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REVIEW

Prognosis of *BRCA*-associated breast cancer: a summary of evidence

L. Bordeleau · S. Panchal · P. Goodwin

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Abstract The purpose of the study is to review the clinical studies relevant to the prognosis and prognostic associations of *BRCA1*- and *BRCA2*-associated breast cancers. Reports of relevant studies obtained from a MEDLINE search and references from these articles were critically reviewed. A number of methodologic limitations have been identified in the early studies. More recent studies have failed to demonstrate, for the most part, a significant overall survival difference between *BRCA*-associated breast cancers and sporadic breast cancers. The risk of in-breast tumor recurrence also appears to be similar in the first 5 years following a breast cancer diagnosis with apparent increase in the risk after 5 years in one study. Many in-breast tumor recurrences are now considered to be second primary breast cancers. There is a significant increase in the risk of contralateral breast cancers in *BRCA* mutation carriers with an estimated 10-year risk ranging from 20–40%. The prognosis of *BRCA*-associated breast cancers appears to be similar to that of sporadic breast cancers based on the current literature. Future data from large prospective cohort studies will be of interest.

L. Bordeleau (✉)
Juravinski Cancer Centre, Department of Oncology, McMaster University, Hamilton, ON, Canada
e-mail: Louise.Bordeleau@jcc.hhsc.ca

S. Panchal
Department of Nursing Oncology, Mount Sinai Hospital, Toronto, ON, Canada

P. Goodwin
Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada

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Introduction

BRCA1 and *BRCA2* mutations account for the majority of hereditary breast and ovarian cancer. Individuals with mutations in these two genes are at an increased risk to develop breast, ovarian, and other cancers. The risk estimates for developing breast cancer (BC) range from 50 to 80% [1], and the age at BC diagnosis is much younger (typically premenopausal) compared to sporadic cases. Since the identification of the *BRCA* genes, there has been a significant interest in the characterization of *BRCA*-associated BCs and its comparison to sporadic BCs. *BRCA1*-associated cancers have distinctive histopathologic features compared to sporadic BCs. They are usually high-grade, poorly differentiated, infiltrating ductal carcinomas, and stain negative for ER, PR, and HER2/neu; they also frequently stain for the presence of basal cytokeratins 5 and 6, overexpress cyclin E and p53, and underexpress p27 [2]. Medullary carcinomas have also been observed more frequently in *BRCA1* mutation carriers, a phenotype characterized by an abundant lymphocytic infiltrate and a smooth margin [3]. *BRCA2*-associated BCs seem to share similar pathologic characteristics with non-carriers although they are more frequently of high grade [4]. All types of hereditary BCs have a low frequency of HER2/neu protein overexpression. Studies using microarray technology have shown that gene expression profiles of *BRCA1*, *BRCA2*, and sporadic BCs differed significantly from each other [5–7]. Tumors from *BRCA1* mutation carriers have been found to be frequently of the basal subtype, whereas *BRCA2* tumors fall mainly within the luminal category.

In addition to the above noted differences in the phenotype and genotype of *BRCA*-associated BCs, numerous studies have been conducted to specifically address the prognosis of *BRCA*-associated BCs. The data acquired from these studies span approximately 20 years, and study designs and populations vary greatly. The purpose of this systematic review is to summarize the literature relating to the prognosis of *BRCA*-associated BCs.

Search strategy and selection criteria

Data for this review were identified by searches of MEDLINE and references from relevant articles using the search terms "*BRCA*", "breast cancer", and "prognosis". Clinical studies relevant to the prognosis of BC in carriers of *BRCA1* or *BRCA2* mutations and published in English-language medical journals were reviewed. The full text of all relevant articles was reviewed, with a particular emphasis on the methodologic aspects of clinical studies. Abstracts were excluded from the review.

Early prognostic studies (prior to 1997)

Prior to the identification of the *BRCA* genes in the early 1980s, it was noted in a registry of cancer prone families that the 5-year survival of patients with "hereditary" BC was better than that observed in the large American College of Surgeons (ACS) series of BC patients (67 vs. 42.2% respectively, $P < 0.05$). Both series had similar stage of disease at presentation; however, patients from cancer prone families had an earlier onset of the disease and had an excess of bilaterality [8]. In the early 1990s, linkage analysis data located the BC gene *BRCA1* to chromosome 17q12-21 [9–11]. Using linkage analysis, Porter al al. reported on the prognosis of *BRCA1*-associated BC when compared to population-based cancer registry in Scotland. The expected 5-year survival rate was 83% in *BRCA1* carriers and 61.1% in an age-matched group ($P < 0.05$) [12].

In view of these findings, Porter et al. published a more comprehensive report looking specifically at penetrance and survival in probable carriers of *BRCA1* gene mutation [13]. Eight BC pedigrees with a high probability of harboring individuals with the *BRCA1* gene mutation were identified through linkage analysis. Sixty-one women were classified as probable *BRCA1* carriers, 35 of whom were diagnosed with BC (13 with bilateral disease). Lifetime penetrance was estimated at 88%. The 5-year survival rate was significantly higher in *BRCA1* carriers than that in an age-matched Scottish population ($P < 0.05$). At approximately the same time, a second major BC susceptibility gene, *BRCA2*, was mapped to the q12-13 region of chromosome 13 [14].

Studies were undertaken by Marcus and colleagues to compare the pathobiologic differences between *BRCA1*- and *BRCA2*-mutation-associated BC (hereditary BC, or HBC) and non-hereditary BC (non-HBC) [15]. Based on linkage analysis and/or family history, 26 families (90 BC cases) were classified as "*BRCA1* related", and 26 families (85 cases) were classified as "other" (most of which were assumed to carry a *BRCA2* mutation). These 52 families (175 cases) were classified as HBC families. Cases were compared with 187 predominantly non-HBC cases. HBC cases presented at lower stage ($P = 0.003$) and earlier age than non-HBC ($P < 0.0001$). *BRCA1*-mutation-associated BC often had distinguishing features such as higher proliferation rates and more frequent aneuploidy when compared to non-HBC cases. There was a non-significant trend toward better crude survival in both HBC groups. In keeping with previous observations, patients with *BRCA1*-associated BC had fewer recurrences ($P = 0.013$) and a trend toward lower specific death rates despite identification of adverse prognostic features.

These reports raised the possibility that patients with hereditary BC may have a different prognosis and even differential host response to BC treatment; however, methodologic limitations have been noted at a very basic level. The use of family history only as a surrogate for genetic testing in these studies could lead to overestimation of the likelihood of a mutation. In addition, the family history can be difficult to properly ascertain and verify, and the definition of high risk is variable. Furthermore, the use of linkage analysis to identify hereditary families required living affected cases potentially biasing survival estimates to longer duration in these families. Many of the next generation of studies addressed these limitations by performing mutation analysis as detailed in the following section.

Next generation prognostic studies (1998–2002)

In the next generation of studies, the prognosis of *BRCA*-associated BC was investigated in studies done in multiple countries using institution-based case identification and direct testing for mutations in the *BRCA*1 and/or *BRCA*2 genes in affected individuals. Some studies have focused on founder mutations in patients with specific ethnic background (mainly Ashkenazi Jewish ancestry). These studies have been summarized in Table 1.

Johannsson et al. described survival rates among patients with breast and ovarian cancer in 21 families from southern Sweden with germ-line *BRCA1* mutations and compared overall survival with that of a population-based group consisting of all breast and ovarian cancer patients diagnosed in Sweden between 1958 and 1995. They also identified a subgroup that was age and stage-matched. They

Table 1 Prognosis in *BRCA1*- or *BRCA2*-associated breast carcinomas

Author	Methodologic aspects of study										
	Gene	Number of patients		Control mutation status known	Matching or adjustment parameters	Complete follow-up	Overall survival		Adjusted or multivariate		Ethnicity-country
		Cases	Controls				Cases (%)	Controls (%)	*P*	*P*	
Johannsson [16]	*BRCA1*	40	27,220	No	Age, calendar year diagnosis	Yes	60	60	.29	–	Sweden
	BRCA2	40	112	No	Age, stage	Yes	60	80	.37	–	
Ansquer[a] [18]	*BRCA1*	15	108	Yes	–	[b]	70	90	<.04	–	France
Gaffney [19]	*BRCA1*	30	8,409	No	Age, diagnosis date, tumor size	Yes	75	70	NS		Utah, United States
	BRCA2	20	8,409	No	Age, diagnosis date, tumor size	Yes	73	70	NS		
Pierce [20]	*BRCA1* & *BRCA2*	71	213	No	Age, diagnosis date	Yes	86	91	0.7		United States & Canada
Verhoog [21]	*BRCA1*	49	196	No	Age, diagnosis date	[b]	63	69	0.88	NS	The Netherlands
Verhoog[c] [22]	*BRCA2*	28	112	No	Age, diagnosis date, tumor size	Yes	73	70	NS	NS	The Netherlands
Loman [23]	*BRCA2*	54	214	No	Diagnosis date, stage	?	73	82	0.059[d]	NS	Sweden & Denmark
Eerola [24]	*BRCA1*	32	59,517[e]	Yes	–	Yes	67	78	>0.05		Finland
	BRCA2	43	284[e]	No	–	Yes	77	78	>0.05		
Goode [25]	*BRCA1*	10	1341	Yes	Age, grade, tumor type	?	Worse	Better	0.047	HR-1.99	United Kingdom
	BRCA2	19	1341	Yes	Age, grade, tumor type	?			0.47	NS	
Robson[f][26]	*BRCA1* & *BRCA2*	30	61	Yes	[g]	[b]	NR	NR	NS		Ashkenazi Jewish/USA
Robson [27]	*BRCA1* & *BRCA2*	28	277	Yes	Age, tumor and nodal stage	[b]	Worse (71.9)	Better (87.2)	0.02	NS	Ashkenazi Jewish/USA
Chappuis [28]	*BRCA1* & *BRCA2*	32	170	Yes	–	Yes	58	82	0.003 [h]		Ashkenazi Jewish/ Canada
Lee [29]	*BRCA1*	35	979	[i]	–	[b]	79	78	NS		Ashkenazi Jewish/USA
	BRCA2	23	979	[i]	–		65	78	NS		
Foulkes [31]	*BRCA1*	16	100	Yes	Age, tumor size, ER, nuclear grade, p53	No	50	90	0.0001	0.01	Ashkenazi Jewish/ Canada
Stoppa-Lyonnet [32]	*BRCA1*	40	142	No[j]	Age, tumor size, nodal stage, ER, PgR, tumor grade	?	80	91	0.002	0.05	France
Moller [33]	*BRCA1*	36	205	Yes	Stage, grade, ER	Yes	63	91	0.04	NS	Norway, Scotland, England and Holland

Table 1 continued

Author	Methodologic aspects of study										
	Gene	Number of patients		Control mutation status known	Matching or adjustment parameters	Complete follow-up	Overall survival		Adjusted or multivariate		Ethnicity-country
		Cases	Controls				Cases (%)	Controls (%)	*P*	*P*	
Hamann [34]	*BRCA1*	36	49[k]	Yes	Age	?	84	87	0.37	NS	Germany

BC, breast cancer; *FHx*, family history; *NR*, not reported; *NS*, not significant

[a] Study included only women with breast cancer diagnosis before age 36

[b] Only cases with complete follow-up data were included in the study; total number of eligible cases without complete follow-up specified

[c] About 17 of 45 cases excluded because of lack of histologic confirmation of breast cancer or lack of consent

[d] Significant difference in breast cancer-specific survival, $P = 0.0033$

[e] About 59,517 population controls, 284 familial controls negative for *BRCA1* or *BRCA2* mutations

[f] Of all eligible cases, 24% identified were not included in the analysis for survival because of inadequate follow-up data

[g] Study included only Ashkenazi Jewish women with breast cancer diagnosis before age 42 years

[h] Significant difference in disease-free survival also reported

[i] In this study, cases and controls were first-degree relatives of Ashkenazi Jewish volunteers who underwent mutation testing for *BRCA1* and *BRCA2*. The mutation status of cases and controls was assumed

[j] No *BRCA1* mutation, *BRCA2* status unknown

[k] Breast cancer patients from families without a *BRCA1* mutation, still considered hereditary cancer

concluded that survival for carriers of a *BRCA1* mutation may be similar to, or possibly worse than, that for breast and ovarian cancer in general (P = NS) [16]. The results were questioned in view of the small sample size, the potential for preferential inclusion of four founder mutations identified in this geographic location, and impact of ovarian cancer diagnosis (following a breast cancer diagnosis) on the survival analysis and outcome [17].

Ansquer et al. identified a series of 123 women diagnosed with BC at a very young age (<36 years) at the Institut Curie, Paris, between 1990 and1995 [18]. Mutation testing was undertaken in all cases, and likely deleterious *BRCA1* mutations were identified in 15 individuals. Mean age at diagnosis, tumor size, and axillary lymph node status were similar between the *BRCA1* and non-*BRCA1* groups, though *BRCA1*-associated BCs were more likely to be grade III ($P < 0.05$) and hormone receptors negative ($P < 0.05$). The OS was worse among the *BRCA1* mutation carriers ($P < 0.04$) and felt to be related to the adverse prognostic features observed. The DFS was similar between groups ($P = 0.19$). Some of the limitations of this study include small sample size and limiting of the mutation analysis to *BRCA1*, which could lead to a dilution effect by assigning *BRCA2* to the control group.

Prognosis and response to radiotherapy in BC patients with *BRCA1/2* mutations were summarized in a retrospective study conducted in Utah [19]. Patients from 12 different pedigrees were cross-referenced with the Utah Cancer Registry. Patients were matched for age, date of diagnosis, and tumor size, and actuarial survival calculations were performed. Despite younger age at presentation, BCs in *BRCA1* and *BRCA2* mutation carriers were found to have similar survival at 5 and 10 years when compared with sporadic BC patients. Pierce and colleagues also published on the effect of radiotherapy after breast-conserving therapy in women with *BRCA*-associated BC in the United States and Canada; similar findings were observed at 5 years [20].

Similar findings were observed in studies conducted in the Netherlands, Sweden, Denmark, Finland, and the United Kingdom [21–25]. In the first report by Verhoog et al., 5-year DFS and OS for 49 Dutch patients from 19 consecutive families with a proven-specific *BRCA1* mutation and one family with strong evidence for linkage to the *BRCA1* gene were similar to DFS and OS in 196 sporadic BC patients matched for age and year of diagnosis; results were unchanged when adjusted for known prognostic factors including tumor size, nodal status, estrogen/progesterone receptor status, and contralateral BC. In a second report by Verhoog et al., DFS and OS of 28 BC patients from 14 consecutive Dutch families with *BRCA2* germ-line mutations were similar to outcomes in 112 sporadic BC patients matched for age and year of diagnosis. Adjustments for a number of prognostic factors including tumor size, nodal status, hormone receptor status, and contralateral BC did not alter the results. *BRCA2*-associated BCs were noted to be more frequently hormone receptor positive, especially progesterone receptor positive. Loman et. al assessed the prognosis and clinical presentation of *BRCA2*-associated BC in 22 families from Sweden and Denmark with *BRCA2* germ-line mutations in comparison with 214 age- and date of diagnosis-matched controls identified among BC patients from South Sweden. More *BRCA2* carriers had node-positive disease and Stage IV disease at presentation ($P = 0.036$ and $P = 0.021$, respectively). A significant difference in BC-specific survival was observed among the *BRCA2*-associated cases; however, this difference was no longer present in multivariate analysis when adjusting for stage. Eerola et al. compared survival rates of 359 familial BC patients (32 patients from *BRCA1*-positive families; 43 patients from *BRCA2*-positive families; 284 patients from *BRCA1/2*-negative BC families) to outcomes in all other patients diagnosed in Finland from 1953 to 1995. There was no significant difference in the overall survival when adjusted for age, stage, and year of diagnosis though the risk of death tended to be higher in *BRCA1* families and lower in *BRCA2* families. The impact of germ-line mutation on survival among women with breast cancer participating in a British population-based study also failed to show a survival difference between *BRCA1/2* mutation carriers and non-carriers.

A number of studies have assessed prognosis of *BRCA*-associated BC in patients of Ashkenazi Jewish (AJ) descent harboring one of three founders mutations: *BRCA1* (185delAG, 5382insC) and *BRCA2* (6174delT). Three studies presented outcomes for both *BRCA1* and *BRCA2* combined [26–28]. In the first report, Robson and colleagues identified 91 AJ women with early onset BC (median age 36 years; range, 21–42). All women underwent genetic testing for the previously mentioned founder mutation, and 30 were found to be carriers. More adverse clinical and histopathologic features were observed in the carrier group; however, the prognosis appeared similar to that of non-carriers. In the second report by Robson et al., a different approach was undertaken. A retrospective review of women of AJ descent undergoing breast-conserving therapy for BC diagnosed during the period from 1980 to 1990 at the Memorial Sloan-Kettering Cancer Centre in the United States. Archival tissue samples were retrieved and tested for the earlier mentioned founder mutations. Genetic results were linked to clinical data, and outcomes were analyzed in univariate and multivariate analyses. Distant DFS was shorter in women with *BRCA1/2* mutations (66.2 vs. 84.3% at 10 years; $P = 0.05$), as was BC-specific survival (71.9 vs. 87.2% at 10 years; $P = 0.02$). In

Table 2 Prognosis in *BRCA1*- or *BRCA2*-associated breast carcinomas (2003–2008)

Author	Methodologic aspects of study									
		No. of patients		Control mutation status known	Matching or adjustment parameters	Complete follow-up	Overall survival		Adjusted or multivariate		Ethnicity-country
	Gene	Cases	Controls				Cases (%)	Controls (%)	*P*	*P*	
Veronesi [35]	*BRCA1* & *BRCA2*	39	86	Yes	Age, tumor grade	69 months	85[a]	55		0.19	Italy
	BRCA1 & *BRCA2*	21	211	Yes		82 months	95	89.6	NS		
Bonadona [36]	*BRCA1*	15	211	Yes		82 months	93.3	89.6	NS		France
Vinodkumar [37]	*BRCA1*	11	18	Yes			34 months+	71 months+	0.05		South India
Robson [38]	*BRCA1*	43	439	Yes	Age, tumor size, nodal status, ER	116 months	62	86	<0.0001[b]	0.01[b]	Ashkenazi Jewish/ United States
	BRCA2	13	439	Yes	Age, tumor size, nodal stage, ER, adjuvant Rx	116 months	84	86	0.76	NS	
Rennert [39]	*BRCA1*	76	1189	Yes	Age, tumor size, lymph-node status, metastasis	Minimum of 10 years	49	51	0.58	0.52	Jewish/Israel
	BRCA2	52	1189	Yes	Age, tumor size, lymph-node status, metastasis	Minimum of 10 years	48	51	0.73	0.42	
Brekelmans [42]	*BRCA1*	223	446	No[c]	Age, year at diagnosis, tumor stag, adjuvant systemic therapy, morphology, grade, ER, B(S)O	5.1 years	50	51	HR = 1.01	HR = 1.47	The Netherlands
Brekelmans [43]	*BRCA1*	223	759	No[c]	Age, year at diagnosis, tumor stag, adjuvant systemic therapy, morphology, grade, ER, B(S)O		50	55	NS	0.15	The Netherlands
	BRCA2	103	759	No[c]	Age, year at BC diagnosis, tumor stage, adjuvant treatment, morphology, histologic grade, ER, B(S)O		61	55	0.32	0.78	
Moller [45]	*BRCA1*	89	318	Yes	Stage, grade, ER		73	92	<0.001		Norway & United Kingdom
	BRCA2	35	318	Yes	Stage, grade, ER		96	92	NS		

BC, breast cancer *FHx*, family history; *NR*, not reported; *NS*, not significant

[a] Projected survival at 20 years

[b] Breast cancer-specific survival

[c] Excluded from control population were any women with at least two family members with breast cancer, or one family member with breast cancer under age 55, or one family member with ovarian cancer at any age

multivariate analysis, tumor stage and nodal status (but not mutation status) were predictive of distant DFS and breast cancer-specific survival. This study specifically addressed the issue of survival bias by utilizing archival tissue for genetic analysis without regard for vital status. Chappuis et al. undertook a similar approach; pathology blocks from 202 consecutive Ashkenazi Jewish women with primary invasive BC were tested for the presence of a founder mutation. A *BRCA1/2* mutation was identified in 16%. *BRCA1/2* mutation carriers had a significantly worse distant DFS compared with women without *BRCA1/2* mutations (58 vs. 82%; $P = 0.003$).

The impact of carrying an AJ founder mutation (either *BRCA 1* or *2*) has been addressed separately in other studies [29–31]. Lee et al. collected blood samples and questionnaire data on 5318 AJ volunteers. The blood samples were tested for the earlier mentioned AJ founder mutations. A novel extension of the kin-cohort method was applied. First, the estimated survival curves of affected relatives of carriers and non-carriers were compared. Second, the prevalence of *BRCA1* and/or *BRCA2* mutations in first-degree relatives of carriers and non-carriers was inferred using estimates of age-specific penetrance from previous report. A second survival analysis was conducted using this quantitative approach. No overall survival difference was observed between affected relatives of carriers and non-carriers using either statistical method. This study is limited by the potential for recall bias of family history and the failure to genotype affected family. Foulkes and colleagues focused on the study of *BRCA1*. Tumor blocks of unselected AJ women with primary BC were assayed for the presence of either of the two *BRCA1* AJ founder mutations. Results for women diagnosed before age 65 at a single institution were initially published; 5-year distant DFS was significantly worse in *BRCA1* mutation carrier ($P = 0.019$). In a later publication focusing on a node-negative population, the research team identified a number of significant prognostic factors on univariate analysis including young age of onset, high nuclear grade, ER negativity, p53 over-expression, and germ-line *BRCA1* mutation. However, on multivariate analysis, only *BRCA1* mutation carrier status remained an independent prognostic factor (0.01).

Additional studies in Germany, France, Norway, Scotland, England, and Holland also evaluated the impact of a *BRCA1* germ-line mutation on BC prognosis [32–34]. In France, the presence of a *BRCA1* mutation was found to have a significant prognostic impact ($P = 0.002$) even when adjusting for known prognostic factors ($P = 0.05$); *BRCA1* germ-line mutation was not found to have a prognostic value in other studies.

As evidenced in this section, data on the outcome of *BRCA1/2*-associated BC were inconsistent in these studies. There are a number of methodologic limitations identified in some, if not most studies described in this section including the following:

1. limited sample size
2. survival bias (a Neyman bias) by including living affected individuals only
3. dilution bias that may occur from the lack of genetic analysis of controls or limited testing of hereditary familial cases (only *BRCA1* for example)
4. limited generalizability in studies of BC families from single center studies
5. lack or limited inclusion of known prognostic factors for BC that would limit one's ability to properly adjust for differences in these variables. This could have a major influence in studies focusing on *BRCA*-associated BC in view of the small sample size and known differential phenotypic presentations of these cancers [2–7]
6. lack of inclusion of factors particularly relevant to *BRCA* mutation carriers that may impact prognosis is not always included such as age of menopause (natural or surgical) and history of subsequent ovarian cancer
7. lack of adjustment for BC treatment
8. use of institutional registry for cases while controls were drawn from population-based registries in some instances.

Prognostic studies in the last 5 years

In the past 5 years, a number of studies have been published with great efforts to overcome the earlier mentioned methodologic limitations (Table 2). Studies with small sample size conducted in South India, Italy, and France during that time have been summarized in Table 2 [35–37]. In one study, *BRCA1*-associated BCs had worse prognosis; in the other two studies, the presence of a *BRCA* mutation did not affect prognosis.

The study reported by Robson et al. expands on a previous report from the same authors [38]. Two retrospective cohorts of AJ women undergoing breast-conserving therapy for invasive BC between 1980 and 1995 were established; archival tissue blocks were tested for the AJ founder mutations. Genotyping was successfully completed in 496 women, of whom 56 (11.3%) were found to carry a *BRCA1* and/or *BRCA2* mutations. After a median f/u of 116 months, BC-specific survival was worse in *BRCA1* mutations carriers but not in *BRCA2* mutation carriers. The presence of a *BRCA1* mutation remained an independent predictor of BC mortality in multivariate analysis. However, *BRCA1* status predicted BC mortality only among women who did not receive chemotherapy ($P = 0.001$). This was the first report incorporating treatment factors

emphasizing the importance of systemic therapy in these patients. The authors acknowledged certain limitations of the study such as significant missing data on the ER/PR status and the inability to conduct a separate analysis of the role of grade.

More recently, Rennert et al. addressed the prognosis of *BRCA*-associated BC in a national population-based study of Israeli women [39]. Data were obtained on all incident cases of invasive BC diagnosed in 1987 and 1988 and recorded in the Israel National Cancer Registry. Tumor blocks or unstained slides from the tumor specimens were analyzed for the three AJ founder mutations. A *BRCA1/2* mutation was identified in 10% of women of AJ ancestry. All subjects were followed for a minimum of 10 years. The adjusted hazard ratios for death from any cause and from BC only were not significantly different between mutation carriers and non-carriers. The interaction between *BRCA1* mutation status and chemotherapy was significant for overall survival ($P = 0.02$) but not disease-free survival. An adverse prognostic effect was seen in carriers who did not receive adjuvant chemotherapy but not in those who received this treatment. Potential limitations of the study included: (1) possible impact of missing data on outcome, (2) lack of inclusion of tumor grade as a known prognostic factor, and (3) type of chemotherapy used and change in the choice of systemic therapies since the completion of the study [40, 41].

Brekelmans et al. selected 223 women with BC from families at the Rotterdam clinic (the Netherlands) with an identified *BRCA1* mutation [42]. All *BRCA-1*-associated BC cases were matched to sporadic BC patients, in a 1:2 ratio, for age and year of diagnosis. No significant differences between the *BRCA1*-associated and sporadic tumors were found with respect to ipsilateral BC recurrence or BC-specific survival. A trend toward a worse overall survival was found for *BRCA1*-associated ductal BC, likely reflecting the increased risk of ovarian cancer death in that group. There was no survival benefit observed from contralateral prophylactic mastectomy. This study included a number of important prognostic factors such as grade, systemic treatments, and B(S)O (bilateral salpingo-oopherectomy), in the multivariate analyses. In the following year, Brekelmans et al. published an expanded analysis that also included data on *BRCA 2*-associated BC and familial (*BRCA* negative) BC [43]. The tumor characteristics of *BRCA2*-associated BC were similar to those of familial *BRCA*-negative BC or sporadic BC, with the exception of a higher risk of contralateral BC and greater frequency of ER positivity in *BRCA2*-associated BCs. No significant differences in overall survival were observed. Independent prognostic factors for BC-specific survival in hereditary BC were tumor stage, adjuvant chemotherapy, histologic grade, ER status, and prophylactic (salpingo-) oophorectomy. Post-relapse survival was worse for *BRCA1* and better for *BRCA2*-associated patients when compared to sporadic patients; however, the differences disappeared after adjustments for ER status, site of first distant metastasis, and distant disease-free interval [44].

BC outcomes in women attending a familial BC surveillance program at collaborating centers in Norway and the UK were investigated by Moller and colleagues [45]. The study identified a worse survival in *BRCA1*-associated BC than in *BRCA2* or mutation-negative BC ($P < 0.001$). This study has a number of limitations such as the selection of a control group from a familial BC surveillance program, the classification of patients with micro-invasion as DCIS rather than invasive cancer, the unexpectedly low 5-year survival associated with DCIS (67%), and the lack of inclusion of important prognostic factors in the analyses.

A number of breast cancer prognostic factors have been examined in long-term breast cancer survivors of the Eindhoven Cancer Registry, a population-based cancer registry in the Netherlands. The role of *BRCA* mutation on overall survival was mixed, often decreasing after correction for stronger well-established prognosticators [46].

In the last 5 years, we have seen significant improvements in the methodology used to conduct survival analyses in this patient population. Despite this, limitations remain and will be difficult to circumvent in future studies given the long observation time required to conduct these analyses. In the future, inclusion of other factors such as the survival impact of surgical (or early) oophorectomy, the use of chemotherapy in general and more specifically relating to the class of agents used, and the role of HER-2 positivity should be considered. Although HER-2 positivity is not frequently observed in this population, it is a well-established prognostic factor. The mutational spectrum for *BRCA1* and *BRCA2* is wide, and as such, the study of penetrance and prognostic impact of specific mutations in each gene will be difficult to properly address. So far, the prognosis of BC has been separately addressed in only one subgroup of patients with specific ethic founder mutations (AJ descent). Finally, other factors (non-neoplastic) may impact the survival of *BRCA* mutation carriers and may need to be considered. Mai and colleagues recently examined the association between the three AJ *BRCA* founder mutations and risk of overall and non-cancer mortality in patients of AJ descents in the Washington D.C. area. They observed an overall association between *BRCA1/2* mutations and reduced life expectancy after excluding deaths following diagnosis of cancers that have been shown to be related to these mutations. The reduction in estimated life expectancy persisted after excluding deaths following any cancer diagnosis as well [47].

Table 3 Risk of in-breast tumor recurrence and contralateral breast cancer (CBC)

Author	Methodologic aspects of study								
		No. of Patients		Risk of in-breast tumor recurrence (%)			Risk of CBC (%)		
	Gene	Cases	Controls	Cases	Controls	*P*	Cases	Controls	*P*
Robson 1998 [26]	*BRCA1* & *BRCA2*	30	61	11 (66 months)	24(44 months)		31 (5 years)	4 (5 years)	0.0007
Verhoog 1998 [21]	*BRCA1*	49	196	14 (5 years)	16(5 years)	0.84	19	5	0.02
Robson 1999 [27]	*BRCA1* & *BRCA2*	28	277	14.9 (5 years)	4.5 (5 years)		14.8 (5 years)	3.7 (5 years)	
				22 (10 years)	6.9 (10 years)	0.25	27 (10 years)	9.5 (10 years)	0.002
Verhoog 1999 [22]	*BRCA2*	28	112				12 (5 years)	2 (5 years)	0.02
Chappuis 2000 [28]	*BRCA1* & *BRCA2*	32	170	6 (5 years)	7 (5 years)	0.93	10 (5 years)	2 (5 years)	0.02
Foulkes 2000 [31]	*BRCA1*	16	99	4.2 (5 years)	12.9 (5 years)	0.1	19.3 (5 years)	2 (5 years)	0.002
Hamann 2000 [34]	*BRCA1*	36	49				24 (5 years); 42 (10 years)	6 (5 & 10 years)	0.04
Loman 2000 [23]	*BRCA2*	54	214				22[a]	10[a]	0.03
Pierce 2000 [20]	*BRCA1* & *BRCA2*	71	213	2	4	0.8	20	2	0.0001
Stoppa-Lyonnet 2000 [32]	*BRCA1*	40	142	17 (5 years)	15 (5 years)	0.16	14 (5 years)	17 (5 years)	NS
Haffty 2002 [48]	*BRCA1* & *BRCA2*	22	105	49 (12 years)	21 (12 years)	0.007	42	9	0.001
Robson 2004 [38]	*BRCA1* & *BRCA2*	56	439	12 (10 years)	8 (10 years)	0.68	27 (10 years)	8 (10 years)	<0.001
Brekelmans 2006 [42]	*BRCA1*	170	446	16 (10 years)	25 (10 years)	0.24	27 (10 years)	5 (10 years)	<0.001
Pierce 2006 [50]	*BRCA1* & *BRCA2*	160	445	24 (15 years)	17 (15 years)	0.19	39 (15 years)	7 (15 years)	<0.001
Bonadona 2007 [36]	*BRCA1* & *BRCA2*	21	211	4.8	15.6	0.328	14.3	7.1	0.21
Brekelmans 2007 [43]	*BRCA1*	223	759	16 (10 years)	21 (10 years)	0.6	25 (10 years)	5 (10 years)	<0.001
Vinodkumar 2007 [37]	*BRCA2*	103	759	17 (10 years)	21 (10 years)	0.6	20 (10 years)	5 (10 years)	<0.001
	BRCA1	11	18				36.4	0	0.03

[a] 75% metachronous in carriers vs. 64% in controls, mean follow-up of 8.1 years

Contralateral BCs (CBCs) and in-breast tumor recurrence

The rates of in-breast tumor recurrence and CBCs have been summarized in Table 3. In most studies, the rate of in-breast tumor recurrence has not been found to be significantly different when compared to sporadic BC except for one study where none of the *BRCA* carriers had undergone an oophorectomy or received tamoxifen in the adjuvant setting [48]. The risk of in-breast tumor recurrence was similar in the first 5 years but diverged (higher in the mutation carriers) at 5–10 years post-diagnosis. The median time to in-breast tumor recurrence in *BRCA* carriers generally exceeds that observed in sporadic disease [20, 49]. In *BRCA* carriers, many in-breast tumor recurrences are considered second primary tumors in view of differing location and histologic appearances. There is no evidence of increased radiation sensitivity or sequelae from adjuvant radiation therapy in breast tissue for *BRCA* carriers compared with controls [20, 50].

The risk of CBCs has been found to be significantly increased in *BRCA* carriers compared with controls with an estimated 10-year risk ranging from 20 to 42% vs. 5 to 6%, respectively. The use of tamoxifen and oophorectomy has been associated with a significant reduction in the risk of CBCs in *BRCA* mutation carriers [51, 52]. Despite the reduction in risk observed with tamoxifen and oophorectomy, the risk of CBCs in *BRCA* mutation carriers still appears to exceed the risk observed in women with sporadic BC. In view of this, prophylactic contralateral mastectomy is often considered in this patient population; however, no survival benefit has been seen with this approach [42].

Conclusions

In this review, we have provided a summary of the literature addressing breast cancer prognosis in *BRCA* mutation carriers. Early studies published in the 1990s had several methodologic limitations and provided inconclusive results. More recent studies have used improved methodology to ascertain prognosis. These studies have failed, for the most part, to demonstrate a significant overall survival difference between *BRCA*-associated breast cancer and sporadic breast cancer; in one study, BRCA*1* status predicted increased breast cancer mortality only among women who did not receive chemotherapy. The study of prognosis in this population remains complex and difficult to address in view of inherent design limitations.

In most studies, the risk of contralateral breast cancer has been found to be significantly increased in *BRCA* carriers with an estimated 10-year risk ranging from 20 to 40%; the risk of in-breast tumor recurrence appears to be similar to the risk observed in women with sporadic breast cancer in the first 5 years following diagnosis. Divergence in rates following this has been observed in one study where no hormone manipulation was utilized. Many in-breast tumor recurrences are considered to be second primary tumors in mutation carriers.

Clinical implications

This review provides reassurance that the overall prognosis of *BRCA*-associated breast cancer is similar to that of sporadic breast cancer; however, the risk of contralateral breast cancer is significantly increased (3% per year) [52]. At this time, the systemic management of *BRCA*-associated breast cancer remains similar to that of sporadic breast cancer. A number of special considerations remain in the local management of *BRCA*-associated breast cancer and prevention of contralateral breast cancer. Many women now opt for prophylactic mastectomy of the contralateral breast (at the time of diagnosis or thereafter). Advantages of this approach include the significant risk reduction of contralateral breast cancer (by up to 97%) [52, 53] and the lack of need for ongoing breast cancer surveillance post-mastectomy. It is to note that no survival benefit has been observed with prophylactic contralateral mastectomy [42]. Much effort is now being directed at the prevention and early detection of breast cancer in this patient population.

Future directions

In the future, data from larger prospective international population-based cohort study will provide invaluable insight into this controversial topic. The treatment of breast cancer in *BRCA* carriers is also being scrutinized with increasing focus on the development and use of novel therapies. The impact of targeted therapies (e.g., Popy (ADP-Ribose) Polymerase inhibitors) and selected chemotherapies (e.g., taxanes, platinum agents) on prognosis and outcome of this patient population will be of great interest.

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