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ORIGINAL ARTICLE

Breast cancer detection among Irish *BRCA1 & BRCA2* mutation carriers: a population-based study

E. M. Walsh · M. P. Farrell · C. Nolan · F. Gallagher · R. Clarke · J. A. McCaffrey · M. J. Kennedy · M. Barry · M. R. Kell · D. J. Gallagher

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Abstract
Background High-risk breast cancer screening for *BRCA1/2* mutation carriers with clinical breast exam, mammography and MRI has reported sensitivity of 100 %, but *BRCA1/2* mutation carriers still present with interval cancers.
Aims We investigated the presentation and screening patterns of an Irish cohort of *BRCA1/2* mutation carriers with breast cancer.
Materials and methods *BRCA1/2* mutation carriers with breast cancer were identified in this retrospective cohort study. Records were reviewed for *BRCA1/2* mutation status, demographics, screening regimen, screening modality, stage and histology at diagnosis.
Results Fifty-three cases of breast cancer were diagnosed between 1968 and 2010 among 60 Irish hereditary breast ovarian cancer (HBOC) families. In 50 of 53 women, the diagnosis of breast cancer predated the identification of *BRCA1/2* mutations. Breast cancer detection method was identified in 47 % of patients ($n = 25$): 80 % ($n = 20$) by clinical breast exam (CBE), 12 % by mammography ($n = 3$), 8 % by MRI ($n = 2$). Fourteen women (26 %) developed a second breast cancer. Ten of these patients (71 %) were involved in regular screening; 50 % were detected by screening mammography, 20 % by MRI and 30 % by CBE alone. Six patients (43 %) had a change in morphology from first to second breast cancers. There was no change in hormone receptor status between first and second breast cancers.
Conclusion In this cohort of Irish BRCA1/2 mutation carriers, compliance with screening was inconsistent. There was a 30 % incidence of interval cancers occurring in women in high-risk screening. Preventive surgery may be a more effective risk reduction strategy for certain high-risk women.

Keywords *BRCA1/2* mutation · Breast cancer · Screening · Interval cancer

E. M. Walsh (✉) · J. A. McCaffrey
Medical Oncology Department, Mater Misericordiae University Hospital, Dublin 7, Ireland
e-mail: Elaine1walsh@gmail.com

M. P. Farrell · F. Gallagher · D. J. Gallagher
Cancer Genetics Service, Mater Misericordiae and Mater Private Hospitals, Dublin 7, Ireland

C. Nolan · F. Gallagher · R. Clarke · D. J. Gallagher
Cancer Genetics Service, St. James's Hospital, Dublin 8, Ireland

M. J. Kennedy
Medical Oncology Department, St James's Hospital, Dublin 8, Ireland

M. Barry · M. R. Kell
Surgery Department, Mater Misericordiae University Hospital, Dublin 7, Ireland

Background

Breast cancer is the most common invasive cancer diagnosed each year in Ireland and represents the second commonest cause of cancer mortality in women [1]. There are approximately 3,000 cases of invasive breast cancer diagnosed per year. In 2010, 650 women died from breast cancer in Ireland, accounting for 16 % of all cancer mortality [2]. Approximately 25 % of breast cancers result from a familial predisposition [3].

Hereditary breast ovarian cancer syndrome (HBOC) is an autosomal dominant syndrome caused by germline mutations in *BRCA1* and *BRCA2*. It is associated with an

increased risk of breast, ovarian, prostate and pancreatic cancers and malignant melanoma. Three to five percent of all breast cancers are associated with *BRCA1/2* germline mutations [3, 4]. A meta-analysis of twenty-two international studies by Antoniou et al. [5] reported the cumulative risk of breast cancer by 70 years of 65 % in *BRCA1* mutation carriers and 45 % in *BRCA2* mutation carriers. The average cumulative ovarian cancer risk by age 70 was 39 % in *BRCA1* mutation carriers and 11 % in *BRCA2* mutation carriers. This is a significant public health issue in the Irish population, where up to 150 cases of breast cancer per year may be caused by *BRCA1/2* mutations.

Breast cancer screening was introduced in Ireland in 2000 and was expanded nationally by 2007. With mammography alone, only 50 % of *BRCA1/2* mutation-associated breast cancers are detected by screening; the other 50 % present as interval cancers, which are diagnosed during the period between screening modalities [6–8]. International guidelines recommend intensive breast cancer screening programmes for *BRCA1/2* mutations carriers [2, 7, 9]. Recommended high-risk breast screening consists of monthly self-breast exam from age 18; clinical breast exam (CBE) every 6 months and annual mammography alternating with annual MRI from age 30 years. This combined approach has a reported sensitivity of 100 % [6, 10]. Even with these internationally recognized intensive screening programmes, *BRCA1/2* mutation carriers can still present with self-detected interval breast cancers [8, 10]. In Ireland, according to National Cancer Registry of Ireland (NCRI) data, the rate of interval cancers in the low-risk *BreastCheck* screening programme is 27 % in the first year after screening, rising to 48 % in the second year after screening. 80 % of interval cancers in this cohort are greater than 1.5 cm diameter, compared to 53 % in the screen-detected cohort. 91 % of interval cancers are grade 2 or 3 compared to 79 % in the screen-detected group [2]. It appears that even in low-risk populations, interval breast cancers are more aggressive than screen-detected cancers.

In this retrospective cohort study, we determined the method of breast cancer presentation and detection in an Irish hereditary breast ovarian cancer (HBOC) harbouring pathogenic germline *BRCA1/2* mutations, and assessed compliance with high-risk screening programmes.

Materials and methods

Cancer genetics programme

A cancer genetics programme was established in St James's Hospital, Dublin in 1992. The cancer genetics database used in this study is comprised of all patients with a pertinent personal or family history of breast or ovarian cancer that were referred to this service for genetic counselling and testing.

Study cohort

This population-based study was carried out by identifying women from the cancer genetics database who had a diagnosis of breast cancer and who carried *BRCA1/2* mutations. This cohort included women treated elsewhere for breast cancer but referred to this centre for cancer genetic risk assessment.

Medical and electronic charts were reviewed for demographics, *BRCA1/2* mutation status, cancer diagnosis, stage, histology, hormone receptor status, screening investigations completed, and breast cancer detection methods.

Compliance with high-risk screening programmes was assessed by review of medical and radiology records. We identified whether breast cancers were diagnosed at screening or as interval cancers.

This study has been approved by a local research ethics committee and has been conducted in accordance with the ethical standards as laid down in the Helsinki Declaration of 1975, as revised in 2000.

Results

First breast cancer

Seventy-three female BRCA1/2 mutation carriers in 60 Irish HBOC kindreds were identified. Fifty-three cases of breast cancer were diagnosed in this cohort between 1968 and 2010 (Table 1). The median age was 42 years (range 24–73). In 50 of 53 women, the diagnosis of breast cancer predated the detection of *BRCA1/2* mutations. Twenty-one women (40 %) had a breast cancer diagnosis at least 5 years prior to a *BRCA1/2* mutation being detected; the longest gap between diagnosis and detection of a mutation was 31 years. Twenty-four women (45 %) in this cohort had a *BRCA1* mutation and twenty-nine (55 %) had a *BRCA2* mutation. The most common *BRCA*1 mutation identified was E143X ($n = 7$ or 29 %). The most common *BRCA2* mutations were 3945delA and 983del4 ($n = 3$ or 10 % each).

Sixteen (30 %) cases of breast cancer were stage I at diagnosis; 23 (43 %) were stage II; four (7.5 %) were stage III and the stage of the remaining 10 cases could not be confirmed.

The majority ($n = 33$ or 62 %) of cancers were invasive ductal carcinomas. Others were lobular ($n = 2$), mixed ($n = 1$), medullary ($n = 1$), undifferentiated ($n = 4$) and twelve cases could not be confirmed. In this cohort,

Table 1 Breast cancer characteristics

	1st cancer		2nd cancer	
Characteristic	*n*	%	*n*	%
	53	100	14	26
Median age	42		45	
Range	24–73		36–68	
BRCA1	24	45	6	43
BRCA2	29	55	8	57
Stage				
I	16	30	9	64
II	23	43	2	14
III	4	8	3	22
Unknown	10	19	–	–
Histology				
Ductal	33	62	12	86
Other	8	15	2	14
Unknown	12	23	–	–
ER status				
Positive	5		6	
BRCA1	0	–	0	–
BRCA2	5	100	6	100
Negative	4		5	
BRCA1	3	75	3	60
BRCA2	1	25	2	40
Unknown	44	83	3	21
Screening				
MMG	9	17	10	71
(+MRI)	–	–	4	
None	17	32	1	7
Unknown	27	51	3	22
Diagnosis	25		10	
CBE	20	80	3	30
MMG	3	12	5	50
MRI	2	8	2	20

hormone receptor status was documented in nine women. Five were oestrogen receptor positive (all 5 *BRCA2* mutation carriers) and four were oestrogen receptor negative (3 *BRCA1* mutation carriers, 1 *BRCA2* mutation carriers).

Nine (17 %) women were undergoing regular mammographic screening at the time of their initial breast cancer detection. Seventeen (32 %) were not in a screening programme and screening details were unavailable for 27 women. Breast cancer detection method was retrospectively identified in 25 patients (47 %) and not known in the remainder. Twenty cases (80 %) of breast cancer were detected by clinical breast exam (CBE). Eighteen of these cases (72 %) were self-detected by the patient and two were detected by a clinician. Three (12 %) cases were detected by mammography alone and two (8 %) detected by MRI alone.

Second breast cancer

Fourteen women (26 %) in this cohort went on to develop a second breast cancer (Table 1). The median age was 45 years (range 36–68). Six patients (43 %) were *BRCA1* mutation carriers; eight (57 %) had a *BRCA2* mutation. Five women (36 %) were known to be *BRCA1/2* mutation carriers at the time of second breast cancer diagnosis. Nine (64 %) were stage I at diagnosis; two (14 %) were stage II; three (21 %) were stage III. 86 % ($n = 12$) were invasive ductal carcinomas. There was one medullary and one lobular subtype. Six patients (43 %) had a change in morphology from first to second breast cancers.

Hormone receptor status was known in eleven of fourteen patients. Six (55 %) were oestrogen receptor positive (all six were *BRCA2* mutation carriers); five (45 %) were oestrogen receptor negative (three *BRCA1* mutation carriers and two *BRCA2* mutation carriers). There was no change in hormone receptor status between first and second breast cancers.

Of the fourteen women who developed a second breast primary, ten (71 %) were involved in regular screening; one patient was not and screening details were unavailable for three patients. All 10 patients involved in screening (Table 2) were having annual mammography and four were also having regular MRI screening. Of the five women who were known to be *BRCA1/2* mutation carriers at the time of second breast cancer diagnosis, four were involved in regular screening. Three of these women (75 %) were enrolled in a high-risk screening programme with annual mammography alternating with MRI; one was having annual mammography only. Seven women had a second breast cancer detected by screening. Five cases were detected by screening mammography and two by MRI. The median age of women presenting with screen-detected cancers was 44 (range 36–57). Four (57 %) of these women had stage I breast cancer detected (two detected by mammography and two by MRI); two (20 %) were stage II (both detected by mammography) and one was stage III (detected by mammography). Three (30 %) interval cancers were detected by CBE alone; two were self-detected and one detected by clinician physical exam (Table 3). All three patients were having annual mammography and two were also having annual MRIs. The median age of those presenting with an interval cancer was 50 (range 45–53). Two cases of interval cancer were stage I and one case was stage III.

There were no ovarian cancer diagnoses among the 14 women in this cohort who developed a second breast cancer. Rates of risk-reducing surgery, either prophylactic

Table 2 Second breast cancer characteristics

2nd cancer-detected in screening	Screen detected		Interval cancer	
Characteristic	*n*	%	*n*	%
	7	70	3	30
Median age	44		50	
Range	36–57		45–53	
BRCA1	3	43	1	33
BRCA2	4	57	2	67
Stage				
I	4	57	2	67
II	2	29	0	–
III	1	14	1	33
Histology				
Ductal	6	86	3	100
Other	1	14	–	–
ER status				
Positive	4	57	1	33.3
BRCA1	–	–	–	–
BRCA2	4	100	1	100
Negative	2	29	1	33.3
BRCA1	2	100	–	–
BRCA2	–	–	1	100
Unknown	1	14	1	33.3
Diagnosis				
CBE	–	–	3	100
MMG	5	71	–	–
MRI	2	29	–	–

Table 3 Interval breast cancer characteristics

Interval cancer characteristics		
Characteristic	*n*	%
	3	30
Median age	50	
Range	45–53	
BRCA1	1	33
BRCA2	2	67
Stage		
I	2	67
II	0	–
III	1	33
Histology		
Ductal	3	100
Other	–	–
ER status		
Positive	1	33.3
BRCA1	–	–
BRCA2	1	100
Negative	1	33.3
BRCA1	–	–
BRCA2	1	100
Unknown	1	33.3
Diagnosis		
CBE	3	100
MMG	–	–
MRI	–	–

mastectomy or bilateral salpingo-oophorectomy in this cohort were not known.

Conclusion

Interval cancers and screening

This population-based retrospective cohort study of Irish *BRCA1/2* mutation carriers has identified fifty-three cases of first breast cancer and 14 cases of a second contralateral breast cancer, with a 30 % rate of interval cancers. These rates are consistent with interval cancer rates reported by the NCRI [2]. Other international studies report rates of interval breast cancers between 2 and 50 % [11, 12]. The reason for variations in interval cancers between studies is not clear but may relate to adherence to high-risk screening programmes as well as differences in the uptake of risk-reducing surgeries. Komenaka et al. [8] found an interval cancer rate of 46 % among patients with *BRCA1/2* mutations who were enrolled in a screening programme. Screening consisted of annual mammography as information regarding the utility of MRI was not yet known at that time. The mean time between last screening and interval cancer detection was 5.1 months; 66 % of these interval cancers occurred less than 6 months after mammography and 50 % less than 3 months after mammogram. 100 % of interval cancers were self-detected. More recently, studies have shown interval cancer rates of <3 % when mammography and MRI are performed at the same time [6, 10] with similar interval rates when these imaging modalities are alternated every 6 months [13]. Some interval cancers may be undetectable despite optimal screening.

The uptake of high-risk screening in this Irish cohort was 75 %. The reasons for this are likely to be multifactorial and may be related to patients' preference and/or the time interval during which patients included in this study were cared for in Ireland. The importance of compliance with screening must be emphasized with patients, and is best monitored though a dedicated high-risk screening programme. Two-thirds of interval cancers in this population were self-detected, emphasizing the importance

of breast awareness in this population; but also highlighting the need for a national, coordinated approach to caring for high-risk women.

Breast cancer characteristics between first and second cancer groups

Hormone receptor status did not change between first and second tumour diagnosis in this cohort. Hormone receptor status was noted in nine women (17 %) with a first breast cancer and eleven (79 %) with a second breast cancer diagnosis. In the first breast cancer group, five (56 %) were oestrogen receptor positive (100 % *BRCA2* mutation carriers) and four (44 %) were oestrogen receptor negative (75 % *BRCA1* mutation, 25 % *BRCA2* mutation carriers). Similarly in the second breast cancer group, six (55 %) were oestrogen receptor positive (100 % *BRCA2* mutation carriers) and five (45 %) were oestrogen receptor negative (60 % *BRCA1* mutation, 40 % *BRCA2* mutation carriers). All *BRCA1* mutation carriers had oestrogen receptor negative disease and all cases of oestrogen receptor positive disease were seen among *BRCA2* mutation carriers. While morphology changed from first to second breast cancers for six women, there was no change in hormone receptor status. Testing for HER-2 overexpression became part of routine histological testing in our institution in 2005. Eleven patients (21 %) in this cohort were diagnosed with a first breast cancer after 2005. Only one case had a HER2 status documented, and was HER2 negative. Of those with a second breast cancer, five (36 %) were diagnosed after 2005. All five cases (100 %) were documented as HER2 negative tumours. There were no documented cases of change in HER2 status between first and second breast cancers. Data regarding the histological tumour grades were not documented in this cohort.

Breast cancer characteristics compared to international cohorts

We observed several differences in breast cancer characteristics in this Irish cohort compared to international studies. 45 % ($n = 24$) had a *BRCA1* mutation and 55 % ($n = 29$) had a *BRCA2* mutation compared with internationally reported incidences of 66 % *BRCA1* mutation and 33 % *BRCA2* mutation rates [14].

The median age of women presenting with screen-detected second cancers in this cohort was 44 years (range 36–57) while the median age of those presenting with an interval cancer was 50 (range 45–53). This contrasts to a study by Scheuer et al. [14] which reported that women with interval cancers are younger than those with screen-detected cancers (mean 41.3 vs 56.7 years; $p = 0.048$).

There was a higher incidence of early stage breast cancers in this cohort of women who developed a second cancer compared to other international series. Combining both the screen detected and interval cancer groups, 60 % of cancers were stage I (two detected by mammography, two by MRI and two interval cancers); 20 % were stage II (both detected by mammography) and 20 % were stage III disease (one detected by mammography; one by CBE). Several other series have shown figures of 27–36 % with stage I disease, 46–53 % with stage II and 7–12 % with stage III/IV disease in *BRCA 1/2* mutation-associated cancers [15–17] which may support the hypothesis of allelic risk heterogeneity, such that different mutations confer different risks [5].

Risk-reducing surgery

No women evaluated in this cohort underwent a prophylactic mastectomy prior to or at the time of breast cancer diagnosis. Over 25 % of women in this cohort developed a second breast cancer. This is supported by Carroll et al. [18] who previously demonstrated a low uptake of prophylactic mastectomies among an Irish *BRCA1/2* cohort. Only nineteen percent of *BRCA1/2* mutation carriers with breast cancer in that study underwent risk-reducing mastectomies. The uptake of prophylactic surgeries has increased worldwide in recent years [19]. It is likely that rates of prophylactic mastectomy in Ireland will increase in keeping with current international trends. Such surgical prevention in genetically predisposed individuals will place an increased demand on already stretched Irish cancer services.

Limitations

This is a single institution retrospective cohort study with small patient numbers. Our results and observations are certainly thought provoking but it has been difficult to ascertain whether the differences we observed in this population are statistically significant. In addition, as this was a retrospective study it may not be as accurate as a prospective equivalent, although it has shown to be an efficient method of study in this context. As a result, we propose that this study should form the basis of a larger, prospective confirmatory study.

Patients were ascertained for this study from a tertiary referral centre. These women then returned to their referring centre for further management. Data as a result are both retrospective and incomplete. A national familial cancer registry would facilitate long-term follow-up of a contemporary cohort of women, and avoid future loss of data as was encountered in this study. Such a registry

would be optimally linked with a national germline DNA biobank.

Conclusion

In conclusion, we identified a 30 % rate of interval cancers among a cohort of Irish *BRCA1/2* mutation carriers. Compliance with high-risk screening programmes was 75 % in this group. For women who are non-compliant with screening, risk-reducing surgery may be a preferable alternative. There may exist a molecular subset of high-risk women prone to developing radiographically occult breast cancer who would similarly be best managed with surgical prevention. This Irish cohort of *BRCA 1/2* mutation-associated breast cancer cases differed from international series. Cancer predisposition is an increasingly central component of cancer care and the limitations of this study highlight the need for a cohesive national genomics programme to monitor screening and direct prevention.

Conflict of interest The authors have no conflict of interest to declare.

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