Dietary patterns during adolescence and risk of colorectal cancer

A population-based study in Iceland

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Fæðumynstur á unglingsárunum og tengsl þess við áhættu á krabbameini í ristli og endaþarmi
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Ágrip

Markmið: Markmið þessarar rannsóknar var að kanna fæðuvenjur á unglingsárum og tengsl þeirra við ristil- og endaþarmskrabbamein.

Aðferðir: Notast var við gögn úr Öldrunarrannsókn Hjartaverndar sem framkvæmd var í Reykjavík á tímabilinu 2002 -2006 en alls tóku 5764 einstaklingar (42% karlar) fæddir á tímabilinu 1907 -1935 þátt. Með samkeyrslu gagnanna við Krabbameinsskrá Íslands fengust upplýsingar um greiningu og dánartíðni vegna ristil- og endaþarmskrabbameins. Notast var við meginhlutagreiningu til að greina fæðumynstur. Notast var við lifunargreiningu til að meta hlutfallslega áhættu á ristil- og endaþarmskrabbameini með 95% öryggismörkum.

Niðurstöður: Á eftirfylgnitímanum (meðaltal 8.2 ár) greindust 136 einstaklingar með ristil- og endaþarmskrabbamein, þar af voru 52 sem dóu af völdum meinsins. Borið saman við þátttakendur sem skoruðu lágt á sterkasta fæðumynstrinu, sem einkennist af mikilli neyslu á söltuðu og reyktu kjöti og fiski, blóðmör og lifrarpylsu, mjólk og mjólkurvörum ásamt hafragraut á unglingsárum sást aukin áhætta á ristil- og endaþarmskrabbameini hjá þátttakendum sem skoruðu meðalhátt (HR 1.63, 95% CI 1.04-2.57). Hinsvegar, sáust ekki marktæk tengsl fyrir þátttakendur sem skoruðu hátt (HR 1.48, 95% CI 0.93-2.37). Þegar gögnunum var lagskipt eftir kyni sást einungis tölfræðilega marktækt samband hjá konum (HR 2.06, 95% CI 1.11-3.84; p-trend =0.02) sem skoruðu hátt á þessu fæðumynstri, en ekki körlum.

Ályktun: Niðurstöður gefa til að kynna að fylgni við fæðumynstur sem samanstendur af mikilli neyslu á söltuðu og reyktu kjöti og fisk á unglingsárunum geti aukið hættu á ristil- og endaþarmskrabbameini meðal kvenna. Kynjamunurinn gæti verið tilkominn vegna hás aldurs þátttakenda við komu í Öldrunarrannsóknina.

Lykilorð: unglingsárin, fæðumynstur, ristilkrabbamein, þáttagreining, faraldsfræði

Abstract

Aims: To examine whether dietary patterns in adolescence are associated with colorectal cancer (CRC).

Methods: We used food frequency data obtained from the AGES Reykjavik study, conducted in Reykjavik, Iceland in the period 2002 -2006 and included 5078 (42% male) participants born between 1907 and 1935. Through linkage to the Cancer Registry, information on CRC diagnosis and mortality was obtained. Principal component analysis was used to extract dietary patterns. We used Cox models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for CRC according to dietary patterns scores in adolescence.

Results: During the follow-up period (mean 8.2), 136 participants were diagnosed with CRC, of whom 52 died due to the disease. The strongest pattern extracted in adolescence was characterized by high consumption of salted and smoked meat and fish, blood and liver sausage, rye bread, milk and milk products and oatmeal (traditional Icelandic diet). For all participants, the middle tertile was associated with CRC (HR 1.63 95% CI 1.04-2.57) when compared to the lowest tertile of the traditional Icelandic diet. However, the highest tertile was not significantly associated with CRC (HR 1.48 95% CI 0.93-2.37). When the analysis was stratified by gender, the results showed that the association with the highest tertile compared to the lowest was only evident for women (HR 2.06 95% CI 1.11-3.84; p trend = 0.02), but not for men.

Conclusion: Our findings suggest that high adherence to a pattern characterized by high consumption of salted and smoked meat and fish during adolescence increases risk of CRC among women late in life. High age at entry to the study might explain the gender difference in our data.

Keywords: adolescence, dietary pattern, colorectal cancer, factor analysis, epidemiology

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Abbreviations

AGES-Reykjavik, the Age/Gene Environment Susceptibility – Reykjavik Study

AICR, American Institute for Cancer Research

ASR, Age-standardized rate

CI, Confidence interval

CRC, Colorectal cancer

BMI, Body max index

DM2, Diabetes mellitus type 2

e.g., for example

FFQ, Food frequency questionnaire

HR, Hazard ratio

i.e., that is

IARC, International Agency for Research on Cancer

NOCs, N-nitroso compounds

OR, Odds ratio

SD, Standard deviation

US, United States

WRCF, World Cancer Research Fund

1 Introduction

Colorectal cancer (CRC) is one of the most frequently diagnosed cancer worldwide, accounting for almost 10% of new cancer cases (6). Worldwide, CRC is a major public health burden, with estimated 1,4 million new cases and almost 694,000 cancer deaths in 2012 (7). Nationwide population based cancer registry has been operating in Iceland since 1955 and reports that the age-standardized rate (ASR) of CRC has increased substantially during the last decades to become one of the most frequently diagnosed malignancies in Iceland (8).

CRC is the combined name for cancer that begins in the colon or/and the rectum, both of which are parts of the large intestine (9). CRC typically starts as a growth in the inner surface of the colon and/or rectum, called a polyp (10). Most polyps are not cancerous but certain types of polyps, called an adenoma can develop into cancer over time. The most common type of CRC is adenocarcinomas (approximately 95%). Other, less common types of CRC include mucinous carcinomas and adenosquamous carcinomas.

Several non-modifiable risk factors for CRC have been established, such as age, family history of adenomatous polyps or CRC, presence of hereditary syndromes, chronic inflammatory bowel disease and ethnicity (11-14). In addition, a number of modifiable risk factors have been associated with CRC, for example, physical inactivity, being overweight and smoking (14). Dietary factors are also believed to play an important role in the prevention and development of this type of cancer. Whilst most studies of CRC have evaluated dietary exposures during adult life there is a lack of research focusing on earlier time periods (1-5).

The aim of this study was therefore to examine whether dietary patterns in adolescence (14 -19 years) were associated with CRC risk later in life among participants of the Age, Gene/Environment Susceptibility (AGES) Reykjavik cohort. Improved knowledge of potential effect of diet during early life on risk of CRC could have a major impact on public health.

1.1 Incidence and mortality of CRC

CRC is the second most frequently diagnosed cancer in females and the third most frequently diagnosed cancer in males worldwide (7). A significant global variation in incidence rates across countries has been observed (with an estimated 10-fold difference across countries, in both sexes, although rates are higher in men than in women in most parts of the world, see figure 1. According to the latest data from 2012, the incidence rates are highest in Australia and New Zealand, Europe and Northern America and lowest in Western Africa and South-Central Asia (6, 7). CRC has been more common in developed countries (accounting for over 65% of new cancer cases) than in underdeveloped countries. In recent years, the incidence rate of CRC has been increasing in certain countries where risk has traditionally been low, including Western Asia and Eastern Europe. Increased incidence rates in these countries may be due to changes in screening activity, changes in dietary and environmental exposures, as well as ageing of the population. In contrast, incidence rates seem to be declining or stabilizing in several countries that have reached high development levels, like Australia, the United States (US), New Zealand and several countries in Western Europe. This is most likely due to increase in screening among aged adults, removal of pre-cancerous adenomas, as well as reduction in risk factors (e.g. smoking) (at least in the US, and probably in other countries as well) (15). In 2012, it was estimated that 447,136 new cases of CRC were diagnosed in Europe (15% of new cancer cases) and 136,490 in the US for 2016 (8% of new cancer cases) (11, 16). In Iceland, CRC is the second most common cancer in males and the third most common in females (8). In 2010 -2014, the ASR in Iceland was 30, 6 per 100,000 for males and 22, 1 per 100,000 for females (17).

CRC is the fourth-leading cause of cancer related deaths worldwide, with almost 694,000 deaths estimated to have occurred in 2012 (accounting for 8, 5% of all cancer deaths) (7). The highest CRC mortality rates in 2012 were in Central and Eastern Europe. In Europe, CRC is the second most common cause of cancer related deaths with almost 215,000 deaths estimated to have occurred in 2012 (accounting for around 12% of all cancer deaths). The lowest mortality rates were in Western Africa, consistent with their low CRC incidence rates. In recent years, CRC mortality rates have been steadily falling in several high-income countries, such as Asia (Japan), North America (Canada and the US) and Oceana (New Zealand and Australia) (18). Similar decline in mortality rates has been observed in most European countries (other than Estonia, Croatia, Latvia, Romania and Russia) (18-20). This may partly be due to increased use of screening and/or improved treatments. Despite these favorable changes, CRC continues to be an ongoing public health burden.

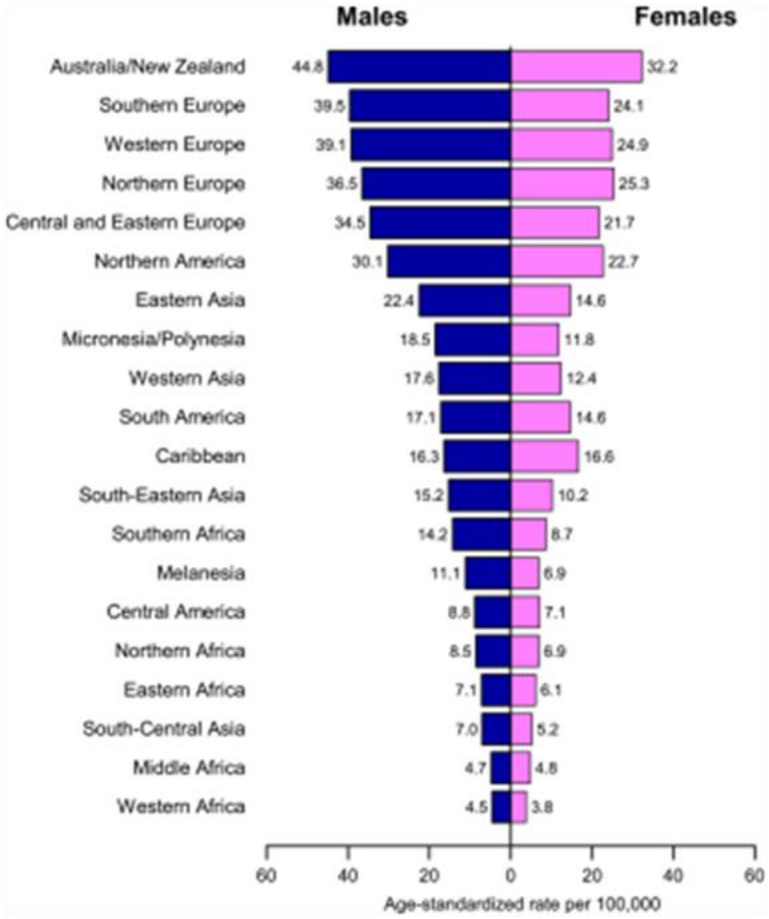

Figure 1 Age-standardized (world standard) incidence rate (per 100,000) for colorectal cancer by gender and world area (7)

1.2 Risk factors

Etiology of CRC is not fully known. Age, family history and ethnicity are among non-modifiable risk factors that have been established for CRC to date (14). Other non-modifiable risk factors include hereditary syndromes and inflammatory bowel disease (21, 22). Incidence of CRC increases markedly with older age and is higher among people with a first-degree relative (e.g. parent or sibling) diagnosed with the cancer. As mentioned previously (see section 1.1, figure 1) there is a significant global variation in the incidence of CRC (7). This variation cannot be completely explained by increased use of screening, but may be partly explained by lifestyle differences between countries. This is further supported by migration studies, which have demonstrated a great difference in CRC incidence among immigrants who move to high-risk areas from low-risk areas (23). These findings illustrate the importance of lifestyle and/or environmental factors in the pathogenesis of CRC. In fact, a number of lifestyle and/or environmental factors have been found to be associated with the incidence of CRC, including obesity, physical activity and dietary factors (14).

1.2.1 Anthropometric measures

There is convincing evidence that excess body weight (defined as body mass index (BMI)) and abdominal fat (defined by waist circumference and/or waist to hip ratio) is associated with increased risk of CRC and the evidence suggests a positive dose-response relationship (14, 24). A recent systematic review and meta-analysis based on 13 cohort studies, which was published in 2015 found that excess weight gain between early adulthood (18 - 21 years) and midlife (~ 40 - 65 years) was associated with 23% higher risk of CRC for those in the highest, compared to lowest, weight gain category (25). Weight gain from midlife to late life showed a similar association, although not as strong. An even stronger association has been observed for excess abdominal fat with an estimated 50% higher risk of CRC when comparing those in the highest, to the lowest, category of waist circumference (26, 27). These results suggest a stronger association between excess abdominal fat and CRC than excess body weight. In 2016, the International Agency for Research on Cancer (IARC) working group concluded that avoidance of weight gain lowers risk of developing CRC (24). These conclusions were based on studies in which confounding, bias and chance could be ruled out with confidence, suggesting that obesity is an independent risk factor for CRC. The link between obesity and CRC appears to be related to insulin resistance and hyperinsulinemia via the insulin- insulin like growth factor pathway, a complex pathway which regulates cell proliferation and cell apoptosis (14, 24, 28, 29). Other suggested mechanisms involve sex hormones, adipocytes and chronic inflammation.

In addition to higher body weight and abdominal obesity, there is convincing evidence that adult attained height is associated with CRC (14, 24). Although, height by itself is unlikely to cause cancer, it is thought as a marker of underlying processes and/or environmental exposures that can affect cancer risk, such as altered hormone profiles, early life nutrition and the rate of sexual maturation (14). The exact biological pathways involved in the association between height and CRC remains unclear, but several pathways have been suggested, including the insulin like growth factor pathway (30). Growth hormone is also known to induce production of insulin-like growth factor I, a major growth-regulating molecule, which plays a major role in determining height in adulthood. Taken together, these findings suggest that obesity and greater adult attained height is associated with CRC risk, but further research is needed to better understand the underlying mechanisms involved, i.e. altered hormone concentration, inflammations and/or rate of sexual maturation.

1.2.2 Physical activity

Results from prospective studies have consistently indicated that higher overall levels of physical activity are inversely associated with the risk of CRC, and the evidence suggests a dose-response relationship (14, 31, 32). The observed dose-response relationship is strong for colon cancer, particularly in males, but there is no evidence for such relationship between physical activity and rectal cancer (14). Existing prospective studies have reported risk reductions of colon cancer up to 40% when comparing high versus low levels of physical activity for both sexes (32, 33). In a systematic review and meta-analysis from 2005, which used data from 19 cohort studies, an increased recreational physical activity was found to be statistically significantly associated with a 20%

decreased risk of colon cancer in males (34). This study reported similar findings for females but not as strong, but no association was found between recreational time physical activity and rectal cancer for either of the sexes. The observed association between recreational time physical activity and colon cancer were very similar across different populations, and the estimates did not change noticeably whether or not studies adjusted for lifestyle factors including smoking status, alcohol consumption and BMI. Estimates from maximally and minimally adjusted analyses tended to be similar, suggesting that the effect of recreational time physical activity on colon cancer risk is not confounded by other factors included. Although there is convincing evidence that physical activity is associated with decreased risk of colon cancer the biological mechanisms through which physical activity may protect against this type of cancer is not known (14). Several mechanisms have been suggested, including decreased inflammation, reduced serum insulin levels and less insulin resistance. In addition, physical activity is known for its role in weight control and obesity prevention, but as mentioned before, obesity has been positively associated with risk of CRC. Despite the relatively strong conclusions that obesity and physical activity are independent risk factors for CRC, there is still need for further research in this field.

1.2.3 Diet

As mentioned earlier, modifiable behaviors are likely to play a large role in the etiology of CRC. Diet might be one of the most important determinants in that regard. As this factor and its association with CRC risk is the main topic of this thesis, it will be discussed in detail in the following sections.

1.2.3.1 Diet in adulthood

According to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report from 2011 there is convincing evidence that high consumption of red and processed meat and alcohol in men, and probably in women, is associated with an increased risk of CRC, while consumption of food containing dietary fiber is associated with a decreased risk (14). Furthermore, the panel considered consumption of milk, calcium and garlic to be probable protective factors.

Red and processed meat

In 2015, the IARC reviewed the available data linking consumption of red and processed meat to CRC (35). Positive association between consumption of processed meat and CRC were found in 12 out of 18 cohort studies and 6 out of 9 case control studies, while positive association between consumption of red meat and CRC were found in 7 out of 14 cohort studies and 7 out of 15 case control studies. In addition, the evidence suggest a dose-response relationship with higher consumption of red and processed meat (36). In the light of these findings the IARC classified consumption of red meat as group 2 carcinogens (i.e. probably carcinogenic to humans) and consumption of processed meat as group 1 carcinogens (i.e. carcinogenic to humans) (35). Despite the strength of the epidemiological evidence, the exact pathways involved in the association between meat consumption and CRC are poorly understood. Red meat contains many compounds, including heme-iron, which promotes formation of endogenous N-nitroso compounds that are considered carcinogenic (36). Not only can there be carcinogenic N-nitroso compounds already in meat, but exogenously N-nitroso compounds

can be formed from nitrites added to meat during processing. Two intervention studies found that high intake of red meat (300 or 420 g/day) elevated levels of DNA adducts, a DNA segment bound to a carcinogen, derived from N-nitroso compounds in rectal biopsies and exfoliated colonocytes isolated from human stool (37, 38). Not only can there be carcinogenic N-nitroso compounds already in meat, but cooking meat using high-temperature methods (e.g. grilling, barbecuing or pan-frying) can generate carcinogenic chemicals (such as heterocyclic amines and polycyclic aromatic hydrocarbons) that may increase cancer risk (39). Studies have shown that these compounds, especially heterocyclic amines, may increase the risk of CRC, particularly in people that are more susceptible to this compound due to genetic predisposition (40-44).

Fiber

Many studies have examined the association between consumption of dietary fiber and CRC but the results have been discordant (45). Several epidemiologic studies have reported a risk reduction of colorectal adenomas and cancer with higher consumption of fiber (46-50). A pooled data collected from 13 prospective studies reported a significant inverse association between dietary fiber consumption and CRC risk, when comparing participants in the highest, to the lowest, quintile of dietary fiber consumption. However, in this study, high consumption of dietary fiber was attenuated and after adjustment for other dietary risk factors, no longer statistically significant. A meta-analysis conducted by the WCRF/AICR in 2011 reported a statistically significant dose-response relationship between dietary fiber consumption and CRC risk with a 10% risk reduction per every 10 g/day increase in dietary fiber consumption (14). In this analysis there was, however, a difference between different food groups containing dietary fiber. As an example, fiber from legumes, fruit and vegetable was not associated with protection from CRC while fiber from grains was. These findings were partially supported by a nested case-control study using data from the European Prospective Investigation into Cancer and Nutrition, published in 2014, which found a protective association between high whole grain consumption via biomarkers of whole-grain rye and wheat and distal colon cancer (51). No association was found between high plasma total alkyl resorcinol concentrations, reflecting high whole-grain wheat and rye intake and overall CRC risk, although risk reduction of overall colon cancer was observed between higher fiber consumption from whole-grain rye and wheat among Scandinavian participants (a population that consumes these products regularly). On the other hand, no association was found between consumption of dietary fiber and colorectal adenomas or cancer in the Nurses' Health study, a large prospective study from the US (52). Similarly, another study from the US, a randomized controlled trial, found no protective effects of fiber, fruit and vegetable intervention on CRC risk (53). The exact pathways through which dietary fiber may protect against this CRC are still not fully understood, but several plausible mechanisms have been suggested. Food containing dietary fiber can dilute fecal content, decreasing transit time and increasing fecal weight, thus limiting the contact between potential carcinogens and the lining of the bowel (45, 54). In addition, anaerobic fermentation of fiber to short-chain fatty acids by the micro flora of the large intestine, have been associated with decreased risk of CRC (55). Short-chain fatty acids, such as butyrate may reduce the risk of CRC by inducing cell differentiation and apoptosis. Furthermore, food containing dietary fiber generally has high content of folate, which may have a protective role in carcinogenesis of CRC (56).

High consumption of dietary fiber may also play an important role in preventing weight gain (45). Therefore, it has been suggested that potential protective effects of dietary fiber consumptions may, at least, partly be mediated through reduced insulin resistance and/or improved weight control. In summary, the evidence from the literature suggests that consumption of foods containing dietary fiber has a protective effect against CRC risk. However, whether only specific types of dietary fiber protects against colorectal adenomas or cancer is unclear, perhaps because assessing intake of whole-grains by using FFQ can be vulnerable to measurements errors, as consumers might find it hard to accurately recognize whole-grain products (51). Also, whole-grain content varies greatly between whole-grain products.

Milk and milk products

Mixed results have been observed from epidemiological studies that have examined the association between milk products and CRC (57). Some studies have reported beneficial association between consumption of total milk products, milk and/or yogurt and CRC (58-64), while other have found no association (65-72). Potential protective effects of milk products may partly be due to their high calcium content, and calcium has been shown to inhibit cell proliferation and promote cell differentiation (73). Dietary calcium may also help protect against CRC through its binding to ionized fatty acids and secondary bile acids in the colon, thus limiting the potential damaging effects of these compounds to the intestinal mucosa. On the other hand, some types of milk products, such as cream and certain cheeses with high saturated fat content, may increase secondary bile acids levels in the colon and therefore increase risk of CRC (74). Saturated fatty acids have also been suggested to promote increased insulin secretion, which may be important since insulin resistance has been linked with increased risk of CRC. Taken together, these findings suggest that milk has a protective role against CRC, but other milk products with high fat content may increase the risk of this cancer. However, a meta-analysis from 2012 found that increased consumption of milk and total milk products was statistically significantly associated with modest risk reduction of CRC, but no association was observed between consumption of cheese or other milk products and CRC risk (57). Therefore, the relationship between other milk products and CRC appears unclear and further research of the subject is needed.

Dietary pattern

As habitual diet consists of thousands of different nutrients and other bioactive compounds that act together, it can be difficult to distinguish the effect of a single dietary component in a mixed diet (75). Therefore, in recent years, more focus has been on exploring the combined effect of various foods included in a dietary pattern rather than individual foods or nutrients (75, 76). To date, a number of studies have assessed the relationship between dietary patterns during adult life and colorectal adenoma or cancer, but little is known about earlier time periods (1-5). Among adults, dietary patterns characterized by high consumption of red and processed meat, potatoes and highly refined grains in adult life have been associated with greater risk of developing colorectal adenoma or cancer, whereas dietary patterns characterized by high consumption of fruits and vegetables have been associated with reduced risk of colorectal adenoma or cancer (77). Despite the fact that colorectal carcinogenesis is a

stepwise progression that can take several decades to evolve (78, 79), few studies have evaluated the potential link between diet in childhood or adolescence and CRC risk (1-5).

1.3 Diet during adolescence and CRC

The few available studies evaluating the association between diet in childhood or adolescence and colorectal adenomas or cancer will be reviewed below.

A prospective cohort study (n=4383) from the UK (the Boyd Orr Cohort) by van Der Pols et al. examined the total childhood (aged up to 19 years) dairy consumption and individual dairy products in relation to CRC incidence and mortality in adult life (2). During the follow-up period (1948 -2005), 53 participants (both genders) were diagnosed and 45 participants died of CRC. High total dairy consumption (median 471 g/day), as compared with low total dairy consumption (median 89 g/day) were found to near-triple the odds of being diagnosed with CRC (Odds ratio (OR) 2.90, 95% CI 1.26-6.65)), independent of meat, fruit and vegetable consumption, as well as other risk factors included. This study reported similar findings for total milk consumption in childhood, although not as strong. In contrast to the Boyd Orr Cohort findings, a case-control study by Cox et al. of 562 cases and 571 controls, found that consumption of school milk in childhood (5 -18 years) was associated with decreased risk of CRC (OR 0.70, 95% CI 0.51-0.96), including dose-response relationship with higher consumption of milk (3).

A prospective cohort study by Ruder et al., published in 2011, examined the relationship between intake of various food groups (e.g. red and processed meat, milk, fruit, grains and vegetables) and nutrients (e.g. fiber, calcium, vitamin A) during adolescence and development CRC (4). Participants (n=292,797) provided retrospective information on frequency of consumption of common foods in adolescence (12 -13 years) at study entry (51 years and older). During the study period (1995 -2006), 3773 subjects (both genders) were diagnosed with CRC. This study found that high vitamin A intake in the adolescence period was associated with reduced risk of colon cancer (HR 0.80, 95% CI 0.71-0.90). Also, this study showed that participants in the highest quintile of vegetables intake (HR 0.81, 95% CI 0.70-0.92) were inversely associated with risk of colon cancer compared with those in the lowest quintile of vegetables intake. Furthermore, this study found a statistically significant increased risks of colon and rectal, when comparing those in the highest, to the lowest, tertile of red meat (HR 1.38, 95% CI 1.16-1.64) or processed meat (HR 1.25, 95% CI 1.06-1.47) consumption. This association was only observed for individuals with high total red meat consumption during both adolescence and adulthood. Analyses stratified on gender showed that female participants in the highest quintile (HR 1.29, 95% CI 1.05-1.59) of fiber consumption during adolescence were positively associated with risk of colon cancer compared to those in the lowest quintile of fiber consumption, but showed a non-significant inverse association among male participants.

A prospective cohort study by Nimptsch et al., published in 2013 examined the association between consumption of processed and unprocessed meat, fish and poultry during adolescence and colorectal adenoma risk later in life among 19,771 middle aged women participating in the Nurses‘ Health Study 2 (1). Participants provided retrospective information on frequency of consumption of common foods in high school (13 -17 years) at study entry (then 34 -51 years of age). During the

study period (1998 -2007), a total of 1494 cases of colorectal adenoma were diagnosed. This study found no association between red meat or fish consumption and risk of colorectal adenomas, but showed that consumption of poultry was associated with lower risk (OR 0.80, 95% CI 0.64-0.99) of total colorectal adenomas when comparing those with highest (≥ 80 g/day) versus lowest (<20 g/day) consumption, independent of meat and fish consumption. Furthermore, this study reported that substitution of 1 portion per day of fish or poultry for 1 portion per day of total red meat consumption was associated with decreased risk of rectal adenomas (OR 0.59, 95% CI 0.37-0.94) and advanced adenomas (OR 0.65, 95% CI 0.45-0.95).

A prospective cohort study by Nimptsch et al., published in 2014 examined the association between dietary patterns during adolescence (13 -17 years) and colorectal adenoma in middle aged women by analyzing data from 17,221 women participating in the Nurses' Health Study 2 (5). During the study period (1998 -2007), 1,299 cases of colorectal adenoma were diagnosed. This study reported that participants in the highest quintile of the prudent pattern score, a dietary pattern characterized by high intake of fish, fruit and vegetables during high school was inversely associated with rectal adenomas (OR 0.45, 95% CI 0.27-0.75), but not colon adenomas compared to those in the lowest quintile. Furthermore, this study reported that participants in the highest quintile of the western pattern score, a dietary pattern characterized by high consumption of red and processed meat, desert, snacks and sweets was positively associated with rectal adenomas (OR 1.78, 95% CI 1.12-2.85) and advanced adenomas (OR 1.58, 95% CI 1.07-2.33), but not associated with colon adenomas or non-advanced adenomas compared to those in the lowest quintile.

In summary, few studies have investigated the association between dietary exposures during childhood or adolescence on colorectal carcinogenesis (1-4). Mixed results have been observed from studies that have examined childhood milk and dairy consumption in relation to CRC (2-4). One cohort study by van Der Pols et al. found that high milk and dairy intake was associated with increased risk of CRC, whereas another cohort study by Ruder et al. found no association with CRC risk and a case-control study by Cox et al. reported inverse association (2-4). For red and processed meat, Ruder et al. found high consumption to be associated with increased risks of colon and rectal cancer, compared to low consumption, whilst Nimptsch et al. found no association but found that substitution of fish or poultry for red meat was associated with decreased risk of rectal adenomas and advanced adenomas (1, 4). However, ascertainment of dietary exposures (37 versus 124 item FFQ) and the outcome (colorectal adenoma versus cancer) was different between the two studies. To date, only one study has addressed the association between dietary patterns in adolescence and colorectal carcinogenesis (5). In that study, Nimptsch found that higher adherence to the prudent pattern was associated with decreased risk of rectal adenomas, whereas higher adherence to the western pattern was associated with increased risk of rectal and advanced adenomas (5). There is a definite lack of research focusing on the role of diet during adolescence on CRC risk and there is no well-established evidence for an etiological role of diet during this particular time period and CRC development later in life. Further research on the subject is needed.

1.4 Aims

The aim of this thesis was to examine whether there is an association between dietary patterns in adolescence and CRC risk. Due to the lack of research focusing on the role of dietary habits during adolescence, our focus was on the potential impact of dietary patterns at this particular time period.

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Article

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Dietary patterns during adolescence and risk of colorectal cancer: A population-based study

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Abstract

Purpose: To examine whether dietary patterns in adolescence are associated with colorectal cancer (CRC) risk.

Methods: We used food frequency data obtained from the AGES Reykjavik study, conducted in Reykjavik, Iceland in the period 2002 -2006 and included 5078 (42% male) participants born between 1907 and 1935. Through linkage to the Cancer Registry, participants were followed for CRC diagnosis and mortality through 2014. We used principal component analysis to extract dietary pattern and Cox models to calculate hazard ratios (HRs) for CRC according to dietary patterns scores in adolescence.

Results: During the follow-up period (mean 8.2), 136 participants were diagnosed with CRC, of whom 52 died due to the disease. The strongest pattern extracted in adolescence was characterized by high consumption of salted and smoked meat and fish, blood and liver sausage, rye bread, milk and milk products and oatmeal (traditional Icelandic diet). For both genders, the middle tertile was associated with CRC (HR 1.63 95% CI 1.04-2.57) when compared to the lowest tertile of adherence with the traditional Icelandic diet. However, the highest tertile was not significantly associated with CRC (HR 1.48 95% CI 0.93-2.37). When the analysis was stratified by gender, the results showed that the association with the highest tertile compared to the lowest was only evident for women (HR 2.06 95% CI 1.11-3.84; p trend = 0.02), not men.

Conclusion: Our findings suggest that high adherence to the traditional Icelandic diet during adolescence increases risk of CRC among women late in life. High age at entry to the study might explain the gender difference in our data.

Keywords: adolescence, dietary pattern, colorectal cancer, factor analysis, epidemiology

Introduction

Dietary factors are believed to have an important role in the prevention and development of colorectal cancer (CRC) [1]. There is convincing evidence that high intake of red and processed meat and alcohol in adult life is associated with increased risk of CRC, whereas high intake of foods containing dietary fiber have been associated with decreased risk of this type of cancer. Mixed results have been observed from studies that have examined the association between individual foods or nutrients during childhood or adolescence and colorectal adenomas (a precursor of CRC) or cancer [2-5].

As habitual diet consists of thousands of different nutrients and other bioactive compounds that act together it can be difficult to distinguish the effect of a single dietary component in a mixed diet [6]. Therefore, in recent years, more focus has been on exploring the combined effect of various foods included in a dietary pattern rather than individual foods or nutrients. A number of studies have assessed the relationship between dietary patterns during adult life and colorectal adenoma or cancer, but little is known about earlier time periods [7-9]. To date, only one study has addressed the association between dietary patterns in adolescence and risk of colorectal adenomas [9]. The study results showed that higher adherence to the prudent pattern, a pattern characterized by high intake of fish, fruit and vegetables was associated with decreased risk of rectal adenomas, whereas higher adherence to the western pattern, a pattern characterized by high consumption of red and processed meat, desert, snacks and sweets was associated with increased risk of rectal and advanced adenomas [10,11].

Colorectal carcinogenesis is a stepwise progression that can take several decades to evolve; therefore, adolescent diet, rather than recent adult diet, may be of significance for CRC risk [10]. Using the population-based Age, Gene/Environment Susceptibility (AGES) Reykjavik cohort, our aim was to examine whether dietary patterns in adolescence (14 -19 years) were associated with CRC risk late in life.

Methods

Study population

This study is based on the AGES-Reykjavik Study which is drawn from the Reykjavik Study (n=30795), a population-based prospective cohort study conducted during the period 1967 -1991 by the Icelandic Heart Association. The AGES-Reykjavik Study was conducted during 2002 -2006 and included 5764 (42% male) surviving participants from the Reykjavik study born between 1907 and 1935 [12]. For this current study, we excluded participants diagnosed with CRC prior to study entry into the AGES-Reykjavik Study (n=99) and participants with missing data (n=587), leaving 5078 participants in our cohort (see fig. 1).

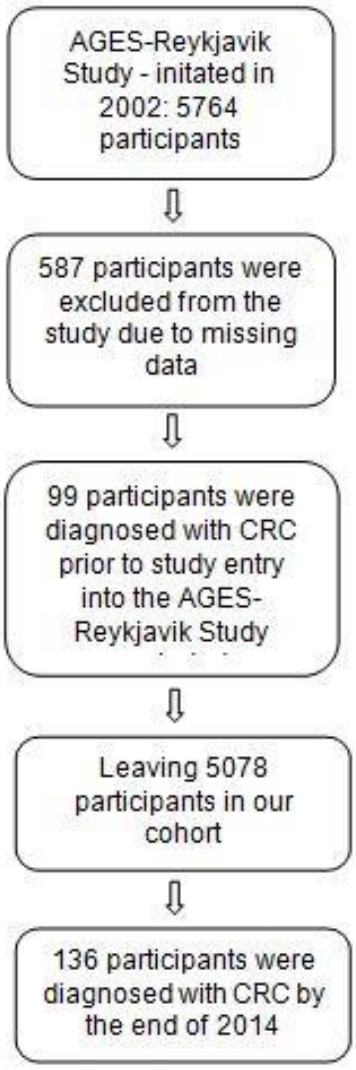

Figure 2 Selection of participants from the AGES-Reykjavik Study, Iceland, 1967 -2014

Assessment of dietary intake

The participants from the AGES-Reykjavik study provided retrospective information on frequency of consumption of common food groups in adolescence (14 -19 years), in midlife (40 -50 years) and at study entry (67 years and older). In the present study, only information on diet in adolescence was used. Participants reported how frequently, on average, they consumed 10 common foods and food groups using a food frequency questionnaire (FFQ). These food groups were meat (including salted and smoked meat), fish (including salted or smoked fish), fish liver oil, blood or liver sausage, rye bread, oatmeal, potatoes, milk and milk products, fruits and vegetables. Possible response categories were; “never”, “less than once a week”, “1-2 times a week”, “3-4 times a week”, “5-6 times a week”, “daily”, and “more than once a day”. At the clinic at study entry a trained interviewer used the AGES-FFQ to collect information on dietary habits [13,14]. The AGES-FFQ has been validated for dietary habits in midlife and in late life [13,14]. Validity of the adolescence dietary assessment cannot be investigated. However, the participants provided information on early-life residency and the dietary data obtained from the AGES-Reykjavik study shows similar residency dependent variation in dietary habits as documented by Sigurjonsson in 1939 [15].

Extraction of dietary patterns

Principal component analysis (PCA) with orthogonal rotation was used on the food groups to extract dietary patterns. This is a data driven method that identifies new components or linear factors (i.e. dietary patterns) by reducing dimension of the data and grouping correlated variables (i.e. food intake) [16]. The components extracted by this method reflect food intake combinations of food groups consumed by each participant. The coefficients defining the components are called factor loadings and represent the correlation between each input variable (i.e. food groups) and the extracted components (table 1). A positive factor loading indicates that the corresponding foods or food groups are positively correlated with the dietary pattern, whereas negative factor loadings indicate an inverse correlation. The number of factors to retain was based on interpretability of the factor loading matrix after varimax rotation, eigenvalues (>1) and a scree plot. Food groups with factor loadings higher than 0.30 or lower than -0.30 were considered important for the interpretability of each dietary pattern. For each dietary pattern extracted, a factor score was calculated, ranking participants on their adherence to that particular pattern.

Assessment of covariates

We retrieved information on potential confounders, collected at study entry to the AGES-Reykjavik Study. We gathered information on age at entry of the study (continuous), education (elementary; secondary; college and university), family history of CRC (no; yes), physical activity since the age of 20 years (never/rarely/occasionally; moderate/high), smoking status (never; ever), alcohol consumption in late life (0 g per week; 1-10 g per week; >10 g per week), and diabetes type 2 (DM2) in midlife (no; yes). We obtained values for body max index in midlife (BMI; continuous) from the Reykjavik Study. We retrieved information on dietary covariates for the adolescence period from the AGES-FFQ.

Follow-up and outcome

The follow-up time began at study entry into the AGES-Reykjavik study and ended at diagnosis of CRC, death or the end of the follow-up period (December 31, 2014). For the mortality analysis, the follow-up ended at time of cancer death, death from other causes, or end of follow-up. We ascertained diagnoses of CRC through linkage with the Icelandic Cancer Registry [17]. The Icelandic Cancer registry covers 99% of all cancers diagnosed in Icelandic residents, so follow up was virtually complete. Cause of death information was obtained from the Directorate of Health [17].

Statistical analyses

PCA with varimax rotation was used to extract dietary patterns. Factor scores for the extracted dietary patterns were calculated and used as exposure variables. Each dietary pattern was divided into tertiles, using the lowest third as a reference category. We used Cox proportional hazard regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for CRC incidence and mortality according to dietary patterns scores in adolescence. The first model (HR^a) was adjusted for age (continuous) at entry into the AGES-Reykjavik Study. The second model (HR^b) was additionally adjusted for gender, BMI in midlife, educational level, family history of CRC and physical activity since the age of 20 years, all categorized as described in Table 1. Adjustment for smoking status, alcohol consumption in late life and DM2 in midlife or the other dietary patterns extracted did not significantly alter our estimates (≤20%) and were therefore not included in the final models. We also ran models with individual dietary components of pattern 1, the only pattern that showed an association with the outcome, categorized as described in Table 4. Gender-stratified analyses were performed using the same models, as described for all participants. Tests for trend were calculated for men and women separately by entering the tertiles of the factor score as a continuous term into the multivariate models (p trend).

We used R core team (2016) for windows for all statistical analysis. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; (https://www.r-project.org/). The study protocol was approved by the Icelandic Ethical Review Board and the Icelandic Data Protection Authority (VSNb2007120014/03-7).

Results

The dietary pattern analysis was based on participants who gave information on frequency of consumption of common foods in adolescence at entry to the AGES-Reykjavik study (n=5089). During the follow-up period (mean 8.2 years), 136 participants were diagnosed with CRC, of whom 52 died due to the disease. Their mean age (±SD) at study entry was 77 years (5.8) and mean age at cancer diagnosis was 76 years (9.9).

Four dietary patterns were identified during adolescence. **Table 1** shows factor loading coefficients between food groups from which the four dietary patterns were extracted and the cumulative variance explained by the patterns. Pattern number 1 (eigenvalue 2.2) was characterized by high consumption of salted and smoked meat, salted and smoked fish, blood and liver sausage, rye bread, milk and milk products and oatmeal. This pattern was labeled as “traditional Icelandic diet”. Pattern number 2 (eigenvalue 1.8) was characterized by high consumption of fruits, vegetables and fish. Pattern number 3 (eigenvalue 1.3) had positive factor loadings for fish oil, oatmeal and blood and liver sausage. Pattern number 4 (eigenvalue 1.2) was positive for meat, fish and potatoes. However, only the traditional Icelandic diet pattern showed an association with the outcome (Supplementary table A) and was therefore selected for further analysis.

Table 2 shows the characteristics of participants providing dietary information in AGES-Reykjavik (n=5078) by tertiles of the traditional Icelandic diet pattern score. Participants with the highest tertile of adherence to the traditional Icelandic diet in adolescence were more likely to be older at study entry, less educated and to consume less alcohol compared to those in the lowest tertile.

Table 3 shows HRs, with 95% CI for colorectal cancer incidence by tertiles of the traditional Icelandic diet score. Compared to the lowest tertile of the traditional diet score during adolescence, the fully adjusted model indicated a positive association with CRC for the mid tertile (HR 1.63, 95% CI 1.04-2.57) and the highest tertile, albeit not statistically significant (HR 1.48, 95% CI 0.93-2.37). Furthermore, the fully adjusted model indicated that participants in the highest tertile of the traditional Icelandic diet score were positively associated with CRC mortality, compared with participants in the lowest tertile, but this association was not statistically significant (HR 2.15, 95% CI 0.92-5.00). When stratified by gender, we found that female participants in the highest tertile were positively associated with CRC later in life compared with females in the lowest tertile (HR 2.06, 95% CI 1.11-3.84; p trend = 0.02). We found no significant association between tertiles of the traditional Icelandic diet and CRC among male participants in our cohort. Our estimates did not change noticeably when additionally adjusting for lifestyle factors including smoking status, alcohol consumption or DM2 (data not shown). Estimates were also similar when we further adjusted for the other dietary patterns extracted from adolescence (data not shown).

Table 4 shows the association between individual dietary components of the traditional Icelandic diet during adolescence and colorectal cancer. No statistically significant associations were found for consumption of individual dietary components of the traditional Icelandic diet and CRC.

Discussion

Findings from this population-based prospective study suggest that high adherence to the traditional Icelandic diet during adolescence may increase the risk of CRC later in life. This dietary pattern was characterized by high consumption of salted or smoked meat and fish with the highest score for factor loading coefficient in the pattern. When the analyses were stratified by gender the results indicated that this association was only evident for women, not for men.

Relatively few studies have explored the association between dietary exposures during childhood or adolescence and colorectal adenoma or cancer [4,2,3,5,9]. Mixed results have been observed from studies that have examined childhood milk and dairy consumption in relation to CRC [4,2,3]. One cohort study by Van Der Pols et al. found that high total childhood milk and dairy intake was associated with increased risk of CRC, whereas another cohort study by Ruder et al. found no association with CRC risk [3] and a case-control study by Cox et al. reported inverse association [4]. For red and processed meat, Ruder et al. found high consumption to be associated with increased risk of colon and rectal cancer compared to low consumption, whilst Nimptsch et al. found no association but found that substitution of one portion of fish or poultry for one portion of red meat was associated with decreased risk of rectal and advanced adenomas [5,3]. However, ascertainment of dietary exposures (37 versus 124 item FFQ) and the outcome (adenomas versus cancer) was different between the two studies.

Most previous studies on dietary exposure in early life have focused on individual foods and nutrients in relation to colorectal carcinogenesis. To distinguish the effect of a single dietary component in a mixed diet can, however, be difficult. Therefore, studying dietary patterns, which allows us to examine the diet as a whole and assess the combined effect of various foods included in a dietary pattern might be more important for disease risk. To date, only one study has addressed the association between dietary patterns in adolescence and colorectal carcinogenesis [9]. In that study, Nimptsch et al. examined the association between dietary patterns during adolescence and colorectal adenoma in middle aged women and found that higher adherence to the prudent pattern, characterized by high intake of fish, fruit and vegetables was associated with decreased risk of rectal adenomas, whereas higher adherence to the western pattern, characterized by high consumption of red and processed meat, deserts, snacks and sweets, was associated with increased risk of rectal and advanced adenomas [9]. In our study, high exposure of salted and smoked meat and fish during adolescence affected women more than men. Different findings for men and women have also been found previously in single nutrient studies, but have not been explored previously for dietary patterns in adolescence. In the study by Ruder et al, high fiber consumption in the adolescence period was associated with increased risk of colon cancer among women, but an inverse, non-significant association was observed among men [3]. The reason for the gender difference in our results cannot be determined in our study. Some possible explanation could be difference in the pathology of CRC between men and women, biological differences in how men and women respond to dietary exposures or other reason [18-21].

The biological mechanism behind the positive association between the traditional Icelandic diet and CRC risk found in our study is unknown but could be due to the effect of salted/ smoked meat and fish

on colorectal carcinogenesis. High consumption of red meat and salted and smoked meat in the adolescence period has been reported in the study group [22]. Red meat contains many compounds, including heme-iron, which promotes formation of endogenous N-nitroso compounds (NOCs) that are considered carcinogenic [23]. In addition, food preservation processes, such as salting or smoking can lead to formation of carcinogenic compounds (e.g. NOCs) that may potentially increase the risk of CRC [24]. Furthermore, fish, in particular fatty fish, is highly susceptible to lipid oxidation, an oxidative degradation process of lipids [25]. It has been reported that addition of salt to fish products induces lipid oxidation of long chain n-3 polyunsaturated fatty acids in fish muscle, a process that can lead to formation of α, β - unsaturated aldehydes, compounds which are currently being considered to play a role in cancer development [26].

A major strength of this study is the ability to study dietary exposures from adolescence in relation to disease risk late in life. This study is also a large and well-established population based cohort with extensive information on covariates, making adjustment for multiple potential confounding factors available. Also, findings from our study were based on incident cases only, thereby limiting the possibility of recall-related errors. Furthermore, record linkage to the Icelandic Cancer Registry, provided detailed and valid assessment for CRC diagnosis and deaths.

A limitation in this study is the fact that information on dietary intake from adolescence was gathered retrospectively through questionnaire at study entry. As a result, non-differential measurement error may be of concern; as there is always an uncertainty in assessing dietary habits many decades back in time [13]. However, it has been demonstrated that dietary recall from childhood and up to four decades later can be as accurate as dietary recall from current diet, especially for foods that are consumed rarely or daily [23]. Another limitation in our study is the lack of information about total energy intake and growth during adolescence. We were, however, able to adjust for BMI values measured in midlife, which correlates with total energy intake [24]. Although we were able to adjust for numerous potential confounding factors in the multivariable-adjusted model, we cannot exclude the possibility of residual confounding by unmeasured covariates in our study. The fact that men tend to be at higher risk than women of getting CRC before the age of 75 that are consistent with men's higher risk of dying from the disease before the age of 75 is another limitation to our study [25]. Mean age at entry to the AGES-Reykjavik study was 77 years. It is therefore possible that those men born in the early 20th century and growing up with high consumption of salted or smoked meat and fish in the adolescence period, were more likely to die before the AGES-Reykjavik study was initiated [26]. Therefore, selection bias may have occurred, that might explain the gender difference in our results.

Conclusion

Our findings indicate that high adherence to the traditional Icelandic diet, including salted and smoked meat and fish, blood and liver sausage, rye bread, milk and milk products and oatmeal during adolescence may increase the risk of CRC among women later in life. These findings additionally indicate that diet during adolescence may be of significance for CRC risk later in life.

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Compliance with ethical standards

Conflict of interest

The authors declare that there is no conflict of interest.

Ethical approval

The study protocol was approved by the Icelandic Ethical Review Board and the Icelandic Data Protection Authority (VSNb2007120014/03-7).

Abbreviations

AGES, age, gene/environment susceptibility

CRC, colorectal cancer

BMI, body mass index

DHA, docosahexaenoic acid

CI, confidence interval

DM2, diabetes mellitus

FFQ, food frequency questionnaire

HR, hazard ratio

NOCs, N-nitroso compunds

PCA, principal component analysis

SD, standard deviation

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Table 1 Factor loading coefficients between food groups and the dietary patterns extracted from adolescence (14 -19 years).

Dietary patterns	Factor loadings coefficient [a, b]
Pattern 1 (the traditional Icelandic diet)	
Salted/smoked meat	0.78
Salted/smoked fish	0.72
Blood and liver sausage	0.59
Rye bread	0.48
Milk and milk products	0.42
Oatmeal	0.35
Pattern 2	
Fruit	0.77
Vegetables	0.77
Fish on bread or in salad	0.64
Pattern 3	
Fish oil	0.73
Oatmeal	0.67
Blood and liver sausage	0.34
Pattern 4	
Meat	0.74
Fish	0.61
Potatoes	0.48

[a] Factor loadings are correlation coefficients between food groups and the extracted factor.
[b] Food groups with factor loadings between 0.30 and -0.30 are not listed.

Table 2 Characteristicis of participants in AGES-Reykjavik Study by tertiles of pattern 1 (the traditional Icelandic diet) in adolescence (14 -19 years).

	Pattern 1 (the traditional Icelandic diet) score [a, b]			
	Lowest tertile (n= 1693)	**Middle tertile (n= 1701)**	**Highest tertile (n=1695)**	p-value
Age in years, mean (±SD)	74.5 (5.2)	76.3 (2.5)	77.6 (5.8)	<0.001
BMI in midlife, mean (±SD)	25.2 (3.6)	25.2 (3.4)	25.3 (3.6)	0.498
Education, n (%)				0.033
Primary/secondary	1353 (79.9)	1377 (81.0)	1419 (83.7)	
College	220 (13.0)	209 (12.3)	165 (9.7)	
University	120 (7.1)	115 (6.8)	111 (6.5)	
Physical activity, n (%)				0.321
Moderate/high	495 (31.2)	533 (33.2)	534 (33.5)	
Family history of colorectal cancer, n (%)				0.311
Yes	203 (12.0)	176 (10.3)	187 (11.0)	
Smoking status, n (%)				0.795
Never	976 (57.6)	972 (57.1)	988 (58.3)	
Alcohol consumption, n (%)				0.002
0 g/week	568 (33.6)	559 (32.9)	660 (39.0)	
1-10 g/week	607 (36.0)	604 (35.6)	565 (33.6)	
>10 g/week	513 (30.4)	536 (31.5)	466 (27.6)	

[a] Pattern 1 (the traditional Icelandic diet) score divided into tertiles.
[b] Participants in the highest tertile had higher adherence to the traditional Icelandic diet than those in the lowest tertile.

Table 3 Hazard ratios (HRs) and 95% confidence intervals (CIs) for colorectal cancer diagnosis by tertiles of pattern 1 (the traditional Icelandic diet) score in adolescence (14 -19 years).

Pattern 1 (the traditional Icelandic diet) score	Cases (%)	Age adj. HR[a] (95% CI)	Adj. HR (95% CI)[b]
All participants		*n=136*	*n= 125*
Lowest tertile	32 (2.1)	1.00	1.00
Mid tertile	51 (3.0)	1.40 (0.92-2.15)	1.63 (1.04-2.57)
Highest tertile	49 (2.9)	1.37 (0.89-2.12)	1.48 (0.93-2.37)
Female participants [c]		*n=75*	*n=68*
Lowest tertile	20 (1.9)	1.00	1.00
Mid tertile	24 (2.5)	1.32 (0.73-2.40)	1.58 (0.83-3.00)
Highest tertile	31 (3.4)	1.78 (1.01-3.14)	2.06 (1.11-3.84)
Male participants [c]		*n=61*	*n=57*
Lowest tertile	16 (2.5)	1.00	1.00
Mid tertile	27 (3.6)	1.40 (0.76-2.61)	1.59 (0.83-3.04)
Highest tertile	18 (2.3)	0.93 (0.47-1.82)	0.93 (0.45-1.92)

[a] Adjusted for age (y; continuous) at entry to the study.
[b] Adjusted for age (y; continuous) at entry to the study, gender, BMI (in kg/m^2; continuous), education (primary/ secondary; college; university), family history of colorectal cancer (no; yes), physical activity (never/ rarely/ occasionally; moderate/ high).
[c] Adjusted for same covariates as in model b, except for gender.

Table 4 Associations between individual dietary components of pattern 1 (the traditional Icelandic diet) in adolescence (14 -19 years) and colorectal cancer.

	Age adj. HR[a] (95% CI)	Adj. HR[b] (95% CI
All participants		
Pattern 1 (the traditional Icelandic diet)	1.11 (0.93-1.34)	1.12 (0.93-1.34)
Salted/smoked meat		
3 times a month or less	1.00	1.00
Once a week or more	1.14 (0.77-1.71)	1.12 (0.75-1.68)
Salted/smoked fish		
3 times a month or less	1.00	1.00
Once a week or more	0.91 (0.61-1.35)	0.90 (0.61-1.39)
Blood and liver sausage		
2 times p/w or less	1.00	1.00
3 times p/w or more	1.10 (0.76-1.58)	1.11 (0.77-1.59)
Rye bread		
Less than daily	1.00	1.00
Daily or more often	1.01 (0.68-1.48)	1.00 (0.68-1.47)
Milk and milk products		
Less than daily	1.00	1.00
Daily or more often	1.22 (0.77-1.91)	1.25 (0.79-1.97)
Oatmeal		
Less than daily	1.00	1.00
Daily or more often	096 (0.63-1.47)	0.97 (0.63-1.49)

[a] Adjusted for age (y; continuous) at entry to the study.
[b] Adjusted for age at entry (y; continuous), gender, BMI (in kg/m^2; continuous), education (primary/ secondary; college; university), family history of colorectal cancer (no; yes), physical activity (never/ rarely/ occasionally; moderate/ high).

Supplementary table A Hazard ratios (HRs) and 95% confidence intervals (CIs) for colorectal cancer diagnosis by tertiles of dietary patterns score in adolescence (14 -19 years)

Dietary patterns	Cases (%)	Age adj. HR[a] (95% CI)	Adj. HR (95% CI)[b]
Pattern 1		*n=136*	*n= 125*
Lowest tertile	32 (2.1)	1.00	1.00
Middle tertile	51 (3.0)	1.40 (0.92-2.15)	1.63 (1.04-2.57)
Highest tertile	49 (2.9)	1.37 (0.89-2.12)	1.48 (0.93-2.37)
Pattern 2		*n=136*	*n=125*
Lowest tertile	47 (2.8)	1.00	1.00
Middle tertile	43 (2.5)	0.95 (0.63-1.44)	1.00 (0.65-1.54)
Highest tertile	46 (2.7)	1.00 (0.66-1.51)	1.02 (0.65-1.59)
Pattern 3		*n=136*	*n=125*
Lowest tertile	40 (2.4)	1.00	1.00
Middle tertile	54 (3.2)	1.38 (0.92-2.08)	1.53 (0.99-2.37)
Highest tertile	42 (2.5)	1.07 (0.69-1.65)	1.21 (0.76-1.92)
Pattern 4		*n=136*	*n=125*
Lowest tertile	45 (2.7)	1.00	1.00
Middle tertile	47 (2.8)	1.05 (0.70-1.58)	1.02 (0.67-1.58)
Highest tertile	44 (2.5)	0.99 (0.65-1.50)	0.96 (0.62-1.48)

[a] Adjusted for age (y; continuous) at entry to the study.
[b] Adjusted for age (y; continuous) at entry to the study, gender, BMI (in kg/m^2; continuous), education (primary/ secondary; college; university), family history of colorectal cancer (no; yes), physical activity (never/ rarely/ occasionally; moderate/ high).