Epidemiology of breast cancer in families in Iceland

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Abstract

The Icelandic Cancer Registry has collected 989 pedigrees of breast cancer patients since 1972. In addition to the probands, the families also include 401 other women with breast cancer, so family information exists for 1390 women with breast cancer out of a total of 2748 diagnosed with the disease from 1910 to 1988. Most of the probands have been selected with care to avoid the bias of selecting families with a known history of breast cancer. After excluding all those who did not conform to the strict selection criteria, 947 pedigrees remained for this analysis. First, second, and third degree relatives all had a significantly increased risk of breast cancer: 2.26, 1.43, and 1.49, respectively. Male relatives also had a significantly increased risk, whereas females related by marriage had not. Of the first degree relatives, sisters had the largest increase in risk.

When pedigrees were classified by the age at diagnosis of breast cancer of the proband, the risk was highest in the relatives of probands who were young at diagnosis. Bilaterality of breast cancer increased the risk in relatives and the highest risk (9.04) was found in sisters of probands with bilateral disease and an age at diagnosis of first cancer of less than 45 years (95% confidence limits 4.14, 17.18).

Sisters consistently have the highest risk, significantly higher than other first degree relatives. This points to an important role of shared environmental aetiological factors acting after birth and it can not yet be excluded that most of the increase in risk can be explained by this. The search for inherited genes must, however, continue because of the important consequences their identification could have for the understanding of carcinogenesis and possible prevention.

That breast cancer occurs more frequently in some families than in others has been suspected for a long time. Several studies have shown an increased risk of breast cancer in close relatives of breast cancer patients. Among the earlier studies are those published by Waaler,¹ Jacobsen,² Woolf,³ Macklin,⁴ and Anderson *et al.*⁵ Since then, a number of epidemiological studies have been published. The subject has recently been thoroughly reviewed by Schneider *et al.*⁶

Familiality is the word which has lately been used for the difference in the risk of a disease between families. Familiality of breast cancer can therefore be defined as the increased risk of breast cancer among relatives of breast cancer patients. This leads to the following questions. Is this increase in risk of breast cancer for relatives of patients with breast cancer significant and is it valid? Is the increase in risk because of shared environmental factors, such as common living conditions, diet, etc, or because of common genes, or a combination of both?

As to the first question, most published studies agree that relatives of breast cancer patients are at a significantly increased risk. As for the question of validity, the most likely biases are those of recall and of selection. The recall bias would come into operation if the information about which relatives have breast cancer is obtained from the breast cancer patients themselves or their relatives. Positive information (that a family member has breast cancer) can be verified but negative information (that a person does not have breast cancer) can only be verified where there is complete population based cancer registration.

Selection bias occurs if families with multiple cases are more likely to be included than those which do not have multiple cases. It can be assumed that the chance occurrence of many cases in a kindred would attract attention and such families would therefore be more likely to be traced and therefore to be available for investigation. In some published studies, however, this has been well taken care of, for example, in studies from northern countries,^{7,8} by selecting families for tracing using criteria that prevent this. It can be accomplished by taking a random sample, or taking all breast cancer cases diagnosed in a defined period, or those who are born in a defined period. There seems, therefore, little doubt that the raised risk is valid.

The Icelandic Cancer Registry has been in operation since 1954.⁹ The information on cancer incidence in the population is likely to be nearly complete for 1955 and later years for cancer at all sites. The incidence of breast cancer up to that time has been the subject of a special study.¹⁰ It is therefore assumed that few, if any, breast cancer cases diagnosed in Icelanders after 1910 are not known to the Cancer Registry.

The tracing of pedigrees of breast cancer patients was started in 1972. By the end of 1990 families of 989 patients had been traced. Of these, 947 patients have been selected by year of birth or year of diagnosis, thus avoiding selection bias.

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In an earlier publication⁸ on 369 families from Iceland it was found that the relative risk for breast cancer for mothers of cases was 1.81 and for sisters it was 2.91. The present study will look at some epidemiological features, such as age at diagnosis and bilaterality of familial breast cancer among relatives of 947 patients with breast cancer.

Materials and methods

BREAST CANCER CASES

Complete cancer registration has been in operation nationwide since 1955.^{9,11} Before that date, a list of all breast cancer cases diagnosed in Iceland since 1910 has been established.¹⁰ These two sources form the complete set of cases used to select probands, to identify breast cancer among the relatives, and to calculate expected numbers.

SELECTION OF PROBANDS

Families have been traced for all patients born between 1834 and 1860 (55 families), all patients born after 1915 and diagnosed before 1985 (725 families), 26 patients born after 1915 and diagnosed in 1985, and patients born in 1865 and 1875 (five patients from each year). Families were also traced for every eighth patient born between 1899 and 1916 (46 families), and for every eighth patient diagnosed between 1954 and 1972 (85 families). Forty-two families did not conform to these selection criteria. These include families which are not yet completely traced, mainly diagnosed in recent years, and families which have aroused special interest. These have not been used for analysis.

CONSTRUCTION OF THE PEDIGREES

The extent to which the family is traced is 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). Next in size 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 1860, the parents have been identified and all their offspring have been traced (55 families). When relatives of other types than those decided in advance for that group of families have been recorded among the family members, these have been excluded from the present analysis.

Information on diagnosis of breast cancer was obtained by comparing the pedigrees with the list of all breast cancer patients from 1910 to 1988, and information on cancer at any other site by matching with the Cancer Registry. Breast cancer, both in situ and invasive, is recorded. The family files are updated for date of death every year.

METHOD FOR ESTIMATING RISK

Since 1910 the incidence of breast cancer has increased greatly. In an earlier publication¹² the multiplicative effects of year of birth and age have been shown and that exponential increase with the year of birth describes the changes in incidence adequately. Moreover we found that the age dependence of the incidence could be adequately described by two exponential curves, one for under 45 years of age and another for over that age.

We obtained the following equations for females:

$$I = 0.005 * \text{Exp} (0.0194 * X + 0.172 * t),$$

t < 45 years,

$$I = 2.5 * \text{Exp} (0.0194 * X + 0.0339 * t),$$

t ≥ 45 years

where I = incidence per 100 000 per year, 1800 + X = calendar year of birth, t = age in years, Exp = the exponential function.

For males the same expressions divided by 100 were used.

In order to calculate the cumulative risk for a person, the incidence equations were integrated from birth or the beginning of the observation period (1910), whichever came later, until the first of three possible endpoints was reached: time at breast cancer diagnosis, death, or the end of the observation period (1988). The expected number of cases was computed as the sum of the cumulative risks of all the subjects.

Multivariate Poisson regression was also used to check the results, and Cox's proportional hazards model was used to test significance of difference in risk between sisters of probands and other first degree relatives. The program EGRET¹³ was used for both types of regression.

Results

In the family collection of the Icelandic Cancer Registry there are 989 pedigrees in which the proband is a breast cancer patient (table 1). In addition, 401 breast cancer patients have been identified among the relatives of these 989 patients, so the Registry has family information on 1390 or 50.6% of the 2748 known breast cancer patients.

The criteria for selecting breast cancer patients for family tracing have been described above. Pedigrees not in accordance with the selection rules (42) were excluded, leaving 947 pedigrees where previous information on breast cancer in the family can be ruled out as contributing to the selection of the family. In the remaining pedigrees there are 68 896 persons, on average 73 family members in each

Table 1 Breast cancer in Iceland 1911 to 1988.

Women diagnosed with breast cancer	2748
Pedigrees drawn	989
Additional patients as relatives	401
Pedigrees selected according to rules	947
Subjects in 947 pedigrees	
Related males	25 625
Related females	24 296
Husbands of relatives	9504
Wives of relatives	8524
Probands	947
Total	68 896

Table 2 Relative risk of breast cancer in families (No of pedigrees 947).

	Obs	Exp	RR	95% conf limits
Female relatives				
First degree	216	95.5	2.26	1.98, 2.59
Sisters	134	50.9	2.63	2.21, 3.13
Daughters	13	7.9	1.65	0.88, 2.82
Mothers	69	36.6	1.88	1.47, 2.39
Second degree	303	212.2	1.43	1.28, 1.60
Third degree	234	157.5	1.49	1.31, 1.70
Fourth to seventh degree	25	21.7	1.15	0.74, 1.70
Total	778	487.6	1.60	1.49, 1.72
Male relatives	13	4.6	2.81	1.49, 4.81
Females related by marriage	213	234.2	0.91	0.79, 1.04

Odds ratio for sisters *v* daughters + mothers = 1.43 (1.09, 1.88), $p=0.01$.

Table 3 Relative risk of breast cancer in families and mean age at diagnosis of the affected relatives by age of proband at diagnosis.

Age of proband at diagnosis	< 45			45-54			> 54		
No of pedigrees	291			332			324		
	N	RR	Age	N	RR	Age	N	RR	Age
First degree relatives	76	2.98	55.4	77	2.20	57.4	63	1.80	56.9
Sisters	44	3.63	51.6	51	2.70	53.7	39	1.96	56.6
Mothers + daughters	32	2.39	60.6	26	1.62	64.6	24	1.62	57.3
Second degree relatives	113	1.70	60.1	92	1.33	60.2	98	1.28	58.8
Third degree relatives	48	2.22	53.5	41	1.24	57.0	145	1.41	55.9

All relative risks in the table are significantly different from 1 at the 5% level except for third degree relatives of probands diagnosed at ages 45 to 54.

Table 4 Relative risk of breast cancer in families: proband with bilateral disease (78 pedigrees).

	Obs	Exp	RR	95% conf limits
First degree female relatives	37	8.4	4.40	3.39, 6.46
Sisters	26	4.9	5.30	3.46, 7.79
Mothers/daughters	11	3.5	3.14	1.57, 5.62
Second degree female relatives	33	17.1	1.93	1.32, 2.72
Third degree female relatives	18	9.3	1.93	1.14, 3.05

Table 5 Relative risk of breast cancer in families: proband with bilateral disease and age at diagnosis of first cancer < 45 (duplicate nuclear families not included) (29 pedigrees).

	Obs	Exp	RR	95% conf limits
First degree female relatives	14	2.6	5.42	2.96, 9.11
Sisters	9	1.0	9.04	4.14, 17.18
Mothers/daughters	5	1.6	3.13	1.01, 7.29
Second and third degree female relatives	23	7.7	2.98	1.89, 4.47

Table 6 Relative risk of breast cancer in families: proband with mother or daughter affected (duplicate nuclear families not included) (74 pedigrees).

	Obs	Exp	RR	95% conf limits
Sisters	13	3.4	3.84	2.04, 6.57
Second degree female relatives	43	15.4	2.79	2.02, 3.77
Third degree female relatives	25	12.2	2.04	1.32, 3.02

pedigree, and of these 24 296 are related females.

Table 2 shows the relative risk of the members of 947 pedigrees by degree of relationship. Among the female relatives the sisters have the highest relative risk of 2.63 (95% confidence limits 2.21, 3.13), where 134 were observed against 50.9 expected. The other first degree relatives have lower relative risks (mothers 1.88 and daughters 1.65). The latter figure is not significant (95% confidence limits 0.88, 2.82) based on only 13 cases where 7.9 were expected. Sisters have a significantly higher risk than the other first degree relatives (mothers and daughters) and the odds ratio is 1.43 (95% confidence limits 1.09, 1.88).

Second and third degree relatives also have significantly raised risks (1.43 and 1.49 respectively) whereas more distant female relatives do not have a significant increase in risk. All female relatives taken together have a risk of 1.60 (95% confidence limits 1.49, 1.72). Male relatives also have higher relative risks (2.81) (95% confidence limits 1.49, 4.81). This is based on only 13 cases, when 4.6 were expected.

Females who have married into the families have a risk not significantly different from 1, which lends credence to the increased relative risks of the relatives.

In table 3 the pedigrees were divided into three groups by the age of the proband. Relative risks of sisters, mothers, and daughters, first degree relatives taken together, second degree relatives, and third degree relatives were computed for each group of pedigrees. For all but third degree relatives of probands diagnosed between 45 and 54 years of age, the relative risks for each group of probands were significantly different from 1 at the 5% level. The relative risks were consistently highest in the group of probands less than 45 years of age at diagnosis, and for first and second degree relatives they were consistently lowest for the group of probands older than 54 years at diagnosis.

Looking at the mean age at diagnosis of the relatives, sisters are the only category to show an increase in mean age at diagnosis with increasing age at diagnosis of the proband. In other categories of relatives there was no consistent pattern.

The relatives of probands with bilateral disease have higher relative risks than relatives of all probands. The sisters of probands with bilateral disease have a relative risk of 5.30 (95% confidence limits 3.46, 7.79), as seen in table 4, compared with sisters of all probands (2.63) (95% confidence limits 2.21, 3.13) (table 2).

The highest relative risks are shown in table 5 where the results are shown for pedigrees where the proband had bilateral disease and at least the first cancer was diagnosed at an age below 45 years. The first degree relatives have a relative risk of 5.42 (95% confidence limits 2.96, 9.11) and the sisters (nine observed when one was expected) had a relative risk of 9.04 (95% confidence limits 4.14, 17.18).

Table 7 Results from multivariate Poisson regression. Odds ratio (95% confidence limits).

Variable	Year of birth		Age at risk		Total
	< 1910	> 1909	< 45 years	> 44 years	
Type of relative (Reference: spouses)					
Mother or daughter	1.98 (1.42, 2.77)	2.25 (1.40, 3.64)	2.03 (1.03, 3.99)	2.09 (1.57, 2.79)	2.18 (1.67, 2.85)
Sister	2.89 (1.87, 4.46)	2.89 (2.20, 3.80)	4.01 (2.52, 6.38)	2.27 (1.77, 2.92)	2.71 (2.16, 3.40)
Second degree relatives	1.42 (1.09, 1.84)	2.02 (1.54, 2.64)	1.82 (1.17, 2.85)	1.59 (1.30, 1.95)	1.69 (1.42, 2.04)
Third degree relatives	1.48 (1.08, 2.03)	1.77 (1.40, 2.23)	2.00 (1.30, 3.05)	1.53 (1.24, 1.89)	1.65 (1.37, 1.99)
Fourth to seventh degree relatives	2.01 (0.63, 6.41)	1.07 (0.67, 1.73)	1.29 (0.60, 2.79)	1.27 (0.76, 2.14)	1.14 (0.73, 1.73)
Proband's age at diagnosis (Reference: > 44 years)					
< 45 years	1.49 (1.21, 1.85)	1.39 (1.14, 1.70)	1.50 (1.09, 2.08)	1.37 (1.16, 1.61)	1.42 (1.23, 1.64)
Laterality of proband's cancer (Reference: unilateral)					
Bilateral	1.40 (1.04, 1.87)	1.25 (0.95, 1.64)	1.66 (1.10, 2.51)	1.27 (1.01, 1.59)	1.33 (1.09, 1.62)

Year of birth (10 year groups 1850–1959) together with age (5 year groups 20+ years) were also variables in the regression (coefficients not shown here).

Table 6 shows the relative risk of relatives if a mother or a daughter is affected. Here, the risk of the sisters is 3.84, higher than that of sisters of all probands, but the difference is not significant at the 5% level.

As can be seen from tables 2, 4, and 5, the relative risk of second and third degree relatives increases according to that of the first degree relatives.

In addition to the computations based on the incidence model for the Icelandic population, a multivariate Poisson regression was performed using only the data from the family file. The results shown in table 7 are consistent with the other results when the relative risk of spouses of relatives (0.91) in table 2 is taken into consideration. This low value could result from the crudeness of the incidence model. Table 7 shows the results of the Poisson regression on the total number of female relatives and also divided according to year of birth or age period of risk of the relative. The independent effects of young age of proband and bilaterality of cancer are clearly seen. Division of the material according to birth

cohorts did not show any noteworthy differences in risk ratios. Division of the risk period at the age of 45 yields mostly higher risk ratios before the age of 45 than after. Sisters have a consistently higher risk than mothers and daughters but not significantly so.

Regression according to the Cox's proportional hazards model was used to test if the sisters had a significantly higher risk than mothers and daughters. Birth cohorts 1875 to 1954 of sisters (1913), mothers (719), and daughters (469) were used. Observation started at the age of 35 and ended at diagnosis of breast cancer. Deaths before the end of 1988 or being alive then without having been diagnosed as having breast cancer were treated as censored data. Variables were sisters versus mothers and daughters and decades of birth. This yielded a hazard ratio of 1.34 for sisters (95% confidence limits 0.96 and 1.88) ($p = 0.09$, NS).

The figure shows graphically the results of plotting the cumulative risk of mothers, sisters, and daughters separately. This was done by computing the Kaplan-Meier estimate for survival using EGRET.¹³ It shows that the cumulative risk of sisters is clearly higher than that of mothers, but the daughters are too few for definite conclusions. If it were only the cohort effect the curve for daughters should show the highest cumulative rate, whereas the last points on the curve for daughters are below those of sisters.

Discussion

SIGNIFICANCE AND VALIDITY

Tables 2 to 6 show the relative risks of breast cancer for the various types of relatives of breast cancer patients. These are consistently significantly higher than 1, whereas the risk for women married to family members is not (table 2). Sisters have the highest relative risk, and the first degree relatives have a higher risk than more distantly related family members (tables 2 to 6). This is in accordance with most published studies. It can therefore be concluded that the increase in risk for relatives of breast cancer patients is significant.

As for validity, bias of selection and of recall have to be considered. It is possible that if more than one family member has the same disease, this will draw attention to that family

Unadjusted cumulative rates for breast cancer incidence of mothers, sisters, and daughters of women diagnosed with breast cancer.

and make it more likely that such a family is selected for tracing. This is likely to have happened in some of the previously published studies. In the present material, this bias has been avoided by defining criteria for selection that do not include any information on breast cancer in the family. The criteria used are those of year of birth or year of diagnosis. Thus, for example, all breast cancer cases born in 1916 or later and diagnosed before 1985 have been selected. The families not conforming to these selection criteria have been excluded from this analysis.

Related to the selection bias is the definition of the extent of family traced. For each selection group, the extent traced has also been defined. If information exists on family members more distantly related than the predefined pedigree size calls for, it has been recorded but excluded from this analysis. This bias may have operated in studies where predefined criteria were not used.

The bias of recall operates where information on the disease is obtained from members of the families, since persons who have been exposed to a serious disease are more likely to know about and remember similar diseases in the family than those who have not been so exposed, and this can lead to spuriously raised relative risks for the family members. In our material this bias should not operate, as the procedure was as follows. First the information on disease is recorded and the Icelandic Cancer Registry has information on all breast cancer cases diagnosed in the population since 1910. This file is considered to be close to complete. After the probands have been selected, tracing is undertaken either from published pedigrees or from the files of the Genetical Committee of the University of Iceland, which has family information for almost all Icelanders alive in 1840 or born since. After the family tree is completed, the individual family members are matched against the files of the Cancer Registry, and thus the bias of recall is avoided. It can therefore be concluded that these common biases do not apply in the present study.

ENVIRONMENT VERSUS GENES

Having established that close relatives of patients with breast cancer are at increased risk for breast cancer themselves, the question arises of how this comes about. Cancers arise from somatic tissues, that is, the normal cells become altered and acquire the characteristics of cancerous cells. These characteristics are unlimited cell division, ability to invade tissues, and ability to travel through the body and set up metastases in other organs. The DNA of cancerous cells differs from that of the cells of the parent organ. In that sense, all cancers are genetic. Alterations of the DNA, mutations, that are required to alter a normal cell to a cancer cell are probably numerous. These mutations may all be acquired after birth, but some may be inherited through the germ cells. Close relatives, sisters for example, share approximately 50% of their genes. It follows,

therefore, that a gene or genes could be responsible for this increased likelihood of having breast cancer. Sisters, however, share many other factors which could influence the risk, such as common living conditions, dietary habits, and social status in general. These too influence the risk of breast cancer. It is further possible that a combination of environmental and genetic factors are at play. Finally, a disease such as breast cancer is likely to have more than one pathogenetic mechanism, thus being aetiologically heterogeneous. These considerations are important, since only by knowing the causes and identifying the pathogenetic mechanisms can methods be devised that are likely to prevent the disease or its harmful consequences.

To resolve the question whether the liability to cancer is inherited, genetic epidemiology has two main types of method at its disposal. These are linkage studies and segregation analysis.

Results of a recently published study¹⁴ indicated linkage between early onset breast cancer and chromosome 17q21. This study was performed on a set of 23 families from various parts of the western world, and the families were said to "share the epidemiologic features characteristic of familial breast cancer, younger age at diagnosis, frequent bilateral disease, and more frequent occurrence of breast cancer among men". These families were highly selected and the gene identified has only been shown to account for a very small proportion of human breast cancer.

Segregation analysis was performed, using the Pointer program,¹⁵ on Danish pedigrees previously published by Jacobsen.² This found that the transmission through the pedigrees of breast cancer was consistent with mendelian, monogenic, dominant inheritance accounting for only a small proportion of the breast cancer in the families.

Studies of unselected twins can, by comparing concordance rates of monozygotic twins with that of dizygotic twins, elucidate the role of heredity in disease. Holm *et al*,¹⁶ in a study of unselected Danish twins, found that the observed number of breast cancer in the co-twin after the diagnosis of breast cancer in the first twin was increased by a factor of nearly six in monozygotic twins and by a factor of about two in dizygotic twins. They found, though, that the pairwise concordance rates between the two groups of twins were not significantly different.

FAMILIAL BREAST CANCER

In addition to the previously cited studies¹⁻⁵ Anderson¹⁷⁻²² of the M D Anderson Hospital in Houston has published extensively on the characteristics of breast cancer in family members of breast cancer patients. He found that relatives of patients with bilateral disease have a higher risk than relatives of patients with unilateral disease; relatives of patients diagnosed before the age of 50 have a higher risk than relatives of patients diagnosed at an older age; and that the relatives of patients with

bilateral disease diagnosed early have the highest risk.

Our study⁸ was population based and found increased relative risk for sisters (2.91) and mothers (1.81). Another population based study from Sweden⁷ was published in 1981 and confirmed the general increase in risk, but not the importance of age at diagnosis or of bilaterality. That study found the relative risk for sisters to be 2.1 and all female first degree relatives 1.7. Table 2 shows 2.63 and 2.26 for sisters and all female first degree relatives respectively.

Ottman *et al*²³ published a population based case control study from California and did not find a significantly raised risk in sisters of patients with unilateral breast cancer but found a relative risk of 10.5 in sisters of patients diagnosed under the age of 40 and with bilateral disease diagnosed under the age of 50. In sisters of patients with bilateral disease, diagnosed between 41 and 50 years of age, the risk was 3.8.

Kelsey and Hildreth²⁴ reviewed familial aggregation of breast cancer. They, and other cited studies, agree that the difference between familial breast cancer and sporadic breast cancer is as follows. (1) The relatives have a raised relative risk. (2) The relative risk is raised more when breast cancer is diagnosed in young women. (3) The relative risk is raised more when the cancer affects both breasts. (4) The relative risk is raised still more when breast cancer is both diagnosed at a young age and affects both breasts.

AGE AT DIAGNOSIS

In table 3 the relative risk for all types of relatives is considerably higher when the proband is less than 45 years of age at diagnosis than if she is 45 years or older. The difference between 45 and 54 and over 54 is similar but less pronounced.

If a number of mutations have to take place before normal breast gland cells degenerate into malignant ones, it is reasonable to assume that if one, or a few, mutations are inherited, it will on average take fewer years to acquire sufficient mutations. On the other hand, if the young age at diagnosis of one family member is solely because of an excessive concentration of environmental risk factors, it can be expected that the same risk factors would also affect their close relatives.

Tables 2 to 6 consistently show that sisters have higher relative risks than all other relatives, and sisters are the ones who share the proband's environment at a young age. The segregation¹⁵ and linkage¹⁴ analyses have indicated that the mode of inheritance is dominant, but if that were so one would expect the relative risks for mothers and daughters to be at least as high as that of sisters.

Height is a significant risk factor for breast cancer in an Icelandic study²⁵ and some, but not all, other studies. It is strongly influenced by environmental factors at young ages, but is also under genetic control. Further studies are needed to clarify whether this observation can

be used to identify linkage between genes influencing height and genes influencing breast cancer risk.

A population based case control study from Sweden⁷ did not find an effect of young age at diagnosis. Tryggvadóttir²⁶ has drawn attention to the effect of length of observation time in influencing the classification of breast cancer into familial and sporadic groups. If the classification takes place at the time of diagnosis of the breast cancer cases, some will be 'wrongly' classified as sporadic, but if the classification is done retrospectively these will be classified as familial because a relative has been diagnosed with breast cancer in the meantime. This could explain the lack of effect of age at diagnosis in the Swedish case control study.

BILATERAL BREAST CANCER

Arguments, similar to those above, that inherited mutations can influence age at diagnosis can also be used for the extent of disease. The counter argument is that a high concentration of environmental risk factors at a young age can influence the extent of disease in the proband as it influences the relative risk of the close relatives. Table 4 shows the sisters of patients with bilateral disease to have a relative risk of 5.30 and table 5 shows that sisters of patients diagnosed with breast cancer before the age of 45 and having bilateral disease have a relative risk of 9.04 compared with the relative risk of sisters shown in table 2 (2.63) and table 3 (1.96, 2.70, and 3.63).

Related to bilaterality is our observation,²⁷ not confirmed by others, that patients with cancer of the right breast are more likely to have relatives with the disease than those with left sided breast cancer. The odds ratio was 1.31 with 95% confidence limits of 1.02, 1.70 ($p = 0.03$).

Conclusions

(1) In this population based study the biases of selection and of recall have been avoided. (2) The relative risk of breast cancer is increased in relatives of patients with the disease. This increase is statistically significant and agrees with the results of most other studies. (3) The increase in relative risk is greater in first degree relatives than in more distant relatives. (4) The increase is greater in sisters than in other first degree relatives. This would indicate the importance of shared environmental factors at young ages. If, however, the increase in risk has a genetic basis, it would speak for recessive inheritance rather than dominant. (5) The increase in risk of breast cancer in male relatives of female patients is significant. (6) Women who have married into the families do not have an increased risk of breast cancer, which argues against the importance of environmental factors acting after the age of marriage. (7) Age at diagnosis below 45 is accompanied by a greater increase in relative risk among the family members than above that age. (8) Bilateral breast cancer substantially increases the

risk among the various groups of relatives. (9) Relatives more distantly related than first degree have a significantly increased risk, supporting the argument for genetic factors. (10) This increase in risk of family members of breast cancer patients has not yet been proven to be genetic except for a linkage study of highly selected pedigrees. The case for environmental factors acting from birth to the age of marriage is strong. The search for genes, both promoting and suppressing, must continue, because of the important consequences their identification could have for the understanding of carcinogenesis and for prevention.

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