Breast cancer incidence and familiality in Iceland during 75 years from 1921 to 1995

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Abstract

Information in the Icelandic Cancer Registry on breast cancer and its collection of breast cancer families has been used to elucidate changes in breast cancer incidence by time period and by age, and the effect of degree of relationship and age on the familial risk of breast cancer. Since 1921 the incidence rates have increased, but the increase is significantly greater (2.06% per year) for ages over 44 years than for ages 20-44 (1.20% per year). It has been shown before that when familial risk is computed, the age of the proband influences the risk for the relatives. However, this study shows that the age of the relative is also important and with increasing age the familial risk decreases.

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The Icelandic Cancer Registry (ICR) has been in operation since 1954. Information on incidence and treatment of breast cancer in Iceland from the last decades of the 19th century to 1955 had been collected, and has been used in previous publications[1] and found to be reliable. This paper makes use of the period from 1921 to 1995.

Table 1 Selection scheme for probands

Year of birth	*Year of diagnosis*	*No of probands*
1834–1860	Unrestricted	55
1865	Unrestricted	5
1875	Unrestricted	5
1899–1916	Unrestricted	46
1915–	1911–1984	725
1915–	1985	26
1954–1972	Unrestricted	85
Total		947

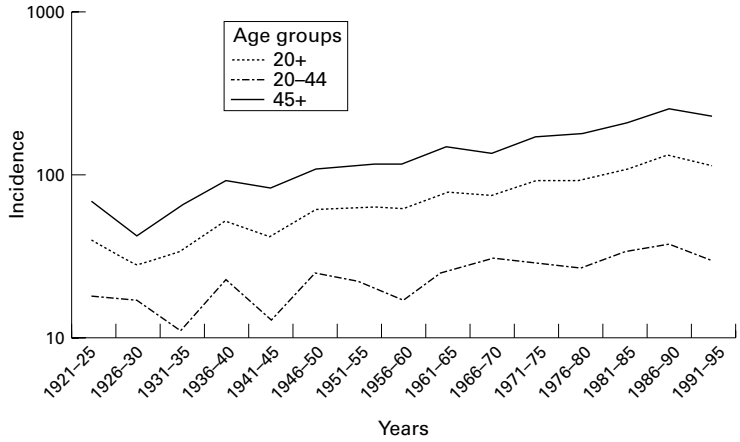

Figure 1 Age standardised breast cancer incidence rates per 100 000 per annum.

Demographic information is of good quality in Iceland. The first census took place in 1703 and listed every member of the population. Numerous censuses took place up to 1960, but in 1952 the National Roster was started and has the identification number of every person. A law on death certification took effect in 1910, and a certificate issued by a doctor exists for all deaths since 1930. Health information is of high quality and hospital and pathology records and paraffin blocks are available for most of the period covered in this report. All this has made construction of family pedigrees relatively easy and reliable. Since 1972 ICR has organised collection of family pedigrees of cancer patients, among them 947 probands with breast cancer who were selected on the basis of year of birth or year of diagnosis and without consideration of family history of cancer. These pedigrees are therefore population based and can be used for epidemiological research.[2–4] A reliable population basis improves the estimates of penetrance for the identified breast cancer genes that will be useful in an ongoing study.

It is intended to make use of this good quality information to describe the dependence of familial risk ratio on the person's age, the age of the relative, the degree of relationship, and the time period.

Material

The material consists of the Icelandic population. In 1921, the average population was 95 500 persons, 46 611 males and 48 889 females.[5] In 1995, the average population was 267 380 persons, 134 038 males and 133 342 females.[6] Information on the demography of Iceland has been collected and published by the Icelandic Bureau of Statistics, which is responsible for the operation of the Icelandic National Roster. Information on breast cancer before 1955 comes from a study previously published[7] in which information from hospital records, death certificates, and doctors' records was collected and analysed. From 1954 onwards the information on breast cancer diagnoses is from the records of the Icelandic Cancer Registry.

Papers on the descriptive epidemiology of breast cancer in Iceland 1955-1984 have been published,[8] as well as on the familiality of breast cancer,[2–4] in a collection of 947 pedigrees of a stratified sample of breast cancer patients and their relatives.

The selection of probands was on the basis of year of birth or year of diagnosis. The

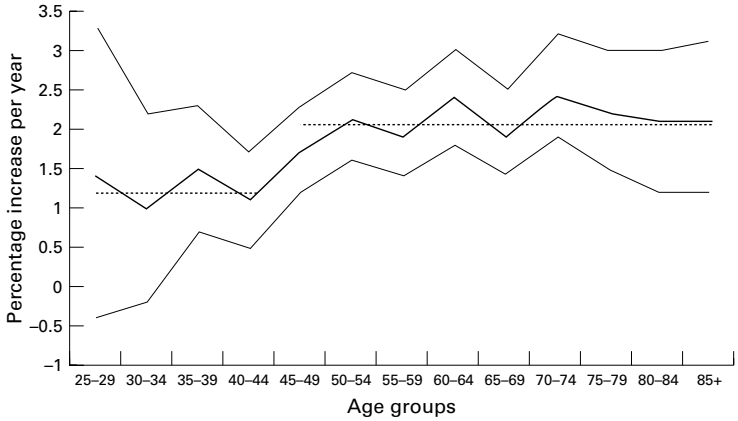

Figure 2 Annual increase in age specific incidence and 95% confidence limits. The horizontal broken lines represent results from the two models for the age groups 20 to 44 and 45 and older.

Table 2 Age coefficients in incidence model

Age	*Coefficients (A)*
20–24	0
25–29	2.061
30–34	2.961
35–39	4.025
40–44	4.675
45–49	0
50–54	0.086
55–59	0.179
60–64	0.271
65–69	0.398
70 –74	0.216
75–79	0.451
80–84	0.493
85–	0.740

scheme for selection of probands is shown in table 1. The extent to which the family was traced was decided in advance. The smallest pedigrees consist of the proband, sibs, parents, uncles and aunts, and grandparents (182 families). There are pedigrees consisting of the proband, all first degree relatives, uncles and aunts, and grandparents (358 families). There are pedigrees consisting of all first and second degree relatives plus first cousins (182 families). Then there are pedigrees consisting of all first, second, and third degree relatives except great grandparents and grandparents' sibs (170 families). For the patients born between 1834 and 1855 (55 families) both parents and all their offspring have been traced. Since the genealogy files in Iceland are considered reliable, so is the tracing of family members in the present study. Cancer in situ is included with breast cancer. The family files are updated for dates of death approximately once a year.

Methods

For age standardisation of incidence rates the "world" population of Segi[9] was used. In order to establish a model of the breast cancer incidence for the population, Poisson regression was applied to each of the age specific five year intervals (25-29, 30-34, etc) to estimate the dependence of the incidence on calendar year. On the basis of this analysis an incidence model was used with different dependence on calendar year according to whether the age of the person was under 45 years or not.

This model was applied to compute the expected values of the cumulative breast cancer risk for first, second, and third degree relatives of the probands stratified into 10 year groups for age of the probands and 10 year groups for the age at risk for the relatives. The observed values for number of breast cancer cases for the relatives were stratified in the same manner and relative risk calculated as the ratio between observed and expected number of cases.

A Poisson model was then fitted to the risk ratios of the relatives, relative to the population. The independent variables were age of proband at diagnosis, time period, age of relative at risk, and degree of relationship and their interactions were tested. This model can be used to estimate breast cancer risk of a relative from one proband. The computations were done using the program package SPIDA.[10]

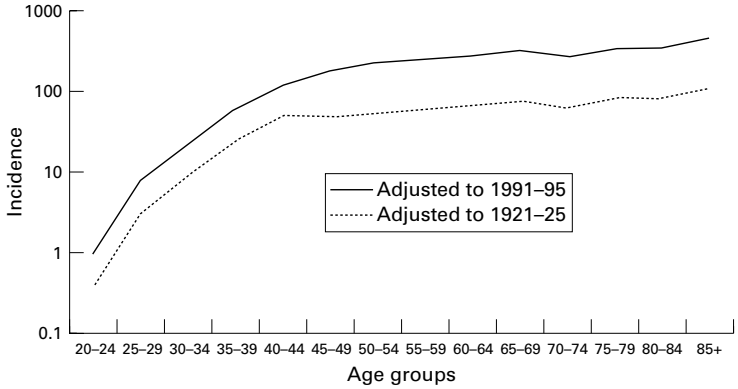

Figure 3 Age specific incidence rates of breast cancer. Results from Poisson regression per 100 000 per annum.

Results

The age standardised breast cancer incidence in Iceland in five year periods, as shown in fig 1, has continued to increase in a similar fashion to what has previously been published.[1 8] This figure shows the truncated rates for age over 19, for age over 44, and for the age group 20-44. Fig 2 shows the results of Poisson regression for the dependence of incidence rates on time period. A separate regression was performed for each age group. The increase by year is greater for age over 44 years than for 20-44 years but the variability within each of these age periods is limited. Separate age adjusted regression for each of these periods shows the difference in increase between these age periods to be significant, 2.06 versus 1.20% per year ($p<0.001$).

For breast cancer incidence the resulting model is found. For age less than 45 years $I=0.336 \star 1.012^{c} \star \exp(A)$. For age 45 years and over $I=29.7 \star 1.0208^{c} \star \exp(A)$. C is the calendar year minus 1900 and A is shown in table 2.

The incidence rates resulting from the two Poisson models are shown in fig 3 adjusted to the periods 1921-1925 and 1991-1995.

In the population based series of 947 breast cancer pedigrees,[2] we showed that the relative risk for first degree relatives was 2.26, for second degree relatives 1.43, and for third degree relatives 1.49, and that the age of the proband influenced the risk. For probands younger than 45 years of age, the risk for first degree relatives was 2.98, but for probands over 54 years of age it was 1.80. Table 3 shows the relative risk for relatives according to age and age of probands for first, second, and third degree relatives. Table 3A is without adjustment for age of proband and time period and table 3B is without adjustment for age of proband and age of relative.

The resulting model for the familial risk ratio of a person (relative) given a first degree relative (proband) is: $RR1=6.95 \star 0.9906^{P} \star 0.998^{R}$, where RR1 is the risk ratio, P is the age

Table 3A Breast cancer risk ratio of relatives of breast cancer probands according to age of relative and degree of relationship

Age of relative	1st degree		2nd degree		3rd degree	
	No of cases	Risk ratio (95% CI)	No of cases	Risk ratio (95% CI)	No of cases	Risk ratio (95% CI)
20–29	2	2.75 (0.33–9.92)	5	4.52 (1.46–10.5)	0	
30–39	24	3.70 (2.37–5.51)	22	2.17 (1.36–3.28)	27	2.02 (1.33–2.95)
40–49	60	2.81 (2.16–3.65)	66	1.94 (1.51–2.82)	77	1.86 (1.50–2.34)
50–59	57	2.12 (1.61–2.75)	70	1.56 (1.22–1.98)	75	1.51 (1.21–1.90)
60–69	60	2 09 (1.61–2.71)	74	1.35 (1.07–1.71)	72	1.50 (1.18–1.89)
70–79	37	2.03 (1.43–2.78)	59	1.31 (1.01–1.71)	38	1.37 (0.96–1.88)
80+	15	1.34 (0.75–2.20)	48	1.33 (0.98–1.76)	20	1.27 (0.78–1.96)

Table 3B Breast cancer risk ratio of relatives of breast cancer probands according to age of proband and degree of relationship

Age of proband	1st degree		2nd degree		3rd degree	
	No of cases	Risk ratio (95% CI)	No of cases	Risk ratio (95% CI)	No of cases	Risk ratio (95% CI)
20–29	21	2.79 (1.73–4.27)	35	1.65 (1.15–2.29)	15	2.96 (1.66–4.88)
30–39	67	2.68 (2.04–3.51)	98	1.98 (1.65–2.93)	51	2.22 (1.65–2.93)
40–49	96	2.32 (1.89–2.86)	103	1.45 (1.19–1.77)	55	1.30 (0.99–1.71)
50–59	54	2.08 (1.57–2.72)	61	1.29 (1.00–1.64)	78	1.32 (1.05–1.65)
60–69	16	1.60 (0.92–2.72)	31	1.38 (0.94–1.97)	59	1.42 (1.09–1.85)
70–79	0		12	1.19 (0.62–2.08)	32	1.90 (1.30–2.68)
80–	1	0.70 (0.02–3.89)	4	0.89 (0.24–2.27)	19	1.92 (1.16–3.00)

Table 3C Breast cancer risk ratio of relatives of breast cancer probands according to calendar period and degree of relationship

Time	1st degree		2nd degree		3rd degree	
	No of cases	Risk ratio (95% CI)	No of cases	Risk ratio (95% CI)	No of cases	Risk ratio (95% CI)
1921–1935	7	1.78 (0.71–3.66)	33	1.60 (1.10–2.26)	11	2.64 (1.32–4.73)
1936–1950	23	2.44 (1.55–3.67)	51	1.47 (1.09–1.94)	12	1.07 (0.55–1.87)
1951–1965	42	2.15 (1.55–2.91)	80	1.62 (1.19–2.02)	42	1.52 (1.09–2.04)
1966–1980	89	2.63 (2.13–3.21)	83	1.43 (1.15–1.79)	91	1.58 (1.28–1.96)
1981–1995	94	2.00 (1.62–2.46)	97	1.54 (1.25–1.87)	153	1.58 (1.34–1.86)

of proband (years), and R is the age of relative (years). The risk ratio for second and third degree relatives is: RR2=0.71 * RR1 and RR3=0.74 * RR1 respectively. The risk ratio did not depend significantly on time period.

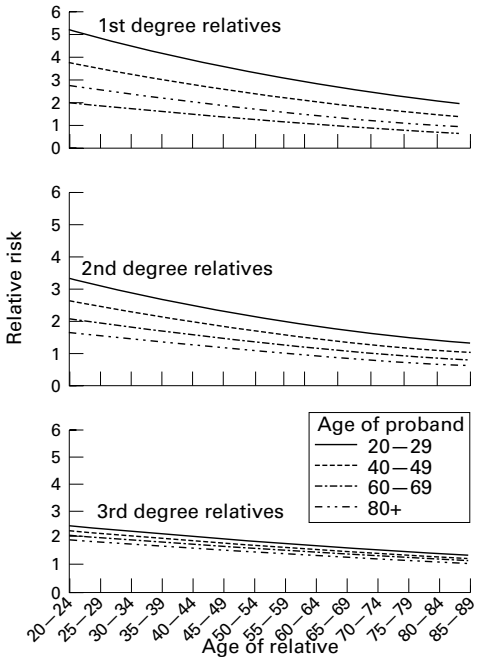

Figure 4 Relative risk of first, second, and third degree relatives of breast cancer patients by age of proband and relative.

In fig 4 the smoothed curves show that for probands and first degree relatives aged 20-29 the relative risk is 5, but for probands and relatives over 70 it is close to 1. For second degree relatives the risk in the age groups 20-29 is over 3 and for third degree relatives it is 2.4.

Table 4 is similar to table 3 for the first degree relatives. It shows that the risk is higher for sisters than for mothers or daughters.

Discussion

The increasing incidence of female breast cancer in Iceland has been previously reported.[1 8 11] This has been observed in other Nordic countries[12–14] and in 1993 the International Agency for Research on Cancer (IARC) published trends in cancer.[15] The majority of populations covered showed an increase in breast cancer incidence rate over time, but the age distribution of the increase differed. In Iceland, as in many other populations shown in the IARC publication,[15] such an increase is greater for women over 44 years of age than in younger women.

The distribution of age specific incidence of breast cancer shows that it is first diagnosed in the third decade of life. It is safe to assume that both genetic and environmental factors play a causative role. The increase in age adjusted incidence over time is more easily explained as resulting from an increase in environmental causes rather than genetics, since the density of environmental factors is more likely to fluctuate over a few decades than genetic factors.

Table 4A Breast cancer risk ratio of first degree relatives of breast cancer probands according to age of relative and type of relationship

	Mothers			Sisters			Daughters		
Age of relative	No of cases	Risk ratio	95% CI	No of cases	Risk ratio	95% CI	No of cases	Risk ratio	95% CI
20–29	0			1	2.67	0.06–14.7	1	3.93	0.06–21.7
30–39	2	1.56	0.18–5.68	17	4.85	2.87–7.75	5	2.95	0.92–6.90
40–49	17	3.50	1.84–5.16	34	2.62	1.74–3.49	9	2.59	1.16–4.94
50–59	14	1.99	0.95–3.03	40	2.26	1.56–2.96	3	1.42	0.30–4.09
60–69	12	1.26	0.55–1.98	44	2.49	1.75–3.22	4	2.67	0.67–6.77
70–79	22	2.62	1.53–3.72	15	1.70	0.84–2.56	0		
80–	8	1.16	0.36–1.96	7	2.10	0.79–4.33	0		

Table 4B Breast cancer risk ratio of first degree relatives of breast cancer probands according to age of proband and type of relationship

	Mothers			Sisters			Daughters		
Age of proband	No of cases	Risk ratio	95% CI	No of cases	Risk ratio	95% CI	No of cases	Risk ratio	95% CI
20–29	3	2.50	0.55–7.26	3	4.68	0.92–1.36	0		
30–39	12	1.55	0.68–2.43	22	3.28	1.91–4.65	1	2.61	0.06–14.5
40–49	35	2.49	1.67–3.32	56	2.56	1.89–3.24	7	4.58	1.89–9.46
50–59	15	1.35	0.67–2.03	56	2.68	1.98–3.38	6	2.09	0.79–4.58
60–69	10	2.67	1.28–4.84	21	1.71	0.98–2.44	6	2.08	0.79–4.46
70–79	0			0			1	0.54	0.06–2.99
80–	0			0			1	0.69	0.06–3.85

Table 4C Breast cancer risk ratio of first degree relatives of breast cancer probands according to calendar period and type of relationship

	Mothers			Sisters			Daughters		
Time period	No of cases	Risk ratio	95% CI	No of cases	Risk ratio	95% CI	No of cases	Risk ratio	95% CI
1921–1935	6	2.16	0.79–4.70	0			1	2.99	0.06–16.5
1936–1950	16	2.50	1.28–3.72	7	3.16	1.28–6.53	0		
1951–1965	21	2.06	1.18–2.94	18	2.23	1.20–3.26	3	2.52	0.55–7.39
1966–1980	20	1.82	1.03–2.62	64	3.10	2.34–3.85	5	2.36	0.79–5.55
1981–1995	12	1.55	0.67–2.43	69	2.11	1.61–2.61	13	1.98	0.90–3.05

Interplay between genetic and environmental factors is very likely. This study shows that the excess risk of familiality is more pronounced in the young, both the relatives of young patients and the young relatives of breast cancer patients, and it diminishes greatly with age.

Latent periods for cancers caused by chemical and physical agents have been studied, but not enough is known about them. It is, however, generally assumed that they are counted in years and decades and probably continue during the lifetime of the person. Biological factors, such as reproductive history, may be shorter lived, as we have shown concerning the effect of age at first birth which diminishes with age in contrast to the effect of parity.[16 17] For hereditary causes, the term roughly inversely corresponding to latent period is penetrance, and for the breast cancer genes BRCA1 and 2 this is being investigated in our material.

The frequency of the BRCA2 gene in the Icelandic population has been estimated as approximately 4 to 6 per 1000.[18 19] The material presented here could serve as a basis for penetrance calculations for these genes.

The familial risk is composed of unknown proportions of hereditary factors and of environmental factors and it is difficult to estimate their relative proportions. It is often argued that if a disease presents at an early age it is more likely to be hereditary, and this is certainly true for some diseases with high penetrance. It is, however, possible to argue that an environmental factor can mimic the genetic effect if the dose is high, since it is known from carcinogenic experiments that high dose will result in earlier presentation.

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