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Original contribution

Subtypes in *BRCA*-mutated breast cancer☆,☆☆

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Summary Approximately 3% to 5% of breast cancer patients are *BRCA1* or *BRCA2* germline mutation carriers. In this study, we correlated the distribution of intrinsic molecular subtypes according to failure pattern in a Danish cohort of *BRCA* germline–mutated breast cancer patients. Tumor tissues from 425 *BRCA* germline–mutated breast cancer patients were analyzed by immunohistochemistry for hormone receptor status, proliferation index (Ki-67), and HER2. Surrogate intrinsic molecular subtypes were assigned according to approximated St Gallen criteria. Annual hazard rates (AHR) were calculated for death and local or distant relapse, contralateral breast cancer, new primary cancer other than breast cancer, or death as first event (disease-free event). Luminal A–like subtype was observed with a frequency of 9% and 35% for *BRCA1* and *BRCA2*, respectively, and for both *BRCA1* and *BRCA2* patients, the luminal B–like subtype was more frequent than the luminal A–like subtype (*BRCA1* 21% and *BRCA2* 40% luminal B–like). No events or deaths were observed for luminal A–like subtype during the first 2.5 and 0 to 5 years, respectively. AHRs for luminal B–like tumors were 5.34% (95% confidence interval [CI], 1.49-1.19) and 1.76% (95% CI, 0.36-3.16) for disease-free event and death, respectively, and those for basal-like were 6.58% (95% CI, 2.98-10.18) and 4.54% (95% CI, 2.69-6.40). A substantial proportion of *BRCA* carriers had luminal A–like subtype, and these were mainly *BRCA2* carriers. Luminal A–like subtype was significantly associated with low AHR the first 5 years after surgery. This study warrants further exploration of the impact of the molecular intrinsic subtypes on survival in *BRCA*-mutated breast cancer patients.

1. Introduction

Approximately 3% to 5% of breast cancer patients are *BRCA1* or *BRCA2* germline mutation carriers. *BRCA* breast cancers are known to present with adverse tumor

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characteristics, and although histologic diagnosis in around 80% of tumors are invasive ductal carcinoma of no special type and thereby similar to noncarriers, most *BRCA* breast cancers are histologic high-grade tumors [1]. A higher prevalence of triple-negative (TN), invasive ductal carcinoma with medullary features [2] are frequently observed in *BRCA1* breast cancers, whereas *BRCA2* breast cancers are histologically and immunophenotypically similar to sporadic breast cancer [3]. The 4 major molecular subtypes of breast cancer, luminal A, luminal B, HER2-enriched, and basal-like, provide prognostic information and show different response to cytotoxic therapy [4]. The concept of intrinsic molecular subtypes was introduced in 2000 by Perou et al [5] by quantitatively measuring gene expression in breast cancer specimens. The tumors clustered in specific subgroups (eg, intrinsic subtypes), which were subsequently shown to be associated with differential prognosis [6]. These findings were validated by others [7,8] and resulted in development of the PAM50 classifier, which, based on the expression of 50 genes, predicts the molecular intrinsic subtypes [9]. Genomic tests are, however, expensive compared with immunohistochemistry (IHC) and require specific technical equipment. A 4-marker IHC-based surrogate definition based on estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67 was suggested as approximation of the intrinsic subtypes, with a Ki-67 cutoff of initial 13.25% [10] and, later in addition, cutoff of PR at 20% [11] to recapitulate the prognostic information. Among the luminal ER-positive breast cancers, luminal A has a significantly better prognosis, and the absolute benefit from addition of chemotherapy is low. On the other hand, luminal B–, HER2-enriched, and basal-like tumors are highly proliferative with a worse prognosis, and consequently, the distinction between luminal A and B subtypes is clinically relevant to identify a low-risk ER-positive population who might be spared chemotherapy [12]. Because most *BRCA* breast cancer patients are premenopausal at diagnosis and present with high-risk factors, intrinsic subtype classification is less investigated in these patients. However, as shown recently, omission of chemotherapy is associated with a worse prognosis in both *BRCA1*- and *BRCA2*-mutated breast cancers [13]. In addition, a large population-based study of *BRCA2* carriers has indicated that ER positivity may be associated with a worse prognosis [14].

The pattern of recurrence and death differ according to ER status in sporadic breast cancer: ER-negative breast cancer has an initially high recurrence rate, opposite to ER-positive breast cancer for which the hazard rate is more constant and exceeds the recurrence rate of ER-negative breast cancer after around 5 years [15]. Higher grade and TN phenotype could lead to the assumption that luminal A subtype is absent or very rare in *BRCA*-mutated breast cancer. Therefore, we decided to investigate the association of the IHC-determined intrinsic subtypes with disease-free survival (DFS) and overall survival (OS) in a large cohort of Danish breast cancer patients with *BRCA1* or *BRCA2* germline mutation.

2. Materials and methods

The National Committee on Health Research Ethics (registration number 33483) and the Danish Data Protection Agency (2009-41-3611) approved the study.

The study is reported according to REMARK criteria [16].

2.1. Patients

Since 1977, Danish women with primary breast cancer have been registered in the Danish Breast Cancer Cooperative Group database including prospectively registered clinical data. Family history of breast and ovarian cancers was added to the Hereditary Breast and Ovarian Cancer registry in 1999 [17]. From the Danish Breast Cancer Cooperative Group database, Danish female *BRCA1/2* carriers with *BRCA* mutation tested between 1997 and July 2011 with primary stage I-III breast cancer diagnosed between 1977 and February 2012 were included. Recently, survival data on patients from the same population diagnosed as having a *BRCA* mutation less than 2 years after breast cancer surgery were published [13]. Five hundred eighty-three patients with a germline *BRCA1* or *BRCA2* mutation were identified. In the present study, all patients with intrinsic subtype assignment and clinical follow-up were included, leaving 425 of 583 *BRCA*-mutated breast cancer patients for analysis. Follow-up for death was complete by linkage to the personal civil registration system in Denmark [13]. Only follow-up beyond *BRCA* testing date was included in statistical analysis.

BRCA mutation testing method, breast cancer treatment, clinical follow-up, and available medical registries were previously described [13]. In brief, patients had clinical follow-up every third month of the first year after primary breast cancer surgery, every sixth month during the following 2 to 5 years, and once a year, 6 to 10 years after primary breast cancer or until a first event. Since 1997, patients suspected of having a germline *BRCA1/2* mutation were referred for genetic counseling and, after risk stratification, offered mutational screening or predictive testing for *BRCA1* and *BRCA2* mutations. Proposed guideline criteria for referral to genetic counseling in 2001 [13] were any of the following: young age at breast cancer diagnosis, first- and second-degree relatives with breast cancer or ovarian cancer, a disease-causing mutation in the family, breast and ovarian cancers in the same individual, and male breast cancer. However, to some extent, patients were referred by other criteria as tumor biology and bilateral breast cancer. Supplementary clinical information was retrieved from the Danish National Patients Register, the Danish Pathology Register, and the Danish Cancer Register as previously described [13]. Mutational screening of the *BRCA1* and *BRCA2* genes for deleterious mutations and variant classification was performed as previously described [13].

2.2. Tissue samples

Formalin-fixed, paraffin-embedded tissue blocks were collected from Danish departments of pathology. Four-micrometer sections from each block were stained with hematoxylin and eosin for identification of tumor areas for preparation of tissue microarray (TMA) and histologic review. Up to four 1.5-μm cores from primarily the invasive tumor front were used for TMA. Review of histologic subtype and grade was performed according to World Health Organization guidelines [18]. The diagnosis of ductal carcinoma with medullary characteristics features was designated for high-grade tumors with pushing margins and syncytial growth pattern in more than 75% of the tumor in association with a pronounced lymphoplasmacytic infiltrate [18].

2.3. IHC/in situ hybridization analysis

IHC was performed for ER, PR, HER2, and Ki-67 with anti-ER SP1 ready-to-use (RTU), anti-PR clone 1E2 RTU, anti-HER2 clone 4B5 RTU, and anti-Ki-67, clone 30-9 RTU (Ventana/Roche, Oro Valley, Arizona, USA). ER and PR were assessed as positive in case of at least 1% positive nuclear staining [19], and HER2 IHC was scored according to standardized guidelines [20]. For HER2 score 2+, HER2 gene status was determined with a gene-protein assay (INFORM Dual ISH DNA Probe cocktail; Ventana) and scored according to guidelines [20,21]. Ki-67 was scored semiquantitatively as percent positive nuclei in hotspots according to national guidelines [20].

2.4. Intrinsic subtype classification

Classification of breast cancer intrinsic subtypes was performed based on a combination of IHC markers for expression of ER, PR, HER2, and Ki-67 approximating the proposed St Gallen subtype classification [22]. For distinction of luminal A and luminal B subtypes, a 20% cutoff for PR [11] and Ki-67 was applied [23]. Currently, there is no consensus on Ki-67 cutoff [24]. Previously, Cheang et al [10] proposed a cutoff of 13.25%; however, for unambiguous applicability, a cutoff of 20% was applied. Luminal A–like subtype was defined as ER positive (≥1% positive nuclei) and HER2 negative, and PR ≥ 20% or Ki-67 < 20%. Luminal B–like subtype was defined as ER positive (≥1% positive nuclei) and HER2 negative, and PR < 20% or Ki-67 ≥ 20%. The HER2 subtype was defined as HER2 3+ or HER2 amplified according to American Society of Clinical Oncology, College of American Pathologists (ASCO CAP) guidelines [21]. Finally, the basal-like subtype was defined as TN. Histologic review, interpretation of IHC and HER2 in situ hybridization and subtype assignment were performed blinded to *BRCA1/2* mutation status.

2.5. Statistical analysis

Differences in proportions of tumor characteristics and treatment between subgroups were tested using the χ^2 test or Fisher exact test as appropriate. Missing values were excluded. Patients were observed from time of definitive breast cancer surgery to death of any cause or disease event defined as local or distant relapse, contralateral breast cancer, new primary cancer other than breast cancer, death as first event, or end of 10-year follow-up, whichever occurred first. To minimize longevity bias, data were left truncated at the time of *BRCA* testing, meaning that only follow-up beyond date of *BRCA* testing was included. For OS, information on vital status for all patients was obtained from the Danish Civil Registration System, and consequently, no patients were lost to follow-up

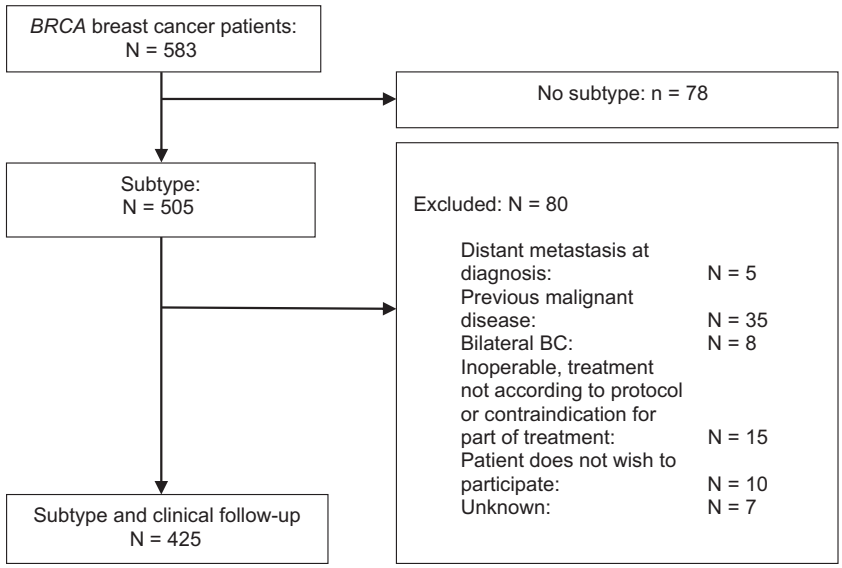

Fig. 1 Consort diagram of study population.

Table 1 Patient and tumor characteristics of patients with subtype assignment (N = 425)

Variable	Patients				
	BRCA1		*BRCA2*		*P*
	n	%	n	%	
Total cases	253	60	172	40	
BRCA test					
≥2 y	109	43	73	42	1.0
<2 y	140	55	94	55	
Unknown	4	2	5	3	
Age (y)					
18-39	112	44	53	31	.009
40-59	123	49	97	56	
≥60	18	7	22	13	
Year of diagnosis					
<2000	72	28	37	22	.1
≥2000	181	72	135	78	
Menopausal status at diagnosis					
Premenopausal	197	78	118	69	.03
Postmenopausal	56	22	54	31	
Subtype					
Luminal A–like	23	9	60	35	<.0001
Luminal B–like, HER2−	52	21	69	40	
HER2+	14	6	11	6	
Basal-like/TN	164	65	32	19	
Histology					
Ductal	218	86	151	88	.0001
Lobular	2	1	12	7	
Other	33	13	9	5	
Histology					
Ductal with medullary features	32	13	8	5	.006
Other	221	87	164	95	
Histology					
Lobular	2	1	12	7	.0005
Other	251	99	160	93	
Tumor size (mm)					
≤10	26	10	25	15	.7
11-20	120	47	73	42	
21-50	101	40	67	40	
>50	6	2	6	3	
Unknown	0	0	1	1	
Grade					
1 and 2	54	21	89	52	<.0001
3	198	78	82	48	
Unknown	1	1	1	1	
Positive lymph nodes					
0	154	61	75	44	.002
1-3 positive	72	28	69	40	
≥4 positive	27	11	28	16	
ER status					
Positive	82	32	138	80	<.0001
Negative	171	68	34	20	
PR status					
Positive	62	25	119	69	<.0001
Negative	191	75	53	31	
HER2 status					
Positive	14	6	11	6	.7
Negative	239	94	161	94	
Ki-67 status					
<20%	50	20	91	53	<.0001
≥20%	198	78	79	46	
Unknown	5	2	2	1	
Surgery					
Mastectomy	135	53	105	61	.1
Breast-conserving surgery	118	47	67	39	
Systemic therapy					
None	31	12	17	10	<.0001
Chemotherapy alone	171	68	53	14	
Chemotherapy and endocrine therapy	37	15	78	45	
Endocrine therapy alone	14	6	24	14	
RRCM					
Yes	113	45	64	37	.1
No	140	55	108	63	
RRSO					
Yes	205	81	141	82	.8
No	48	19	31	18	

and were censored if alive at the date of data retrieval (September 23, 2016) [13]. Median potential follow-up time from the date of surgery and date of *BRCA* test was calculated using the Kaplan-Meier method. Annual hazard rates (AHRs) of death and DFS event were estimated as the number of events divided by the sum of person-years in the given time interval. Because of limited number of events, hazard rates were estimated in periods of 0 to 2.5, 2.5 to 5.0, and 5 to 10 years after surgery for DFS event, and 0 to 5, 5 to 10, and 10 to 20 years for death, giving the average annual hazard in these intervals. For 9 patients with missing *BRCA* test date, the date was set to January 1, 1999, if definitive surgery was performed before that date and otherwise to the date of definitive surgery.

3. Results

Four hundred twenty-five patients had subtype assigned and clinical follow-up. By left truncating at the date of *BRCA* testing, only follow-up time *beyond* the date of *BRCA* testing contributed to the analysis of failure rate. Twelve patients died before *BRCA* testing, leaving 413 patients with follow-up for death (Fig. 1). Fifty-nine had a DFS event out of 290 patients with clinical follow-up for DFS event after the date of *BRCA* test. Of these, 34 (12%) had local or distant relapse, 9 (3%) had contralateral breast cancer, 5 (2%) died as first event, and 11 (4%) had a new primary cancer other than breast cancer. Ninety-six of 413 patients with follow-up for death exceeding the date of *BRCA* test died. Estimated median potential follow-up time from *BRCA* testing was 8.8 and 6.6 years for OS and DFS, respectively. Median potential

Table 2 Patient and tumor characteristics according to subtype (n = 413)

	Luminal A–like		Luminal B–like		HER2+		Basal-like		*P*
	n	%	n	%	n	%	n	%	
Total cases	75	18	120	29	25	6	193	47	
BRCA test after BC surgery (y)									
<2	42	56	70	58	12	48	110	57	.8
≥2	33	44	50	42	13	52	83	43	
BRCA									
1	21	28	52	43	14	56	161	83	<.0001
2	54	72	68	57	11	44	32	17	
Year of diagnosis									
<2000	16	21	27	23	7	28	52	27	.7
≥2000	59	79	93	78	18	72	141	73	
Age (y)									
18-39	27	36	36	30	7	28	90	47	.07
40-59	43	57	69	58	15	60	86	45	
≥60	5	7	15	13	3	12	17	9	
Definitive surgery									
Mastectomy	44	59	71	59	13	52	102	53	.7
Breast-conserving surgery	31	41	49	41	12	48	91	47	
Chemotherapy									
Yes	61	81	82	68	18	72	169	88	.05 [a]
No	14	19	38	32	7	28	24	12	
Endocrine therapy									
No	23	31	49	41	14	56	187	97	<.0001
Yes	52	69	71	59	11	44	6	3	
RRCM									
No	46	61	67	56	17	68	108	56	.6
Yes	29	39	53	44	8	32	85	44	
RRSO									
No	11	15	22	18	4	16	33	17	.9
Yes	64	85	98	82	21	84	160	83	
Tumor size (mm)									
0-20	49	65	69	58	12	48	109	56	<.0001
21-49	25	33	47	39	12	48	77	40	.03
≥50	1	1	3	3	1	4	7	3	
Unknown	0	0	1	1	0	0	0	0	
Lymph node status									
Negative	30	40	60	50	11	44	123	63	.001
Positive	45	60	60	50	14	56	69	36	
Unknown	0	0	0	0	0	0	1	1	
Histology									
Ductal	67	89	110	92	24	96	159	82	<.0001
Lobular	7	9	4	3	0	0	0	0	
Other	1	1	6	5	1	4	34	18	
Histology									
Ductal with medullary histology	75	100	6	5	1	4	33	17	<.0001
Other	0	0	114	95	24	96	160	83	
Malignancy grade									
1 and 2	56	75	51	43	12	48	17	9	<.0001 [b]
3	19	25	69	57	13	52	174	90	<.0001 [c]
Unknown	0	0	0	0	0	0	2	1	

[a] Test of treatment difference between luminal A–like and luminal B–like within the luminal-like subgroup.
[b] Test of the difference between grade 1 and 2 *vs* grade 3 between all subtypes.
[c] Test of the difference between grade 1 and 2 *vs* grade 3 between luminal A– and B–like in luminal-like subgroup.

Table 3 Annualized hazard rates of death in years 0 to 5, 5 to 10, and 10 to 20 and of DFS event and recurrence in years 0 to 2.5, 2.5 to 5, and 5 to 10 [a]

	Hz and 95% CI (%)							
	<2½ y		Year 5		Year 10		Year 20	
Death (n = 413)								
All			2.71	1.73-3.69	2.89	1.89-3.89	3.34	2.12-4.56
Luminal A			0	0	5.21	2.21-8.20	7.32	2.71-11.92
Luminal B			1.76	0.36-3.16	2.68	0.95-4.40	4.39	1.73-7.05
Basal-like			4.54	2.69-6.40	1.98	0.70-3.26	2.14	0.76-3.53
DFS-event (n = 290)								
All	4.97	2.85-7.09	3.97	2.31-5.63	4.13	2.21-6.05		
Luminal A	0	0	3.99	0.16-7.83	6.01	0.90-11.12		
Luminal B	5.34	1.49-9.19	4.29	1.18-7.40	3.96	0.56-7.36		
Basal-like	6.58	2.98-10.18	3.45	1.10-5.81	3.25	0.69-5.80		
Recurrence [a] (n = 290)								
All	4.47	2.45-6.49	3.41	1.86-4.95	2.91	1.29-4.54		
Luminal A	0	0	2.99	0-6.33	6.01	0.90-11.12		
Luminal B	4.58	1.00-8.15	4.29	1.18-7.40	3.96	0.56-7.36		
Basal-like	6.03	2.58-9.48	3.02	0.82-5.23	1.08	0-2.58		

Abbreviations: CI, confidence interval; Hz, hazard ratio.

[a] Recurrence was defined as local or distant recurrence, contralateral breast cancer, or death, censoring new primary cancer other than breast cancer.

follow-up time from breast cancer surgery was 12.2 and 8.1 years, respectively.

3.1. Patient characteristics

Patient and tumor characteristics of the full cohort (N = 425) are listed according to affected *BRCA* gene in Table 1 and according to intrinsic subtype for patients alive when *BRCA* tested (n = 413) in Table 2. Most patients were diagnosed after the year 2000 and were *BRCA* tested less than 2 years after surgery. This did not vary according to subtype. *BRCA1* carriers were younger ($P = .0088$) and had less nodal involvement ($P = .0005$) compared with *BRCA2* carriers. No disparity in treatment, year of surgery, and time from surgery to *BRCA* testing between *BRCA1* and *BRCA2* patients was observed (Table 1); however more *BRCA1* patients had received risk-reducing contralateral mastectomy (RRCM) as compared with *BRCA2* patients. *BRCA1* status was associated with medullary features ($P = .0056$) and higher grade ($P < .0001$). *BRCA2* status was associated with lobular histology ($P = .0005$).

3.2. Subtypes

Overall, 20%, 28%, 6%, and 46% of breast cancers were of luminal A–like, luminal B–like, HER2-positive, and basal-like subtype, respectively. Most *BRCA1* carriers had basal-like (65%) subtype, whereas *BRCA2* carriers predominantly had a luminal-like subtype (75%). Luminal A–like subtype was assigned with a frequency of 9% and 35% in *BRCA1* and *BRCA2* carriers, respectively. In contrast, HER2-positive subtype was rare, irrespective of affected gene (Table 1). Basal-like subtype was associated with high tumor grade ($P < .0001$), medullary histologic features ($P < .0001$), and absence of lymph node metastases ($P = .001$). More luminal B–like as compared with luminal A–like tumors were high grade ($P < .0001$). Luminal A– and B–like tumors were smaller compared with non–luminal-like tumors (Table 2). Among patients with luminal-like subtype, a higher proportion of luminal B–like compared with luminal A–like subtypes were not treated with chemotherapy ($P = .05$, 19% luminal A–like versus 32% luminal B–like); however, no disparity in surgery (mastectomy versus breast-conserving surgery), RRCM, or risk-reducing salpingo-oophorectomy (RRSO) between subtypes was observed.

3.3. AHRs according to subtypes

AHRs of death increased with time for patients with luminal-like subtypes, whereas they decreased for patients with basal-like subtype (Table 3 and Fig. 2). The first 5 years after breast cancer surgery, no deaths occurred among patients with luminal A–like subtype, and similarly, in years 0–2.5, no DFS event was observed but with increasing AHR in the subsequent periods. Basal-like subtype showed a reverse failure pattern with high AHR in the early years and decreasing in the subsequent periods. Luminal B–like subtype showed an increasing AHR of death in all periods but was exceeded by luminal A–like subtype after approximately 5 years. Luminal B–like AHR of DFS-event was high in the beginning and then only decreased slightly and not to the same extent as basal-like subtype but was exceeded by luminal A–like subtype at around 5 years. Breast cancer–related events (eg, censoring new primary cancers other than breast cancer) showed similar failure pattern.

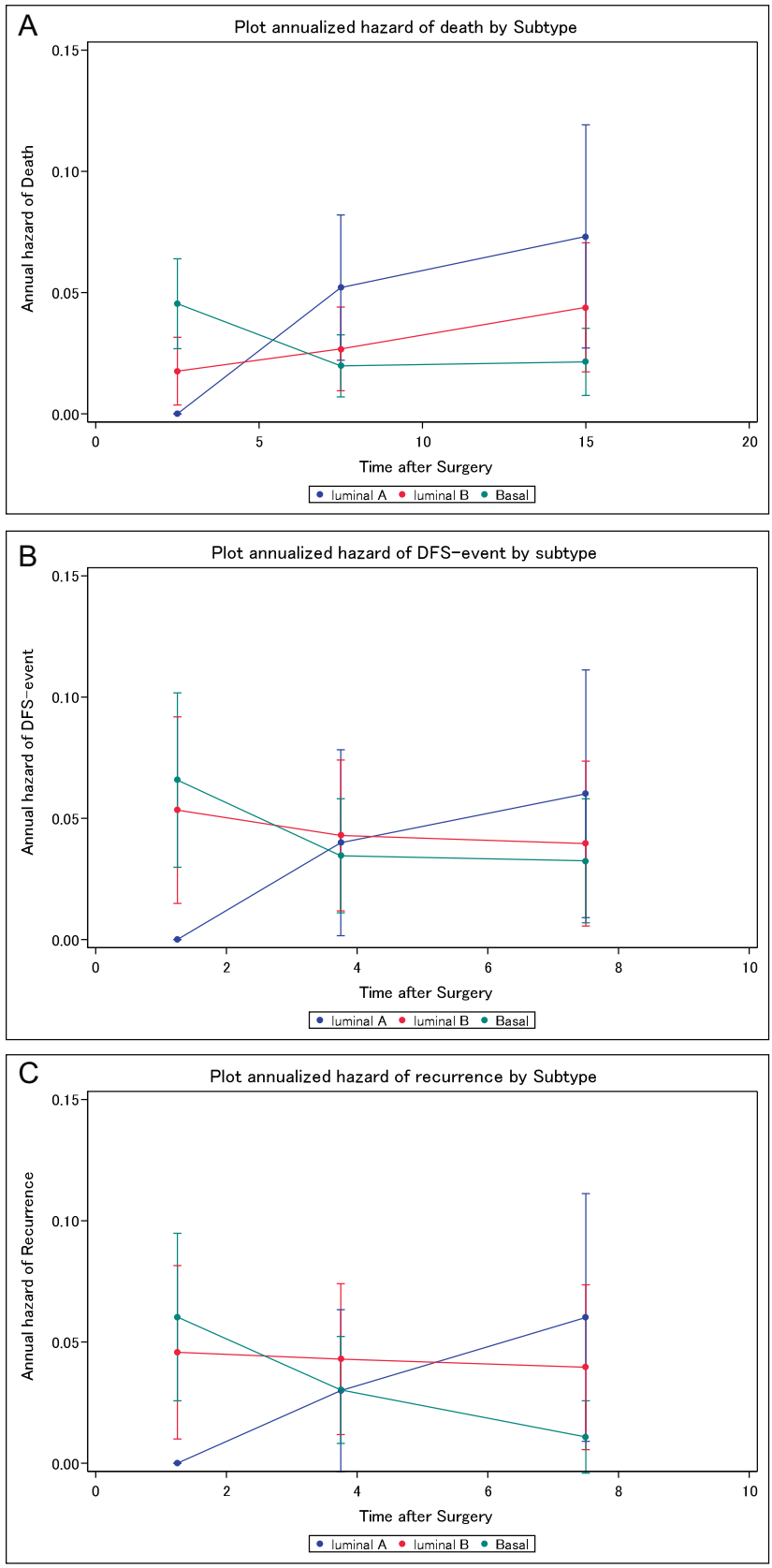

Fig. 2 Plots of annualized hazard rates for death (A), DFS event (B), and recurrence (C) according to luminal A–like, luminal B–like, and basal-like subtypes. Recurrence was defined as local or distant relapse, contralateral breast cancer, or death as first event, censoring new primary cancer other than breast cancer.

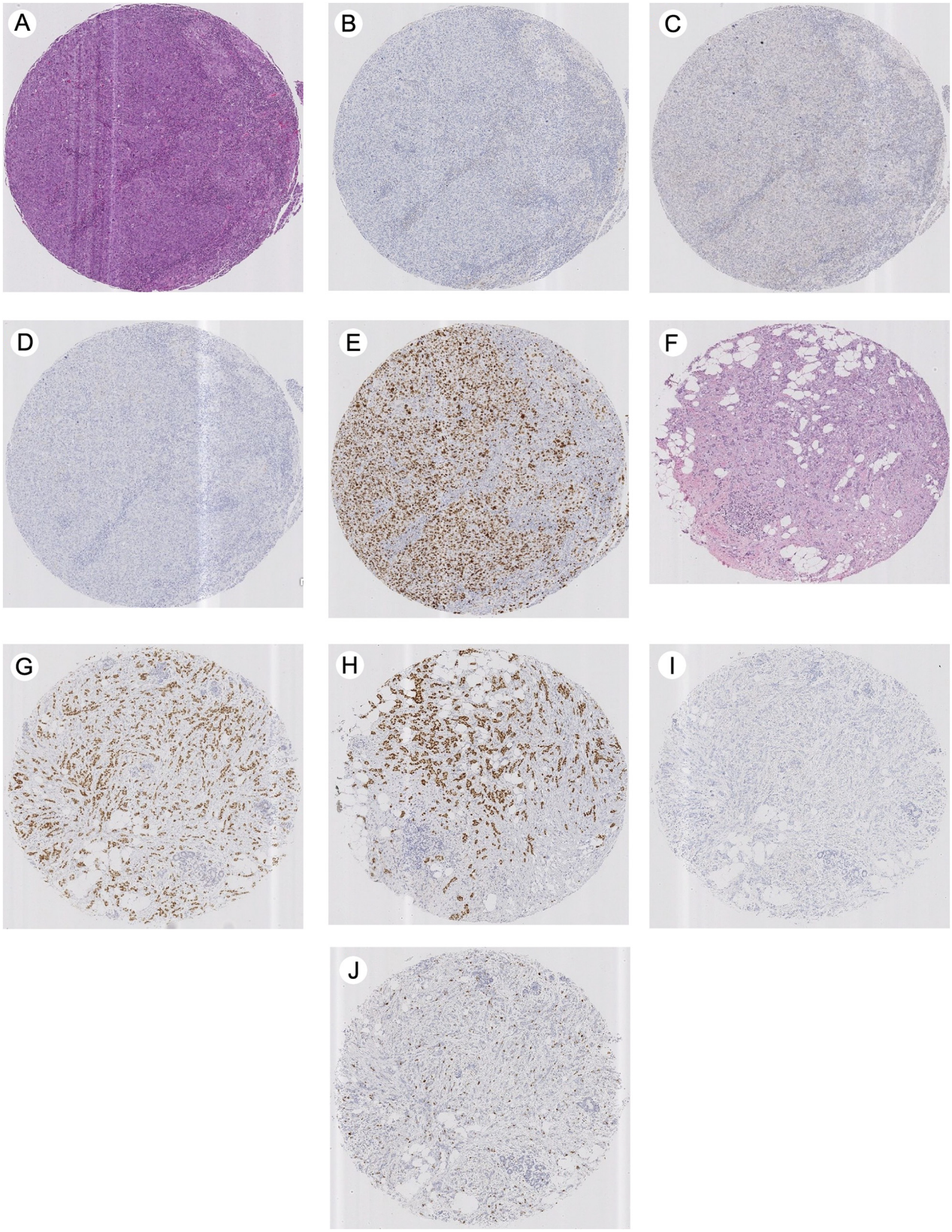

Fig. 3 Morphology and IHC stainings of one *BRCA1* tumor categorized as basal-like and one *BRCA2* tumor categorized as luminal A–like subtype. A, Hematoxylin and eosin of the *BRCA1* tumor showed invasive ductal carcinoma with medullary features. IHC stainings were ER < 1% (B), PR < 1% (C), HER2 IHC score 0 (D), and Ki-67 score of 90% positive (E). F, The *BRCA2* tumor was invasive ductal carcinoma, not otherwise specified and luminal A–like subtype. ER was 95% positive (G), PR expression was 100% positive (H), HER2 had IHC score 0 (I), and Ki-67 was 10% (J).

4. Discussion

Failure patterns differed relative to intrinsic subtype in the cohort of Danish breast cancer patients with germline *BRCA1/2* mutation. The results suggests that *BRCA* carriers with luminal A–like subtype have a significantly better prognosis the first 5 years after breast cancer surgery compared with luminal B–like and basal-like subtype [25].

Distribution of subtypes according to affected gene confirms previous reports of association of TN/basal-like subtype with *BRCA1* and luminal subtype with *BRCA2* [1] (Fig. 3). In accordance with the observed high proliferation, luminal B–like subtype was somewhat more frequent than luminal A–like, confirming the high proliferation and malignancy grade described previously [3,26,27].

The strengths of this study are the large and nationwide population of *BRCA* carriers. This is likely the first study to describe hazards according to subtypes in *BRCA* germline–mutated breast cancer patients.

There are, however, some potential limitations. Selection of patients with low mortality (eg, luminal A–like subtype), consequently affecting the subtype distribution, cannot be ruled out. Assuming this, a higher proportion of luminal A–like subtype among breast cancer patients *BRCA* tested later than 2 years after primary breast cancer surgery as compared with less than 2 years after breast cancer surgery (Table 2) could be expected. There were no such observations. In addition, longevity bias was minimized by left truncation.

The lack of analytical validity for Ki-67 is well known [28] and could have affected subtype distribution. Against a PAM50 gold standard, a proportion of IHC-luminal-B like tumors would be luminal A–like and to a minor extent HER2-enriched or basal-like [29,30]. However, Waddell et al [31] found a similar proportion of luminal A–like *BRCA2* breast cancers in a population enriched for family history of breast cancer using the PAM50 classifier. Because of tumor heterogeneity, the use of TMA might have affected the Ki-67 analysis, but the contribution of up to 4 tissue cores per tumor should have diminished this issue.

An initial lower failure rate has previously been described for luminal A subtype compared with non–luminal A subtypes in sporadic breast cancers [8,25,32]. Hazard rates according to intrinsic subtypes are not reported for *BRCA* carriers. Other studies have investigated the prognostic association of ER status in *BRCA1* and *BRCA2* patients and report a similar prognostic association as for sporadic breast cancers [33,34]. One exception is, however, the Icelandic study of *BRCA2* carriers with a specific founder mutation [14]. Jonasson et al reported *BRCA2* mutation as a predictor of a worse survival in ER-positive breast cancer, however, not among ER-negative breast cancer. Whether these results apply only to this specific founder mutation is unknown. Interestingly, recent results from the Prospective Outcomes in Sporadic versus Hereditary breast cancer (POSH) study [35] showed that young *BRCA1* breast cancer patients with TN breast cancer had a lower mortality compared with noncarriers the first 2 years after diagnosis. In that cohort, patients were selected based on early-onset breast cancer but not according to family history. Furthermore, all patients were *BRCA* tested within the first year of primary breast cancer diagnosis. Although conclusions are limited to selected populations (eg, age <40 years and founder mutations), the studies suggested that subtypes may have a different impact in breast cancer progression according to carrier status and affected *BRCA* gene.

In conclusion, in our study, a substantial proportion of *BRCA* carriers had luminal A–like subtype, and these were largely *BRCA2* carriers. Luminal A–like subtype was significantly associated with a low hazard rate the first 5 years after surgery, and the results suggest that *BRCA1* and *BRCA2* carriers with a luminal A–like subtype have an excellent prognosis the first 2½ years after diagnosis. Because of sample size, any exploration of different failure patterns according to intrinsic subtypes within the *BRCA1* and *BRCA2* subgroups or by age groups was not feasible. However, this study in combination with current knowledge of breast cancer subtypes and survival in *BRCA*-associated breast cancer warrants further exploration of these associations.

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