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Neoplastic diseases in families of breast cancer patients

H Tulinius, G H Olafsdottir, H Sigvaldason, L Tryggvadottir, K Bjarnadottir

Abstract

Objective **– To investigate whether the risk of cancer at all sites, and at individual sites other than breast, prostate, ovaries, and endometrium, is increased among relatives of breast cancer patients compared with the general population.**

Design **– A cohort of family members of breast cancer patients was established. The probands were chosen by year of birth or time of diagnosis. Any influence of knowledge of the cancer experience of the relatives has been avoided. The risk estimates are based on expected numbers computed from age and time specific incidence rates for the Icelandic population.**

Setting **– Iceland.**

Subjects **– The population of Iceland.**

Main outcome measures **– Relative risks by degree of relatedness and age of proband.**

Results **– The relative risk of cancer at all sites is raised for males and females. This is more than expected based on the known familial risk of breast cancer, prostate, and ovarian cancer. The excess risk of breast, prostate, and ovarian cancer is confirmed, but not that of cancer of the endometrium. The risk of cancer of the pancreas in both sexes and the stomach and kidneys in females is significantly raised. No evidence was found for decreased risk for any cancer type.**

Conclusions **– The risk of cancer at all sites in relatives of breast cancer patients is increased. In addition to the risk of breast, prostate, and ovarian cancer, the risk of pancreas cancer and cancer of the stomach and kidneys in females is raised, but the last mentioned observations need further confirmation.**

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Numerous reports have appeared on the increased risk of breast cancer among relatives of breast cancer patients. Fewer articles have been published on the distribution of neoplastic disease at various other sites among relatives of breast cancer patients. A report on 34 selected families of breast cancer patients from the USA, and cancer in their relatives, was published in 1973.[1] A study from Switzerland on first degree relatives of 229 breast cancer patients diagnosed between 1981 and 1987 did not find a significant increase in relative risk (RR) for all sites in both sexes, but for females only. In addition to significantly increased RR for cancer of the breast, they found RR for cancer of the oesophagus, stomach, and brain to be significantly increased in both sexes, and cancer of the colon and endometrium in females.[2]

The Icelandic Cancer Registry was founded in 1954 by the Icelandic Cancer Society. In 1972 an agreement was made with the International Agency for Research on Cancer (IARC), the Genetical Committee of the University of Iceland, and the Department of Pathology of the University of Iceland to collect genealogical information with the purpose of evaluating the risk of cancer to family members of patients with neoplastic diseases. Such excess familial risk, if found, can be genetic, environmental, or both, and the investigation aims at resolving that problem, as well as quantifying the relative importance of inheritance and environment. The ultimate aim is to identify genes involved so that information about the gene products can lead to understanding of the pathogenesis and consequently enable prevention and cure of the diseases. This collaboration has lead to several publications.[3–9]

The purpose of the present investigation is to estimate the frequency of malignant diseases, at all sites and at individual sites, in relatives of women who have been diagnosed as having breast cancer, in order to gain a better perspective of the familial risk of cancer in man.

Material and methods

The cancer risk of family members of 947 randomly selected women with breast cancer was analysed. The study base is thus the same as in our previous publication,[9] except that no persons have now been excluded because of year of birth or age, and that the family members have been followed up for malignant diseases until the end of 1991 by record linkage with the Icelandic Cancer Registry. The material has been collected in such a way that most of the serious biases are avoided. The breast cancer cases, for whom pedigrees were collected, were a random sample of all breast cancer cases diagnosed in the Icelandic population, selected either by year of diagnosis or by year of birth. The pedigrees are of predetermined types of relatives, thus avoiding the pitfall of having more information about those family members in whom the occurrence of cancer is thought to be more common. The information on which family members have been diagnosed with a malignant disease was obtained only by record linkage with the Icelandic Cancer Registry, which is thought to have almost complete information on malignant neoplasms in the Icelandic population. The collection of material has been described in previous publications.[8 9]

Icelandic Cancer Registry, Skógarhlíð 8, PO Box 5420, 125 Reykjavik, Iceland
H Tulinius
G H Olafsdottir
H Sigvaldason
L Tryggvadottir
K Bjarnadottir

Correspondence to Professor Tulinius.

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STATISTICAL METHODS

In a previous study,[9] computation of expected numbers was based on incidence rates of spouses of probands and spouses of relatives of probands whereas the present investigation uses the rates in the general population.

The risk period for cancer was taken as 1955–1991. Each person was assumed to be at risk from the beginning of the period or from birth, if born later, until the end of 1991, death, or diagnosis of cancer, whichever came first.

In computing the RR for cancer at all sites combined, two methods were considered; first, counting only the first primary cancer and defining the end of the risk period of cases as the time of diagnosis and, secondly, counting all primary cancers and defining the end of the risk period as time of death or end of 1991. Both methods were used.

Observed cases of cancer and years of risk in family members were classified according to sex, five year age intervals, five calendar year intervals, degree of relatedness to the breast cancer proband (first, second, third, and fourth degree), and age at diagnosis of the proband. Incidence figures classified according to the site of cancer, sex, five year age intervals, and five year calendar periods were obtained from the Icelandic Cancer Registry. The expected number of cases was calculated as the sum of products of years of risk and the corresponding incidence figures. Relative risks were computed as the ratio between observed and expected numbers. In addition to the RRs specific to the degree of relatedness, a composite RR was compared using the following weights: first degree, 1; second degree, 1/2; third degree, 1/4; and fourth degree, 1/8. It should be kept in mind that one test out of 20 would be classified as significant, even in the case of no real connection, if the level of significance chosen is 5%.

Results

Table 1 shows the total material used and the number of observed malignant neoplasms diagnosed in the years 1955 to 1991. The number of malignancies diagnosed was 1977 in 21 364 male relatives and 2309 in 20 442 female relatives.

Table 2 shows the observed number of cases and RRs of malignant neoplasms in relatives of breast cancer patients by degree of relatedness and for all relatives weighted by degree of

Table 1 People under study

	Study population		*All cancers*	
	No in Pedigree	*No alive 1955*	*No of persons*	*No of tumours*
Probands	947	879		
Male relatives	25 021	21 364	1842	1977
Female relatives	23 702	20 442	2099	2309
Husbands	9314	8284	909	971
Wives	8367	7621	884	969
Total	67 351	58 590	5734	6226

Table 2 Observed numbers of cases and relative risk of malignant neoplasms by relatedness to breast cancer probands

		Degree of relatedness									
		First		*Second*		*Third*		*Fourth*		*Weighted*	
		No obs	*RR*	*No obs*	*RR*	*No obs*	*RR*	*No obs*	*RR*	*RR*	*95% conf limits*
All sites first primaries	Males	424	1·20***	737	1·04	591	1·02	90	1·06	1·10***	1·05; 1·16
All sites first primaries	Females	505	1·43***	798	1·15***	687	1·14**	109	1·11*	1·26***	1·21; 1·32
Breast	Females	192	2·17***	213	1·43***	247	1·54***	35	1·27	1·76***	1·63; 1·91
Prostate		89	1·27*	172	1·15	105	0·94	9	1·22	1·16**	1·04; 1·30
Ovary		36	1·53*	43	1·05	35	0·85	7	0·91	1·22*	1·00; 1·47
Endometrium		24	1·20	33	0·99	23	0·67	4	0·95	1·02	0·81; 1·28
Stomach	Males	77	1·10	141	0·90	98	0·99	7	0·90	0·99	0·88; 1·12
Stomach	Females	38	1·08	122	1·35**	49	1·00	3	0·86	1·20*	1·04; 1·40
Pancreas	Males	25	1·66*	38	1·20	16	0·68	3	1·43	1·30*	1·04; 1·64
Pancreas	Females	18	1·39	29	1·04	17	0·84			1·14	0·88; 1·47
Lung	Males	45	1·11	63	0·98	69	0·96	7	0·86	1·03	0·88; 1·21
Lung	Females	38	1·27	50	1·03	50	0·95	11	1·69	1·12	0·94; 1·34
Colon and rectum	Males	43	1·12	66	0·84	64	1·03	4	0·66	0·98	0·84; 1·15
Colon and rectum	Females	44	1·08	78	0·88	56	0·89	5	0·83	0·96	0·82; 1·13
Kidney	Males	21	1·07	36	0·92	37	1·05	5	1·14	1·00	0·81; 1·25
Kidney	Females	15	1·10	43	1·53**	21	0·96	3	1·03	1·25	0·99; 1·60
Bladder	Males	26	1·13	41	0·99	40	1·01	2	0·42	1·04	0·85; 1·28
Bladder	Females	8	0·76	17	0·71	17	1·02	1	0·59	0·78	0·56; 1·09
Brain	Males	15	1·30	20	1·05	19	0·87	13	1·71	1·15	0·87; 1·50
Brain	Females	15	1·26	15	0·90	23	1·03	7	1·03	1·08	0·82; 1·42
Thyroid	Males	10	1·37	13	1·08	13	0·99	5	1·72	1·20	0·86; 1·69
Thyroid	Females	21	1·21	43	1·31	21	0·69	7	0·95	1·15	0·92; 1·44
Leukaemia	Males	15	1·46	21	1·01	22	1·20	5	0·68	1·21	0·92; 1·58
Leukaemia	Females	7	0·93	14	0·88	7	0·54	4	0·93	0·85	0·58; 1·24
Cervix		22	1·05	26	0·82	46	1·18	13	1·37	1·01	0·81; 1·25
All sites multiple primaries	Males	463	1·16**	781	0·97	639	0·98	94	1·04	1·05*	1·00; 1·10
All sites multiple primaries	Females	580	1·42***	866	1·11**	746	1·09*	117	1·08	1·24***	1·18; 1·29

For individual sites risk estimates are based on first primary diagnosed at that site. * Significant at 0·05% level. ** Significant at 0·01% level. *** Significant at 0·001% level

relatedness. A significantly increased risk was found for cancer at all sites for first degree female relatives, RR = 1·43 (95% CL 1·31; 1·56) and for first degree male relatives, RR = 1·20 (95% CL 1·09; 1·32). Second, third, and fourth degree female relatives also had a significantly raised risk for cancer at all sites, but not male relatives. These figures are computed by counting only the first primary in each person. When counting all cancers slightly lower numbers are obtained, but still significantly increased.

Female first degree relatives had significantly increased risk for breast cancer (2·17) and ovarian cancer (1·53), and males for prostate cancer (1·27) as previously reported.[8,9] The weighted RRs were 1·76, 1·22, and 1·16 respectively, all significant. In addition, the female second degree relatives had a significant increase in risk for stomach cancer (1·35) and the weighted RR was 1·20 (95% CL 1·04, 1·40). Male first degree relatives had an increased RR for cancer of the pancreas (1·66) and the weighted RR was 1·30 (95% CL 1·04, 1·64). Second degree relatives had a significant increased RR for kidney cancer (1·53).

Table 3 shows the RRs for relatives of breast cancer probands, comparing probands diagnosed before the age of 45 (table 3A) with those diagnosed after that age (table 3B). For relatives of young probands, the RR is increased for cancer at all sites in both sexes. Furthermore the RRs are increased for breast cancer and stomach cancer in female relatives and for cancer of the prostate and pancreas in male relatives. In female relatives of postmenopausal breast cancer patients, an increased risk was found for cancer of the pancreas.

Discussion

The main purpose of our investigation was to find out whether the relatives of women diagnosed with breast cancer were at increased risk of neoplastic diseases at all sites, and at any sites in addition to breast, prostate, ovaries, and endometrium.[8,9]

The most important finding is that relatives of breast cancer patients are at significantly increased risk of having neoplastic diseases in general. This is true even if the excess number of breast, prostate, and ovarian cancers is subtracted. The present analysis confirmed the previous findings on breast, prostate, and ovarian cancer, but not on cancer of the endometrium. An explanation is not obvious, but it should be pointed out that in the previous study[9] the association was only significant when the weighted average RR was used, and not when looked for in each degree of relatedness separately. Furthermore the reference group in the former study consisted of wives of relatives, whereas in the present study the comparision group is the entire Icelandic population.

The reason for this choice is that spouses may have a lower RR than the population in general. In our material, husbands have an RR of 0·87 (CL 0·82; 0·93) and wives rates of 0·93 (CL

Table 3A Observed numbers of cases and relative risk of malignant neoplasms by relatedness to a premenopausal (younger than 45) breast cancer proband

		Degree of relatedness									
		First		Second		Third		Fourth		Weighted	
		No obs	RR	No obs	RR	No obs	RR	No obs	RR	RR	95% conf limits
All cancer	Males	114	1·27*	252	1·08	82	1·05	3	1·38	1·16**	1·05; 1·28
All cancer	Females	153	1·57***	274	1·21**	111	1·29**	5	2·10	1·37***	1·25; 1·50
Breast	Females	70	2·66***	87	1·75***	53	2·21***	2	2·47	2·22***	1·93; 2·55
Prostate		18	1·07	69	1·36*	10	0·73			1·20	0·96; 1·50
Ovary		9	1·31	17	1·23	8	1·37	2	9·81*	1·29	0·91; 1·83
Stomach	Males	21	1·29	55	1·08	19	1·47	1	4·25	1·18	0·95; 1·47
Stomach	Females	14	1·70*	42	1·49*	5	0·78			1·52*	1·16; 1·99
Pancreas	Males	8	2·16*	12	1·13	3	0·98			1·51*	0·99; 2·30
Pancreas	Females	2	0·59	5	0·53	2	0·75			0·57	0·28; 1·15
Kidney	Males	8	1·53	10	0·76	7	1·53			1·14	0·75; 1·72
Kidney	Females	7	1·90	15	1·58	1	0·34			1·61*	1·05; 2·46

Table 3B Observed numbers of cases and relative risk of malignant neoplasms by relatedness to a postmenopausal (45 and older) breast cancer proband

		Degree of relatedness									
		First		Second		Third		Fourth		Weighted	
		No obs	RR	No obs	RR	No obs	RR	No obs	RR	RR	95% conf limits
All cancer	Males	310	1·17**	485	1·02	509	1·02	87	1·06	1·09*	1·02; 1·15
All cancer	Females	352	1·38***	524	1·12**	576	1·11*	104	1·09	1·23***	1·16; 1·29
Breast	Females	122	1·96***	124	1·26*	194	1·42***	33	1·23	1·59***	1·44; 1·75
Prostate		71	1·33*	103	1·04	95	0·97	9	1·26	1·15*	1·01; 1·31
Ovary		27	1·62*	26	0·96	27	0·77	5	0·67	1·19	0·94; 1·49
Stomach	Males	56	1·05	86	0·80	79	0·91	6	0·79	0·92	0·80; 1·06
Stomach	Females	23	0·86	80	1·29*	44	1·03	3	0·88	1·08	0·90; 1·29
Pancreas	Males	17	1·49	26	1·23	13	0·63	3	1·48	1·23	0·94; 1·61
Pancreas	Females	16	1·67*	24	1·29	15	0·85			1·35*	1·02; 1·78
Kidney	Males	13	0·90	26	1·00	30	1·04	5	1·17	0·97	0·75; 1·25
Kidney	Females	8	0·80	28	1·51*	20	1·06	3	1·06	1·12	0·84; 1·50

For individual sites risk estimates are based on first primary diagnosed at that site. * Significant at 0·05% level. ** Significant at 0·01% level. *** Significant at 0·001% level.

0·87; 1·00). This may be because cancer occurring at a young age may prevent marrying. This is supported by the observation on prostate cancer that husbands have a RR close to 1 or 0·97 (CL 0·84; 1·12). Cancer of the prostate occurs nearly exclusively after the age of 45. Another possibility is that persons who never marry may have a different (higher) cancer risk. For breast cancer it is well known that nulliparous women are at an increased risk.[10 11]

Cancer of the pancreas shows an increased frequency in these pedigrees. For males the RR is significantly raised for first degree relatives (1·66) and for all degrees of relatedness (1·30). For females the rise is not significant for probands at all ages. When the pedigrees are classified by the age of the proband at diagnosis, the RRs are significantly raised for first degree relatives and for weighted average for male relatives of younger probands. For females the weighted average and the RR for first degree relatives of older probands are also raised.

The RR for cancer of the stomach for females is significantly raised for second degree relatives (1·35) and for all relatives (1·20). For the relatives of younger probands this is also true for first degree relatives (1·70), second degree relatives (1·49), and all relatives (1·52). An increased risk for stomach cancer has previously been reported by Swiss researchers.[2]

Females have an increased risk for cancer of the kidney. This is significant only for second degree relatives of all probands (1·53), for weighted average of relatives of probands younger than 45 years of age (1·61), and second degree relatives of the older probands (1·51).

It is not possible to say how many of these observations are the effects of multiple significance testing.

These studies do not indicate that the ratio of multiple primary neoplasms in relation to single primaries is raised in relatives of breast cancer patients. The rates are lower as shown in table 2. Further, no evidence was found for a significantly decreased risk at any site.

Comparing the pedigrees of those breast cancer patients diagnosed young with those where the proband is diagnosed at 45 years or older showed that many of the important RRs are higher in the former group. It is usually assumed that diagnosis at an early age of a disease which may have genetic or environmental causes, or both, indicates a genetic component in the risk. Another interpretation is possible, namely an environmental risk factor of unusually great magnitude would also lead to young age at diagnosis.

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