

RESEARCH ARTICLE

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# Lympho-vascular invasion in BRCA related breast cancer compared to sporadic controls

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## Abstract

**Background:** Germline mutations in the BRCA1 gene predispose to the development of breast cancer, exhibiting a specific histological phenotype. Identification of possible hallmarks of these tumors is important for selecting patients for genetic screening and provides insight in carcinogenetic pathways.

Since BRCA1-associated breast cancers have pushing borders that prevent them from easily reaching vessels and are often of the medullary (like) type that is known to have a low rate of lympho-vascular invasion (LVI), we hypothesized that absence of LVI could characterize BRCA1 related breast cancer.

**Methods:** A population of 68 BRCA1 related invasive breast cancers was evaluated for LVI by an experienced breast pathologist blinded to mutation status, and compared to a control group matched for age, grade and tumor type.

**Results:** LVI was present in 25.0% of BRCA1 related cases, compared to 20.6% of controls ( $P = 0.54$ ,  $OR = 1.29$ ,  $CI 0.58-2.78$ ).

**Conclusion:** LVI is frequent in BRCA1 germline mutation related breast cancers, but seems to occur as often in sporadic controls matched for age, grade and tumor type. Apparently, these hereditary cancers find their way to the blood and lymph vessels despite their well demarcation and often medullary differentiation.

## Background

About 5-10% of all breast cancer cases are due to a hereditary predisposition. The two most important genes that, when bearing a germline mutation, predispose to breast cancer, are the BRCA1 and BRCA2 genes. It has been estimated that 5.3% of breast cancers occurring in women under forty years and 1.1% of breast cancers in women from 50 to 70 years are due to mutations in either of these genes[1]. Both genes are considered to be tumor suppressor genes that play a role in DNA repair [2-6] and mammary stem cell differentiation[7,8].

Mutation carriers have an increased life-time risk of developing breast cancer of 57% and 40% and of developing ovarian cancer of 40% and 18% for BRCA1 and BRCA2 respectively[9].

BRCA1 related breast carcinomas have a distinct histopathological phenotype. They have been shown to be more often of the ductal and medullary type, of high grade and to show a high mitotic activity index (MAI)

and necrosis [10,11]. An expansive growth pattern is also a prominent feature of this phenotype. Pushing margins have been reported to be significantly more often present and to cover a larger area of the tumor in BRCA1 and -2 related breast cancers[12,13]. In addition, specific immunohistochemical, gene expression and genomic alteration profiles have been described putting this hereditary subgroup apart from other breast cancer subtypes. These tumors usually do not express the estrogen and progesterone receptors and are almost always HER-2/*neu* negative ("triple negative")[10]. Furthermore, accumulation of p53[10] and overexpression of vimentin[14], EGFR [15], HIF-1 $\alpha$ [16], p-cadherin, and cytokeratins 5/6 and 14[17] are associated with BRCA1 mutations. At the gene-expression level these tumors cluster together with the basal-like subgroup[18]. BRCA2 related breast cancers are most often of luminal type and seem phenotypically harder to recognize[11].

Unraveling genotype, morphology and immunophenotype of BRCA-germline mutation related breast cancer has several advantages. Established biomarkers help the pathologist to recognize these hereditary cancers, which

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can help to trigger analyzing family history and to decide on mutation testing in patients at borderline risk, based on family history only. Tools that help to select patients for screening are wanted, since genetic screening is time-consuming and expensive. Further, an established phenotype can help to pin down the pathogenicity of so called "unclassified variant" mutations. Lastly, insight into carcinogenic pathways may offer opportunities to develop new targeted therapies for treatment and prevention of hereditary breast cancer.

Locoregional and systemic spread of breast cancer cells to respectively the lymph nodes and distant organs occurs after invasion of tumor cells into the lymphatic channels and the blood vessels. Although lymphatics and blood vessels of the breast can basically be discerned using immunohistochemical markers, this is in practice not usually done and lymphatic and blood vessel invasion is lumped as "lympho-vascular invasion" (LVI). LVI is present in approximately 15% of invasive ductal breast carcinomas, but its frequency differs widely among studies (5-50%). It is unusual to find LVI in lobular carcinomas[19]. LVI correlates with the presence of lymph node metastases[20,21] and is, not unexpectedly, a poor prognostic sign [22-24]. We hypothesized that LVI is negatively associated with BRCA1 germline mutations for three reasons. First, BRCA1 associated breast cancers are known to have pushing borders. Such an expansive growth pattern would mean that adjacent structures are pushed aside, rather than infiltrated, so that blood and lymph vessels may not be easily reached and invaded by tumor cells. In ER-negative breast cancer it has been shown that the presence of pushing margins correlates with the absence of LVI and lymph node negative status[25]. In endometrial carcinomas LVI has also been associated with a diffusely infiltrative and almost never with an expansive growth pattern[26].

Second, since the presence of LVI strongly correlates with lymph node metastases, low rates of LVI are likely to result in relatively frequent negative axillary nodal status. Indeed, a trend has been reported toward a higher percentage of lymph node negative, BRCA1-positive breast cancers as compared with controls[27]. In addition, the strong correlation between tumor size and nodal status described for sporadic breast cancer patients, was absent in BRCA1 mutation carriers[28].

Third, BRCA1 related breast cancers are frequently (11-19%) of the medullary tumor type, in contrast to 1% of sporadic cancers[29]. A high percentage of BRCA1 mutations has indeed been reported in medullary breast carcinomas[30]. Medullary carcinomas are associated with a significantly lower LVI rate of 6%[31].

Five studies have previously evaluated LVI in BRCA related breast cancer, some finding more and some less LVI compared to controls, but significance was not

reached [13,32-35], due to small populations (n = 8-32) and lack of correction for confounders like grade, thus not allowing definite conclusions.

We therefore set out to compare frequency of LVI in a large set of BRCA1 related breast cancers with well matched sporadic controls.

## Methods

### Study group

A population of 68 patients with hereditary invasive breast cancer, due to a germline mutation in the BRCA1 gene, was studied. A control group of 68 breast cancer patients unselected for family history and with no known mutation (further denoted "sporadic") was selected by case matching for age, tumor type and histologic grade as much as possible. All tumors could be coupled to a tumor with the same grade. The next step was matching for age, using a window of 5 years. Some tumor types were so rare, that after matching for age, no match for type could be found. They were therefore matched to invasive ductal carcinomas. Matching for these features was deemed necessary because these characteristics are significantly different between sporadic and BRCA related tumors and have been shown to be associated with the presence of LVI[36]. We excluded all "sporadic" cases for which a strong family history of breast cancer in the pathology report or electronic patient files was mentioned and all cases of which cumulative breast cancer risk exceeded 30% based on family history in the patient file[37]. MAI was assessed as before[38]. Growth pattern was reported to be expansive if pushing margins were observed in >50% of the tumor circumference[13]. Anonymous use of redundant tissue for research purposes is part of the standard treatment agreement with patients in our hospitals[39]. The protocol for use of the redundant tissue was approved by the science committee of the UMC Utrecht Biobank. Clinical data were retrieved from the pathology report and patient files. 71.3% of patients underwent an axillary lymph node dissection, the remaining 28.7% only underwent a sentinel node biopsy Breast conserving therapy was performed in similar rates in hereditary and sporadic patients.

### Lympho-vascular invasion

All available Hematoxylin-eosin (H&E) stained slides of all tumors were retrieved from our archive and screened for LVI by an experienced breast pathologist (PvD) blinded to BRCA mutation status. For the determination of LVI status we used criteria for identification as postulated by Rosen: "Evaluation is limited to tissue peripheral to the carcinoma, intralymphatic tumor emboli usually do not conform exactly to the space in which they lie, endothelial nuclei should be present and coexistent blood vessels are confirmatory evidence." [40]

Since many of the hereditary cases and some of the sporadic cases were referrals for which only one slide with tumor was available, we selected for each matched pair (case and control) the same number of slides to end up with a comparable number of slides assessed for LVI in both groups. For all patients with only one slide available, we selected for the match the H&E from the block on which immunohistochemistry (IHC) had been done. If no IHC had been done, the slide with the largest tumor area was selected. Although not including all slides might result in some false negatives and thereby lead to an underestimation of LVI frequency in our study group, this would apply to both the hereditary and sporadic in a similar manner and thereby does not influence our comparison between both groups.

### Statistics

Frequencies of LVI in hereditary cases and sporadic controls were compared by Chi-square test and Fischer exact test and odds ratios (OR) were calculated with 95% confidence intervals. Continuous data for both groups (e.g. MAI) were compared by Mann-Whitney U test. When features were significantly associated with both BRCA mutation status and the presence of LVI, statistical analysis of these possible confounders took place by calculating ORs stratified for specific subgroups (corrected by Mantel-Haenszel procedure) and logistic regression for significant features. All statistical analyses were performed using SPSS 15.0.

## Results

### Patients and tissues

Anonymous use of redundant tissue for research purposes is part of the standard treatment agreement with patients in our hospital [41], in compliance with the Helsinki Declaration. The research protocol for this study was approved by the Scientific Advisory Committee of the UMC Utrecht Biobank.

In the BRCA1 group, median tumor size was 1.8 cm compared to 2.6 for controls ( $p = 0.003$ ), median MAI was 22 vs 20 in controls (n.s.), and median age was 40 in both cases and controls (n.s.). Invasive ductal carcinomas were slightly more prevalent in the sporadic group (n.s.). Table 1 shows the further features of the BRCA1 population and the sporadic control group. BRCA1 related patients more frequently had negative lymph nodes (67.2% compared to 50.8% in controls), but this difference was not statistically significant ( $P = 0.06$ ). Expansive growth pattern was present in 47% of BRCA1 related tumors, compared to 41% in sporadic controls (n.s.). Multifocality (more than one invasive intramammary tumor nodule) was present in 21.8% of sporadic tumors, compared to 25% of BRCA1 related tumors (n.s.). All BRCA1 related carcinomas had a negative HER-2/*neu* receptor status when assessed, whereas in the control group 23.5%

was positive ( $P = 0.005$ ). Both ER and PR receptor status were more often negative in the BRCA1 related group (72.7% and 75.4% for ER and PR respectively, compared to 48.3% and 54.5% in controls;  $P = 0.005$  and  $P = 0.016$ , respectively).

### Lympho-vascular invasion

Frequencies of LVI in the BRCA1 related breast cancer and sporadic controls are shown in table 1. 25.0% of hereditary cases were positive for LVI, compared to 20.6% of controls, which was not statistically significant ( $P = 0.54$ , OR = 1.29, 95% CI = 0.58-2.78). Also when stratifying for tumor type, we did not find a significant difference between sporadic and BRCA related carcinomas (table 2). There was a much lower rate of LVI in medullary and metaplastic carcinomas.

No significant confounders were identified by stratified analysis and ORs, adjusted for confounding by Mantel Haenszel procedure, were not significantly different from the crude ORs. Therefore, further analysis of confounders by means of logistic regression was deemed unnecessary.

## Discussion

The aim of this study was to evaluate the absence of LVI as a putative biomarker in BRCA1 germline mutation related breast cancer. Our data did however not show the expected lower rate of LVI in BRCA related tumors.

Five studies have evaluated LVI in BRCA related breast cancer. None of the studies found a significant correlation between mutation status and LVI. Only one study statistically corrected for histologic tumor grade, by means of stratification[32]. This study compared 32 BRCA1 related tumors to 334 unmatched controls. LVI was reported in 31.6% and 25.3% of the cases for BRCA1 related and sporadic tumors, respectively. This result was not significant ( $P = 0.29$ ). Correction for other possible confounders (e.g. age, tumor type and size) did not take place. In four other studies no matching or statistical correction for confounding was performed at all[13,33-35]. Relatively small populations evaluated ( $n = 8-32$ ), in addition to the lack of correction for grade and other confounders make it impossible to draw definite conclusions from these five studies.

Rates of LVI in the present study (22.8%) were above the average rate described in literature (15%)[19]. We had indeed expected to find a higher rate of LVI than described in literature, since our population consisted mostly of high-grade carcinomas and high grade has been associated with higher rates of LVI. In populations consisting of solely grade 3 breast cancers, 35-46% of patients were reported to contain LVI[22,42-44]. In three of these four studies immunohistochemical staining for endothelial walls was used for identification of LVI, which might explain the higher rates found in these specific studies compared to our study employing just H&E[22,43,44].

**Table 1: Characteristics of BRCA1 related breast cancers and sporadic controls evaluated for frequency of lympho-vascular invasion**

		Sporadic control group (n = 68)		BRCA1 group (n = 68)		P-value	OR	95% CI
		Number	Percentage	Number	Percentage			
Tumour Type	invasive ductal carcinoma	58	85.3%	55	80.9%	0.83		
	invasive (ducto)lobular carcinoma	3	4.4%	3	4.4%			
	invasive medullary and metaplastic carcinoma	7	10.3%	10	14.7%			
Histologic grade	1	3	4.4%	2	2.9%	0.88 <sup>a</sup>		
	2	13	19.1%	14	20.6%			
	3	52	76.5%	52	76.5%			
Tumour size	<2 cm	24	35.3%	37	59.4%	0.02 <sup>a</sup>		
	2-5 cm	36	52.9%	22	35.9%			
	>5 cm	8	11.8%	9	4.7%			
	unknown	0		4				
Lymph node status	N0	33	50.8%	39	67.2%	0.06 <sup>a</sup>		
	N1	21	32.3%	17	29.3%			
	N2	9	13.8%	1	1.7%			
	N3	2	3.1%	1	1.7%			
	unknown	3		10				
Growth pattern	infiltrative	40	58.8%	36	52.9%	0.49	1.31	0.64-2.50
	expansive	28	41.2%	32	47.1%			
HER-2/ <i>neu</i> status	negative	26	76.5%	31	100.0%	0.005 <sup>b</sup>		
	positive	8	23.5%	0	0.0%			
	unknown	34		37				
ER status	negative	28	48.3%	48	72.7%	0.005 <sup>a</sup>	0.38	0.18-0.79
	positive	30	51.7%	18	27.3%			
	unknown	10		2				
PR status	negative	30	54.5%	49	75.4%	0.016 <sup>a</sup>	0.42	0.19-0.92
	positive	25	45.5%	16	24.6%			
	unknown	13		3				
Lympho-vascular invasion	negative	54	79.4%	51	75.0%	0.54 <sup>a</sup>	1.29	0.58-2.87
	positive	14	20.6%	17	25.0%			

a. P-value obtained with a Chi-square test. b. P-value obtained with a Fischer's exact test

Further, there is no real consensus on the definition of LVI, sometimes including intratumoral LVI, interobserver discordance has been reported [45-47] and case selection differed between studies, possibly contributing to the wide range of frequencies reported. Retraction artefacts and intraductal carcinoma are in some cases hard to distinguish from LVI and can lead to false positives whereas tumor emboli filling up the entire lumen of a vessel sometimes make it hard to detect LVI and may result in false negatives. However, topographic conditions, like other accompanying vessels usually help making the diagnosis LVI[45]. In addition, when LVI seems questionable at one location very often there is clearer LVI present elsewhere in the section.

To deal with interobserver discordance as mentioned, the same observer evaluated all slides. Therefore, potential interobserver bias is of little influence on our comparison between sporadic and hereditary breast cancer. In addition, several studies have shown that regarding equivocal cases as negative did not influence the predictive value of LVI[45,46].

An explanation for the fact that we found lower LVI frequencies, than described in the literature for grade 3 cancers, may lie in that fact that we did not evaluate all slides of all tumors, in order to match for number of evaluated slides per case, so that we may have missed LVI in cases where it is not present in all the slides. To get an impression of the magnitude of this potential reduction, we also assessed LVI in all slides available in the sporadic group. We then found an about 1.5 times higher rate of LVI (30.9%) if we considered all available slides in the sporadic group instead of only those slides used after slide number matching.

In order to find a LVI effect contributable to BRCA1 mutation and not to another feature associated with the BRCA1 phenotype, it was deemed necessary to match for features associated with LVI. Unfortunately, this matching has a downside. By case-matching to select controls, we likely preferentially select some hidden BRCA1/2 mutation carriers (age, histologic type and grade effect), as well as some tumors that have no known BRCA mutation but show a similar phenotype (type, grade effect) by e.g. promoter hypermethylation of BRCA1/2 or a mutation in another gene involved in the BRCA pathway. 9-22% of sporadic breast cancers have been described to show promoter hypermethylation of BRCA1 or loss of heterozygosity at the BRCA1 locus and these tumors are largely ER and PR negative, of ductal and medullary type, and high grade [48-52]. These are all also features of tumors with a mutation in BRCA1. One study selected 7 sporadic tumors with a BRCA1 phenotype, and found that 3 out of 7 showed promoter hypermethylation of BRCA1[53]. Selecting "sporadic" controls with a BRCA1 like phenotype might make it harder to find differences between sporadic and BRCA related carcinomas. This

might explain why we did not find the expected correlation between expansive growth pattern and BRCA1 mutation status as was described in literature. The absence of a higher frequency of pushing margins in our BRCA1 related group, is a possible explanation for the unexpected similar rates of LVI found in both groups.

We further looked into features that were associated with both LVI and BRCA mutation status such as age, tumor type, tumor size, nodal status, grade, ER and PR [19,21,22,42-44], to exclude and correct for possible confounders. No significant differences were found between cases and controls for age, nodal status and grade. Contradictory with literature, we did not find a significantly higher MAI in our hereditary group. Since cases were matched for tumor grade and MAI (as a constituent of grade) strongly correlates with grade, a difference was not expected here. Invasive ductal carcinomas were slightly more prevalent in the sporadic group. This is due to the fact that case matching could not always be performed for type in the case of rare tumor types and these were matched to ductal carcinomas. Stratification for tumor type shows a much lower rate of LVI in medullary and metaplastic carcinomas, which is consistent with literature[31]. A significantly lower rate of ER, PR and HER-2/*neu* expression was found in the BRCA1 related group. This is consistent with what we know from literature about BRCA1 related tumors, mostly showing a triple-negative receptor status[54]. ER and PR negative status have been associated with high LVI rates. No significant correlation between HER-2/*neu* status and LVI has been described [19,55]. In our study ER status was not significantly associated with LVI and neither was PR or HER-2/*neu* status. When stratified separately for ER, PR and HER-2/*neu* status, no significant differences for LVI status between cases and controls were found.

In our control group tumor size was slightly larger than in the BRCA1 related group. This has not been reported in literature. Since several studies noted that tumor size is significantly associated with LVI, this is a possible confounder. These studies reported high frequencies (58-69%) of LVI in tumors with a diameter bigger than 5 cm[42,43], although the one reporting the highest rates used immunohistochemistry to detect LVI. In our study LVI in tumors bigger than 5 cm was not significantly higher, so this does not likely play an important role here. The significant difference in tumor size between cases and controls was largely based on a difference in distribution between the group up to 2 cm and the group from 2-5 cm, but between these groups no significant differences in LVI rates were found.

## Conclusions

LVI seems to occur as much in BRCA1 germline mutation related breast cancers as in sporadic controls. Apparently, these hereditary cancers find their way to the blood

**Table 2: Frequency of lympho-vascular invasion (LVI) in BRCA1 associated breast cancer compared to matched sporadic controls, stratified for tumor type.**

Tumour type	LVI	Sporadic control group (n = 68)		BRCA1 group (n = 68)		Total (n = 136)		OR	95% CI	P-value
		Number	Percentage	Number	Percentage	Number	Percentage			
Invasive ductal carcinoma	negative	45	77.6%	39	70.9%	84	74.3%	1.42	0.61-3.32	0.42 <sup>a</sup>
	positive	13	22.4%	16	29.1%	29	25.7%			
Invasive lobular carcinoma	negative	2	66.7%	3	100.0%	5	83.3%	0.40	0.14-1.17	1 <sup>b</sup>
	positive	1	33.3%	0	0.0%	1	16.7%			
Invasive medullary and metaplastic carcinoma	negative	7	100.0%	9	90.0%	16	94.1%	0.56	0.37-0.87	1 <sup>b</sup>
	positive	0	0.0%	1	10.0%	1	5.9%			

a. Chi-square test. b. Fischer's exact test

and lymph vessels despite their well demarcation and often medullary type differentiation.

#### Competing interests

The authors declare that they have no competing interests.

#### Authors' contributions

MRHV collected samples, performed LVI assessment, carried out statistics and data interpretation, and drafted the manuscript. PG participated in the conception and design of the study, supervised collection of samples, and critically revised the manuscript. JB contributed with samples, participated in data interpretation and critically revised the manuscript. EW selected patients, participated in the conception and design of the study, and critically revised the manuscript. PJD performed LVI assessment, participated in the conception and design of the study, supervised statistics, and helped to draft the manuscript. All authors read and approved the final manuscript.

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