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Review

Management of *BRCA1/2* associated breast cancer: A systematic qualitative review of the state of knowledge in 2006

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ABSTRACT

Introduction: The optimal clinical management of breast cancer (BC) arising in *BRCA1/2* mutations carriers is a difficult issue complicated by the risk of subsequent malignancies and by the potential differences in response to local and systemic therapies.
Aim: Systematically review the difference in outcome after breast conservation therapy (BCT) and uni-or bilateral mastectomy in *BRCA1/2* related BC.
Material and methods: We selected 20 studies, for which we evaluated the methodology, the characteristics of the populations, biases, confounding risk factors and outcomes.
Results: All studies are retrospective, entailed by numerous biases. They varied with respect to patients' number, selection, and confounding factors. Hereditary BC patients carried an increased risk of ipsilateral recurrence in 5/17 studies, a worse survival in 4/14, an increased risk of contralateral BC in 14/16.
Conclusion: Except for contralateral risk, the presence of a *BRCA* mutation does not seem to offer additional prognostic information. Large prospective trials, stratified for risk reduction strategies are warranted.

1. Introduction

Hereditary susceptibility caused by mutations in autosomal dominant genes is responsible for about 5% to 10% of all breast cancers and about 7% to 10% of all ovarian cancers.[1] Mutations in *BRCA1* or *BRCA2* are thought to be responsible for the majority of these hereditary breast and ovarian cancers. However, the proportion of mutation-related breast cancer may be lower than listed in some common information sources (1 to 2%).[2] Women who carry these *BRCA1* or *BRCA2* mutations have an estimated lifetime breast cancer risk between 60% and 85% and a lifetime ovarian cancer risk between 26% and 54% for *BRCA1*, and between 10% and 23% for *BRCA2*.[3–6] Specific *BRCA* founder mutations are clustered, with high prevalence rates, among certain ethnic groups, such as Ashkenazi Jews, and among families in the Netherlands, Iceland, Poland and Sweden.[7,8] Although their mechanism of action is not yet fully elucidated, it is assumed that these genes play a key role in important cellular pathways including response to DNA damage, and interact with other proteins involved in DNA repair

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and apoptosis.[9] It has also been suggested that *BRCA* heterozygosity may confer increased sensitivity to ionising radiation and to certain chemotherapy regimens.[10,11] Although some studies have evaluated the benefits and harms of genetic testing for inherited breast cancer susceptibility and suggested recommendations concerning clinical practice for high risk women, there are few guidelines regarding the management of a newly diagnosed breast cancer in a patient with proven *BRCA1/2* genetic predisposition.[12–14] The optimal clinical management of such a patient is complex since it also has psychological, ethical and social implications. Furthermore, treatment is complicated by the risk of subsequent malignancies and by the potential differences in response to local and systemic therapies.[10,11]

Since 1991, breast conservation therapy associated with radiation therapy (BCT) is considered to be the preferred surgical option in early-stage disease.[15] This consensus was reached after analysis of several thorough, prospective, randomised, clinical trials among which some have been recently updated with a median follow up of 20 years.[16,17] All of these studies confirm that survival is the same in breast cancer patients treated by BCT or mastectomy.[18] In early stage breast cancer, the cumulative incidence of a recurrence in the ipsilateral breast is estimated between 8.8 and 14.3% after 20 years of follow up. The risk of ipsilateral recurrence may be reduced by chemotherapy in patients treated with BCT.[16,19] However the situation may be different in *BRCA* mutations carriers.

Three studies recently reported that genetic cancer risk assessment at the time of breast cancer diagnosis and prior to definitive treatment, significantly influences the women's choice of treatment.[20–22] Schwartz et al. observed that about half of the women found to carry a deleterious *BRCA1/2* mutation, chose bilateral mastectomy as their primary treatment, compared with 24% of those in whom no mutation or a mutation of unknown significance was found and 4% of those who declined to be tested.[20] The rate of bilateral mastectomy was higher among patients diagnosed with stage II or III breast cancer, compared with stage 0 or I. The high selection of bilateral mastectomy not only among women with confirmed *BRCA1/2* mutation but also among women with negative results (24%), undoubtedly raises questions since the single, strongest predictor of patients' surgical choice was the physician's recommendation.[23] Although rapid genetic testing may be challenging, one may wonder whether physicians have enough compelling data to make such counselling to newly diagnosed breast cancer patients. To answer this question we conducted a systematic review to determine the difference in outcome after breast conserving-therapy and uni-or bilateral mastectomy in *BRCA1/2* related breast cancer.

2. Materials and methods

Using online databases (Medline, PubMed, Cancerlit, Cochrane Controlled Trials Register and Google), we conducted literature searches to identify all published reports concerning the outcome of breast cancer in *BRCA1/2* patients, according to the type of loco-regional therapy modality. Since the major breast cancer predisposing genes *BRCA1* and *BRCA2* were identified in 1994 and 1995, respectively, we looked for articles published between 1994 and 2006.[24,25] The search strategy for articles included, in various combinations, the following keywords: *BRCA1, BRCA2, and breast cancer, breast neoplasm, surgical treatment, surgery, breast conserving- therapy, mastectomy, lumpectomy, prognosis, outcome, survival, contralateral breast cancer, chemotherapy, tamoxifen and radiotherapy.* If reports identified by these criteria referred to other papers not identified in the initial search, these were also reviewed when relevant to surgical breast cancer management and outcome in patients with *BRCA1/2* mutations. The search was complemented by consulting review articles, and breast cancer

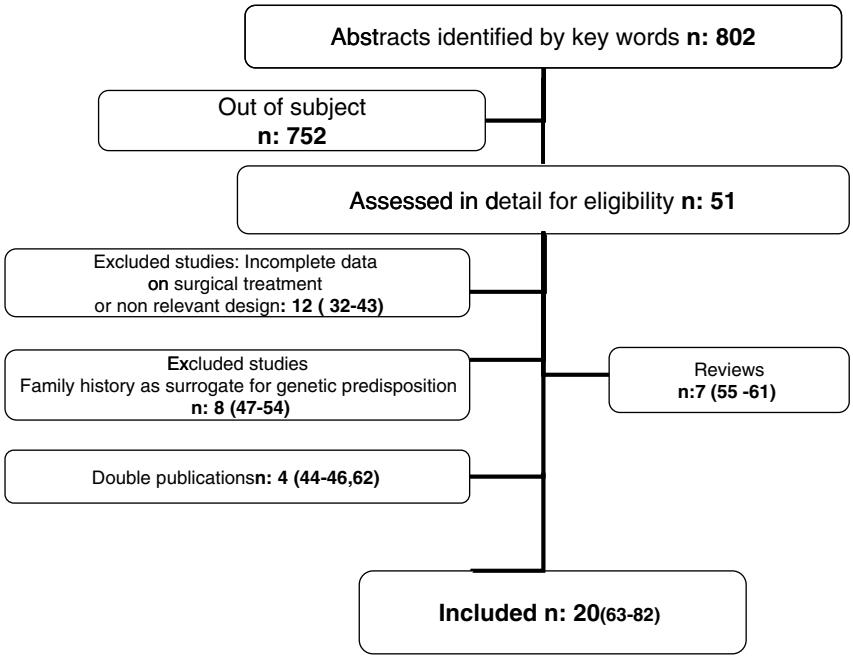

Fig. 1 – Selected/unselected studies.

conference proceedings. All available abstracts were reviewed and the full text of an article was consulted by a different reader when eligibility was ambiguous.

To be included in this review, studies were required to be written in English or French, to contain data on genetic testing methodology (even partial), information on surgical and radiation treatment and, information on at least one of the following endpoints: ipsilateral breast tumour recurrence (IBTR), contralateral breast cancer (CBC), distant metastasis (M), distant disease free survival (DDFS) and overall survival (OS). The following prognostic factors were considered: tumour size, lymph node status, histological type, oestrogen (ER) and progesterone receptors (PgR), histological grade, and HER-2 receptor.[26–28] Studies that ascertained only genetic status on the basis of familial pedigree without genetic testing were excluded. Although we recognise that the type of molecular analysis strategies is important,[29] we did not classify all the studies according to the used strategies. Because interpreting ipsilateral breast tumour recurrence (IBTR) and mortality requires a relatively long follow-up, we excluded studies with a follow up of less than 5 years for the genetic cohort. Data were extracted from the manuscripts using a standardised methodology.[30,31]

We retrieved 802 abstracts using these keywords. 752 were found to be irrelevant to the topic and 51 full-text papers were selected from the remaining abstracts (Fig. 1). We then excluded eight studies which used a family history as a surrogate marker of genetic predisposition,[47–54] 12 reports with incomplete data about the surgical treatment or non relevant design,[32–43] three papers for double publications,[44–46] seven review articles[55–61] and, one article which has been recently updated.[62] We retrieved 20 relevant studies.[63–82]

3. Results

Finally, we considered 20 studies for which we evaluated the methodology, the characteristics of the studied populations, the treatment regimens, confounding breast cancer prognostic factors, and outcome.

3.1. Characteristics of the studied populations

Among the 20 studies we found no randomised trials. Sixteen studies were described as retrospective by their authors. In the other four studies some data were prospectively collected. However, since other data were also retrospectively collected, we considered that the four trials used a retrospective design[67,71,78,79] (Table 1). In nine studies, affected carriers were matched to breast cancer patients selected from cancer registries and based on age at onset and period of diagnosis (*n*: 5); stage at diagnosis was also used as additional matching criteria (*n*: 2) as was the length of follow up (*n*: 2). In four studies, *BRCA1*/*BRCA2* mutations were sought in archival tissue from Ashkenazi Jewish women who had undergone treatment for cancer, and in whom the clinical outcomes were known (Table 1). Among the remaining seven unmatched studies, five performed genetic testing in a cohort of patients either with familial breast cancer,[71,73] bilateral breast cancer,[78] or with early onset breast cancer (<42 years),[69,74] and two studies were not controlled but based on a subset of proven affected carriers followed and assessed for different endpoints.[70,79] Only four studies gave data on the mean time between BC diagnosis and genetic testing ranging from 34 to 43 months,[70–73] and no study provided data on the mean time between genetic testing and enrolment. Some have attempted to limit the impact of longevity bias by either removing the index cases from the cases group,[64,65,69] or by ensuring that the follow up of controls was at least equal to the time-interval between diagnosis and genetic testing in cases,[72] or by excluding patients whose time interval between diagnosis and genetic counselling was longer than 3 years,[71] or by including deceased women.[79]

Most of the studies determined median observation time which varied between 4.2 years and 14.5 years. Only two studies presented the outcome results with a median follow up of at least 10 years. In four studies, the follow up was significantly longer in the hereditary cohort (Table 1). Age was reported in 19 studies, in various fashions. Median age data were provided for the entire population in seven studies (ranging from 36 years to 46 years). In 12 studies median age was given in relation to mutation status (ranging from 33.7 years to 49 years). Among these studies nine found that mutation carriers were significantly younger than sporadic cases. In one study, patients were classified as being younger or older than 50 years of age (Table 1). Only three studies provided data about ethnicity (black, white, other and Jews).[63,74,75] Five studies used religious preference as a surrogate for ethnicity; patients declaring themselves to be of Ashkenazi Jewish origin were defined as such[67–69,76,77] (Table 1). Only five studies gave details on menopause status.[63,65,66,71,72]

3.2. Genetic testing

The assessed type of *BRCA* germline mutations was *BRCA1* in five studies, *BRCA2* in one and both *BRCA1*/*BRCA2* in 14 studies. Genetic testing methods were detailed and/or referenced in 16 studies; two authors did not mention this information and two authors stated that mutation analysis was not performed for every genetic case, assuming a high probability to be carrier based on family history and pedigree analysis.[64,81] Ten authors out of 20 mentioned the number of tested mutations which varied between 3 and 71.[65–69,71,76,77,81,82] Among them, five authors looked specifically for the three dominant mutations in the Ashkenazi population (*BRCA1*: 185delAG, 5382insC; *BRCA2*: 6174delT).[67–69,76,77] The number of patients with *BRCA* mutations varied between 4 and 123 (*BRCA1*), and between 5 and 37 (*BRCA2*), respectively. One study included 491 patients supposed to be carriers, of whom 411 had been tested for *BRCA1* and *BRCA2* but more details on genetic testing methods are not available.[79] In only 13 out of the 20 genetic cohorts did all the patients undergo mutation analysis.[67,68,70–78,81,82] Affected mutation carriers were identified by familial cancer risk clinics in 12 studies (Europe, *n*: 8;[64–66,71–73,80,81] US, *n*: 4.[69,70,79,82] Among the 18 controlled reports, the sporadic group had undergone genetic testing in nine studies[65,67,68,71,73,74,76–78] although in one study, *BRCA2* testing was not possible for all patients,[65] and in another one, variants of unknown significance were described in the sporadic cohort.[74] In the remaining nine controlled studies, a negative family history (with variable definitions) was used

Table 1 – Characteristics of tie studies and studied populations

Authors (year) (reference)	Design Period follow up	Studied population		Mutation	No. of mutations	Cases/ controls	Age Years (range)	Ethnicity/ menopause status	Median follow up years
Brekelmans (2006) [64]	Retrospective Matched 1:2 1980–2001	Family Cancer Clinic, Rotterdam Women with BC and *BRCA1: n* = **223** (53 *BRCA1* index patients excluded).	Matched for age and year of diagnosis with **446** sporadic cases untested and without family history.	*BRCA1*	NA	**223/446**	39(23–82)	NA/NA	Cases 9.1[a]/43 Controls 5.1
Verhoog (1999) [65]	Retrospective Matched 1:4 1960–1996	Family Cancer Clinic, Rotterdam Women with BC and *BRCA2*:*n* = 45; **28** eligible.	Matched for age and year of diagnosis with **112** sporadic cases untested and without family history.	*BRCA2*	8	**28/112**	46 (32–85)	NA/ Pre menopausal: cases = 76.9% Controls = 9.8%	NA
Seynaeve (2004) [66]	Retrospective Matched 1:2 1980–1990	Family Cancer Clinic, Rotterdam Women with hereditary BC who underwent BCT: *n* = **87** HBC pts, including 21 *BRCA1*, 5 *BRCA/2* carriers and 61 unspecified HBC.	Matched for age and period of diagnosis with **174** BCT sporadic cases untested and without family history.	*BRCA1BRCA2*	13	**87/174**	BRCA: 38.7 Controls 45.9	NA/ Pre menopausal BRCA = 80.8% Controls = 60%	6.1
Robson BC Res (2004) [67]	Retrospective 1980–1995	Multi institutional collaboration, USA and Canada. Two retrospective cohorts of AJ women undergoing BCT for invasive BC (*n* = 584) were established. Genotyping for AJ *BRCA1/BRCA2* founder mutation using archived tissue blocks was successful in **496** women; of whom **56** (11.3%) carried a *BRCA1/2* founder mutation.		*BRCA1 BRCA2*	3	**56/440**	*BRCA1:* < 50 = 70%	AJ/NA	9.6
Goffin (2003) [68]	Retrospective 1980–1995	Canada single institution (McGillUnhersity) A historical cohort of 292 AJ women 65 years or younger with invasive BC was tested using archived tissue blocks for *BRCA1/2* founder mutations: **278** were eligible; of whom **30** *BRCA1* carriers.		*BRCA1*	3	**30/248**	Cases 46.7 Controls 53.8	AJ/NA	8.0
Robson (1998) [69]	Retrospective 1992–1995	USA (MSKCC)-Clinical genetic service A cohort of **91** AJ women ascertained during studies of the genetics of early-onset breast cancer (<42 years), underwent testing for the *BRCA1/2* founder mutations; of whom **30** *BRCA1/2* carriers.		*BRCA1 BRCA2*	3	**30/61**	36 (21–42)	AJ/NA	5.2

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Table 1 – *continued*

Authors (year) (reference)	Design Period follow up	Studied population		Mutation	No. of mutations	Cases/ controls	Age Years (range)	Ethnicity/ menopause status	Median follow up years
Robson Cancer (2004)[70]	Retrospective *1992–2003*	USA (MSKCC)-Clinical genetic service Participants (*n* = **87**) in genetic testing protocols were identified who (1) were found to have *BRCA* mutations and (2) reported a history of invasive BC treated with BCT. Among these *BRCA1* =**62** and *BRCA2* =**25**.		*BRCA1BRCA2*	NA	**87**	43(27–82)	NA/NA	6.3
Stoppa -Lyonnet (2000)[71]	Retrospective[b] *1991–1998*	France, Institut Curie -Family Cancer Clinic A cohort of **183** patients with in vasive BC and with a familial history of breast and/or ovarian cancer, were tested for *BRCA1* mutation: *n* = **40** (22%) *BRCA1*. France Institut Curie-Family Cancer Clinic		*BRCA1*	27	**40/143**	Cases 41 Controls 43	NA/ Pre menopausal: cases = 85% Controls = 77%	Cases 7.5 Controls 4.5
Kirova (2005)[72]	Retrospective Matched 1 :2 *1981–2000*	Women with a family history of breast and/ or ovarian cancer, treated with BCT, tested for *BRCA* mutations: *n* = **131** pts (*n* = **27** *BRCA1/2*).	Matched for age at diagnosis, year of treatment and period of follow up with **261** patients without FH	*BRCA1BRCA2*	NA	**131/261**	43	NA/ Pre menopausal: cases = 77.7%[b] Controls = 75.9%	8.7
Delaloge (2003)[73]	Retrospective	IGR France- Family Cancer Clinic Women from genetic clinic (*n* = **96**) who were treated with BCT and of whom **37** are *BRCA1*, **16** *BRCA2* and **43** neither gene mutation carriers.		*BRCA1 BRCA2*	NA	**53/43**	*BRCA1/2*: 36.7/43 Control 46	NA/NA	9.5
Pierce (2006)[63]	Retrospective Matched 1:3 *1980–1987*[c]	USA (Michigan) and Canada-Radiation Oncology Multi institutional A total of 160 women with *BRCA1* (*n* = **123**) and *BRCA2* (*n* = **37**) mutation and stage I or II BC treated with BCT	Matched for age, date of diagnosis and observation time with **445** women with sporadic BC and BCT	BRCA1 BRCA2	NA[c]	**160/445**	Cases 40.1 Controls 41.0	Cases white = 91% Controls white = 83% Pre menopausal: Cases = 74% Controls = 75%	Cases 7.9 Controls 6.7

Haffty (2002)[74]	Retrospective 1975–1998	USA - Yale University (New Haven) Women (*n* = **290**) with BC diagnosed at age 42 years or younger and who underwent BCT; 66 had died, so 234 potential participants of whom **127** consented for sequencing of *BRCA1* and *BRCA2*. Finally **15** *BRCA1* and 7 BRCA2 carriers are found.		BRCA1 BRCA2	NA	**22/105**	Cases 33.7 Controls 37.3	Cases Jewish 41% Controls Jewish 12% NA	12.7
Turner (1999)[75]	Retrospective Matched 1:1 1973–1994	USA- Yale University. 52 BC treated with LRT who developed an IBTR within the prior irradiated breast Genetic testing was done for 52 locally recurrent pts (*n* = **8** *BRCA1/2*)	Matched for age, date of diagnosis and stage, to 52 controls BC pts treated with LRT without IBTR. Genetic testing was done for 15 of the matched control patients under age 40 (*n* = **1** *BRCA1/2*).	BRCA1 BRCA2	NA	**52/52**	49.5	A[d] /NA	14.5
Chappuis (2000)[76]	Retrospective *1986–1995*	Canada (McGill University) Pathology blocks from **202** consecutive AJ women with invasive BC were tested for the three common *BRCA1/2* founder mutations;**32** (16%) *BRCA1/2*.		BRCA1 BRCA2	3	**32/170**	Cases 48 Controls 53.7	AJ/NA	6.4
ElTamer (2004)[77]	Retrospective *1989–1999*	USA Columbia-Presbyterian Comprehensive Breast Centre 715 patients younger than 65 years of age and of Jewish descent were identified; 487 pts were tested using the tissue blocks for the common mutations:**30** *BRCA1* and **21** *BRCA2* carriers identified (10.36%).		BRCA1BRCA2	3	**51/436**	Cases 48 Controls 50.8	AJ/NA	Cases[e] 7.6 Controls 4
Bremer (2003)[78]	Retrospective[b]	Germany Clinics of Ob Gyn - Medical School Hanover Unselected hospital-based cohort of **110** patients with bilateral BC tested for mutations *BRCA1* (*n* = **4**) and *BRCA2* (*n* = **5**).		BRCA1 BRCA2	NA	**9/101**	Cases[f] 42.5 Controls[f] 55.3	NA/NA	6
Metcalfe (2004)[79]	Retrospective[b] *1975–2000*	Canada- Multi institutional - Cancer Genetic Clinics 1139 pts from 337 families with *BRCA1/2* mutations diagnosed with stage I/II BC at age 65 years or younger; 439 were ineligible, **491** of the remaining 700 eligible cases (70%) were enrolled. Ninety-two of the **491** (187%)were deceased.		BRCA1 BRCA2	NA	**491**	42.1	NA/NA	9.2

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Table 1 – *continued*

Authors (year) (reference)	Design Period follow up	Studied population		Mutation	No. of mutations	Cases/ controls	Age Years (range)	Ethnicity/ menopause status	Median follow up years
Eccles (2001) [80]	Retrospective Matched[g] *1959–1996*	UK - Multi institutional - Genetic **304** women with familial and sporadic BC with either diagnosed at age < 40 years or bilateral BC:**142** eligible: **75** *BRCA1* tested + **67** (FH+) mutation unknown	Matched partially to 49 out of 1 62 pts without family history and mutation unknown (FH-).	*BRCA1*	NA	**142/162**	37	NA/NA	7
Johannsson (1998) [81]	Retrospective Matched *1958–1995*	Sweden, **71** BRCA1 -associated cancer patients (33 BC, 7 breast and ovarian cancer, and 31 ovarian cancerpts from 21 families with *BRCA1* germline mutations).	Compared with that of a population- based comparison group that consisted of all other invasive BC (n = 28,281) and OC (n = 7011) diagnosed during 1958 to 1995, as well as an age- and stage-matched control group	*BRCA1*	8	**40/112**	Cases 43.5 Controls 44.9	NA/NA	NA
Gaffney (1998) [82]	Retrospective Matched 1:117 *1957–1994*	USA-Multi institutional (five facilities in Utah) BC pts with mutations of *BRCA1*(n = **30**) or *BRCA2* (n = **20**)	Matched for age, date of diagnosis and tumour size with multiple controls. And cross-referenced with the Utah Cancer Registry (UCR).	*BRCA1 BRCA2*	12	**50/8.409**	Cases 47.5[b] Controls 60	NA/NA	8.6

NA not available, **HBC** hereditary breast cancer, **BCT** breast conserving therapy, **MSKCC** Memorial Sloan-Kettering Cancer Centre, New York, **AJ** Ashkenazi Jews,**IGR** Institut Gustave Roussy Paris, **FH** family history, **LRT** lumpectomy with radiation therapy, **IBTR** ipsilateral breast tumour recurrence.

a Data without 53 *BRCA1* index patients excluded.

b Interpreted data.

c 71 mutations were described in the previous publication [62].

d Data available in sub groups.

e Data for *BRCA1*.

f Data for primary tumour.

g 49 pts in the controls group with no FH, were matched for -age (5 years) and - year of diagnosis (5 years) of a case (a case being defined as a woman with a significant FH).

Table 2 – Characteristics of breast cancers

Authors (year) (Reference)	T status		N status			Grade			Histology			Oestrogen recepter			Progesterone receptor			
		Cases (%)	Controls (%)		Cases (%)	Controls (%)		Cases (%)	Controls (%)		Cases (%)	Controls (%)		Cases (%)	Controls (%)		Cases (%)	Controls (%)
Brekelmans (2005) [64]	**Mean size mm**[a]	23.9 (1–98)	25.3 (4–98)	**N0**	104(61)	201(45)	I	1(1)	21(5)	**Ductal**	146(86)	394(88)	**Neg**	77(45)	108(24)	**Neg**	64(38)	86(19)
	T1	81(48)	194(43)	**N+ ⩽ 3**	35(21)	111(25)	II	12(7)	76(17)	**Lobular**	6(3)	40(9)						
	T2	62(36)	154(34)	**N+ ⩾ 4 N+**	16(9)	106(24)	III	93(55)	200(45)	**Medullary Tubular**	12(7) 0	9(2) 3(1)	**Pos**	29(17)	216(48)	**Pos**	31(18)	158(35)
	T3/T4	11(6)	41(9)	no unknown	10(6)	6(1)	**ND**	63(37)	149(33)	**Other**	1(1)	0	**ND**	64(38)	122(27)	**ND**	75(44)	202(45)
	ND	16(9)	57(13)	**ND**	5(3)	22(5)				**ND**	5(3)	0						
Verhoog (1999) [65]	**⩽2 cm**	10(37)	53(54.6)							**NST**	23(82.1)	98(89.1)						
	2–5 cm	13(48.1)	34(35.1)	**Neg**	17(63)	56(52.8)				**Lobular**	1(3.6)	7(6.4)	**Neg**	1(6.7)	10(15.6)	**Neg**	0	14(23.3)
	⩾5 cm	4(14.8)	4(4.1)					**ND**		**Mixted Medullary**	2(7.1) 2(7.1)	2(1.8)	**Pos**	14(93.3)	54(84.4)	**Pos**	12(100)	46(76.7)
	Chest wall	0	6(6.2)	**Pos**	10(37)	50(47.2)				**Mucinous other**	0 0	1(0.9) 2(1.8)	**ND**	13	48	**ND**	16	52
	ND	1	15	**ND**	1	6				**ND**	0	2						
Seynaeve (2004) [66]	**⩽2 cm**[b]	52(60)	121(69.5)	**Neg**	20(23)	49(28.0)	I	4(4.6)	3(1.7)	**Ductal**	74(85.0)	147(84.5)						
	2–5 cm	17(19.5)	35(20.1)	**Pos**	61(70)	117(67.8)	II	16(18.4)	29(16.7)	**Mixted**	2(2.3)	6(3.4)						
	⩾5 cm	0	1(0.6)	**ND**	6(7.0)	8(5.0)	III	47(54.0)	92(52.9)	**Medullary Mucinous**	2(2.3) 3(3.4)	7(4.0) 4(2.3)		**ND**		**ND**		
	ND	18(21)	17(9.8)				**ND**	20(23.0)	50(28.7)	**Other ND**	4(4.6) 2(2.3)	5(2.9) 5(2.9)						
Robson BC Res (2004)[67]	**T1**[c]	29(67)	324(74)	**Neg**	23(53)	262(60)							**Neg**	27(63)	98(22)			
	T2	11(26)	97(22)	**Pos**	18(42)	149(34)		**ND**			**ND**		**Pos**	6(14)	197(45)	**ND**		
	ND	3(7)	19(4)	**ND**	2(5)	29(6)							**ND**	10(23)	145(33)			
Goffin (2003) [68]	**Mean size**			**Neg**[d]	19(66)	122(54)	I	1(3)	72(29)				**Pos**	7(23)	165(68)			
	mm	20	16	**Pos**	10(34)	103(46)	II	8(27)	104(42)		**ND**		**Neg**	23(77)	77(32)	**ND**		
	N = 266	(15–50)	(10–140)				III	21(70)	70(28)									
Robson (1998) [69]	**Is**	1(3.3)	2(3.3)	0	13(46.4)	32(54.2)				**Ductal**	23(76.7)	53(86.9)						
	1	14(46.7)	37(60.7)	**1–3**	8(28.6)	17(28.8)				**Medullary**	3(10)	1(1.6)						
	2	12(40)	15(24.6)	**4–9**	2(7.1)	5(8.5)	III	21/21	32/54 (59.2)	**Lobular**	1(3.4)	2(3.3)	**Pos**	7/23 (30.4)	37/56 (66)	**Pos**	7/23 (30.4)	29/55 (52.7)
	3	0	3(4.9)							**DCIS**	2(6.7)	1(1.6)						
	4	2(6.7)	1(1.6)	**10+**	5(17.9)	5(8.5)				**LCIS**	0	1(1.6)						
		ND	1(3.3)	3(4.9)							**Other/ND**	1(3.3)	3(4.9)					

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Table 2 – *continued*

Authors (year) (Reference)	T status		N status			Grade			Histology			Oestrogen recepter			Progesterone receptor			
		Cases (%)	Controls (%)		Cases (%)	Controls (%)		Cases (%)	Controls (%)		Cases (%)	Controls (%)		Cases (%)	Controls (%)		Cases (%)	Controls (%)
Robson Cancer (2004) [70]	T1	71(74.7)		Neg	28(29.5)		1	2 (2.1)		Ductal	84(88.4)		Pos[e]	34(35.8)				
	T2	22(23.2)		Pos	63(66.3)		2	7 (7.4)		Medullary	7(7.4)							
			ND			ND	3	70(73.7)	ND	Tabular	1(3.2)	ND	Neg	45(47.4)			ND	
	ND	1(1.1)		ND	4(4.2)		ND	16(16.8)		Lobular	3(3.2)		ND	16(16.8)				
Stoppa-Lyonnet (2000) [71]	T0[f] or T1	13 (31)	70 (47)	Neg Pos	19(70) 8(30)	69(60) 46(40)	1–2 3	13 (43) 17 (57)	76 (73) 28 (27)	Ductal Lobular	28(67) 4(9)	108(72) 12(8)	Pos Neg	10(32) 21(68)	60(63) 35(37)	Pos Neg	11(35) 20(65)	66(72) 32(28)
	⩾ T2	29 (69)	80 (53)	No ax dissect	15	35	ND	12	46	Medullary Other	4(9) 6	0 30(20)	ND	11	55	ND	11	52
Kirova (2005)[72]	Tnp[g]	3(10.3)	49(18.1)	N0	26(89.7)	243(70.5)	1,2	9(31.1)	166(81.0)	Ductal Lobular	17(65.4) 3(11.5)	216(82.1) 16(6.1)	Neg	11(47.8)	33(20.9)	Neg	11 (47.8)	34 (21.7)
	T1–T2	26(89.7)	212(78.2)				3	14(68.9)	39(19)	Medullary other	3(11.5) 2(7.7)	2(0.8) 12(4.5)	Pos	12(52.2)	125(79.1)	Pos	12 (52.2)	123 (78.3)
	T3	0	1(0.4)	N1	3(10.3)	26(29.5)	ND	6	66	DCIS	1(3.9)	17(6.5)	ND	6	113	ND	6	114
	TX	0	9(3.3)							ND	3	8						
Delalogе (2003) [73]	Mean size mm	BRCA1 32 BRCA2 27	20		ND		3	BRCA1(76) BRCA2 (37)	(26)		ND		Pos(%)	BRCA1(19) BRCA2 (73)	(70)		ND	
Pierce (2006) [63]	T1	110(70)	292(67)	Neg	115(75)	276(66)	I–II	27(24)	146(56)	Ductal	136(85)	375(85)	Pos	32(23)	211(63)	Pos	29(24)	168(60)
	T2	48(30)	147(33)	Pos	39(25)	143(34)	III	84(76)	117(44)	Lobular Medullary	3(2) 17(11)	30(7) 16(4)	Neg	106(77)	122(37)	Neg	91(76)	113(40)
Haffty (2002) [74]	T1	17(77)	77(73)	No dissection	4(18)	15(14)				Ductal	82(78)	15(68)	ND	8(36)	25(24)	ND	10(45)	31(29)
	T2	4(18)	19(18)	Neg	13(59)	73(70)		ND		DCIS Lobular Medullary	9(8) 5(5) 5(5)	1(5) 0 6(27)	Neg	11(50)	37(35)	Neg	9(41)	39(37)
	Tis	1(5)	9(9)	Pos	5(23)	17(16)				other	4(4)	0	Pos	3(14)	43(41)	Pos	3(14)	35(34)
Turner (1999)[75]	Mean size mm [h]	17	17		ND			ND		ND		ND			ND			
Chappuis (2000) [76]	<2 cm ⩾2	17(53)	98(58)	N0	19(63)	99(62)	1	1(3)	52(31)	Ductal	28(90)		pos	11(34)	115(68)			
		15(47)	72(42)				2	9(28)	67(39)	Medullary	1(3)		Neg	21(66)	54(32)			
	median	1.7	1.5	N+	11(37) BRCA1 14(50)	60(38) 262	3	22(69)	51(30)	other	2(7)							
		BRCA1		NO	BRCA2	(69)					BRCA1			BRCA1			BRCA1	
El Tamer (2004) [77]	Median size mm	20 BRCA2 1.5	1.5	N +	15(78) BRCA1 14(50) BRCA2 4(21)	117 (31)		ND		Medullary	0 BRCA2 1(4.7)	4(0.9)	Neg	15(68) BRCA2 2(14.2)	65(19.5)	Neg Neg	15(71.4) BRCA2 7(50)	112(34)

Bremer (2003) [78]	**Tis**[1]	4(3)	0	**Neg**[i]	5(45)	69(59)								**Pos**[i]	6(55)	65(56)					
	T1/T2	84(72)	9(82)	**Pos**	6(55)	32(27)								**Neg**	4(45)	15(13)					
	T3/T4	12(10)	2(18)					**ND**			**ND**							**ND**			
	ND	17(15)	0	**ND**		16								**ND**	1(1)	37(31)					
Metcalfe (2004) [79]	**Size**						**1**	13(2.6)		**Medullary**	43(8.8)			**Pos**	146(29.7)			**ND**			
	0–2 cm	324(66)		**Pos**	160(32.6)		**2**	93(18.9)		**Ductal**	410(83.5)			**Neg**	213(43.4)						
	2–5 cm	167(34)		**Neg**	331(67.4)		**3**	214(43.6)		**Lobular**	16(3.3)			**Equivocal**	12(2.4)						
							ND	171(34.8)		**other**	19(3.9)			**ND**	120(24.4)						
Eccles (2001) [80]	**Mean**	25	2.6	**Pos**	37(26)	57(35)															
	size	+/−	+/−	**Neg**	66(47)	96(59)			**ND**			**ND**				**ND**				**ND**	
	mm	1.4	1.6	**ND**	39(27)	9(6)															
Johannsson (1998)[81]	**Stage 1**	19(47)	52(46)																		
	2	18(45)	53(47)	**NO**	4	6								**Pos**	3(8)	53(47)	**pos**	3(8)		53(47)	
	3	3(7)	7(6)						**ND**	**ductal**	100%		89%	**Neg**	24(60)	31(28)	**Neg**	24(60)		27(24)	
	4	0	0	**N+**	14	47								**ND**	13(33)	28(25)	**ND**	13(33)		32(29)	
Gaffney (1998)[82]	**Mean**			**Neg**[k]																	
					15(44)		**1**[k]	2(6)													
	size	22								**Medullary**	3(9)										
	mm[j]			**pos**	17(50)		**2**	4(12)		**BRCA1**			221/8409			**ND**				**ND**	
	BRCA1						**3**	11(32)		**BRCA2**			(2.6)								
	BRCA2	31		**ND**	2(6)		**ND**	17(50)			1(4)										

Tnp tumour non palpable, **ND** no data = unknown, **NST** no special type.

a Data for *BRCA1* unselected group after exclusion of 53 index patients tested, versus controls.

b Data for the entire hereditary group including 61 unspecified hereditary breast cancer, versus controls.

c Data for *BRCA1* versus controls.

d Data available for 254 patients.

e ER or PR together.

f Data including 9 synchronous invasive breast cancer; 2 in the genetic cohort and 7 in the sporadic cohort (tumours total = 192).

g Data for 29 tumours arising in 27 *BRCA1/2* carriers

h Data for 15 matched index cases with ipsi breast tumour recurrence (IBTR) and 15 control (no IBTR) under age 40.

i Data extracted from the oral presentation of the abstract, oestrogen and progesterone receptors together.

j The T size andN status matched closely with a large retrospective study of over 24,000 sporadic BC.

k Data for *BRCA1*; no differences with *BRCA2*.

Table 3a – Local and systemic treatment and outcome

Authors (year) (reference)	Local treatment	Cases (%)	Controls (%)	Adjuvant chemotherapy	Cases (%)	Controls (%)	Adjuvathormonal therapy	Cases (%)	Controls (%)	IBTR	Cases (%)	Controls (%)	DFS/ DDFS	Cases (%)	Controls (%)	OS/BCSS	Cases (%)	Controls (%)
Brekelmans (2005) [64]	BCT	76(46)	241(54)		84 (51)	208 (48)	*0.04	12 (8)	62 (15)	5 years	12%	14%	DDFS5 years	68%	60%	OS 5 years	69%	74%
	Mastec	85(51)	189(42)															
	Biopsy	5(3)	15(4)							10 years[a]	16%	25%	DDFS10 years[b]	60%	49%	OS 10 years[c]	50%	51%
Verhoog (1999)[65]	BCT	10(36)	56(50)	ND			ND			ND			DFS 5 years	52%	52%	OS 5 years	74%	75%
	Mastec	18(64)	46(41)															
Seynaeve (2004)[66]	ALL BCT				15 (17.2)	33 (19.4)		3 (3.4)	4 (2.3)	5 years	14.6%	7%	ND			OS 5 years	78%	82%
										10 years[d]	30%	16%				OS 10 years[e]	59%	73%
Robson BC Res (2004)[67]	ALL BCT			*0.02	24 (56)	156 (35)	*0.01	10 (23)	190 (43)	5 years			DDFS 10 years[g]	66.2%	84.3%	BCSS 10 years[g]	BRCA1 62%	86%
										10 years[f]	12%	8%					BRCA2 74.5%	
Goffin (2003)[68]	BCT	25(83)	163(78)		17 (57)	112 (46)		9 (32)	120 (52)	ND			DDFSRR[h]	1.2	1.0	OS RR[i]	1.4	1.0
	Mastec	5(17)	55(22)															
Robson (1998)[69]	BCT	9(32)	25(42)		23 (82)	47 (80)		5 (18)	16 (27)	Crude rate	1/9 11%	6/25 24%	DFS 5 years	65%	69%	ND		
	Mastec	19(68)	34(58)															
Robson Cancer (2004)[70]	ALL BCT			+/− Tam	70 (73)		+/− Chemo	28 (29.5)		5 years	11.2%		DFS 5 years	92.9%		OS 5 years	95.6%	
										10 years	13.6%		DFS 10 years	87.3%		OS 10 years	89.4%	
Stoppa-Lyonnet (2000)	BCT		(74)	ND			ND			5 years	17%	15%	Meta Free[j]	18%	84%	OS 5 years[k]	49%	85%
	Mastec		(16)															
Kirova (2005)[72]	ALL BCT		BRCA1 (38) BRCA2 (28)	(25)	*0.04	BRCA1 (7) BRCA2 (13)	(6)	Crude rate	BRCA1 24% BRCA2 22%	19%	ND	ND						
Delaloge (2003)[73]	ALL BCT			ND	BRCA2 37%		ND		BRCA 2 63%	10 years	BRCA1 9%	12%	ND			OS 10 years	BRCA1 80%	88%
Pierce (2006)[63]	ALL BCT			*0.007	(69)	(58)		(22)	(29)	10 years	12%	9%	ND			ND		
										15 years[l]	24%	17%						
Haffty (2002)[74]	ALL BCT				13 (54)	46 (44)	*0.05	0	16 15%	5 years	22%	18%	p			p		
										10 years[m]	41%	19%						
Turner (1999)[75]	ALL BCT			ND				0 < 40 years	0 < 40 years	Crude Rate	LRT+IBTR 8 BRCA1/2	LRT 1 BRCA1/2	ND			All alive		
Chappuis (2000)[76]	BCT		189(64)	*0.03	21 (68)	74 (46)	ND			5 years	6%	7%	DDFS 5 years[n]	58%	82%	q		
	Mastec	13(6)																

El Tamer (2004)[77]	BCT	21(41)	220(51)	* 0.001	*BRCA1* (63)	139 (31)	ND			5 years[o]	23%		12.5%	ND		OS 5 years	*BRCA1* 90.7%	91.2%
	Mastec	30(59)	216(49)		*BRCA2* (47)												*BRCA* 2 94.7%	
Bremer (2003)[78]	BCT	(82)	(61)		(46)	(33)		64%	52%	5 years[p]	29%		6%	ND	ND			
	Mastec	(12)	(39)															
Metcalfe (2004)[79]	BCT	191(39.6)		296 (61.4)			144 (29.9)			10 years	11.5%			ND		ND		
	Mastec	254(52.7)																
	Bilat Mastec	37(7.7)																
Eccles (2001)[80]	BCT	72(51)	83(51)		41 (29)	37 (23)		54 (33)	62 (37)	10 years	18%		21%	[q]		[q]		
	Mastec	70(49)	79(49)															
Johansson (1998)[81]	PM+/−RT	12	22	ND			ND			ND				ND		OS 5 years months	64	85
	TM+/−RT	28	54															
Gaffney (1998)[82]	**BCT**		7(12)		**ND**			**ND**		**7 BCT** for total population		**1/7 IBTR** for Total population			**ND**	OS 5 years	75%	59%
	Mastec		49(56)													OS 10 years	70%	NA

OS/BCSS overall survival; **BCT** breast conserving therapy; **RR** relative risk; **IBTR** ipsilateral breast tumour recurrence; actuarial risk of local relapse rate 5 years and 10 years; **DFS/DDFS** disease-free survival or distant diseases free survival according to the study; **PM** partial mastectomy; **TM** total mastectomy; **RT** radiation therapy.

a *p*: NS; HR multi 0.67 (0.34–1.32 95%CI) adjusted for tumour stage, adjuvant systemic therapy, tumour morphology, histologic grade, ER and bilateral (salpingo)ovariectomy (BSO).

b HR uni, *p*:0.03; HR multi, *p*:NS.

c HR multi, *p*:NS.

d $p = 0.05$; after adjustment for age and T size, *p*=NS for *BRCA*1.

e *p*=NS.

f For women not using tamoxifen $p = 0.05$.

g DDFS; $p = 0.05$; *BRCA*1 mutation remained an independent predictor of breast cancer mortality in multivariate analysis of the group of women who did not receive chemotherapy ($p = 0.001$).

h In the Cox multivariate model, greater tumour size (RR 2.4), higher nuclear grade (Grade 3 versus Grade 1, RR 3.8; Grade 2 versus Grade 1, RR 2.4), and positive lymph node status (RR 2.0) remained statistically significant but p53 IHC status did not.

i In the multivariate model, in node-negative patients, only positive *BRCA*1 mutation status (RR 3.5) was significantly associated with higher mortality.

j $p = 0.05$; analysis limited to 110 pts whose interval between diagnosis and genetic counselling was less than 3 years.

k $p = 0.02$; analysis limited to 110 pts whose interval between diagnosis and genetic counselling was less than 3 years.

l $p = 0.19$.

m $p = 0.007$ for IBTR uni and multivariate analyses; all patients remain disease free after treatment of their IBTR.

n $p = 0.003$ for DPS; when OS was considered, age ($p = 0.02$), tumour size ($p = 0.004$), grade ($p = 0.0001$), ER status ($p = 0.0001$), *BRCA*1/2 status ($p = 0.001$), and $p27^{Kip1}$ expression ($p = 0.001$) were all prognostic factors in univariate analysis, only $p27^{Kip1}$ expression and nuclear grade retained significance in multivariate analysis (RR, 6.4; $p = 0.01$; and RR, 2.0; $p = 0.05$, respectively).

o $p = 0.05$ but NS in multivariate analysis.

p $p = 0.022$.

q The RFS was worse in the family history + group compared to the FH−group and approached statistical significance (log rank test, $p = 0.0563$); OS_p = NS. .

* P: significant.

Table 3b – Outcome data: summary of the studies reporting an increased contralateral breast cancer (BC) risk, or local recurrence risk, or a decreased overall survival (OS) or breast cancer specific survival (BCSS) or disease free survival (DFS) or distant disease free survival (DDFS) in the genetic cohorts

Outcome in the genetic cohort	Increased risk of contralateral BC	Increased risk of local recurrence	Decreased OS/BCSS	Decreased DDFS/DFS
No studies associated with worse outcome *(reference)*	14[63–67,69,70,72,74–77,79,80]	5[66,74,75,77,78]	3[67,68,71]	3[67,71,76]
No studies not associated with worse outcome *(reference)*	2[71,82]	12[63,64,67,69–73,76,79,80,82]	10[64–66,70,73,75–77,81,82]	6[64,65,68–70,74]
Outcome not detailed *(reference)*	4[68,73,78,81]	3[65,68,81]	7[63,69,72,74,78–80]	11[63,66,72,73,75,77–82]

as a surrogate for the absence of mutation in the sporadic cohorts.

3.3. *Characteristics of breast cancers*

Only seven out of the 20 studies provided data on tumour stage[63,71,74–76,79,81] and only eight on nodal status[63,68,69,72,76,77,79,81] for the entire studied population (Table 2). However, most controlled studies reported some data on tumour size and nodal status and found no difference between cases and controls (*n*: 13), while one reported larger tumour size for *BRCA2* cancers but less lymph node invasion as compared to sporadic cancers.[65] One study reported a larger mean size for *BRCA1* cancers as well as more N1 or N2 nodal status[71] and, another one reported more T1 N0 tumours in the genetic group associated with more screen detected cancers in the genetic cohort (11% versus 6%).[64] Finally, one author found more stage 0 breast cancers (ductal carcinoma *in situ*) in *BRCA2* carriers when compared with *BRCA1*[77] (Table 2). Fourteen studies presented details on histological type; five of them noted significantly more medullary subtypes in *BRCA1* mutations[63,64,71,74,82] and one noted that all medullary carcinomas were found in *BRCA1* carriers[72] (Table 2). Twelve studies detailed information about the histological grade and most observed an increased incidence of grade III tumours in *BRCA1* germline mutation carriers as compared with sporadic cases.[63,64,68,69,71–73,76] Only in four out of eight studies in which patients were exclusively treated by BCT, was information on histological margins available.[63,66,74,75] In one of these, the presence of *in situ* component was described.[66] In half of the reviewed reports, the receptor status was missing in a large proportion of patients (more than 20%). There was no information at all about ER in four studies[66,75,80,82] and about PgR in ten studies[66–68,70,73,75,78–80,82](Table 2). In 12 controlled studies, breast cancer patients of the genetic groups had, more frequently, ER- negative tumours (Table 2). One study provided details about p53 expression assessed using immunohistochemistry[68] and another one about $p27^{Kip1}$.[76]

3.4. *Treatment*

In no study was surgical and adjuvant systemic treatment randomly assigned. Eight studies included patients who were treated exclusively by BCT. Four among them provided details on radiation therapy, including received doses.[63,66,70,72] In 12 studies, patients were treated either by BCT or total mastectomy (Table 3). Three among these studies did not determine surgical treatment according to genetic status. However, they reported that BCT was performed, respectively, in 74%, 64% and 12% of the entire selected population. The nine remaining studies reported surgical treatment according to genetic status and in three, there was a higher proportion of patients treated with total mastectomy than with BCT. These studies included patients who were followed from 1957 to 1994, 1960 to 1996 and 1975 to 2000, respectively (Table 3). Finally, from 17 reports, we retrieved a total of 827 mutation carriers treated by BCT and 531 mutation carriers treated by total mastectomy. Based on medical records, no increased radiation toxicity was noted by two authors.[79,82] Fifteen studies mentioned the number of patients treated with adjuvant chemotherapy (CT), which ranged from 5 to 296 in the genetic cohorts (Table 3). Only three of these studies detailed the type of CT as anthracycline-based, CMF-based or other. The incidence of CT administration in carriers of *BRCA* mutations varied between 19.2% and 82% (mean = 53%). In some studies (*n*: 4) mutation carriers received statistically more CT than patients in control groups (Table 3). Data on hormonal therapy (HT) were reported in 13 studies and the frequency of administration in mutation carriers ranged from 0% to 64% (mean = 22.4%). The number of carriers who received HT varied between none to 144. Although in most studies (12/13), *BRCA* carriers received HT less often than controls, this was only statistically significant in four studies (Table 3). Only three studies reported data on rates of oophorectomy.[63,64,79] One of them, an uncontrolled study, provided data on its timing.[79]

3.5. *Outcome*

3.5.1. *Ipsilateral breast tumour recurrence (IBTR)*

We retrieved 17 reports which addressed the issue of ipsilateral breast tumour recurrence (IBTR) in *BRCA1/2* carriers using various designs and methodologies (Table 3). Eight controlled studies including 2947 patients found no significant difference between genetic cases (*n*: 837) and sporadic cases (2110) with respect to IBTR (5-year risk of local relapse ranging between 2% and 17 % for the genetic cohort and, between 4% and 15% for the sporadic cohort; 10-year risk of local relapse ranging from 12% to 18% for the genetic cohort, and from 8% to 25% for the sporadic cohort). Four studies including 982 patients noted a statistically higher IBTR risk in the genetic cohort (5-year risk of local relapse ranging from 14% to 29% for the genetic cohort, and from 6% to 18% for the sporadic cohort; 10-year risk of local relapse ranging between 30% and 41% for the genetic cohort, and between 16% and 19% for

the sporadic cohort). However, none of the studies reporting an increased IBTR risk among hereditary breast cancer patients addressed the effect of adjuvant HT on recurrence risk either because no patients received tamoxifen[74,77] or because sample sizes were too small.[66,78] In addition, the increased IBTR risk, noted by some authors, did not compromise overall survival. Furthermore, seven studies observed that genetic carriers had a higher probability of developing a second primary breast cancer (metachronous primary) rather than true recurrence (synchronous primary). This was based either on longer time interval to local recurrence,[63,72,75,80] and/or different location and histology.[63,66,74,75,78,80] Two uncontrolled cohort studies reported a 10-year actuarial risk of local relapse rate of 11.5% and 13.6% respectively.[70,79] Turner et al., looking only at patients experiencing recurrence, found a high proportion of *BRCA1/2* mutation carriers in a subgroup of patients younger than 40 years of age.[75] Local recurrence after total mastectomy was reported in two studies without conclusive data.[77,78]

3.5.2. *Survival outcome*

Nine studies addressed survival outcomes: disease free survival (DFS) or distant disease free survival (DDFS) or metastasis free interval (MFS) or relapse free interval (RFS) (Table 3). Two studies found that genetic carriers had worse DDFS as compared to controls after multivariate analyses: 5-year DDFS 58% versus 82% and 10-year DDFS of 66.2% versus 84.3% respectively.[67,76] In a subgroup analysis, one author reported that *BRCA1* patients had a worse MFS.[71] Fourteen controlled studies provided information on overall survival (OS) or breast cancer specific survival (BCSS). Most did not show adverse survival outcome for *BRCA* carriers (11/14). After subgroup analyses, two authors reported significantly worse OS in mutation carriers who did not receive CT[67] or in node

Table 4 – Contralateral breast cancer

Author *(reference)*		Contralateral BC		*P*	Remark		
		Cases	Controls				
Brekelmans 2005[64]	**5 years**	16%	3%	< 0.001	*BRCA1* Index cases	5 years 18%	10 years 26%
	10 years	27%	5%		Unselected *BRCA1*	16%	27%
Verhoog 1999[65]	**5 years**	12%	2%	0.02			
Seynaeve C EJC 2004[66]	**Incidence**	13.8%	6.3%	0.06	*BRCA1* inc HBC inc		23.1% 10.8%
Robson Br C Res 2004[67]	**10 years**	*BRCA1* 27% *BRCA2* 32%	8%	<0.0001	Risk lower in *BRCA* receiving Tam(NS)		
Goffin 2003[68]				**ND**			
Robson 1998[69]	**5 years**	31%	4%	0.0007	**Incidence**	40%	8.2%
Robson 2004[70]	**10 years**	37.6%			*BRCA1* inc *BRCA2* inc		15 5
Stoppa-Lyonnet 2000[71]	**5 years**	14%	17%	NS			
Kirova 2005[72]	**Incidence**	*BRCA1* 37% *FH+* 18.3%	7.3%	0.0001			
Delabge 2003[73]				**ND**			
Pierce 2006[63]	**10 years** **15 years**	25% 39%	3% 7%	0.0001	Risk lower in *BRCA* receiving Tam ($p = 0.05$)		
Haffty 2002[74]	**5 years** **10 years**	22% 31%	4% 7%	0.001			
Turner 1999[75]	**Incidence**	*BRCA1* 63%					
Chappuis 2000[76]	**5 years**	10%	2%	0.02			
El Tamer 2004[77]	**5 years**	*BRCA1* 23% *BRCA2* 19%	12%	0.05			
Bremer 2003[78]				**ND**			
Metcalfe 2004[79]	**5 years** **10 years**	16.9% BRCA132% BRCA2 24.5%			97 Cont BC/336 without PM Risk lower in *BRCA* receiving Tam (0.05) Risk lower if BSO (0.03)		
Eccles 2001[80]	**Incidence**	35.9%	16%	0.0007			
Johannsson 1998[81]				**ND**			
Gaffney 1998[82]	**Incidence**	*BRCA1* 13% *BRCA2* 10%					

ND no data; **PM** prophylactic mastectomy; **BSO** bilateral salpingo-oophorectomy; **ContBC** contralateral breast cancer, **Tam** tamoxifen; **Inc** incidence.

negative *BRCA1* patients;[68] one study, in which details on adjuvant treatment were not available, found a worse OS in the genetic cohort.[71]

3.5.3. *Contralateral breast cancer (Table 4)*

Sixteen of the 20 studies addressed the issue of contralateral breast cancer; among them, one specifically assessed the risk of contralateral breast cancer in a cohort of *BRCA* carriers[79] and one series selected a population of bilateral breast cancer patients and looked at the local relapse rate after radiotherapy according to *BRCA* status.[78] Most studies found a higher risk of contralateral breast cancer for germline mutation carriers as compared to sporadic cases (5-year actuarial risk of contralateral breast cancer ranging from 10% to 31% for genetic cases and from 2% to 12% for sporadic cases; 10-year actuarial risk of contralateral breast cancer ranging from 25% to 31% for genetic cases and from 4% to 8% for the sporadic cases) (Table 4). In addition, three out of four authors evaluated the effect of adjuvant systemic therapy on contralateral breast cancer risk, and found a lower risk in *BRCA* carriers receiving tamoxifen compared to those who did not.[63,67,79] This difference was not statistically significant in the study by Robson et al.,[67] and disappears after correction for other confounding factors such as age, mutation and other treatments in the study by Metcalfe et al.[79] One author found that bilateral-salpingo-oophorectomy significantly decreased contralateral breast cancer risk in a large series of *BRCA1* and *BRCA2* mutation carriers (HR = 0.41; 95% CI = 0.18 to 0.90; *P* 0.03).[79] The combination of bilateral-salpingo-oophorectomy and tamoxifen was particularly effective in women younger than 50 years of age (HR = 0.09; 95% CI = 0.01 to 0.68). In the same uncontrolled series, after a mean follow-up period of 9.2 years, one contralateral breast cancer (in the chest wall) occurred among the 146 women treated with bilateral, prior, or delayed contralateral mastectomy. In contrast, there were 97 contralateral breast cancers diagnosed among the 336 women who kept the contralateral breast.

4. Discussion

Despite the large number of *BRCA1/2* patients who have been included in the several reviewed studies (*n*: 51), no published randomised or prospective study was found. All of the reviewed studies were retrospective with the well known associated biases such as collection and selection. In addition, the studies varied with respect to different confounding factors, numbers of patients, selecting and testing of cases and control groups, ethnic background or specific mutations. Most controlled matched studies (7/9), assessed patients selected from Family Cancer Clinics. Most authors recognised that selection biases may exist in such clinics or pedigree-based studies, all of which favourably influence prognosis: the preferential inclusion of women who are alive and have consented to undergo genetic testing, as compared with women who died early before undergoing genetic analysis.[83,84] Furthermore, such design may also influence the evaluation of other outcomes such as bilateral breast carcinoma or ovarian carcinoma since both may spuriously be more prevalent among mutation carriers.[84] In support of longevity biases, we observed that in some studies, follow up was significantly longer in mutation carriers than in control patients.[63,64,71,77] Similarly, we noted a longer mean time from diagnosis to genetic testing in women experiencing IBTR or contralateral breast cancer compared with those not experiencing these outcomes,[70] suggesting that women with longer survival are more likely to experience these events. We found that many studies differ in the way of selecting control groups and defining family history of breast cancer. Despite a restrictive definition for positive family history in some sporadic cohorts, a potential for misclassification of mutation carriers in the control sporadic cohort was possible in 16 studies. These disparate control groups imply that some hereditary cases might have been included, tending to dilute any differences between the two groups and confounding the results. In addition, since the retrospective design encountered in the majority of the reports has led to a high frequency of missing data concerning major prognostic factors such as nodal status, histological grade and ER, the power of most of the reviewed studies was limited.

On the other hand, it has not been well established that *BRCA1* and *BRCA2* can be combined in outcome analyses.[83] For example, it has been suggested that ER-negative status is an intrinsic feature of *BRCA1*-related breast cancer,[85] while many *BRCA2*-related tumours are ER-positive. There also exists the possibility that the location of the mutation may affect disease severity and thus, studies of populations with different mutation spectra may differ in outcomes.[86–88] Interpretation of genetic test results is not always straightforward because the sensitivity and specificity of molecular analysis strategies may vary with the laboratory techniques employed, the proportion of the gene tested, and the structural nature of the mutations present in the gene.[11,89] The occurrence of *BRCA1/2* variants of uncertain significance, often missense mutations, further complicates genetic assessment,[90,91] but most authors did not provide information on how these variants were tested. Ethnic background could also cause difficulties in the results interpretation since recurrent mutations are widely dispersed and are not readily identifiable in some ethnic groups.[92] However, no reviewed study specifically addressed these issues.

The issue of breast cancer recurrence after BCT in *BRCA1* and *BRCA2* mutation carriers was addressed in 17 studies. Most studies did not definitely detect an increased risk of IBTR. Young age but not *BRCA* status was found to be associated with an increased risk of local recurrence among hereditary breast cancer patients in some reviewed studies.[67,72,73] In accordance with a recent report suggesting that *BRCA1* and *BRCA2* mutations do not play a major role in chromosomal radio sensitivity *in vitro*, no increased risk of radiation toxicity was found in this review.[93] However, no study mentioned radiation toxicity as a primary or secondary endpoint. Pierce and colleagues using Radiation Therapy Oncology Group (RTOG) /European Organization for Research and Treatment of Cancer (EORTC) Radiation Morbidity Scoring, found no evidence of increased radiation sensitivity or sequelae in breast tissue heterozygous for a *BRCA1/2* germline mutation compared with controls.[62] Recently, Andrieu and colleagues analysed retrospectively a cohort of *BRCA1/2* carriers and found that chest X-rays were associated with a small increased risk of BC. Although this information is interesting,

the methodology is quite different since it relates to exposure to chest X-rays in BRCA unaffected women.[94]

Four studies noted a higher IBTR risk in women with BRCA1/2 germline mutations; there were severe limitations, however, to the latter studies precluding definitive conclusions. For instance, in the case control study by Seynaeve and colleagues, an increase in IBTR in the hereditary group after 5 years was reported (14% versus 7%).[66] However, when only the 26 proven BRCA1/2 mutation carriers were considered, no difference was found, reflecting the heterogeneity of the hereditary group which included unspecified hereditary breast cancer patients and proven BRCA1 and BRCA2 carriers. In the study by El Tamer and colleagues, a higher 5-year actuarial risk of IBTR in BRCA1 and BRCA2 patients as compared to non- carriers was seen (23% versus 12.5%) but when assessed over time in a Kaplan–Meier curve, that difference was no longer significant.[77] This may be due to the low power of these studies in view of the small number of events and the short follow up. In an unselected cohort of bilateral breast cancer patients, Bremer and colleagues described an actuarial 5-year local relapse rate of 29% in BRCA1/2 patients and of 6% in non carriers.[78] However, the size sample is again limited since only 11 patients had suffered from local relapse after radiotherapy. Finally, in the study by Haffty and colleagues, a subgroup of 127 patients under the age of 42 years was tested for genetic mutations; among the 22 mutation carriers identified, the actuarial risk of developing IBTR at 12 years was 49%. However, 66 deceased patients were not included, which may limit the robustness of the estimate.[74] The proper method to address the issue of IBTR in mutation carriers is to prospectively evaluate the recurrence frequency in a population of patients who have deleterious BRCA mutations and compare it to a matched control group with a follow up of at least 10 years.[95] To our knowledge, no such study has yet been published. Furthermore, one should also note the absence of adequate data regarding the effect of systemic adjuvant therapy on IBTR in mutation carriers. For these reasons we consider that currently there are no sufficient data to preclude BCT in patients with early stage breast cancer and BRCA mutations.

There appears to be no clear difference in survival rates between patients with hereditary breast cancer and age-matched patients with sporadic breast cancer. Four studies included in this review suggested worse survival for BRCA1 patients but all had small number of patients.[67,68,71,76] In addition, since in no study treatment was randomly assigned, a comparison between treatment groups is problematic and must be interpreted cautiously. Chappuis and colleagues, assessing 32 BRCA carriers, did find worse distant DDFS in mutation carriers as compared to sporadic cases, but there were no significant differences in OS between the two groups. The high proportion of small tumours (57% less than 2 cm; *n*: 17) and the low proportion of lymph node-positive patients (38%; *n*: 20) may have influenced the results.[76] Furthermore, since three out of the four studies restricted genetic testing to the three founder mutations described among Ashkenazi descent, their results may not be applicable to all women with BRCA1/BRCA2 mutations. In a prevalent cohort of hereditary breast cancer, assessed in a family cancer clinic, Stoppa-Lyonnet and colleagues found worse OS and MFS in BRCA1 carriers as compared to non carriers. However, the author acknowledged that non-BRCA1 familial breast cancer cases are probably an heterogeneous group since it may include BRCA2 mutation carriers, carriers of gene(s) still unidentified, sporadic cases with a family history of breast cancer occurring by chance and finally some carriers of BRCA1 mutations that escaped detection.[71]

The majority of the reviewed studies found a consistent 2–3-fold higher risk of contralateral breast cancer for mutation carriers, ranging from 25% to 31% at 10 years and estimated to be of 2.5–3% per year. As suggested by a recent review, this finding indicates that while BCT remains an option for women with BRCA-associated breast cancer, they must be closely monitored for second primary cancers.[59] Metcalfe and colleagues showed that in women treated with bilateral, prior, or delayed contralateral mastectomy the residual breast cancer risk is almost zero.[79] The available evidence shows that bilateral mastectomy may be another viable option, which will substantially reduce the risk of subsequent breast cancers in this group of patients.[12,96,97] However, the potential benefits of contralateral or bilateral prophylactic mastectomy on breast cancer mortality in BRCA carriers remain unanswered.[98] In addition, despite recent reports showing that most women (83%) are satisfied with contralateral prophylactic mastectomy, every woman should be correctly informed about the potential long term adverse effects including body image disruption, impaired sexual function, and the potential for re-operations following reconstruction.[99,100] Furthermore, a substantial proportion of patients, even when faced with high risks of second events, will not accept this option and a women's choice towards risk reduction strategies may differ from one country to another.[101–103] Finally, such a decision should be discussed in relation to the prognosis of the primary tumour and should not be taken in haste. Managing contralateral risk is part of a long term strategy which also includes bilateral salpingo-oophorectomy and tamoxifen.[104–108] In a retrospective case control study, which included 250 BRCA1/2 women with bilateral BC and 566 BRCA/2 with unilateral BC; the authors observed that the risk of contralateral breast cancer was reduced by more than 50% in carriers of BRCA1 and BRCA2 mutations when tamoxifen was given as treatment for the initial breast cancer; surprisingly, tamoxifen was almost equally effective in BRCA1 and BRCA2 carriers.[108] Although some patients with BCT were included, the investigators did not assess the effect of tamoxifen on the subsequent risk of IBTR. They also noted no additional effect of oophorectomy and tamoxifen which is in contrast with the results of the cohort study by Metcalfe and colleagues who reported that this combination was particularly effective in reducing contralateral breast cancer risk among young women.[79]

5. Conclusion

In this review we found conflicting results with respect to the outcome of breast cancer in BRCA1 and BRCA2 carriers that could be explained by various methodological flaws in the published studies. Despite a decade of reports about BRCA testing, epidemiology and molecular biology, no definitive conclusions can be made about the prognosis of BRCA1- or BRCA2-associ-

ated tumours when compared with sporadic breast cancers. Until now, except for increased risk of contralateral breast cancer, the presence of a *BRCA* mutation does not seem to offer additional prognostic information to the standard prognostic factors used for breast cancer. Although data are limited, BCT remains, today, a reasonable option for genetically predisposed breast cancer patients. A number of unanswered questions remain when managing these patients: the magnitude of risk for subsequent malignancies, the modifying effect of adjuvant systemic therapy and the need and timing of risk reduction surgical options to prevent subsequent cancers. Furthermore, risk reduction strategies like bilateral salpingo-oophorectomy, tamoxifen or other hormonal agents such as aromatase inhibitors and SERM's have not yet been correctly evaluated in such patients, nor has the survival impact of specific chemotherapy regimens been demonstrated. Although there is now substantial evidence that surveillance by magnetic resonance imaging (MRI) is more sensitive than mammography for women at high hereditary risk, the optimal surveillance strategy for early detection of a second primary breast cancer in affected carriers is not yet known.[109–112] In this era of tailored therapies and translational research, it will be very important to compare the benefits of different treatments in women with hereditary breast cancer.[113,114] Advising these women is not so much a question of whether or not they should have genetic testing with their cancer diagnosis but rather whether the results could alter treatment decisions as well as follow up strategies and risk reduction options. To answer this fundamental question and to assist these patients, large prospective studies are warranted.[115] Such studies should be properly designed and stratified for risk reduction strategies (such as bilateral salpingo-oophorectomy, prophylactic mastectomy and hormonal agents), since for instance, it has recently been reported that bilateral salpingo oophorectomy may reduce mortality.[103] The ultimate goal is to ensure that these women and their physicians use information gained from genetic testing in an optimal way leading to improved clinical and psychosocial outcomes.

Conflict of interest statement

None declared.

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