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Malignancies in Families of Women with Medullary, Tubular and Invasive Ductal Breast Cancer

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Abstract—*Breast cancer seems to represent a heterogeneous group of neoplasia originating from the parenchymal epithelium of the mammary gland. Family studies combined with genetic epidemiological analyses and histological evaluations were used to gain an insight into this nosological entity. Special emphasis was given to the type and frequency of neoplasia in close relatives.*

This study represents pedigrees of 36 *histologically defined pure tubular and* 22 *pure medullary breast cancer patients as well as* 171 *with the invasive ductal form. The incidence of cancer in the first degree relatives of all three groups is compared to that of the local population. The first degree relatives did not have a higher risk (RR) for the neoplastic diseases. However, breast cancer occurs more frequently in the female relatives of all three groups. Other cancers have different relative risks.*

INTRODUCTION

BREAST CANCER tends to cluster in certain families [1]. An increased breast cancer risk for relatives of breast cancer patients has been amply documented [2–7], and even an autosomal dominant pattern of transmission of the susceptibility to breast cancer in specific families had already been suggested in 1950 [8]. Genetic epidemiology has provided statistical methodologies to investigate genetic models of disease transmission in pedigrees. Segregation analyses are consistent with the suspected autosomal dominant mode of inheritance in selected pedigrees [9–11].

Attempts to correlate biological and histological markers with an increased breast cancer risk have had limited success. The pathological aspects of familial breast cancer are not unequivocal [12]. Breast cancer with a similar histology appeared to cluster and medullary carcinomas tended to be overrated in families with breast cancer aggregations [12]; this has recently been corroborated [13]. In a previous study, we did not find specific familial associations of other cancers with a particular histopathological type [14]. However, there was a preponderance of malignancies of the breast, the gynaecological and gastrointestinal systems and of soft tissue tumours in families of index patients with tubular or medullary breast cancer. Additional families of patients with tubular and medullary breast cancer have been evaluated in order to determine the relative risk for developing neoplasia in first degree relatives.

PATIENTS AND METHODS

Each index patient of an unselected hospital based series with a histologically verified pure tubular or pure medullary breast cancer was interviewed by a physician using the same detailed questionnaire with special emphasis on the age of all family members as well as the cause of death. The anamnestic data about deceased relatives were verified as far as possible by reviewing medical reports. The malignancies were diagnosed between 1981 and 1987 in the German speaking part of Switzerland. All histological diagnoses were confirmed by the same pathologist (J.T.) according to *Histological Typing of Breast Cancer* [15]. The occurrence of malignancies in these families was compared with that of the families of 171 index patients with the

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invasive ductal form of breast cancer detected in the same time period and hospitals. They had also been interviewed by one of us (A.G.) with the same questionnaire. The incidence of malignancies in the first degree relatives of all three forms was compared to that occurring in the general population of the same geographical region. The population data were collected between 1969 and 1982.

The patient information of all first degree relatives was entered into a data bank and various statistical analyses were performed with the program 'DISEASES'. This program calculates, using the data of the population-based Regional Cancer Registry of both counties of Basel, the age and sex specific probability of developing a specific malignancy. The first part of the program uses non-stationary Markov chains to compute the expected values in the population [16–18]. In a second step, the program compares the observed and the expected numbers of patients with malignancies within the whole group or family, and computes whether the differences that occur are due to chance alone. The test was selected according to the number of expected cases. If the latter was greater or equal than 10, chi-square analysis was used; if the expected frequency was less than 10 but greater than or equal to 5, a binomial distribution was used and, for less than expected cases, a Monte-Carlo procedure [19] was employed.

The comparisons between the study groups, one with each other, were carried out with the help of contingency tables.

Two hundred and twenty-nine women with breast cancer, of whom 36 had pure tubular, 22 pure medullary and 171 invasive ductal type fulfilled the requested histological criteria, were presently alive, resident in Switzerland, and were willing to participate in this study. The anamnestic data were verified by consulting medical reports. Six (16.7%) of the probands with tubular, seven (31.8%) with medullary and 27 (20%) with invasive ductal neoplasia were diagnosed as having premenopausal breast cancer. The biographical data of the index patients are summarized in Table 1. Although the median ages of diagnosis differ, the age distributions at the time of diagnosis in the three groups were statistically similar when the Kolmogorov-Smirnov test was employed. These findings deviate from the generally accepted assumption that patients with medullary breast carcinoma are youngest at diagnosis and have short intervals between menarche, first pregnancy and diagnosis [20].

The number of relatives in the families of the index patients in the three histological groups are given in Table 2. It is worthy of note that the average number of first degree relatives per proband was lowest in the families of index patients with medullary breast cancer with only 5.4 per proband while there were 6.6 relatives in the other two groups. On average, index patients with invasive ductal or tubular breast cancer had more sisters than those with medullary breast cancer. The percentages of women without children in the three groups were the following: 20% in the families of women with tubular breast cancer, 13% in the group with medullary carcinoma and 27% in the invasive ductal group. The average number of children among the remaining women was slightly over two, with an average of 2.14 for mothers with tubular form, 2.2 for mothers with medullary breast carcinoma, and 2.08 for mothers with invasive ductal carcinoma.

For illustration, some pedigrees are shown of probands with tubular or medullary carcinoma of

Table 1. Biographical data of the index patients according to the three histological types of breast cancer

Biographical information	Tubular	Medullary	Invasive ductal
Age at diagnosis			
range	40–86	30–79	24–91
median	60	54	56
Age at menarche			
range	10–19	10–17	8–22
median	14	14	14
Age at first childbirth			
range	21–40	21–39	15–42
median	27	25	27
Age at menopause			
range	31–56	37–55	31–58
median	47	46	48
Length of reproductive period			
range	17–41	23–42	18–44
median	33	32	34

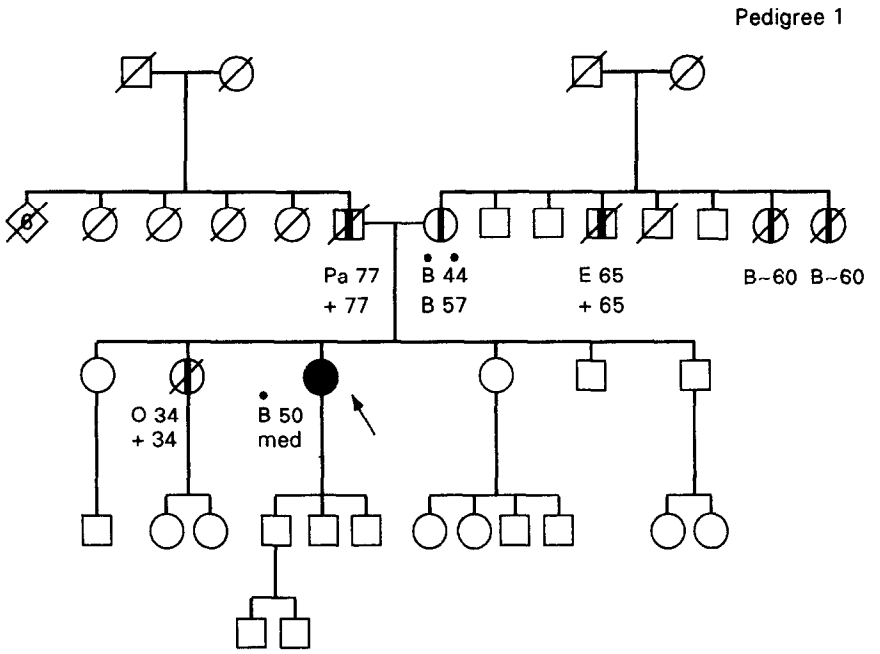

Fig. 1. Pedigree 1. The index patient is suffering from a medullary breast cancer on the right side, diagnosed 13 years after hysterectomy at the age of 50 years. Her mother had bilateral breast cancer at the age of 44 and 57 years. The father of the proband had a pancreatic carcinoma at the age of 77 years of which he died the same year. One of the two sisters of the index patient had ovarian cancer at the age of 34 years of which she died the same year. Both sisters of the mother also suffered from breast cancer at the age of about 60 years. One of the five brothers of the mother had oesophageal cancer at the age of 65 years and died soon after refusing an operation. On the maternal side in this family a preponderance of breast and ovarian carcinomas seems to exist.

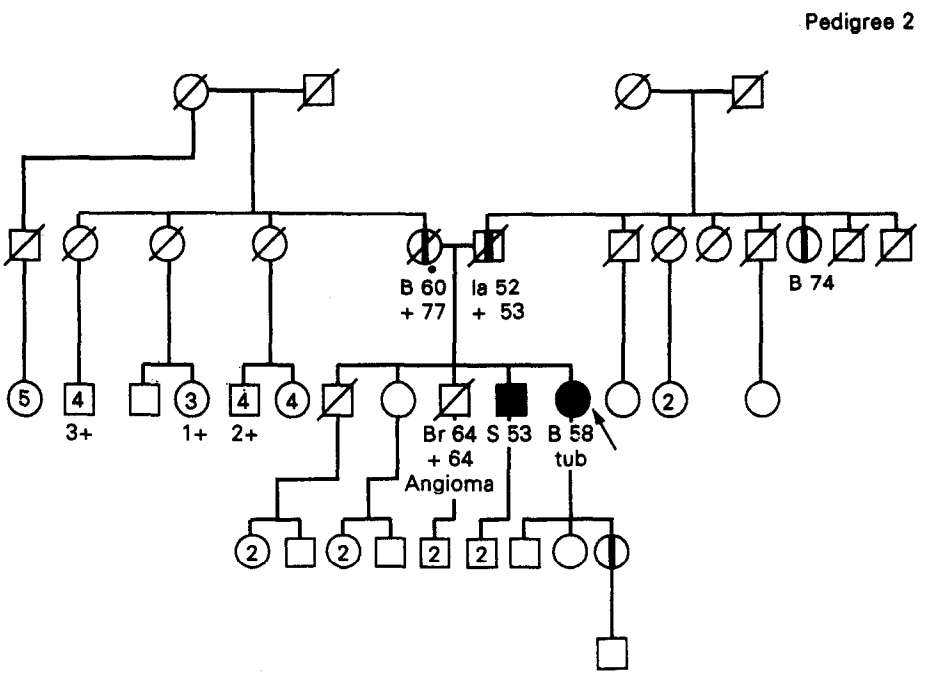

Fig. 2. Pedigree 2. The index patient herself is suffering from a postmenopausal tubular breast cancer on the right side. Her mother had breast cancer on the left side at the age of 60 and died at the age of 77. Her father died early at the age of 53 of a laryngeal carcinoma after having been a cigar smoker. One brother of the patient died at the age of 64 years from a benign angioma in the brain and the only brother who is still alive suffers from a histologically verified stomach cancer. One of the two daughters of the proband had a serious dysplasia at the cervix uteri but still no cancer at the age of 31 years. One of the sisters of the father suffers from a breast cancer diagnosed at the age of 74 years. With the occurrence of breast, laryngeal, brain and stomach tumours among seven first degree relatives of the nuclear pedigree, this family seems to have a high probability of a familial cancer syndrome.

the breast and a pertinent accumulation of other tumours among their relatives.

The circles stand for women and the squares for men. The crossed family members have already died. The circle marked with an arrow points out our index patient. Solid circles and squares mark persons with a histologically proven malignancy and the signs with a bar only designate family members with a tumour of undetermined histology. In the case of breast cancer patients the small spots

Table 2. Number of relatives in the families of the index patients with breast cancer

Relatives (*n*)	Histology of breast cancer: Tubular *n*	Tubular (%)	Medullary *n*	Medullary (%)	Invasive ductal *n*	Invasive ductal (%)
Index cases	36		22		171	
1st degree relatives	239		119		1126	
1st degree females	117	(100%)	56	(100%)	571	(100%)
mothers	36	(30.7%)	22	(39.3%)	170	(29.8%)
sisters	50	(42.8%)	16	(28.6%)	286	(50.1%)
daughters	31	(26.5%)	18	(32.1%)	115	(20.2%)

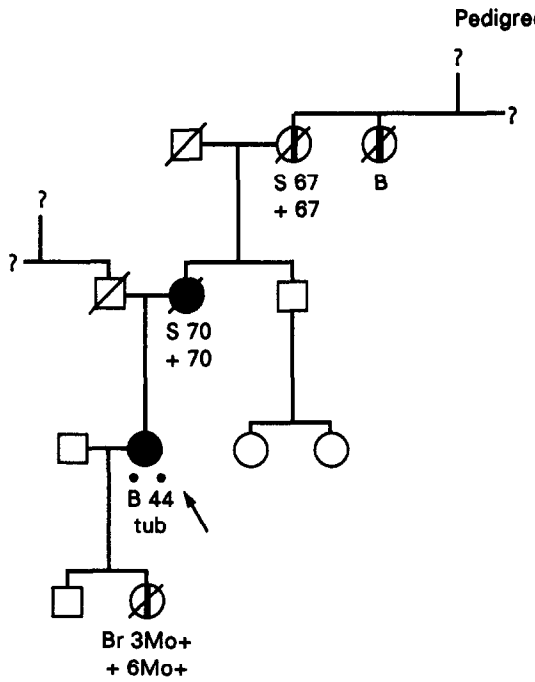

Fig. 3. Pedigree 3. The index patient has a bilateral premenopausal breast cancer of tubular histology. Her mother died at the age of 70 years of a histologically verified stomach cancer. The only daughter of the proband had a brain carcinoma of which she died at the age of 6 months. The grandmother on the maternal side also had a stomach cancer of which she died at the age of 67 years. The sister of this grandmother died of breast cancer. Within this small pedigree there is a substantially increased incidence of tumours among female members, an accumulation of gastrointestinal, breast and brain tumours.

indicate the side of the tumour. The letter below persons with a malignancy is an abbreviation for the kind of tumour, followed by a number indicating the age at diagnosis. If the patient has already died, this is noted a line below with a '+' followed by the age at death. The abbreviations of the malignancies are the following: B = breast cancer, Bl = urinary bladder carcinoma, Br = brain carcinoma, Cu = corpus uteri carcinoma, E = oesophageal cancer, La = laryngeal carcinoma, Le = leukaemia, O = ovarian carcinoma, P = prostatic cancer, Pa = pancreatic carcinoma, Sa = sarcoma, S = stomach cancer. With histologically verified breast cancers, the histological type is also mentioned: duc = invasive ductal carcinoma, tub = tubular carcinoma and med = medullary carcinoma.

RESULTS AND DISCUSSION

Cancer risk for all types of malignancies

The relatives of those women with tubular breast cancer had a relative risk of developing a malignancy that was 0.98 which was not statistically significant (n.s.) at the 95% confidence limit. In this group there were 42 first degree relatives who developed cancer, nearly the same as expected (43). The relative risk for females was 1.11 (n.s.) and for males only 0.88 (n.s.). In the group of women with medullary breast cancer, the relative risk that a first degree relative might develop any type of cancer was smaller (0.84, n.s.). In this group, there were 13 malignancies while more than 15 were expected. The relative risk for females was 0.81 (n.s.) in these cases while the relative risk for males was 0.87 (n.s.). Neoplasms did not occur more frequently in the families of tubular or medullary breast cancer patients than in the general population.

In comparison, there were 181 malignancies in the first degree relatives of patients who had invasive ductal breast cancer while nearly 162 were expected. The relative risk for developing any type of cancer was 1.12 (n.s.). Notice that the relative risk for females was 1.5. It was significantly higher [$P = 0.0001$; 95% confidence limits for the relative risk (RR) 1.30–1.72] than expected from the population data; and, in contrast, the relative risk for males was 0.78 ($P = 0.015$), which is significantly lower (95% confidence limits for RR = 0.636–0.943) than what is expected. No statistically significant difference among the three groups could be found when the contingency tables were used.

Occurrence of breast cancer in relatives

It is generally accepted that when a caucasian woman in a family has breast cancer, the risk of developing the same malignancy is more than 2–3 times higher when compared with a women lacking such a family history. Such a risk factor is obtained when the different types of breast malignancies are

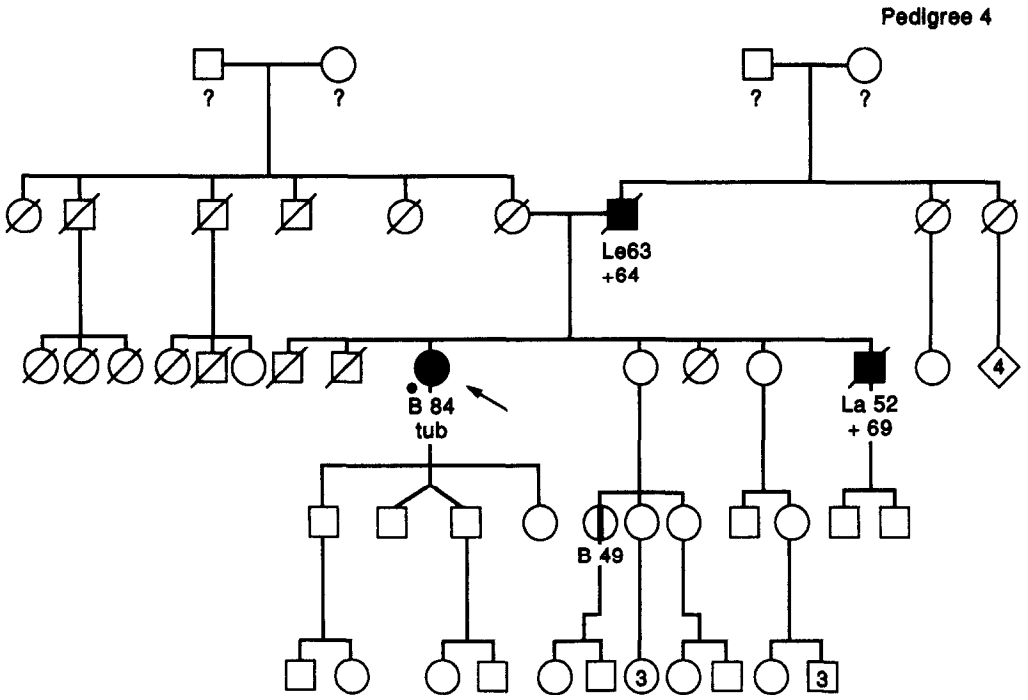

Fig. 4. Pedigree 4. The index patient has right-sided postmenopausal breast cancer of tubular histology. Her father suffered from leukaemia at the age of 63 and died 1 year after diagnosis. One of her three brothers who was non-smoker had a laryngeal carcinoma at the age of 52 years and he died 17 years after the treatment. One niece of the patient who is living in the United States also has breast cancer diagnosed at the age of 49 years. Although this pedigree is large and not very informative, it seems likely that a genetic factor plays a role in the development of malignancy.

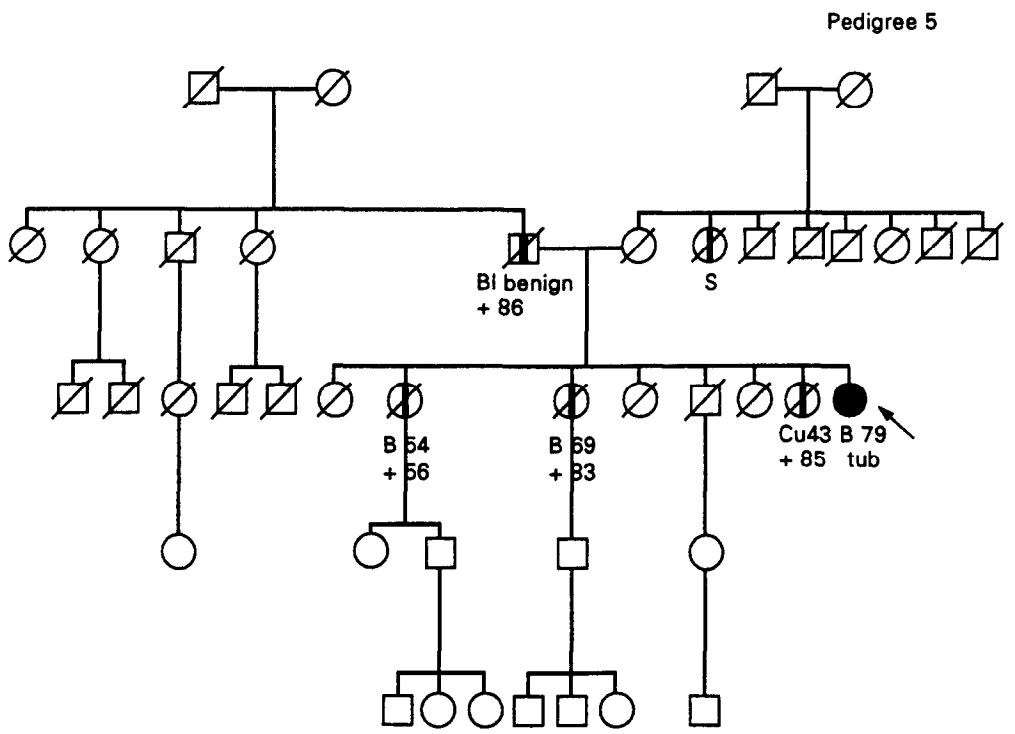

Fig. 5. Pedigree 5. The index patient herself suffers from postmenopausal tubular breast cancer on the right side. Her father had a benign tumour of the urinary bladder and died at the age of 86 years. Three of the six sisters of the proband also had a tumour, two of them breast cancer at the ages of 54 and 69 respectively and the other had a corpus uteri carcinoma at the age of 43 years. An aunt on the maternal side died of stomach cancer. In this family an accumulation of breast and gynaecological tumours seems to occur.

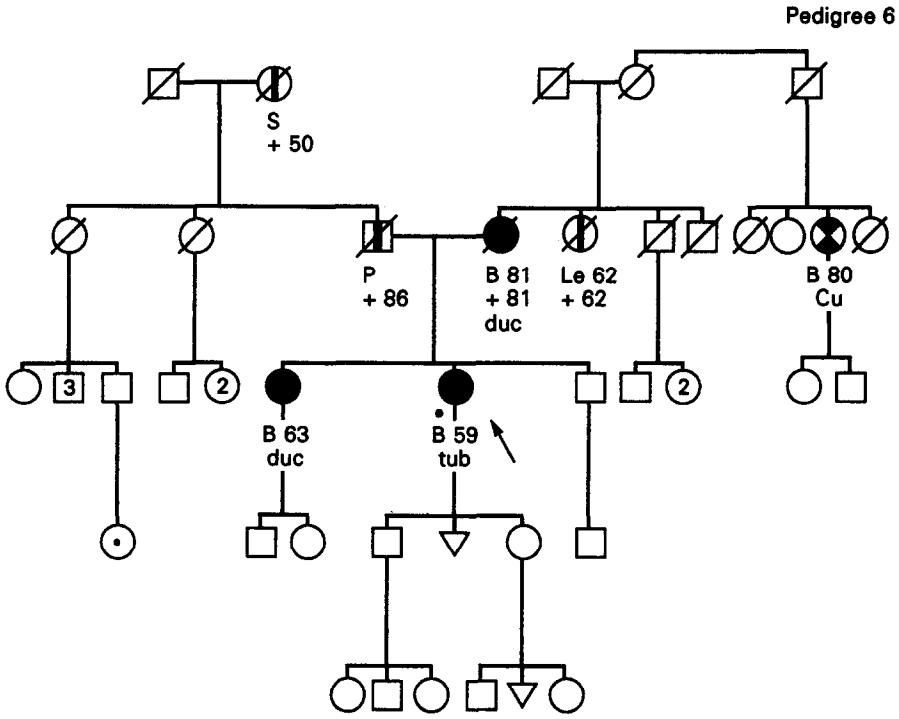

Fig. 6. Pedigree 6. The index patient has postmenopausal tubular breast cancer. Her mother developed an invasive ductal breast cancer at the age of 81 years and died of it the same year. The father died at the age of 86 of a prostatic cancer. The only sister of the proband also suffers from an invasive ductal breast cancer diagnosed at the age of 63 years. The only maternal aunt had leukaemia of which she died at the age of 50 years. There is another half-aunt on the maternal side who is suffering from both breast cancer and corpus uteri carcinoma at the age of 80 years. The malignancies in these relatives occurred relatively late, but there is nevertheless a substantially increased incidence of tumours in this family with a preponderance of breast cancer and tumours of the SBLA syndrome.

collectively categorized as one clinical entity. It was our goal to determine whether a more refined risk factor can be ascertained when the pathological diagnosis of the index patient is also considered. In all three groups of this study together, 56 breast cancers were observed among female first degree relatives although only 27 were expected. That indicates an increased relative risk of developing breast cancer in first degree relatives of more than 2 ($P = 0.0001$; 95% confidence interval for R between 1.70 and 2.64). Three families have been found in this study with an unusual aggregation of breast cancers (pedigrees 1–3). Calculating the relative risk of breast cancer in the three histological groups separately, an increase of more than twice could be reported in families of index patients with tubular or invasive ductal tumours (Table 3), whereas, in the families with medullary breast cancer, the increase was less than 2 and because of the small number not statistically significantly higher than in the population (Table 3). With contingency tables there was no statistically significant difference between the three different histological groups.

Familial associations of breast cancer with other malignancies

Women with breast cancer might have relatives with a disproportionately greater number of other specific types of neoplasia. It has been proposed that in some of these families the same predisposition leads to a defined set of malignancies: familial association of mammary and ovary tumours [21, 22], familial association of breast and gastrointestinal tumours [23] including adenocarcinomas of the colon and endometrium [24], the Li-Fraumeni/SBLA syndrome [25], Morbus Cowden and the Muir-Torre's syndrome.

The malignancies observed in the first degree relatives were categorized into three groups:

(a) Gynaecological tumours which also occur only in females and could also be influenced by factors such as: hormones, hormone modulators, as well as the sexual and/or reproductive history of the individual [21, 22].

(b) Gastrointestinal cancers which can occur associated with breast cancer in some of the said genetic entities, e.g. familial adenocarcinomatosis [22, 23].

(c) Malignancies belonging to the so-called Li-Fraumeni/SBLA syndrome [25]. Individuals of families with this syndrome, besides breast cancer, are affected with a variety of different malignancies including soft tissue sarcomas, brain tumours, leukaemias, lung or larynx cancer and adrenocortical tumours.

In this study, several families of which six are shown have been found which could be assigned to one of these genetic entities (pedigrees 1–6).

Table 3. Occurrence, relative risk and P-value of malignancies in families of index patients with tubulary, medullary or invasive ductal breast cancer

Primary site	Tubular and Medullary Observed	Tubular and Medullary Relative risk	Tubular and Medullary *P*-value	Tubular Observed	Tubular Relative risk	Tubular *P*-value	Medullary Observed	Medullary Relative risk	Medullary *P*-value	Invasive ductal Observed	Invasive ductal Relative risk	Invasive ductal *P*-value
Breast	13	2.05	0.0062	10	2.11	0.0200	3	1.89	n.s.	43	2.15	0.0001
Oesophagus	0	0	n.s.	0	0.00	n.s.	0	0.00	n.s.	6	4.77	0.0010
Stomach	4	1.70	n.s.	3	1.73	n.s.	1	1.62	n.s.	19	2.96	0.0001
Colon	3	0.86	n.s.	2			1			11	1.18	*
Liver	2	2.57	n.s.	2			0			4	1.97	n.s.
Pancreas	2	2.14	n.s.	0			2			3	1.17	n.s.
Gall bladder	1	2.35	n.s.	1			0			1	0.86	n.s.
Larynx	2	—	n.s.	2			0			2	1.75	n.s.
Lung and bronchus	5	0.76	n.s.	4	0.83	n.s.	1	0.56	n.s.	13	0.75	n.s.
Bones and joints	2	1.65	n.s.	1			1			5	1.46	n.s.
Melanoma of skin	3	2.43	n.s.	2	2.22	n.s.	1	2.99	n.s.	2	0.54	n.s.
Corpus uteri	4	2.74	n.s.	4	3.37	0.0050	0	0.00		17	3.69	0.0001
Ovary	2	2.16	n.s.	1			1			3	1.00	n.s.
Prostate gland	5	1.09	n.s.	3	0.89	n.s.	2	1.66	n.s.	8	0.72	n.s.
Testes	1	1.22	n.s.	1			0			1	0.41	n.s.
Urinary bladder	1	0.75	n.s.	1			0			2	0.57	n.s.
Brain and CNS	1	1.16	n.s.	1			0			8	3.08	0.0052
Hodgkin's disease	0			0								
Leukaemias	0			0			0			1	0.88	n.s.
Adrenocortical gland	0			0			0			5	1.15	n.s.
							0			1	1.82	n.s.
Gynaecological tumors	7	2.33	0.0325	6	2.65	0.0265	1	1.34	n.s.	23	2.39	0.0001
SBLA syndrome	23	1.28	n.s.	18	1.36	†	5	1.05	n.s.	77	1.50	0.0002
Any malignancy	55	0.94	n.s.	42	0.98	n.s.	13	0.84	n.s.	181	1.12	‡

*n.s. for both sexes together. For females alone RR = 2.17; $P = 0.0254$.

†n.s. for both sexes together. For females alone RR = 1.74; $P = 0.0349$.

‡n.s. for both sexes together. For females alone RR = 1.50; $P < 0.0001$, for males alone RR = 0.78; $P = 0.0152$.

(a) *Gynaecological tumours.* In two of the three study groups, the relative risk of first degree relatives for developing a cancer of this type is 2–3 times higher than expected in the population. In the pedigrees of tubular breast cancer patients, six neoplasms occured although less than three were expected. The relative risk, therefore, was nearly 3-fold higher than expected (Table 2). Among the relatives of probands with medullary breast cancer, only one ovarian tumour has been reported. Because of this small number, statistical analysis is of no significance. A total of 23 gynaecological neoplasias were diagnosed in the families of the invasive ductal breast cancer patients while nearly 10 were expected. The resulting relative risk was about 2.5 times higher than expected (Table 2). Again, no statistically significant differences among the three study groups could be demonstrated with contingency tables. Taking in account the different hormone dependent malignancies separately, there was an increase of 3 times for every tumour in families of patients with tubular or invasive ductal breast cancer while the number in the families with medullary breast cancer was too small for statistical analyses (Table 2).

(b) *Gastrointestinal cancers.* An increased relative risk has been observed for the kin of patients with invasive ductal breast cancer only: 5 times higher for oesophageal cancer, 3 times for stomach cancer and 2 times for colon cancer in female relatives, while the risk for males was lower (Table 2). In the two groups of patients with tubular or medullary breast cancer, again, the number of individuals was too small to arrive at statistically significant results.

(c) *Malignancies of the spectrum of the Li-Fraumeni/S-BLA syndrome.* In the kinship of probands with invasive ductal breast cancer, the relative risk for brain tumours was 3-fold higher than in the general population. When considering only female relatives, the relative risk was even greater than 4.5 (Table 2). This difference between males and females may implicate the role of female hormones in the development of this type of neoplasia.

In conclusion, certain neoplasms seem to occur in the relatives of breast cancer patients more frequently than in the general population. However, categorizing the diseases of the index patients into tubular, medullary and invasive ductal, significant differences in relative risk could not be found and the suggestion of the previous study in finding such differences could not be confirmed with statistically significant results. Therefore, we were unable to identify a histological marker which can clearly define susceptibilities predisposing individuals to breast or other neoplasms.

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