The Breast 49 (2020) 81–86

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Breast cancer surveillance for *BRCA1/2* mutation carriers – is "early detection" early enough?

Rinat Bernstein-Molho [a, d], Bella Kaufman [a, d], Merav A. Ben David [a, d, 1], Miri Sklair-Levy [b, d], Dana Madoursky Feldman [b], Dov Zippel [b], Yael Laitman [c], Eitan Friedman [b, c, d, *]

[a] *Breast Cancer Center, Oncology Institute, Chaim Sheba Medical Center, Tel-Hashomer, Israel*
[b] *The Meirav High-risk Clinic - Chaim Sheba Medical Center, Tel-Hashomer, Israel*
[c] *Oncogenetics Unit, Institute of Genetics, Chaim Sheba Medical Center, Tel-Hashomer, Israel*
[d] *Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel*

ARTICLE INFO

Article history:
Received 27 September 2019
Received in revised form
22 October 2019
Accepted 24 October 2019
Available online 6 November 2019

Keywords:
BRCA1 BRCA2
Surveillance
Early diagnosis
Intensive screening
Risk-reducing surgeries

ABSTRACT

Background: Annual MRI screening is associated with a significant reduction in advanced-stage breast cancer diagnosis in *BRCA1/2* mutation carriers. The impact that early detection has on subsequent oncological treatment is less frequently reported. In this study we compared disease stage and therapeutic approaches in *BRCA1/2* mutation carriers who developed breast cancer while adhering to the recommended surveillance scheme ("known carriers"), with women who became aware of their *BRCA* mutation status after breast cancer diagnosis ("latent carriers").

Methods: Data on tumor characteristics, disease stage, and therapeutic decisions were collected on *BRCA1/2* mutation carriers treated for breast cancer at the Chaim Sheba Medical Center.

Results: Data were available for 298 *BRCA1/2* carriers. Median follow-up was 77.4 months (range, 3.5–520). Age at diagnosis was not statistically different between known carriers ($n = 96$; median age at diagnosis 44.7 years) and latent carriers ($n = 202$; 43.7 years); $p = 0.8284$. Of known carriers, 19.8% were diagnosed with carcinoma in situ vs. 5% of latent carriers ($p = 0.0012$). Stage T1N0 disease was diagnosed in 54/96 (56.3%) of known carriers vs. 59/202 (29.2%) of latent carriers ($p < 0.00001$). Neoadjuvant or adjuvant chemotherapy was administered to 46/96 (47.9%) of known carriers compared with 162/202 (80.2%) of latent carriers ($p < 0.00001$).

Conclusions: While early stage breast cancer was diagnosed frequently among known *BRCA1/2* carriers under tight surveillance, almost half of these women were treated with chemotherapy. Healthy *BRCA1/2* mutation carriers should be informed about these rates while discussing risk-reducing surgical options.

Introduction

Germline mutations in *BRCA1* or *BRCA2* genes confer a significantly increased lifetime risk of developing breast cancer (BC), estimated at up to 6 times that of the average risk population [1]. Healthy women who carry a deleterious mutation in *BRCA1/2* are counseled about BC risk-management options including a tight surveillance scheme from 25 to 30 years of age, chemoprevention, and risk-reducing surgeries [2]. While admittedly bilateral risk reducing mastectomy (BRRM) is the most effective method for actively reducing BC risk among *BRCA1/2* mutation carriers [3,4], rates of *BRCA1/2* carriers who opt for this option are below 50% in most countries [5–8]. Data regarding survival benefits of BRRM over intensive surveillance are conflicting, primarily due to the lack of prospective trials [9]. The American Cancer Society recommendations for surveillance of female *BRCA1/2* mutation carriers from 2007 included magnetic resonance imaging (MRI) of the breast and annual mammography [10]. Annual MRI screening has been shown to be the most sensitive screening tool for high-risk women and associated with a significant reduction in the incidence of advanced-stage BC in *BRCA1/2* mutation carriers [11–15]. Based on

* Corresponding author. Oncogenetics Unit, Sheba Medical Center Tel- Hashomer, 52621, Israel.
E-mail addresses: eitan.friedman@sheba.health.gov.il, feitan@tauex.tau.ac.il (E. Friedman).
[1] Present address - Oncology Institute, Assuta Medical Center, Ramat Hahayal, Tel Aviv.

https://doi.org/10.1016/j.breast.2019.10.012

these findings, population screening for *BRCA1/2* mutations, at least for populations exhibiting founder mutations was suggested [16–19], to facilitate early detection in young mutation carriers who may not be aware of their risk. However, to what extent such early detection in female *BRCA1/2* carriers who adhere to the recommended early detection scheme affects oncological treatment decisions has sparsely been reported [9,20].

The purpose of the present study was to assess stage at diagnosis and therapeutic approaches in Israeli *BRCA1/2* mutation carriers and compare these parameters in women who developed BC while adhering to the recommended surveillance scheme ("known carriers"), with BC cases who became aware of their *BRCA* mutation status after BC diagnosis ("latent carriers"). Noteworthy, the Israeli population has the highest prevalence of *BRCA1/2* mutation carriers, when most of the mutations are limited to one of the 3 founder Ashkenazi Jewish mutations [21]. Yet, the rate of uptake of BRRM among *BRCA1/2* mutation carriers is less than 20% [8]. No studies have been done so far to explain these low rates, or whether these rates have changed in Israel over time.

Methods

Retrospective data were collected on female *BRCA1/2* mutation carriers treated for BC at the Chaim Sheba Medical Center, including both the Oncology Institute and the Meirav Center for Breast Health's high-risk clinic.

Since 2007, the surveillance scheme for asymptomatic *BRCA1* and *BRCA2* mutation carriers in our center follows mostly the ACS [10] and NCCN guidelines [2]. All mutation carriers undergo biannual clinical breast examination from the age of 25, annual breast MRI starting at age 25 years, alternating with annual mammography and sonography starting at age 35 years. Self-developed guidelines also include clinical breast examination and sonography every 3 months in pregnant and breastfeeding *BRCA1/2* mutation carriers. These surveillance guidelines and systemic BC treatment protocols for early stage disease have not changed in our center since 2007.

The Meirav Center high-risk clinic offers all *BRCA1* and *BRCA2* mutation carriers the early detection scheme outlined above. All registered *BRCA1*/*BRCA2* mutation carriers attending the high-risk clinic who were diagnosed with breast cancer were included in the study. Carriers who underwent BRRM and cancer free carriers as of June 2019 were excluded from the study. None of the known mutation carriers was treated with chemo-preventive agents. All adhered to the recommended screening scheme.

The latent carriers were identified during oncological treatment and follow-up at the Oncology Institute. These patients started follow-up at the Meirav Center high-risk clinic only after completing their oncological treatment. There were no data available on the rate of adherence to the population recommended screening (in Israel starting at age 50 in general population, and recommended from age 40 for women with first-degree relatives with BC) among latent carriers.

Data were reviewed from January 2007 to May 2019. For latent mutation carriers in whom BC was diagnosed prior to 2007 (19%), the date of first diagnosis was referred as the start of follow-up period. The main variables evaluated were tumor characteristics, age and stage at diagnosis, and therapeutic approaches.

Relevant demographic and clinical features were compared between known and latent carriers or between *BRCA1*-and *BRCA2*-mutation carriers by using the student t-test and the chi-square test, as appropriate. Analyses were conducted using SPSS version 25 (SPSS, Inc).

The study was approved by the ethics committee of the Chaim Sheba Medical Center, and given its retrospective nature and lack of direct patient contact, was exempt from obtaining patients written informed consent. Notably, all patients consented for the initial *BRCA* testing and data acquisition as part of the Oncogenetics counseling process.

Results

Overall, relevant clinical information was available for 298 *BRCA1/2* associated BC cases. Median follow-up time from BC diagnosis was 77.4 months (range, 3.5–520). All known carriers were diagnosed with BC after January 2007. Among latent carriers, 163/202 (81%) were diagnosed after January 2007.

Clinical characteristics - Known carriers included 96 women (median age at diagnosis 44.7 years [range 27.8–80.3 years]), 71 (74%) were *BRCA1* mutation carriers, 23 (24%) *BRCA2* mutation carriers, and two (2.1%) carried mutations in both genes. Latent carriers included 202 women (median age at diagnosis 43.7 years (range 23.8–75 years), $p = 0.8284$. Of latent carriers 118 (58%) were *BRCA1* mutation carriers and 84 (42%) harbored a *BRCA2* mutation. Additional relevant clinical data are summarized in Table 1.

Tumor features - Of known carriers, 19/96 (19.8%) were diagnosed with ductal carcinoma in situ (DCIS) vs. 10/202 (5%) in the group of latent carriers ($p = 0.0001$). Stage T1N0 disease was diagnosed in 54/96 (56.3%) of known carriers vs. 57/202 (28.2%) of latent carriers ($p < 0.00001$). Node-positive disease was diagnosed in 11/96 (11.5%) of known carriers vs. 98/202 (48.5%) of latent carriers ($p < 0.00001$). Metastatic disease was diagnosed at presentation in none of the known carriers vs. 4/202 (2%) of latent carriers ($p = 0.1637$). Tumor characteristics in each group and separately for *BRCA1* and *BRCA2* mutation carriers are summarized in Table 2.

Therapeutic decisions- The treatment regimens for all participants are summarized in Table 3. Chemotherapy was recommended for 49/96 (51%) of the known carriers (including all BC stages), 46 of them (47.9%) received either neoadjuvant ($n = 12$) or adjuvant ($n = 34$) chemotherapy (74% of them for triple-negative disease). Three additional patients refused for the recommended chemotherapy, two of them with triple-negative T1bN0 disease and one with triple-negative T1cN0 disease. Among the 46 patients receiving chemotherapy, 38 (83%) were *BRCA1* mutation carriers, and 8 (17%) were *BRCA2* mutation carriers. Among the 73 known *BRCA1* mutation carriers, 38 (52%) received chemotherapy compared with 8/23 (35%) of the known *BRCA2* mutation carriers. Patients with invasive disease for whom chemotherapy was not recommended ($n = 28$) had triple-negative T1aN0 disease ($n = 8$) or low-risk stage I ER-positive disease ($n = 20$). Six of the 28 patients with invasive ER-positive/Her2-negative disease in this group had OncotypeDx testing - 3 of them had recurrence scores (RS) between 18 and 20, one had $RS = 26$ (was not recommended chemotherapy in 2014), two had high RS (35, 42) and received chemotherapy. Radiotherapy was given to 41/96 (42.7%) of known carriers, 30 (73%) following lumpectomy without nodal involvement, 2 (5%) post-lumpectomy with regional nodal irradiation, and additional 9 (22%) had postmastectomy irradiation due to nodal involvement ($n = 8$) or T3N0 disease ($n = 1$).

Of latent carriers, 162/202 (80.2%) received either neoadjuvant ($n = 74$) or adjuvant ($n = 88$) chemotherapy ($p < 0.00001$), 59.3% of them for triple-negative disease, 61% of them with *BRCA1* mutation. Twelve of the 75 patients with invasive ER-positive/Her2-negative disease in this group underwent OncotypeDx testing - 9 of them had RS between 9 and 24, additional 3 patients had high RS (32, 35, 41) and received chemotherapy. Radiotherapy was delivered to 168/202 (83.2%) of latent carriers, 65 (38.7%) of them following lumpectomy without nodal involvement, 59 (35.1%) of them post-lumpectomy with regional nodal irradiation, and additional 44 (26.2%) had postmastectomy irradiation due to nodal involvement

Table 1
Clinical data of known vs latent *BRCA1/2* mutation carriers.

	All	Known carriers	Latent carriers	P-value
Number of pts	297	96	202	
Median follow-up, months (range)		47.9 (3.7–141)	81.3 (3–491)	
Median age at diagnosis, months (range)		44.7 (27.8–80.3)	43.7 (23.8–75)	0.828
BRCA1 carriers age at diagnosis, mean (SD) [a]		43.6 (11.24)	44.0 (11.1)	0.81
BRCA2 carriers age at diagnosis, mean (SD)		49.8 (13.85)	47 (9.46)	0.26
Mutation in, No. (%)				
BRCA1		**71 (74)**	**118 (58)**	0.0076
185delAG		39 (55)	69 (58.5)	
5382insC		12 (17)	21 (17.8)	
Other		4 (5.6)	14 (11.9)	
Not specified		16 (22.5)	14 (11.9)	
BRCA2		**23 (24)**	**84 (42)**	0.0026
6174delT		18 (78)	66 (78.6)	
8765delAG		2 (9)	4 (4.8)	
Other		0	12 (14.3)	
Not specified		3 (13)	2 (2.3)	
Both		**2 (2)**	0	
Performed BSO, No. (%)		68 (71)	173 (85.6)	0.0028
(*% of them prior to BC diagnosis*)		*66.2*	*2*	
First diagnosed by, No. (%)				
MRI		56 (58.3)	5 (2.5)	<0.00001
Mammography		17 (17.7)	43 (21.3)	0. 4697
US		9 (9.4)	9 (4.5)	0.0986
Self-Palpation [b]		14 (14.6)	131 (64.9)	<0.00001
Unknown		0	14 (6.9)	0.0085
Diagnosed during pregnancy or postpartum, No. (%)		9 (9.4)	18 (8.9)	0.8884
Recurrent disease, No. (%)				
Ipsilateral recurrence		2 (2.1)	23 (11.4)	0.0069
Contralateral second primary		4 (4.2)	33 (16.3)	0.0031
Distant recurrence		3 (3.1)	20 (9.9)	0.0401
Non-BC after BC diagnosis		0[c]	8 (4)[d]	0.0473
Status at last follow-up, No. (%)				
Alive without disease		93 (95.8)	178 (88.1)	0.0338
Alive with disease		0	16[e] (7.9)	<0.00001
Deceased		3 (3.1)	8[f] (4)	0.7014

Abbreviations: BC, Breast cancer; BSO, bilateral salpingo-oophorectomy; NS, non-significant.
[a] Including 2 carriers of both *BRCA1* and *BRCA2* mutations.
[b] Interval tumors in the "known carriers" cohort/tumors first discovered by the patient and not by population screening in the "latent carriers" cohort.
[c] Seven women had cancer prior to BC diagnosis: Ovarian cancer (n = 3), Uterine cervix cancer (n = 1), Gastric cancer (n = 1), Colon cancer (n = 1), Parotid gland Merkel cell tumor (n = 1).
[d] Pancreatic cancer (n = 1), Non-Hodgkin Lymphoma (n = 1), Ovarian cancer (n = 1), Rectal cancer (n = 1), Bladder cancer (n = 1), Chronic myelogenous leukemia (n = 1), Thyroid cancer (n = 1), Endometrial cancer (n = 1). Additional patient had Ovarian cancer prior to BC (performed genetic testing only after BC diagnosis).
[e] Including one patient with Ovarian cancer on treatment.
[f] Including three patients with non-BC related deaths.

(n = 36) or T2-3N0 disease (n = 6) and additional two for T1N0 disease (unspecified reasons).

Risk reducing surgeries - BRRM was performed on 60/96 (62.5%) of the known carriers, 73% of them at the time of primary tumor resection and the rest – at a later stage. Among latent carriers, 82/202 (40.6%) underwent BRRM, 44% at the time of primary tumor resection ($p < 0.001$).

Recurrent disease – as shown in Table 1, despite early diagnosis and recommended oncological treatment, 3/96 (3.1%) of the known carriers had metastatic recurrence between 20 and 44 months of initial diagnosis and died of BC. All three were *BRCA1* mutation carriers and received adjuvant chemotherapy - one for T2N0 triple-negative tumor, one for T1cN0 ER-positive disease (with Oncotype Dx recurrence score of 38), and one for T2N1 ER-positive lobular carcinoma. Among latent carriers, 20 women (10%) had distant BC recurrence, of whom 15 (75%) remain alive with disease and 5 deceased.

Discussion

In the present study, in line with previously reported studies [12,14,15], diagnosis of early stage disease (DCIS or T1N0) was significantly more prevalent in the group of known *BRCA1/2* mutation carriers adhering to the recommended tight surveillance scheme that stresses the importance of bi-annual breast imaging – MRI alternating with mammography [2,10]. Therefore, our findings further support the previously suggested population screening for *BRCA1/2* mutations, at least for founder mutations, where these exist [16–18]. It should be noted that interval cancers were not infrequent (14.6%) among known carriers, 12/14 of them with *BRCA1* mutation. Biannual MRI screening has been recently suggested as more beneficial screening strategy, especially for *BRCA1* mutation carriers [23], but this is still not considered as standard of care. There are no data on the rate of adherence of any of the latent carriers to the population recommended BC screening (starting at age 50 in Israel). As has previously been reported [16,17], in nearly 50% of Jewish *BRCA* mutation carriers there is no family history suggestive of inherited predisposition. Thus, it seems likely that 50% of the latent carriers in our study who are under age 50 were not screened prior to being diagnosed with breast cancer. In addition, it seems plausible that if a significant proportion of "latent carriers" were enrolled in early detection programs (e.g. awareness programs) or tailored screening for higher-risk populations because of family history, a substantial proportion of screened tumors

Table 2
Tumor characteristics in known vs latent *BRCA1/2* mutation carriers.

	Known carriers N = 96			Latent carriers N = 202		
	BRCA1	*BRCA2*	P-value	*BRCA1*	*BRCA2*	P-value
Number of patients (%)	73 (**76**)[a]	23 (**24**)		117 (**58**)	85 (**42**)	
Stage at diagnosis						
DCIS, No. (**%**)	14/73 (**19.2**)[a]	5/23 (**21.7**)	NS	3/117 (**2.6**)	7/85 (**8.2**)	NS
T1N0, No. (**%**)	41/73 (**56.2**)	13/23 (**56.5**)	NS	34/117 (**29**)	23/85 (**27**)	NS
T1aN0	10/41 (24)	1/13 (7.7)	NS	1/34 (2.9)	1/23 (4.3)	NS
T1bN0	16/41 (39)	6/13 (46.15)	NS	3/34 (8.8)	2/23 (8.7)	NS
T1cN0	15/41 (37)	6/13 (46.15)	NS	21/34 (61.8)	15/23 (65)	NS
T1(unknown)N0	0	0		9/34 (26.5)	5/23 (22)	NS
T2-3N0, No. (%)	11/73 (**15**)	1/23 (**4.3**)	NS	19/117 (**16.3**)	13/117 (**11**)	
Node-positive disease, No. (**%**)	7/73 (**9.6**)	4/23 (**17.4**)	NS	60/117 (**51.3**)	38/85 (**44.7**)	NS
Bilateral disease, No. (%)	4/73 (**5.5**)[c]	0		3/117 (**2.6**)	2/85 (**2.4**)[d]	NS
Metastatic at presentation, No. (%)	0	0		0	4	NS
Invasive disease cases [b]	**60**[c]	18		**119**[d]	**77**	
Triple-negative, No. (**%**)	42/60 (**70**)	3/18 (**17**)	0.0002	84/119 (**70.6**)	19/77 (**25**)	0.0001
ER-positive Her2-negative, No. (**%**)	14/60 (**23**)	14/18 (**78**)	0.0001	27/119 (**22.7**)	48/77 (**62**)	0.0001
Her2-positive, No. (**%**)	4/60 (**7**)	1/18 (**5**)	NS	8/119 (**6.7**)	10/77 (**13**)	NS

Abbreviations: DCIS, ductal carcinoma in situ; NS, non-significant.
[a] Including 2 carriers of both *BRCA1* and *BRCA2* mutations.
[b] Excluding DCIS.
[c] Four of 59 patients with invasive carcinomas had bilateral disease - 3 of them with both triple-negative tumors (calculated as single case) and 1 had triple-negative and ER-positive tumors (calculated as an additional case).
[d] Five of 115 patients with invasive carcinomas had bilateral disease – 1 of them with both triple-negative tumors (calculated as single case), 3 of them with triple-negative and Her2-positive tumors and 1 had triple-negative and ER-positive tumors (each of these patients calculated as two cases). One additional patient had bilateral DCIS.

Table 3
Treatments delivered in known vs latent *BRCA1/2* mutation carriers.

	Known carriers N = 96			Latent carriers N = 202		
	BRCA1	*BRCA2*	P-value	*BRCA1*	*BRCA2*	P-value
Number of patients (%)	73 (**76**)[a]	23 (**24**)		118 (**58**)	84 (**42**)	
Chemotherapy, No. (**%**)	**46 (48)**	**162 (80)**	<0.00001			
Overall	38/73 (**52**)	8/23 (**35**)	0.2276	99/118 (**84**)	63/84 (**75**)	0.166
Adjuvant	29/38 (76)	5/8 (63)		52/99 (52.5)	36/63 (57)	
Neoadjuvant	9/38 (24)	3/8 (37)		47/99 (47.5)	27/63 (43)	
Refused recommended treatment [b]	3	0		2	0	
Chemotherapy by tumor types						
Triple-negative disease	31/38 (**81.6**)	3/8 (**37.5**)	0.0325	78/99 (**79**)	19/63 (**30**)	0.0057
ER-positive Her2-negative	3/38 (**7.9**)	4/8 (**50**)	0.0134	13/99 (**13**)	34/63 (**54**)	0.0001
Her2-positive	4/38 (**10.5**)	1/8 (**12.5**)	0.8705	8/99 (**8**)	10/63 (**16**)	0.1998
Surgery, No. (%)						
Lumpectomy only	21/73 (28.2)	13/23 (56.5)	0.0295	50/118 (42.4)	46/84 (54.8)	0.1167
Unilateral Mastectomy	1/73 (1.4)	1/23 (4.3)	0.9722	10/118 (8.5)	10/84 (11.9)	0.5717
Synchronous bilateral mastectomy as primary surgery	36/73 (49.3)	8/23 (34.8)	0.3272	26/118 (22)	10/84 (11.9)	0.0954
Metachronous bilateral mastectomy following lumpectomy	15/73 (20.5)	1/23 (4.3)	0.1344	32/118 (27.1)	14/84 (16.7)	0.1151
No surgery					4[c]	
Radiotherapy, No. (**%**)	**41 (42.7)**	**168 (83.2)**	<0.00001			
Overall	27/73 (**37**)	14/23 (**61**)		96/118 (**81.4**)	73/84 (**87**)	
Post-lumpectomy, node-negative disease	20/27 (74)	10/14 (71)	0.8561	34/96 (35)	31/71 (44)	0.3576
Post-lumpectomy with regional nodal radiation	1/27 (4)	1/14 (7)	0.6278	36/96 (37.5)	23/71 (32)	0.604
Postmastectomy radiation	6/27 (22)	3/14 (21)	0.9536	27/96 (28)	17/71 (24)	0.66811

Abbreviations: DCIS, ductal carcinoma in situ.
[a] Including 2 carriers of both *BRCA1* and *BRCA2* mutations.
[b] All patients had triple-negative disease, two of them with stage T1bN0 and one with stage T1cN0.
[c] Metastatic at presentation.

would have been diagnosed by imaging rather than by self-palpation. As shown in Table 1, almost 2/3 of the cancers in the latent carrier group were first discovered by self-palpation and not by screening. Taken together these considerations make a selection bias less likely.

Despite early stage BC diagnosis, almost 50%, of known carriers were treated with chemotherapy, with higher proportion of *BRCA1* mutation carriers, mostly because of higher prevalence of triple-negative tumors. In addition, 3% of those patients died of recurrent disease despite early stage BC diagnosis. These findings raise two important, clinically relevant questions. First, is there over-treatment of stage I triple-negative disease? Most international guidelines recommend “considering” adjuvant chemotherapy for triple-negative breast cancer (TNBC) at stage T1bN0 up to age 70

years, and recommend giving adjuvant chemotherapy for T1cN0 disease and lymph node positive disease [24–26]. Unfortunately, at present there are no validated tools to predict which patients who fit these criteria can be adequately and successfully treated without chemotherapy. Previous studies suggested that TNBC can be molecularly dissected to different subtypes, each showing a distinct biological behavior [27]. However, these tools have not attained widespread clinical use or have been prospectively validated as predictive tools to resolve this therapeutic dilemma. Although a 70-gene assay (MammaPrint™) was validated in a small cohort of TNBC to predict risk of distant recurrence [28], this assay is not recommended for routine treatment decisions in TNBC [29].

The second clinically relevant issue raised is to what extent this information could impact the specific healthy *BRCA1/2* mutation carrier's decision on risk-reducing surgeries. Discussion with a *BRCA1/2* mutation carrier regarding surveillance and risk-reducing options depends on the specific clinical scenario and age of the mutation carrier. For a healthy 30-year-old *BRCA1* carrier, BRRM is an attractive option for active BC risk reduction. While the data regarding survival benefit of BRRM over intensive surveillance have been conflicting so far, recent analysis of the Dutch large multi-center cohort study showed that BRRM was associated with lower mortality then surveillance during a mean follow-up of 10.3 years, mostly for *BRCA1* mutation carriers [9]. In that study the data presented (but not discussed) show that 62% of the *BRCA1* mutation carriers and 39% of the *BRCA2* mutation carriers in the Dutch series were treated with chemotherapy, in line with the data presented herein. Chéreau et al. also reported high proportion of aggressive tumors requiring adjuvant chemotherapy in a small cohort (21 patients) of "known" mutation carriers undergoing intensive screening [20]. However, 67% of carriers in that study were previously diagnosed with BC, unlike the present study, where all known carriers were newly diagnosed with BC in the course of adhering to the recommended follow-up scheme.

Currently, there is a limited ability to better define specific personal BC risk and the variable penetrance rates affected by factors such as mutation location, ethnicity, specific family history, modifier genes, environmental exposures and life style habits [30]. Counseling for BRRM is very complex and delicate: it usually involves discussion of extent of cancer risk reduction/protection, risks associated with surgeries, and breast reconstructive options. It is also important to address the psychological and quality-of-life aspects of BRRM [31]. It is plausible that BRRM decision making can sometimes be driven primarily by the desire to avoid cancer diagnosis and treatment even more than by any survival advantage [32]. Therefore, it is crucial for asymptomatic mutation carriers, especially those harboring *BRCA1* mutations, to understand and be aware of the high rates of chemotherapy used even when early stage BC detection is indeed attained.

There are several inherent limitations to this study. This is a single institution study, with a limited number of participants and a very well-defined, narrow spectrum of *BRCA1/2* mutations. There also could be a selection bias in the known carriers' cohort, who could possibly become aware of their mutation status because of significant family history, and therefore were more motivated to follow the recommended surveillance scheme. There were also differences in the distribution of *BRCA1* vs *BRCA2* mutations in known compared with latent mutation carriers.

To the best of our knowledge, this is one of a few studies to assess the treatment approaches in an admittedly relatively small cohort of known *BRCA1/2* mutation carriers diagnosed with early stage BC who adhered to the recommended surveillance scheme. Obviously, more studies with larger numbers of mutation carriers of diverse ethnicities and longer follow up are needed to validate the data presented herein. If validated, the possibility of being treated with chemotherapy or radiotherapy should be discussed with every *BRCA1/2* carrier, especially *BRCA1* mutation carriers, since this may be an additional factor to influence a woman's decision to undergo BRRM.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

All authors declare that they have no conflict of interest.

Acknowledgments

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The authors did not have any writing assistance.

References

[1] King M-C, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in *BRCA1* and *BRCA2*. Science 2003;302:643–6. https://doi.org/10.1126/science.1088759.

[2] NCCN guidelines for detection, prevention, & risk reduction. Available from: https://www.nccn.org/professionals/physician_gls/#detection.

[3] Evans DGR, Baildam AD, Anderson E, Brain A, Shenton A, Vasen HFA, et al. Risk reducing mastectomy: outcomes in 10 European centres. J Med Genet 2009;46:254–8. https://doi.org/10.1136/jmg.2008.062232.

[4] Rebbeck TR, Friebel T, Lynch HT, Neuhausen SL, van 't Veer L, Garber JE, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE study group. J Clin Oncol 2004;22:1055–62. https://doi.org/10.1200/JCO.2004.04.188.

[5] Evans DGR, Lalloo F, Ashcroft L, Shenton A, Clancy T, Baildam AD, et al. Uptake of risk-reducing surgery in unaffected women at high risk of breast and ovarian cancer is risk, age, and time dependent. Canc Epidemiol Prev Biomark 2009;18:2318–24. https://doi.org/10.1158/1055-9965.EPI-09-0171.

[6] Metcalfe KA, Birenbaum-Carmeli D, Lubinski J, Gronwald J, Lynch H, Moller P, et al. International variation in rates of uptake of preventive options in BRCA1 and BRCA2 mutation carriers. Int J Cancer 2017;122:22. https://doi.org/10.1002/ijc.23340. n.d.

[7] Skytte A-B, Gerdes A-M, Andersen MK, Sunde L, Brøndum-Nielsen K, Waldstrøm M, et al. Risk-reducing mastectomy and salpingo-oophorectomy in unaffected BRCA mutation carriers: uptake and timing. Clin Genet 2010;77:342–9. https://doi.org/10.1111/j.1399-0004.2009.01329.x.

[8] Laitman Y, Vaisman Y, Feldman D, Helpman L, Gitly M, Shimon SP, et al. Rates of risk-reducing surgery in Israeli BRCA1 and BRCA2 mutation carriers. Clin Genet 2014;85:68–71. https://doi.org/10.1111/cge.12149.

[9] Heemskerk-Gerritsen BAM, Jager A, Koppert LB, Obdeijn AI-M, Collée M, Meijers-Heijboer HEJ, et al. Survival after bilateral risk-reducing mastectomy in healthy BRCA1 and BRCA2 mutation carriers. Breast Canc Res Treat 2019;177:723–33. https://doi.org/10.1007/s10549-019-05345-2.

[10] Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, et al. American cancer society guidelines for breast screening with MRI as an adjunct to mammography. CA A Cancer J Clin 2007;57:75–89. https://doi.org/10.3322/canjclin.57.2.75.

[11] Stoutjesdijk MJ, Boetes C, Jager GJ, Beex L, Bult P, Hendriks JHCL, et al. Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer. JNCI J Natl Cancer Inst 2001;93:1095–102. https://doi.org/10.1093/jnci/93.14.1095.

[12] Kriege M, Brekelmans CTM, Boetes C, Besnard PE, Zonderland HM, Obdeijn IM, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 2004;351:427–37. https://doi.org/10.1056/NEJMoa031759.

[13] Kuhl CK, Schrading S, Leutner CC, Morakkabati-Spitz N, Wardelmann E, Fimmers R, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol 2005;23:8469–76. https://doi.org/10.1200/JCO.2004.00.4960.

[14] Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans DG, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). The Lancet 2005;365:1769–78. https://doi.org/10.1016/S0140-6736(05)66481-1.

[15] Warner E, Hill K, Causer P, Plewes D, Jong R, Yaffe M, et al. Prospective study of

breast cancer incidence in women with a BRCA1 or BRCA2 mutation under surveillance with and without magnetic resonance imaging. J Clin Oncol 2011;29:1664–9. https://doi.org/10.1200/JCO.2009.27.0835.
[16] Metcalfe KA, Poll A, Royer R, Llacuachaqui M, Tulman A, Sun P, et al. Screening for founder mutations in BRCA1 and BRCA2 in unselected jewish women. J Clin Oncol 2009;28:387–91. https://doi.org/10.1200/JCO.2009.25.0712.
[17] Gabai-Kapara E, Lahad A, Kaufman B, Friedman E, Segev S, Renbaum P, et al. Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. Proc Natl Acad Sci 2014;111:14205–10. https://doi.org/10.1073/pnas.1415979111.
[18] Manchanda R, Loggenberg K, Sanderson S, Burnell M, Wardle J, Gessler S, et al. Population testing for cancer predisposing BRCA1/BRCA2 mutations in the ashkenazi-jewish community: a randomized controlled trial. JNCI J Natl Cancer Inst 2015;107. https://doi.org/10.1093/jnci/dju379.
[19] Patel S, Legood R, Evans DG, Turnbull C, Antoniou AC, Menon U, et al. Cost effectiveness of population based BRCA1 founder mutation testing in Sephardi Jewish women. Am J Obstet Gynecol 2018;218:431. https://doi.org/10.1016/j.ajog.2017.12.221. e1-431.e12.
[20] Chéreau E, Uzan C, Balleyguier C, Chevalier J, de Paillerets BB, Caron O, et al. Characteristics, treatment, and outcome of breast cancers diagnosed in BRCA1 and BRCA2 gene mutation carriers in intensive screening programs including magnetic resonance imaging. Clin Breast Canc 2010;10:113–8. https://doi.org/10.3816/CBC.2010.n.022.
[21] Warner E, Foulkes W, Goodwin P, Meschino W, Blondal J, Paterson C, et al. Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. J Natl Cancer Inst 1999;91:1241–7.
[23] Guindalini RSC, Zheng Y, Abe H, Whitaker K, Yoshimatsu TF, Walsh T, et al. Intensive surveillance with biannual dynamic contrast-enhanced magnetic resonance imaging downstages breast cancer in BRCA1 mutation carriers. Clin Cancer Res 2019;25:1786–94. https://doi.org/10.1158/1078-0432.
[24] NCCN Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf (accessed October 13, 2017).
[25] Curigliano G, Burstein HJ, Winer EP, Gnant M, Dubsky P, Loibl S, et al. De-escalating and escalating treatments for early-stage breast cancer: the st. Gallen international expert consensus conference on the primary therapy of early breast cancer 2017. Ann Oncol 2017;28:1700–12. https://doi.org/10.1093/annonc/mdx308.
[26] Untch M, Thomssen C, Bauerfeind I, Braun M, Brucker SY, Felberbaum R, et al. Primary therapy of early breast cancer: evidence, controversies, consensus. Geburtshilfe Frauenheilkd 2019;79:591–604. https://doi.org/10.1055/a-0897-6457.
[27] Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Investig 2011;121:2750–67. https://doi.org/10.1172/JCI45014.
[28] Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, et al. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 2016;375:717–29. https://doi.org/10.1056/NEJMoa1602253.
[29] Krop I, Ismaila N, Andre F, Bast RC, Barlow W, Collyar DE, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American society of clinical Oncology clinical practice guideline focused update. J Clin Oncol Off J Am Soc Clin Oncol 2017;35:2838–47. https://doi.org/10.1200/JCO.2017.74.0472.
[30] Milne RL, Antoniou AC. Modifiers of breast and ovarian cancer risks for BRCA1 and BRCA2 mutation carriers. Endocr Relat Cancer 2016;23:T69–84. https://doi.org/10.1530/ERC-16-0277.
[31] Hartmann LC, Lindor NM. The role of risk-reducing surgery in hereditary breast and ovarian cancer. N Engl J Med 2016;374:454–68. https://doi.org/10.1056/NEJMra1503523.
[32] Hoskins LM, Greene MH. Anticipatory loss and early mastectomy for young female BRCA1/2 mutation carriers. Qual Health Res 2012;22:1633–46. https://doi.org/10.1177/1049732312458182.