

ORIGINAL ARTICLE

The effect of a single *BRCA2* mutation on cancer in Iceland

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Dr H Tulinius, Icelandic Cancer Registry, Skogarhlid 8, PO Box 5420, 125 Reykjavik, Iceland; hrafnt@krabb.isRevised version received 28 March 2002
Accepted for publication 2 April 2002**Objective:** To estimate the risk of malignant diseases in families of probands with the same mutation in the *BRCA2* gene.**Design:** A cohort study using record linkage of a breast cancer family resource and the Icelandic Cancer Registry.**Setting:** Iceland.**Subjects:** Families of 995 breast cancer patients, from which 887 were tested for a single founder 999del5 mutation; 90 had the mutation and 797 did not.**Results:** Relatives of probands with the mutation had significantly increased relative risk (RR) of breast cancer. For first degree relatives, the RR was 7.55 (95% CI 6.04 to 9.03) but was 1.72 (95% CI 1.49 to 1.96) in first degree relatives of probands without the mutation. For prostate and ovarian cancer, the first and second degree relatives of probands with the mutation had a significantly increased RR, but in families of probands without the mutation no significant familial risk was found.**Conclusions:** The 999del5 mutation in the *BRCA2* gene explains a substantial proportion of familial risk of breast cancer in Iceland, but significant familial risk remains in relatives of probands without the mutation. For prostate and ovarian cancer, the mutation accounts for most of the familiarity observed in families of breast cancer patients.

MATERIAL AND METHODS

The study base

The population based Icelandic Cancer Registry has existed since 1954 and has published cancer incidence for Iceland since 1955.^{15 16} The file on breast cancer has been extended to cover the time since 1910.¹⁷

Precoded information

Samples, and all information, stripped of personal identifiers, was precoded in accordance with the requirements of the Icelandic Data Commission.

Family collection

The collection of breast cancer pedigrees began in 1972,¹⁷ then by selecting every eighth case diagnosed between 1955 and 1972 ordered by date of diagnosis. This was supplemented with several groups of cases, either all cases diagnosed in a defined period, or all cases born in the same year and diagnosed before a defined year. The method of proband selection has been described in a previous publication.¹ Information on cancer diagnoses up to and including 31 December 1999 has been added to the information in the pedigrees. The probands in this report are 995 females diagnosed with breast cancer from 1 January 1910 to 31 December 1985. In that time period, 2401 females and 25 males were diagnosed with breast cancer.

The family file contains 995 families with a total of 58 409 family members, 28 806 females and 29603 males. The mean size of the families is thus 59 persons, the median is 31 persons, and the range from one (eight families in which no relative was in the Icelandic population) to 1309 members. The file has been updated for dates of death and cancer diagnoses before 1 January 2000. For statistics, all first, second, and third degree relatives available from the families were included. For the period 1921-1999 for breast cancer, 17 782 women and 18 418 men contributed risk years, and for other cancers the period 1955-1999 was used with 14 781 females and 15 118 males.

For the 995 probands, 851 affected relatives were identified in the pedigrees. This gives a total of 1846 breast cancer cases, in 1600 females and 12 males. The difference, 234 cases, is because the same person can be both a proband and an affected relative and can occur in more than one family. The probands are 41.4% of all female breast cancer patients in Iceland during the 75 year period 1910 to 1985. Of the 1612 individual breast cancer cases in the pedigrees, 198 could not be investigated for *BRCA2* mutations. This leaves 1414 breast cancer patients investigated.

The classification of the families was done on the probands, so that in 90 families the probands were positive for *BRCA2*, for 797 the proband was negative, and in 108 the proband could not be classified.

Laboratory methods

Samples for DNA extraction were obtained from the Department of Pathology of the University of Iceland (tissue samples) and the Biological Specimen Bank of the Icelandic Cancer Society (blood samples) for all breast cancer cases. The *BRCA* classification was carried out in two laboratories, the Molecular and Cell Biology Research Laboratory of the Icelandic Cancer Society (1255 samples) and at the Laboratory of Cell Biology, Department of Pathology of the University of Iceland (196 samples).

DNA extraction from paraffin embedded tissue samples was carried out as previously described.^{12 18} Exon 9 fragments of the *BRCA2* gene were PCR amplified from genomic DNA using primers as previously published.⁶ The fragments were heat denatured and run on a 6% denaturing polyacrylamide gel.^{12 18} *BRCA2* mutants were identified by the presence of an extra band, slightly smaller than the normal PCR fragment.

Statistical methods

Incidence figures for the Icelandic population are available for breast cancer for 1921-1999 and for cancers at other sites for 1955-1999. These figures are stratified according to gender,

age (five year intervals), and calendar time (five year intervals).

The risk years of relatives of breast cancer probands were stratified in a similar manner and further according to the degree of relatedness to the proband, and whether the proband was *BRCA2* positive or negative.

For each of these strata, the observed number of cases was counted and the expected number calculated as the product of incidence and risk years. Poisson regression was applied to the breast cancer results where the number of cases was the dependent variable and the expected number was the exposure time variable. The explaining variables tested were age of relative, degree of relatedness, and *BRCA2* status of proband and the result was risk relative to the population. Because *BRCA2* status of the proband could be expected to interact with the other variables, products of *BRCA2* status and age of relative and degree of relatedness were also included.

The familial risk accounted for by the *BRCA2* mutation was calculated by subtracting the familial risk of relatives of mutation negative probands from that of relatives of all probands and is calculated as a percentage of the total familial risk.

The data used in the Poisson regression were from the 887 families of probands where *BRCA2* mutation status could be ascertained, 90 families of mutation positive probands, and 797 families where probands were negative for the *BRCA2* mutation.

Relative risk was computed according to the model shown in the Appendix. Absolute risk was computed by using incidence rates in the population 1995-1999 assuming the prevalence of *BRCA2* in the population to be 0.5% and multiplying by the relative risks found.

Cumulative incidence was calculated by summing the incidence figures found by multiplying the population incidence figures by the relative risk found by the model for each five year age group up to the specified age and multiplying by 5.

RESULTS

BRCA2 mutation status of probands and cases

Of the 995 probands, 887 were informative for *BRCA2* status, 797 negative and 90 or 10.1% positive. Of family members diagnosed with breast cancer (first, second, and third degree relatives) 894 were informative for *BRCA2*, 714 negative and 180 (20.1%) positive. There were 259 first degree relatives, 187 negative and 72 positive (27.8%), there were 310 second degree relatives, 248 negative and 62 positive (20.0%), and there were 325 third degree relatives, 279 negative and 46 positive (14.2%).

Breast cancer risk

Table 1A gives the breast cancer risk ratio of relatives of breast cancer probands adjusted for age and calendar period by *BRCA2* status. In all families, the risk is significantly increased for first, second, and third degree relatives, relative risks 2.18, 1.52, and 1.52, respectively. In the families of probands with the mutation, these are 7.55, 3.18, and 2.58. In the families of probands without the mutation, these are 1.72, 1.36, and 1.33. All these ratios are significantly increased. Comparing the risks in families of probands without the mutation with the risks in all families shows that in this material the mutation accounts for 39%, 31%, and 37% for first, second, and third degree relatives, respectively.

Among the first degree relatives, the sisters have consistently greater risk than the mothers and the daughters regardless of *BRCA2* status. Thus, in families of all probands both the mothers and daughters have a risk of 1.92 (not shown in table 1), but the sisters have a risk of 2.37. This difference is not statistically significant ($p=0.06$). The values for the families of *BRCA2* positive probands are 5.74 for mothers and daughters and 9.02 for sisters ($p=0.03$). For families of *BRCA2* negative

Table 1 Cancer risks

Relative	Observed	O/E	95% confidence interval
<i>(A) Risk of breast cancer in relatives of female probands</i>			
<i>Females</i>			
All probands, 995 families			
Mother	81	1.92	1.54 to 2.37
Sister	184	2.37	2.04 to 2.68
Daughter	30	1.94	1.32 to 2.75
1st degree	295	2.18	1.95 to 2.43
2nd degree	391	1.52	1.37 to 1.67
3rd degree	371	1.52	1.37 to 1.63
<i>BRCA2 positive probands, 90 families</i>			
Mother	20	5.51	3.51 to 7.99
Sister	50	9.02	6.95 to 11.1
Daughter	6	6.67	2.48 to 13.9
1st degree	76	7.55	6.04 to 9.03
2nd degree	74	3.18	2.50 to 3.87
3rd degree	49	2.58	1.93 to 3.36
<i>BRCA2 negative probands, 797 families</i>			
Mother	59	1.61	1.24 to 2.05
Sisters	122	1.79	1.50 to 2.12
Daughter	19	1.68	1.01 to 2.60
1st degree	200	1.72	1.49 to 1.96
2nd degree	271	1.36	1.20 to 1.52
3rd degree	221	1.33	1.16 to 1.50
<i>Males</i>			
All probands, 995 families			
1st degree	7	5.04	2.02 to 10.3
2nd degree	3	1.10	0.23 to 3.21
3rd degree	8	3.20	1.35 to 6.30
<i>BRCA2 positive probands, 90 families</i>			
1st degree	6	66.7	24.6 to 143
2nd degree	1	4.51	0.14 to 25.1
3rd degree	1	5.65	0.16 to 31.2
<i>BRCA2 negative probands, 797 families</i>			
1st degree	1	0.85	0.02 to 4.73
2nd degree	2	0.97	0.12 to 3.50
3rd degree	1	0.56	0.01 to 3.12
<i>(B) Risk of prostate cancer in relatives of female probands</i>			
All probands, 995 families			
1st degree	156	1.33	1.13 to 1.55
2nd degree	251	1.22	1.07 to 1.37
3rd degree	212	1.05	0.91 to 1.19
<i>BRCA2 positive probands, 90 families</i>			
1st degree	34	4.79	3.27 to 6.32
2nd degree	37	2.21	1.57 to 3.02
3rd degree	13	0.92	0.49 to 3.12
<i>BRCA2 negative probands, 797 families</i>			
1st degree	110	1.08	0.89 to 1.29
2nd degree	177	1.15	0.98 to 1.32
3rd degree	146	1.03	0.86 to 1.20
<i>(C) Risk of ovarian cancer in relatives of female probands</i>			
All probands, 995 families			
1st degree	46	1.48	1.08 to 1.96
2nd degree	67	1.32	1.00 to 1.63
3rd degree	52	0.92	0.67 to 1.17
<i>BRCA2 positive probands, 90 families</i>			
1st degree	13	5.22	2.80 to 8.77
2nd degree	15	3.26	1.84 to 5.32
3rd degree	8	1.75	0.76 to 3.42
<i>BRCA2 negative probands, 797 families</i>			
1st degree	31	1.16	0.78 to 1.64
2nd degree	44	1.13	0.80 to 1.46
3rd degree	36	0.94	0.63 to 1.24
<i>(D) Risk of stomach cancer in relatives of breast cancer probands</i>			
<i>Females</i>			
All probands, 995 families			
1st degree	46	1.10	0.81 to 1.46
2nd degree	141	1.39	1.17 to 1.61
3rd degree	62	1.03	0.77 to 1.29
<i>BRCA2 positive probands, 90 families</i>			
1st degree	5	1.78	0.57 to 4.10
2nd degree	30	3.08	2.09 to 4.34
3rd degree	6	1.19	0.44 to 2.57
<i>BRCA2 negative probands, 797 families</i>			
1st degree	37	1.05	0.74 to 1.44
2nd degree	97	1.22	0.98 to 1.46
3rd degree	44	1.05	0.74 to 1.35

contd

Table 1 continued

Relative	Observed	O/E	95% confidence interval
<i>Males</i>			
All probands, 995 families			
1st degree	97	1.21	0.99 to 1.47
2nd degree	175	0.99	0.85 to 1.13
3rd degree	117	0.98	0.80 to 1.16
BRCA2 positive probands, 90 families			
1st degree	13	2.40	1.29 to 4.05
2nd degree	34	1.91	1.33 to 2.63
3rd degree	15	1.77	0.99 to 2.89
BRCA2 negative probands, 797 families			
1st degree	73	1.08	0.85 to 1.35
2nd degree	118	0.88	0.72 to 1.04
3rd degree	75	0.87	0.67 to 1.07
<i>(E) Risk of kidney cancer in relatives of breast cancer probands</i>			
<i>Females</i>			
All probands, 995 families			
1st degree	20	1.04	0.64 to 1.62
2nd degree	49	1.39	1.00 to 1.78
3rd degree	35	1.09	0.73 to 1.45
BRCA2 positive probands, 90 families			
1st degree	5	3.57	1.15 to 8.22
2nd degree	1	0.30	0.01 to 1.67
3rd degree	1	0.37	0.01 to 2.05
BRCA2 negative probands, 797 families			
1st degree	13	0.79	0.41 to 1.35
2nd degree	43	1.59	1.12 to 2.07
3rd degree	26	1.19	0.73 to 1.65
<i>Males</i>			
All probands, 995 families			
1st degree	27	0.96	0.64 to 1.39
2nd degree	49	0.97	0.70 to 1.24
3rd degree	58	1.14	0.85 to 1.43
BRCA2 positive probands, 90 families			
1st degree	6	2.84	1.21 to 6.12
2nd degree	4	0.87	0.23 to 2.21
3rd degree	2	0.55	0.07 to 1.52
BRCA2 negative probands, 797 families			
1st degree	20	0.83	0.50 to 1.28
2nd degree	38	1.00	0.68 to 1.32
3rd degree	42	1.18	0.82 to 1.53
<i>(F) Risk of cancer at all sites in relatives of female probands</i>			
<i>Females</i>			
All probands, 995 families			
1st degree	671	1.43	1.34 to 1.52
2nd degree	1036	1.21	1.15 to 1.28
3rd degree	979	1.16	1.09 to 1.23
BRCA2 positive probands, 90 families			
1st degree	108	3.39	2.88 to 3.89
2nd degree	138	1.83	1.57 to 2.09
3rd degree	97	1.46	1.20 to 2.01
BRCA2 negative probands, 797 families			
1st degree	515	1.27	1.17 to 1.37
2nd degree	775	1.18	1.11 to 1.26
3rd degree	646	1.12	1.04 to 1.20
<i>Males</i>			
All probands, 995 families			
1st degree	609	1.24	1.15 to 1.33
2nd degree	991	1.12	1.06 to 1.18
3rd degree	901	1.06	1.00 to 1.12
BRCA2 positive probands, 90 families			
1st degree	87	2.54	2.08 to 3.00
2nd degree	151	1.93	1.67 to 2.19
3rd degree	71	1.18	0.93 to 1.43
BRCA2 negative probands, 797 families			
1st degree	476	1.14	1.05 to 1.23
2nd degree	696	1.04	0.97 to 1.11
3rd degree	614	1.04	0.96 to 1.12

probands the risk for mothers and daughters is 1.63 and for sisters it is 1.79 ($p=0.50$). The excess risk of sisters is thus largely accounted for by the *BRCA2* mutation.

Table 1A also shows the breast cancer risk for male relatives. This is significantly increased for first and third degree

relatives of all probands, and significant for first degree relatives of probands carrying the mutation, but not for relatives of probands without the mutation.

Cancers at other sites

Previous studies from Iceland have found an increased risk of cancer of the prostate, ovaries, stomach, pancreas, and kidneys in relatives of females with breast cancer.^{3,4}

Table 1B gives the prostate cancer risk ratio of relatives in the families of breast cancer probands adjusted for age and calendar period by *BRCA2* status. In all families together, the familial increase in risk is significant for first and second degree relatives, 1.33 and 1.22, but not for third degree relatives. In the families of probands with the mutation, these risks are 4.79 and 2.21, respectively. In the families of probands without the mutation, no significant familial increase in prostate cancer risk was found, indicating that in this material the familiarity of prostate cancer is confined to the families with a mutation in the *BRCA2* gene.

Table 1C shows the ovarian cancer risk ratio of relatives in the families of breast cancer probands adjusted for age and calendar period by *BRCA2* status. In all families together, the familial excess risk is significant for first and second degree relatives, relative risk is 1.48 and 1.32, but not for third degree relatives. In the families of probands with the mutation these are 5.22 and 3.26 respectively, but in the families of breast cancer patients without the mutation, no significant increase in the familial risk was found.

The information on stomach cancer is shown in table 1D. In all families, the female second degree relatives have a familial relative risk of 1.39 (95% CI 1.17 to 1.61). This is stronger for relatives of *BRCA2* positive probands, 3.08 (2.09 to 4.34), but is not significant in relatives of *BRCA2* negative probands. No significant difference in risk was found for the first or third degree relatives. For the males, however, no families or relatives of negative probands show a significant familial risk, but the relatives of *BRCA2* positive probands have significantly increased relative risk for first degree relatives, 2.40 (1.29 to 4.05), and for second degree relatives, 1.91 (1.33 to 2.63). For third degree relatives, the relative risk is 1.77 (0.99 to 2.89).

Table 1E gives the results for cancer of the kidneys. In all families, the female first, second, and third degree relatives are at increased risk, but with statistical significance only for second degree relatives, 1.39 (1.00 to 1.78). In families of mutation positive probands, only the risk of first degree relatives is significant, and in the families of relatives of mutation negative probands the results are similar to those for all families. For the males, only the first degree relatives in the families of mutation positive probands have significantly raised risk.

An effect of the mutation in increasing the familial risk was tested for cancers of the pancreas, colon and rectum together, endometrium, melanoma, and thyroid and none was found (results not shown).

Table 1F shows the results for any cancer at any site for female and male relatives. For all families together, the familial excess risk for females is significant in first, second, and third degree relatives, 1.43, 1.21, and 1.16, respectively. For males these are 1.24, 1.12, and 1.06, respectively. In the families of probands carrying the mutation, the familial relative risk is significantly increased for all relatives for females and first and second degree relatives for males. The risk ratios are 3.39, 1.83, and 1.46 for females and 2.54 and 1.93 for males. In the families of probands without the mutation, the relative risks are significantly increased for all degrees of relatedness for females, but for males only the risk in first degree relatives is significantly increased.

Age at diagnosis

The mean age at diagnosis of first breast cancer of all probands tested for *BRCA2* is 49.59 years. For *BRCA2* negative probands

Table 2 Incidence of female breast cancer per 10⁵ per annum by age of relative and *BRCA2* status. Results from a model based on Poisson regression

Age of relative	<i>BRCA2</i> positive proband: degree of relatedness				<i>BRCA2</i> negative persons
	"0" degree*	1st degree	2nd degree	3rd degree	
25-29	47	32	22	15	4
30-34	63	42	29	19	6
35-39	516	350	237	160	53
40-44	969	656	444	301	114
45-49	1380	935	633	428	185
50-54	1306	884	599	405	199
55-59	1553	1052	712	482	270
60-64	1787	1210	819	554	354
65-69	1603	1085	735	498	363
70-74	999	676	458	310	258
75-79	1070	724	491	332	314
80-84	876	593	402	272	294
85-89	796	539	365	247	304
<i>Cumulative incidence</i>					
70 years	46%	31%	21%	14%	7.7%
90 years	65%	44%	30%	20%	13.6%

*Extrapolation to 100% sharing of genes.

it is 50.01 and for *BRCA2* positive probands 45.84 years. The mean age of breast cancer in the Icelandic Cancer Registry was, in the period 1955-1999, 59.92 years and for first diagnosed breast cancer it was 59.77.

Results of the Poisson model

Table 2 shows the incidence of female breast cancer per 10⁵ per annum by age of relative and *BRCA2* status based on a Poisson model. It also shows the cumulative incidence of female breast cancer at the age of 70 and at the age of 90 for first, second, and third degree relatives, as well as an extrapolation to total sharing of genes, or being a *BRCA2* mutation carrier. It can be seen that the effect of the *BRCA2* mutation declines markedly with age. When comparing relatives of *BRCA2* positive probands with those of *BRCA2* negative probands, first degree relatives under 35 years of age have a more than seven-fold higher incidence, whereas for those 80 years and older the increase is less than two-fold. The model is shown in the Appendix.

DISCUSSION

This is an investigation of the impact of a single founder mutation in the *BRCA2* gene on cancer incidence in the Icelandic population. Recorded linkage between a population based collection of 995 families of women diagnosed with breast cancer and the Icelandic Cancer Registry was used. Familiality of breast cancer in first degree relatives is 2.18 which is similar to that previously reported.¹ Classification of the families by *BRCA2* mutation status (the Icelandic founder mutation 999del5) of the proband indicates that this *BRCA2* gene mutation explains a substantial part of the familiality of breast cancer in Iceland, but not all, since the risk remains significant in the families of probands without the mutation. In contrast, the mutation explains most of the excess familial risk of prostate and ovarian cancer observed in relatives of breast cancer patients.

As already stated, the selection rules for the probands aimed at preventing preferential selection of families with many breast cancer cases. These rules have, however, affected the mean age at diagnosis since probands were selected among all cases born in a certain year and diagnosed before a stated year. This has led to a lower mean age at diagnosis in this material compared with the general population, which probably

explains why the proportion of *BRCA2* mutation carriers among probands is higher than previously reported from Iceland.^{11 19}

The results show that 40% of the familial risk of breast cancer is explained by the 999del5 mutation. This may seem high, but should be looked at in light of the fact that *BRCA1* mutation is very rare in Iceland. Therefore, over half of the familial risk remains unexplained, as only a small proportion of this can be accounted for by the very rare mutation in the *BRCA1* gene.

The results for breast cancer show that there remains significant familiality in the 797 families of probands negative for the mutation. Female first degree relatives of probands have a risk of 1.72 and are at 39% increased risk for breast cancer compared with the Icelandic population. This familiality is unlikely to be because of the *BRCA1* mutation, since it has been shown to be rare in the Icelandic population.^{8 12} This has not yet been investigated in this material nor the possibility of other *BRCA2* or *BRCA1* mutations. The possible existence of further *BRCA* genes should also be kept in mind.²⁰ Other factors can be suggested, such as polymorphisms and variants, of, for example, the *BRCA* or *TP53* genes, which may increase the risk to a smaller degree than the identified mutations.^{22 23} Common variants in a number of gene classes, including genes involved in steroid hormone and carcinogen metabolism, may act as low penetrance susceptibility alleles.^{23 24} Some of the items mentioned above could explain that segregation analysis on the same material indicates a codominant mode of inheritance for familial breast cancer²⁵ and familial breast and prostate cancer.²⁶ Genes important in the carcinogenic process may interact with environmental risk factors and this is the only mechanism by which genetics can have played a role in the increase in the incidence of breast cancer observed in Iceland and many other populations during the past several decades.

The Poisson model shows that the effect of the mutation declines with increasing age of the relative, so that in the youngest age group there is a more than seven-fold increase in breast cancer risk whereas in the two oldest groups it is less than two-fold. This is in accordance with the observation that mutation carriers are younger at diagnosis than those without the mutation. It also agrees with the assumption that environmental causes are relatively more important in the older age groups than in the young. The cumulative incidence to age 70 in the *BRCA2* group is 31% for first degree relatives and to age 90 it is 44%, which is similar to previously published figures from Iceland.¹⁹ The extrapolation to the theoretical 0th degree relatives should represent the mutation carrier assuming that the effect of the mutation is mainly dominant. Although there are clear differences in risk of penetrance of cancer between families,⁹ this extrapolation shows that for a group of assumed mutation carriers the average cumulative incidence is 46% at the age of 70 and 65% at the age of 90. Similarly, the age specific and cumulative incidence for relatives can be deduced from the model. It should be kept in mind that this is based on the unusual situation that only one *BRCA2* mutation is important in this population.

In table 2, the age distribution of breast cancer incidence for relatives of mutation positive probands, as well as relatives of mutation negative probands, shows an increase up to the age group 60-64, but at older ages there is no increase in the risk, rather a decrease. This is particularly pronounced for the extrapolation to "0th" degree, or mutation carriers, but can also be seen in the relatives of negative probands. Raw incidence figures for first and second degree relatives of *BRCA2* show the same tendency (data not shown). One explanation for the absence of risk increase after the age of 64 could be that the incidence calculations include only first diagnosed breast cancer, whereas second primary breast cancers are counted in the incidence as published by cancer registries. Furthermore, mutation carriers are diagnosed at younger ages than

non-carriers and therefore reduced numbers are at risk. Finally, the estimation of the prevalence of the 999del5 mutation in the Icelandic population is inaccurate, since it is based on a total of five carriers out of 1019 persons studied.^{10 11}

Sisters have a consistently greater risk than mothers or daughters, as has been discussed in previous publications,^{1 2} implying recessive inheritance. This difference is far more pronounced in relatives of probands positive for the mutation, which suggests an interaction between the truncation of the *BRCA2* gene and an environmental risk factor, for example, diet early in life, affecting sisters in the same manner since they grow up together, whereas mothers and daughters do not share the same environment at the same age.

The importance of *BRCA2* in the excess risk of male breast cancer has previously been reported from Iceland.^{9 10 27} The present results show that *BRCA2* mutation is important for male breast cancer, accounting for all excess risk in first degree relatives. The small number of cases did not permit further analysis.

For cancers at other sites than the breast in relatives of breast cancer patients, we have previously published significantly increased risk for cancers of the prostate, ovaries, stomach in females, pancreas in males, and kidneys in females.^{3 4} A recent paper on the effects of mutations in the *BRCA2* gene on risk of cancer in other organs than the breast²⁸ using collections of families at high risk of breast cancer from 20 different centres in Europe and North America including Icelandic data, the Breast Cancer Linkage Consortium (BCLC), showed statistically significant increase in risks for prostate cancer, estimated RR = 4.65, pancreas RR = 3.51, gallbladder and bile duct RR = 4.97, stomach (both sexes together) RR = 2.59, and malignant melanoma RR 2.58. A previous publication²⁹ estimated familial relative risks from the Utah Population Database. For probands with breast cancer, they found significantly increased familial relative risks for cancers of the colon, prostate, thyroid, and non-Hodgkin's lymphoma. Their relative risk for prostate cancer was 1.23. The present study confirms our previous findings on cancer of the prostate, ovaries, stomach, and kidneys, but not on the pancreas. It is in agreement with the BCLC study concerning stomach cancer and the Utah study concerning prostate cancer. The *BRCA2* mutation explains all excess familial risk of two hormone related cancers, those of the prostate and ovaries. Further, the excess risk of stomach cancer is in accordance with a previous publication.⁴

In the population of Iceland of around 280 000 persons (95 000 around 1920), mutation in the *BRCA1* gene is rare but the frequency of the 999del5 mutation in the *BRCA2* gene is estimated to be around 0.5%. This study shows that the *BRCA2* mutation accounts for all the excess risk for cancer of the prostate, ovaries, stomach, and some of the excess of cancer of the kidneys in females, found in relatives of breast cancer patients. On the other hand, it should be stressed that there is a significant residual familiarity of breast cancer of 1.72 for first degree relatives in families of probands negative for this mutation.

This unusual situation of having a population in which only one mutation of the *BRCA2* gene is present, and *BRCA1* mutation carriers are rare, makes it easier to calculate the risk that can be attributed to that mutation. It should, however, be kept in mind that the effects of other mutations, in this gene in this or other populations, might not be the same.

These results, although important, cannot be directly translated into recommendations for actions for prevention. For that, our knowledge of the intermediate steps in the pathogenesis from gene to cancer is insufficient. More research on these, as well as on the action of genes that might alleviate the effect of genes like *BRCA2*, is urgently needed.

APPENDIX

Formula obtained from Poisson regression on the dependence of relative risk of breast cancer of women relatives on *BRCA2* status of proband.

$$I_{\text{calc}} = \exp(C_0 + C_1 * A + C_2 * B + C_3 * B * A + C_4 * S + C_5 * B * S) * I_{\text{pop}}$$

where

I_{calc} = calculated incidence rate.

I_{pop} = population incidence rate.

A = age of the relative, years.

B = *BRCA2* positive proband set at 1.

BRCA2 negative proband set at 0.

S = degree of relatedness.

The following values were found for the coefficients (95% CI):

$C_0 = 0.954$ (0.573 to 1.335)

$C_1 = -0.0052$ (-0.0103 to -0.0001)

$C_2 = 3.242$ (2.489 to 3.995)

$C_3 = -0.0262$ (-0.0376 to -0.0148)

$C_4 = -0.133$ (-0.230 to -0.036)

$C_5 = -0.390$ (-0.599 to -0.181)

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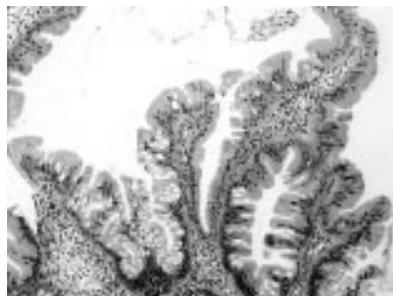
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ECHO

Serrated adenoma and APC gene mutation



Stained histological section of a serrated adenoma.



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A small study suggests that serrated adenoma may be a form of familial adenomatous polyposis (FAP) and not a separate type of colorectal cancer.

Three serrated adenomas were found separately in three out of 11 Japanese patients from three families with FAP. Colorectal polyps numbered <100 in each of the three, and all serrated adenomas were found in the rectum. All three patients with serrated adenomas had mutations in the adenomatous polyposis coli (*APC*) gene—two proximal to the site of the gene, at codon 161, 332 and the third at the most distal site, codon 1556. Mutations in the other patients were located between codons 554 and 1324.

The rate of occurrence of serrated adenoma in the study was 30 times that in the general population so *APC* mutation may influence pathogenesis of serrated adenoma. The genetic results are compatible with a recent report describing colonic polyposis of <100 polyps as attenuated FAP so serrated adenoma may actually be a phenotype of FAP.

All 11 patients had a total colonoscopy and multiple biopsies of polyps with a convoluted surface appearance suggesting serrated adenoma and confirmed as such by their characteristic appearance in histological stained sections.

The *APC* gene was screened by PCR of DNA from blood leucocytes and the protein truncation test. Complementary DNA was synthesised by reverse transcription of mRNA from blood leucocytes, amplified by PCR with *APC* gene primers, and the PCR products translated in vitro and determined as full or truncated proteins by gel electrophoresis.

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