Can a Phenotype for Recessive Inheritance in Breast Cancer be Defined?

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Background:

While a dominant inheritance of breast cancer (vertical inheritance) is well known, less is known about a possible recessive inheritance (horizontal inheritance).

Material and methods:

In a clinical series of 1677 breast cancer patient's family history was scored as vertical (grandmother-aunt-mother-sister-daughter) or horizontal (sister-sister) and related to histopathological tumor type, presence of germline mutations, bilaterality, multifocality, screening, parity, hormone replacement therapy (HRT) use and age at diagnosis. Prognosis was estimated by also adding tumor size, lymph node status, distant metastases and hormone receptor status at diagnosis into a Cox proportional hazard model.

Results:

Excluding mutations carriers, a horizontal family history (5% of all cases) was significantly associated with tubular tumor type (OR=3.87(1.44-10.41). A vertical family history (23% of all cases) was significantly related to tumor multifocality (OR=2.30(1.51-3.50)), tumor bilaterality (OR=2.08(1.44-3.00)) and screening detection (OR=1.50(1.10-2.05)).

No significant difference in survival could be seen between patients with none, horizontal or vertical family history. However, germline mutation carriers (*BRCA1/2*, *TP53* or *CDKN2A*, present in 1.5% of the cases) had a significantly worse survival. Screening detected cases, HRT ever users and patients with estrogen receptor positive tumors had a significantly better survival adjusting for age at diagnosis, tumor size, lymph node status and presence of distant metastases at diagnosis.

Conclusion:

Factors associated with a horizontal family history were found, defining a possible phenotype for a recessive inheritance: tubular breast cancer.

Key words:

Familial breast cancer

Horizontal inheritance

Recessive inheritance

Tubular breast cancer

Vertical inheritance

Abbreviations:

HRT – Hormone Replacement Therapy

OR – Odds Ratio

CI – Confidence Intervals

HR – Hazard Ratio

ER – Estrogen Receptor

PgR – Progesterone Receptor

LCIS – Lobular Carcinoma in situ

DCIS – Ductal Carcinoma in situ

BC – Breast Cancer

Introduction

Twin studies suggest that most familial aggregation in breast cancer results from inherited susceptibility (1, 2). *BRCA1*, *BRCA2* and other known susceptibility genes account for approximately 20% of this effect (3), the high-susceptibility genes (such as *PTEN, STK11, TP53*) together with moderate- susceptibility (such as *CHK2, ATM, PALB2, BRIP1*) account for around 2%, whereas approximately 4% is credited to the low-susceptibility genes (such as *FGFR2, TOX3, MAP3K1, LSP1*)(4, 5), this leaves approximately 75 % of all familial breast cancer unexplained.

While a dominant inheritance of breast cancer (vertical inheritance) is well known, less is known about a possible recessive inheritance (horizontal inheritance). With the exception of rare syndromes like Ataxia-Telangiectasia, where homozygote and heterozygote carriers have an increased risk for breast cancer, it has been more difficult to identify recessive genes for breast cancer (6). However, a number of segregation analyses have raised the possibility of an existence of a recessive gene (7-11). Additionally, a recent study from Scotland found a higher risk for breast cancer in sisters than other relatives in high risk families suggesting the possibility of a recessive inheritance (12).

We have previously in a preliminary report described a possible relationship between lobular breast cancer, late age at diagnosis and a horizontal inheritance (13). In the present study we have investigated whether tumor biology, tumor histology and some breast cancer risk factors are related to a horizontal vs. a vertical inheritance/family history of breast cancer, aimed at defining a candidate phenotype for a recessive inheritance. In the present study, patients with the strongest family history (often vertical) were offered genetic screening for *BRCA1*, *BRCA2*, *TP53* and

CDKN2A. In further analyses mutation carriers of these genes were separately analyzed to allow us to investigate a family setting without the strong dominant genes.

Material and methods

In a clinical series of 1676 breast cancer patients (median age 56, range 23-89) family history was scored as vertical (grandmother-aunt-mother-sister-daughter), horizontal (sister-sister), or none and related to histopathological tumor type, presence of germline mutations, bilaterality, multifocality, screening, parity, Hormone Replacement Therapy (HRT) and age at diagnosis. Families that both had a horizontal and a vertical disease transmission were scored as vertical. After excluding germline mutation carriers of *BRCA1*, *BRCA2*, *TP53* and *CDKN2A*, only breast cancer was considered in the family history. Due to lack of information concerning HER-2/neu and histologic grade, more than 70% missing, they were not considered in any calculations.

Pathological slides were not re-examined, and the diagnosis determining treatment was used. Besides retrieving information from hospital records and pathological reports, patients underwent a standardized oral interview about family history, environmental/ reproductive risk factors, screening history and patient delay. Information from our population based cancer registry and census registry was used for finding new incident contralateral breast cancer as well as date of diagnosis, death and confirming diagnosis of relatives.

The Department of Oncology, University Hospital, Lund has a population-based catchment area, serving the Southern Health Care region in Sweden with adjuvant and metastatic treatment of breast cancer. Follow-up of the patients was performed until Jan 1st, 2009.

Families with three affected breast or ovarian cancer cases with at least one diagnosed before age 50, families with two affected breast or ovarian cancer cases with at least one diagnosed before

age 40 and single patients diagnosed with breast cancer before age 30 have been offered genetic counseling and mutation screening according to the national cancer care program of Sweden.

Binary logistic regression was used to estimate factors associated with horizontal versus vertical inheritance. As a control group for the histopathological groups a combined group of mixed histopathologies, undefined adenocarcinomas and other rare tumors was used. Odds ratios (OR) were estimated with 95% Confidence Intervals (CI).

Prognosis was estimated by adding tumor size, lymph node status, distant metastases and hormone receptor status at diagnosis into a Cox proportional hazard model adjusting for age at diagnosis, risk factors and tumor biology factors simultaneously. Hazard Ratio (HR) was estimated using a 95% CI.

Results

During follow-up 856 patients (48.5%) died, the median follow-up time was 15 years, range 0.5-29 years. A germline mutation of *BRCA1/2*, *TP53* or *CDKN2A* was present in 1.2% of the cases. Around 4% of the cases were mutation screened according to the screening criteria. A vertical family history was present in 23% and a horizontal in 5% of the cases. A multifocal and bilateral tumor was present in 10% respectively. Seventeen percent were nulliparous at diagnosis and median number of children were 2 (range 0-9). Ever users of HRT were 18.8%. Estrogen receptor (ER) status was known for 65% (68% ER-positive, 32% ER-negative), Progesterone receptor (PgR) status for 63% (58%PgR-positive, 42% PgR-negative). (Table 1)

Mutation carriers added up to 16 in total; 9 (0.89%) *BRCA1*, 5 (0.5%) *BRCA2*, *CDKN2A* and *TP53* 1 (0.10%) respectively, none of which were present in tubular or mucinous breast cancer.

The median tumor size was 20 mm (range 3mm-503mm). Forty-four percent were node negative.

Pure ductal, lobular, tubular, medullary, mucinous cancers were present in 41%, 8.5%, 2.6%, 1.8%, and 1.5% respectively, a mixture of or very rare histopathological types were present in 36.7%. In situ cancers constituted 8%.

In the following analyses mixed tumor types, very rare tumor types and non-invasive cancers were excluded if not stated otherwise.

Excluding mutation carriers, but including non-invasive cancers, the following factors were significantly related to a horizontal family history: tubular tumor type (OR=3.87(1.44 – 10.41))

and age at diagnosis. A vertical family history was significantly associated with tumor multifocality (OR=2.08(1.44-3.00)) and screening detection (OR=1.50(1.10-2.05)), and when adding ER- and PgR-status into the model tumor multifocality (OR=2.30(1.51-3.50)) were significantly associated (Table 2).

No significant difference in survival could be seen between patients with no, horizontal or vertical family history, however, germline mutation carriers had a significantly worse survival. (Figure 1) Screening detected cases, HRT-ever users, patients with ER-positive tumors had a significantly better survival adjusting for age at diagnosis, tumor size, lymph node status and presence of distant metastases at diagnosis (Table 3). The reason why the survival of germline mutations is only displayed for 180 months and not the full 350 months is that genetic screening started in 1994. Therefore, the follow-up is only 15 of the 29 years for germline mutation carriers.

Discussion

The main finding in this study was that a vertical family history was associated to multifocality and more often occurred in breast cancer patients detected via screening, while a horizontal family history was associated to patients with tubular breast cancer.

The association between higher age at diagnosis and horizontal family history can be explained by that it is most likely easier to find a patient with vertical family history at an earlier age compared to finding a patient with horizontal family history as the mother/grandmother of the patient with a vertical inheritance would be older and having a higher risk by age at developing breast cancer then a potential sister of a patient with a horizontal inheritance and thereby pin pointing the family pattern. In a similar manner multifocality is easier detected in families with vertical family histories vs. horizontal family histories. Therefore, since most studies aimed at finding hereditary breast cancer are focused on cases diagnosed at a young age they would subsequently miss cases with recessive inheritance occurring in an older population. This is also true for some registry-based studies, such as results from the Swedish Multigeneration Registry linked to the Cancer registry and not incorporating cases older than 62 years of age.

Another striking observation is the strong association between a horizontal family pattern and tubular breast cancer. Tubular breast cancer is a rare tumor type constituting around 1-5% of all breast cancer and have been studied in relationship to family history (14). A relationship was found, but the finding was within the range of chance, which probably was due to small the number of cases in the study. However, an old publication from 1980 inferred an overall relationship between tubular breast cancer and familiarity (15). Our data, also looking at

inheritance pattern, suggest that indeed patients with tubular breast cancer have a strong family history and could be a candidate phenotype for recessive inheritance.

Survival did not differ between patients having a horizontal vs. a vertical family tree with breast cancer. The small group of mutation carriers did however have a worse survival. Conventional prognostic factors such as large tumor size, tumor involved lymph node status, distant metastases and low estrogen receptor content showed, as expected, a worse prognosis. In line with most previous findings HRT ever users had a better prognosis (16, 17), while screening detected cases had a better prognosis, again in line with literature (18).

Patients are referred in a population based setting to the Department of Oncology from the Southern Health Care Region being the responsible university clinic for radio- and chemotherapy. As the case series here was slightly younger than the mean age in the cancer registry some older cases and cases only operated without adjuvant therapy (stage I) may not be referred. Overall we receive around 60% of all breast cancer cases for therapy. Therefore our results may not fully be applicable to stage I or more, and older patients.

In the present study we have not been able to study the histopathological tumor types of relatives to see if there is a concordance in diagnosis between family members. Likewise bilateral tumor cases need to be studied among familial cases in order to find out if there is a relationship between the primary tumor and the contralateral tumor.

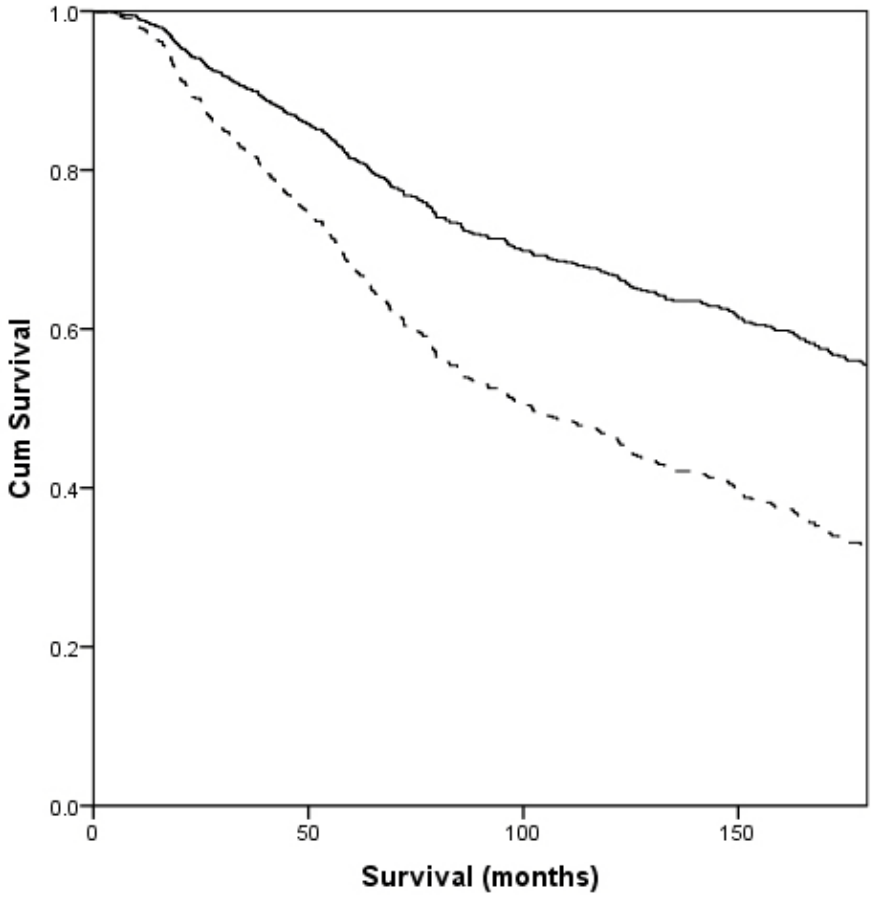
We choose only to study pure histopathological groups and used patients with mixed histologies as a part of the control group, therefore we cannot make any statements regarding possible relationships between individuals with mixed histologies and inheritance.

In summary:

A possible phenotype for recessively inherited breast cancer has been described encompassing patients with sister-sister family history of breast cancer, displaying the tumor types tubular. Another feature of these families is a higher age at diagnosis compared with breast cancer families having a dominant inheritance pattern. The phenotype is not significantly associated with a worse survival.

Figure 1. Survival analysis for mutation carriers and patients with a horizontal family pattern vs. all others

a. Germline mutation carriers vs all other breast cancer cases (overall survival)



b. Horizontal breast cancer cases vs all other breast cancer cases (overall survival)

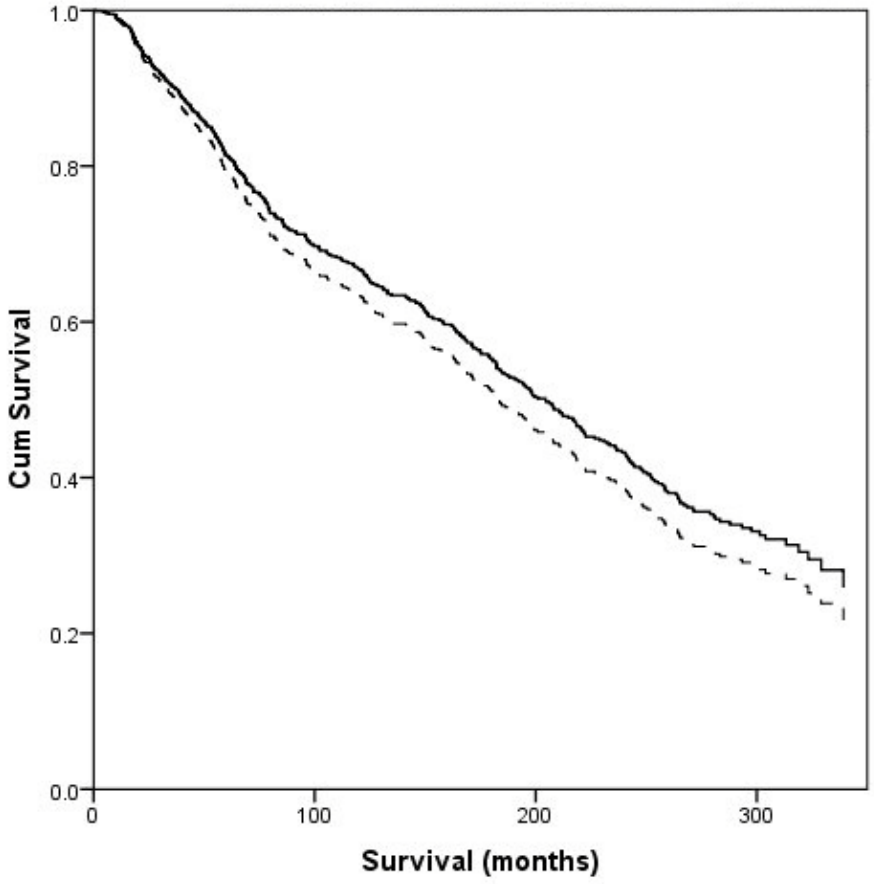


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Figure Legends:

Figure 1 **a.** Survival for mutation carriers (dotted line) compared to all others (whole line). The model was adjusted for age at diagnosis, tumor size, number of positive lymph nodes, and occurrence of distant metastases

b. Survival for patients with a horizontal family history (dotted line) compared to all others (whole line). The model was adjusted for age at diagnosis, tumor size, number of positive lymph nodes, and occurrence of distant metastases

Table 1 – Tumor type, age, tumor stage, histologic grade, hormone receptor status and family history for all patients, and vertical and horizontal family history. DCIS – ductal carcinoma in situ.

		All	(%)	Vertical	(%)	Horizontal	(%)
Histopathology (y/n)	All	1676	100	379	100	84	100
	Ductal	694	41	162	43	33	3
	Lobular	142	8	30	8	11	13
	Tubular	43	3	8	2	7	8
	Medullary	27	2	5	1	0	0
	Mucinous	25	1	5	1	1	1
	DCIS	104	6	29	8	3	4
	LCIS	27	2	8	2	0	0
	Other	614	37	132	35	29	34
Age at diagnosis	Median (range)	56 (23-89)		52 (24-86)		63 (29-87)	
	20-29	14	1	4	1	1	1
	30-39	132	8	42	11	0	0
	40-49	401	24	114	30	11	13
	50-59	448	27	101	27	22	26
	60-69	420	25	80	21	22	26
	70-79	225	13	34	9	24	29
	80-89	35	2	3	1	4	5
Tumor stage	0	84	5	21	6	4	5
	I	462	28	133	35	17	20
	II	678	40	123	32	39	46
	III	366	22	83	22	16	19
	IV	28	2	4	1	2	2
	Unknown	58	3	15	4	6	7
ER - status	Positive	744	44	195	51	36	43
	Negative	351	21	76	20	16	19
	Unknown	581	35	108	28	32	38
PgR - status	Positive	611	36	163	43	31	37
	Negative	446	27	98	26	20	24
	Unknown	619	37	118	31	30	36
Family history	One 1st degree relative with BC	220	13	146	39	72	86
	Two or more 1st degree relatives with BC	26	2	13	3	12	14

Table 2 – Binary Logistic Regression

Vertical and horizontal family history vs. no family history in relation to histopathology, bilaterality, multifocality and screening. Numbers in bold are significant, $p \leq 0.05$. Adjusted for age at diagnosis, excluding mutation carriers for *BRCA1*, *BRCA2*, *TP53* and *CDKN2A,* n=20.

	Vertical Family history N=360		Horizontal family history N=84	
N=1645 Variables	OR	95.0% CI for OR (lower-upper)	OR	95.0% CI for OR (lower-upper)
Ductal y/n	1.08	0.77-1.53	0.82	0.44-1.54
Lobular y/n	0.81	0.48-1.36	1.42	0.63-3.22
Tubular y/n	0.73	0.31-1.68	**3.87**	**1.44-10.41**
Medullary y/n	0.66	0.21-2.00	0.00	0.00-0.00
Mucinous y/n	0.93	0.33-2.62	0.66	0.08-5.30
DCIS y/n	1.01	0.61-1.67	0.71	0.23-2.24
LCIS y/n	1.04	0.52-2.05	0.55	0.07-4.28
Other BC	1.00	-	1.00	-
Multifocality y/n	**2.08**	**1.44-3.00**	1.22	0.58-2.58
Bilaterality y/n	1.26	0.85-1.87	0.84	0.34-2.04
Screening y/n	**1.50**	**1.10-2.05**	0.73	0.39-1.36

Table 3 – A Cox proportional hazard model calculating prognosis for horizontal and vertical family history, germline mutation carriers, hormone receptor status, parity, HRT usage, histopathology, multifocality, bilaterality, tumor size, lymph node positivity, occurrence of distant metastasis, screening detection and youngest relative with breast cancer. The model was adjusted for age at diagnosis.

	HR	95.0% CI for HR (Lower-Upper)	p-value
Horizontal y/n	1.10	0.74-1.63	0.646
Vertical y/n	1.03	0.81-1.30	0.811
Germline mutation carriers	**1.90**	**0.99-3.65**	**0.055**
ER-status y/n	**0.76**	**0.60-.96**	**0.023**
PgR-status y/n	1.05	0.83-1.31	0.700
No. of children	1.00	0.92-1.08	0.922
HRT y/n	**0.65**	**0.49-0.85**	**0.002**
Ductal y/n	1.18	0.93-1.51	0.181
Lobular y/n	1.36	0.95-1.94	0.090
Tubular y/n	0.73	0.34-1.61	0.439
Multifocality y/n	0.92	0.58-1.44	0.708
Bilaterality y/n	1.20	0.89-1.63	0.235
Tumor size:	1.00	1.00-1.00	
0.2 - 5 cm	**1.30**	**1.04-1.61**	**0.019**
> 5 cm	**2.07**	**1.54-2.78**	**0.000**
No. of positive Lymph nodes:	1.00	1.00-1.00	
1-3	**1.34**	**1.08-1.65**	**0.008**
>3	**1.92**	**1.50-2.45**	**0.000**
Distant metastasis y/n	1.79	0.91-3.55	0.093
Screening y/n	**0.63**	**0.43-0.94**	**0.023**