Advances in Breast Cancer Research, 2015, 4, 87-99
Published Online October 2015 in SciRes. http://www.scirp.org/journal/abcr
http://dx.doi.org/10.4236/abcr.2015.44010

Familial versus Sporadic Breast Cancer: Different Treatments for Similar Tumors?

Ellen G. Engelhardt[1], Mieke Kriege[2], Maartje J. Hooning[2], Caroline Seynaeve[2], Rob A. E. M. Tollenaar[3], Christina J. van Asperen[4], Margreet G. E. M. Ausems[5], Lonneke V. van de Poll-Franse[6], Stella Mook[7], Senno Verhoef[8], Matti A. Rookus[1], HEBON Collaborators[9], Marjanka K. Schmidt[1,10]

[1]Division of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands
[2]Family Cancer Clinic, Department of Medical Oncology, Erasmus MC-Daniel den Hoed Cancer Centre, Rotterdam, The Netherlands
[3]Department of Surgery, Leiden University Medical Centre, Leiden, The Netherlands
[4]Department of Clinical Genetics, Leiden University Medical Centre, Leiden, The Netherlands
[5]Department of Medical Genetics, University Medical Centre Utrecht, Utrecht, The Netherlands
[6]Eindhoven Cancer Registry, Comprehensive Cancer Centre South, Eindhoven, The Netherlands
[7]Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands
[8]Family Cancer Clinic, Netherlands Cancer Institute, Amsterdam, The Netherlands
[9]Hereditary Breast and Ovarian Cancer Netherlands (HEBON) Collaborators (see end of article for full list of HEBON collaborators and affiliations)
[10]Division of Molecular Pathology, Netherlands Cancer Institute, Amsterdam, The Netherlands
Email: mk.schmidt@nki.nl

Received 14 July 2015; accepted 27 September 2015; published 30 September 2015

Abstract

Objective: It is unclear if and to what extent family history of breast/ovarian cancer or *BRCA*1/2-mutation carriership influences breast cancer treatment strategy. We investigated whether treatment differed between patients from *BRCA*1/2 families and those unselected for family history. Methods: We included 478 *BRCA*1/2-related patients referred for genetic testing before or after diagnosis. Two references were used: 13,498 population-based and 6896 hospital-based patients. Surgical treatment and adjuvant chemotherapy use was analyzed using logistic regression models, stratified by tumor size, nodal status, age at and period of diagnosis, and estrogen receptor status (ER). Results: *BRCA*1/2 cases aged 35 - 52 years at diagnosis and/or with tumors < 2 cm were more likely to have undergone a modified radical mastectomy (Odd Ratios (OR) ranging from 2.8 to 5.1) compared to the references. This effect was most pronounced in patients treated after 1995 (OR 5.7 to 10.3). Compared to the reference groups, chemotherapy was more often administered to *BRCA*1 and ER-negative *BRCA*1/2-cases irrespective of age and nodal status (OR 1.9

How to cite this paper: Engelhardt, E.G., *et al.* (2015) Familial versus Sporadic Breast Cancer: Different Treatments for Similar Tumors? *Advances in Breast Cancer Research*, **4**, 87-99. http://dx.doi.org/10.4236/abcr.2015.44010

to 24.3). Conclusion: After 1995 treatment of *BRCA*1/2-associated patients consisted notably of more mastectomies and adjuvant chemotherapy than their population-based counterparts with the same tumor characteristics. There is a need to be aware of such differences in daily practice and interpretation of survival studies on *BRCA*1/2 mutation carriers.

Keywords

***BRCA*1/2, Familial, Breast Cancer, Treatment, Adjuvant Chemotherapy, Mastectomy, Breast Conserving Therapy**

1. Introduction

*BRCA*1 and *BRCA*2 mutation carriers have an increased risk of developing breast cancer at a young age. These mutations confer a lifetime-risk of 50% - 80% whereas the breast cancer risk of the general Dutch population is 13% [1] [2]. Approximately 2% - 3% of all breast cancer cases can be attributed to a mutation in the *BRCA*1 or *BRCA*2 gene [3].

Nowadays the most important prognosticators of long-term (*i.e.* ≥10-year) survival in sporadic breast cancer patients are still the traditional factors such as tumor size, nodal status, tumor grade, age at diagnosis and ER status [4]. Current evidence suggests that these prognostic factors are also relevant for survival of *BRCA*2-related breast cancer patients, while they are possibly less strong prognosticators for *BRCA*1-related breast cancer [5]-[7]. It is still under debate whether survival in *BRCA*1 carriers is different from that of non-carriers. One out of two reviews based on limited evidence concluded that *BRCA*1 carriers have a worse overall and progression-free survival time compared to non-carriers [8] [9]. Current guidelines on breast cancer treatment do not take genetic status into account [10] [11].

In the Netherlands, breast cancer treatment guidelines for local therapy (surgery/radiotherapy) existed on a regional level as far back as the early 1970's. Breast conserving surgery was introduced in the mid-eighties following the publication of the European Organization for Research and Treatment of Cancer (EORTC) 10801 trial [12], while the first national Dutch guideline regarding adjuvant systemic therapy was implemented by the Dutch Institute for Healthcare Improvement [13] in 1998 following the presentation of the meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [14], initiating a wider use of adjuvant systemic therapy most notably for node negative breast cancer [14] [15]. Continuous improvements in breast cancer treatment over the past decades, including local and systemic adjuvant therapy and the introduction of breast cancer screening, have played an important role in improving long-term breast cancer survival [16] [17].

In the Netherlands, Family Cancer Clinics were established in the early 1990's, and after the identification of the breast cancer susceptibility genes *BRCA*1 and *BRCA*2 in 1994 and 1995, respectively, referral for genetic testing and counselling became more frequent. Nowadays, breast cancer genetic counselling has become common practice in the Netherlands. Especially female breast cancer patients diagnosed at a young age (<35 years) or those with a (extensive) family history of breast and/or ovarian cancer are referred for genetic testing [18]. The uptake of preventive surgery by women with a *BRCA*1/2 mutation in the Netherlands—with 35% opting for prophylactic mastectomy and 49% for salpingo-oophorectomy—is relatively high compared to other western countries [19]-[21]. Several studies have shown that preventive salpingo-oophorectomy not only reduces the risk of developing ovarian/fallopian tube cancer, but also reduces the breast cancer risk in *BRCA*1/2-mutation carriers by 50% - 72%; whereas bilateral prophylactic mastectomy reduces the risk of breast cancer by approximately 90% - 95% [21]-[24]. Furthermore, prophylactic salpingo-oophorectomy has been shown to improve the overall and cancer-specific survival, including breast cancer-specific survival, in *BRCA*1/2-mutation carriers [21] [23] [25], while data on a beneficial effect of preventive mastectomy on survival are not yet available.

While the influence of genetic status or family history of breast/ovarian cancer on the decision making regarding prophylactic surgery (*i.e.* prophylactic mastectomy or salpingo-oophorectomy) has been the subject of several studies, it has never been explored whether a family history of breast/ovarian cancer and/or knowledge of *BRCA*1/2-carriership affect choices for breast cancer treatment [26]. Therefore the aim of the current study was to determine whether patients from *BRCA*1 and *BRCA*2 families received more extensive breast cancer treatment compared to sporadic breast cancer cases.

2. Methods

2.1. Patient Selection and Data Collection

For the current case-case study, which was conducted as part of the Hereditary Breast and Ovarian cancer Netherlands (HEBON) Resource study, females in *BRCA*1/2 families diagnosed with breast cancer between 1980 and 2007 were identified through the Gene-Environment Research in Hereditary Breast and Ovarian cancer Netherlands (GEO-HEBON) database [27]. All breast cancer patients who underwent genetic counselling and were (partly) treated at the Antoni van Leeuwenhoek hospital, Amsterdam, Erasmus MC-Daniel den Hoed cancer clinic, Rotterdam, Leiden University Medical Centre or University Medical Centre Utrecht were selected from the GEO-HEBON database (n = 590). Cases with distant metastases at diagnosis or only a ductal carcinoma in situ were excluded (n = 112), leaving 366 *BRCA*1 and 112 *BRCA*2 breast cancer cases for analyses. These 478 breast cancer patients consisted of women who were genotyped as *BRCA*1/2 mutation carrier before breast cancer diagnosis (n = 36), women who were genotyped as *BRCA*1/2 mutation carrier after breast cancer diagnosis (n = 383), and women who had not (yet) undergone genetic testing, but belonged to proven *BRCA*1/2 families and were a first degree family member of a proven mutation carrier (= obligate carrier) (n = 59). These *BRCA*1/2-familial cases are all referred to as *BRCA*1/2 cases in this paper, keeping in mind that the majority of these patients were treated for breast cancer not yet knowing that they were a *BRCA* mutation carrier, as *BRCA*-testing started in 1995 approximately. From July 2009 until January 2010 for all eligible patients detailed information on tumor characteristics, surgical and systemic treatment for the primary breast cancer, and follow-up data regarding local recurrence, distant metastases, other primary tumors and death was extracted from medical records, the GEO-HEBON and other existing (clinical) oncology databases.

We used two reference populations, a general population-based sample of breast cancer cases from the Comprehensive Cancer Centre South database (n = 13,498) [28] and a hospital-based case series from the Antoni van Leeuwenhoek cancer-specialized hospital (NKI-AVL), Amsterdam (n = 6896), applying the same exclusion criteria as for the *BRCA*1/2 cases. The patients from the hospital-based series were diagnosed with breast cancer between 1987-2000 [29]. The cancer hospital-based reference group was included in addition to the population-based reference group (mainly treated in general hospitals), to account for possible differences in treatment strategy between cancer-specialized and general hospitals.

Primary breast cancer treatment included local surgery, consisting of either a modified radical mastectomy or breast conserving therapy aiming at radical excision, followed by adjuvant radiotherapy (on indication after modified radical mastectomy, and always after breast conserving therapy). Also, adequate treatment of the axillary lymph nodes was performed, consisting of either systematic axillary dissection or sentinel lymphadenectomy (SN-procedure, as of the year 2000 approximately). The clinical decision to opt for a modified radical mastectomy or breast conserving surgery was largely based on tumor size (in combination with tumor location and breast volume). Adjuvant systemic therapy (*i.e.* chemotherapy and/or hormonal therapy) was administered after local therapy depending on the patient's age/menopausal status (≤52 years premenopausal, >52 years postmenopausal), tumor stage (tumor size, and nodal status), and later also depending on tumor characteristics (e.g. differentiation grade and hormone receptor status). Since the latter part of the 1990s hormone receptor status, mainly ER status, became an important discriminating factor regarding the type of systemic treatment; a positive ER status was recognized as a predictive factor for efficacy of endocrine therapy, while in case of negative ER status only chemotherapy was considered [13] [30].

2.2. Ethical Standards

The HEBON Resource study was approved by the Review Board of the NKI-AVL, and according to Dutch law, no further institutional Review Board approval was needed. The use of all data in this manuscript, including that of the two control cohorts, complies with Dutch laws and follows the Scientific Codes published by the Dutch federation of Biomedical Scientific Societies [31].

2.3. Statistical Analysis

In order to quantitatively assess breast cancer treatment, we divided treatment into two dichotomous variables, namely 1) type of surgical treatment (modified radical mastectomy versus breast conserving therapy) and 2) use of adjuvant chemotherapy (yes versus no). Only 10% of *BRCA*1/2 cases had received both chemotherapy and

hormonal therapy.

Odds ratio's for undergoing a modified radical mastectomy (versus breast conserving therapy) and for receiving chemotherapy were calculated using multivariate logistic regression analyses for *BRCA*1 and *BRCA*2 cases compared to population- and cancer hospital-based reference groups. A priori we expected the *BRCA*1/2 cases to be younger and to have different tumor characteristics. Based on these differences, but also based on covariates, which might influence breast cancer treatment decisions, we decided for which characteristics we would stratify and/or adjust our analyses. Logistic regression models for surgery were stratified for tumor size (≤2 cm and >2 cm) age at breast cancer diagnosis (<35, 35 - 52, >52) and period of breast cancer diagnosis (≤1995, >1995 (introduction of *BRCA*1/2 mutation testing in the Netherlands) and ≤1998, >1998 (paradigm shift in adjuvant treatment). Analyses for chemotherapy were stratified for nodal status (negative, positive), age at breast cancer diagnosis (<35, 35 - 52, >52) and period of breast cancer diagnosis (≤1995, >1995 and ≤1998, >1998). Additionally the logistic models for chemotherapy were also run for ER negative cases only (with *BRCA*1 and *BRCA*2 patients combined due to small numbers). In the logistic regression models for surgery and for chemotherapy, covariates included were differentiation grade (1, 2, 3, and missing), nodal status (node negative, node positive, and missing), tumor size (≤2 cm, >2 cm, and missing), estrogen receptor status (positive, negative, and missing), age at breast cancer diagnosis (<35 years, 35 - 52, and >52), unless the model was stratified for that factor. In the analyses for *BRCA*1 cases versus the reference groups, stratified for multiple factors, only cases with grade 3 tumors were included since grade 1 and grade 2 tumors are rare in *BRCA*1 cases. All statistical analyses were performed using SPSS Inc.18. A two-sided p of <0.05 was considered significant.

3. Results

Of the 478 *BRCA*1/2 breast cancer patients included, 419 were identified as *BRCA*1 (N = 323) or *BRCA*2 (N = 96) mutation carriers themselves, and 59 obligate mutation carrier. Breast cancer was diagnosed before 1995 in 256 (54%) of the *BRCA*1/2 cases and after 1995 in 222 (46%). Of the 222 *BRCA*1/2 cases diagnosed after 1995, 36 (16%) were aware of their own carriership status and 16 (7%) were aware of a *BRCA*1 or *BRCA*2 mutation in their family at breast cancer diagnosis and treatment.

Characteristics of *BRCA*1/2 cases and of the two reference groups are shown in **Table 1**. Mean age at breast cancer diagnosis was 41 and 44 years for *BRCA*1 and *BRCA*2 patients, respectively, compared with 57 years and 55 years for the population-based and hospital-based reference groups, respectively. The majority of the *BRCA*1 and *BRCA*2 patients had grade 3 tumors (88% and 69%, respectively), while this was only 32% and 31% for the population-based and hospital-based reference groups, respectively. The majority of the *BRCA*1 tumors were ER negative (77%) compared with 25% of the *BRCA*2 tumors and 23% of the tumors in both reference groups.

We had data on prophylactic surgery for 408 of the 478 *BRCA*1/2 cases; 24 of them underwent a prophylactic salpingo-oophorectomy and 56 a mastectomy within 1 year of the diagnosis of the primary tumor (no data available for reference groups).

3.1. Type of Surgery

Figure 1 shows unadjusted trends in chemotherapy and surgical treatment per year. Type of surgical treatment by tumor size and nodal status for the two reference groups is shown in **Table 2(a)** and for the *BRCA*1/2 cases in **Table 2(b)**. Within the *BRCA*1/2 cases having a tumor ≤ 2 cm, 64% of those identified as mutation carrier prior to their breast cancer diagnosis underwent a modified radical mastectomy compared to 35% of *BRCA*1/2 cases who had not yet been referred for genetic testing. For the population- and hospital-based reference groups these percentages were 27% and 20%, respectively. *BRCA*1/2 cases with a tumor ≤ 2 cm more often had a mastectomy and received chemotherapy (53%) than the general population- and hospital-based reference groups (<30%) (**Table 2(c)**). So, *BRCA*1/2 cases with tumors ≤ 2 cm underwent a modified radical mastectomy 1.6 to 3.1 times more often than the population- and hospital-based cases, respectively (**Table 3**), while there were no significant differences in type of surgery between *BRCA*1/2 cases and the reference patients with tumors > 2 cm. After stratification for age at diagnosis, *BRCA*1/2 cases aged 35 - 52 years were significantly more likely to undergo a modified radical mastectomy compared to the reference population cases. If we stratified for tumor size and age at diagnosis (only enough cases for the *BRCA*1 subgroup), the higher percentage of modified radical mastectomy in *BRCA*1 cases only remained significant in the subgroup of patients diagnosed between 35 - 52 years and having a tumor ≤ 2 cm. In patients treated before 1995, we did not observe a higher rate of modified radical

Table 1. Population characteristics.

	Clinical genetic centers		Reference groups	
	*BRCA*1	*BRCA*2	Population based	Hospital based
Medical centers, patients (N)				
Antoni van Leeuwenhoek hospital	79	30	NA	6896
Erasmus MC- Daniel den Hoed Cancer Center	212	44	NA	NA
Leiden University Medical Center	51	36	NA	NA
University Medical Center Utrecht	24	2	NA	NA
Comprehensive Cancer Center South	NA	NA	13498	NA
Total (N)	366	112	13498	6896
Diagnosis year (N (%))				
Range	1980-2006	1981-2006	1980-2007	1987-2000
1980-1990	110 (30)	35 (31)	3860 (28)	1541 (22)
1991-2000	202 (55)	49 (44)	5112 (38)	5355 (78)
2001-2010	54 (15)	28 (25)	4526 (34)	0
Age at diagnosis (N (%))				
Mean age (range)	41 (19 - 72)	44 (31 - 81)	57 (20 - 81)	55 (23 - 81)
<35 years	108 (30)	16 (14)	359 (3)	266 (4)
35 - 52 years	211 (58)	76 (68)	4782 (35)	2998 (43)
>52 years	47 (12)	20 (18)	8357 (62)	3632 (53)
Differentiation grade (N (%))				
Grade 1	1 (<1)	4 (6)	1523 (22)	1053 (19)
Grade 2	29 (12)	17 (25)	3091 (46)	2724 (50)
Grade 3	210 (88)	46 (69)	2168 (32)	1727 (31)
Missing	126	45	6716	1392
Tumor diameter (N (%))				
≤2 cm	172 (52)	51 (52)	7064 (54)	3529 (52)
>2 cm	157 (48)	47 (48)	6087 (46)	3320 (48)
Missing	37	14	347	47
Estrogen receptor (N (%))				
Negative	189 (77)	19 (25)	2196 (23)	1050 (23)
Positive	56 (23)	57 (75)	7443 (77)	3536 (77)
Missing	121	36	3859	2310
Nodal status (N (%))				
Negative	225 (66)	49 (47)	6624 (55)	3143 (48)
Positive	115 (34)	56 (53)	5348 (45)	3435 (52)
Missing	26	7	1526	318

NA = not applicable.

mastectomy in *BRCA*1/2 cases with a tumor ≤ 2 cm compared to the reference groups, while *BRCA*1 cases with tumors ≤ 2 cm diagnosed after 1995 had higher odds of undergoing a modified radical mastectomy compared to the population-based (OR = 5.8, 95% CI 3 - 11.2) and the hospital-based cohort (OR = 10.3, 95% CI 4.8 - 22.3) (**Table 3**). The analyses stratified for prior or post 1998 showed similarly increased odds for undergoing modified radical mastectomy in the *BRCA*1/2 cases diagnosed after 1998 (data not shown).

3.2. Adjuvant Chemotherapy

Administration of chemotherapy in relation to negative or positive nodal status is shown in **Table 2(a)** and **Table 2(b)** for the reference and *BRCA*1/2 groups, respectively. Chemotherapy was more often administered in

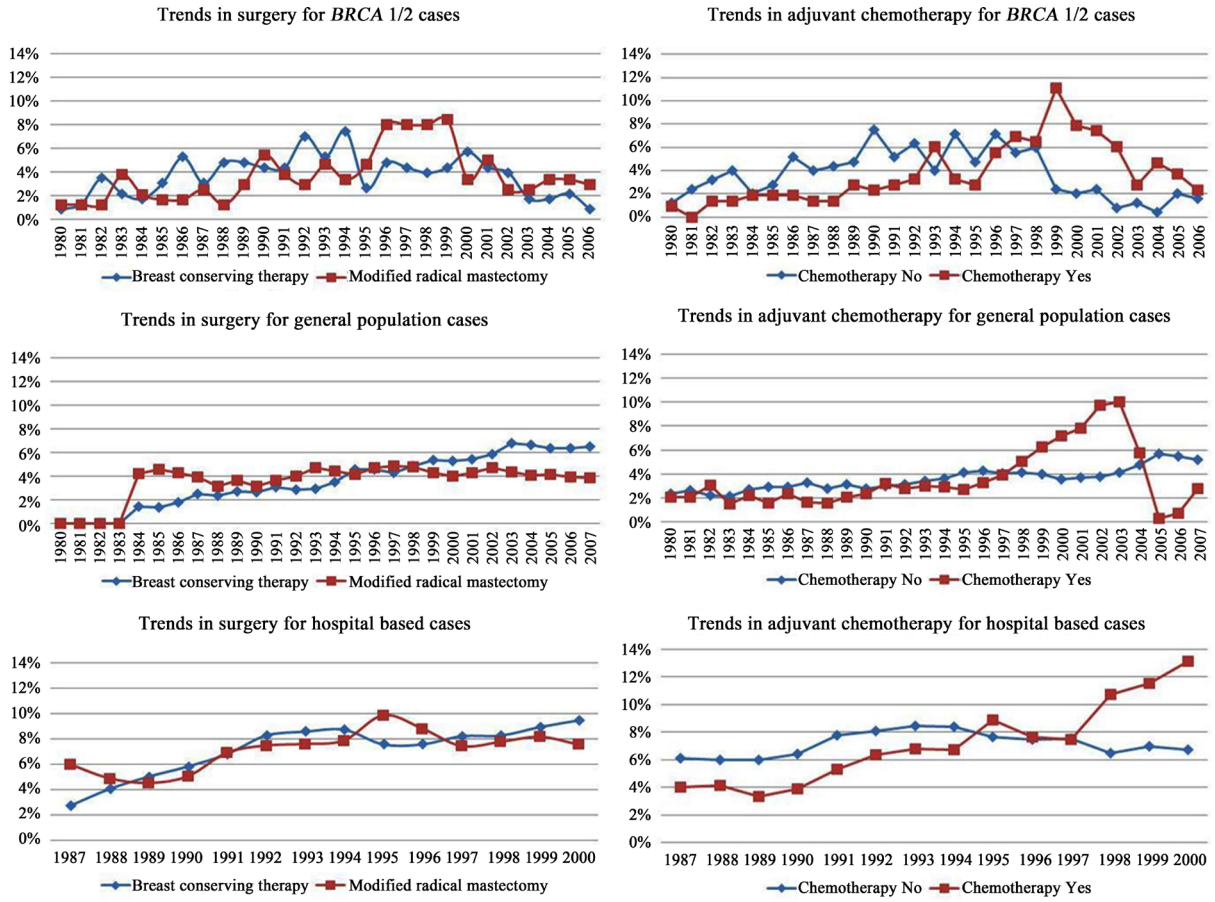

Figure 1. Trends in surgical and adjuvant chemotherapy for population subgroups.

node-negative *BRCA*1/2 patients genotyped prior to their breast cancer diagnosis (73%) compared to *BRCA*1/2 patients who had not yet been tested (17%; **Table 2(b)**); at least partly related to the fact that more chemotherapy was given in later years of diagnosis. *BRCA*1 and ER-negative (*BRCA*1and *BRCA*2 combined) cases across all ages and irrespective of lymph node involvement had higher odds of receiving chemotherapy compared to both reference groups while a higher odds for of receiving chemotherapy in *BRCA*2 cases was especially observed in the node positive subgroup and in the subgroups of 35 - 52 years and >52 years at diagnosis (**Table 4**). The higher odds of receiving chemotherapy in *BRCA*1/2 cases compared with the reference groups was observed in patients treated before as well as after 1995, but numbers were too small for adjusted analyses (**Table 4**). Node positive *BRCA*1 cases treated both prior to and after 1998 had increased odds of receiving chemotherapy compared to the population-based cases (OR = 5,95% CI 2.4 - 10.2; OR = 4.1, 95% CI 1.2 - 14.2). Moreover, node negative *BRCA*1 cases treated after 1998 also showed significantly increased odds of receiving chemotherapy compared to the population reference group (OR = 13.1, 95% CI 5.8 - 29.4) (other data for this comparison not shown). In the current study data regarding hormonal therapy was also collected, however, the numbers of *BRCA*1/2 patients receiving adjuvant hormonal therapy were too small (57 cases) to perform separate analyses.

4. Discussion

Overall we found that *BRCA*1/2 cases more often underwent a modified radical mastectomy, especially *BRCA*1 and *BRCA*2 cases diagnosed after 1995 with tumours ≤ 2 cm, and more often received adjuvant chemotherapy, especially in *BRCA*1 cases and/or ER-negative tumors, compared to unselected breast cancer cases with similar tumor characteristics from hospital- and population-based reference groups. These findings highlight the importance of taking type of treatment into account when comparing survival between mutation carriers and sporadic cases, something which is rarely done by studies published so far, as demonstrated by a recent systematic review

Table 2. (a)Type of surgery and administration of chemotherapy for the reference groups; (b) Type of surgery and administration of chemotherapy by tumor subgroup in relation to timing of DNA testing; (c) Type of surgery and administration of chemotherapy by nodal status for each study population.

(a)

		Population-based[1]	Hospital-based[1]	P[2]
	Type of surgery (*N* (%))			
≤2 cm	Breast conserving therapy	4758 (73)	2649 (80)	**<0.001**
	Modified radical mastectomy	1836 (27)	643 (20)	
>2 cm	Breast conserving therapy	1803 (35)	1240 (41)	**<0.001**
	Modified radical mastectomy	3324 (65)	1793 (59)	
	Adjuvant chemotherapy (*N* (%))			
Node negative	Yes	277 (4)	132 (4)	0.967
	No	6347 (96)	3011 (96)	
Node positive	Yes	1773 (33)	1477 (43)	**<0.001**
	No	3575 (67)	1958 (57)	

[1]Numbers of patients varies due to missing values.
[2]P values from Chi-square tests; because these are unadjusted for patient and tumor differences between the references populations, these should not be interpreted as differences in treatment practices between these populations.

(b)

		Clinical Genetic Centers		P[3]
		DNA test pre breast cancer diagnosis[1,2]	DNA test post breast cancer diagnosis[2]	
	Type of surgery (*N* (%))			
≤2 cm	Breast conserving therapy	10 (36)	106 (65)	**0.011**
	Modified radical mastectomy	18 (64)	57 (35)	
>2 cm	Breast conserving therapy	10 (43)	58 (39)	0.441
	Modified radical mastectomy	13 (57)	89 (61)	
	Adjuvant chemotherapy (*N* (%))			
Node negative	Yes	24 (73)	34 (17)	**<0.001**
	No	9 (27)	169 (83)	
Node positive	Yes	14 (88)	107 (81)	0.677
	No	2 (12)	25 (19)	

[1]DNA test pre breast cancer diagnosis means that either the case herself or a family member had undergone BRCA genetic testing and received the results of the test prior to the woman included being diagnosed with breast cancer.
[2]Numbers of patients varies due to missing values
[3]P values from Chi-square tests; because these are unadjusted for patient and tumor differences between the pre-and post-breast cancer diagnoses tested carriers, these should not be interpreted as differences in treatment practices between those groups.

(c)

	Treatment		Population			P[1]
	Adjuvant chemotherapy	*Type of surgery* (*N* (%))	*BRCA* 1/2 *cases*	*General population-based*	*Cancer hospital-based*	
Node negative	No	Breast conserving therapy	130 (63)	3488 (62)	2223 (81)	**<0.001**
		Modified radical mastectomy	75 (37)	2114 (38)	531 (19)	
	Yes	Breast conserving therapy	30 (45)	144 (55)	90 (71)	**0.001**
		Modified radical mastectomy	36 (55)	118 (45)	36 (29)	
Node positive	No	Breast conserving therapy	6 (21)	1330 (43)	702 (39)	**0.008**
		Modified radical mastectomy	22 (79)	1799 (57)	1087 (61)	
	Yes	Breast conserving therapy	50 (36)	697 (44)	609 (44)	0.155
		Modified radical mastectomy	90 (64)	884 (56)	780 (56)	

[1]P values from Chi-square test; because these are unadjusted for patient and tumour differences, these should not be interpreted as differences in treatment practices between groups.

Table 3. Odds of undergoing a modified radical mastectomy versus breast conserving therapy for *BRCA1/2* cases compared to population- and cancer hospital-based cases.

Subgroup			N	*BRCA*1/2 cases versus population-based cases		*BRCA*1/2 cases versus hospital-based cases	
				Unadjusted	Adjusted[1]	Unadjusted	Adjusted[1]
				OR (95%-CI)	OR (95%-CI)	OR (95%-CI)	OR (95%-CI)
Cases stratified by tumour diameter							
BRCA 1	≤2 cm		171	1.7 (1.2 - 2.3)	1.6 (1.2 - 2.3)*	2.7 (1.9 - 3.7)	2.9 (2.0 - 4.2)*
	>2 cm		156	0.7 (0.5 - 0.9)	0.8 (0.6 - 1.1)	0.9 (0.6 - 1.2)	1.5 (1.0 - 2.2)*
BRCA 2	≤2 cm		51	2.0 (1.1 - 3.4)	1.9 (1.1 - 3.3)*	3.1 (1.8 - 5.5)	3.1 (1.7 - 5.6)*
	>2 cm		47	1.2 (0.6 - 2.1)	1.3 (0.7 - 2.4)	1.5 (0.8 - 2.7)	1.9 (1.0 - 3.7)
Cases stratified by age at breast cancer diagnosis							
BRCA 1	<35		107	0.8 (0.5 - 1.3)	0.8 (0.5 - 1.4)	1.0 (0.7 - 1.6)	1.4 (0.8 - 2.4)
	35 - 52		205	1.4 (1.1 - 1.9)	1.5 (1.1 - 2.0)*	1.8 (1.4 - 2.4)	2.5 (1.8 - 3.5)*
	>52		42	1.3 (0.7 - 2.4)	1.2 (0.6 - 2.3)	1.6 (0.9 - 2.9)	1.8 (0.9 - 3.7)
BRCA 2	<35		16	1.0 (0.4 - 2.8)	1.0 (0.3 - 3.0)	1.3 (0.5 - 3.7)	1.3 (0.4 - 4.1)
	35 - 52		76	2.0 (1.3 - 3.2)	1.9 (1.1 - 3.1)*	2.6 (1.6 - 4.1)	2.6 (1.5 - 4.4)*
	>52		20	2.3 (0.9 - 5.6)	2.4 (0.9 - 6.8)	2.7 (1.1 - 6.7)	4.4 (1.5 -12.9)*
Cases stratified by age at breast cancer diagnosis and tumour diameter							
BRCA 1(*only grade 3 tumours included*	<35	≤2 cm	27	2.1 (0.8 - 5.9)	x^2	1.8 (0.7 - 4.9)	x^2
		>2 cm	34	0.4 (0.2 - 0.9)	0.5 (0.2 - 1.4)	0.7 (0.3 - 1.7)	1.4 (0.5 - 4.0)
	35 - 52	≤2 cm	63	2.5 (1.5 - 4.4)	2.8 (1.6 - 4.8)*	3.5 (2.0 - 6.2)	5.1 (2.7 - 9.8)*
		>2 cm	54	1.2 (0.7 - 2.1)	1.5 (0.8 - 2.6)	1.1 (0.6 - 2.0)	1.9 (1.0 - 3.7)
	>52	≤2 cm	11	0.6 (0.1 - 2.7)	0.6 (0.1 - 2.9)	0.6 (0.1 - 2.7)	0.9 (0.1 - 5.0)
		>2 cm	12	0.8 (0.2 - 2.4)	0.9 (0.3 - 2.9)	0.9 (0.3 - 2.8)	2.4 (0.6 - 9.3)
BRCA 2[2]							
Cases stratified by year of diagnosis and tumour diameter							
BRCA 1 (*only grade 3 tumours included*	≤1995	≤2 cm	53	0.8 (0.4 - 1.6)	x^2	0.9 (0.4 - 1.7)	x^2
		>2 cm	37	0.5 (0.3 - 1.1)	0.8 (0.4 - 1.8)	1.0 (0.5 - 1.9)	2.4 (1.1 - 5.3)*
	>1995	≤2 cm	48	5.7 (3.0 - 10.7)	5.8 (3.0 - 11.2)*	6.5 (3.4 - 12.6)	10.3 (4.8 - 22.3)*
		>2 cm	63	1.0 (0.6 - 1.8)	1.0 (0.6 - 1.8)	0.9 (0.5 - 1.6)	1.5 (0.8 - 2.8)
BRCA 2[2]							

[1]Model with surgery (modified radical mastectomy versus breast conserving therapy) adjusted for: differentiation grade (grade 1 & 2 (ref), grade 3 and missing), nodal status (node positive (ref), node negative and missing), age at breast cancer incidence (<35 years, 35 - 52 years (ref) and > 52 years, tumour diameter (≤2 cm (ref), >2 cm, missing). All models were adjusted for the above-mentioned factors, unless the model was stratified for that factor.
[2]Insufficient cases to run the model.
*Statistically significant ($P < 0.05$) (indicated only for adjusted ORs).

that found that of 66 studies assessing the survival of *BRCA*1/2 mutation carriers, only 8 corrected for confounding by adjuvant treatment [32]. Current evidence suggests that contrary to currently held beliefs, if confounding by treatment is taken into account, differences in survival between *BRCA*1/2 mutation carriers and sporadic breast cancer patients if any are likely to be small.

The Dutch guidelines for breast cancer treatment do not differ specifically for *BRCA*1/2 cases and sporadic breast cancer cases. Breast conserving surgery was introduced in 1986 following the EORTC 10,801 trial [12]. Age by itself and tumor size have been shown to be important factors in the choice of type of breast cancer surgery, but even within the Netherlands there is variance between hospitals [33]. In our analysis, we found an increased probability of more extensive surgery in *BRCA*1/2 cases with a tumor ≤ 2 cm, both compared to the NKI-AVL cancer hospital-based (where 22% of the *BRCA*1/2 cases had also been treated) as well as to the

Table 4. Odds of receiving chemotherapy for *BRCA*1/2 cases compared to population-based and cancer hospital-based cases.

Subgroup			N	*BRCA*1/2 cases versus population-based cases		*BRCA*1/2 cases versus hospital-based cases	
				Unadjusted	**Adjusted[1]**	**Unadjusted**	**Adjusted[1]**
				OR (95%-CI)	OR (95%-CI)	OR (95%-CI)	OR (95%-CI)
Cases stratified by nodal status							
BRCA 1	Negative		223	8.8 (6.4 - 12.1)	1.9 (1.3 - 2.7)*	8.8 (6.2 - 12.4)	2.5 (1.7 - 3.8)*
	Positive		115	9.6 (5.9 - 15.6)	4.3 (2.4 - 7.6)*	6.3 (3.9 - 10.2)	2.7 (1.4 - 5.3)*
BRCA 2	Negative		49	2.6 (1.0 - 6.6)	0.9 (0.3 - 2.4)	2.6 (1.0 - 6.6)	1.2 (0.5 - 3.4)
	Positive		56	9.3 (4.7 - 18.4)	4.4 (2.0 - 9.7)*	6.1 (3.1 - 12.1)	2.7 (1.1 - 6.5)*
ER-negative only BRCA 1/2 *combined*	Negative		142	4.6 (3.1 - 6.8)	2.0 (1.3 - 3.1)*	24.3 (15.2 - 38.9)	x[b]
	Positive		65	8.4 (4.1 - 17.1)	3.8 (1.8 - 8.3)*	8.4 (4.1 - 17.0)	2.6 (1.0 - 6.7)
Cases stratified by age at breast cancer diagnosis							
BRCA 1	<35		108	1.6 (1.1 - 2.5)	3.2 (1.8 - 5.8)*	1.1 (0.7 - 1.7)	2.4 (1.2 - 4.7)*
	35 - 52		205	1.6 (1.2 - 2.2)	2.5 (1.8 - 3.6)*	1.0 (0.8 - 1.3)	2.5 (1.6 - 3.7)*
	>52		44	5.4 (2.7 - 10.7)	3.7 (1.7 - 8.0)*	6.0 (3 - 12.1)	7.8 (3.5 - 17.7)*
BRCA 2	<35		16	1.2 (0.4 - 3.2)	1.0 (0.3 - 3.3)	0.8 (0.3 - 2.2)	0.3 (0.1 - 1.1)
	35 - 52		76	2.3 (1.5 - 3.6)	2.5 (1.4 - 4.5)*	1.4 (0.9 - 2.2)	1.9 (1.0 - 3.7)
	>52		19	5.4 (2.7 -10.7)	3.5 (1.0 - 12.2)	4.8 (1.6 - 14.6)	7.4 (2.1 - 26.0)*
ER-negative only BRCA 1/2 *combined*	<35		69	2.0 (1.1 - 3.6)	3.8 (1.8 - 8.2)*	1.3 (0.7 - 2.5)	3.8 (1.2 - 12.1)*
	35 - 52		122	1.5 (1.0 - 2.2)	2.1 (1.3 - 3.3)*	1.3 (0.9 - 1.8)	4.1 (2.3 - 7.3)*
	>52		20	2.4 (0.9 - 6.2)	2.7 (1.0 - 7.7)	8.6 (3.2 - 22.8)	39.1 (8.9 - 173)*
Cases stratified by year of diagnosis and nodal status							
BRCA 1(*only grade* 3 *tumours included*)	≤1995	Negative	64	2.6 (0.8 - 9.0)	x[2]	1.9 (0.6 - 5.9)	x[2]
		Positive	28	11.2 (4.1-30.3)	10.3 (2.3 - 46.7)*	7.1 (2.7 - 18.9)	8.6 (1.8 - 40.6)*
	>1995	Negative	68	7.8 (4.5 - 13.5)	x[2]	4.3 (2.4 - 7.8)	2.8 (1.5 - 5.2)*
		Positive	37	12.9 (3.9 - 42.3)	6.6 (1.9 - 22.3)*	6.7 (2 - 22.2)	x[2]
BRCA 2[b]							
ER-negative only BRCA 1/2 *combined*	≤1995	Negative	62	4.5 (1.1 - 18.3)	1.2 (0.2 - 5.9)	4.8 (1.3 - 18.2)	x[2]
		Positive	27	8.5 (3.2 - 22.9)	3.8 (1.1 - 13.0)*	7.0 (2.6 - 18.5)	1.9 (0.5 - 7.1)
	>1995	Negative	80	5.8 (3.5 - 9.6)	3.0 (1.7 - 5.2)*	38.8 (21.5 - 70.2)	x[2]
		Positive	38	8.3 (2.9 - 23.7)	5.0 (1.7 - 14.9)*	9.9 (3.5 - 28.1)	x[2]

[1]Model with surgery (modified radical mastectomy versus breast conserving therapy) adjusted for: differentiation grade (grade 1 & 2 (ref), grade 3 and missing), nodal status (node positive (ref), node negative and missing), age at breast cancer incidence (<35 years, 35 - 52 years (ref) and >52 years, tumour diameter (≤2 cm (ref), >2 cm, missing). All models were adjusted for the above-mentioned factors, unless the model was stratified for that factor.
[2]Insufficient cases to run the model.
*Statistically significant (P < 0.05) (indicated only for adjusted ORs).

population-based reference group. It seemed that particularly after 1995, the *BRCA*1/2 cases were more likely to receive a modified radical mastectomy for smaller tumors, but we lacked power to investigate the effects of knowledge of *BRCA*-carriership. It is known that a part of the affected *BRCA*1/2 cases also choose for a contralateral preventive mastectomy (in combination with a modified radical mastectomy of the affected breast) to prevent contralateral breast cancer [20], which might play a role in the higher rate of modified radical mastectomies observed in *BRCA*1/2 cases in this study. Unfortunately, in the current study it is unknown how many *BRCA*1/2 cases underwent a contralateral mastectomy. Our observations also may reflect the (early) perception of many physicians that more extensive surgery for mutation carriers would be better in the long term. Possibly, effects of a general time trend of increased use of modified radical mastectomy in patients < 50 years also played a role [33].

Both node positive and node negative *BRCA*1/2 cases were more likely to receive chemotherapy for ER-negative tumors. Until the publication of the EBCTCG review results in 1997 [14] and the implementation of the first Dutch guidelines on adjuvant systemic breast cancer treatment in 1998, adjuvant systemic treatment was rarely used in node-negative breast cancer in the Netherlands. Since then adjuvant systemic therapy in node negative patients has become more commonplace and included in the guideline for those patients from whom a 10-year survival gain of at least 3% - 5% is expected [13] [14]. This might partly explain our observation that node negative *BRCA*1/2 cases were more likely to receive chemotherapy especially after 1998. Another explanation for this observation might be the growing awareness that *BRCA*-associated breast cancer frequently metastasized and was possibly more sensitive to chemotherapy [34] [35].

The current study confirmed the high prevalence of high-grade tumors in *BRCA*1 and *BRCA*2 cases (88% and 69%) described in the literature [9]. Nowadays differentiation grade is a factor of consideration regarding the use of adjuvant systemic therapy in node-negative breast cancer given the fact that the cumulative 10-year survival of high grade tumors has been estimated to be 30% - 78% compared to 90% - 94% for breast cancers with the lowest differentiation grade tumors [4]. However, in the current Dutch treatment guidelines a high-grade tumor alone is not considered sufficient justification for prescribing adjuvant systemic therapy [13], and effects we found were consistent also when only comparing grade 3 tumors. Moreover, in the period that the majority of the included cases were diagnosed, grade was not yet a relevant factor used in clinical decision-making. Unfortunately, we do not have information on other tumor markers such as EGFR, E-cadherin and ki67. Also, the majority of patients were treated before the nationwide introduction of Trastuzumab.

Despite the unique results of the current study, we are aware of some limitations. Ideally we would have compared *BRCA*1/2 cases to sporadic cases from the same hospitals. Young women (<40 years) treated at a general hospital were more likely to undergo breast conserving therapy compared to those treated at a teaching or academic hospital [36]. Also, a pronounced difference in the use of adjuvant systemic therapy at a hospital level was found though this did not appear to be associated with type of hospital [36]. The variations in treatment observed could be due to a delayed introduction of new techniques or implementation of new scientific insights. Importantly, overall we observed similarly increased odds, or at least overlapping confidence intervals, for the *BRCA*1/2 cases for receiving more extensive treatment compared to both the population-based and the cancer hospital-based reference groups. Secondly, the current multicenter study included a sizeable study population and had a long follow up; the treatment data is largely complete, yet a large proportion of tumor characteristics, such as tumor differentiation grade and ER-status are missing, partly due to the work-up and the factors considered during the period of treatment. Also, possibly just a few of the 59 obligate *BRCA*1/2 carriers (obligate based on mendelian inheritance) might have turned out to be *BRCA*1/2 mutation negative would they have been tested individually. Further, since no testing was performed in the reference population, there might have been some mutation carriers in these populations. However, it is unlikely that this affected the results given the large number of patients in the reference groups and the small proportion of mutation carriers expected. In addition, selection bias may have occurred as patients who were included in the GEO-HEBON cohort if they had responded to a mailed questionnaire. This could have led to the selection of those in better physical condition or the more motivated patients. If a more extensive treatment has led to a better survival, this is overrepresented in the selected cohort. Further, another draw-back of our study was the small numbers in specific subgroup analyses, producing wide confidence intervals. Also, a proportion of the *BRCA*1/2 mutation carriers were not aware of their *BRCA* status at the time of diagnosis and treatment. However, it is worth noting that although they were not aware of their *BRCA* status, family history was known and was considered an important prognostic factor. Finally, reasons driving treatment decisions were not clearly identifiable in this study, given the retrospective study design.

Currently, as far as we know, there is little information available regarding the influence of having breast cancer in the family or being a *BRCA*1/2 mutation carrier on the clinical breast cancer treatment decision process. Most studies evaluated factors influencing the decision whether or not to undergo additional preventive surgery in high risk populations, showing that *BRCA* test results are one of the most important factors in combination with the carrier's age and personal circumstances (e.g. marital status, having children) for this decision [19]. It is unknown whether these factors also play a role in decisions on breast cancer treatment for *BRCA*1/2 mutation carriers, additionally, we do not know whether the differences in treatment for *BRCA*1/2 cases observed in this study were driven by the choice of the patient or the physician. Over the last decades shared decision-making has been promoted in clinical practice and a large proportion of patients favors this trend [37]. Yet, exploration

of whether breast cancer surgeons and oncologists who shared decision-making with their patients, felt comfortable with this approach, and whether they perceived any barriers to implementation, showed a substantial gap between the high self-reported comfort levels with shared decision-making (87% - 89%) and the self- reported use (56% - 69%) [38] [39]. The physicians reported that time constraints and patient's knowledge and psychological state were the most important factors inhibiting shared decision-making [38] [39].

Conclusion

In conclusion, we found evidence of different breast cancer treatment strategies in *BRCA*1/2-associated compared to sporadic cases with similar tumor characteristics, including more mastectomies and administration of adjuvant chemotherapy among *BRCA*1/2 cases. Although it is unknown which factors exactly played a role in the treatment decision among *BRCA*1/2 mutation carriers and sporadic patients, respectively, and whether treatment choice was driven by the patient or the physician, the results of the current analyses highlight the importance of the need to be aware of such differences in daily practice and interpretation of survival studies on *BRCA*1/2 mutation carriers.

Acknowledgements

We would like to thank all patients and Esther Janssen, Kiki Jeanson, GittyJaanen, Petra Bos, Jannet Blom and Twiggy van Cronenburg for their assistance with data collection.

Authors' Contributions

MKS, MJH and CS designed the study; EGE, MKS, MJH, MK, CJvA, MGEMA, LVvdPF, SM and MAR collected the data; EGE and MKS performed the data analyses; EGE, MKS, MJH, MK and CS interpreted the data and wrote the paper; EGE, MKS, MK, MJH, CS, RAEMT, CJvA, MGEMA, LVvdPF, SM, SV, MAR read and approved the final version of the manuscript.

Funding

Dutch Cancer Society grants NKI2009-4363 and DDHK 2009-4318; NWO 184.021.007 (BBMRI-NL); Netherlands Organization of Scientific Research grant NWO/Zon-MW 91109024 (HEBON Resource).

Conflict of Interest

The authors declare that they have no conflict of interest.

Full List of HEBON Collaborators and Affiliations

The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON) consists of the following Collaborating Centers: Coordinating center: Netherlands Cancer Institute, Amsterdam, NL: M.A. Rookus, F.B.L. Hogervorst, F.E. van Leeuwen, S. Verhoef, M.K. Schmidt, J.L. de Lange; Erasmus Medical Center, Rotterdam, NL: J.M. Collée, A.M.W. van den Ouweland, M.J. Hooning, C. Seynaeve, C.H.M. van Deurzen, I.M. Obdeijn; Leiden University Medical Center, NL: C.J. van Asperen, J.T. Wijnen, R.A.E.M. Tollenaar, P. Devilee, T.C.T.E.F. van Cronenburg; Radboud University Nijmegen Medical Center, NL: C.M. Kets, A.R. Mensenkamp; University Medical Center Utrecht, NL: M.G.E.M. Ausems, R.B. van der Luijt; Amsterdam Medical Center, NL: C.M. Aalfs, T.A.M. van Os; VU University Medical Center, Amsterdam, NL: J.J.P. Gille, Q. Waisfisz, H.E.J. Meijers-Heijboer; University Hospital Maastricht, NL: E.B. Gómez-Garcia, M.J. Blok; University Medical Center Groningen, NL: J.C. Oosterwijk, A.H. van der Hout, M.J. Mourits, G.H. de Bock. The Netherlands Foundation for the detection of hereditary tumours, Leiden, NL: H.F. Vasen.

References

[1] Antoniou, A., Pharoah, P., Narod, S., Risch, H., Eyfjord, J., Hopper, J., *et al.* (2003) Average Risks of Breast and Ovarian Cancer Associated with *BRCA*1 or *BRCA*2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies. *The American Journal of Human Genetics*, **72**, 1117-1130. http://dx.doi.org/10.1086/375033

[2] Kiemeney, L., Lemmers, F., Verhoeven, R., Aben, K., Honing, C., de Nooijer, J., *et al*. (2008) De kans op kanker voor Nederlanders. *Nederlands Tijdschrift voor Geneeskunde*, **152**, 2233-2241.

[3] Boyle, P. and Levin, B., Eds. (2008) World Cancer Report 2008. International Agency for Research on Cancer (IARC), Geneva, 1-6-2010.

[4] Soerjomataram, I., Louwman, M., Ribot, J., Roukema, J. and Coebergh, J. (2008) An Overview of Prognostic Factors for Long-Term Survivors of Breast Cancer. *Breast Cancer Research and Treatment*, **107**, 309-330. http://dx.doi.org/10.1007/s10549-007-9556-1

[5] Brekelmans, C., Seynaeve, C., Menke-Pluymers, M., Brüggenwirth, H., Tilanus-Linthorst, M., Bartels, C., *et al*. (2006) Survival and Prognostic Factors in BRCA1-Associated Breast Cancer. *Annals of Oncology*, **17**, 391-400. http://dx.doi.org/10.1093/annonc/mdj095

[6] Foulkes, W., Reis-Filho, J. and Narod, S. (2010) Tumor Size and Survival in Breast Cancer—A Reappraisal. *Nature Reviews Clinical Oncology*, **7**, 348-353. http://dx.doi.org/10.1038/nrclinonc.2010.39

[7] Tutt, A., Robson, M., Garber, J., Domchek, S., Audeh, M., Weitzel, J., *et al*. (2010) Oral Poly(ADP-Ribose) Polymerase Inhibitor Olaparib in Patients with *BRCA*1 or *BRCA*2 Mutations and Advanced Breast Cancer: A Proof-of-Concept Trial. *The Lancet*, **376**, 235-244. http://dx.doi.org/10.1016/S0140-6736(10)60892-6

[8] Bordeleau, L., Panchal, S. and Goodwin, P. (2010) Prognosis of BRCA-Associated Breast Cancer: A Summary of Evidence. *Breast Cancer Res Treat*, **119**, 13-24. http://dx.doi.org/10.1007/s10549-009-0566-z

[9] Lee, E., Park, S., Park, B., Kim, S., Lee, M., Ahn, S., *et al*. (2010) Effect of *BRCA*1/2 Mutation on Short-Term and Long-Term Breast Cancer Survival: A Systematic Review and Meta-Analysis. *Breast Cancer Research and Treatment*, **122**, 11-25. http://dx.doi.org/10.1007/s10549-010-0859-2

[10] Goldhirsch, A., Ingle, J., Gelber, R., Coates, A., Thürlimann, B., Senn, H., *et al*. (2009) Thresholds for Therapies: Highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2009. *Annals of Oncology*, **20**, 1319-1329. http://dx.doi.org/10.1093/annonc/mdp322

[11] Maughan, K., Lutterbie, M. and Ham, P. (2010) Treatment of Breast Cancer. *American Family Physician*, **81**, 1339-1346.

[12] Litiere, S., Werutsky, G., Fentiman, I.S., Rutgers, E., Christiaens, M.R., Van Limbergen, E., *et al*. (2012) Breast Conserving Therapy versus Mastectomy for Stage I-II Breast Cancer: 20 Year Follow-Up of the EORTC 10801 Phase 3 Randomised Trial. *The Lancet Oncology*, **13**, 412-419. http://dx.doi.org/10.1016/S1470-2045(12)70042-6

[13] NABON (2012) Breast Cancer, Dutch Guideline, Version 2.0. http://www.oncoline.nl/mammacarcinoom

[14] Early Breast Cancer Trialists' Collaborative Group (1998) Polychemotherapy for Early Breast Cancer: An Overview of the Randomised Trials. *The Lancet*, **352**, 930-942. http://dx.doi.org/10.1016/S0140-6736(98)03301-7

[15] Vervoort, M., Draisma, G., Fracheboud, J., Poll-Franse, L. and de Koning, H. (2004) Trends in the Usage of Adjuvant Systemic Therapy for Breast Cancer in the Netherlands and Its Effect on Mortality. *British Journal of Cancer*, **91**, 242-247. http://dx.doi.org/10.1038/sj.bjc.6601969

[16] Vos, E., Linn, S. and Rodenhuis, S. (2006) Effects and Costs of Adjuvant Chemotherapy for Operable Lymph Node Positive Breast Cancer with HER2/Neu Overexpression. *Nederlands Tijdschrift voor Geneeskunde*, **150**, 776-780.

[17] Early Breast Cancer Trialists' Collaborative Group (2005) Effects of Chemotherapy and Hormonal Therapy for Early Breast Cancer on Recurrence and 15-Year Survival: An Overview of the Randomised Trials. *The Lancet*, **365**, 1687-1717. http://dx.doi.org/10.1016/S0140-6736(05)66544-0

[18] Devilee, P., Tollenaar, R. and Cornelisse, C. (2012) From Gene to Disease; from BRCA1 or BRCA2 to Breast Cancer. *Nederlands Tijdschrift voor Geneeskunde*, **144**, 2549-2551.

[19] Klitzman, R. and Chung, W. (2010) The Process of Deciding about Prophylactic Surgery for Breast and Ovarian Cancer: Patient Questions, Uncertainties, and Communication. *American Journal of Medical Genetics*, **152A**, 52-66. http://dx.doi.org/10.1002/ajmg.a.33068

[20] Meijers-Heijboer, H., Brekelmans, C., Menke-Pluymers, M., Seynaeve, C., Baalbergen, A., Burger, C., *et al*. (2003) Use of Genetic Testing and Prophylactic Mastectomy and Oophorectomy in Women with Breast or Ovarian Cancer from Families with a *BRCA*1 or *BRCA*2 Mutation. *Journal of Clinical Oncology*, **21**, 1675-1681.

[21] Rebbeck, T., Kauff, N. and Domchek, S. (2009) Meta-Analysis of Risk Reduction Estimates Associated with Risk-Reducing Salpingo-Oophorectomy in BRCA1 or BRCA2 Mutation Carriers. *Journal of the National Cancer Institute*, **101**, 80-87. http://dx.doi.org/10.1093/jnci/djn442

[22] Domchek, S., Friebel, T., Neuhausen, S., Wagner, T., Evans, G., Isaacs, C., *et al*. (2006) Mortality after Bilateral Salpingo-Oophorectomy in BRCA1 and BRCA2 Mutation Carriers: A Prospective Cohort Study. *The Lancet Oncology*, **7**, 223-229. http://dx.doi.org/10.1016/S1470-2045(06)70585-X

[23] Rebbeck, T., Friebel, T., Lynch, H., Neuhausen, S., van't Veer, L., Garber, J., *et al*. (2004) Bilateral Prophylactic Mas-

tectomy Reduces Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers: The PROSE Study Group. *Journal of Clinical Oncology*, **22**, 1055-1062.

[24] Graves, K., Peshkin, B., Halbert, C., DeMarco, T., Isaacs, C. and Schwartz, M. (2007) Predictors and Outcomes of Contralateral Prophylactic Mastectomy among Breast Cancer Survivors. *Breast Cancer Research and Treatment*, **104**, 321-329. http://dx.doi.org/10.1007/s10549-006-9423-5

[25] Domchek, S., Friebel, T. and Singer, C. (2010) Association of Risk-Reducing Surgery in *BRCA*1 or *BRCA*2 Mutation Carriers with Cancer Risk and Mortality. *Japan Automobile Manufacturers Association*, **304**, 967-975. http://dx.doi.org/10.1001/jama.2010.1237

[26] Klaren, H., van't Veer, L., van Leeuwen, F. and Rookus, M. (2003) Potential for Bias in Studies on Efficacy of Prophylactic Surgery for *BRCA*1 and *BRCA*2 Mutation. *Journal of the National Cancer Institute*, **95**, 941-947. http://dx.doi.org/10.1093/jnci/95.13.941

[27] Pijpe, A., Manders, P., Brohet, R., Collée, J., Verhoef, S., Vasen, H., *et al*. (2010) Physical Activity and the Risk of Breast Cancer in BRCA1/2 Mutation Carriers. *Retreats—Breast Cancer Recovery*, **120**, 235-244. http://dx.doi.org/10.1007/s10549-009-0476-0

[28] Sukel, M., van de Poll-Franse, L., Nieuwenhuijzen, G., Vreugdenhil, G., Herings, R., Coebergh, J., *et al*. (2008) Substantial Increase in the Use of Adjuvant Systemic Treatment for Early Stage Breast Cancer Reflects Changes in Guidelines in the Period 1990-2006 in the Southeastern Netherlands. *European Journal of Cancer*, **44**, 1846-1854. http://dx.doi.org/10.1016/j.ejca.2008.06.001

[29] Mook, S., Schmidt, M., Rutgers, E., van de Velde, A., Visser, O., Rutgers, S., *et al*. (2009) Calibration and Discriminatory Accuracy of Prognosis Calculation for Breast Cancer with the Online Adjuvant! Program: A Hospital-Based Retrospective Cohort Study. *The Lancet Oncology*, **10**, 1070-1076. http://dx.doi.org/10.1016/S1470-2045(09)70254-2

[30] Bontenbal, M., van Putten, W., Burghouts, J., Baggen, M., Ras, G., Stiegelis, W., *et al*. (2000) Value of Estrogenic Recruitment before Chemotherapy: First Randomized Trial in Primary Breast Cancer. *Journal of Clinical Oncology*, **18**, 734.

[31] Council of the Dutch Federation of Medical Scientific Societies Code of Conduct for Medical Research. http://www.federa.org/sites/default/files/bijlagen/coreon/code_of_conduct_for_medical_research_1.pdf

[32] van den Broek, A., Schmidt, M., van't Veer, L., Tollenaar, R. and van Leeuwen, F (2015) Worse Breast Cancer Prognosis BRCA1/BRCA2 Mutation Carriers: What's the Evidence? A Systematic Review with Meta-Analysis. *PLoS ONE*, **10**, e0120189. http://dx.doi.org/10.1371/journal.pone.0120189

[33] Siesling, S., van de Poll-Franse, L.V., Jobsen, J.J., Repelaer van Driel, O.J. and Voogd, A.C. (2005) Trends and Variation in Breast Conserving Surgery in the Southeast and East of the Netherlands over the Period 1990-2002. *Nederlands Tijdschrift voor Geneeskunde*, **149**, 1941-1946.

[34] Bayraktar, S. and Glück, S. (2012) Systemic Therapy Options in BRCA Mutation-Associated Breast Cancer. Breast *Cancer Research and Treatment*, **135**, 355-366. http://dx.doi.org/10.1007/s10549-012-2158-6

[35] Kriege, M., Seynaeve, C., Meijers-Heijboer, H., Collee, J., Menke-Pluymers, M., Bartels, C., *et al*. (2009) Sensitivity to First-Line Chemotherapy for Metastatic Breast Cancer in *BRCA*1 and *BRCA*2 Mutation Carriers. *Journal of Clinical Oncology*, **27**, 3764-3771.

[36] van Steenbergen, L., Poll-Franse, L., Wouters, M., Jansen-Landheer, M., Coebergh, J., Struikmans, H., *et al*. (2010) Variation in Management of Early Breast Cancer in the Netherlands, 2003-2006. *European Journal of Surgical Oncology*, **36**, S36-S43. http://dx.doi.org/10.1016/j.ejso.2010.06.021

[37] Degner, L., Kristjanson, L., Bowman, D., Sloan, J., Carriere, K., O'Neil, J., *et al*. (1997) Information Needs and Decisional Preferences in Women with Breast Cancer. *Journal of the American Medical Association*, **277**, 1485-1492. http://dx.doi.org/10.1001/jama.1997.03540420081039

[38] Step, M., Siminoff, L. and Rose, J. (2009) Differences in Oncologist Communication across Age Groups and Contributions to Adjuvant Decision Outcomes. *Journal of the American Geriatrics Society*, **57**, S279-S282. http://dx.doi.org/10.1111/j.1532-5415.2009.02512.x

[39] Charles, C., Gafni, A. and Whelan, T. (2004) Self-Reported Use of Shared Decision-Making among Breast Cancer Specialists and Perceived Barriers and Facilitators to Implementing This Approach. *Health Expectations*, **7**, 338-348. http://dx.doi.org/10.1111/j.1369-7625.2004.00299.x