The role of adolescence growth rate and diet across the lifespan in breast cancer risk

Álfheiður Haraldsdóttir

Thesis for the degree of Philosophiae Doctor

Supervisors:

Laufey Steingrímsdóttir

Jóhanna Eyrún Torfadóttir

Doctoral committee:

Unnur Anna Valdimarsdóttir
Laufey Tryggvadóttir
Hans-Olov Adami

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Álfheiður Haraldsdóttir

Ritgerð til doktorsgráðu

Leiðbeinendur:

Laufey Steingrímsdóttir

Jóhanna Eyrún Torfadóttir

Doktorsnefnd:

Unnur Anna Valdimarsdóttir
Laufey Tryggvadóttir
Hans-Olov Adami

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Ágrip

Bakgrunnur og markmið: Fyrri rannsóknir hafa gefið vísbendingar um mikilvægi lífsháttа snemma á ævinni í þróun brjóstakrabbameins. Markmið þessarar rannsóknar var að efla þekkingu tengslum vaxtarhraða í æsku og mataræðis á lífsleiðinni við brjóstakrabbameinsáhættu.

Efniviður og aðferðir: Þrjár vísindagreinar liggja að baki þessari ritgerð. Í fyrstu greininni var notast við gögn úr bæði Reykjavíkur- og Öldrunarrannsókn Hjartaverndar. Reykjavíkurrannsóknin, sem hófst árið 1967, beindist hér að 9,340 konum, fæddum á árunum 1908 – 1935, sem gáfu upplýsingar um búsetu í æsku við komu í rannsóknina og höfðu ekki áður greinst með brjóstakrabbamein. Búseta í æsku var hér notuð sem vísbending um matarvenjur í æsku, sem voru mjög breytilegar eftir landshlutum á fyrri hluta 20.aldar. Upplýsingar um vaxtarhraða frá unglingsaldri fram á fullorðinsár var auk þess að finna fyrir 991 konu (fæddar 1915 – 1935) úr Reykjavíkurrannsókninni og stuðst var við þau gögn í þriðju greininni.

Í fyrstu og annarri grein voru nýtt gögn úr Öldrunarrannsókn Hjartaverndar þar sem alls tóku þátt 3,326 konur á árunum 2002 – 2006. Þessi rannsókn takmarkaðist við um það bil 2800 konur, sem ekki voru greindar áður með brjóstakrabbamein og gáfu upplýsingar um fæðuvenjur sínar á unglingsaldri, á miðjum aldri og efri árum. Hér var megin áhersla lögð á algeng matvæli á Íslandi á fyrri hluta 20. aldar, eða fisk, mjólk, kjöt og heilkornavörur.

Í öllum þremur greinunum voru Cox aðhvörfslíkön notuð til að reikna út áhættuhlutföll (HR) og 95% öryggismörk (95% CI), og leiðrétt var fyrir mögulegum gruggunarþáttum. Notast við meginþáttagreiningu (e. principal component analysis) til að greina mismunandi fæðumynstur. Með samtengingu við Krabbameinsskrá var þátttakendum fylgt eftir, með tilliti til greiningar og dánarorsakar vegna brjóstakrabbameins, frá komu í rannsókn eða vaxtarmælingu út rannsóknartímann (út árið 2013 fyrir grein I, 2014 fyrir grein II og 2015 fyrir grein III). Upplýsingar um dánarorsök voru fengnar hjá Embætti landlæknis.

Niðurstöður: Í fyrstu greininni var eftirfylgni þátttakenda í Reykjavíkurransóknninni að meðalatali 27,3 ár og á því tímabili greindust 744 konur með brjóstakrabbamein. Helstu niðurstöður voru að 22% minni hætta

var á brjóstakrabbameini hjá konum sem bjuggu í sjávarþorpum fram á fullorðinsár, samanborið við konur sem ólust upp á höfuðborgarsvæðinu (95% CI 0.6, 1.0). Í Öldrunarrannsókninni greindist 91 kona með brjóstakrabbamein á eftirfylgnitímanum sem náði út árið 2013, og spannaði að meðaltali í 8,2 ár. Konur sem borðuðu mikinn fisk um miðjan aldur, eða meira en fjóra skammta á viku voru í 54% minni áhættu á að fá brjóstakrabbamein borið saman við þær sem borðuðu fisk sjaldnar, eða minna en tvo skammta á viku (95% CI 0.2, 1.0). Einnig komu fram vísbendingar um að há fiskineysla á unglingsárum gæti tengst lægri áhættu á brjóstakrabbameini, bæði hjá konum sem borðuðu meira en fjóra skammta á viku (HR 0.7, 95% CI 0.4, 1.1) og hjá þeim sem voru með háa fylgni við fæðumynstur sem meðal annars einkenndist af fiskneyslu (HR 0.6, 95% CI 0.4, 1.0). Við tölfræðiúrvinnslu í grein II náði eftirfylgnin í Öldrunarrannsókninni út árið 2014, og á því tímabili voru alls 97 konur greindar með brjóstakrabbamein. Helstu niðurstöður voru að dagleg neysla á rúgbrauði á unglingsárum og miðjum aldri tengdist aukinni áhættu á brjóstakrabbameini (HR 1.7, 95% CI 1.1, 2.6; HR 1.8, 95% CI 1.1, 2.9) borið saman við neyslu á rúgbrauði sjaldnar en daglega. Aftur á móti reyndist viðvarandi mikil neysla á haframjöli vera verndandi gegn meininu (HR 0.4, 95% CI 0.2, 0.9). Ekki fundust nein tengsl á milli neyslu á einstaka fæðutegundum á efri árum við brjóstakrabbamein. Hins vegar voru konur sem höfðu háa fylgni við fæðumynstur sem einkenndist af mikilli neyslu af kökum, sætindum og gosdrykkjum á efri árum í 60% aukinni áhættu á að greinast með brjóstakrabbamein (HR 1.6, 95% CI 1.0, 2.7) á miðað við þær sem voru með lægstu fylgnina. Til voru upplýsingar um hæð 991 kvenna við 13 ára aldur og af þeim greindust 117 konur með brjóstakrabbamein á eftirfylgdartímanum (grein III). Eftirfylgd spannaði frá hæðarmælingu 13 ára fram til loka árs 2015, eða að meðaltali í 66 ár. Konur sem uxu hraðast frá 13 ára aldri þar til fullorðinshæð var náð (7,8 cm að meðaltali á ári) reyndust í aukinni áhættu á brjóstakrabbameini (HR 2.3, 95% CI 1.3, 4.1) samanborið við konur sem uxu hægast frá 13 ára aldri fram að fullorðinshæð (2,6 cm að meðaltali á ári).

Ályktun: Niðurstöður þessara lýðgrunduðu rannsókna benda til að búseta, mataræði og vaxtarhraði tengist á brjóstakrabbameinsáhættu síðar á ævinni. Þannig tengist hraður vaxtarhraði á unglingsárum og rúgbrauðsneysla (sem og á miðjum aldri) aukinni áhættu en fiskneysla og haframjöl öllu jafnan lægri áhættu. Þessar niðurstöður undirstrika þannig mikilvægi lífsháttа yfir ævina í þróun meinsins, og þá sérstaklega fyrri hluta hennar.

Lykilorð: Brjóstakrabbamein, unglingsár, fiskur, lýsi, rúgbrauð, haframjöl, heilkornavörur, mjólk, kjöt, vöxtur, hæð

Abstract

Background and aims: Previous studies have provided evidence for the importance of early life environment on breast cancer development. The aim of this study was to advance knowledge on the association of growth rate in early life and lifelong dietary habits and on breast cancer later in life.

Materials and methods: Three papers form the foundation of this thesis. In the first one, data from the population-based Reykjavik Study and AGES-Reykjavik cohort was used. The Reykjavik Study was established in 1967, and for this study, 9,340 women born between 1908 and 1935, who had information on early residence and were not diagnosed with breast cancer were included. Among extensive data on numerous health related factors, participants provided information on early life residence, here used as a proxy for dietary habits in early life, at study entry. Also, from the Reykjavik Study, a total of 991 participants had information on growth rate in adolescence, used for analysis in the third paper.

In the first and second paper, data from the sub-cohort AGES-Reykjavik Study was used. Between the years 2002 – 2006, a total of 3,326 women entered the study. For dietary analyses in the study, information on dietary habits in adolescence, midlife and late life was available for approximately 2800 women, who were free of breast cancer at study entry. The main emphasis was on common food items in Iceland in the early 20th century, such as fish, milk, meat and whole grain products.

For all analyses, Cox regression models were used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) and adjustments were made for potential covariates. Principal component analysis was used to identify dietary patterns. Breast cancer diagnosis was ascertained through the nationwide Icelandic Cancer Registry. Information on cause of death was obtained from Directorate of Health. Participants were followed from either study entry or time of height measurement until diagnosis of breast cancer, death, or until the end of the observation period December 31st, 2013 for study I, 2014 for study II and 2015 for study III), whichever occurred first.

Results: For the residence analysis, 744 women were diagnosed with breast cancer for an average follow-up of 27.3 years in the Reykjavik Study. A 22% lower risk of breast cancer was observed among women who lived through

the puberty period in coastal villages, when compared with women who were raised in the capital area (95% CI: 0.6, 1.0).

For the AGES-Reykjavik cohort, 91 women were diagnosed with breast cancer during an average follow-up of 8.2 years throughout 2013. An indication of lower risk of breast cancer among women with high fish consumption (more than 4 portions per week) was observed for the adolescence period (HR 0.7, 95% CI, 0.4, 1.1). In addition, a marginal inverse association was observed for women with high adherence with dietary pattern that included fish (HR 0.6, 95% CI 0.4, 1.0). For the midlife period, a statistically significant risk reduction was observed for women with high fish consumption (HR 0.46, 95% CI 0.22, 0.97) compared to those with lower fish consumption. For analysis of other dietary factors in the AGES-Reykjavik study, the follow-up was through 2014, and here, a total of 97 women were diagnosed with breast cancer. For both adolescence and midlife, daily consumption of rye bread was positively associated with breast cancer (HR 1.7, 95% CI 1.1, 2.6; 1.8, 95% CI 1.1, 2.9, respectively). In contrast, persistent high consumption of oatmeal was inversely associated with breast cancer (HR 0.4, 95% CI 0.2, 0.9). No single type of food in late life was associated with breast cancer risk. However, women with high adherence to a dietary pattern characterized by pastries, sweets and soda had a 60% increased risk of breast cancer when compared with women with lower adherence (HR 1.6, 95% CI 1.0, 2.7).

A total of 991 women had available information on height at age 13 (paper III). Of them, 117 women were diagnosed with breast cancer during a mean follow-up of 66 years. Women in the highest tertile of growth rate from age 13 until adult height (7,8 cm mean annual increase) had an increased risk of breast cancer (HR 2.3, 95% CI 1.3, 4.1) when compared with women in the lowest tertile (2,6 cm mean annual increase).

Conclusion: The result of this population-based data suggest that residence, diet and fast growth rate in adolescence are associated with the risk of breast cancer later in life. While fast growth rate and high consumption of rye bread in adolescence (and midlife) may increase the risk of breast cancer, consumption of fish and oatmeal seem to reduce this risk. These results highlight the importance of environmental exposures throughout the life course in the development of the disease, particularly in early life.

Keywords: Breast cancer, adolescence, diet, fish, fish oil, milk, meat, whole grains, oatmeal, rye bread, growth rate, height

Acknowledgements

I have always believed there is some ultimate truth out there when it came to science and facts. I still believe this, but I have learned that the path to both unveil and understand it is neither clear nor easy and will never end. More importantly, I have also learnt that the common saying “the more you learn, the less you know” is indeed true. This journey has also both humbled and shaped me, but hopefully also trained me properly enough so I can continue to learn and contribute to this mysterious world that science is.

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Contents

List of abbreviations

ALA, α–linolenic acid

AGES, Age, Gene/Environment Susceptibility Study

AICR, American Institute of Cancer Research

BMI, body mass index

CDC, cancer detection clinic

CI, confidence interval

CLA, conjugated linoleic acids

CUP, Continous Update Project

DHA, *docosahexaenoic acid*

EPA, eicosapentaenoic acid

EPIC, The European Prospective Investigation into Cancer and Nutrition

ER+/ER-, estrogen receptor positive/negative

FFQ, food frequency questionnaire

GLOBOCAN, Global Cancer Statistics

HCAs, heterocyclic amines

HR, hazard ratio

HRT, hormonal replacement therapy

IGF-1, insulin-like growth factor 1

GUTS, Growing Up Today Study

NHS, Nurses Health Study

NHS II, Nurses Health Study II

OC, oral contraceptive

PAHs, polycyclic aromatic hydrocarbons

PCA, principal component analysis

PR+/PR-, progesteron receptor positive/negative

SD, standard deviation

TDLU, terminal ductal lobular units

Vs., versus

WHO, World Health Organization

25(OHD)D, 25-hydroxy-vitamin-D

n-3 LC-PUFA, omega-3 long chain polyunsaturated fatty acids

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List of original papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-III):

I. Haraldsdottir A, Steingrimsdottir L, Valdimarsdottir UA, Aspelund T, Tryggvadottir L, Harris TB, Launer L, Mucci L, Giovannucci EL, Adami HO, Gudnason, V. Torfadottir JE. **Early Life Residence, Fish Consumption and Risk of Breast Cancer**. *Cancer Epidemiol Biomarkers Preven* 2017 Mar;26(3):346-354.

II. Haraldsdottir A, Torfadottir JE, Valdimarsdottir UA, Adami HO, Aspelund T, Tryggvadottir L, Thordardottir M, Birgisdottir BE, Harris TB, Launer L, Gudnason V, Steingrimsdottir L. **Dietary habits in adolescence and midlife and risk of breast cancer in older women**. *PLoS One* 2018 May;13(5).

III. Haraldsdottir A, Steingrimsdottir L, Maskarinec G, Adami HO, Aspelund T, Valdimarsdottir UA., Bjarnason R, Thorsdottir I, Halldorsson TI, Gunnarsdottir I, Tryggvadottir L, Gudnason V, Birgisdottir BE, Torfadottir, JE. **Growth rate in childhood and adolescence and risk of breast and prostate cancer: a population-based study**. *Manuscript*.

In addition, some unpublished data is presented.

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Declaration of contribution

I, Álfheiður Haraldsdóttir, planned the research work for the papers that form the foundation for this thesis in close collaboration with my supervisors. I conducted all statistical analysis for papers I-III in close collaboration with my supervisor and a statistician. I also drafted all manuscripts and revised in close collaboration with my co-authors. I wrote this thesis with the solid guidance of my supervisor and doctoral committee.

1 Introduction

According to the World Health Organization (WHO), „cancer is a generic term for a large group of diseases characterized by the growth of abnormal cells beyond their usual boundaries that can then invade adjoining parts of the body and/or spread to other organs“. Cancers have various anatomic and molecular subtypes and can affect almost all parts of the body and were estimated to account for almost 10 million deaths in 2018, making it the second leading cause of death worldwide (1). Cancer incidence and mortality are rapidly growing worldwide. The reasons for this trend are complex but involve aging and growth of populations and shifts in prevalence and distribution of risk factors for cancer (2). According to WHO, between 30% and 50% of all cancer deaths could be prevented by modifying or avoiding key risk factors like tobacco products and alcohol, maintaining a healthy body weight, exercising regularly and addressing infection-related risk factors (3).

The most common cancer among women is breast cancer, accounting for approximately 2.1 million newly diagnosed cases in 2018, or 25% of all cancer cases among women. Many of the well established risk factors for breast cancer, such as physical inactivity, obesity in later life and alcohol consumption, are modifiable (4). Diet is estimated to contribute to breast cancer risk, although studies on adult women are not conclusive. It has therefore been suggested that dietary exposures might need to take place during adolescence, a sensitive developmental stage in breast tissue maturation (5). The focus of this thesis will therefore be on diet across the lifespan. As there is currently a gap in the literature regarding diet in adolescence and the risk of breast cancer, the emphasis will mainly be on that period. Improved knowledge of the link between diet and breast cancer can further enhance understanding of the disease and have an important public health impact.

1.1 Breast cancer

The breast consists mainly of glandular epithelium in lobes and ducts (milk channels), connective tissue that supports those structures and the surrounding adipose tissue. During a woman´s life, the breast tissue goes through three major stages of development, or first during embryonic life, then puberty and finally with pregnancy and lactation. These developmental stages are mainly driven by estrogen, progesterone, insulin and growth factors (6). Breast cancer cells are generally formed from normal cells because of mutation of cellular DNA and/or RNA. The development from mutagenic initiation through breast tumor promotion until presentation of symptoms can last for decades (7).

Although breast cancer generally has been referred to as a single disease, there are up to 21 distinct histological subtypes and at least four different molecular subtypes that differ in terms of risk factors, presentation, response to treatment, and outcomes (8). The two most common types of invasive breast cancers are infiltrating ductal carcinoma and infiltrating lobular carcinoma. Approximately 90-95% of all breast cancers fall into these two categories. Around 80% of breast tumors are of the ductal type although the relative incidence of lobular cancer increases with age (9, 10). Most breast cancer subtypes are hormone related, and tumors are often classified according to whether the tumor cells contain hormone receptors or not. The most common categorization is based on whether estrogen (ER+) and progesterone receptors (PR+) are present. Tumors without these receptors are referred to as estrogen receptor negative (ER-) or progesterone receptor negative (PR-). Two thirds of all breast tumors have estrogen receptor tumors and the carcinogenic stimulating effect of estrogen on ER+ tumors are well established (11). The effect of progesterone on breast cancer risk and receptors is not as clear (12). Women with hormone receptor positive tumors have usually better prognosis than women with hormone receptor negative tumors, as the latter ones tend to have higher pathological grade and are more difficult to treat (13). Breast cancer is categorized by menopausal status into premenopausal and postmenopausal breast cancer. Menopause usually takes place around the age of 50 and studies have found that effects of risk factors, can differ depending on whether the cancer is diagnosed before or after menopause (14, 15).

Overall, breast cancer is a heterogenous disease, where majority of tumors are driven by hormonal mechanisms and often categorized by hormonal receptors status and menopause.

1.2 Epidemiology of breast cancer

In the 2018 report from the Global Cancer Statistics (GLOBOCAN) breast cancer is estimated to be the most common cancer among women in 154 countries out of the 185 included in the report. It also accounted for approximately 2.1 million estimated new cases in 2018, or 25% of all cancer cases among women (2). This is a similar proportion as seen in the 2012 GLOBOCAN report (16) but 2% higher than the 2008 estimates (17). The worldwide age-standardized incidence rate of breast cancer is highest in Australia/New Zealand, North America, and more high-income parts of Europe. The highest incidence rate was observed in Belgium, or 113 per 100.000. The incidence rate is relatively lower in Africa, South-America and Asia, particularly Central Asia, where the lowest rate was observed (26 per 100.00, country not specified) (2).

Breast cancer incidence in high-income countries has increased during the last decades, particularly between 1980 and late 1990s, or by 30% (18). This increase has mostly been linked with introduction of population-based screening mammography (19, 20) and the increasing prevalence of risk factors such as obesity, earlier age at puberty, increased alcohol consumption, use of hormone replacement therapy (HRT), and having children later in life (18, 21, 22). However, a decrease or plateau in incidence has been observed since the early 2000s (18), particularly for the age group 50 – 69 years. This decrease has been hypothesized to be related to the concurrent reduction in the use of HRT (23, 24). Other explanations include a plateau in participation rates in mammographic screening (25, 26) and screening saturation, that can occur when a screening test reaches a plateau in the incidence rate due to a reduced pool of undiagnosed prevalent cases (27).

It is not clear if or how geographic or temporal variations in rates relate to specific etiologic factors. There has been rapid increase in breast cancer incidence in certain countries in South America, Africa, and Asia, where rates have been historically relatively low. This trend is most likely related to complex social and economic transitions (28). These factors are older age when first child is born, having fewer children, decreased level of physical activity and increased prevalence of obesity. Dietary habits have also changed, and alcohol intake increased. Simultaneously, life expectancy is higher, access to screening programs has increased, and women in these countries are more aware of breast cancer in general (2, 18, 29).

In most high-income countries, the five-year survival rate for women diagnosed with stage I or II breast cancer is between 80 and 90% and in the US, there was an average 1.8% decrease in mortality rates per year in the period 2007 – 2016 (30). For stages III and IV, the five-year survival rate is around 24%. Still, breast cancer is the leading cause of all cancer deaths in women in over 100 countries, particularly in less developed countries, with the highest mortality rate in Fiji, or 25.5 per 100.000 (2).

In the Nordic countries, breast cancer accounted for 26% of all incident female cancers during the years 2011 – 2015 and 14% of all cancer deaths in the same period. In 2015, the age-standardized rate was 86 per 100.000 (31). The incidence of breast cancer in Iceland (based on 5-year averages) has been steadily increasing over the past decades, with the highest rate observed in 2012 or 94 per 100.000 but was 85 per 100.000 in 2017 (see figure 1). On average, 210 women were diagnosed annually during the years 2013 – 2017. Similarly, on average, 50 women died each year due to breast cancer during the same period. The mean age at diagnosis was 62 years and breast cancer accounted for 27% of new female cancer cases in 2013 – 2017. Regular screening mammography has been available for Icelandic women aged 40 – 69 years since 1987 (32).

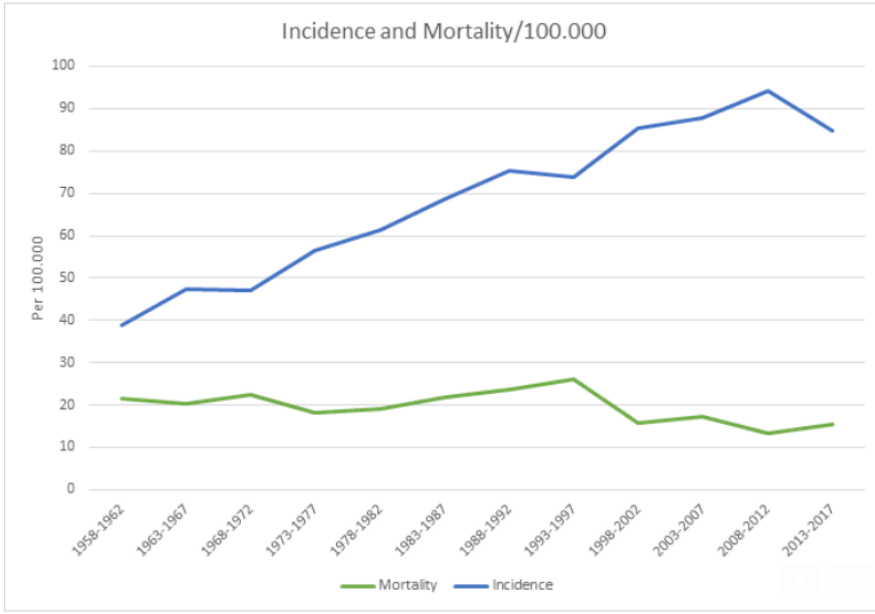

Figure 1: Incidence and mortality of breast cancer per 100.000 1955 - 2017 in Iceland (32).

To sum up, the worldwide breast cancer incidence has mostly been increasing over the last decades. However, a downward trend was observed in many developed countries during the last decade and the incidence seems to be going down since 2012 in Iceland. Still, this is the most frequently diagnosed cancer among females, particularly in high-income countries. The incidence is rapidly increasing in several lower-income countries going through a transition phase, although still relatively low.

1.3 Risk factors

WHO defines a risk factor as „any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury" (1). Well established risk factors for breast cancer include low age at menarche, high age at first pregnancy, use of exogenous hormones, frequent alcohol intake, not breastfeeding, low physical activity, high adult weight as well as several factors related to the host, such as genetic factors (33).

Yet, having one or more risk factors does not always result in the development of a disease. Consequently, women with one or more risk factors for breast cancer may never develop the disease while women with no known risk factors can also present with breast cancer. The different effect of the same exposures may be explained by individual genetic variations, polymorphism and somatic mutations. Duration of exposures, intensity and other factors could also be of importance for this difference (34).

However, it has been shown that risk factors like high bodyweight, alcohol consumption, low physical activity, not breastfeeding and use of menopausal hormone therapy were associated with more than one-third of postmenopausal breast cancers in the US (United States) (35). Another US study found that 28% of cancer cases were attributable to factors such as excess body weight, alcohol intake, poor diet and physical inactivity (36). In the Italian section of the European Prospective Investigation into Cancer and Nutrition study (EPIC), it was estimated that 30% of postmenopausal breast cancer cases could be avoided with increased physical activity, maintaining BMI below 25 and by limiting alcohol consumption to one drink per day (37).

Important knowledge on lifestyle related risk factors and cancer has been established through the work of The Continuous Update Project (CUP), an ongoing program that is led and managed by The World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR). The main purpose of this project is to continuously analyze and re-evaluate global research on the effect of diet and physical activity on cancer risk and survival.

In short, peer-reviewed published data on the subject is continuously being added to the CUP database and then it is systematically reviewed by a team of experts. A second independent panel then evaluates and interprets the evidence collected and categorizes as 1) convincing (strong evidence), 2) probable (strong evidence), 3) limited-suggestive, 4) limited-no conclusion 5) substantial effect on risk unlikely (strong evidence). Based on the panel´s conclusion, the third report was published in 2018 (4).

For clarity, risk factors for breast cancer will be categorized into three major groups in the upcoming overview (see flowchart 1). The first category includes factors that are related to the individual, often referred to as unmodifiable or host factors, such as age, race and family history. The second category includes reproductive factors such as age at menarche and age at first childbirth. Due to the purpose of the thesis, more emphasis will be on the third category, where modifiable factors such as diet, alcohol consumption, physical activity and BMI are covered.

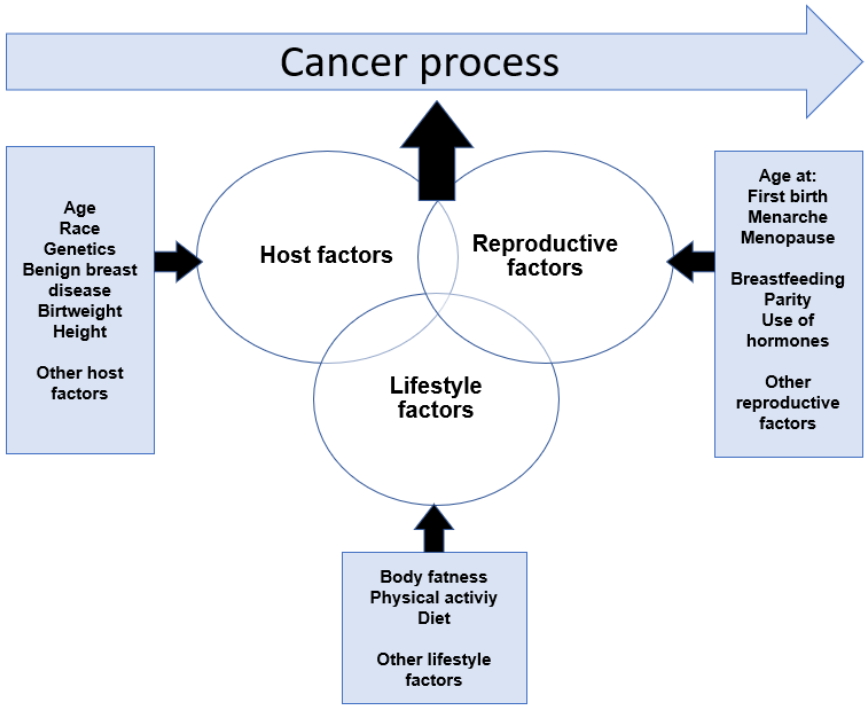

Figure 2: Overview of risk factors for breast cancer

1.3.1 Host factors

Female gender is a major risk factor for breast cancer, but women are almost 100 times more likely to get the disease than men. As for most cancers, the risk of cell mutation increases with advanced age. Individual breast cancer risk steadily increases from the age 20, with a slight inflection in incidence around the age of menopause. Most breast cancers are however diagnosed after menopause, or two out of three cases (5, 38).

Incidence of breast cancer also varies by ethnic groups. In the US, the age-adjusted rate is highest for Caucasian women, followed by African Americans, Asians, Hispanics and Native Americans (39). It is estimated that 5-10% of breast cancers are hereditary (40) and relative risk for women is doubled if they have a parent, sibling or a daughter diagnosed with breast cancer before the age 50. This risk further increases with increased number of first-degree relatives with the disease (41). Two genes have been identified (BRCA1 and BRCA2), which code for proteins that help protect against breast cancer. Pathogenic mutations in those genes confer a highly increased risk of breast cancer and women with these mutations have a cumulative breast cancer risk before age 80 that ranges up to 72% (42). In the Icelandic population, a founder BRCA2 mutation is highly prevalent and is carried by 6% – 8% of all Icelandic women with breast cancer, and an estimated 24% of Icelandic women diagnosed with breast cancer, before age 40 age carry this mutation (43-45). The prevalence of this mutation is 0.7% in the general Icelandic population (46), and it accounts for nearly 40% of familial breast cancers diagnosed in Iceland (47).

Although categorized as benign conditions, hyperplasia, defined as increase in the reproduction rate of its cells, and atypical hyperplasia, an accumulation of abnormal cells in the breast can both severely increase the risk of breast cancer later in life. The same applies for lobular carcinoma in situ, an uncommon condition where abnormal cells form in the milk glands and mammographic density, a measure of the amount of radiopaque fibroglandular as opposed to fat tissue in the breast (48). Women who have undergone radiation therapy at some point were also found to have an increased risk of breast cancer later in life (49-51).

Birthweight might also be of some importance as premenopausal women with birthweight of <5.5 lbs. have been found at decreased risk of breast cancer compared with women who were 8.5 lbs. or more when born. This association has not been observed for postmenopausal women (4, 52). Adult height has also been associated with both pre- and post menopausal breast

cancer. A recent meta-analysis using data from 159 prospective cohorts found a 17% increased risk of both pre- and post menopausal breast cancer per every 10-cm increase in height (53). Similarly, CUP found a 6% increased risk of premenopausal breast cancer for every 5-centimeters increase in height. For postmenopausal breast cancer, this risk was 9% (4).

1.3.2 Reproductive factors

1.3.2.1 Menarche and menopause

Mean age at menarche has been declining during the past 100 years in North-America and Europe and young age at menarche has repeatedly been linked with both pre- and postmenopausal breast cancer risk (54). A study from 2012, where data from 117 epidemiological studies were analyzed, found 5% increased risk of breast cancer for every earlier year at menarche. Breast cancer risk also independently increased by 3% for every year older at menopause (55). An Icelandic study found that mean age at menarche declined from 14.9 years to 13.5 years in successive cohorts of Icelandic women born 1900 to around 1950. In cohorts born 1951 – 1967 the mean age at menarche remained stable (56).

Early menarche is mainly thought to increase the risk of breast cancer through induction of early proliferation of undifferentiated mammary gland cells and elevation of the total number of menstrual cycles in a women's lifetime. Increased frequency of menstrual cycles causes both elevated lifetime exposure to estrogen and higher frequency of menstrual related cell divisions, increasing the risk of random genetic errors and tumor initiation (57).

1.3.2.2 Age at first birth, parity and breastfeeding

Over the centuries it has been observed that nuns are more likely to develop breast cancer compared to women in the general population, and studies conducted in the early 20th century suggested that having children decreased the risk of breast cancer when compared with women who did not have them (58). Later studies have confirmed this, but it was also observed that women who had their first child early, or around age 18 years had less risk of breast cancer when compared with those whose first birth was after age of 35 years or more (59-61). Yet, the association between pregnancy and breast cancer is complex, as pregnancy has also been associated with an increase in short-term risk of breast cancer, followed by a long-term protection later in life. A recent pooled analysis of 15 prospective studies found that compared with

nulliparous women, parous women had an increased risk for breast cancer that peaked about 5 years after birth, before 30% risk reduction was observed approximately 30 years later. The short-term risk was greater for women who were older at first birth (62). Multiparity is also thought to further reduce the risk of breast cancer (63). The risk reduction observed for age of parity is thought to be associated with a shorter time period between menarche and age at first birth, and favorable long-term changes in women´s hormonal environment (5).

Breastfeeding, in addition to childbearing, is also thought to reduce the risk of breast cancer. According to the Collaborative Group on Hormonal Factors in Breast Cancer the risk reduction is estimated to be 4.3 – 4.5% for every 12 months of breastfeeding (64). The CUP estimated 2% decrease of breast cancer risk (type unspecified) per 5 months of duration of breastfeeding (4).

1.3.2.3 Oral contraceptives

Multiple studies have been conducted on oral contraceptive (OC) usage and risk of breast cancer over the years. A large pooled analysis with a total of 54 studies, mainly from case-control studies from the 1970s and 1980s, was conducted in 1996. Compared with never users, current OC users had a 24% increased risk of breast cancer. This risk gradually decreased after stopping, and no risk was observed for women who had stopped taking OC for 10 years or more (65). A meta-analysis including only case-control studies on premenopausal women was published in 2006. Women who ever used OC had a 19% increased risk of premenopausal cancer compared with non-users. The risk was greatest for parous women who used OCs for four years or more before first full-term pregnancy (66). Another meta-analysis, that included 13 prospective studies, found a marginal 8% risk increase for breast cancer when ever users were compared with never users. A dose-response analysis, that was based on five eligible studies, showed 14% increased risk of breast cancer for every ten-years' increment of OC use (67). A recent Danish cohort study of 1.8 million women found a 20% increased risk among current users and recent users, amount to one extra breast cancer for every 7690 women using hormonal contraception for one year (68).

1.3.2.4 Hormonal replacement therapy

Multiple studies have been conducted on the association between HRT on breast cancer risk. The largest pooled analyses on the subject were conducted by the Collaborative Group on Hormonal Factors in breast cancer

in 1997 and 2019. The former analysis included 51 studies and found a 2.3% increased risk of breast cancer for each year of use in current user of HRT, and for those who ceased use 1 – 4 years earlier. These effects seemed to wear off five years after stopping use of HRT (69). At this time little was known about the effects of various HRT regimens. The latter analysis, that included 58 studies, found twofold risk of breast cancer after 5 – 14 years of use of regimens containing oestrogen-progesteron blends, and increased risk of 30% in users of ostrogen-only preparations. Dependent on duration, the risk of breast cancer persisted up to 10 years after cessation of HRT. It was also estimated that five years of HRT, starting at age 50 years, would increase breast cancer incidence at ages 50 – 69 years by one in every 50 users and that HRT use had caused 1 million breast cancer out of 20 million diagnosed in the world since 1990 (70). After the Women´s Health Initiative (WHI) trials were be stopped in 2002 due to severe side affects of HRT (71), the use of menopausal hormone therapy in most western countries decreased substantially. Subsequently, the incidence of breast cancer also dropped (72), supporting the relationship between hormone replacement treatment and breast cancer risk.

Taken together, reproductive factors are of great importance for breast cancer risk, particularly age at menarche and age at first birth. While young age at menarche increases the risk of breast cancer, young age at first birth can reduce this risk later in life. Nevertheless, temporary risk of breast cancer can also be present a few years after birth. Multiparity and breastfeeding can also further reduce the risk of breast cancer. The risk of breast cancer from the OC use seems to be most dominant among current users and usually subsides few years after usage is stopped. Similar trend is observed for the use of HRT, although a recent study found that this increased risk could persist up to 10 years after cessation of HRT.

1.3.3 Physical activity, body fatness and alcohol consumption

1.3.3.1 Physical activity

In meta-analyses from 2013 and 2019, a 12% and 13% risk reduction were observed among women categorized in the highest group of physical activity when compared with women in the lowest activity group. This association was more pronounced in premenopausal women (73, 74). In the CUP, both regular and vigorous physical activity were found protective against postmenopausal breast cancer, while risk reduction was only observed for vigorous physical among premenopausal women (4). A recent Nordic study

estimated that total elimination of insufficient physical activity could reduce the number of postmenopausal breast cancer cases by approximately 3500 or 0.6% in the Nordic countries in the period 2016 – 2045. For Iceland, this reduction was estimated to be a total of 57 women or 0.8% of expected cases (75).

1.3.3.2 Body fatness

The term BMI (body max index) is commonly used to classify underweight, overweight and obesity in adults and is defined as the weight in kilo grams divided by the square of the height in meters (kg/m^2). BMI under 18.5 is classified as underweight, BMI from 18.5 – 25 normal weight, BMI 25 – 30 overweight, and BMI > 30 obese (76). A recent meta-analysis of 31 studies found a 33% increased risk of postmenopausal breast cancer among women in the highest BMI category when compared with the lowest one. No association was observed for premenopausal women (77). The CUP defines body fatness by BMI, waist-hip ratio and waist circumference. For every increase of 5 kg/m^2, a 7% decreased risk was reported for premenopausal women. No firm conclusion could be drawn from results on waist-hip ratio and waist circumference or adult weight gain. On the other hand, postmenopausal women had a 12% increase of breast cancer risk for every 5 kg/m^2 increase in BMI and every 10 cm increase in waist circumference was also linked with 11% increased risk of postmenopausal breast cancer. For adult weight gain, every 5 kg increase in weight were found to increase the risk of postmenopausal breast cancer by 6% (4). It was estimated that cancer burden for postmenopausal breast cancer from 2016 – 2045 could be reduced by 7% in the Nordic countries, with total elimination of overweight and obesity. This would mean 9.4% fewer breast cancer cases in Iceland in the same time period (78).

1.3.3.3 Alcohol

In a 2015 dose-response meta-analysis, with 118 studies included, women with light, moderate and heavy consumption of alcohol were at increased risk of breast cancer by 4%, 23%, and 61%, respectively (79). A meta-analysis that focused on lighter drinking observed 4% increased risk for ≤ 0.5 drink/day, 9% for ≤ 1 drink/day and13% for 1 – 2 drinks/day (80). The CUP observed an increased risk of 5% for premenopausal breast cancer for each 10g increase of ethanol consumption per day. This risk was 9% for postmenopausal women (4). Total elimination of alcohol consumption could reduce the cancer burden for postmenopausal breast cancer by 4.9% in the

Nordic countries in 2016 – 2045. This would mean 3.2% fewer breast cancer cases in Iceland in the same time period (81).

Taken together, the CUP concluded that vigorous physical activity reduces the risk for both pre- and postmenopausal breast cancer. At the same time, greater body fatness before menopause probably protects against premenopausal breast cancer while greater body fatness throughout adulthood is a convincing risk factor for postmenopausal breast cancer. The reason for the different effect of obesity on the different types of breast cancer is not all clear but thought to emphasize their different etiology. CUP considers alcohol consumption as a probable cause of premenopausal breast cancer and convincing cause of postmenopausal breast cancer. Simultaneously, other studies found that elimination of obesity, alcohol consumption and insufficient physical activity would reduce the future risk of postmenopausal breast cancer substantially. These results highly suggest the importance of further identifying and reducing harmful effects of modifiable risk factors for breast cancer.

1.3.4 Nutrition in adulthood

Diet has been estimated to contribute to the etiology of breast cancers and multiple studies have been conducted on the topic. However, the effects of diet on breast cancer have not been uniformly confirmed and currently alcohol is the only dietary factor that is defined as a convincing risk factor for postmenopausal breast cancer. Presently there is also limited evidence that non-starchy vegetables, food containing carotenoids, and diet high in calcium may reduce the risk of both pre and postmenopausal breast cancer and that dairy products may reduce the risk of premenopausal breast cancer (4).

1.3.4.1 Nutrition assessment

The most commonly used tools for dietary assessment are 24-hour recall, food frequency questionnaire (FFQ) and food records or diaries for a defined number of days (82). Each method has different strengths and weaknesses. The FFQ is a questionnaire designed to estimate habitual dietary intake where participants are asked their typical frequency of consumption over a specific period. Available responses are usually close end multiple-choice format and the range depends on the item in question. FFQ can be brief and usually self-administered but can also be checked by an interviewer. Participants eating habits are not affected but they might be required the to recall their diet in the past. A 24-hour recall can capture a detailed description

of food intake very well and does not change dietary habits. However, collection of data can be time-consuming, dependent on well trained interviewers and does not always represent everyday intake. Food records or diaries are to be completed by participants at the time of consumption for a specific period. Although this method does not rely on memory, it can affect usual dietary habits of participants (82, 83).

All studies using self-report on dietary intake face some methodological problems. Data collection on dietary habits is sensitive to information bias, or misclassification, especially when more distant recall of dietary intake is required from the participants. Misclassification can be both differential and non-differential, often depending on the study design involved. Differential information bias, or recall bias, is more pronounced in case-control studies, as cases might recall their diet differently than controls, based on knowledge of the disease involved. This type of misclassification can either exaggerate or underestimate an association. On the other hand, non-differential bias affects all participants and the bias is therefore in the direction of the null value (83-85).

1.3.4.2 Fish and fish products

Fish is an important food item, particularly as it contains substances that are hard to come across in other foods. Among these substances are the long chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFA) eicosapentaenoic acid (EPA) and docohexaenoic acid (DHA). EPA and DHA are mainly found in fatty fish such as salmon, herring and tuna for example and are commonly referred to as marine derived PUFAs (86). n-3 LC-PUFAs play an important role in cell membrane structure, fluidity, and cell signaling (87), and studies on animals have shown that marine derived n-3 PUFA can suppress mammary tumors in rats and slow down growth and metastasis of human breast cancer cells in nude mice (88, 89) via multiple mechanism (90).

Fish, particularly fatty fish, is also rich in vitamin D and hypothesized to reduce the risk of breast cancer by multiple cellular pathways (91-93). Results of meta-analyses on serum vitamin D levels and breast cancer, measured as 25-hydroxy-vitamin-D (25(OH)D) remain inconclusive as beneficial effects have mostly been observed in case-control studies while no association is found in studies with prospective design (94-96). Serum 25(OH)D is lower among those with higher body mass index and lower physical activity levels, both commonly documented outcomes after a diagnosis of breast cancer (97, 98). A meta-analysis from 2014 found a weak inverse association between both vitamin D intake and serum 25(OH)D levels

and breast cancer risk. Studies included on vitamin D intake were mostly prospective while a great majority of the blood 25(OH)D analysis were nested case-control studies. Among women already diagnosed with breast cancer, high serum 25(OH)D levels were also significantly associated with lower breast cancer mortality (99).

Dietary studies on adult consumption of fish and marine n-3 PUFA and breast cancer risk have been inconsistent. In a review from 2003 (100) no association was observed for breast cancer is US derived studies (101, 102). Inverse association was observed for studies from Norway and Japan, both countries with tradition of high fish consumption. In the Japanese study, an inverse association for breast cancer was observed for women with more than five servings of dry fish per week when compared with women who consumed one serving or less per week (103). One Norwegian study found that women who had poached fish for dinner at least five times per month were at less risk of breast cancer compared to women who had fish in this form twice a month or less. However, no association was detected between overall frequency of fish for dinner and breast cancer risk (104). The other Norwegian study found 30% reduced risk of breast cancer mortality for wives of fishermen compared with women who were married to unskilled workers (105). In addition, 19 case control studies of were also identified in the review. Most of them showed either no association or a very weak inverse association between fish consumption and breast cancer (100).

A meta-analysis from 2013 found no association for total fish consumption and breast cancer. These results were based on 11 studies and no distinction appears to have been made between fatty or lean fish, that could possibly explain these results (106). Similar results have been observed for more recent studies. A Japanese study, with relatively high daily consumption (an average of 126 g of fish per day) found no association for fish consumption and breast cancer, independent of menopausal status or type of fish. No association was observed for total n-3 PUFA either (107). American case-control study observed no association with total fish consumption, although a positive association was observed between consumption of tuna and breast cancer risk. No further distinction was made between types of fish (108). No association for fish consumption and breast cancer was observed in the Black Women´s Health Study (109), and neither in the Swedish Women´s Lifestyle and Health cohort (type of fish unspecified) (110).

Stronger associations with breast cancer have been observed in epidemiological studies looking specifically on n-3 PUFA intake. A meta-

analysis from 2013 found a 14% risk reduction for breast cancer among women with the highest intake of marine derived n-3 PUFA. This was based on 17 eligible studies and the association was stronger in postmenopausal women. In addition, a dose-response analysis that included eight studies, indicated that a 0.1g/day increment of dietary marine n-3 PUFA was associated with 5% lower risk of breast cancer (106). To the best of knowledge, only one study has examined the effect of supplemental fish oil, rich in n-3 PUFA, and found that current use of fish oil was associated with 32% reduced risk of breast cancer for postmenopausal women aged 56 – 76 years (111).

1.3.4.3 Milk and dairy products

Milk and other dairy products contain a variety of bioactive compounds of interest for breast cancer development. It has been hypothesized that consumption of dairy can increase serum levels of insulin like growth factor 1 (IGF-1) (112) which in return increases the risk of breast cancer (113-116). IGF-1 is a mitogen that plays an important role in almost every organ of the human body by regulating cell proliferation, differentiation and apoptosis (117).

Dairy products are often rich in fat, which have been speculated to increase the risk of breast cancer, although this association remains unclear. A meta-analysis from 2016, that included 24 studies on total dietary fat and fatty acids intake, and seven studies on serum fatty acids found no association with breast cancer (118). On the other hand, milk also contains calcium and conjugated linoleic acids (CLA) and is often fortified with vitamin D, all of which are hypothesized to have beneficial effects against breast cancer. In vitro studies have suggested that calcium and vitamin D have favorable effects on breast cancer cells (91, 92), although observational studies on vitamin D show controversial results, as discussed previously in the thesis. In vitro studies, and studies on animals have shown beneficial effects of CLA against carcinogenesis in the mammary gland (119, 120). However, data from population studies on dietary CLA intake and risk of breast cancer are sparse and results conflicting (121-123). According to the CUP, diet high in calcium is categorized as limited-suggestive evidence for both pre- and postmenopausal breast cancer while evidence on vitamin D are limited with no conclusion (4).

Two recent meta-analysis have been conducted on dairy consumption and breast cancer risk. In the former one included 18 studies and found 15% reduced risk for breast cancer was observed when the highest category of

total dairy consumption was compared with the lowest one. A weak negative association was observed for milk consumption. Based on limited number of studies, subgroup analyses suggested that these associations were strongest for low-fat dairy intake in premenopausal women. In addition, a beneficial dose-response relationship with breast cancer risk was observed for total dairy consumption, although not for milk consumption (124). The second meta-analysis included 22 prospective cohort studies and five case-control studies. Both high (>600 g/day) and modest (400 – 600 g/day) dairy consumption reduced the risk of breast cancer, by 10% and 6% respectively. In a subgroup analysis on types of dairy, this association was only of significance for yogurt and low-fat dairy (125). Another meta-analysis on dietary protein sources and risk of breast cancer was published in 2016. A total of 7% risk reduction was observed for high intake of skim milk, and 10% risk reduction was found for yogurt consumption. No association was observed for total or whole milk intake (126). The CUP found similar results for premenopausal women, or 5% risk reduction for every increase of 200g of dairy products (4).

1.3.4.4 Red meat

Red and processed are proposed to play a role in breast cancer via several pathways. Red meat is rich in both heme iron and non-heme iron, that cause oxidative stress that can lead to DNA damage (127) and epidemiological studies have shown positive association of cancer and iron intake (128, 129). Another mechanism linking red meat and breast cancer development involves heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs). These compounds are both by-products that are produced in the process of high-temperature cooking, such as grilling or charring red meat (130, 131). Some, although not all (132) epidemiological studies have shown positive association between HCA and PAH (133). Also, as hormones such as testosterone, estradiol, estradiol benzoate and progesterone are approved in US animal production, accumulation of these hormones in animal tissues might affect breast cancer risk (134-136). However, a recent review concluded that current evidence on the subject were too limited to conclude on this association (137). Finally, processed meat undergoes treatments like curing, smoking, or salting to modify and improve their shelf life, color, and taste. The preservatives nitrates can reform into nitrites in the oral cavity. Nitrites can react with amines and amides in the stomach and form N-nitroso compounds, most of which are known carcinogens (138).

A meta-analysis published in 2015 included 14 prospective studies on meat and 12 studies on processed meat. An increased risk of 10% was observed for the highest category of red meat consumption and for each increase of 120 g/day. This risk was 8% for high consumption of processed meat and increased by 9% for each increase of 50 g/day. When stratified by menopausal status, the risk was more pronounced in postmenopausal women, for both red meat and processed meat (139). In another meta-analysis, only processed meat was associated with a 6% increased risk of total breast cancer and this risk was only visible in postmenopausal women with stratification for menopausal status (140). In a yet another meta-analysis, when comparing the highest to the lowest category, unprocessed red meat consumption was associated with a 6% higher breast cancer risk (1.06, 95%CI 0.99, 1.14) and processed meat consumption was associated with a 9% higher breast cancer risk (141).

1.3.4.5 Whole grain products

Whole grain is a grain of any cereal and pseudo cereal that contains the endosperm, germ, and bran, while refined grains retain only the endosperm. Whole grains contain various micronutrients, and non-nutrients that are lost in the refining process, some of importance for cancer prevention (142). A recent meta-analysis of 11 observational studies on total whole grain consumption and breast cancer found a 16% risk reduction for women with high consumption, although this association was only observed in case control studies (143).

One of the most important substance in whole grains is fiber, a type of carbohydrate that the body is unable to digest. Fiber is hypothesized to reduce breast cancer risk by for example lowering the body´s estrogeon concentration (144-148). Other proposed anti carcinogenic effects of fiber include enhanced immunity and production of various anti-inflammatory cytokines (149). Fiber can also increase glucose absorption, reduce insulin secretion and hyperinsulinemia, wich lead to a better glycemic control (150, 151), which may be of importance as higher serum insulin levels have been associated with increased breast cancer risk (152, 153). Also, foods containing high amounts of whole grains and fiber have been found to be inversely associated with weight gain, a risk factor for breast cancer (154). A recent umbrella review of 18 meta-analysis on fiber intake and breast cancer observed a risk reduction for high consumption of fiber, in the range of 7% – 15% (155).

Whole grains are also rich in various antioxidants, including vitamin E and beta-carotene as well as important trace minerals like selenium, zinc, copper and manganese, which have all been inversely linked with breast cancer (148). Some whole grain products, like oatmeal, contain the polysaccharide beta-glucan. Beta-glucan can be found in the cell wall of bacteria, fungi, and in cereals such as barley and oats. Beta-glucans are proposed to have in vitro anticancer properties (156, 157), although data on this association in humans is still very limited (158).

Other important compounds found in certain types of whole grains are phytoestrogens, or dietary estrogens. Phytoestrogens are naturally occurring compounds that are structurally and/or functionally like mammalian estrogens and their active metabolites. Phytoestrogens are mainly thought to reduce the risk of breast cancer by inhibiting a conversion of androstenedione and testosterone to estradiol, and consequently lower the amount of circulating estrogen in the body (159, 160). Other proposed protective mechanisms include stimulation of apoptosis, antioxidant activity and competitive binding to estrogen receptors (161-163). The most studied phytoestrogens are isoflavones, which are present in berries, wine, grains and nuts, but are most abundant in soybeans and other legumes. Another subgroup of phytoestrogens are lignans, which are found in many fiber-rich foods such as berries, seeds (particularly flaxseeds), grains (mostly rye), nuts and fruits (164). Dietary lignans are converted into the enterolignans enterodiol and enterolactone, also called mammary lignans, by the gut microbiome. Enterolignans can be measured in plasma and urine (165). A meta-analysis from 2010 found no association for total lignan exposure (intake or biomarker-based) with overall breast cancer risk. However, high intake of lignans was associated with 14% reduced risk of breast cancer in postmenopausal women Breast cancer risk was also inversely associated with calculated enterolignan exposure, but not with blood or urine enterolactone concentrations (166). No association with breast cancer was observed between plant lignans or the estimated enterolignans intake in a recent German case control study on postmenopausal women (167).

1.3.4.6 Dietary pattern

Diet is a complex exposure variable where combined effects of correlated foods or nutrients consumed together can confound each other. Therefore, greater emphasis has been put on the use of dietary patterns as an alternative and complementary approach in research on diet and different health outcomes over the last decades. The most common method used in

studies on diet and cancer are the priori indices and factor analysis. The priori indices is a theoretical driven method that is usually based on interpretation of the literature on diet and health, and the patterns are constructed from dietary recommendation or guidelines (168, 169), such as the Mediterranean diet for example (170). Factor analysis is an empirically driven method that uses standard multivariate statistical method, most commonly principal component analysis (PCA), to define dietary patterns based on dietary information usually collected from FFQ or dietary records. PCA aggregates food items or food groups based on which foods tend to be consumed or avoided by the same person. Everyone in the dataset gets a score for each pattern derived based on adherence to the pattern and each pattern can then be used as a continuous exposure variable when analyzing the association with the outcome of interest (168, 169).

For breast cancer and dietary patterns, a systematic review on studies that used factor analysis techniques and/or principal component analysis was conducted on 26 eligible studies in 2014. Mediterranean dietary pattern and diets composed largely of vegetables, fruit, fish, and soy were associated with a decreased risk of breast cancer. Only one study showed a significant increase in risk associated with the “Western” dietary pattern, characterized by high intakes of red meat, processed meat, food high in saturated fat, refined grains and sugary drinks. Diets that included alcoholic beverages were associated with increased risk of breast cancer (171). However, a recent systematic review and meta-analysis containing 32 eligible articles found a 14% increased risk of total breast cancer for women with high adherence to “Western” dietary pattern while high adherence to prudent dietary pattern was associated with an 18% risk reduction. Prudent pattern or similar patterns usually have high loadings of fruits, vegetables, fish, whole grains, and low-fat dairy products. Interestingly, stronger association for the “Western” pattern was observed among postmenopausal women while the prudent pattern was only of significance among premenopausal women (172).

To sum up this chapter, fish, meat, milk and whole grain products all include various substances of importance for breast cancer risk. However, results form epidemiological studies have not been entirely conclusive on the effect of these food items on breast cancer risk. According to the CUP (4), and relative to these items, diet high calcium holds the strongest evidence and is categorized as limited-suggestive evidence for risk reduction of both pre- and postmenopausal breast cancer. Dairy products are also categorized as limited-suggestive in decreasing breast cancer risk, but for premenopausal

cancer only. Fish, meat, and whole grain products are currently categorized as limited evidence with no conclusion and further research is needed on the topic.

1.4 Exposures in adolescence

As breast cancer can take decades to develop (7, 173), a possible explanation for inconclusive results on adult diet and breast cancer could be timing of exposure in the studies. Possibly some dietary exposures may need to take place at times when the mammary tissue is undergoing extensive modeling or re-modeling, such as during puberty in the adolescence period. Most breast malignancies originate in the terminal ductal lobular units (TDLU), a common structure found in the mammary glands. During puberty, when the mammary glands are developing, through regulation of sex steroids and growth hormones, the number of TDLU increases considerably and carcinogenic exposures at that point may result in higher risk of breast cancer (174). Indeed, women exposed to the atomic bombs in Japan in the first two decades of their life had higher risk of breast cancer compared with those who were older at the time of exposure, suggesting a greater susceptibility to breast carcinogens earlier in life (175, 176). Similar patterns are found in migration studies where women are immigrating from a country with a low incidence of breast cancer to a country of higher incidence. The incidence among first generation immigrants is usually unchanged, but begins to gradually rise with second and third grade immigrants (177, 178), suggesting significant early environmental component in the development of the disease. Some studies also suggest higher risk among the first generation if migration took place in childhood (22).

These effects of early life radiation and migration suggest the importance of early environmental exposures in the development and progression of breast cancer.

1.4.1 Dietary exposures

1.4.1.1 Nurses Health Study

Available studies on diet in adolescence and breast cancer later in life are relatively few. An important information source on the subject is the Nurses Health Study (NHS), established 1976 in the US. The NHS consists of 121.700 women aged 30 – 55 years at study entry. The original focus of the study was on contraceptive methods, smoking, cancer, and heart disease, but has expanded over time to include research on many other lifestyle

factors. Every two years, cohort members receive a follow-up questionnaire with questions about diseases and health-related topics, including smoking, hormone use, and menopausal status. In 1980, the first 24-item food-frequency questionnaire (FFQ) about diet between the ages of 12 and 18 years was sent out for the NHS. Participants were aged 46 – 55 years when answering the FFQ. A response rate of at least 90% has been achieved in most follow-up cycles of questionnaires. The Nurses Health Study II (NHS II), was established in 1989 and a total of 116, 671 women aged 25 – 43 years entered the study. In 1991, the first food-frequency questionnaire was collected, and continues to be administered at four-year intervals (179). In 1998, approximately half of NHS II participants (n = 47,355) completed a detailed validated (180) 124-item FFQ on diet in high school. Response rates to NHS II questionnaires are 85 – 90% for each two-year cycle. The women were aged 33 – 52 years when filling out the FFQ on high school diet (179).

1.4.1.2 Diet in adolescence

Little is known on fish consumption in adolescence and the risk of breast cancer and currently available studies are US-based, where fish freqency of fish consumption is generally reported as low (181, 182) . A nested case-control study from the NHS, with 843 eligible cases, found no association for fish consumption between ages 12 – 18 years (183). A prospective study from the NHS II, with 13 years of follow-up, also found no association for adolescent fish consumption and breast cancer risk for approximately 44,000 pre- and postmenopausal women (184). Another US-based case-control study on approximately 3,000 women found no association for fish consumption at ages 12 – 13 years in premonopausal women aged 45 and younger (185).

Some studies on vitamin D exposure in adolescence have suggested a positive association with breast cancer risk. A Canadian case-control study found that breast cancer risk was reduced for women who had frequent sun exposure, engaged in outdoor activities, used cod liver oil and drank milk frequently, all used as a proxy for vitamin D exposure. This association was strongest when the exposure took place between ages 10 – 19 years (186). As for fish consumption, no association on adolescence vitamin D intake and breast cancer was observed in the nested case-control study from NHS (183). Based on approximately 29,000 participants in the NHS II who returned a FFQ in 1998, women in the highest quintile of vitamin D intake between ages 12 – 18 years had a 21% lower risk (95% CI 0.61, 1.01) of proliferative benign breast disease when compared with the lowest quintile

(187). Using the same data, no association was observed for total adolescent polyunsaturated fat consumption and premenopausal breast cancer risk (188). To the best of knowledge, no studies have been conducted particularly on adolescence n-3 PUFA consumption and breast cancer risk.

Two studies on meat intake in adolescence and breast cancer risk have been conducted in NHS II. The first one included 39,268 premenopausal women who also completed the FFQ in 1998. After 7 years of follow-up, a marginal positive association was observed for the highest quintile of red meat intake for premenopausal breast cancer (1.34, 95% CI, 0.94, 1.89) along with 20% increased risk for every additional 100 g of daily red meat consumption (189). Using the same data from the NHS II, but this time with 44,231 participants, women in the highest quintile of total red meat consumption in adolescence were at 43% higher risk of premenopausal breast cancer after 13 years of follow-up. No association was observed for postmenopausal women. Replacement of one serving/day of total red meat with one serving of combination of poultry, fish, legumes, and nuts was associated with a 15% lower risk of total breast cancer and 23% lower risk of premenopausal breast cancer (184).

Two studies on adolescent milk consumption and breast cancer risk have been conducted in NHS II. After 7 years of follow-up, no association was observed between either total dairy or milk consumption and breast cancer among the 39,268 premenopausal women who were included (188). Similarly, no association between total dairy consumption and total breast cancer was found in a more recent study where approximately 44,000 women were included and prospectively followed for 17 years (190).

Results from the Boyd-Orr cohort, with 65 years of follow-up, found no association for dairy consumption and breast cancer risk (191) and neither did an American case-control study from 1986 (185).

Very few studies on early life consumption of whole grains and breast cancer are currently available. During 15 years of follow-up among approximately 44,000 participants in the NHS II, no association was observed for adolescent intake of either whole grains or foods containing refined grains, and premenopausal breast cancer. However, among women with dietary data available for both early adulthood (questionnaire completed in 1991) and adolescence, an inverse association for premenopausal breast cancer was observed for the highest quintile of combined adolescent and early adulthood intake of whole grains. However, this association was no longer significant after further adjustment for fiber intake (192). Another study

from the NHS II showed that high intake of dietary fiber in adolescence was inversely associated with lower breast cancer risk (HR 0.84; 95% CI 0.70, 1.01). This risk reduction became 25% for women with high intake of fiber in both adolescence and early adult life (193).

A Canadian case-control found that higher phytoestrogen intake (both isoflavones and lignans) during adolescence was associated with 30% reduced breast cancer risk (194). Soy is rich in isoflavone and an inverse association for soy consumption in adolescence and breast cancer has been observed in some studies, although mainly among Asian women (195, 196).

To the best of knowledge, only two studies have been conducted on dietary pattern in adolescence and breast cancer, both from NHS II. In the former one, the association between adolescent dietary patterns and a diet quality index, the Alternative Healthy Eating Index (AHEI) and breast cancer was examined among women who completed a 124-item FFQ about their high-school diet. A marginal inverse association was observed between the prudent dietary pattern and premenopausal breast cancer. No association was observed between the "Western" pattern or the "fast-food" pattern. Results were similar for each of these patterns when both premenopausal and postmenopausal breast cancer were considered together (197). The second study investigated the association between an adolescent and early adulthood inflammatory dietary pattern and breast cancer. The inflammatory dietary pattern was identified by higher intake of sugar-sweetened and diet soft drinks, refined grains, red and processed meat, margarine, corn and other vegetables, fish and lower intake of green leafy vegetables, cruciferous vegetables and coffee. Inflammation dietary pattern in adolescence and early adulthood was associated with 35% and 41% increased incidence of premenopausal breast cancer, respectively. This association was not observed for postmenopausal breast cancer (198).

To sum up, studies on adolescent diet are too few to draw any firm conclusion from. However, similar with diet in adulthood, epidemiological data indicate that high consumption of red meat may increase premenopausal breast cancer risk while persistent consumption of whole grains and fiber may reduce the breast cancer risk. For both adolescence and adulthood, no strong association has been found for fish consumption. The protective effect observed for adult dairy consumption has not been visible in studies on adolescents. More studies are needed on adolescent diet and breast cancer, particularly on the postmenopausal type.

1.4.2 Growth rate in puberty

Despite inconclusive outcomes on studies on diet and cancer, effects of diet can also be mediated through rate of growth (4, 199). Indeed, adult height, a well established risk factor for breast cancer and a marker of linear growth, is mainly determined by inheritance and rate of growth during developmental phases like fetal, childhood and puberty (4).

Puberty usually starts around age 12 for girls and age 14 for boys and during this period, the hypothalamic pituitary ovarian axis regulates production of ovarian hormones, including estrogen and progesterone, who generally associated with the development and growth of normal breasts but are also risk factors for breast cancer (200-203). This is followed by increase in serum levels of growth hormone (GH) and IGF-1, or insulin like growth factor 1. GH is produced in the anterior pituitary gland and then released into the blood stream where it stimulates the liver to produce IGF-1, that in return, stimulates growth in almost every cell in the body (204). During puberty the levels of GH can triple (200), and there is high correlation between growth rate during puberty and increase of serum IGF-1 levels (205).

High levels of IGF-1 have also been linked with increased risk of breast cancer (114-116) and it is hypothesized that these effects might somewhat be mediated through diet (206). It is known that adequate supply of both energy and protein is essential for the maintenance of IGF-1 production (207) and as stated earlier in the thesis, high intake of dairy and milk has been associated with higher levels of IGF-1 (112, 208, 209). High consumption of energy and protein have also been linked with higher levels of IGF-1 (209). As mechanism of growth is controlled by similar hormonal and growth factor signaling pathways as breast cancer development the intensity of the height growth during puberty might be of importance regarding the risk of breast cancer.

Studies on growth rate and breast cancer that are based on actual height measurements are sparse but have suggested a positive association for rate of growth and breast cancer. In a British birth cohort study of approximately 2,500 women, a height increase of one standard deviation (SD) between ages 11 – 15 years was associated with 29% increased risk of breast cancer, and risk estimates for 1 SD between age 7 – 11 years indicated 17% increased risk of breast cancer. No association was observed for height increase from age 15 to adult height (measured at age 36) (210), possibly as women had already reached their adult height. In a study on approximately

117,000 Danish women where early life measurement from school records were used, each 5 cm increase in height from age 8-14 years was associated with 17% increased risk of breast cancer (211). Another Danish study, where school records were also used found that tallness at age 7 and 13 years was positively associated with breast cancer in a cohort of approximately 13,500 women. This association was independent of high proportion of breast density (212). In a Finnish study on 3,447 women born 1924 – 1933, women with high stature at ages 7 – 15 years had increased risk of developing breast cancer later. However, no association was observed for growth velocity during the same time period (213). In the American Growing Up Today Study (GUTS), girls with the most rapid growth between ages 9 to 15 years had an increased risk of benign breast disease, a risk factor for breast cancer later in life (214).

Similar results were observed for studies where early life anthropometric factors were estimated. In the NHS cohort (n = 65,000), women with the highest estimated peak height velocity (> 8.9 cm per year) had 31% increased risk for premenopausal breast cancer and 40% for postmenopausal, when compared with those in the lowest quintile (≤ 7.6 cm per year). Peak height velocity was estimated using age at menarche and adiposity at age 10, assessed with pictograms. These associations persisted after controlling for age at the birth of a first child, parity, adult adiposity, and age at menopause (215). Among women who participated in the Minnesota Breast Cancer Family Study cohort, there was an positive association for self-reported height at ages 7, 12 and 18 and breast cancer (216).

Early life body fatness is also of importance for breast cancer risk. In a review from 2009, where 45 studies were identified, majority of studies reported that women with greater BMI at age 18, or among those who perceived their body fat higher relative to others during childhood, were at approximately 20 – 50% decreased risk of breast cancer. This association was more predominant for premenopausal breast cancer (217). Later studies have confirmed this finding (212, 218-220) and the CUP concluded that body fatness in young adulthood (18 – 30 years) protects women against both pre- and postmenopausal breast cancer (4). The mechanism for the inverse association between early life body fatness and breast cancer risk are not completely understood, but might involve lower levels of sex hormones in obese young women (221), effects of adipose tissue derived estrogens on breast differentiation (222) and lower serum concentration of IGF-1 (114).

Based on both estimated and actual measurements, growth rate, height and weight in early life may be associated with breast cancer risk later in life, although the mechanism is not all clear.

1.4.2.1 Prostate cancer

Prostate cancer, the most frequently diagnosed cancer in men, is also hormonal-dependent cancer and has some underlying biological similarities with breast cancer (223). The most established risk factors for this cancer are age, family history, race and being overweight or obese (224). As studies on growth rate and prostate cancer are currently lacking, analysis on prostate cancer and growth rate will also be conducted. Previous studies using the same data as current thesis found that rural residency in the first 20 years of life was marginally associated with increased risk of advanced prostate cancer, particularly among men born before 1920. In addition, daily milk consumption in adolescence was associated with a 3-fold risk of advanced prostate cancer (225). High intake of salted or smoked fish in early and later life was also found to be associated with a 2-fold increased risk of advanced prostate cancer while fish oil consumption in later life reduced this risk (226). Finally, daily rye bread consumption in adolescence was associated with a decreased risk of prostate cancer diagnosis, particularly advanced disease (227).

1.5 Residence based dietary habits in Iceland in the early 20th century

The diet of Icelanders in the early 20th century was largely limited to locally produced food, such as fish from the sea and livestock at the farm, in addition to imported grain, mostly rye. The most common characteristics of traditional Icelandic diet around 1900, according to food consumption statistics, were very high consumption of fish and dairy. The fish included fresh, dried, and salted fish, and based on food supply statistics, the average consumption was estimated to be as high as 430 kg/male equivalents/year which translates to around 650g day. Dairy consumption consisted mostly of milk, butter, and especially the cheese-like product skyr and total average consumption was 1.4 kg/male equivalent/day. Fruits and vegetables were very rare, and no grains were grown in the country. All cereals, mostly rye but also barley and oats were imported from Denmark. Rye bread was a common food in both rural areas and on the coast and by the turn of the 20th century, the average consumption of rye was estimated as high as a 175 g/day/male equivalent, based on import statistics. Rye was also used in

porridge and mixing in blood and liver sausages. Barley and oats were also important grains used in porridge while wheat was almost unknown. Fish liver oil, usually from cod liver fish oil, was widely used both as a condiment and for frying and valued as a health remedy and given to children and adults and is still commonly practiced widely. The use of fish oil was most common in coastal areas, especially in the West fjords(228, 229). This diet persisted to some extent until the middle of the 20th century, even though the diet became more varied and less dependent of fish, dairy and rye.

However, until the mid-20th century, most of Iceland had very limited infrastructure that yielded in a relative isolation of many regions. Consequently, there were differences in food access and considerable variability in dietary habits between residence areas in Iceland in early and mid-20th century. In 1939, Professor Júlíus Sigurjónsson studied dietary habits and food availability among 56 households around the country on behalf of the Icelandic Nutrition Council. Dietary habits were studied in four coastal villages, five different rural areas, and the capital area Reykjavík. On average, each home submitted 12 weekly reports, or one report for one week each month. Included were all the main types of food in Iceland, and the daily quantity consumed of each food in the household was recorded in a blank column on the form. The form had one column for each day of the week. As dietary information was based on the whole household rather than individuals, calculations on nutrient intake and food quantities was done using the adult male-equivalents for the household. Males aged 14 – 59, doing light work were given an index of 1.0, adult women were given an index of 0.8 and children in the household got an index according to their age. Results were based on adult male diet equivalents. The main results from the study were that residence in coastal villages showed pattern of high fish intake and low milk and meat intake compared to rural areas and Reykjavik, see table 1. Furthermore, consumption of milk was four times higher in rural areas compared to coastal villages and twice that of the Reykjavik area (230).

Residence	Milk	Fish	Meat	Rye	Butter	Fruit	Vegetables
Reykjavik	**625**	**213**	**133**	**78**	**23**	**9**	**6**
Coastal villages	**356**	**354**	**106**	**98**	**3**	**5**	**1**
Rural areas	**1367**	**140**	**177**	**113**	**21**	**3**	**6**

Table 1. Example of adult male diet in 1939, g/day (0.8 for women)(230)

1.6 Study motivation

In 1967, the Icelandic Heart Association initiated the Reykjavik Study, a population based prospective cohort where all men and women living in the capital area in December 1966 and born 1907 – 1935 were identified and invited to participate in the study (N = 30,795). Along with detailed health related information, participants also provided information on early life residence (231). A subgroup of participants was later enrolled in the AGES-Reykjavik study in 2002, with the aim of studying the process of aging. At study entry, the participants (n = 5,764) completed a questionnaire on dietary habits in youth, midlife and at present (232). In addition, the nationwide Icelandic Cancer Registry was established in 1954 in Iceland (233).

As studying early life dietary exposures can be challenging due to lack of variation in intake patterns, the need for follow-up during many decades and the possibility of recall bias among participants (5) this setting gives an exceptional opportunity to examine the effect of diet in adolescence, by using early life residence as a proxy for dietary habits, and breast cancer risk later in life. In addition, information from the AGES-Reykjavik study provides an opportunity to study dietary habits across the life span and the Reykjavik Study also holds information on height and weight from age 8 – 13 years for a portion of the participants.

The findings of this study will not only shed a light on the importance of the adolescent period, in terms of diet and growth rate, for subsequent breast cancer development but also provide valuable knowledge on how dietary habits across the lifespan can affect breast cancer risk later in life. This work is an important contribution to the knowledgebase on dietary causes of cancer and will possibly lay foundation for early dietary intervention.

2 Aims

The overarching aim of the thesis was to advance knowledge on the influence of early life growth rate and lifelong dietary habits on breast cancer risk later in life. The main emphasis of the study was on the adolescence period where the focus point was on food items that varied by residential areas in the early 20th century in Iceland and are of known relevance for breast cancer development. To further investigate how early life exposures, affect breast cancer risk, the effects of growth rate in childhood and adolescence was also explored.

2.1 Paper I

Using the population-based Reykjavik Study data, the aim was to determine if different residence (Reykjavik area, coastal village or rural/farming area) in early life, used a as a proxy for diet, is associated with the risk of breast cancer risk in later life. Data from the AGES-Reykjavik sub cohort was also used to further explore the association between consumption of fish and fish liver oil and breast cancer later in life.

2.2 Paper II

Using the sub-cohort AGES-Reykjavik study, the aim was to investigate the association between high consumption of meat, milk and whole-grain products, in early, midlife and late life and breast cancer risk later in life.

2.3 Paper III

Using a unique growth data from the Reykjavik Study, the aim of this study was to explore the association between growth rate in childhood (age 8 – 13 years) and adolescence (age 13 – 15 years) and risk of breast cancer. The secondary aim was to explore whether height, weight and BMI, measured at ages 8, 13 and in adulthood were associated with risk of breast cancer.

To further explore the effect of growth on hormonal dependent cancers, the same analyses were executed for prostate cancer.

3 Materials and methods

3.1 Study population

3.1.1 Reykjavik Study - Paper I and III

The Reykjavik Study is a population-based prospective cohort that was initiated in 1967 by the Icelandic Heart Association. The main objective of the Reykjavik Study was to examine risk factors for cardiovascular diseases. All men and women born between 1907 and 1935 and were living in the Reykjavik metropolitan area in December 1966 were identified (n = 30,795) and a random sample of 27,281 people was invited to participate. A total of 19,381 people entered the study in six stages from 1967 until 1996 (71% response rate). The Reykjavik Study included detailed medical examination and health related questionnaires, including questions on place of birth and residence history (231, 234, 235). For this study (n = 10,049), only data from the first clinical visit at the study entry was used. Women who were diagnosed with breast cancer prior to entry (n = 139) and for who follow-up was incomplete (n = 6) were excluded. Women who resided in a combination of coastal village and rural area and women without available information on residence were also excluded (n = 564). This left 9,340 women the analysis.

In 1929, the two main elementary schools in Reykjavik started recording yearly height and weight measurements of their students. Growth rate analyses include participants of the Reykjavik Study who had information on both; 1) height at age 8 and 13 years, and adult height at entry to Reykjavik Study and 2) weight at ages 8 and 13 years. Available data for the height growth rate analysis between ages 8 – 13 years included 702 women and 689 men. The analysis between age 13 until adult height was reached consisted of 991 women and 1,067 men. For simplification, the defined period between 8 – 13 years in our study will be referred to as childhood while the period between age 13 until adult height is reached will be referred to as adolescence.

3.1.2 The AGES-Reykjavik Study - Paper I and II

The Age, Gene/Environment Susceptibility–Reykjavik Study (AGES-Reykjavik Study), a sub-cohort of the Reykjavik Study was initiated in March

2002. The main objectives of the study were to explore how genetic, behavioral, and environmental risk factors are associated with complex traits and diseases that manifest later in life. A total of 11,549 Reykjavik Study cohort members were still alive in 2002 and 8,030 individuals were randomly chosen to participate. By February 2006, when the study ended, 5,764 (71.8%) had entered the study, thereof 3,326 women, born 1908 – 1935 (232). For all dietary analysis, women who were diagnosed with breast cancer prior to AGES-Reykjavik Study entry (n = 196) were excluded, leaving 3,130 women in the study. Our analyses included individuals responding to the dietary questions, ranging from 2,854 - 2,882 in the adolescent period, from 2,864 - 2,879 in the midlife period, and 2,865 - 2,883 in the late life period, depending on the question.

3.2 Exposure classification

3.2.1 Residence – Paper I

The aim of paper I was to determine if different residence (Reykjavik area (or capital area), coastal village or rural/farming area) in early life, used a as a proxy for diet, affects the risk of breast cancer diagnosis.

All participants of the Reykjavik Study provided information on residence of 5 years or more from birth throughout their lifetime. Although all participants were living in the greater Reykjavik area at the time of recruitment of the study, approximately two thirds of participants were born and raised outside of the capital area before moving there. From the data collected, a total of 245 communities were identified. For the purpose of this study, every non-urban community was classified as either rural area or coastal village or combination of both using the 1974 National Land Survey of Iceland and the Icelandic Historical Statistics on population density by region in 1940 and fish catch by place of processing in 1942. Rural areas were classified areas away from the sea or areas by the sea which had no fishing industry and defined as densely populated. On the other hand, coastal villages were classified as areas by the sea with fishing industry and classified as densely populated (225, 236).

3.2.2 Dietary habits in adolescence, midlife and later life – Paper I and II

Using the sub-cohort AGES-Reykjavik Study, the aim was to investigate whether high consumption of fish, fish oil, meat, milk and whole-grain

products, in early, midlife and late life, affects breast cancer risk later in life.

In the AGES-Reykjavik Study, participants provided information on dietary habits in adolescence (between the ages 14 and 19), midlife (between the ages 40 and 50) and intake at study entry (between ages 66 and 96) using a food frequency questionnaire (FFQ). The questions in the FFQ represented common food and food groups from these periods. The section on diet in adolescence included 16 questions on food items such as fish (total fish intake, fish in a salad or as topping and salted or smoked fish intake) fish oil, meat (total meat intake and salted or smoked meat), milk and milk products, fruit, vegetables, rye bread and flatbread, blood or liver sausage, oatmeal and potatoes. The midlife section additionally included a question on whole wheat bread, but it was not common in the Icelandic diet until the middle of the 20th century. The late life section also had additional questions on cake, cookies, fruit juice, soft drinks, pastry, candy tea and coffee. In total, the FFQ included 63 questions, 16 from the adolescent period, 17 from the midlife period, and 30 from the late life period (237).

The participants reported frequency of intake during each period. In general, for fish, fish in salad or as topping on bread, meat, milk and milk products, fruit, vegetables, rye bread and flatbread, blood or liver sausage, oatmeal and muesli, potatoes, and whole wheat bread, seven response were available; 1) never 2) less than once a week 3) 1 – 2 times a week 4) 3 – 4 times a week, 5) 5 – 6 times a week, 6) daily, and 7) more than once a day. For fish oil the categories were the same except for the last option. The categories for salted or smoked meat and salted or smoked fish were;1) never 2) less than once a month 3) 1 – 3 times a month 4) 1 – 2 times a week 5) 3 – 6 times a week, and 6) daily or more often.

3.2.2.1 Fish and fish oil consumption - Paper I

The FFQ included three questions on fish consumption, 1) fish in salad or as topping on bread 2) fish as a main meal and 3) salted or smoked fish (included in the question on main meal). Weekly intake of fish as a main meal and fish in salad or as topping on bread was converted and combined into total fish portions per week (p/w) and then into to daily intake. The estimated average portion for a main meal (150g) was based on nationwide survey (238). Therefore, never was converted to zero per day, less than once a week to 0.07 per day, 1 – 2 times per week to 0.21 per day, 3 – 4 times per week to 0.5 per day, 5 – 6 times per week to 0.79 per day, daily to 1 per day, and more than once a day to 1.5 per day. Fish in salad or as topping on bread was estimated to be 40 g and the number of portions of fish in salad or

as topping of a fish meal was therefore calculated as 0.27 (40/150). The daily estimate of fish in salad or as topping on bread was therefore multiplied with 0.27 and computed with the daily estimated intake of fish meals. The total outcome was multiplied with seven to get total portions per week (239) .

To observe the effect of very high intake of fish and retain sufficient proportions for meaningful analysis, total fish consumption in adolescence was divided into three groups for both periods; high (> 4 portions p/w), moderate (>2 – 4 portions p/w) or low (≤ 2 portions p/w). For adolescence, the low intake group represented 49%, the medium group 11% and the high group contained 40%. Only 13 participants (0.5%) never ate fish or fish topping on bread in adolescence. To maintain coherency, same categorization was used for midlife and later life. The proportion was 27% in the highest category, 62% in the middle one and 11% in the lowest. Here, only seven participants, or 0.2% never consumed fish. For later life the proportion was 15% for the highest category, 57% for the middle one and 28% for the lowest one. The FFQ did not contain questions on the type of fish. However, cod and haddock were the fish most commonly consumed in the early 20th century as well as today (238).

Responses for fish oil was divided into never and daily or less. For adolescence, the proportion is 43% for never consumers and 57% for daily and less. For midlife this proportion was 33% vs. 67% and 27% vs. 73% for later life.

3.2.2.2 Meat, milk and wholegrain consumption - Paper II

Two separate questions were asked regarding meat consumption in all time periods. One included total consumption of meat and ground meat as a meal (hereafter referred to as meat). The other question (included in the total meat consumption) concerned intake of corned meat, corned meat sausage, or any kind of salted/smoked meat (hereafter referred to as salted or smoked meat). For all periods, meat consumption was divided into 2 times or less per week and 3 times or more per week. For the adolescence period, the proportion was 33% vs. 67% while for the midlife period these proportions were 42% vs. 58% and same for the late life consumption. For salted or smoked meat, low intake was defined as 3 times per month or less and high as once per week or more for both periods. The proportions for adolescence was 67% vs. 33% and 77% vs. 23% in midlife. In late life, the proportion was 97% vs. 3% and therefore, the categories were divided differently in the analysis or for late life or, less than once a month vs. once a month or more or 75% vs. 25%.

For all time periods, information on milk consumption included frequency of intake of milk and milk products (hereafter referred to as milk). The participants predominantly consumed whole, unpasteurized cow´s milk in early life, particularly in rural areas in the early 20th century. During the study period, only one type of low-fat milk has been fortified with 0.38 ug of vitamin D per 100 grams of milk, or since 1990s. Consumption of milk was divided into less than daily vs. daily or more. For adolescence, these proportions were 24% vs. 76%, 44% vs. 56% for midlife period and 53% vs. 47%.

Rye bread consumption was assessed by one question on intake of rye bread and flatbread made of rye (hereafter referred to as rye bread). Consumption of rye bread was divided into less than daily vs. daily or more. The proportions for the adolescence period were 49% vs. 51%, 66% vs. 34% in the midlife period and 75% vs. 25% for late life. For midlife, the question on oatmeal also included muesli, but will be referred to as oatmeal in both periods. For both periods, consumption of oatmeal was divided into low (4 times a week or less) and high (5 times a week or more). The proportions were 62% vs. 38% for the adolescence period and 76% vs. 24% for the midlife. In late life this was 65% vs. 35%. Consumption of whole wheat bread in Iceland did not become common until the middle of the 20th century and was therefore only included in the midlife and late life sections of the FFQ. The division for whole wheat bread was less than daily (43%) and daily and more (57%) and for late life this division was 65% for less than daily and 35% for more than daily.

3.2.3 Validation of the AGES-FFQ

The FFQ designed for the AGES-Reykjavik cohort has been validated for midlife and current dietary habits. The adolescent intake cannot be directly validated as data on individual food intake from this period is not available. However, the data from the AGES-Reykjavik study on adolescence diet shows similar distribution of intake according to residence in rural and coastal fishing areas, as observed in the household survey from 1939 (225, 230).

For the midlife validation, validity was assessed by comparing answers from the FFQ from the AGES-Reykjavik study to dietary data from the 1990 Icelandic National Dietary Survey. A total of 107 women who had participated in the national survey in 1990 were recruited to answer the midlife AGES FFQ in 2008 – 2009. Main results were that questions on fish as a meal, meat and milk were found to be within acceptable range ($r = 0.26 – 29$) to rank individuals according to intake. Correlation between questions on rye

bread and flat bread and whole wheat bread was low, or r = 0.07 and 0.05, respectively. Fish liver oil was ranked highest, or r = 0.56. Validation of intake of fish in a salad or as topping on bread, salted or smoked meat, and salted or smoked fish could not be assessed as information from the two methods were not comparable (237).

For late life dietary habits, validity was assessed by comparing answers from the FFQ to weighed food records. A total of 128 participants from the IceProQualita study, aged 65 years and older, completed the AGES FFQ and subsequently filled out a 3-day weighed food record within 2 weeks (240, 241). Here, all questions were found acceptable to rank individuals according to intake (r = 0.28 - 0.48), except for meat (r = 0.11) and fish meal (r = -0.02). As for midlife, the validity of intake of salted or smoked meat and salted or smoked fish could not be assessed since methods could not be compared (241).

3.2.4 Growth rate – Paper III

The aim of this study was to explore the association of rate of growth height in childhood (age 8 – 13 years) and adolescence (age 13 – 15 years) with the risk of breast cancer.

Childhood height and weight measured at yearly examinations in two schools in Reykjavik were documented by school health professionals. These growth measures were later stored at the National Archives of Iceland and later linked with available participants in the Reykjavik Study (242). Adult height was measured at Reykjavik Study entry and recorded to the nearest 0.5 cm without shoes.

Growth rate was defined as the difference between two height measurements divided by the time between them in years. Growth velocity (velocity = Δx/time) per year was calculated for height (cm), between ages 8 – 13 years and from age 13 until adult height. Women were estimated to have reached attained adult height at age 15, and for men this age was 17 (243, 244). All growth velocity estimates were categorized into tertiles and will be referred to as low, medium and high.

3.3 Follow-up and ascertainment of outcome

For papers I and II, participants were followed from their entry into the study until their diagnosis of breast cancer, death, or the end of the observation period. In the residence analysis (paper I), participants in the Reykjavik Study

entered the study between the years 1967 and 1996 and follow-up ended on December 31st, 2013. For the fish and fish liver oil analyses (paper I), participants entered the AGES-Reykjavik Study between the years 2002 – 2006 and follow-up ended December 31st, 2013. For the analyses on meat, milk and whole grain products (paper II), also conducted on participants in the AGES-Reykjavik cohort, the follow-up ended December 31st, 2014. For paper III, the growth rate analyses, participants with height measurement at age 8 and at age 13 were followed from when the measurement took place until December 31st, 2015.

Breast cancer diagnoses ascertained through the nationwide Icelandic Cancer Registry (233). Information on the cause of death was obtained from the Directorate of Health. Due to Iceland's computerized national roster and each person's unique personal identification numbers, follow-up was virtually complete (245).

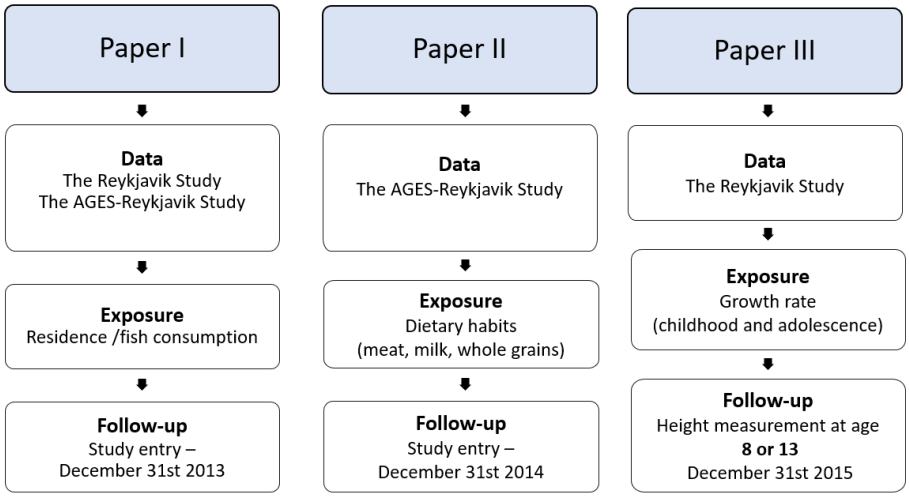

Figure 3. Overview of data, exposures and follow-up for paper I, II and III

3.4 Covariate assessment and statistical analysis

3.4.1 Residence – Paper I

As before, the major aim of paper I was to determine if different residence (Reykjavik area (or capital area), coastal village or rural/farming area) in early life, used a as a proxy for diet, affects the risk of breast cancer diagnosis.

From the Reykjavik Study we retrieved baseline information on age at entry (continuous), height (continuous), year of birth (1908 – 1914 , 1915 –

1919 , 1920 – 1924, 1925 – 1929 , 1930 – 1935), education (primary, secondary, college/university), BMI (continuous), parity (no children, 1 – 2, 3 and more), and physical activity (no, yes).

As data on reproductive history were generally not collected in the Reykjavik Study, information on potential reproductive confounders for breast cancer was obtained from the Cancer Detection Clinic Cohort (CDC cohort), established 1964. This cohort includes data collected as part of nationwide, centralized cervical- and breast cancer screening programs. All Icelandic women aged 20 – 69 years are invited to visit the CDC every other year for screening cancer of the cervix (from the age of 20) and breast (from 40 years of age). When data from the two cohorts were linked, about 91% of women in the Reykjavik Study had attended the Cancer Detection Clinic at least once. This was to be expected, as it has been shown previously that women born in the first decades of the 20th century are not well represented in the CDC databank (15). From the CDC cohort we primarily retrieved information on age at menarche and age at first birth. Information on age at menarche had 933 missing values and information on age at first birth had 924 missing values, which we were able to reduce to 683 by adding information on parity from the Reykjavik Study. We also evaluated information on the total months of breastfeeding (never, 1 – 6 months, 7 months and more), the use of hormonal replacement therapy (HRT) (never, ever) and use of oral contraceptives (never, ever).

In attempt to compensate for the missing values for the variables "age at menarche" (10%) and “age at first birth” (7%) a separate sensitivity analysis was conducted for the residence analysis. Here, a multiple imputation was used to predict missing values for age at menarche, by mean matching after stratifying the variables: age at entry, birth cohort and education. In this analysis, missing values for “age at first birth” were included in the analysis as a special category.

Cox proportional hazard regression models were used to calculate hazard ratios (HR) and 95% confidence intervals (95 % CI) for the diagnosis of breast cancer by residence (coastal village or rural area) in early life. Residence in the capital area was the reference category. In line with WHO´s definition of the adolescence period (246), we also stratified our data into three categories, based on women’s age when they moved away from their first residence in rural areas and coastal villages: 1) age 11 and younger, 2) between the ages of 12 and 19, and 3) at age 20 and older. Residence in the capital area was also the reference group. The first model was adjusted for

age (continuous) at entry into the Reykjavik Study. The second model was additionally adjusted for birth cohort, education, parity, physical activity, BMI and height, categorized as described in table 1. The third model was additionally adjusted for age at menarche and age at first birth, obtained from the CDC cohort. Other variables from the CDC cohort were not included due to high number of missing values.

3.4.2 Dietary habits – Paper I and II

From the AGES-Reykjavik Study, information on potential confounders were mainly retrieved from a lifestyle questionnaire that participants completed at study entry. For all analysis in paper I and II , we evaluated information on age at entry (continuous), education (primary, secondary, college/university), age at menarche (continuous), age at first birth (none, age 24 and younger, 25 and older), family history of breast cancer (mother, sister and/or daughter ever diagnosed with breast cancer), hormonal replacement therapy (never, ever), use of oral contraceptive (never, ever), year of birth (1908 – 1919 , 1920 – 1924 , 1925 – 1929, 1930 – 1935) and physical activity in adolescence and midlife (never/rarely, occasionally, moderately/often). From the Reykjavik Study we retrieved values on body mass index (BMI) and height from the midlife period (both continuous). We also evaluated use of use of alcohol in midlife (never, ever) and late life (g/d), and information on first residence (capital area, coastal villages, rural area, combination of coastal villages and rural areas). Information on selected dietary covariates for each time period was retrieved from the AGES-FFQ.

. For all dietary analyses, in all time periods, Cox proportional hazard regression models were used to calculate HR and 95 % CI for incident breast cancer. For all analysis (fish, fish liver oil, milk, meat, salted and smoked meat, rye, oatmeal and whole wheat bread), women with lower consumption (referent) were compared with women with higher consumption. Only total fish consumption had three categories.

All dietary analyses were adjusted for age at entry, education, age at menarche, age at first birth, as well selected contemporary dietary covariates. For adolescence and midlife analysis, we used midlife BMI, collected at entry to the Reykjavik Study. We also adjusted the midlife and late life analysis for concurrent alcohol consumption. The analysis on fish and fish oil were also adjusted for family history of breast cancer. Other potential covariates were excluded as they did not alter any estimates. For the dietary analysis in paper II, some missing values of covariates were observed for age at first birth (n =

211), that was included as a special category in the analysis. The 21 missing values for BMI were replaced with the mean BMI value of the participants of the study or 25. The 177 missing values for age at menarche were replaced with the mean age of menarche in the cohort, or 14 years.

To assess the potential effects of longitudinal dietary habits on breast cancer risk we pooled consumption of each food item in adolescence and midlife into one variable with four categories; 1) low in both adolescence and midlife; 2) low in adolescence and high in midlife; 3) high in adolescence and low in midlife; and 4) high in both adolescence and midlife. For this analysis, the first category (low consumption in both periods) was used as a reference. Adjustments were made for same factors as described for the adolescent period. This analysis was conducted on food items investigated in paper II, or meat, smoked or salted meat, milk, rye bread and oatmeal.

3.4.3 Dietary pattern

Principal component analysis was used to identify dietary patterns from the AGES-FFQ, including all dietary data available. This method is data driven and forms new linear factors (dietary patterns) by reducing data dimension and grouping correlated variables (food intake). For each pattern, a new variable is created, ranking participants on their adherence to that particular pattern. Each variable/pattern was further divided into tertiles, or low, medium, and high adherence to each pattern. Cox proportional hazard regression was used to test association between adherence to adolescence, midlife and late life patterns and breast cancer risk, using the lowest tertile as a reference. For all time periods, adjustments were made for age at entry, BMI, education, age at menarche, and age at first child, using the same cut offs as previously described for individual exposures in adolescence and midlife.

For the rye bread, oatmeal and dietary pattern analyses in paper II, we also tested for trend in the hazard ratios for the first category, using polynomial contrasts.

3.4.4 Growth rate – Paper III

Here, the major aim of this study was to explore the association of rate of growth height in childhood (age 8 – 13 years) and adolescence (age 13 – 15 years) with the risk of breast and prostate cancer. The secondary aim was to explore whether height, weight and BMI measured at ages 8, 13 and in adulthood were associated with these cancers.

All analyses were adjusted for age at study entry (as a continuous variable). birth cohort (1915 – 1924, 1925 – 1929, 1930 – 1935), education (primary, secondary, college/university), and growth measurements at the beginning of the growth rate period. For example, for childhood growth rate between ages 8 – 13 years, adjustment was made for height at age 8 etc. In the second Cox model among women, additional adjustment was made for age at menarche (continuous). Missing information on age at menarche (n = 58) were replaced with the mean age at menarche (13.6 years) among women included in the adolescence analysis. The effects of further adjustment for adult height, physical activity and parity (women only) were also explored. The trend for HR for the categories relative to the first category was calculated using polynomial contrasts. The risk for height growth rate between age 8 until adult height was reached was also calculated, using same adjustments. For breast cancer, an analysis on adolescence growth rate stratified by birth cohort (1915 – 1924, 1925 – 1929, 1930 – 1935) was also conducted.

Cox proportional hazard regression models were used to calculate HR and 95% CI between growth rate and risk of breast and prostate cancer, using the lowest tertile as a reference category. A linear regression for average increase in growth rate per year in cm was also conducted. Cox regression models were used to calculate risk estimates for 1 increase in Z-score for height, weight and BMI at ages 8 and 13 using the same adjustments as above. These analyses were also conducted for height, weight and BMI collected at Reykjavik Study entry. The analysis on adult height was also adjusted for growth rate in adolescence among the 991 women with available information on growth rate, and interaction between adult height and growth rate in adolescence was also tested.

With information from the AGES-Reykjavik cohort, milk consumption in adolescence was evaluated between tertiles of growth rate in childhood and adolescence.

For coherency, all HR estimates in the thesis will be presented with one decimal in the text. However, as results are presented with two decimals in paper I, results from paper I will be presented with 2 decimals in the tables in the result chapter.

SPSS software, version 22.0 - 25.0 in was used in all statistical analyses (SPSS Inc., Chicago, Illinois; www.spss.com), along with R Core Team (2014). R: A language and environment for statistical computing. R

Foundation for Statistical Computing, Vienna, Austria; (http://www.R-project.org/).

The study protocol was approved by the Icelandic Ethical Review Board and the Icelandic Data Protection Authority (VSN -17-189/VSN b2007120014/03-7) (www.vsn.is).

4 Results

For the analysis on early life residence, a total of 9,340 women were included. Among them, the mean age at entry into the Reykjavik Study was 53.9 years (SD = 9.9). During an average follow-up of 27.3 years, 744 were diagnosed with breast cancer. The mean age at diagnosis was 69.7 years (SD = 11.0) and sixty-five women (9%) were diagnosed before the age of 55.

The dietary analyses were based on information from the AGES-Reykjavik, a sub-cohort from the Reykjavik Study. After exclusion of women with known breast cancer, 3130 women were left in the study, and the range of women with available dietary data was 2,854 – 2,883. Among them, the mean age at entry was 77.0 years (SD = 6.0). For paper I, the mean follow-up time was 8.2 years (SD = 3.1; from study entry through 2013) and during that time, 91 women were diagnosed with breast cancer and their mean age at diagnosis was 81.2 years (SD = 6.5). For the dietary analysis on meat, milk and whole grains, the mean follow-up time was 8.8 years (SD = 3.1; from study entry through 2014). During that time, 97 women were diagnosed with breast cancer, with mean age at diagnosis 81.4 years (SD = 6.5).

The mean age at study entry for the 991 women with available height measurements for the adolescence period was 49.4 years (SD 7.5). During a mean follow-up time of 66.1 years (SD 10.9), 117 women were diagnosed with breast cancer, with mean age at diagnosis 65.7 years (SD 12.3). For the childhood period, the mean age at entry was 48.7 years (SD 7.6) and during a mean follow-up time of 70 years 83 women were diagnosed with breast cancer, with a mean age of 65.4 years (SD 12.5).

4.1 Early life residence and fish consumption – Paper I

4.1.1 Early life residence

In the Reykjavik Study, all participants lived in the capital area at time of entry. However, as seen in table 2, only 37% were born and raised in the capital area; 35% were born and raised in a coastal village, and 28% were born and raised in a rural area. The average duration of first residence was longest in the capital area because most of the women born there never moved away. A higher proportion of women raised in the capital area had college/university degrees and exercised more frequently than women raised

in other areas. They were also taller than women in costal and rural areas. Women with first residence in rural areas had fewer children on average and were older when having their first child while women raised in coastal villages were on average older at menarche.

Table 2. Characteristics of participants according to location of first residence

Location of first residence **Reykjavik Study**	**Reykjavik area** n = 3474 (37%)		**Coastal village** n = 3262 (35%)		**Rural area** n = 2604 (28%)	
Mean, SD						
Duration of first residence	44.7	(15.3)	20.6	(11.5)	19.0	(7.8)
Height, cm,	163.7	(5.7)	162.6	(5.7)	162.5	(5.6)
Education	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Primary	1746	(50)	1766	(54)	1522	(58)
Secondary	1342	(39)	1288	(40)	900	(35)
College/University	386	(11)	208	(6)	182	(7)
Birth cohort						
1908 -1914	462	(13)	525	(16)	516	(20)
1915 -1919	526	(15)	592	(18)	548	(21)
1920 -1924	727	(21)	703	(22)	594	(23)
1925 -1929	774	(22)	726	(22)	501	(19)
1930 -1935	985	(28)	716	(22)	444	(17)
Children						
None	310	(9)	351	(11)	359	(14)
1-2	928	(27)	880	(27)	799	(31)
3 or more	2200	(64)	2004	(62)	1421	(55)
Regular physical activity	947	(27)	730	(22)	496	(19)
Age at menarche ≥ 14	1603	(46)	1680	(52)	1195	(46)
Age at first birth ≥ 25	1016	(29)	1003	(31)	1049	(40)
Dietary habits in adolescence **AGES-Reykjavik Study**	**Reykjavik area** n = 1159 (39%)		**Coastal village** n = 1017 (34%)		**Rural area** n = 783 (26%)	
5 times p/w or more	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Meat	13	(1)	17	(2)	67	(9)
Fish	411	(39)	440	(47)	224	(31)
Fish oil	482	(45)	410	(44)	232	(33)
Daily or more						
Milk	783	(74)	664	(71)	601	(84)
Rye bread	458	(43)	417	(45)	450	(64)
No intake						
Fruits	280	(26)	319	(34)	354	(50)
Vegetables	175	(17)	198	(21)	177	(25)
Once a week or more						
Salted or smoked fish	466	(44)	450	(48)	458	(65)
Salted or smoked meat	255	(24)	270	(29)	348	(49)
Marginal food deprivation	315	(27)	323	(32)	292	(37)

Participants were asked the question; did you always get enough to eat when you growing up? Four possibilities for answer were given; 1) always got more than enough 2) I got enough but no more, 3) Sometimes I did not get enough and 4) I was often hungry as a youngster. The last three answers were combined into one category i.e. marginal food deprivation.

Table 2 also presents the differences in consumption of common food items in adolescence by first residence. This analysis was conducted for participants who later entered the AGES-Reykjavik Study and had available information on first residence and dietary habits. When looking at consumption of meat stratified by early life residence, the proportion of women who consumed meat 5 times a week or more often was higher for women who grew up rurally or 9% vs. 2% for both the Reykjavik area and coastal villages. Similar pattern was observed for consumption of milk, rye bread and for salted or smoked meat, where high consumption of these items was most common in rural areas. On the other hand, high consumption of fish, or 5 times a more per week, was most commonly found in coastal villages or 47% vs. 33% in rural areas and 39% in Reykjavik. Yet, the highest proportion for salted or smoked fish was found in rural areas, or 65% vs. 48% in coastal villages and 44% in Reykjavik.

As seen in table 3, compared to women born and raised in the capital area, early life residence in coastal villages and rural areas were both weakly associated with a lower risk of breast cancer diagnosis, HR = 0.9 (95% CI 0.7, 1.0), and HR = 0.9 (95% CI 0.7, 1.1), respectively. When looking at the duration of residence from birth outside the capital area, we observed an inverse association for breast cancer diagnosis only among women who lived beyond the puberty period (at least to age 20 years or longer) in coastal villages, compared to women residing in the capital area (HR = 0.8, 95% CI 0.6, 1.0). No statistically significant associations were observed between any length of residence and breast cancer in the rural areas.

Table 3. Breast cancer risk by location of first residence and duration of stay

	No. of participants	Mean duration of residency, years (SD)	HR	95% CI
Location of first residence				
Reykjavik	3474	44.7 (15)	1.00	Ref.
Coastal village	3262	20.6 (11)	0.87	0.72, 1.04
Rural area	2604	19.0 (8)	0.88	0.73, 1.07
Age when moving away from coastal village				
1 – 11 y	523	7.3 (2)	1.11	0.80, 1.54
12 – 19 y	1253	16.1 (2)	0.88	0.69, 1.13
20 y and older	1484	29.1 (12)	0.78	0.61, 0.99
Age when moving away from rural area				
1 – 11 y	426	7.8 (2)	1.05	0.73, 1.51
12 – 19 y	881	16.0 (2)	0.85	0.64, 1.13
20 y and older	1293	24.6 (6)	0.85	0.67, 1.09

Sensitivity analyses

When imputed missing indicators were used for age at menarche and age at first child, the pooled risk estimates for women who lived beyond the puberty period in coastal villages attenuated slightly (HR = 0.83, 95% CI: 0.66, 1.04).

Changes in dietary habits

Table 4 shows how dietary habits among the participants have changed from adolescence to late life. The strongest correlation for those two time periods was found for rye bread ($p = 0.313$ $p < 0.001$). Meat consumption showed negative correlation, suggesting a shift in consumption between regional areas and/or social groups during this study period. Correlation of other food times was relatively low, suggesting changed dietary habits among participants. The proportion of women eating 2 portion or less of fish lowered from 49% in adolescence to 11% in midlife, although the proportion was 28% in late life. At the same time, high fish consumption declined from 40% having 4 portions per week in adolescence down to 15% for current diet. Only 3% reported salted or smoked fish once a week or more while this proportion was 50% in adolescence. Likewise, consumption of salted and smoked meat had also decreased or from 33% reporting consumption once a week down to 3% for current consumption. The correlation coefficients between food items in adolescence and midlife were in general higher, or between 0.38 – 0.50, highest for rye bread, although negative correlation (- 0.19 $p < 0.001$) was also observed for meat consumption (see paper II).

Table 4. Dietary habits of participants through different time periods

	Adolescence n (%)	Midlife n (%)	Late life n (%)	Spearman's ρ	*P*
Fish					
≤ 2 portions p/w	1425 (49)	326 (11)	808 (28)	0.080	<0.001
> 2 up to 4 portions p/w	311 (11)	1781 (62)	1638 (57)		
> 4 portions p/w	1146 (40)	772 (27)	437 (15)		
Salted/smoked fish					
3 times a month or less	1388 (49)	2017 (70)	2772 (97)	0.091	<0.001
Once p/w or more	1466 (51)	849 (30)	97 (3)		
Fish liver oil					
Never	1233 (43)	950 (33)	788 (27)	0.216	<0.001
Daily or less	1639 (57)	1920 (67)	2077 (73)		
Rye bread					
Less than daily	1452 (51)	1918 (67)	2152 (75)	0.313	<0.001
Daily or more	1406 (49)	957 (31)	715 (25)		
Milk and milk products					
Less thank daily	695 (24)	1247 (44)	1517 (53)	0.259	<0.001
Daily or more	2176 (76)	1617 (56)	1355 (47)		
Meat					
2 times or less p/w	958 (33)	1203 (42)	1199 (42)	-0.090	<0.001
3 times or more p/w	1908 (67)	1668 (58)	1679 (58)		
Salted/smoked meat					
3 times a month or less	1930 (67)	2210 (77)	2782 (97)	0.121	<0.001
Once or more p/w	932 (33)	654 (23)	95 (3)		
Oatmeal					
4 times or less p/w	1791 (63)	2175 (76)	1868 (65)	0.121	<0.001
5 times or more p/w	1065 (37)	690 (24)	1009 (35)		
Vegetables					
Never	585 (20)	163 (6)	122 (4)	0.172	<0.001
6 times p/w or less	2175 (76)	2485 (87)	2338 (81)		
Daily or more	105 (4)	213 (7)	410 (14)		
Fruit					
Never	1013 (35)	114 (4)	29 (1)	0.092	<0.001
6 times p/w or less	1784 (62)	2501 (87)	1719 (60)		
Daily or more	68 (3)	256 (9)	1127 (40)		

4.1.2 Fish consumption

Women with high fish consumption in adolescence were younger at first childbirth and had the highest consumption of meat, fish liver oil and salted fish, compared to women with lower fish consumption. Women with high intake of fish in midlife were more physically active, consumed less meat, less salted fish, less rye bread and less alcohol, drank more milk and were unlikely to have used OC, compared to women with lower fish intake in

midlife. Only small proportion, or 2% and 0.8% reported fish consumption as a meal as never or less than once a week in adolescence and midlife, respectively. This proportion was 2.5% for current consumption.

Table 5 presents HR and 95% CI for consumption of fish, fish oil and breast cancer in three time periods. For fish consumption, compared to women consuming two portions or less per week in adolescence, women with high consumption (> 4 portions p/w), showed lower risk of breast cancer, albeit not statistically significant (HR 0.7, 95% CI 0.4, 1.1). For the midlife period, high consumption of fish was significantly associated with lower risk of breast cancer (HR 0.5, 95% CI 0.2, 1.0). This was not observed for late life. When information on early life residence was added to the models, our estimates did not change considerably. No significant association was found between fish liver oil or salted fish and breast cancer risk in any time period, although consuming salted or smoked fish once a week or more was found marginally protective for breast cancer.

Table 5. Breast cancer risk by consumption of fish, fish liver oil and salted or smoked fish in adolescence, midlife and late life

	Adolescence		Midlife		Late life	
	HR	95% CI	HR	95% CI	HR	95% CI
Fish						
≤ 2 portions	1.00	Ref.	1.00	Ref.	1.00	Ref.
> 2 up to 4 portions	1.19	0.61, 2.31	0.81	0.45, 1.47	0.92	0.55, 1.51
> 4 portions	0.71	0.44, 1.13	0.46	0.22, 0.97	1.61	0.86, 3.00
Fish liver oil						
Never	1.00	Ref.	1.00	Ref.	1.00	Ref.
Daily or less	1.10	0.71, 1.69	0.96	0.62, 1.49	1.31	0.79, 2.16
Salted or smoked fish*						
3 times a month or less	1.00	Ref.	1.00	Ref.	1.00	Ref.
Once p/w or more	0.89	0.58, 1.38	0.58	0.33, 1.02	0.99	0.30, 3.23

*For late life, the categories were less than once a month vs. once a month or more

4.2 Consumption of meat, milk and whole grains – Paper II

The major characteristics of women with high consumption of meat in adolescence were older age at study entry, lower level of education, and older when having their first child, when compared with women with low consumption. They also consumed more salted or smoked meat and more salted and regular fish. Similar pattern was observed for women with high consumption of rye bread when compared with women with lower consumption, except they were also less physically active. Women with high milk consumption (daily or more often) had lower BMI in midlife, were more often raised in rural areas, and had more frequent consumption of cod liver oil, salted or smoked fish, total fish, meat, and oatmeal.

Table 6 presents HR and 95% CI for meat, milk and whole grain products breast cancer in three time periods. The reference group for all food items is the relevant lower consumption category. For adolescence, no statistically significant association was found for meat, salted and smoked meat and milk consumption, as seen in table 4. For whole grain products, a positive association was observed between high consumption of rye bread (daily or more often) in adolescence and breast cancer risk (HR 1.7, 95% CI 1.1, 2.6, P_{trend} = 0.043), compared with lower consumption (less than daily). No significant association was observed for oatmeal consumption. No difference was observed with further adjustment for early life residence.

For midlife, no significant association was observed for meat and milk consumption, although a marginally positive association was observed for high consumption (weekly or more) of salted and smoked meat (HR 1.6, 95% CI 1.0, 2.6) compared with women with low consumption (less than once a week). For whole grain products, no association was observed for whole wheat bread while a statistically significant positive association was observed for high consumption (more than daily) of rye bread (HR 1.8, 95% CI 1.1, 2.9, P_{trend} = 0.007) when compared with lower consumption (less than daily). No significant association was observed for oatmeal or whole wheat bread. No difference was observed for any of the risk estimates when early life residence was added to the model. No association was observed for analysis on late life.

Table 6. Breast cancer risk by dietary habits in adolescence, midlife and late life

	Adolescence		Midlife		Late life	
	HR	95% CI	HR	95% CI	HR	95% CI
Meat						
2 times or less p/w	1.0	Ref.	1.0	Ref.	1.0	Ref.
3 times or more p/w	1.3	0.8, 2.0	1.0	0.6, 1.4	1.3	0.8, 2.0
Salted or smoked meat*						
Three times a month or less	1.0	Ref.	1.0	Ref.	1.0	Ref.
Once p/w or more	1.4	0.9, 2.2	1.6	1.0, 2.6	1.1	0.3, 3.5
Rye bread						
Less than daily	1.0	Ref.	1.0	Ref.	1.0	Ref.
Daily or more	1.7	1.1, 2.6	1.8	1.1, 2.9	1.3	0.8, 2.1
Milk						
Less than daily	1.0	Ref.	1.0	Ref.	1.0	Ref.
Daily or more	0.7	0.4, 1.1	1.1	0.7, 1.7	0.9	0.6, 1.3
Oatmeal						
4 times or less p/w	1.0	Ref.	1.0	Ref.	1.0	Ref.
5 times or more p/w	0.7	0.5, 1.2	0.6	0.4, 1.1	1.2	0.8, 1.8
Whole wheat bread						
Less than daily			1.0	Ref.	1.0	Ref.
Daily or more			0.8	0.5, 1.3	1.0	0.6, 1.5

*For late life, the categories were less than once a month vs. once a month or more

Long-term consumption

A positive association was observed for combined high rye bread consumption in adolescence and midlife a (HR 2.1, 95% CI 1.2, 3.5, P_{trend} = 0.045), when low consumption in adolescence and midlife was used as a reference category. An inverse association was observed between breast cancer risk and high consumption of oatmeal in both adolescence and midlife (HR 0.4, 95% CI 0.2, 0.9, P_{trend} = 0.032). No association was observed for milk, meat, and smoked or salted meat.

4.3 Dietary pattern

Four dietary patterns were extracted for the adolescent and midlife period while six patterns for late life. Factor loading coefficients for those patterns are presented in table 7. For adolescence, the pattern containing rye bread, blood liver sausage, salted meat, salted fish, and oatmeal represents traditional Icelandic diet in the earlier half of the 20th century. High adherence to this pattern was not significantly associated with breast cancer risk (HR 1.3, 95% CI 0.8, 2.3). Marginal inverse association was observed for the highest adherence to a pattern of fish, blood/liver sausage, oatmeal, fish oil, and milk in adolescence (HR 0.6, 95% CI 0.4, 1.0). No association was observed for any pattern in midlife, including the dietary pattern including rye bread consumption.

Table 7. Factor loading coefficient for dietary pattern in adolescence, midlife and late life

Late life	FLC[a, b]	Midlife	FLC[a, b]	Adolescence	FLC[a, b]
Pattern 1		***Pattern 1***		***Pattern 1***	
Raw vegetables	0.69	Fish as a side	0.39	Bloodsausage	0.60
Boiled/fried vegetables	0.66	Blood/liver sausage	0.55	Salted meat	0.79
Fruits	0.65	Salted meat	0.79	Salted fish	0.73
Pure fruit juice	0.49	Salted fish	0.75	Rye bread	0.46
Fish as a side	0.32	***Pattern 2***		Oatmeal	0.38
Pattern 2		Fish as a side	0.58	Milk	0.40
Salted fish	0.71	Fruit	0.74	***Pattern 2***	
Salted meat	0.61	Oatmeal	0.32	Fish meal	-0.31
Blood sausage	0.56	Vegetables	0.77	Fish as a side	0.64
Fish as a side	0.44	Fish oil	0.43	Fruit	0.76
Pattern 3		***Pattern 3***		Vegetables	0.76
Cultured milk products	0.60	Potatoes	0.66	***Pattern 3***	
Milk	0.54	Rye bread	0.38	Fish meal	0.34
Oatmeal/muesli	0.46	Whole bread	0.63	Blood sausage	0.33
Rye bread	0.44	Milk	0.51	Oatmeal	0.63
Fish oil	0.48	***Pattern 4***		Fish oil	0.74
Pattern 4		Meat	-0.73	Milk	0.31
Candy	0.78	Fish meal	0.60	***Pattern 4***	
Cookies/cakes/pastry	0.70	Blood sausage	0.33	Meat	0.73
Sweetened juice/carbonated beverages	0.58	Rye bread	0.32	Fish meal	0.58
Pattern 5		Oatmeal	0.41	Potatoes	0.48
Fish meal	0.73	Fish oil	0.31		
Potatoes	0.69				
Whole wheat bread	0.32				
Pattern 6					
Meat meal	0.77				
Salted meat	0.36				
Oatmeal/muesli	-0.32				
Fish meal	-0.36				

[a] Factor loading coefficient (FLC) are correlation coefficients between food groups and the extracted factor.

[b] Food groups with factor loading between 0.30 and -0.30 are not listed.

For late life, high adherence to the sweet pattern, characterized by consumption of candy, cookies, cake, pastry, sweetened juice and carbonated beverages was associated with increased risk of breast cancer (HR 1.6, 95% CI 1.0, 2.7). For pattern 6, characterized by high consumption of meat, fish and milk, women in the second tertile were found at increased risk of breast cancer (HR 2.0, 95% CI 1.2, 3.3) while the third tertile was not of significance (HR 1.1, 95% CI 1.2, 3.3)

4.4 Growth rate – Paper III

When looking at major characterists of women in the highest teritile of growth in the adolescence period, they were on average shorter, had the slowest growth rate in childhood, weighed less at ages 8 and 13 years, and had a later menarche than women in the lowest growth rate tertile in the same period. Women in the highest growth tertile were also taller in adult life, weighed less at study entry and were more prevalent in the older birth cohorts.

Table 8 presents growth rate in tertiles during childhood and adolescence and the risk of breast cancer. For women in the highest tertile of growth rate in adolescence, an increased risk of breast cancer (HR 2.3, 95% CI 1.3, 4.1) was observed when compared with women in the lowest tertile (P_{trend} = 0.006). These estimates attenuated without adjustment for height at age 13 (HR 1.8, 95% CI 1.0, 3.0). Adjustment for adult height, physical activity or parity did not affect these estimates. A marginal association was observed for linear regression of average growth rate per year in adolescence (HR 1.1, 95% CI 1.0, 1.2). When growth rate analysis for breast cancer in adolescence was stratified by birth cohort (1915 – 1924, 1925 – 1929, 1930 – 1935), a significant threefold increased risk was observed among women born 1915 – 1924 and 1925 – 1929, but not for the youngest cohort.

Table 8. Breast cancer risk by growth rate in childhood and adolescence

Growth rate period	Mean growth per year in cm (SD)	HR	95% CI
Childhood (ages 8 - 13 years)			
Low	4.9 (0.5)	1.0	Ref.
Medium	5.7 (0.2)	1.1	0.6, 1.9
High	6.5 (0.3)	1.5	0.8, 2.7
Adolescence (age 13 – adult height)			
Low	2.6 (0.8)	1.0	Ref.
Medium	4.8 (0.6)	1.6	1.0, 2.6
High	7.8 (1.7)	2.3	1.3, 4.1

Growth rate in childhood was not significantly associated with breast cancer (HR 1.5, 95% CI 0.8, 2.7). The estimate for linear regression of average growth per year in childhood was 1.2 (95% CI 0.9, 1.7). No difference in milk consumption in adolescence was found between tertiles of growth in childhood and adolescence, for both men and women. No association was observed for growth rate between age 8 years and adult height was reached.

We observed positive association for increase of on Z-score of adult height and weight at study entry and breast cancer, or 20% and 10% respectively. Adjusting for growth rate in the analysis did not change our results on adult height estimates (n = 991). For prostate, cancer, no association was observed, neither for growth rate nor adult estimates.

5 Discussion

5.1 Main findings

In the Reykjavik Study, prolonged residence in a coastal village for the first 20 years of life or longer was associated with a lower risk of breast cancer, when compared to residence in the capital area. In the AGES-Reykjavik subgroup analysis on dietary habits, high fish consumption during midlife was associated with a lower risk of breast cancer while an association was marginally suggested between fish consumption in adolescence and breast cancer risk.

Surprisingly, daily consumption of rye bread during both adolescence and midlife was positively associated with breast cancer in the AGES-Reykjavik cohort. Meanwhile, persistent high consumption of oatmeal in adolescence and midlife was associated with lower risk of breast cancer. However, no dietary pattern in either adolescence or midlife that included rye bread was significantly associated with breast cancer risk. In addition, a dietary pattern in adolescence that consisted of fish, blood/liver sausage, oatmeal, fish oil, and milk was marginally associated with a lower risk of breast cancer. Current dietary habits in late life were not found to be associated with breast cancer, although high adherence to dietary pattern that contained foods high in sugar was found to increase the risk.

The results further indicate that growth rate adolescence represents an important period for breast cancer risk. Indeed, our data showed that women in the highest tertile of growth rate in adolescence had an increased risk of breast cancer when compared with women in the lowest tertile.

Overall, the results of the study suggest that early life environment may have an important role in breast cancer risk later in life. Moreover, our data shows that midlife dietary habits are also of importance in this context.

5.2 Comparison with other studies and possible mechanism

5.2.1 Paper I and III

Previous studies on fish consumption in adolescence (183-185, 216) and young adulthood (247) have not reported any association with breast cancer.

More research has been conducted on midlife fish consumption and breast cancer, although overall, they have not produced any strong beneficial association either (100, 106-108, 110). The studies with the strongest association originate from Norway and Japan (103-105), both countries where high consumption of fish is traditional, like in Iceland (228, 230, 238). It is therefore possible that consumption of fish in most prior studies has not been high enough to show any beneficial association like observed in ours. However, vitamin D and marine derived n-3 PUFA, the most common substances in fish that are linked with risk reduction for breast cancer are mainly found in fatty fish and fish liver oil (106, 111, 187, 248). The most common fish types consumed in Iceland are the lean species haddock and cod, containing only modest amounts of vitamin D, or about 0.9 µg per 100g and 0.3 g of n-3 PUFA per 100g (249). However, as the female breast tissue undergoes increased cellular proliferation between menarche until the terminal differentiation with first full term pregnancy (5), this period could be of great importance for environmental exposures such as diet. The anti-cancer effect of uniquely high consumption of lean species through adolescence into adulthood can therefore not be excluded for women with prolonged residence in coastal villages.

However, fish liver oil, a common supplement in Iceland, is also rich in vitamin D and marine derived n-3 PUFA. One possible explanation for not finding an inverse association between fish oil consumption and breast cancer might be due to the unusually high amount of retinol (30,000µg per 100g) found in Icelandic fish liver oil for most of the 20th century. Retinol can interfere with the absorption, transportation and conversion to vitamin D's active form (250, 251). Consequently, the high consumption of fish rather than fish liver oil may have promoted better absorption and utilization of vitamin D. Also, because of high levels of EPA and DHA in both diet and plasma of the Icelandic population (252), beneficial threshold for breast cancer risk might have already been reached in our study population.

Furthermore, lean fish is also rich in both selenium and iodine, nutrients that some studies have linked with anticancer effect (253-256). Another explanation for the finding on prolonged residence in coastal villages could also involve energy intake. Fish has lower energy content than meat per 100g (249) and lower energy intake was reported in people residing in coastal villages in the first half of the 20th century (230). Studies have found anorexic women at reduced risk for breast cancer, particularly those with early onset of anorexia (257, 258) and Norwegian studies found the incidence of breast cancer was lower than expected among women who went

through puberty during the second World War, where food availability was somewhat limited (259, 260). Low energy intake has also been linked with reduction in mammary tumors in rodents (261, 262). In the Reykjavik Study, women raised in coastal villages were on average shorter in adulthood and started menarche later then women in the capital area, both factors that can be affected by low energy intake prior and during adolescence (169, 263-265).

However, low energy intake, particularly around adolescence, has also been associated with increased rate of breast cancer (266, 267) and whether energy restriction causes increased or decreased risk of cancer may depend on it's duration and intensity (267). It has been hypothesized completion of severe energy restriction causes amplified response of the hormone factor signaling GH-IGF axis, that consequently might cause carcinogenic response (268, 269). On the other hand, continuous moderate energy restriction might enable the body's metabolism to adapt by responding with lower circulating IGF-1 (270, 271).

Although information on diet and energy intake are lacking for all participants in the Reykjavik Study, and data on growth rate is restricted to a small subsample in the capital area only, the different effect of energy restriction on breast cancer risk may also explain the observed risk for fast growth rate in adolescence (paper III). Indeed, this increased risk of breast cancer was mostly driven by girls who had slower growth rate in childhood, were on average 8 cm shorter at age 13, and, interestingly, started menarche later compared with girls the in lowest tertile in adolescence. It is therefore possible that around age 13, shorter girls experienced hefty growth spurt to obtain their genetically set final height. The mechanism involved have affected levels of growth hormones and this might possibly explain why fast growth rate in adolescence was linked with increased breast cancer risk while a protection was observed for women with prolonged stay at coastal villages. Also, the association for growth rate was strongest for older women in the cohort, or those who went through adolescence during the economic recession in the 1930's in Iceland, which might have affected both quantity and quality of nutrition sources (229, 272). Furthermore, the mechanism involved may have canceled out the beneficial effect of late menarche in relation to breast cancer risk.

For paper III, other explanation for the increased risk observed among women with fast growth rate in adolescence (tertile 3) could be that these same women were, on average, also taller in adult life than women in the

lowest tertile. Yet, risk estimates for adult height and breast cancer were not altered with adjustment for growth rate in adolescence. In addition, no interaction was observed between growth rate in adolescence and adult height for breast cancer. Growth rate and adult height might therefore be independent risk factors of breast cancer. Also, we can not exclude the effect of other environmental factors that might affect growth, such as infections and quality of housing in reference to mold for example (273, 274).

5.2.2 Paper II

Most of available epidemiological data on adult consumption of food rich in whole grains show either inverse (275, 276) or no association (277, 278). Results from the NHS II suggest that high consumption of whole grains in adolescence can reduce the risk of premenopausal breast cancer (192), although rye bread consumption does not seem to have been included in the question on total wholegrain consumption. As whole grains are a diverse group and contain different types of dissimilar bioactive compounds (279), each type of grain may act differently on breast cancer genesis. Most prior studies on whole grains have not disentangled whole grain consumption by types of grains and only few studies have specifically addressed consumption of rye bread, a common whole grain product in the Nordic countries, in relation to breast cancer. Two Danish studiers found no association with neither total consumption of whole grains nor where the types were separated, including rye (277, 280). However, higher alkylresorcinol C17:0/C21:0 ratio in adipose tissue, reflecting higher relative whole grain rye intake, was associated with a higher risk of postmenopausal breast cancer (280).

Rye bread is rich in lignans, a group of bioactive compounds with phytoestrogenic activity that is are also commonly found in wheat, oats, and barley, legumes, oilseeds, and various fruits and vegetables (281). A Canadian case control study found that high adolescent intake of lignans reduced the risk of breast cancer. However, although rye bread was included in the diet assessment of the study, it was not commonly consumed, and these results can also be confounded by other healthy eating habits (194). A meta-analysis on adult lignan and enterolignan exposure also observed mostly favorable effects for breast cancer, although the sources of dietary lignans are not available (166). However, phytoestrogens also express weak estrogenic affinity and can act both as agonists and antagonists in breast tumors, although this mechanism is considered complex (163, 279, 282, 283). As longitudinal exposure to estrogens, exemplified by early menarche,

late menopause, and use of hormonal replacement therapy, are considered risk factors for breast cancer (202, 284) it is possible that long term exposure to phytoestrogens via rye bread consumption may have somewhat similar effect. Indeed, the analysis on dietary habits through different time-periods showed that the highest correlation between consumption in adolescence and late life was for rye bread, and the analysis on long term consumption of rye bread showed that the risk was strongest for women with high consumption of rye bread in both adolescence and midlife.

However, the rye grain also has some other bioactive compounds of unknown concentration that may be of significance in this context (285). Also, common toppings for rye bread may contain other potentially carcinogenic compounds. Furthermore, potentially carcinogenic compounds could form when the old-style rye flatbread, a traditional Icelandic bread included in the question on rye bread, is baked or charred directly on a hot plate. However, no significant results were observed for any dietary pattern that included high rye bread consumption, neither in adolescence nor the midlife period, suggesting that rye bread in the total diet might not be of major concern for cancer risk.

In contrast to our results on rye bread, frequent long-term consumption of oatmeal was found to be protective against breast cancer. Similar to rye, yet containing only half the amount of phytoestrogen (279), oatmeal is rich in fiber, which is thought to reduce breast cancer risk via multiple pathways (286-288). Indeed, two studies on fiber intake in adolescence and early adulthood found an inverse association with breast cancer (193, 289). However, when analyzed separately, only fiber from fruit and vegetables was protective effects against breast cancer in one study (193) whereas the main sources of fiber in the other study were not clear (289). Although we cannot exclude the influence of fiber to be responsible for our beneficial results, oatmeal also contains multiple bioactive compounds, including the polysaccharide beta-glucan, which is proposed to have some anticancer properties. However, data on this association is still limited (157, 158). The inclusion of muesli as part of the question on oatmeal might act as proxy for consumption of other healthy food items. This is further supported by the borderline risk reduction for breast cancer found with high adherence to a dietary pattern in adolescence that included oatmeal, fish, fish oil, milk, and blood- and liver sausage. This further indicates possible anticancer properties of oatmeal and possible other food items in that particular dietary pattern.

5.3 Dietary pattern in late life

The only dietary pattern that was statistically associated with breast cancer in the study was high adherence in late life with the “sweet pattern”. This pattern was characterized by frequent consumption of food items like sweets, cookies, cake, pastry, sweetened juice and carbonated beverages. These results are in line with studies investigating similar food consumption. A recent French cohort study found 18% increased risk of breast cancer for every additional 100ml consumption of sugary drinks. High consumption of fruit juice was not found of significance for breast cancer, although a positive association was observed for total cancer (290). Similar results were observed in a recent Spanish study on postmenopausal women (291). In a population-based US derived case-control study, high consumption of dessert foods, sweet beverages, and food items with high content of added sugars were positively associated with breast cancer (292). Finally, A Canadian study found women in the highest tertile of intake of desserts (including biscuits, brioches, cakes, puffs and ice-cream) and sugars (including sugar, honey, jam, marmalade and chocolate) had increased risk of breast cancer, independent of age, body mass index, total energy intake and other covariates (293).

A few plausible mechanisms for the association between high adherence to sweet pattern and breast cancer risk exist. High consumption of food rich in sugar can enhance weight gain, a known risk factor for postmenopausal breast cancer (4). Nevertheless, our results were independent of BMI. The glycemic index or glycemic load in food with high sugar content could also contribute to this association, as they are associated with hyperinsulinemia and type 2 diabetes, both potentially involved in breast carcinogenesis (294). However, a recent study from the Reykjavik and AGES-Reykjavik cohorts suggest that a diagnosis of type 2 diabetes may only add a very small, if any, additional breast cancer risk among the women in the cohort (295). However, high glycemic load is also associated with increased proinflammatory markers, such as C reactive protein, and systemic inflammation is suggested to increase the risk of several cancers, including breast cancer (296, 297).

These results indicate that diet high in sugars in late life may be associated with breast cancer carcinogenesis. However, these effects might also be of importance in the adolescence and midlife period as questions on pastries, soda and candy were not included in the FFQ for these time periods in present study.

5.4 Strength and weaknesses

For both they Reykjavik Study and the AGES-Reykjavik cohort, the major strengths are the population-based data, the prospective design and the extensive covariate information that allows for control for several potential confounding factors. The record linkage of both cohorts to the Icelandic Cancer Registry, founded in 1954 and estimated to have 99% completeness (233) ensured both detailed and valid assessment of the outcome and high prospect of capturing the majority of cancer diagnosis. The growth analysis is also based on actual measurements, and as all participants were living in Reykjavik at study entry, they had equal access to the public health care system and therefore had the same chance of getting diagnosed with breast cancer (298). The dietary data in the AGES-Reykjavik cohort also hold the ability to study dietary factors across the life course, using a validated FFQ for midlife and late life. Currently, retrospective dietary information is of great importance as prospective gathering of dietary exposures in adolescence could span many decades of follow-up. As only incident breast cancer cases were used in the dietary analyses, the risk of differential recall bias is limited.

Our studies are possibly subjected to selection bias. Despite the population-based design it is possible that participants of the Reykjavik cohort differ from those who did not participate. Those who ended up participating might be more health conscious, and therefore have more favorable distribution of risk factors. Similarly, when the AGES-Reykjavik Study was initiated, a large fraction of the participants in the Reykjavik Study was deceased and this cohort might therefore include healthier individuals than in the general population, resulting in a survival bias and it is challenging to predict how such a bias affects our estimates.

The study retrospective dietary assessment may have caused some non-differential measurement error as there is always uncertainty in assessing dietary habits stretching over a 40-to-50-year period (299) and the adolescence diet in this study cannot be validated. Yet, food-related memory from childhood to four decades later can be as accurate as food-related memory of current diet (180, 300, 301), especially for food items eaten rarely or daily (300). Also, diet in Iceland during the adolescent period was quite simple, included very few foods and showed little day to day variation (230), which should make the recall easier. Also, as seen in table 4, the correlation between adolescent and current diet is generally low, reflecting the changes in availability of food items for the period. Furthermore, the data on dietary habits, stratified by residence, is also in line with previously documented

residence-based difference in dietary habits, probably reflecting the limited infrastructure in the country during the first decades of the 20th century. Yet, as most of the older cohort was deceased at the time when the AGES-Reykjavik Study was initiated it might not completely reflect the diversity of dietary habits of the older participants in the study. However, as those analyses were all based on incident breast cancer cases, any misclassification should not be differential with respect to the outcome.

Also, the FFQ used has only crude information on quantity of food items consumed and we are not able to adjust for cooking methods, single nutrients, total intake of fat, fiber, and energy and we do not have information on types or quantities of condiments. Furthermore, the validation on current diet in late life showed low correlation for fish meals, rye bread and whole-grain bread (241). Consequently, late life fish consumption was not included in paper I, although it is included in the thesis. The reasons for lack of validity of some of the food items in late life are possibly the inability of the reference method (3-day food record) to adequately reflect intake of foods that are consumed infrequently. The validation on midlife food consumption showed that participants were mostly acceptably ranked while there was a low correlation for rye bread consumption (237). However, as rye bread consumption is still relatively common in the current diet of Icelanders (228) and has not been studied thoroughly in relation to breast cancer, rye bread was included in paper II. Also, in the same study, using data on men, daily rye bread consumption was associated with lower risk of prostate cancer (227). Also, the AGES-FFQ does not hold information on age of menopause or BMI for adolescence and the results from the AGES cohort are based on older women diagnosed with breast cancer and these results might not apply for women diagnosed earlier in life.

In the Reykjavik Study, the classification of residence into rural areas and coastal villages is based on geographical and historical evidence that does not consider variability of remoteness or isolation. In addition, we do not have complete information on reproductive factors like the use of HRT and oral contraceptives and breastfeeding for all women in the residence and growth analysis, although it is unlikely that these factors are affected by exposures like residence and growth rate. For the growth analysis, available information on growth in early life is only available for small proportion of participants, from one area of the country. Also, our calculation for growth rate of height in adolescence is based on estimation of the time adult height is reached. Another limitation are the few cases of incident breast and prostate cancer, particularly with advanced prostate disease. Because many of our

participants grew up during times of economic recession of the 1930s, possibly with restricted caloric intake, our findings may not be generalizable to all girls growing up today but perhaps particularly to those living in developing countries undergoing economic transition. Lack of statistical power may have prevented us to observe real associations as statistically significant and limited the detail in subgroup analyses. Finally, as in any observational study, we cannot exclude the possibility that unmeasured confounders may account for some observed associations and, as our analyses are based on older women in Iceland, the generalizability of the results might be limited.

6 Summary and conclusions

The results of this population-based study indicate that growing up in costal villages and corresponding very high fish consumption may be associated with a decreased risk of late life breast cancer. In contrast, daily rye bread consumption, in both adolescence and midlife, was associated with increased risk of breast cancer diagnosed late in life. The data further suggest that high intake of sugar may also increase this risk while high persistent oatmeal consumption might lower breast cancer risk. In addition, rapid growth, especially among women who were shorter in the beginning of the adolescence period, may also increase late life breast cancer risk.

Breast cancer is among the most important public health challenges in modern times and primary prevention holds the greatest promise to reduce suffering from this disease. Our results indicate that environmental exposures throughout the lifespan are of significance for breast cancer carcinogenesis, particularly in early life, although the midlife period is also of importance. This work is also an important contribution to the extending base of knowledge on dietary causes of cancer. Although we stand by our results, larger population-based prospective studies are needed to further advance knowledge on early life exposures of importance for breast cancer and to better map critical time-windows for the development of the disease.

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Original publications

Paper I

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Early Life Residence, Fish Consumption, and Risk of Breast Cancer

Alfheidur Haraldsdottir[1,2], Laufey Steingrimsdottir[1,3], Unnur A. Valdimarsdottir[2,4,5], Thor Aspelund[2,6], Laufey Tryggvadottir[7,8], Tamara B. Harris[9], Lenore J. Launer[9], Lorelei A. Mucci[4,10], Edward L. Giovannucci[4,10,11], Hans-Olov Adami[4,5], Vilmundur Gudnason[6,8], and Johanna E. Torfadottir[2,3]

Abstract

Background: Little is known about fish intake throughout the life course and the risk of breast cancer.

Methods: We used data on the first residence of 9,340 women born 1908 to 1935 in the Reykjavik Study as well as food frequency data for different periods of life from a subgroup of the cohort entering the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study ($n = 2,882$).

Results: During a mean follow-up of 27.3 years, 744 women were diagnosed with breast cancer in the Reykjavik Study. An inverse association of breast cancer was observed among women who lived through the puberty period in coastal villages, compared with women residing in the capital area [HR, 0.78; 95% confidence interval (CI), 0.61–0.99]. In the subgroup analysis of this Icelandic population, generally characterized by high fish intake, we found an indication of lower risk of breast cancer among women with high fish consumption (more than 4 portions per week) in adolescence (HR, 0.71; 95% CI, 0.44–1.13) and midlife (HR, 0.46; 95% CI, 0.22–0.97), compared with low consumers (2 portions per week or less). No association was found for fish liver oil consumption in any time period, which could be due to lack of a reference group with low omega-3 fatty acids intake in the study group.

Conclusions: Our findings suggest that very high fish consumption in early to midlife may be associated with a reduced risk of breast cancer.

Impact: Very high fish consumption in early adulthood to midlife may be associated with decreased risk of breast cancer. *Cancer Epidemiol Biomarkers Prev; 26(3); 346–54. ©2016 AACR.*

Introduction

Increasing evidence suggests that dietary factors play an important role in both the prevention and development of breast cancer (1), although no clear relation has been established (2). A meta-analysis from 2013 examined the association between breast cancer and intake of fish as well as n-3 polyunsaturated fatty acids (n-3 PUFA; ref. 3). A risk reduction for breast cancer was observed for high intake of marine derived omega-3 PUFA, mainly consisting of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). No association was found for total fish consumption, where information on different species (lean and fatty fish) was lacking (3). Recent studies have also reported nonsignificant association between total fish intake and breast cancer (4–6). The associations between hormone receptor status of breast tumors and fish consumption are unclear (7).

A possible explanation for inconsistent results could be the timing of the exposure measurement. Cancers can have a long latency period from initiation to cancer detection, making different exposure periods of potential importance, rather than just around the time of detection (8). Dietary habits in early life, especially around puberty when the mammary tissue is growing and maturing (9–11), may therefore be of significance for breast cancer risk.

Few studies have specifically explored the potential link between fish consumption in adolescence and breast cancer risk and none of these studies has reported significant associations (12–15). Some (16, 17), but not all studies (15), on vitamin D, an important component in certain types of fish, have reported an inverse association with breast cancer in the adolescent period. However, studying dietary exposure in early-life is challenging due to the need for follow-up for many decades or alternatively, relying on dietary data from distant recall which are often susceptible to bias (18).

According to an Icelandic dietary survey from 1939–1940, dietary patterns differed greatly between rural and coastal areas

[1]Faculty of Food Science and Human Nutrition, University of Iceland, Reykjavik, Iceland. [2]Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavik, Iceland. [3]Unit for Nutrition Research, University of Iceland and Landspitali National University Hospital Reykjavik, Reykjavik, Iceland. [4]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [5]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [6]The Icelandic Heart Association, Kopavogur, Iceland. [7]The Icelandic Cancer Registry, Reykjavik, Iceland. [8]Faculty of Medicine, University of Iceland, Reykjavik, Iceland. [9]Laboratory of Epidemiology and Population Sciences, Intramural Research Program, National Institute on Aging, Bethesda, Maryland. [10]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. [11]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Alfheidur Haraldsdottir, University of Iceland, Eiriksgata 29, Reykjavik 101, Iceland. Phone: 354-543-4956; Fax: 354-543-1331; E-mail: alh1@hi.is

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in the early and mid-20th century. In this population, characterized by high fish intake, fish consumption was substantially higher in coastal villages than in other parts of the country. For example, average fish consumption was 140 grams per day (g/d) in rural areas, 213 g/d in the capital area and 354 g/d in coastal villages (19). Parallel to our earlier studies on prostate cancer (20–22), this variation provides us with a unique opportunity to prospectively explore the impact of high fish consumption in adolescence on the risk of breast cancer. By using the population-based data of the Reykjavik Study, we investigated whether residence (as a proxy for diet) in adolescence was associated with the risk of breast cancer. Furthermore, using validated food frequency data from a subgroup of the Reykjavik Study participating in the Age, Gene/Environment Susceptibility (AGES) Study, our aim was to explore whether diet in both adolescence and midlife was associated with breast cancer risk.

Materials and Methods

Residence analysis—Reykjavik Study

Population. The Reykjavik Study is a population-based prospective cohort. The Icelandic Heart Association initiated the study in 1967. All women born between 1908 and 1935 and living in the capital area in December 1966 were invited to participate (23). 10,049 women entered the study (71% response rate), in six stages from 1967 until 1996 (24). We excluded women who were diagnosed with breast cancer prior to entry and for who follow-up was incomplete ($n = 145$).

Exposure assessment—classification of residence. Participants provided information on residence at birth and throughout their lives. Classification of early residence has been described in our earlier studies (20). In short, every community ($n = 245$) in Iceland was classified into 4 categories: capital area, coastal villages, rural areas, and combinations of coastal villages and rural areas (20). We excluded participants without available information on residence ($n = 238$) and those whose first residence was a combination of coastal village and rural area ($n = 341$), since it would be hard to draw any dietary-based conclusions for this particular group. This left 9,340 women in the residence analysis.

Covariate assessment—Reykjavik Study. From the Reykjavik Study we retrieved baseline information on age at entry (continuous), height (continuous), year of birth (1908–1914, 1915–1919, 1920–1924, 1925–1929, 1930–1935), education (primary, secondary, college/university), body mass index (BMI; continuous), parity (no children, 1–2, 3 and more), and physical activity (no, yes; see Table 1).

Covariate assessment—cancer detection clinic cohort. Because data on reproductive history were generally not collected in the Reykjavik Study, information on potential reproductive confounders for breast cancer was obtained from the Cancer Detection Clinic Cohort (CDC cohort), established in 1964. This cohort includes data collected as part of nationwide, centralized cervical- and breast cancer screening programs. All Icelandic women aged 20 to 69 years are invited to visit the CDC every other year for screening cancer of the cervix (from the age of 20) and breast (from 40 years of age; ref. 25). When data from the two cohorts were linked, about 91% of women in the Reykjavik Study had attended the Cancer Detection Clinic at least once. For this study, information closest to the study's endpoint (breast cancer diagnosis, death, or end of the year 2013) was retrieved and linked with our data. From the CDC cohort we primarily retrieved information on age at menarche (continuous) and age at first birth (none, 24 and younger, 25 and older). The variable "age at menarche" had 933 missing values. The variable "age at first birth" had 924 missing values, which we were able to reduce to 683 by adding information on parity from the Reykjavik Study. We placed the 241 women who had missing values in "age at first birth" from the CDC cohort, and had no children at entry to the Reykjavik Study in the "no birth" category. We categorized the 113 women who were classified as childless in the CDC cohort but had a child according to the Reykjavik Study, into the "25 and older" category, because women were at least 33 years of age upon entry into the Reykjavik Study.

We also evaluated information on the total months of breastfeeding (never, 1–6 months, 7 months and more), the use of hormonal replacement therapy (HRT; never, ever) and use of oral contraceptives (never, ever).

Follow-up and outcome. Participants were followed from their entry into the study (between 1967 and 1996) until their diagnosis of breast cancer, death, or the end of the observation period (December 31, 2013). We ascertained breast cancer diagnoses through the nationwide Icelandic Cancer Registry (26). Information on the cause of death was obtained from the Directorate of Health. Because of Iceland's computerized national roster and each person's unique personal identification numbers, follow-up was virtually complete (27). Information on the receptor status of the tumors was only used in the analysis of residence. We had information on receptor status in 76% of cases for estrogen receptor (ER) positive or negative tumors and 74% of cases for progesterone receptor (PR) positive or negative tumors. Receptor status was further categorized as ER/PR positive, ER/PR negative, ER positive PR negative (28).

Statistical analyses

We used Cox proportional hazard regression models to calculate HRs and 95% confidence intervals (95% CI) for the diagnosis of breast cancer by residence (coastal village or rural area) in early life, from the time of entry into the Reykjavik Study. Residence in the capital area was the reference category. In line with WHO's definition of the adolescence period (29), we also stratified our data into three categories, based on women's age when they moved away from their first residence in rural areas and coastal villages: (i) age 11 and younger, (ii) between the ages of 12 and 19, and (iii) at age 20 and older. Residence in the capital area was also the reference. The first multivariable model was adjusted for age (continuous) at entry into the Reykjavik Study. The second model (HR^a) was additionally adjusted for birth cohort, education, parity, physical activity, BMI and height, categorized as described in Table 1. The third model (HR^b) was additionally adjusted for age at menarche and age at first birth, obtained from the CDC cohort.

Because age both at menarche and at first birth are strong risk factors for breast cancer (2), a sensitivity analysis was conducted in order to compensate for the missing values for these variables. Multiple imputation was used to predict missing values for "age at menarche" (10% missing) by mean matching after stratifying the variables: age at entry, birth cohort and education. Missing values

Table 1. Characteristics of female participants in the Reykjavik Study according to location of first residence, Iceland, 1967–2013

	Location of first residence						
	Reykjavik area (n = 3,474)		Coastal village (n = 3,262)		Rural area (n = 2,604)		P[a]
Duration of first residence							
Mean (SD)	44.7	(15.3)	20.6	(11.5)	19.0	(7.8)	0.001
Median	47		18		19		
Age at study entry[b]							
Mean (SD)	52.8	(9.6)	54.2	(9.7)	54.9	(10.2)	0.001
Median	52		54		54		
Age at diagnosis							
Mean (SD)	68.6	(10.8)	70.5	(10.7)	70.4	(11.4)	0.078
Median	68		72		71		
Height (cm)[e]							
Mean (SD)	163.7	(5.7)	162.6	(5.7)	162.5	(5.6)	0.001
Median	164		163		163		
BMI (kg/m^2)[e]							
Mean (SD)	25.1	(4.3)	25.2	(4.3)	25.1	(4.2)	0.903
Median	25		25		25		
Education, n (%)							
Primary	1746	(50)	1766	(54)	1522	(58)	0.001
Secondary	1342	(39)	1288	(40)	900	(35)	
College/University	386	(11)	208	(6)	182	(7)	
Birth cohort, n (%)							
1907–1914	462	(13)	525	(16)	516	(20)	0.001
1915–1919	526	(15)	592	(18)	548	(21)	
1920–1924	727	(21)	703	(22)	594	(23)	
1925–1929	774	(22)	726	(22)	501	(19)	
1930–1935	985	(28)	716	(22)	444	(17)	
Children, n (%)							
None	310	(9)	351	(11)	359	(14)	0.001
1–2	928	(27)	880	(27)	799	(31)	
3 or more	2200	(64)	2004	(62)	1421	(55)	
Regular physical activity, n (%)							
Yes	947	(27)	730	(22)	496	(19)	0.001
Age at menarche[c], n (%)							
≤13 y	1543	(44)	1249	(38)	1137	(44)	0.001
≥14 y	1603	(46)	1680	(52)	1195	(46)	
Missing values	328	(9)	333	(10)	272	(10)	
Age of birth of first child[c], n (%)							
≤24 y	1904	(55)	1684	(52)	1014	(39)	0.001
≥25 y	1016	(29)	1003	(31)	1049	(40)	
Missing values	250	(7.2)	239	(7.3)	194	(7.5)	
Ever use HRT[c,e], n (%)							
Yes	942	(27)	880	(27)	649	(25)	0.004
Ever use oral contraceptive, n[c,e]							
Yes	791	(23)	622	(19)	422	(16)	0.001
Total months of breastfeeding[c,e], n (%)							
Never	347	(10)	361	(11)	332	(13)	0.001
1–6 months	787	(23)	725	(22)	496	(19)	
≥7 months	1525	(44)	1387	(43)	1099	(42)	
Fish consumption in adolescence[d] (n = 2,898), n (%)							
≤2 portions p/w	594	(52)	448	(45)	397	(51)	0.001
>2 up to 4 portions p/w	105	(9)	78	(8)	128	(17)	
>4 portions p/w	441	(39)	463	(47)	244	(32)	
Meat consumption in adolescence[d] (n = 2,881), n (%)							
2 times or less p/w	372	(33)	277	(28)	307	(40)	0.001
3–4 times p/w	744	(66)	688	(70)	389	(51)	
5 times p/w or more	17	(2)	17	(2)	70	(9)	
Milk consumption in adolescence[d] (n = 2.886), n (%)							
Less than daily	304	(27)	283	(29)	125	(16)	0.001
Daily or more	833	(73)	700	(71)	641	(84)	

Abbreviation: HRT, hormone replacement therapy.

[a]P values are based on χ^2 tests, except for length of residence, age at entry, age at diagnosis, height and BMI, where one-way ANOVA test was used.

[b]Participants underwent the first clinical examination (first visit) between 1967 and 1996.

[c]Information retrieved from the CDC cohort.

[d]Data were available only for women who entered the AGES-Reykjavik Study in 2002–2006.

[e]Values were missing for 36 women on height; 88 women on BMI; 2,471 women on use of HRT; 2,422 women on use of oral contraceptive; 2,281 women on breastfeeding.

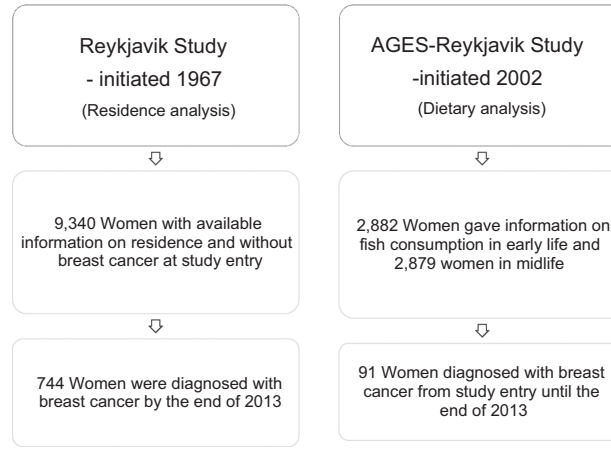

Figure 1.
Selection of participants from the Reykjavik Study and the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, Iceland, 1967–2013.

for "age at first birth" were included in the analyses as a special category (7% missing). Other variables from the CDC cohort were not included due to even higher number of missing values.

In addition, we calculated HR and 95% CI for tumor receptor status according to residence in early life. As above, the first model was adjusted for age only, while the second model (HR^a) was additionally adjusted for birth cohort, education, parity, regular exercise, BMI and height (data shown in Supplementary Table S1).

Dietary analysis—the AGES-Reykjavik study

Exposure measurement—ascertainment of dietary habits. The AGES-Reykjavik Study, a sub-cohort from the Reykjavik Study, was initiated in 2002. Of the women participating in the Reykjavik Study, 3,326 were randomly enrolled between 2002 and 2006, as described by Harris and colleagues (23). Participants entering the AGES-Reykjavik Study provided retrospective information on dietary habits in early life (ages 14–19), in midlife (ages 40–50), as well as current diet in late life (ages 66–96). Participants received careful instructions at the clinic on the filling out of a validated food frequency questionnaire (AGES-FFQ; refs. 30, 31; Fig. 1). There were three questions on fish consumption in the FFQ. The first one concerned the frequency of fish meals per week (p/w; salted or smoked fish included). The second question concerned the weekly frequency of using fish as a topping on bread and in salad, and the third one was on the frequency of salted or smoked fish intake p/w. Total fish intake was based on the first two questions. Possible response categories were; (i) never, (ii) less than once a week, (iii) 1–2 times a week, (iv) 3–4 times a week, (v) 5–6 times a week, (vi) daily, and (vii) more than once a day. Because of the different amounts of fish consumed as a meal or topping on bread, we used information on average portion size from the Icelandic national nutrition surveys (32, 33) to estimate total fish consumption p/w. One portion of fish was estimated to be 150 g for fish as a main meal and 40 g for fish as a bread topping. Numerical values for portions of fish were calculated accordingly (22). Total fish consumption was divided into three groups, that is, high (>4 portions p/w), moderate (>2–4 portions p/w) or low ($\leq$2 portions p/w). The FFQ did not contain questions on the type of fish. However, cod and haddock were the fish most commonly consumed in the early 20th century as well as today (32, 33).

Fish liver oil intake (liquid or capsules) is a cultural tradition in Iceland (33). It was also assessed for each period of life, using one question with the same response alternatives as were used for fish meals, omitting the last option of more than once a day.

The FFQ designed for the AGES-Reykjavik Study has been validated for both midlife and current dietary habits later in life (30, 31). In short, the correlation between the reference method and the AGES-FFQ for midlife was r = 0.58, $P = 0.001$ for fish oil consumption. The question on midlife fish consumption showed a lower correlation but was still within the acceptable range ($r = 0.281$, $P = 0.004$; ref. 31). Because of the low validity for overall current fish intake in late life, these data were not used to study breast cancer risk (30).

Covariate assessment. From the AGES-Reykjavik Study, we retrieved information, gathered at entry, on age (continuous), year of birth (1908–1919, 1920–1924, 1925–1929, 1930–1935), education (primary, secondary, college/university), age at first birth (none, age 24 and younger, 25 and older), family history of breast cancer (mother, sister and/or daughter ever diagnosed with breast cancer), use of hormonal replacement therapy (never, ever), use of oral contraceptive (never, ever), use of alcohol in midlife (never, ever), BMI in late life (continuous), alcohol consumption in late life (0, 1–10 g/week, >10 g/week) and physical activity in midlife and late life (never/rarely, occasionally, moderately/often). From the Reykjavik Study we retrieved values on BMI in midlife (continuous) and height in midlife (continuous).

Information on dietary covariates was retrieved from the AGES-FFQ. For all periods, selected covariates on consumption were milk, salted or smoked fish, rye bread, meat, total fish and fish liver oil. The cutoff points can be seen in Table 2. We also included information on first residence, categorized into four places as described in residence analysis.

Table 2. Multivariable analysis of breast cancer by location of first residence and duration of stay

	Number of participants	Mean duration of residency, years (SD)	IR per 1,000 person years	Age-adjusted HR (95% CI)	HR[a] (95% CI)	HR[b] (95% CI)
Location of first residence				*n* = 744	*n* = 731	*n* = 664
Reykjavik	3474	44.7 (15)	3.15	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref).
Coastal village	3262	20.6 (11)	2.72	0.86 (0.72–1.02)	0.89 (0.75–1.06)	0.87 (0.72–1.04)
Rural area	2604	19 (8)	2.85	0.89 (0.74–1.06)	0.91 (0.75–1.09)	0.88 (0.73–1.07)
Age when moving away from coastal village[a]						
1–11 y	523	7.3 (2)	3.15	1.00 (0.73–1.37)	1.06 (0.77–1.46)	1.11 (0.80–1.54)
12–19 y	1253	16.1 (2)	2.71	0.86 (0.68–1–08)	0.89 (0.71–1.13)	0.88 (0.69–1.13)
20 y and older	1484	29.1 (12)	2.58	0.81 (0.65–1.01)	0.83 (0.66–1.04)	0.78 (0.61–0.99)
Age when moving away from rural area[b]						
1–11 y	426	7.8 (2)	3.19	1.01 (0.71–1.42)	1.01 (0.71–1.43)	1.05 0.73–1.51)
12–19 y	881	16.0 (2)	2.70	0.84 (0.65–1.10)	0.88 (0.67–1.16)	0.85 (0.64–1.13)
20 y and older	1293	24.6 (6)	2.86	0.88 (0.70–1.10)	0.89 (0.71–1.12)	0.85 (0.67–1.09)

NOTE: HR[a] adjusted for age at entry, birth cohort, education, physical activity, parity, height, and BMI in midlife, and HR[b] additionally adjusted for age at menarche and age at first child.

Abbreviations: CI, confidence interval; IR, incidence rate; *n*, number of breast cancer diagnosis in analysis.

[a]Data on duration of residency in coastal village were missing for 2 women.

[b]Data on duration of residency in rural area were missing for 4 women.

Statistical analyses and follow-up—dietary analysis. We used Cox proportional hazard regression models to calculate HR and 95% CI for incident breast cancer, from entry to the AGES-Reykjavik Study, according to total fish consumption in adolescence and midlife, using the lowest category as a referent. The same method was used for the fish liver oil analyses, adding late life consumption.

For both exposures, in all time periods, the first model was adjusted for age (as a continuous variable) at entry. For the adolescent period, information on education, family history of breast cancer, BMI in midlife, age at menarche and age at first child was added to the second model (HR[a]). In the third model (HR[b]), information on dietary factors: rye, milk, meat, salted or smoked fish, fish (for the fish liver oil analysis) and fish liver oil (for the fish analysis) were added. The same models, as described for adolescence, were used for both midlife and late life periods, except information on alcohol consumption was added as a covariate in the second model (HR[a]) as well as current values for BMI and dietary factors. Further adjustment for physical activity, use of oral contraceptives or HRT did not significantly change our results and were therefore not included in the models.

Participants were followed from their entry into the study until a diagnosis of breast cancer, death or the end of the observation period (December 31, 2013). We ascertained breast cancer diagnosis and the cause of death the same way as described for the residence analysis (26).

For all statistical analysis we used SPSS software, version 22.0 (SPSS Inc.; www.spss.com) and R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; (http://www.R-project.org/). The study protocol was approved by the Icelandic Ethical Review Board and the Icelandic Data Protection Authority (VSN b2007120014/03-7).

Results

Residence analysis

We included 9,340 women in our analysis of early life residency (Fig. 1). The mean age at entry into the Reykjavik Study was 53.9 years (SD = 9.9). All participants lived in the capital area at study entry, but only 37% were born and raised in the capital area; 35% were born and raised in a coastal village, and 28% were born and raised in a rural area. During an average follow-up of 27.3 years, 744 (8%) were diagnosed with breast cancer. The mean age at diagnosis was 69.7 years (SD = 11) and 65 women (9%) were diagnosed before the age of 55.

Table 1 presents the baseline characteristics of the study population by first residence. The average duration of first residence was longest in the capital area because most of the women born there never moved away. A higher proportion of women raised in the capital area had college/university degrees, were taller and exercised more frequently than women raised in other areas. Women with first residence in rural areas had fewer children on average and were older when having their first child. Women raised in coastal villages were on average older at menarche and also reported the highest frequency of fish consumption in adolescence in the AGES-Reykjavik Study.

Compared to women born and raised in the capital area, early life residence in coastal villages and rural areas were both weakly associated with a lower risk of breast cancer diagnosis, HR, 0.87; 95% CI, 0.72–1.04, and HR, 0.88; 0.73–1.07, respectively. When looking at the duration of residence from birth outside the capital area, we observed a significant inverse association for breast cancer diagnosis only among women who lived beyond the puberty period (at least to age 20 years or longer) in coastal villages, compared with women residing in the capital area (HR, 0.78; 95% CI, 0.61–0.99). No statistically significant associations were observed between any length of residence and breast cancer in the rural areas (Table 2).

In the final model (HR[b]) we included adjustment variables (age at menarche and age at first child) obtained from the CDC cohort. When we conducted sensitivity analysis, using imputed missing indicators for these variables, the pooled risk estimates for women who lived beyond the puberty period in coastal villages attenuated slightly (HR, 0.83; 95% CI, 0.66–1.04).

When data were analyzed by hormone receptor status, we found a borderline significant association between women with first residence in coastal village and ER/PR negative status and ER positive/PR negative status, adjusted for major risk factors (HR, 0.64; 95% CI, 0.41–1.01 and HR, 0.60; 95% CI, 0.35–1.03, respectively; Supplementary Table S1).

Dietary analyses

The dietary analyses were based on participants providing information on fish and fish oil intake at different time periods

at their time of entry into the Reykjavik-AGES cohort. During the follow-up through 2013 (mean 8.2 years), 91 women were diagnosed with breast cancer. Their mean age at entry was 77.0 years (SD = 6.0) and their mean age at diagnosis was 81.2 years (SD = 6.5).

Table 3 shows the characteristics of the subpopulation providing information on fish consumption in early (n = 2,882) and midlife (n = 2,879). Women with high fish consumption in early life were younger at first childbirth and also had the highest consumption of meat, fish liver oil and salted fish, compared with women with lower fish consumption. Women with high intake of fish in midlife were more physically active, consumed less meat, less salted fish, less rye bread and less alcohol, drank more milk and used less oral contraceptives, compared with women with lower fish intake in midlife.

Table 4 presents HRs, with 95% CI for breast cancer by total fish and fish liver oil intake. Compared with women consuming two portions or less per week in adolescence, women with high consumption (>4 portions p/w), showed lower risk of breast cancer, albeit not statistically significant (HR, 0.71; 95% CI, 0.44–1.13). For the midlife period, we found statistically significant risk reduction among women with high fish consumption (HR, 0.46; 95% CI, 0.22–0.97) compared with lower fish consumption. When information on early life residence was added to the models, our estimates did not change considerably. No significant association was found between fish liver oil consumption and breast cancer risk in any time period.

Discussion

In this population-based prospective cohort study, we did not observe a strong association between residence and breast cancer. However, prolonged stay in a coastal village for the first 20 years of life or longer was associated with a lower risk of breast cancer, compared to residence in the capital area. In the subgroup analysis on dietary habits, high fish consumption during midlife was associated with a lower risk of breast cancer while suggestive association was observed for consumption in adolescence.

Risk reduction for breast cancer has previously been linked with vitamin D (17, 34, 35) and marine derived n-3 PUFA (3, 34) frequently found in fatty fish and fish liver oil. However, to our best knowledge, no study has found an association between adolescent total fish consumption and breast cancer risk (12–15), and studies on adult total fish consumption have not found strong beneficial association either (5, 6, 36–38). Haddock and cod, the most common fish types consumed in Iceland are lean species containing only modest amounts of vitamin D or about 0.9 μg/100 g and 0.3 g of n-3 PUFA/100 g (39). Nevertheless, we cannot exclude their contribution due to the uniquely high amounts of fish consumed in our cohorts, when compared with previous studies. The observed discrepancy with our analysis on fish liver oil, a common supplement in Iceland, rich in vitamin D and n-3 PUFA, might be due to the unusually high amount of retinol (30,000 μg/100 g) found in Icelandic fish liver oil for most of the 20th century. Retinol can interfere with the absorption, transportation and conversion to vitamin D's active form (40, 41). Consequently, the high consumption of fish rather than fish liver oil may have promoted better absorption and utilization of vitamin D. Icelandic fish liver oil also contains n-3 PUFA. However, the Icelandic population has high levels of EPA and DHA in both diet and plasma (42). It might therefore be possible that the study population has already reached a beneficial threshold level of marine derived n-3 PUFA for breast cancer risk.

However, the observed risk reduction for women residing beyond puberty in coastal villages could also be due to lower total energy intake in adolescence, previously linked with risk reduction for breast cancer (43, 44). The total energy intake of people residing in coastal villages in the first half of the 20th century was lower than in other areas (19). In addition, as seen in Table 1, we observed a statistically significant regional difference showing lower adult height and higher age at menarche on average among women born and raised in coastal villages, which are both important factors in evaluating childhood nutritional status and the possible risk of future breast cancer (45). During the period between menarche and first-term pregnancy, the breast tissue in women undergoes increased cellular proliferation, and breast cancer risk accumulates rapidly up to the terminal differentiation accompanying the first full-term pregnancy (10). This period of early adulthood is therefore possibly of great importance for environmental exposure such as diet.

Also, risk factors have been shown to vary in their relevance to breast tumors depending on hormonal receptors status (28). Analogous to the findings on diet in previous studies (46, 47), we observed borderline inverse association between early life residence in coastal villages and ER/PR–negative tumors. This suggest a stronger environmental influence for ER-negative tumors, where hormonal factors might be less dominating (47). Our finding for ER-positive and PR-negative tumors might also indicate the importance of PR status of tumors.

Major strengths of our study are the distinct residency-based variations in early life fish consumption, the ability to study dietary factors across the life span as well as the established population-based cohorts with extensive covariate information. In addition, the record linkage to the nationwide Cancer Registry of Iceland provided detailed and valid assessment of the outcome. A major limitation of our study is that information on the frequency of fish consumed during midlife and adolescence is retrospective in nature. As a result, there may be a nondifferential measurement error, and there is always uncertainty in assessing dietary habits stretching over a 40-to-50-year period (48). Yet, food-related memory from childhood to four decades later can be as accurate as food-related memory of current diet, especially for food items eaten rarely or daily (49), possibly explaining no dose response found for fish consumption in adolescence as few women reported consumption from 2 up to 4 portions per week (30). Also, we do not have information on cooking methods in our study. However, information from a national nutrition survey conducted in 1990 showed that 64% of total fish consumed as a main meal was boiled or baked (32). Another limitation of our study is the lack of information about total energy intake and growth in early life. We were only able to adjust for body mass index measured in midlife, which may only indirectly indicate total energy intake (50). Also, the classification of residence into rural areas and coastal villages is based on geographical and historical evidence that does not consider variability of remoteness or isolation. Finally, we do not have complete information

Table 3. Characteristics of female participants in the AGES-Reykjavik Study by weekly fish intake in adolescence and midlife

	Fish intake in adolescence							Fish intake in midlife						
	≤2 portions (*n* = 1,425)		>2 up to 4 portions (*n* = 311)		>4 portions (*n* = 1,146)		*P*[a]	≤2 portions (*n* = 326)		>2 up to 4 portions (*n* = 1,781)		>4 portions (*n* = 772)		*P*[a]
Age at study entry														
Mean (SD)	76.2	(5.6)	77.3	(6.0)	76.5	5.5	0.013	74.8	(5.4)	76.2	(5.6)	77.6	(5.6)	0.001
Median	76		77		76			74		76		77		
Age at diagnosis														
Mean (SD)	80.3	(6.1)	80.3	(5.4)	81.3	(6.6)	0.784	75.6	(3.2)	81.5	(6.2)	81.9	(5.9)	0.003
Median	80		78		82			75		82		82		
Height[b] (cm)														
Mean (SD)	164.1	(5.4)	164.4	(5.6)	164.1	(5.3)	0.643	164.5	(5.3)	164.2	(5.4)	164.0	(5.3)	0.312
Median	164		164.5		164			164.5		164		164		
BMI[b] (kg/m^2)														
Mean (SD)	24.8	(3.6)	24.8	(4.4)	25.1	(3.8)	0.073	25.0	(4.05)	24.9	(3.7)	25.0	(3.9)	0.860
Median	24.3		24		24.5			24		24.4		24.3		
Education, *n* (%)														
Primary	592	(42)	121	(39)	524	(46)	0.116	163	(50)	755	(42)	317	(41)	0.005
Secondary	626	(44)	147	(47)	475	(41)		138	(42)	765	(43)	345	(45)	
University/College	207	(14)	43	(14)	147	(13)		25	(8)	261	(15)	110	(14)	
Birth cohort, *n* (%)														
1907–1919	143	(10)	50	(16)	128	(11)	0.071	23	(7)	180	(10)	117	(15)	0.001
1920–1924	324	(23)	75	(24)	267	(23)		52	(16)	405	(23)	208	(27)	
1925–1929	452	(32)	89	(29)	371	(32)		104	(32)	563	(32)	245	(32)	
1930–1935	506	(36)	97	(31)	380	(33)		147	(45)	633	(36)	202	(26)	
Age at menarche, *n* (%)														
≤13 y	639	(45)	148	(48)	502	(44)	0.469	147	(45)	789	(44)	350	(45)	0.900
≥14 y	784	(55)	162	(52)	643	(56)		179	(55)	988	(56)	422	(55)	
Ever pregnant, *n* (%)														
Yes	1308	(92)	286	(93)	1068	(93)	0.464	300	(92)	1638	(92)	721	(94)	0.488
Age at birth of first child, *n* (%)														
≤24 y	832	(59)	177	(58)	739	(65)	0.023	204	(64)	1080	(61)	462	(61)	0.489
≥25 y	457	(33)	106	(35)	318	(28)		88	(28)	545	(31)	247	(33)	
Physical activity, *n* (%)														
Never	639	(48)	133	(46)	520	(48)	0.894	154	(51)	837	(50)	301	(42)	0.001
Rarely/occasionally	289	(22)	67	(23)	224	(21)		76	(25)	354	(21)	150	(21)	
Moderate/high	393	(30)	87	(30)	329	(31)		73	(24)	474	(29)	261	(37)	
Family history of breast cancer, *n* (%)														
Yes	240	(17)	50	(16)	188	(16)	0.926	65	(20)	292	(16)	121	(16)	0.206
Meat consumption, *n* (%)														
2 times and less p/w	606	(43)	166	(53)	186	(16)	0.001	113	(35)	671	(38)	418	(54)	0.001
3 times and more p/w	808	(57)	144	(47)	956	(84)		211	(65)	1105	(62)	352	(46)	
Milk consumption, *n* (%)														
Less than daily	371	(26)	67	(22)	256	(22)	0.045	161	(50)	777	(44)	308	(40)	0.009
Daily and more	1046	(74)	243	(78)	887	(78)		160	(50)	996	(56)	460	(60)	
Rye consumption, *n* (%)														
Less than daily	778	(55)	142	(46)	532	(47)	0.001	246	(76)	1236	(69)	435	(57)	0.001
Daily or more	632	(45)	168	(54)	606	(53)		79	(24)	542	(31)	334	(43)	
Fish liver oil consumption, *n* (%)														
Less than daily	640	(45)	139	(45)	454	(40)	0.017	124	(38)	604	(34)	221	(29)	0.005
Daily and more	778	(55)	171	(55)	690	(60)		202	(62)	1172	(66)	546	(71)	
Salted fish consumption, *n* (%)														
3 times a month or less	728	(52)	169	(55)	491	(43)	0.001	268	(83)	1275	(72)	471	(61)	0.001
Once a week or more	684	(48)	141	(46)	641	(57)		57	(17)	495	(28)	297	(39)	
Consumption of alcohol, *n* (%)														
Yes								223	(69)	1067	(60)	428	(56)	0.001
Ever use HRT, *n* (%)														
Yes								99	(31)	486	(28)	210	(28)	0.536
Ever use oral contraceptives, *n* (%)														
Yes								122	(38)	512	(29)	198	(26)	0.001

Abbreviation: HRT, hormone replacement therapy.
[a]*P* values are based on χ^2 tests, except for length of residence, age at entry, age at diagnosis, height and BMI, where one-way ANOVA test was used.
[b]Information retrieved upon entry into the Reykjavik Study.

on reproductive factors like the use of HRT and oral contraceptives and breastfeeding for all women in the residence analysis, and we cannot exclude unmeasured confounders in our study.

Our data imply that very high fish consumption in early to midlife may be associated with a decreased risk of breast cancer. However, we need larger prospective studies to further clarify the effects of very high fish consumption on breast cancer risk.

Table 4. Multivariable analysis of breast cancer by weekly fish and fish liver oil consumption

	IR per 1,000 person years	Age-adjusted HR (95% CI)	HR[a] (95% CI)	HR[b] (95% CI)
Adolescence (14–19 years)[a]				
Fish consumption		*n* = 91	*n* = 90	*n* = 88
≤2 portions	4.04	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
>2 up to 4 portions	4.44	1.09 (0.57–1.20)	1.13 (0.59–2.17)	1.19 (0.61–2.31)
>4 portions	3.21	0.79 (0.51–1.25)	0.74 (0.47–1.17)	0.71 (0.44–1.13)
Fish liver oil consumption				
Never	3.62	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Daily or less	3.88	1.07 (0.71–1.62)	1.07 (0.70–1.63)	1.10 (0.71–1.69)
Midlife (40–50 years)[b]				
Fish consumption		*n* = 91	*n* = 90	*n* = 90
≤2 portions	5.05	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
>2 up to 4 portions	4.07	0.80 (0.44–1.42)	0.82 (0.46–1.48)	0.81 (0.45–1.47)
>4 portions	4.07	0.47 (0.23–0.99)	0.47 (0.23–0.99)	0.46 (0.22–0.97)
Fish liver oil consumption				
Never	3.90	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Daily or less	3.70	0.95 (0.61–1.46)	0.97 (0.62–1.51)	0.96 (0.62–1.49)
Late life (66–96 years)[c]				
Fish liver oil consumption		*n* = 91	*n* = 88	*n* = 88
Never	3.05	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Daily or less	4.05	1.34 (0.81–2.22)	1.33 (0.81–2.20)	1.31 (0.79–2.16)

NOTE: All portions are based on weekly consumption.

Abbreviations: CI, confidence interval; *n*, number of breast cancer diagnoses in analysis.

[a]Adolescence: HR[a] adjusted for age upon entry, education, family history of breast cancer, BMI in midlife, age at first child and age at menarche. HR[b] additionally adjusted for intake of milk, rye, meat, fish liver oil (in fish analyses), salted/smoked fish in adolescence and fish (for fish liver oil analyses).

[b]Midlife: HR[a] adjusted for same covariates as in HR in adolescence plus use of alcohol in midlife. HR[b] Additionally adjusted for same food items as in adolescence, replaced with midlife values.

[c]Late life: HR[a] adjusted for same covariates as in midlife except values for body mass index and alcohol consumption in late life were replaced for midlife values.HR[b] additionally adjusted for same food items as in midlife and adolescence, replaced with late life values.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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Authors' Contributions

Conception and design: A. Haraldsdottir, L. Steingrimsdottir, U.A. Valdimarsdottir, T.B. Harris, J.E. Torfadottir

Development of methodology: A. Haraldsdottir, L. Steingrimsdottir, U.A. Valdimarsdottir, J.E. Torfadottir

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Tryggvadottir, T.B. Harris, V. Gudnason

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. Haraldsdottir, L. Steingrimsdottir, U.A. Valdimarsdottir, T. Aspelund, L.A. Mucci, E.L. Giovannucci, H.-O. Adami, J.E. Torfadottir

Writing, review, and/or revision of the manuscript: A. Haraldsdottir, L. Steingrimsdottir, U.A. Valdimarsdottir, T. Aspelund, L. Tryggvadottir, T.B. Harris, L.J. Launer, L.A. Mucci, E.L. Giovannucci, H.-O. Adami, V. Gudnason, J.E. Torfadottir

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Haraldsdottir, T. Aspelund, V. Gudnason

Study supervision: L. Steingrimsdottir, U.A. Valdimarsdottir, T. Aspelund, V. Gudnason, J.E. Torfadottir

Other (developed the core study AGES): L.J. Launer

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Early Life Residence, Fish Consumption, and Risk of Breast Cancer

Alfheidur Haraldsdottir, Laufey Steingrimsdottir, Unnur A. Valdimarsdottir, et al.

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Paper II

PLOS ONE

RESEARCH ARTICLE

Dietary habits in adolescence and midlife and risk of breast cancer in older women

Alfheidur Haraldsdottir[1,2]*, Johanna E. Torfadottir[2], Unnur A. Valdimarsdottir[2,3,4], Hans-Olov Adami[3,4], Thor Aspelund[2], Laufey Tryggvadottir[5,6], Marianna Thordardottir[6], Bryndis E. Birgisdottir[1,7], Tamara B. Harris[8], Lenore J. Launer[8], Vilmundur Gudnason[6,9], Laufey Steingrimsdottir[1,7]

1 Faculty of Food Science and Human Nutrition, University of Iceland, Reykjavik, Iceland, **2** Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavik, Iceland, **3** Department of Epidemiology, Harvard T.H Chan School of Public Health, Boston, Massachusetts, United States of America, **4** Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, **5** The Icelandic Cancer Registry, Reykjavik, Iceland, **6** Faculty of Medicine, University of Iceland, Reykjavik, Iceland, **7** Unit for Nutrition Research, University of Iceland and Landspitali National University Hospital, Reykjavik, Iceland, **8** Laboratory of Epidemiology and Population Sciences, Intramural Research Program, National Institute on Aging, Bethesda, Maryland, United States of America, **9** The Icelandic Heart Association, Kopavogur, Iceland

* alh1@hi.is

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Abstract

Recent studies indicate that lifestyle factors in early life affect breast cancer risk. We therefore explored the association of high consumption of meat, milk, and whole grain products in adolescence and midlife, on breast cancer risk. We used data from the population based AGES-Reykjavik cohort (2002–2006), where 3,326 women with a mean age of 77 years (SD 6.0) participated. For food items and principal component derived dietary patterns we used Cox proportional models to calculate multivariate hazard ratios (HR) with 95% confidence intervals (95% CI). During a mean follow-up of 8.8 years, 97 women were diagnosed with breast cancer. For both adolescence and midlife, daily consumption of rye bread was positively associated with breast cancer (HR 1.7, 95% CI 1.1–2.6 and HR 1.8, 95% CI 1.1–2.9, respectively). In contrast, persistent high consumption of oatmeal was negatively associated with breast cancer (0.4, 95% CI 0.2–0.9). No association was found for other food items or dietary patterns that included rye bread. High rye bread consumption in adolescence and midlife may increase risk of late-life breast cancer whilst persistent consumption of oatmeal may reduce the risk.

Introduction

During adolescence the female mammary tissue undergoes extensive modeling or re-modeling. Consequently, researchers have hypothesized that breast tissue may be particularly susceptible for initiation of breast tumors during this period [1, 2]. There is increasing evidence on the importance of adult midlife diet and risk of breast cancer [3] while available studies on the impact of diet during adolescence on breast cancer risk are scarce and somewhat inconsistent [4]. Studying early life diet can be challenging due to potential misclassification bias, the need for a long follow-

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up and limited variation in food intake between participants. Interestingly, there was considerable variability in dietary habits between residency areas in Iceland in early and mid 20th century due to relative isolation of regions and differences in food access. This variation was observed to be strongest for the most common food items consumed at that time, or meat, rye, milk products, fish and fish oil [5]. These products are also of interest in this context because of their diverse bioactive compounds [6, 7] as well as their wide-spread use in modern Western diets.

In the Nurses' Health Study, women in the highest quintile of red meat consumption in adolescence had significantly higher risk of breast cancer than women in the lowest quintile [8–10]. A recent meta-analysis of 14 prospective studies [11] on adult red- and processed meat consumption reported a slightly increased breast cancer risk and similar results were observed in the NIH-AARP Diet and Health Study [12]. In contrast, no association with either childhood or adult milk consumption and risk of breast cancer has been found [13–18]. High total dietary fiber intake in early adulthood was associated with significantly lower breast cancer risk [19], as was total high adolescent consumption of lignans [20], a common phytoestrogen commonly found in whole grains [21]. High consumption whole grain food intake in adolescence and early adulthood was associated with lower risk of premenopausal breast cancer risk but not with post-menopausal risk [22]. Available studies on total adult whole grain consumption and breast cancer risk have either suggested a negative [22–24] or no association [25, 26].

For this study we used data from the population based AGES-Reykjavik Study, which is derived from a population with considerable variation in dietary habits in adolescence. Using the same cohort, we have previously observed a preventive role of very high fish intake in adolescence and midlife for breast cancer [27] and also the importance of earlier diet for prostate cancer risk [28–30]. In the present study our aim was to explore the effects of high consumption of meat, milk, and whole grain products in adolescence and midlife on breast cancer risk later in life, with a main emphasis on the adolescence period.

Materials and methods

Study population

We used data from the Age Gene Environment Susceptibility (AGES)—Reykjavik Cohort Study of the Icelandic Heart Association, a sub-cohort of the population based Reykjavik Study initiated in 1967 [31]. The AGES-Reykjavik Study examinations began in 2002 and at that time 11,549 Reykjavik Study cohort members were still alive. Thereof, 8,030 individuals were randomly invited to the study and of these, 5,764 individuals (thereof 3,326 women) participated between 2002–2006 (72% response rate). Extensive data were collected during clinical examinations, including information on food intake in adolescence, midlife and present old age. For our analysis we used data from the first clinical examination [32]. For this study, we excluded women who had been diagnosed with breast cancer prior to study entry (n = 196), leaving 3130 women in our study.

Dietary assessment in early life and midlife

At study entry, the participants completed a food frequency questionnaire (FFQ) on diet in adolescence (between the ages of 14 to 19 years), in midlife (between the ages 40 to 50 years), and at study entry (late life). For this analysis we only use questions from the adolescent and midlife period.

The FFQ was especially designed for this project and provides information on frequency of intake of 10 common foods and food groups consumed in adolescence and 11 in midlife. For both adolescence and midlife, 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 [33]. An additional question on

consumption of whole wheat bread was included for the midlife period, but this type of bread was uncommon in the adolescent period. As previously stated, for this analysis our main focus is on meat, including salted and smoked meat, milk, rye bread, oatmeal and whole wheat bread. We have previously published analysis on fish and cod liver oil from this same cohort [27] while analysis on fruits and vegetables were not conducted due to very low consumption on a daily basis for both adolescence and midlife. However, all food groups, as described above, were included in the dietary pattern analysis (see supporting information).

Two separate questions were asked regarding meat consumption. One included total consumption of meat and ground meat as a meal (hereafter referred to as meat). The other question (included in total meat consumption) concerned intake of corned meat, corned meat sausage, or any kind of salted/smoked meat (hereafter referred to as salted or smoked meat). Information on milk consumption included frequency of intake of milk and milk products (hereafter referred to as milk). Rye bread consumption was assessed by one question on intake of rye bread and flatbread made of rye (hereafter referred to as rye bread). For midlife, the question on oatmeal also included muesli, but will be referred to as oatmeal in both periods.

For meat, milk, rye bread, oatmeal, and whole wheat bread, the frequency of consumption was classified into; 1) never, 2) less than once a week, 3) 1–2 times a week, 4) 3–4 times a week, 5) 5–6 times a week, 6) daily, and 7) more than once a day. For salted or smoked meat, the following response categories were: 1) never, 2) less than once a month, 3) 1–3 times a month, 4) 1–2 times a week 5) 3–6 times a week 6) daily or more often.

For both adolescence and midlife, meat consumption was divided into two categories. low (2 times or less per week) and high (3 times or more per week). Consumption of salted or smoked meat was also divided into two categories, with low intake defined as 3 times per month or less and high as once per week or more. Consumption of milk, rye bread and whole wheat bread (midlife only) was divided into two categories (less than daily and daily or more). Consumption of oatmeal was divided into low (4 times a week or less) and high (5 times a week or more).

The FFQ has been validated for midlife and late life [33, 34]. In short, midlife dietary habits were validated by comparing the results in the AGES-FFQ (n = 107) with detailed dietary data gathered from the same individuals 18–19 years previously in a National nutrition survey conducted in 1990. The main results were that the correlation coefficients for most of the food items were within an acceptable range [33].

Covariate assessment

Information on potential confounders was mainly retrieved from a lifestyle questionnaire, completed at entry to the AGES-Reykjavik Study. We collected information on age at entry to the study (continuous), age at menarche (continuous), family history of breast cancer (mother, sister and/or daughter ever diagnosed with breast cancer), education (primary, secondary, college/university), use of hormonal replacement therapy (never, ever), oral contraceptive (never, ever), use of alcohol in midlife (yes, no), and physical activity in adolescence and midlife (never/rarely, occasionally, moderately/often). We also retrieved information on ever being pregnant (y/n) and age at first birth (continuous), and combined this information into one variable (no births, age 24 and younger, 25 and older). From the Reykjavik Study we retrieved values on body mass index (BMI) and height from the midlife period (both continuous). Information on dietary covariates was retrieved from the AGES-FFQ (Fig 1).

Selected dietary covariates on concurrent consumption included, milk, meat, salted and smoked meat, oatmeal, and rye bread, depending on the exposure (see cut offs above). We also used information on fish consumption, ($\leq$ 2 portions p/w vs. >2–4 portions p/w vs. > 4portions p/w) and on salted and smoked fish (3 times a month or less vs. once a week or more).

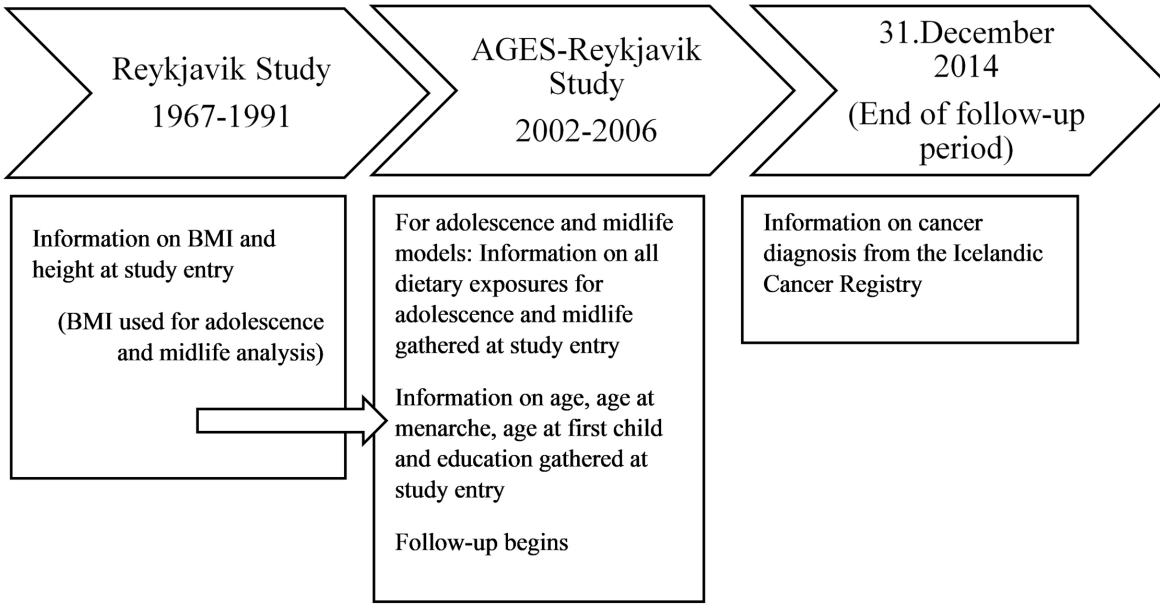

Fig 1. Timeline of examination points in the study.

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As residence dependent variance in food consumption existed during the adolescence period [5] we also added information on place of residence when growing up in our models (capital, coastal village, rural area, and combination of coastal village and rural area) collected in the Reykjavik Study.

Ascertainment of outcome

We ascertained breast cancer diagnosis through the nationwide Icelandic Cancer Registry [35]. Information on cause of death was obtained from Directorate of Health. Due to the computerized national roster and unique personal identification numbers for each person, follow-up was virtually complete (99%) [35]. Participants were followed from the study entry (between 2002 and 2006) to diagnosis of breast cancer, death, or until the end of the observation period (December 31, 2014), whichever occurred first.

Statistical analysis

For both adolescence and midlife, Cox proportional hazard regression models were used to calculate hazard ratio (HR) and 95% confidence interval (95% CI) for incident breast cancer. For all exposures in the adolescent period the first model was adjusted for age (as a continuous variable) at entry. Depending on exposure, all other food items under study (meat, salted and smoked meat, milk, rye bread, oatmeal) plus information on fish and salted and smoked fish were then added simultaneously to the second model (see cutoffs above in *covariates assessment*). Further adjustments were then made for education (3 categories), BMI (continuous) in midlife, age at first child birth (3 categories) and age at menarche (continuous).

After combining information on ever being pregnant and age at first birth in to one variable we had missing values for 211 women. The missing values were included in the multivariable

analysis as a special category. We also replaced the 21 missing values for BMI with the mean BMI value of the participants of the study, or 25. The 177 missing values for age at menarche were replaced with the mean age of menarche in the cohort, or 14 years. We did not replace missing values for food items, neither for exposures or covariate variables.

For midlife, the same types of models were presented, except here midlife measures for all food consumption were used. Also, information on consumption of alcohol and whole wheat bread was added to the multivariate midlife model.

For both periods,further adjustment for family history of breast cancer, height, and physical activity, family history of breast cancer, hormonal replacement therapy or oral contraceptive did not change our risk estimates (data not shown) and were therefore not included in our final statistical models.

To assess the potential effects of longitudinal dietary habits on breast cancer risk we pooled consumption of each food item in adolescence and midlife into one variable with four categories; 1) low in both adolescence and midlife; 2) low in adolescence and high in midlife; 3) high in adolescence and low in midlife; and 4) high in both adolescence and midlife. For this analysis, the first category (low consumption in both periods) was used as a reference. Adjustments were made for same factors as described for the adolescent period. We also performed Spearman´s correlation test between consumption on food items under study in adolescence and midlife.

To further examine whether the association observed for rye bread and oatmeal persisted when other food items commonly consumed were included we also used principal component analysis to identify dietary patterns from the AGES-FFQ, including all dietary data available. This method is data driven and forms new linear factors (dietary patterns) by reducing data dimension and grouping correlated variables (food intake). For each pattern, a new variable is created, ranking participants on their adherence to that particular pattern [36]. Each variable/pattern was further divided into tertiles, or low, medium, and high adherence to each pattern. We used Cox proportional hazard regression to test association between adherence to adolescence and midlife patterns and breast cancer risk, using the lowest tertile as a reference. For both adolescence and midlife, adjustments were made for age at entry, BMI, education, age at menarche, and age at first child, using the same cut offs as previously described for individual exposures in adolescence and midlife. We also tested for trend in the hazard ratios for the first category, using polynomial contrasts (data shown in S1 and S2 Tables).

For all statistical analysis we used SPSS software, version 24.0 (SPSS Inc., Chicago, Illinois; www.spss.com) and R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; (http://www.R-project.org/).

The study protocol was approved by the Icelandic Ethical Review Board and the Icelandic Data Protection Authority (VSN b2007120014/03-7).

Results

The mean age at study entry was 77.0 years and standard deviation (SD) 6.0. The mean follow-up time was 8.8 years (SD = 3.1). During that time, 97 women were diagnosed with breast cancer, with mean age at diagnosis 81.4 years (SD = 6.5). The dietary analyses were based on participants who provided information on diet in midlife and adolescence when entering the AGES-Reykjavik cohort and were free of breast cancer.

Diet in adolescence

Table 1 shows characteristics of the population that provided data on meat (n = 2,866), milk (n = 2,871), and rye bread (n = 2,858) consumption in adolescence. When compared with women with low consumption of meat in adolescence, women with high consumption of meat

Table 1. Characteristics of female participants in the AGES–Reykjavik Study (2002–2006) according to consumption of rye bread, meat and milk in adolescence.

	Rye bread					Meat					Milk				
	N = 2858					N = 2866					N = 2871				
	Low		High			Low		High			Low		High		
	Less than daily		*Daily or more*			*2 times or less per week*		*3 times or more per week*			*Less than daily*		*Daily or more*		
	n = 1452		n = 1406		*P value*	n = 958		n = 1908		*P value*	n = 695		n = 2176		*P value*
Age at study entry															
Mean (SD)	75.2	(5.3)	77.8	(5.7)	0.001	76.1	(5.8)	76.6	(5.5)	0.001	76.3	(5.7)	76.5	(5.6)	0.549
Median	74		78			75		76			75		76		
Height (cm)*															
Mean (SD)	164.4	(5.2)	163.9	(5.5)	0.012	164.3	(5.4)	164.1	(5.4)	0.001	163.9	(5.1)	164.2	(5.5)	0.202
Median	164.5		164			164		164			164		164		
BMI (kg/m^2)*															
Mean (SD)	24.9	(3.7)	25.0	(3.8)	0.520	24.8	(3.8)	25.0	(3.8)	0.001	25.3	(3.9)	24.8	(3.7)	0.010
Median	24		24.5			24		24			24.5		24		
Education, n (%)															
Primary	560	(39)	667	(47)	0.001	358	(37)	874	(46)	0.001	316	(46)	915	(42)	0.232
Secondary	665	(46)	572	(41)		446	(47)	792	(42)		292	(42)	951	(44)	
University/College	227	(15)	167	(12)		154	(16)	242	(12)		87	(13)	310	(14)	
Birth cohort, n (%)															
1908–1919	85	(6)	236	(17)	0.001	104	(11)	216	(11)	0.016	73	(11)	247	(11)	0.386
1920–1924	285	(20)	373	(26)		205	(21)	456	(24)		157	(23)	505	(23)	
1925–1929	470	(32)	435	(31)		283	(30)	621	(33)		209	(30)	699	(32)	
1930–1935	612	(42)	362	(26)		366	(38)	615	(32)		256	(37)	725	(33)	
Location of first residence, n (%)															
Reykjavik	603	(42)	458	(33)	0.001	351	(37)	712	(38)	0.001	283	(41)	783	(37)	0.001
Coastal village	515	(36)	417	(30)		267	(28)	666	(36)		270	(39)	664	(31)	
Rural area	259	(18)	450	(33)		277	(30)	437	(23)		113	(17)	601	(28)	
Combination of coastal village and rural area	53	(4)	50	(4)		45	(5)	58	(3)		18	(3)	86	(4)	
Age at menarche, n (%)															
≤ 13 y	669	(46)	609	(43)	0.147	447	(47)	836	(44)	0.147	309	(45)	978	(45)	0.824
≥ 14 y	782	(54)	794	(57)		510	(53)	1069	(56)		385	(55)	1195	(55)	
Age at first birth, n (%)															
No children	101	(7)	111	(8)	0.003	81	(8)	132	(7)	0.017	40	(6)	173	(8)	0.172
≤ 24 y	927	(64)	804	(57)		544	(57)	1197	(63)		441	(63)	1300	(60)	
≥ 25 y	404	(28)	472	(34)		317	(33)	557	(29)		205	(30)	673	(31)	
Physical activity															
Never	600	(44)	685	(52)	0.001	405	(46)	881	(49)	0.179	310	(47)	977	(48)	0.499
Rarely/occasionally	335	(25)	242	(19)		202	(23)	376	(21)		153	(23)	426	(21)	
Moderate/high	426	(31)	377	(29)		281	(32)	526	(30)		194	(30)	615	(31)	
Family history of breast cancer															
Yes	235	(16)	238	(17)	0.593	147	(15)	330	(17)	0.186	121	(17)	355	(16)	0.499
High intake of other food groups															
Fish (> 4 portions p/w)	532	(37)	606	(43)	0.001	186	(19)	956	(50)	0.001	256	(37)	887	(41)	0.045
Salted fish (once p/w or more)	600	(42)	861	(62)	0.001	450	(47)	1008	(53)	0.002	255	(37)	1210	(56)	0.001
Oatmeal (≥ 5 times p/w)	377	(26)	686	(49)	0.001	353	(37)	710	(38)	0.840	132	(19)	932	(43)	0.001
Salted or smoked meat (once p/w or more)	356	(25)	575	(41)	0.001	334	(35)	595	(31)	0.053	146	(21)	783	(36)	0.001
Milk (daily or more)	974	(67)	1185	(84)	0.001	733	(77)	1432	(75)	0.328					

(*Continued*)

Table 1. (Continued)

	Rye bread					Meat					Milk				
	N = 2858					N = 2866					N = 2871				
	Low		High			Low		High			Low		High		
	Less than daily		*Daily or more*			*2 times or less per week*		*3 times or more per week*			*Less than daily*		*Daily or more*		
	n = 1452		n = 1406		*P value*	n = 958		n = 1908		*P value*	n = 695		n = 2176		*P value*
Meat ≥ 3 times p/w)	944	(65)	953	(68)	0.122						473	(68)	1432	(66)	0.328

Abbreviations: SD, standard deviation.

*Measured in midlife—at entry to the Reykjavik Study

P values are based on Chi-square tests, except for age at entry, height and BMI, where One-Way ANOVA test was used

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(3 times or more p/w) were older at study entry, less educated, and older when having their first child. They also consumed more salted or smoked meat and more salted and regular fish. Women with high milk consumption (daily or more often) had lower BMI in midlife, were more often raised in rural areas, and had more frequent consumption of cod liver oil, salted or smoked fish, total fish, meat, and oatmeal. When compared with less than daily rye bread consumption, women who consumed rye bread daily or more often were older when entering the study, had lower education level, were more commonly raised in rural areas, were older upon first birth, and less physically active. They also consumed fish more frequently, particularly salted or smoked fish as well as milk, oatmeal, and meat, including salted or smoked meat.

Table 2 presents hazard ratios, with 95% CI, for breast cancer and diet in adolescence. No statistically significant association was found for meat, salted and smoked meat and milk consumption. For whole grain products, we found a positive association between high consumption of rye bread (daily or more often) in adolescence and breast cancer risk (HR 1.7, 95% CI

Table 2. Multivariate analysis of breast cancer risk by meat, milk and whole grain intake in adolescence.

	Meat		Salted or smoked meat		Milk		Rye bread		Oatmeal	
	N = 2866		N = 2862		N = 2871		N = 2858		N = 2856	
	Low	High	Low	High	Low	High	Low	High	Low	High
	2 times or less p/w	*3 times or more p/w*	*3 times a month or less*	*Once p/w or more*	*Less than daily*	*Daily or more*	*Less than daily*	*Daily or more*	*4 times or less p/w*	*5 times or more p/w*
	n = 958	n = 1908	n = 1930	n = 932	n = 695	n = 2176	n = 1452	n = 1406	n = 1791	n = 1065
Breast cancer (%)	28 (2.9)	68 (3.6)	61 (3.2)	36 (3.9)	29 (4.2)	68 (3.1)	41 (2.8)	55 (3.9)	68 (3.8)	29 (2.7)
Age adjusted HR	1.0	1.2	1.0	1.3	1.0	0.8	1.0	1.5	1.0	0.7
(95% CI)	(ref.)	(0.8–1.9)	(ref.)	(0.8–1.9)	(ref.)	(0.50–1.2)	(ref.)	(1.0–2.2)	(ref.)	(0.5–1.2)
Multivariate HR*	1.0	1.3	1.0	1.4	1.0	0.7	1.0	1.7	1.0	0.7
(95% CI)	(ref.)	(0.8–2.0)	(ref.)	(0.9–2.2)	(ref.)	(0.4–1.1)	(ref.)	(1.1–2.6)	(ref.)	(0.5–1.2)

Abbreviations: CI, confidence interval; HR, hazard ratio: p/w, per week

*Multivariate HR; adjusted for age at entry, education, body mass index in midlife, age at first child and age at menarche. All food items under study (meat, salted and smoked meat, milk, rye bread, oatmeal) plus information on fish and salted and smoked fish were then added simultaneously to the multivariate model. The multivariate analysis included 2810 women, thereof 95 with breast cancer.

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1.1–2.6), when compared with lower consumption (less than daily). No significant association was observed for oatmeal consumption. When adding early life residence to the multivariate model the risk estimates for high rye bread consumption increased (HR 1.8, 95% CI 1.2–2.9). No difference was observed for other estimates.

We further divided rye bread consumption into three groups (two times or less per week, 3–6 times per week, and daily or more) and explored the association with breast cancer risk, where we found a significant trend across the groups, HR 1.0 (95% CI 0.5–2.0) and HR 1.7 (95% CI 0.9–3.2), respectively ($P_{trend} = 0.043$).

Midlife diet

For midlife (Table 3), no significant association was observed for meat and milk consumption, although a marginally positive association was observed for high consumption (once per week or more) of salted or smoked meat (HR 1.6, 95% CI 1.0–2.6) compared with women with low consumption (3 times a month or less). For whole grain products, no association was observed for whole wheat bread while a statistically significant positive association was observed for high consumption (daily or more) of rye bread (HR 1.8, 95% CI 1.1–2.9) when compared with lower consumption (less than daily). No significant association was observed for oatmeal. No difference was observed for any of the risk estimates when early life residence was added to the model.

Rye bread consumption in midlife was further divided into three groups (two times or less per week, 3–6 times per week, and daily or more). Compared with the group with the lowest consumption, the risk estimates for 3–6 times per week and daily or more were 1.4 (95% CI 0.8–2.4) and 2.3 (95% CI 1.3–4.1), respectively ($P_{trend} < 0.01$).

Long term consumption

Table 4 presents Spearman's correlation between dietary habits in adolescence and midlife. The strongest correlation was found for rye bread consumption ($\rho = 0.50$, $P = 0.001$) and the lowest for meat consumption ($\rho = -0.19$, $P = 0.001$).

Table 5 presents long term consumption for meat, salted or smoked meat, milk, rye bread, and oatmeal with low consumption in adolescence and midlife as a reference category. A positive association was observed for high rye bread consumption in adolescence and midlife (HR 2.1, 95% CI 1.2–3.5). An inverse association was observed between breast cancer risk and high consumption of oatmeal in both adolescence and midlife (HR 0.4, 95% CI 0.2–0.9) ($P_{trend} = 0.07$). No association was observed between breast cancer and meat, salted or smoked meat and milk.

Supplementary material—dietary pattern

Four dietary patterns were extracted for the adolescent period. Factor loading coefficients for those patterns are presented in S1 Table. One pattern containing rye bread in addition to blood liver sausage, salted meat, salted fish, and oatmeal represents traditional Icelandic diet in the earlier half of the 20th century. High adherence to this pattern was not significantly associated with breast cancer risk (HR 1.3 95% CI 0.7–2.1). Borderline inverse association was observed for the highest adherence to a pattern high in consumption of fish, blood/liver sausage, oatmeal, fish oil, and milk in adolescence (HR 0.6, 95% CI 0.4–1.0) ($P_{trend} = 0.049$) (S2 Table).

Four dietary patterns were also extracted for the midlife period. No association was observed for any of those patterns, including the dietary pattern including rye bread consumption (data not shown).

Discussion

In this population based cohort, daily consumption of rye bread during both adolescence and midlife was positively associated with breast cancer. Conversely, we found reduced risk for breast cancer among women who consumed oatmeal persistently both in adolescence and midlife. However, no dietary pattern in either adolescence or midlife that included rye bread was significantly associated with breast cancer while a pattern in adolescence that represented fish, blood/liver sausage, oatmeal, fish oil, and milk seemed to be protective for breast cancer. We also observed borderline risk of breast cancer with high midlife consumption of salted or smoked meat. No association was found between high milk intake and breast cancer risk in either period.

To the best of our knowledge, no study has specifically addressed adolescent consumption of rye bread, a common whole grain product in the Nordic countries, in relation to late-life breast cancer. A few studies have analyzed total adolescent consumption of lignans, a common phyto-estrogen in whole grain cereals—such as rye, wheat, oats, and barley—but also in legumes, oil-seeds, and various fruits and vegetables [37]. A Canadian case control study found that high adolescent intake of lignans reduced the risk of breast cancer. However, although rye bread was included in the diet assessment of the study, it was not commonly consumed and these results can also be confounded by other healthy eating habits [20]. Results from the Nurses' Health Study suggest that high consumption of whole grains in adolescence can reduce the risk of pre-menopausal breast cancer [22]. However, the main difference between this study and ours was rye bread does not seem to be included in total wholegrain consumption in the Nurse´s Health Study questionnaire. Also, the women in our cohort were all post-menopausal with a high mean age at diagnosis, and therefore possibly different carcinogenic process [38].

The few studies on total whole grain consumption in adults and breast cancer have either suggested a protective [23, 24] or no association [25, 26]. The major difference between most

Table 3. Multivariate analysis of breast cancer risk by meat, milk and whole grain intake in midlife.

	Meat		Salted or smoked meat		Milk		Rye bread		Oatmeal		Whole wheat bread	
	N = 2871		N = 2864		N = 2864		N = 2875		N = 2768		N = 2865	
	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
	2 times or less p/w	*3 times or more p/w*	*3 times a month or less*	*Once p/w or more*	*Less than daily*	*Daily or more*	*Less than daily*	*Daily or more*	*4 times or less p/w*	*5 times or more p/w*	*Less than daily*	*Daily or more*
	n = 1203	n = 1668	n = 2210	n = 654	n = 1247	n = 1617	n = 1918	n = 957	n = 2094	n = 674	n = 1238	n = 1627
Breast cancer (%)	41 (3.4)	56 (3.4)	71 (3.2)	26 (4.0)	41 (3.2)	56 (3.5)	57 (3.0)	40 (4.2)	81 (3.7)	16 (2.3)	44 (3.6)	53 (3.3)
Age adjusted HR	1.0	1.0	1.0	1.3	1.0	1.1	1.0	1.5	1.0	0.6	1.0	0.9
(95% CI)	(ref.)	(0.6–1.5)	(ref.)	(0.8–2.1)	(ref.)	(0.7–1.6)	(ref.)	(1.0–2.3)	(ref.)	(0.4–1.1)	(ref.)	(0.6–1.4)
Multivariate HR*	1.00	1.0	1.0	1.6	1.0	1.1	1.0	1.8	1.0	0.6	1.0	0.8
(95% CI)	(ref.)	(0.6–1.4)	(ref.)	(1.0–2.6)	(ref.)	(0.7–1.7)	(ref.)	(1.1–2.9)	(ref.)	(0.4–1.1)	(ref.)	(0.5–1.3)

Abbreviations: CI, confidence interval; HR, hazard ratio.

*Multivariate HR; adjusted for age at entry, education, body mass index in midlife, alcohol consumption in midlife, age at first child and age at menarche. All food items under study (meat, salted and smoked meat, milk, rye bread, oatmeal and whole wheat bread) plus information on fish and salted and smoked fish were then added simultaneously to the multivariate model. The multivariate analysis included 2813 women, thereof 97 with breast cancer.

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Table 4. Dietary habits among participants through different time periods.

	Adolescence	Midlife	Spearmans´s ρ	*P*
	n (%)	n (%)		
Rye bread			0.50	0.001
Less than daily	1452 (51)	1918 (67)		
Daily or more	1406 (49)	957 (31)		
Milk and milk products			0.44	0.001
Less than daily	695 (24)	1247 (44)		
Daily or more	2176 (76)	1617 (56)		
Meat			-0.19	0.001
2 times or less p/w	958 (33)	1203 (42)		
3 times or more p/w	1908 (67)	1668 (58)		
Salted or smoked meat			0.36	0.001
3 times a month or less	1930 (67)	2210 (77)		
Once or more p/w	932 (33)	654 (23)		
Oatmeal			0.38	0.001
4 times or less p/w	1791 (63)	2715 (76)		
5 times or more p/w	1065 (37)	690 (24)		
Vegetables			0.38	0.001
Never	585 (20)	163 (6)		
6 times p/w or less	2175 (76)	2845 (87)		
Daily	105 (4)	213 (7)		
Fruit			0.24	0.001
Never	1013 (36)	114 (4)		
6 times p/w or less	1784 (62)	2501 (87)		
Daily	68 (2)	256 (9)		

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of these and the present study is that we disentangled whole grain consumption into rye, whole wheat bread and oatmeal. Different types of whole grains contain dissimilar bioactive compounds [7] which may act differently on breast cancer genesis.

A Danish study [25] reported no association between neither total adult consumption of whole grains nor when analyzed separately (rye bread, whole grain bread, and oatmeal) with breast cancer. However, the women in the Danish cohort were younger at study entry and at diagnosis (average age 56 years) than participants in the AGES-Reykjavik Study (average age 77 years). This might reflect a previously reported difference in characteristics of diagnosed breast tumors in older women (over 70) compared with those in younger women [38]. Indeed, we found no association for rye bread when a separate analysis was made for women who were already diagnosed with breast cancer at study entry (mean age at diagnosis 64 years, data not shown).

Prolonged exposure to rye bread might therefore possibly explain the observed risk found in our cohort. Rye bread is rich in lignans, which can be converted into enterolignans by the gut microbiome. Enterolignans have been suggested to enhance breast cancer risk reduction [7, 39, 40]. However, they can also express weak estrogenic affinity and can act both as agonists or antagonists in breast tumors. although this mechanism is considered complex [7, 41–43]. Nevertheless, longitudinal exposure to estrogens, exemplified by early menarche, late menopause, and use of hormonal replacement therapy, are considered as a major risk factors for breast cancer [44]. Therefore, it may be hypothesized that long term exposure to phytoestrogens via rye bread consumption may have a similar effect. Indeed, our analysis on dietary

Table 5. Breast cancer risk by longitudinal intake of meat, milk and whole grains.

	Adolescence	Midlife	N	Breast cancer (%)	Age adjusted HR (95% CI)	Multivariate HR (95% CI)*
Meat						
	Low	Low	275	5 (1.8)	1.0, (ref.)	1.0, (ref.)
	Low	High	681	23 (3.4)	1.8 (0.7–4.8)	1.9 (0.7–5.2.1)
	High	Low	921	35 (3.8)	2.1 (0.8–5.4)	2.0 (0.9–5.6)
	High	High	980	33 (3.4)	1.8 (0.7–4.7)	2.0 (0.8–5.3)
Salted or smoked meat						
	Low	Low	1682	52 (3.1)	1.0, (ref.)	1.0, (ref.)
	Low	High	239	9 (3.8)	1.3 (0.6–2.6)	1.3 (0.6–2.6)
	High	Low	517	19 (3.7)	1.2 (0.7–2.1)	1.4 (0.8–2.5)
	High	High	412	17 (4.1)	1.4 (0.8–2.5)	1.6 (0.8–2.9)
Milk						
	Low	Low	567	24 (4.2)	1.0, (ref.)	1.0, (ref.)
	Low	High	122	5 (4.1)	1.0 (0.4–2.5)	0.9 (0.3–2.4)
	High	Low	674	17 (2.5)	0.6 (0.3–1.1)	0.6 (0.3–1.1)
	High	High	1492	51 (3.4)	0.8 (0.5–1.3)	0.8 (0.5–1.3)
Rye bread						
	Low	Low	1304	34 (2.6)	1.0, (ref.)	1.0, (ref.)
	Low	High	145	7 (4.8)	2.1 (0.9–4.8)	2.4 (1.0–5.4)
	High	Low	597	22 (3.7)	1.5 (0.9–2.6)	1.7 (1.0–3.0)
	High	High	807	33 (4.1)	1.7 (1.0–2.8)	2.1 (1.2–3.5)
Oatmeal						
	Low	Low	1577	59 (3.7)	1.0, (ref.)	1.0, (ref.)
	Low	High	206	9 (4.4)	1.1 (0.6–2.3)	1.0 (0.5–2.1)
	High	Low	584	22 (3.8)	1.0 (0.6–1.7)	1.0 (0.6–1.7)
	High	High	478	7 (1.5)	0.4 (0.2–0.9)	0.4 (0.2–0.9)

Abbreviations: CI, confidence interval; HR, hazard ratio.

For meat; low stands for 2 times or less p/w; high for 3 times or more p/w.

For salted or smoked meat; low stands for 3 times a month or less; high stands for once p/w or more.

For oatmeal; low stands for 4 times and less p/w; high stands for 5 times or more p/w.

For milk and rye bread low stands for less than daily; high stands for daily or more.

*Multivariate HR; adjusted for age at entry, education, body mass index in midlife, age at first child and age at menarche. With the exception of the food item under study each time—all other food items in adolescence (meat, salted and smoked meat, milk, rye bread, oatmeal) plus information on fish and salted and smoked fish in adolescence were then added simultaneously to the multivariate model.

All multivariate analysis includes 95 breast cancer events.

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habits through different time-periods shows that the highest correlation between consumption in adolescence and midlife was found for rye bread. The rye grain also has some other bioactive compounds of unknown concentration [45] that may be of significance in this context. Also, common toppings for rye bread, like smoked meat, may contain other potentially carcinogenic compounds. Furthermore, potentially carcinogenic compounds could be formed when the old-style rye flatbread, a traditional Icelandic bread included in the question on rye bread, is baked or charred directly on a hot plate. Thus, these data point towards carcinogenic effects of some compounds in the rye bread or its cooking method. However, no significant results were observed for any dietary pattern that included high rye bread consumption, neither in adolescence nor the midlife period, suggesting that rye bread in the total diet might not be of major concern for cancer risk.

In contrast to our results on rye bread, frequent long-term consumption of oatmeal was found to be protective against breast cancer. Similar to rye, yet containing only half the amount of phytoestrogen [7], oatmeal is rich in fiber, which is thought to reduce breast cancer risk via multiple pathways [46–48]. Indeed, two studies on fiber intake in adolescence and early adulthood found an inverse association with breast cancer [19, 49]. However, when analyzed separately, only fiber from fruit and vegetables was protective effects against breast cancer in one study [19] whereas the main sources of fiber in the other study were not clear [49]. Although we cannot exclude the influence of fiber to be responsible for our beneficial results, oatmeal also contains multiple bioactive compounds, including the polysaccharide beta-glucan, which is proposed to have some anticancer properties. However, data on this association is still limited [50, 51]. The inclusion of muesli as part of the question on oatmeal might also act as proxy for consumption of other healthy food items. This is further supported by the borderline risk reduction for breast cancer found with high adherence to a dietary pattern in adolescence that included oatmeal, fish, fish oil, milk, and blood- and liver sausage. This further indicates possible anticancer properties of oatmeal and possible other food items in that particular dietary pattern.

A major strength of our study is the prospective design and the well-established population-based AGES cohort with its extensive covariate information. The record linkage to the nationwide Cancer Registry of Iceland ensures detailed and valid assessment of the outcome with a virtually complete follow-up [35], where all participants had equal access to the public health care system at study entry. Also, the especially designed validated FFQ used for assessment of food consumption in adolescence and midlife additionally gives a rare opportunity for evaluation of longitudinal consumption in relation to cancer diagnosis. However, the FFQ used has only crude information on quantity of food items consumed and we are not able to adjust for cooking methods, single nutrients, total intake of fat, fiber, and energy and we do not have information on types or quantities of condiments. Also, the dietary data are retrospective in nature and there is always risk of non-differential recall bias when dietary habits 40–50 years earlier are assessed [52]. Validation for the adolescent period is not possible. However, food-related memory from childhood to four decades later have been found to be accurate as food-related memory of current diet, especially for food items eaten rarely or daily [53]. Indeed, our data somewhat represents the residency based difference that existed in Iceland and it should be noted that diet in Iceland during the adolescent period was quite simple, with very few food items available and little day to day variation [5],making the recall easier. The results of the validation study for midlife FFQ did however find low correlation for rye bread consumption ($r = 0.507$, $p = 0.066$). Furthermore, as our results are based on older women diagnosed with breast cancer, we cannot draw any firm conclusion for women diagnosed earlier in life. We also do not have information on age of menopause or BMI for adolescence. Finally, we cannot exclude any unmeasured confounding affecting our results or that our findings are due to chance.

Conclusion

In conclusion, our results suggest that rye bread consumption in both adolescence and midlife is associated with increased risk of breast cancer diagnosed late in life. Conversely, persistent high consumption of oatmeal in adolescence and midlife was associated with decreased risk. Collectively, these data suggest that dietary exposure during both adolescence and midlife period might be critical for breast cancer development in older women. These associations need to be confirmed in future studies, and our findings also call for further studies on potential mechanisms involved.

Supporting information

S1 Table. Factor loading coefficient for dietary pattern in adolescence.
(DOCX)

S2 Table. Hazard ratios (HR) and 95% confidence intervals (95% CI) for breast cancer diagnoses by tertiles of dietary pattern in adolescence.
(DOCX)

Author Contributions

Data curation: Laufey Tryggvadottir, Tamara B. Harris, Lenore J. Launer, Vilmundur Gudnason.

Formal analysis: Alfheidur Haraldsdottir, Marianna Thordardottir.

Methodology: Alfheidur Haraldsdottir, Johanna E. Torfadottir, Unnur A. Valdimarsdottir, Hans-Olov Adami, Thor Aspelund, Marianna Thordardottir, Bryndis E. Birgisdottir, Laufey Steingrimsdottir.

Project administration: Johanna E. Torfadottir, Unnur A. Valdimarsdottir, Laufey Steingrimsdottir.

Supervision: Johanna E. Torfadottir, Laufey Steingrimsdottir.

Writing – original draft: Alfheidur Haraldsdottir.

Writing – review & editing: Johanna E. Torfadottir, Unnur A. Valdimarsdottir, Hans-Olov Adami, Thor Aspelund, Laufey Tryggvadottir, Marianna Thordardottir, Bryndis E. Birgisdottir, Vilmundur Gudnason, Laufey Steingrimsdottir.

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Paper III

Growth rate in childhood and adolescence and risk of breast and prostate cancer: a population-based study

Alfheidur Haraldsdottir[1,2], Laufey Steingrimsdottir [2,3], Gertraud Maskarinec[4], Hans-Olov Adami[5,6], Thor Aspelund[1], Unnur A. Valdimarsdottir[1,5,7], Ragnar Bjarnason[8,9], Inga Thorsdottir[3,10], Thorhallur I. Halldorsson[2,3,11], Ingibjorg Gunnarsdottir [2,3], Laufey Tryggvadottir[9,12], Vilmundur Gudnason[9,13], Bryndis E. Birgisdottir[2,3], Johanna E. Torfadottir[1,12]

[1]Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavik, Iceland.
[2]Faculty of Food Science and Human Nutrition, University of Iceland, Reykjavik, Iceland.
[3]Unit for Nutrition Research, University of Iceland and Landspitali National University Hospital, Reykjavik, Iceland.
[4]University of Hawaii Cancer Center, Honolulu, Hawaii, United States of America.
[5]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.
[6]Clinical Effectiveness Research Group, Institute of Health, University of Oslo, Oslo, Norway.
[7]Department of Epidemiology, Harvard T.H Chan School of Public Health, Boston, Massachusetts, United States of America.
[8]Clinic and University, Children's Medical Center, Landspítali University Hospital, Reykjavik, Iceland.
[9]Faculty of Medicine, University of Iceland, Reykjavik, Iceland.
[10]School of Health Sciences, University of Iceland, Reykjavik, Iceland.
[11]Centre for Fetal Programming, Department of Epidemiology Research, Statens Serum Institute, Copenhagen S, Denmark.
[12]The Icelandic Cancer Registry, Reykjavik, Iceland.
[13]The Icelandic Heart Association, Kopavogur, Iceland.

Correspondence to:
Alfheidur Haraldsdottir
Faculty of Food and Science and Nutrition
University of Iceland
Eiriksgata 29
101 Reykjavik
Iceland
alh1@hi.is
Tel: +354-543 4956
Fax: +354-543 1331

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ABSTRACT

Growth rate is regulated by hormonal pathways that might affect early cancer development. We explored the association between rate of growth in height from age 8 to 13 (childhood) years and from age 13 to adult height (adolescence), and risk of breast and prostate cancer. Participants were 2,037 Icelanders born 1915 – 1935, who took part in the Reykjavik Study established 1967. Height measures were obtained from school records and at study entry. We used multivariable Cox regression models to calculate hazard ratios (HR) with 95% confidence intervals (CI) of breast and prostate cancer by rates of growth in tertiles. During a mean follow-up of 66 years (women) and 64 years (men), 117 women were diagnosed with breast cancer and 118 men with prostate cancer (45 w/advanced). Women in the highest tertile of growth rate in adolescence had increased risk of breast cancer (HR 2.3, 95% CI 1.3, 4.1) compared with women in the lowest tertile. A suggestive association was observed for women in the highest tertile in childhood (HR 1.5, 95% CI 0.8, 2.7) while data on prostate cancer was inconclusive. Rapid growth, particularly in adolescence may increase breast cancer risk.

INTRODUCTION

Being tall in adulthood has consistently been associated with an increase in pre- and postmenopausal breast cancer risk whilst the association for prostate cancer is inconclusive (1, 2). Growth in childhood and puberty is both affected by genetic and environmental factors (3). It has been hypothesized that levels of growth hormones during puberty, like growth factors and estrogens, might play a role in cancer risk in adulthood (4). The few studies on growth patterns in childhood and adolescence with actual measurements have suggested that the rate of growth affects future breast cancer risk (4, 5). In one study, high stature at age 7 – 15 years increased the risk of developing breast cancer but no association was observed in growth velocity analysis (5). To our knowledge, no studies have been conducted on growth rate during childhood and adolescence and prostate cancer risk. However, some studies, although not all (6) have found that high stature in childhood and adolescence may increase prostate cancer incidence and mortality (7-9).

Using unique childhood growth data along with adult demographic and lifestyle information from the Reykjavik Study, we explored the association of rate of growth between ages 8 to 13 years and from age 13 to adult height with risk of breast and prostate cancer. Our secondary aim was to explore whether height, weight and BMI measured at ages 8, 13 and in adulthood were associated with risk of these cancers.

METHODS

Study cohort

We used data from the Reykjavik Study, a population-based prospective cohort, initiated in 1967 by the Icelandic Heart Association. All individuals born between 1907 and 1935 living in the capital area in December 1966 were identified (N = 30,795). A random sample of 27,831 were invited and 19,381 participants entered the study (71% response rate) as previously described (10, 11). Approximately one third of participants grew up in Reykjavik (12, 13). In 1929, the two main elementary schools in Reykjavik started recording yearly height and weight measurements of their students (14).

Our growth analyses include participants who had information on; 1) height at age 8 and 13 years, 2) height at age 13 and adult height at enrollment. Available data for the height growth rate analysis between ages 8 – 13 years included 702 women and 689 men. The analysis between age 13 until adult height was reached consisted of 991 women and 1,046 men (Figure 1). The period between 8 – 13 years will hereafter be referred to as childhood and the period between age 13 until adult height is reached as adolescence. For the adolescence analyses we used adult height measurement from the Reykjavik Study entry, mean age at entry 49.4 years for women and 48.0 for men.

In secondary analyses on height, weight and BMI, we included all participants with available relevant information measured at age 8, age 13 and adulthood (Reykjavik Study entry) (Figure 1).

Collection of exposure and covariate data

Childhood height and weight measured at yearly examinations in two schools in Reykjavik were documented by school health professionals. These growth measures were later stored at the National Archives of Iceland and later linked with available participants in the Reykjavik Study (14). Adult height was measured at Reykjavik Study entry and recorded to the nearest 0.5 cm without shoes. Available childhood data for participants of the Reykjavik Study were linked with individually unique personal identification number.

At enrollment, we retrieved information on age, education (primary, secondary, college, university) and birth cohort (1915 – 1919, 1920 – 1924, 1925 - 1929, 1930 – 1936). We also used information on growth in childhood and adolescence (continuous; data collection described above). As data on reproductive history were not collected in the Reykjavik Study, information on age at menarche (continuous) was obtained from the Cancer Detection Clinic Cohort (CDC cohort), where multiple data was collected as part of a nationwide, centralized cervical- and breast cancer screening program (15).

Approximately 91% of participants in the Reykjavik Study had entered the CDC cohort at least once. Missing information on age at menarche (58 values for adolescence and 32 values for childhood) were replaced with the mean age at menarche (13.6 years) among women included in the adolescence analysis.

Follow-up and outcome

Follow-up time was calculated from the first measurement until diagnosis of breast/prostate cancer, death, or end of follow-up, whichever occurred first (December 31st, 2015). In analyses of growth during childhood (8 – 13 years), follow-up started at age 8 years and in analyses of growth during adolescence (age 13 – adult height) the follow-up started at age 13. Breast and prostate cancer diagnoses were ascertained through linkage to the nationwide Icelandic Cancer Registry (16) and information on the cause of death from the Directorate of Health. Due to Iceland's computerized national roster and each individual's personal identification number, follow-up was virtually complete (17).

For prostate cancer, information on TNM-stage (I, II, III and IV) and cause of death was available for a total of 88% of cases from either medical records or Directorate of Health. Advanced disease was defined as death from prostate cancer or stage III (tumor extending through prostatic capsule (T3, NX/0 and MX/0)) or IV (locally advanced or metastatic disease (T4, NX/0, MX/0; or any T, N1 and/or M1) at diagnosis.

Statistical analyses

Growth rate was defined as the difference between two height measurements divided by the time between them. We calculated growth velocity (velocity = Δx/time) per year for height (cm), between ages 8 – 13 years and from age 13 until adult height. We used age 15 years to estimate adult height for women and age 17 for men (18, 19). We also analyzed height growth rate between age 8 until adult height was reached. All velocity estimates were categorized into tertiles and will be referred to as low, medium and high.

We used Cox proportional hazard regression models to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) of breast and prostate cancer, contrasting hazards across tertiles in growth rates. We also conducted linear regression for average increase in growth rate per year in cm.

For all analyses, we first adjusted for age at study entry (as a continuous variable). We then further adjusted for birth cohort (1915 – 1924, 1925 – 1929, 1930 – 1935), education (primary, secondary, college/university), and growth measurements at the beginning of the growth rate period. For example, for childhood growth rate between ages 8 – 13 years, we adjust for height at age 8 etc. In the second Cox model among women, we additionally adjusted for age at menarche (continuous). We also explored how adjustment for adult height, physical activity and parity affected our estimates for growth rate. We calculated the trend for HR for the categories relative to the first category, using polynomial contrasts. We also calculated the risk for height growth rate between age 8 until adult height was reached, using same adjustments. For breast cancer, we also analyzed adolescence growth stratified by birth cohort (1915 – 1924, 1925 – 1929, 1930 – 1935).

Cox regression models were also used to calculate risk estimates for 1 increase in Z-score for height, weight and BMI at ages 8 and, 13 using the same adjustments as in growth rate analyses. This analysis was also conducted for height, weight and BMI collected at Reykjavik Study entry. We also analyzed adult height adjusted for growth in adolescence among 991 women with available information and tested interaction between adult height and growth rate in adolescence.

We used SPSS software, version 25.0 in all statistical analyses (SPSS Inc., Chicago, Illinois; www.spss.com). The study protocol was approved by the Icelandic Ethical Review Board and the Icelandic Data Protection Authority (VSN -17-189) (www.vsn.is).

RESULTS

Breast cancer

The mean age at study entry among the 991 women with available height measurements for the adolescence period was 49.4 years (SD 7.5). During a mean follow-up time of 66.1 years (SD 10.9), 117 women were diagnosed with breast cancer at a mean age of 65.7 years (SD 12.3). For the childhood period, the mean age at entry was 48.7 (SD 7.6) and during a mean follow-up time of 70 years 83 women were diagnosed with breast cancer at a mean age of 65.4 years (SD 12.5).

Table 1 presents characteristics of study participants by tertiles of growth rate in adolescence. On average, women in the highest growth rate tertile between the age 13 to adulthood were shorter, had the slowest growth rate in childhood, weighed less at ages 8 and 13 years and had a later menarche

than women in the lowest growth rate tertile. Women in the highest growth tertile were also taller in adult life, weighed less at study entry and were more prevalent in the older birth cohorts. Characteristics of study participants by tertiles of growth rate in childhood (8 to 13 years) are shown in supplementary table 1.

Table 2 presents growth rate in tertiles during childhood and adolescence and risk of breast cancer. For women in the highest tertile (mean increase per year 7.8 cm) of growth rate in adolescence, we found an increased risk of breast cancer (HR 2.3, 95% CI 1.3, 4.1) when compared with women in the lowest tertile (mean increase per year 2.6 cm), with a P_{trend} = 0.006. These estimates attenuated without adjustment for height at age 13 (HR 1.8, 95% CI 1.0, 3.0). Adjustment for adult height, physical activity or parity did not attenuate our estimates on adolescence growth rate. A marginal association was observed for linear regression of average growth rate per year in adolescence (HR 1.1, 95% CI 1.0, 1.2).

For the childhood period, we observed no significant association with breast cancer risk: HR 1.5 (95% CI 0.8, 2.7) for highest versus lowest tertile. The estimate for average growth per year in childhood was 1.2 (95% CI 0.9, 1.7). No association was observed between age 8 years and adult height.

We observed an increased risk of breast cancer for increase of each 1 z-score in adult height and weight at study entry, or 20% and 10% respectively (table 4). Adjusting for growth rate in the analysis did not change our results on adult height estimates (n = 991). No association was found for childhood measures and interactions between growth rate in adolescence and adult height was not significant (p = 0.13). When growth rate analysis in adolescence was stratified by birth cohort (1915 – 1924, 1925 – 1929, 1930 – 1935), we found a significant threefold increased risk among women born 1915 – 1924 and 1925 – 1929 (supplemental table 3).

Prostate cancer

Among the 1,046 men with measurements on adolescence growth, the mean age at study entry was 48.0 years (SD 6.9). During a mean follow-up time of 64.2 years (SD 10.0), 118 men were diagnosed with prostate cancer, thereof 45 had advanced disease. The mean age at diagnosis was 72.7 (SD 7.1) for all prostate cancer cases and 71.7 (SD 7.5) for men with advanced disease. For childhood growth, mean age at entry 47.3 years (SD 7.1). During a mean follow-up time of 68.8 years (SD 10.1) 77 men

were diagnosed with prostate cancer, thereof 29 with advanced disease. The mean age at diagnosis for total cases was 71.3 (SD 6.6) and 70.4 (SD 8.0) for advanced disease only.

Table 1 presents characteristics of study participants by tertiles of growth rate in adolescence. Men in the highest tertile were on average both shorter and weighed less at ages 8 and 13 compared with men in the lowest tertile. At entry, men in the highest tertile were however taller and had a lower BMI. Characteristics of study participants by tertiles of growth rate in childhood (8 to 13 years) are shown in supplemental table 1.

Table 3 presents growth rate in childhood and adolescence and risk of prostate cancer. Overall, no significant association was found for any growth marker, neither for total nor for advanced prostate cancer. No significant association was observed for linear regression of average growth rate per year nor for increase in Z-score for height, weight and BMI at ages 8,13, and adult measurment (table 4). Interaction between rate of growth and adult height was not significant ($p = 0.42$).

DISCUSSION

In this population-based prospective study, we found that faster growth rate distinctly in adolescence was associated with more than twofold increased risk of breast cancer risk, with a highly significant dose-response trend. The group that grew fastest in adolescence was on average shorter in the beginning of this period. Our data also provide some evidence that fast growth in childhood might increase the risk of breast cancer, although they are inconclusive with respect to prostate cancer risk. As thoroughly studied, we also observed increased risk of breast cancer for each increase in z-score for adult height and adult weight (1, 20, 21) but not for advanced prostate cancer.

Our results are mostly in line with the few available studies on growth rate and breast cancer risk. In the National Survey of Health and Development British birth cohort, an increase of one standard deviation in height between ages 7 to 11 and 11 to 15 years were associated with 17% and 29% increased risk of breast cancer, respectively. However, no association was observed for increase in height from age 15 until adult height was reached, possibly as most participants might have reached or be close to their final height at that age (22). Likewise, in a Danish study of 117.000 women each 5 cm increase in height between ages 8 and 14 years was associated with 17% increased risk of breast cancer (23).

The mechanism behind the observed association between growth rate in childhood and adolescence and breast cancer risk is unclear. As women in the highest tertile were taller in adult life

than women in the lowest tertile, adult height, a known risk factor for breast cancer might explain these findings. However, when we adjusted for growth rate in adolescence, risk estimates for adult height and breast cancer were not altered. In addition, no interaction was observed between growth rate in adolescence and adult height for breast cancer. Growth rate and adult height might therefore be independent risk factors of breast cancer. Also, menarche usually starts when pubertal growth spurt declines (19) and as observed in table 1, women with the fastest growth spurt in adolescence had menarche later than women in the lowest tertile. As this is in contrast with the well-established evidence on age at menarche and breast cancer risk (24), the mechanism for fast growth rate might therefore override any beneficial effects of later menarche in this context.

Rapid growth can leave less time for repair of DNA damage caused by exposures to carcinogenic factors, and permanent cell DNA damage can cause cancer (25). Also, the puberty process entails increases in level sex steroids, growth hormone (GH) and insulin like growth factor 1 (IGF-1). High levels of endogenous estrogen is a well-established risk factor for breast cancer (24, 26). Also, high levels of IGF-1, that correlate with increase in height (27) have been linked with increased risk of breast cancer (28-30) and during puberty, these levels can triple (31).

Energy restriction in early life has a been linked with breast cancer risk (32), and in our study, girls who grew fastest during adolescence had had slower growth rate in childhood and were on average 8 cm shorter at age 13 compared with girls in the lowest tertile. It is therefore possible that around age 13, shorter girls experienced hefty growth spurt to obtain their genetically set final height. This might have affected levels of growth hormones and explain the association with breast cancer risk observed for the adolescent period. Indeed, it has been hypothesized that completion of severe energy restriction can cause amplified response of the hormone factor signaling GH-IGF axis, which consequently might cause carcinogenic response (33, 34). Furthermore, of women in the highest tertile in the adolescence period, 33% and 37% are born during the years 1915 – 1924 and 1925 – 1929, respectively, and some of them might therefore have gone through sensitive times of growth during the depression years in Iceland (1930 – 1939), which might have affected both quantity and quality of nutrition sources (35, 36). Indeed, when we stratified our analysis by birth cohort, our risk estimates for the older birth cohorts are unaffected while risk estimates for women born 1930 – 1935 were lower and not statistically significant (supplemental table 2).

However, we can also not exclude the effect of other environmental factors that might affect growth, such as infections and quality of housing in reference to mold for example (37, 38).

Although exposure to IGF-1 has previously been linked with prostate cancer (29) we observed no significant association between growth rate or height or weight at any age and risk of prostate cancer. Our analysis on advanced prostate cancer was underpowered and, hence, we therefore interpret the results between growth rate and advance prostate cancer as inconclusive.

A major strength of our study is the population-based prospective design with actual measurements, and extensive data available on social- and lifestyle factors from adolescence to midlife. Also, as the nationwide Cancer Registry of Iceland was founded in 1955, when the oldest participants of the Reykjavik Study were around age 40, the record linkage ensured both detailed and valid assessment of the outcome and high prospect of capturing the majority their cancer diagnosis (16). In addition, the health care system provides the study participants with equal access to medical care (39).

A limitation of our study is the few numbers of incident breast and prostate cancer cases, particularly with advanced disease. Also, our height growth rate calculation for adolescence is based on estimation of the time adult height is reached. Because many of our participants grew up during times of economic recession of the 1930s, possibly with restricted caloric intake, our findings may not be generalizable to all girls growing up today but perhaps particularly to those living in developing countries undergoing economic transition.

We conclude that rapid growth, especially among adolescent women who were shorter in the beginning of the adolescence period, may increase breast cancer risk. Underlying mechanisms are not clear and need further study. The association for growth rate and advanced prostate cancer needs further studies.

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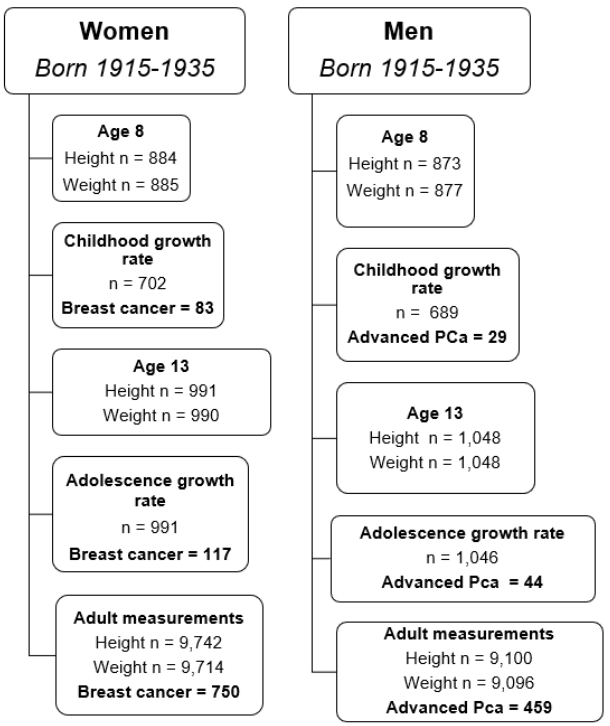

Figure 1 Number of participants entering the study with available measurements of height
PCa: Prostate cancer

Table 1. Characteristics of study participants split by tertiles of growth rate (mean per year) between age 13 until adult height

	Growth rate from age 13 – adult height							
	***Women* (n = 991)**				***Men* (n = 1,046)**			
Childhood and adolescence values	Low n = 359	Medium n = 304	High n = 328	*P value*	Low n = 349	Medium n = 359	High n = 338	*P value*
Mean (SD)								
Weight at age 8 (kg)	26.9 (3.3)	26.0 (3.3)	24.2 (2.9)	0.001	26.9 (3.1)	26.1 (3.0)	24.9 (2.8)	0.001
Weight at age 13 (kg)	50.0 (6.9)	45.4 (6.3)	39.4 (5.7)	0.001	48.3 (7.3)	41.9 (5.9)	38.3 (4.9)	0.001
Height at age 8 (cm)	128.6 (4.7)	127.5 (4.8)	125.3 (4.5)	0.001	129.4 (5.1)	128.2 (4.8)	126.7 (5.0)	0.001
Height at age 13 (cm)	158.5 (5.4)	156.0 (5.1)	150.3 (5.7)	0.001	159.5 (6.8)	152.7 (6.4)	149.8 (6.0)	0.001
BMI at age 8 (kg/m²)	16.3 (1.4)	15.3 (1.4)	15.4 (1.2)	0.001	16.0 (1.2)	15.8 (1.1)	15.5 (1.0)	0.001
BMI at age 13 (kg/m²)	19.8 (2.2)	18.6 (2.0)	17.4 (1.9)	0.001	18.9 (2.0)	17.9 (1.8)	17.0 (1.5)	0.160
Growth rate p/y in childhood (cm)	6.1 (0.6)	5.8 (0.6)	5.1 (0.6)	0.001	6.1 (0.8)	5.1 (0.6)	4.7 (0.6)	0.001
Growth rate 8 – 13 years (%)								
Low	34 (13)	62 (27)	141 (65)	0.001	21 (8)	88 (37)	128 (63)	0.001
Medium	96 (37)	84 (37)	67 (31)		49 (20)	112 (48)	61 (30)	
High	129 (50)	81 (36)	8 (4)		179 (72)	35 (15)	15 (7)	
At study entry								
Mean (SD)								
Age, y	49.8 (8.2)	48.7 (7.2)	49.7 (7.1)	0.128	47.8 (6.8)	48.1 (6.8)	48.2 (6.8)	0.732
Height (cm)	163.7 (5.4)	165.7 (4.9)	165.9 (5.4)	0.001	176.8 (5.9)	177.6 (5.9)	180.3 (6.1)	0.001
Weight (kg)	69.5 (12.3)	67.5 (11.3)	67.0 (11.6)	0.017	83.6 (13.5)	82.4 (12.4)	82.0 (12.6)	0.231
BMI (kg/m²)	25.9 (4.4)	24.6 (3.9)	24.3 (4.1)	0.001	26.7 (4.1)	26.1 (3.5)	25.2 (3.4)	0.001
Age at menarche	12.7 (1.1)	13.6 (1.0)	14.3 (1.2)	0.001				
Birth cohort, n (%)								
1915-1924	93 (26)	73 (24)	109 (33)	0.001	93 (27)	108 (30)	123 (36)	0.024
1925-1929	100 (28)	113 (37)	121 (37)		110 (31)	111 (31)	110 (33)	
1930-1935	166 (46)	118 (39)	98 (30)		146 (42)	140 (39)	105 (31)	
Education, n (%)								
Primary	158 (44)	140 (46)	163 (50)	0.387	88 (25)	100 (28)	86 (25)	0.828
Secondary	169 (47)	130 (43)	131 (40)		190 (54)	184 (51)	175 (52)	
College/University	32 (9)	34 (11)	32 (10)		71 (20)	75 (21)	77 (23)	

Table 2. The risk of breast cancer by growth rate (mean per year) in tertiles in childhood and adolescence

Growth rate period	Mean growth per year in cm (SD)	Event/no event	Age-adjusted HR	95% CI	HR	95% CI
Childhood (ages 8 - 13 years) [a]						
Low	4.9 (0.5)	27/210	1.0	Ref.	1.0	Ref.
Medium	5.7 (0.2)	26/221	1.0	0.6, 1.8	1.1	0.6, 1.9
High	6.5 (0.3)	30/188	1.3	0.8, 2.2	1.5	0.8, 2.7
P_{trend}* 0.161			*Per mean increase p/y (cm)*		1.2	0.9, 1.7
Adolescence (age 13 – adult height) [b]						
Low	2.6 (0.8)	31/328	1.0	Ref.	1.0	Ref.
Medium	4.8 (0.6)	39/265	1.4	1.0, 2.5	1.6	1.0, 2.6
High	7.8 (1.7)	47/281	1.6	1.2, 3.5	2.3	1.3, 4.1
P_{trend}* 0.006			*Per mean increase p/y (cm)*		1.1	1.0, 1.2
Age 8 – adult height [a]						
Low	4.8 (0.3)	27/268	1.0	Ref.	1.0	Ref.
Medium	5.5 (0.1)	30/264	1.1	0.7, 1.9	1.1	0.6, 1.8
High	6.0 (0.3)	44/250	1.6	1.0, 2.6	1.4	0.9, 2.4
P_{trend}* 0.160			*Per mean increase p/ y (cm)*		1.3	0.9, 1.9

a: Adjusted for age, education, birth cohort, height at 8 years of age and age at menarche
b: Adjusted for age, education, birth cohort, height at 13 years of age. age at menarche
*P_{trend} for hazard ratios for the categories relative to the first category, using polynomial contrasts

Table 3. The risk of total and advanced prostate cancer by growth rate (mean per year) in tertiles in male participants in childhood and adolescence

Growth rate period	Mean change per year in cm (SD)	Event/no event	Age-adjusted HR	95% CI	HR	95% CI
Total PCA						
Childhood (ages 8 - 13 years) [a]						
Low	4.5 (0.4)	28/209	1.0	Ref.	1.0	Ref.
Medium	5.2 (0.2)	22/201	0.9	0.5, 1.5	0.9	0.5, 1.5
High	6.3 (0.6)	27/202	1.1	0.6, 1.8	1.1	0.6, 1.9
P_{trend}*0.789			*Per mean increase p/y (cm)*		1.1	0.8, 1.4
Adolescence (age 13 – adult height) [b]						
Low	4.3 (1.0)	40/309	1.0	Ref.	1.0	Ref.
Medium	6.2 (0.3)	38/321	0.9	0.6, 1.4	0.9	0.6, 1.5
High	7.6 (0.5)	40/298	0.9	0.6, 1.5	0.9	0.5, 1.5
P_{trend}* 0.682			*Per mean increase p/y (cm)*		1.0	0.8, 1.1
Age 8 – adult height [a]						
Low	5.1 (0.2)	28/264	1.0	Ref.	1.0	Ref.
Medium	5.6 (0.1)	48/266	1.5	0.9, 2.4	1.5	0.9, 2.4
High	6.1 (0.3)	29/237	1.0	0.6, 1.7	1.0	0.6, 1.7
P_{trend}* 0.971			*Per mean increase p/y (cm)*		1.1	0.7, 1.6
Advanced PCA[#]						
Childhood (ages 8 - 13 years) [a]						
Low	4.5 (0.4)	11/209	1.0	Ref.	1.0	Ref.
Medium	5.2 (0.2)	6/201	0.6	0.2, 1.6	0.7	0.3, 1.9
High	6.3 (0.6)	12/202	1.2	0.5, 2.8	1.4	0.6, 3.3
P_{trend} *0.424			*Per mean increase p/y (cm)*		1.2	0.8, 1.9
Adolescence (age 13 – adult height) [b]						
Low	4.3 (1.0)	19/309	1.0	Ref.	1.0	Ref.
Medium	6.2 (0.4)	12/321	0.6	0.3, 1.3	0.5	0.2, 1.1
High	7.6 (0.6)	14/298	0.7	0.4, 1.4	0.5	0.2, 1.1
P_{trend}*0.103			*Per mean increase p/y (cm)*		0.9	0.7, 1.1
Age 8 – adult height [a]						
Low	5.1 (0.2)	10/264	1.0	Ref.	1.0	Ref.

Medium	5.6 (0.1)	21/266	1.9	0.9, 4.0	1.9	0.9, 4.0
High	6.1 (0.3)	13/237	1.3	0.5, 2.9	1.3	0.5, 2.9
P_{trend}*0.614			*Per mean increase p/y (cm)*		1.0	0.5, 2.0

a: adjusted for age, birth cohort, education, and height at 8 years of age
b: adjusted for age, birth cohort, education and height at 13 years of age
*P_{trend} for hazard ratios for the categories relative to the first category, using polynomial contrasts
#Advanced disease was defined as men who died from prostate cancer or had stage III or IV at diagnosis

Table 4. The risk of breast and prostate cancer per 1-unit increase in height, weight and BMI Z-score at ages 8, 13, and at Reykjavik Study entry

	Height	**Weight**	**BMI**
	HR per 1 z-score increase (95% CI)	HR per 1 z-score increase (95% CI)	HR per 1 z-score increase (95% CI)
Breast cancer			
Age 8	0.9 (0.8, 1.3)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)
Age 13	1.1 (0.9, 1.4)	1.0 (0.8, 1.3)	1.0 (0.8, 1.2)
At study entry	1.2 (1.1, 1.3)	1.1 (1.1, 1.2)	1.1 (1.0 1.2)
Total prostate cancer			
Age 8	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)	1.0 (0.8, 1.2)
Age 13	1.0 (0.9, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)
At study entry	1.0 (1.0, 1.1)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)
Advanced prostate cancer			
Age 8	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)
Age 13	1.0 (0.7, 1.3)	0.9 (0.6, 1.2)	0.8 (0.6, 1.2)
At study entry	0.9 (0.8, 1.0)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)

All analysis are adjusted for age, education, birth cohort and age at menarche (women only)

Supplemental Table 1. Characteristics of study participants split by tertiles of growth rate (mean per year) between ages 8-13 years

	Growth rate between ages 8 – 13 years							
	***Women* (n = 702)**				***Men* (n = 689)**			
Childhood and adolescence values,	Low n = 237	Medium n = 247	High n = 218	*P value*	Low n = 237	Medium n = 223	High n = 229	*P value*
Mean (SD)								
Weight at age 8 (kg)	25.5 (3.7)	25.9 (3.4)	25.9 (2.9)	0.323	25.4 (3.0)	26.1 (3.2)	26.7 (2.8)	0.001
Weight at age 13 (kg)	42.2 (7.7)	46.3 (7.0)	49.3 (6.4)	0.001	39.3 (5.1)	43.0 (6.2)	48.6 (6.9)	0.001
Height at age 8 (cm)	126.7 (5.0)	127.3 (5.0)	127.7 (4.6)	0.089	126.8 (5.0)	128.4 (5.0)	129.5 (4.9)	0.001
Height at age 13 (cm)	151.3 (5.7)	156.0 (5.0)	160.0 (4.8)	0.001	149.3 (5.4)	154.5 (5.1)	161.1 (6.0)	0.001
BMI at age 8	15.8 (1.5)	16.0 (1.4)	15.9 (1.3)	0.583	15.8 (1.1)	15.8 (1.2)	15.9 (1.1)	0.266
BMI at age 13	18.3 (2.5)	19.0 (2.3)	19.2 (2.1)	0.001	17.6 (1.6)	18.0 (1.9)	18.7 (2.0)	0.001
Growth rate p/y in adolescence (cm)	6.5 (2.5)	4.5 (2.0)	3.5 (1.3)	0.001	6.9 (1.0)	6.3 (1.0)	4.6 (1.4)	0.001
Growth rate 13 – adult height (%)								
Low	34 (14)	96 (39)	129 (59)	0.001	21 (9)	49 (22)	179 (78)	0.001
Medium	62 (26)	84 (34)	81 (37)		88 (37)	112 (50)	35 (15)	
High	141 (60)	67 (27)	8 (4)		128 (54)	61 (28)	15 (7)	
At study entry								
Mean (SD)								
Age, y	48.6 (7.7)	49.2 (7.4)	48.3 (7.8)	0.363	47.5 (7.7)	47.1 (7.1)	47.3 (6.9)	0.864
Height (cm)	164.4 (5.5)	165.0 (5.1)	167.1 (5.1)	0.001	177.0 (6.0)	179.5 (5.9)	179.4 (6.3)	0.001
Weight (kg)	80.3 (11.7)	83.6 (13.2)	86.0 (13.4)	0.001	66.2 (11.2)	69.1 (11.6)	70.2(12.5)	0.001
BMI (kg/m^2)	24.5 (4.1)	25.4 (4.2)	25.1 (4.3)	0.061	25.6 (3.3)	25.9 (3.6)	26.7 (4.1)	0.003
Age at menarche	14.0 (1.2)	13.3 (1.0)	13.0 (1,0)	0.001				
Birth cohort, n (%)								
1915-1924	36 (15)	43 (17)	26 (12)	0.001	43 (18)	30 (14)	33 (15)	0.003
1925-1929	116 (49)	87 (35)	66 (30)		104 (44)	70 (31)	76 (33)	
1930-1935	85 (36)	117 (48)	126 (58)		90 (38)	123 (55)	120 (52)	
Education, n (%)								
Primary	104 (44)	102 (41)	93 (43)	0.646	63 (27)	52 (23)	45 (20)	0.482
Secondary	106 (45)	125 (51)	105 (48)		127 (53)	120 (54)	132 (57)	
College/University	27 (11)	20 (8)	20 (9)		47 (20)	47 (23)	52 (23)	

Supplemental table 2. Breast cancer risk for women with fast growth rate (mean cm per year) in adolescence split by birth cohorts

	Birth cohort		
	1915-1924 n = 275/BC = 31	**1925-1929** n = 334/BC = 39	**1930-1935,** n = 382/BC = 47
HR, 95% CI			
High (tertile 3)	3.3, 1.0, 10.9	3.2, 1.1, 9.1	1.3, 0.5, 3.4

Reference group was the lowest fast growth (tertile 1)