Research Article

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

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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

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

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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 breast-feeding (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.

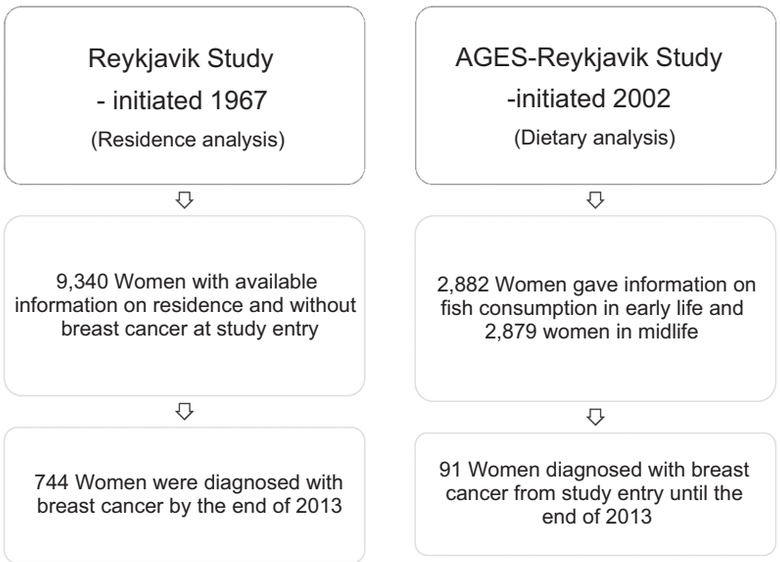

Figure 1.
Selection of participants from the Reykjavik Study and the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, Iceland, 1967–2013.

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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