62 (3.7)

Abbreviations: BMI, body mass index; cm, centimeters; kg, kilogram; m, meter; SD, standard deviation

[a] Consuming rye bread daily

[b] Consuming rye bread less than daily

[c] Consuming oatmeal five times per week or more

[d] Consuming oatmeal four times per week or less

[e] Data on residency is missing for 55 men

[f] At the same time (adolescence/midlife) when rye bread and otamel consumption was high or low. High consumption in adolsecence is shown for all particpants (n=2,268)

Table 2

Prostate cancer by rye bread intake in early- and midlife

Adolescence (14-19 years of age)			**Age adjusted OR (95% CI)**	**OR[a] (95% CI)**	**OR[b] (95% CI)**
Advanced (n= 62)	**Non-PCa (n)**	**PCa (n)**			
n = 1,978					
Low intake	1,025	35	1.00	1.00	1.00
High intake	891	27	0.68 (0.40-1.15)	0.68 (0.39-1.16)	0.47 (0.27-0.84) *
Localized (n=280)	**Non-PCa (n)**	**PCa (n)**			
n = 2,196					
Low intake	1,025	152	1.00	1.00	1.00
High intake	891	128	0.89 (0.68-1.15)	0.87 (0.67-1.14)	0.83 (0.63-1.09)
Total (n=342)	**Non-PCa (n)**	**PCa (n)**			
n = 2,258					
Low intake	1,025	187	1.00	1.00	1.00
High intake	891	155	0.84 (0.66-1.07)	0.84 (0.66-1.07)	0.76 (0.59-0.98) **

Midlife (40-50 years of age) Age			**adjusted OR (95% CI)**	**OR[a] (95% CI)**	**OR[b] (95% CI)**
Advanced (n= 63)	**Non-PCa**	**(n) PCa (n)**			
n = 1,977					
Low intake	1,338	42	1.00	1.00	1.00
High intake	576	21	0.93 (0.54-1.62)	0.96 (0.55-1.67)	0.87 (0.49-1.54)
Localized (n=283)	**Non-PCa (n)**	**PCa (n)**			
n = 2,197					
Low intake	1,338	202	1.00	1.00	1.00
High intake	576	81	0.85 (0.64-1.13)	0.84 (0.63-1.13)	0.84 (0.63-1.13)
Total (n=346)	**Non-PCa (n)**	**PCa (n)**			
n = 2,260					
Low intake	1,338	244	1.00	1.00	1.00
High intake	576	102	0.87 (0.67-1.13)	0.87 (0.67-1.12)	0.85 (0.65-1.12)

Abbreviations: CI, confidence interval; OR, odds ratio

[a]djustment made for birth year, age at study entry in midlife, education, family history of prostate disease, going to a physician regularly, height in midlife, BMI in midlife, and type 2 diabetes in midlife

[b]Additional adjustments made for fish-, fish liver oil-, meat-, and milk intake

*Bootstrap OR and 95% CI for advanced prostate cancer: 0.47 (0.27-0.81)

**Bootstrap OR and 95% CI for total prostate cancer: 0.76 (0.60-0.97)

Table 3

Prostate cancer by oatmeal intake in early- and midlife

Adolescence (14-19 years of age)	Age adjusted OR (95% CI)			OR[a] (95% CI)	OR[b] (95% CI)
Advanced (n= 60)	**Non-PCa (n)**	**PCa (n)**			
n = 1,973					
Low intake	1,183	39	1.00	1.00	1.00
High intake	730	21	0.73 (0.42-1.27)	0.71 (0.40-1.24)	0.67 (0.37-1.20)
Localized (n=282)	**Non-PCa (n)**	**PCa (n)**			
n = 2,195					
Low intake	1,183	164	1.00	1.00	1.00
High intake	730	118	1.11 (0.86-1.44)	1.07 (0.82-1.39)	1.02 (0.82-1.42)
Total (n=342)	**Non-PCa (n)**	**PCa (n)**			
n = 2,255					
Low intake	1,183	203	1.00	1.00	1.00
High intake	730	139	1.03 (0.81-1.31)	0.99 (0.78-1.26)	0.99 (0.77-1.27)

Midlife (40-50 years of age)	Age adjusted OR (95% CI)			OR[a] (95% CI)	OR[b] (95% CI)
Advanced (n= 63)	**Non-PCa (n)**	**PCa (n)**			
n = 1,979					
Low intake	1,441	41	1.00	1.00	1.00
High intake	475	22	1.45 (0.85-2.48)	1.37 (0.79-2.37)	1.33 (0.75-2.38)
Localized (n=280)	**Non-PCa (n)**	**PCa (n)**			
n = 2,196					
Low intake	1,441	205	1.00	1.00	1.00
High intake	475	75	1.06 (0.80-1.41)	1.01 (0.76-1.35)	1.05 (0.78-1.43)
Total (n=343)	**Non-PCa (n)**	**PCa (n)**			
n = 2,259					
Low intake	1,441	246	1.00	1.00	1.00
High intake	475	97	1.12 (0.87-1.46)	1.07 (0.82-1.39)	1.10 (0.83-1.44)

Abbreviations: CI, confidence interval; OR, odds ratio

[a]Adjustment made for birth year, age at study entry in midlife, education, family history of prostate disease, going to a physician regularly, height in midlife, BMI in midlife, and type 2 diabetes in midlife

[b]Additional adjustments made for fish-, fish liver oil-, meat-, and milk intake

Table 4

Prostate cancer by longitudinal rye bread intake

Total prostate cancer (n= 338) Adolescence	Midlife	Number	OR[a] (95%CI)
Low[b]	Low	1083	1.00
Low	High[c]	123	0.82 (0.47-1.43)
High	Low	491	0.75 (0.55-1.03)
High	High	554	0.74 (0.54-1.00)

Advanced prostate cancer (n =59) Adolescence	Midlife	Number	OR[a] (95%CI)
Low	Low	942	1.00
Low	High	112	1.36 (0.50-3.72)
High	Low	432	0.44 (0.21-0.96)
High	High	485	0.53 (0.27-1.06)

[a]Adjustment made for birth year, age at study entry in midlife, education, family history of prostate disease, going to a physician regularly, height in midlife, BMI in midlife, and type 2 diabetes in midlife, fish-, fish liver oil-, meat-, and milk intake in adolescence

[b]Consuming rye bread less than daily

[c]Consuming rye bread daily or more