Breast Cancer Incidence and Early Diagnosis in a Family History Risk and Prevention Clinic: 33-Year Experience in 14,311 Women

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Abstract

*Purpose:*Women at increased familial breast cancer risk have been offered screening starting at an earlier age and increased frequency than national Screening Programmes for over 30years. There are limited data on longer-term largescale implementation of this approach on cancer diagnosis.

*Methods:*Women at our institution at ≥17% lifetime breast cancer risk have been offered enhanced screening with annual mammography starting at age 35 or 5-years younger than youngest affected relative, with upper age limit 50 for moderate and 60 for high-risk. Breast cancer pathology, stage and receptor status were assessed as well as survival from cancer diagnosis by Kaplan-Meier analysis.

*Results:*Overall 14,311 women were seen and assessed for breast cancer risk, with 649 breast cancers occurring in 129,119.5 years follow up (post-prevalent annual incidence=4.55/1,000). Of 323/394 invasive breast cancers occurring whilst on enhanced screening, most were LN negative (72.9%), T1 (≤20mm,73.2%) and stage-1 (61.4%). Ten-year breast cancer specific survival was 91.3%(95%CI=87.4–94.0) significantly better than the 75.9%(95%CI=74.9-77.0) published for England in 2013-2017. As expected, survival was significantly better for women with screen detected cancers(p<0.001). Ten-year survival was particularly good for those with diagnosed ≤40 at 93.8% (n=75;95%CI=84.2–97.6). Women with lobular breast cancers had worse 10-year survival at 85.9% (95%CI=66.7–94.5). Breast cancer specific survival was good for 119 *BRCA1/2* carriers with 20-year survival in *BRCA1*:91.2%(95%CI=77.8-96.6) and 83.8% (62.6-–93.5) for *BRCA2*

*Conclusions:*Targeted breast screening in women aged 30-60 years at increased familial risk is associated with good long-term survival that is substantially better than expected from population data.

Introduction

Breast cancer (BC) is the most common cancer in females with approximately 54,500 women diagnosed annually in the UK (2016) and remains the leading cause of premature death in women aged 30-60 years.[1] Epidemiological studies suggest that ~4-5% of BC is caused by high-risk genes,[2] but twin studies suggesting ~27% have inherited factors.[3] The cloning of *BRCA1* and *BRCA2* in 1994-1995[4,5] allowed predictive testing to identify which women had highest risk. Other high-penetrance BC genes (lifetime-risk >40%) including *TP53, PTEN, CDH1*, *STK11* and *PALB2* have also been identified,[6,7] as well as moderate-risk genes (lifetime-risk 20-30%) *ATM* and *CHEK2*.6

Family history risk and prevention clinics (FHRPC) began appearing in 1987.[8] A method of triage was developed such that women with moderate BC risk (lifetime-risk 17-29%) were managed in local FHPRCs and high-risk women (lifetime risk ≥30%) were referred to genetics clinics.[9] This process was endorsed in the UK by the National Institute for Health and Care Excellence (NICE) in 2004 whose guidance covered recommendations on BC risk assessment, genetic testing, surveillance and risk reducing surgery.[10] Most FHRPCs offered pragmatic annual breast screening from five years before the earliest BC diagnosis in the family or from 35 years whichever was earlier.[9] NICE originally advised annual mammographic screening only from 40-49 years for moderate and high-risk individuals, but updated the guidance in 200610 to include MRI screening for women at the highest risk after the publication of a number of MRI screening trials.[11-14] In 2013, following publication of the FH01 study, annual mammographic screening in women aged 40-49 at moderate and high-risk[15] was fully endorsed by NICE and annual mammography for high-risk women from 50-59 years.10 Since then, screening with annual mammography between ages 35-39 years has also been shown to detect BC at earlier stages with anticipated improvement in survival.[16] The outcomes from a largescale systematic approach utilising family history to enhance early detection rates by mammography screening has not yet been published to our knowledge.

A FHRPC was established in Manchester in 1987[17] and was the forerunner to other similar clinics in Europe. We report here the outcome of risk assessment and surveillance in 14,311 women referred to the Manchester FHPRC clinic between 1987-2020.

Materials And Methods

Women with a BC family history, but unaffected personally, have been referred to the FHRPC at the Nightingale Centre Withington/Wythenshawe hospital since 1987. Their lifetime and residual risk of BC has been assessed using questionnaire information on family history and standard risk factors using Claus tables and the Tyrer-Cuzick programme.[1,17-19] Women were classified as being high-risk (lifetime-risk ≥30%), moderate-risk (lifetime-risk-17-29%) or average/population risk (lifetime-risk-<17%). Average-risk women were returned to primary care with reassurance and information on breast awareness and advised to start or continue screening from age 50. Moderate-risk and high-risk women were offered ‘enhanced’ surveillance (annual mammography and clinical breast examination (CBE)) starting at 35years or 5years younger than youngest affected relative (earliest age 30). With upper age limit 50 for moderate and 60 for high-risk. For high-risk women ‘enhanced’ surveillance continued at 12-18 monthly intervals from 50-60 years of age and started as young as age 30 (if *BRCA1/2* or youngest relative <35). Women from families eligible for genetic testing (20% *BRCA1/2* likelihood 2004-2013, 10% likelihood >2013) were referred to Genetics. Women with proven *BRCA1/2* pathogenic variants (PVs) in the family were offered targeted testing for their familial variant. In contrast, unaffected women (without BC) with a significant family history have only been offered a full *BRCA1/2* screen since 2013 if an affected family member is unavailable and their *a priori* likelihood of a *BRCA1/2* PV is ≥10%.[11] *BRCA1/2* pathogenic variant (PV) carriers have been offered annual MRI screening aged 30-50 years since 2006.10 However, some aged 35-50 years had MRI screening through the MARIBS trial from 1997.[12] Women with lifetime BC risks ≥25%, including *BRCA1/2* carriers, have had bilateral risk-reducing mastectomy (BRRM) discussions since 1994.

All FHRPC women seen from 1987 (including discharged) had assessment of vital (living/dead) and cancer status through the regional cancer registry and NHS systems in December-2012. Post 2012, deaths were notified to the clinic and BC incidence was only assessed in those under ongoing surveillance. Women were censored for BC incidence at: BC diagnosis, BRRM, or death, if none, at last mammography (latest March 2020) or 01/12/2012. Data on all BCs occurring in the screening programme including interval cancers occurring within 18-months of last mammogram were collated. This included pathology (invasive–ductal, lobular, ductal carcinoma *in situ* (CIS)), tumour size, lymph node (LN) status and oestrogen(ER)/progesterone and HER2 receptor status.

HER2 testing was only available from 2005. ER+HER2- and triple negative BC (TNBC) groups include HER2 untested from <2005 as only 8.6% (6/70) and 7.3% (10/137) of subsequent tests on invasive ductal cancer for ER- and ER+ respectively were also HER2+. Vital status was established on all BC cases in April-2020 and causes of death confirmed from cancer records and death certification.

BCs were defined as detected 'on programme' if they were diagnosed at screening episodes or within 18-months (interval cancers). Most women off programme were discharged to population breast screening on the 3-yearly basis NHS breast screening programme aged 50 if moderate-risk and 60 if high-risk.

In addition to clinical *BRCA1/2* (including *CHEK2* c.1100delC) testing where indicated by likelihood of a *BRCA1/2* PV, many families received testing of affected members through the Familial BC Study (FBCS) and 1300 women (900 without BC) consenting to the FHrisk study had testing of an extended panel of BC genes through the BRIDGES study.[20]

Annual incidence rates

Annual incidence rates were calculated excluding cancers at prevalent screen. The *BRCA1* and *BRCA2* PV carrier groups were eligible for follow up from testing date or date of clinic entry which ever was later. PV carriers tested after BC diagnosis were included in the untested group if their family PV was known at diagnosis or to the appropriate risk category at clinic entry if their family PV was identified after diagnosis. Likewise, those testing negative for their family *BRCA1/2* PV were eligible from date of negative test and excluded from prospective analysis as a PV carrier if testing was after diagnosis. All other women were grouped with their original risk category including the small group of 31 women with other known moderate/high risk gene PVs at entry. The 16 patients with neurofibromatosis-1 (NF1) were classified as moderate risk.[21]

Statistical methods

BC incidence was calculated excluding cancers detected on prevalence screen. Survival was assessed by Kaplan-Meier analysis and the log rank test to compare survival curves for categorical variables. Chi-squared tests were used to compare categorical variables. Differences in pathology variables in cancers on the screening programme used the high risk *BRCA1/2* negative group as the reference. *BRCA1* and *BRCA2* incidence and in those testing negative, was only assessed from date of mutation report. All p values were based on two-sided tests and were considered statistically significant if <0.05. Analyses were performed using Stata version 14.

The study was approved by the Central Manchester Research Ethics Committee (10/H1008/24).

Results

Study Population

A total of 14,311 women without BC, born between 1920 and 2003 (median: 1966), had their risk of BC assessed (Figure 1). Age at entry ranged from 16-81 years (median=39.9; IQR=33.9-46.9). Detailed study population characteristics are described (Table-1) according to final known genetic status. Seven-hundred-and-thirty-six women (5.1%) have been identified as *BRCA* PV carriers (*BRCA1*=364, *BRCA2*=372)–Table 1. Two-hundred-and-seventy-two (37.0%) of these were referred into the FHRPC as known PV carriers unaffected by BC. The remainder were identified after clinic entry (Figure-1). As such 298/14,311 (2.1%) were identified as BRCA PV carriers with no known PV in the family at clinic entry. Overall BRCA testing in the individual woman or affected family member has completed in 4168(29.1%) clinic attenders. Of 649 women with BC, 539-(83.1%) had known BRCA status.

Follow-up time

There have been 129,119.5 women-years follow up with 649 BCs (588 post-prevalent), resulting in annual incidence of 4.55/1,000. This excluded 45 prevalent asymptomatic screen detected cancers (0.31%) and a further sixteen women who developed symptomatic BC between referral and clinic attendance. Therefore, there were 61 total prevalent cancers (0.43%-61/14311). Within the enhanced screening programme there were 63972.4 years follow up, 349 (2.4%) women developed BC following prevalence screen (incidence=5.46/1000). Four-hundred-and-fifty-five women (455/14311-3.2%) have undergone pre-symptomatic BRRM with seven occult BCs (1.5%) diagnosed at surgery. The remaining 239 cancers occurred after clinic discharge making a total of 255 (including 16 pre-prevalent scan) off programme. Breast cancer incidence by risk group is shown in table 2. Incidence post prevalence in *BRCA1* was 1.73% and in *BRCA2* 1.55% annually from date of mutation report. The low rate in untested women reflects those at 25% risk and very young women prior to testing. Carriers of known PVs in other genes were included in the lifetime risk category known at entry due to low numbers.

Cancers

The age and known PV carrier status of the women with BCs are shown in table-3. Cancer pathology on the FHRPC enhanced screening programme is shown in table-4. *BRCA1*-related BCs were more likely grade 3 and oestrogen receptor negative (ER-) than cases in the high-risk BRCA negative cohort as expected (p<0.0001 for both). Tumours from women who tested BRCA PV negative in the high-risk cohort were more likely to be grade 1 than both *BRCA1 (*p<0.001) and *BRCA2* (p=0.04) tumours. Only 36/394 (9%) women with cancers in the enhanced screening programme had no genetic testing compared with 84/255 (32.9%) of those off programme. Of the cancers in the enhanced screening programme 70 (17.9%) were carcinoma *in situ* (CIS) with a higher proportion seen on prevalent screen (33.3%- supplementary-table-1). The majority of invasive cancers were LN negative (72.9%), small (≤20mm-73.2%) and stage-1 (61.4%). *BRCA1/ BRCA2* PV associated cancers were smaller overall with 75.0% and 85.4% being ≤20mm respectively, potentially reflecting MRI screening in these groups. Overall deaths were lower in women screened on the enhanced-programme (13.8%) compared with off-programme (20.8%)-(Table-3), although off-programme women were older. Of the deaths with *BRCA1/2* PVs, 7/16 were unrelated to BC; *BRCA1*-4/8 (ovarian(n=2), carcinosarcoma

uterus(n=1),pancreatic(n=1)) *BRCA2*-3/8 (ovarian,lung cancer,old-age). Only one each *BRCA1* and *BRCA2* deaths in carriers were BC related in women on MRI screening (2/38). In total 34/54(63%) of deaths in women with cancers detected in the enhanced screening programme were BC related.

BC deaths, as expected, were more frequent in women with symptomatic interval cancers (supplementary-table-1,Figure 2a). Incident screen detected 10-year survival was 91.9%-(95% CI=86.7–95.1) vs interval 80.2% (95%CI=68.6–87.9) (p<0.001); prevalence screen survival 94.5%-(95%CI=79.8–98.6) vs incidence screen (p=0.052). The pathologies with the highest proportion of BC deaths were lobular (23.3%,10-year survival=85.9%(95%CI=66.7–94.5)) triple negative (14.3%;10-year-survival=83.5% (95%CI=72.7–90.3)) and high-grade ER+HER2- cancers (13.0%;10-year-survival=88.5%(95%CI=74.3–95.1)) although numbers in each group were relatively small limiting statistical comparison. As expected, the lowest proportion of BC specific deaths was noted in those with grade-1 tumours (2.4%; 10-year-survival=95.5%(95%CI=70.7–99.3)) and CIS (2.8%;10-year-survival=98.2%(95%CI=87.6–99.7)), although BC specific survival was also excellent in grade-2 ER+HER2- BC (10-year-survival=95.1%(95%CI=85.3–98.4). Nearly all triple negative BC deaths occurred in the first 5-years-(Figure 2b).

Although overall survival was worse in those diagnosed >50 years (10-year=83.5%-≤40 years-10-year=93.5%,p=0.04; 41-50 years-10-year=88.8%,p=0.025-Supplementary figure-1), BC specific survival was virtually identical for all age groups, with 10-year ≤40years survival 93.8% (95%CI=84.2–97.6-supplementary-table-1; Figure-2c). For the ≤40years group with invasive BC (n=58), 5, 10 and 20-year overall survival was 92.2% (80.5-97.0), 92.2% (80.5-97.0) and 79.9% (59.9-90.6). Survival was not significantly different between *BRCA1, BRCA2* and non-BRCA carriers on enhanced screening (Figure-2d) with 20-year BC specific survival particularly good in 60 *BRCA1* carriers at 91.5%-(78.5–96.8) compared to 59 *BRCA2* at 85.1%-(64.1–94.3) and 275 non-BRCA 84.7%-(76.5–90.3). The *BRCA2* survival curve crossed over *BRCA1* after 10 years. Only 51 BRCA carriers were aware of their status at BC diagnosis. Kaplan-Meier curves comparing BRCA PV carriers who knew their status at diagnosis versus those who did not and BRCA carriers who had MRI versus those who only had mammography are shown in Supplementary Figures 2&3. Survival in the known carriers and MRI screened (90.6%, 95%CI=80.3-95.7%) and 90.1% (95%CI=62.6– 97.7%) 10-year survival respectively), but this was not significantly better than the controls who did not know their status (94.8%; 95%CI=68.0-93.2%) and those not undergoing MRI (87.0%: 95%CI=80.6–94.8%). We also carried out a time dependency analysis and this did not show any advantage to knowing the BRCA status (Supplementary-Figure-4)

Five and 10-year BC specific survival in those with BC detected on programme vs off programme screening was:5-year 94.1%-(95%CI=91.0–96.1) vs 94.3%-(95%CI=90.5-96.6) and 10-year 91.0%-(95%CI=87.2–93.7) vs 90.4%-(95%CI=85.7–93.4) respectively.

Discussion

The current study is, to our knowledge, the largest study on systematic local approaches to BC risk assessment and surveillance. In total 649 (4.5%) of 14311 women developed BC with the majority (394[62%]) detected on enhanced screening. The majority of BCs were detected at stages 0/1-(270/394-68.5%) with only 94/394-(23.5%) interval cancer, seven of which were asymptomatic at BRRM. There were expected BC associations with *BRCA1* grade-3 ER-HER2-significantly more frequent than high-risk BRCA-negative group (p<0.0001). Pure CIS was less frequent in *BRCA1* and more frequent in *BRCA2*.22 There appears to be a stronger signal for low grade BC (28%) in those testing negative for PVs in high-risk genes suggesting a potential feature of yet to be discovered moderate/high-risk genes.

We have reported a mean annual rate of incident prospective BCs in *BRCA1/2* PV carriers of 1.6% (1.55% *BRCA2*, 1.73% *BRCA1*),[23] consistent with currently published 69-72% risks by age 80 years[24,25] when extrapolated over a 50-year risk period. This study also provides support for the current NICE recommended annual MRI screening surveillance strategy [11] as there was only one death in a *BRCA2* carrier among MRI screened women. This continues to provide efficacy evidence for MRI as an alternative to BRRM.[26] Indeed, nearly half the deaths (44%) in *BRCA1/2* PV carriers with BCs were due to other cancers-(6/16) or old age (1/16).

BC specific survival was excellent with 10-year survival rates of 91.3%-(95%CI=87.4–94.0) noticeably higher than current 10-year BC survival in England of all women presenting with primary BC of 75.9% (95%CI=74.9-77.0; 2013-2017 data).[27] Of particular note is that the 10-year invasive BC survival ≤40years of 92.2%-(95%CI=80.5–97.0) had lower 95%CI above -the UK population based POSH (Prospective-study-of-Outcomes-in-Sporadic-versus-Hereditary-BC) trial. This trial consisted of women presenting with primary BC ≤40years between 2000-2008.[28] The study found 10-year survival of 73·4%-(67·4–78·5) for *BRCA1/2* vs 70·1%-(67·7–72·3) for non BRCA BC compared to lower 95%CI of 86.9% in our population. Indeed, the Kaplan-Meier curves continued to drop towards 50% by 15 years in POSH28 far below the 20-year survival from our study of 85.3% (77.1–90.7)), and indeed the lower 95% CI. Thus, even allowing ~18-months lead-time16 survival of women with invasive cancers ≤40 who undergo annual screening is likely significantly better than unscreened women as suggested by the FH02 study[16].

As expected, women with interval BCs had higher mortality. Most presented within 12-months with known poorer survival.[29] Interestingly stage 2 or more Breast cancer was not different between incident and prevalent cases (27.6% versus 26.7%) among screened population and this is reflected by similar survival rates. This is partly explained by the higher rates of DCIS (33% versus 20.5%). Although women presenting with triple negative cancers had relatively low 5-year survival, at 10-15 years this was no worse than for those with high-grade ER+HER2- BC. Interestingly, invasive lobular BC, known to have higher interval cancer rates29 presumably poorer mammographic sensitivity, was associated with the worst survival. Individuals with a higher risk of lobular cancer including those with *CDH1* pathogenic variants, LCIS or lobular BC family history should be considered for MRI breast screening.

There are some limitations to the present study. Genetic testing was only carried out in a minority of the screened population although it was performed on the great majority of enhanced programme BCs (91%) and assessment of incidence rates based on gene testing was not the primary study aim. Most women with BCs had panel testing, allowing extrapolation of likely frequencies of other common familial genes (*ATM,CHEK2,PALB2*). We do not have follow up for all women after December-2012, but were able to check vital status and cause of death for all women with BC.

In conclusion, the present study has demonstrated good survival from family history based enhanced-screening approach over a 33-year period. Overall and BC specific survival is very good and substantially better than would be expected from population statistics and especially ≤40 years who would not otherwise qualify for screening. MRI screening is of benefit to *BRCA1/2* carriers and could also be utilised in those at high risk of lobular cancer who are otherwise less well served by mammography.

Declarations

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Conflicts of interest/Competing interests

DGE has received consultancy fees from Astrazeneca and Springworks

There are no other conflicts

Availability of data and material (data transparency)

Raw data available on request

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Tables

Table 1: Risk and gene PV status of all 14311 women assessed at the Manchester FHRPC

gene/risk	number	breast cancer	%BC	RRM	%RRM	deceased	median age at entry	IQR	Proportion of clinic
BRCA1	366	77	21.04%	121	33.24%	20	35.7	31.0-42.5	2.54%
BRCA2	374	78	20.86%	101	27.15%	19	36.9	31.9-45.0	2.60%
ATM	18	9	50.0%	0	0.00%	0	41.7	37.9-45.0	0.11%
CDH1	7	2	28.57%	4	57.14%	0	35.1	33.9-46.8	0.05%
STK11	2	0	0.00%	0	0.00%	0	38.4		0.01%
PTEN	5	2	40.00%	1	20.00%	1	35.8	35.3-36.5	0.03%
PALB2	13	6	46.15%	0	0.00%	0	38.0	34.3-42.0	0.09%
CHEK2	18	7	38.89%	2	11.11%	0	39.5	30.7-44.9	0.13%
NF1	16	0	0.00%	0	0.00%	0	41.8	40.9-44.2	0.11%
TP53	7	3	42.86%	0	0.00%	1	32.1	27.5-34.8	0.05%
Negative for *BRCA1* in family	267	5	1.87%	7	2.62%	0	37.5	32.1-44.4	1.87%
Negative for *BRCA2* in family	271	10	3.69%	6	2.21%	3	39.4	32.5-45.4	1.89%
untested for *BRCA1* in family	115	2	1.74%	1	0.87%	0	34.5	31.5-40.9	0.80%
untested for *BRCA2* in family	135	1	0.74%	2	1.48%	1	38.3	31.7-46.1	0.94%
negative for other actionable gene	13	0	0.00%	2	15.38%	0	36.2	34.0-42.3	0.09%
untested for other gene	10	0	0.00%	0	0.00%	0	35.1	28.2-42.3	0.07%
No known high or moderate risk gene in family or individual including untested									
high	4939	217	4.39%	171	3.46%	69	39.7	34.7-47.0	34.53%
moderate risk	5234	181	3.46%	37	0.71%	73	40.3	34.2-46.5	36.59%
Average/population risk	2501	48	1.92%	0	0.00%	82	41.5	33.9-34.7	17.48%
Total	14311	649	4.51%	455	3.18%	269			100.00%

RRM-Risk reducing mastectomy; IQR-Interquartile range; BC-Breast cancer

Table 2: Incidence rates for breast cancer by *BRCA1/2* and risk group

	number	follow up	BC	BC annual rate	prevalent	% prevalent
*BRCA1**	309	1738.39	30	1.73%	2	0.65%
*BRCA2**	312	1811.26	28	1.55%	2	0.64%
moderate in screening	5293	28087.29	100	0.36%	19	0.36%
high risk in screening	5129	30392.28	192	0.63%	29	0.57%
moderate off screening		22091.61	83	0.38%	N/a	
High risk off screening		13298.49	81	0.61%	N/a	
Average	2509	23924.80	49	0.20%	1	0.04%
Negative for family *BRCA2*	218	1458.97	6	0.41%	0	
Negative for family *BRCA1*	194	1379.21	4	0.29%	0	
Untested for family *BRCA1+*	167	2390.28	7	0.29%	3	1.80%
Untested for family *BRCA2+*	180	2546.92	8	0.31%	5	2.78%
	14311	129119.52	588		61	

* includes 31 tested on research basis who have not had clinical testing including 7 *BRCA1/2* with breast cancer +includes women tested after censor and follow up in women who later tested positive or negative but these numbers not included in total women. BC-breast cancer

Table 3: Gene status in women with breast cancer with age at diagnosis and whether on or off programme

gene/risk	Total breast cancer	On screening program	median age	range	IQR	died	% died	Off screening programme	median age	range	IQR	died	% died
BRCA1	77	60	43.2	29.5-61.3	36.6-48.7	8	13.79%	17	42.5	27.7-66.4	38.0-53.5	3	17.65%
BRCA2	78	59	46.9	28.7-77.1	39.3-52.0	8	13.79%	19	54.2	40.4-71.4	48.7-60.3	3	15.79%
ATM	9	8	47.4	39.8-53.36	46.0-52.5	1	16.67%	1	41.6	41.0		0	0.00%
CDH1	2	1	50.3			1	100.00%	1	51.3			1	100.00%
PTEN	2	2	39.9	38.4-41.4		0	0.00%	0				0	
PALB2	6	6	44.7	41.6-46.5	44.5-45.4	1	16.67%	0				0	0.00%
CHEK2	7	4	43.4	35.6-46.1	36.9-44.1	0	0.00%	3	64.4	54.4-74.5		3	100.00%
TP53	3	1	24.1	24.1		0	0.00%	2	32.4	28.9-35.9		1	50.00%
negative for family *BRCA1*	5	3	54.3	47.4-56.9		0	0.00%	2	51.2			0	0.00%
negative for family *BRCA2*	10	4	54.1	49.7-59.3	51.2-57.3	1	25.00%	6	52.2	44.5-53.1	49.8-52.6	0	0.00%
Untested *BRCA1*	2							2	53.8	41.5-66.0		1	50.00%
Untested *BRCA2*	1							1	56.5			0	0.00%
Average risk negative *BRCA1/2*	22	3	55.0	48.3-64.9		3	100.00%	19	55.9	31.4-66.6	51.6-58.3	4	21.05%
Moderate risk negative *BRCA1/2*	121	78	47.9	34.3-65.5	44.5-52.1	14	17.50%	43	56.2	30.2-78.1	48.5-65.4	5	11.63%
High risk negative *BRCA1/2*	176	131	49.7	29.6-66.6	44.9-54.8	14	10.53%	45	54.7	32.1-79.2	50.1-67.3	9	20.00%
Average risk no testing	26	0				0		26	55.7	41.3-86.6	51.8-63.0	11	42.31%
Moderate risk no testing	61	17	48.4	34.4-64.0	46.4-53.4	1	5.88%	44	55.3	27.6-71.1	51.1-62.6	10	22.73%
High risk no testing	41	17	45.9	33.0-63.0	44.8-54.8	2	11.11%	24	56.7	35.5-71.1	47.7-64.6	2	8.33%
Total	649	394				54	13.81%	255				53	20.78%

IQR-Interquartile range; BC-Breast cancer

Table 4: Pathology details by genetic testing and risk group of breast cancers identified on the screening programme

gene/risk	*BRCA1*	*BRCA2*	*ATM*	*CDH1*	*PTEN*	*PALB2*	*CHEK2*	*TP53*	Negative for family BRCA mutation	Average risk	Moderate risk negative *BRCA1/2*	High risk negative *BRCA1/2*
On breast screening programme	60	59	8	1	2	6	4	1	7	3	78	131
Timing of cancer diagnosis												
Prevalent	5	7	0	0	0	0	1	0	1	1	17	9
Incident	37	42	8	1	2	4	2	1	6	0	43	87
Interval % interval	18 (30.0%)	10 (16.9%)	0 0.0%	0 0.0%	0 0.0%	2 33.3%	1 25.0%	0 0.0%	0 0.0%	2 66.7%	18 23.1%	35 26.7%
Interval at BRRM	2	2		1			1					1
Type of cancer												
IDC Grade 1	0	3	0	0	0		1	0	0	1	10	26
P value Grade 1	<0.0001	0.004									0.18	Reference
IDC Grade 2	7	18	2	0	1	2	1	0	2	0	25	35
IDC Grade 3	48	21	1	0	0	4	1	1	3	0	25	32
% Grade 3	80.0%	35.6%	12.5%	0.0%	0.0%	66.7%	25.0%	100.0%	42.9%	0.0%	32.1%	24.4%
Grade 3 vs high risk no PV*	<0.0001	0.24									0.73	Reference
ILC	0	3	1	1	0	0	0	0	0	2	5	17
P value*	<0.0001	0.1									0.16	Reference
CIS	5	14	4	0	1	0	1	0	2	0	13	21
% CIS	8.3%	23,7%	50.0%	0.0%	50.0%	0.0%	25.0%	0.0%	28.6%	0.0%	16.7%	16.0%
P value*	0.18	0.08									1.0	Reference
Cancer characteristics												
LN negative in invasive % LN^0	40 72.7%	34 75.6%	4 100.0%	1 100.0%	1 100.0%	4 66.7%	3 100.0%	1 100.0%	3 60.0%	1 33.3%	46 70.8%	80 72.7%
Stage 1	35	30	250.0%	0	0	2	3	1	3	1	36	69
% of invasive	63.6%	66.7%		0.0%	0.0%	33.3%	100.0%	100.0%	60.0%	33.3%	55.4%	62.7%
Invasive≤20mm	39	36	1	0	0	2	3	1	4	1	48	82
%	73.6%	83.7%	33.3%	0.0%	0.0%	33.3%	100.0%	100.0%	80.0%	33.3%	73.8%	74.5%
ER-	42	14	0	0	0	1	0	0	0	1	22	16
	<0.0001	0.05									0.004	Reference
HER2+	0	2	0	0	0		0	0	0	0	7	5

BRRM: bilateral risk reducing mastectomy. IDC: invasive ductal carcinoma. ILC: invasive lobular carcinoma. CIS: carcinoma *in situ*. LN: lymph node; PV-Patho

*p values were compared with high risk PV negative for *BRCA1, BRCA2* and moderate only due to numbers

Figures

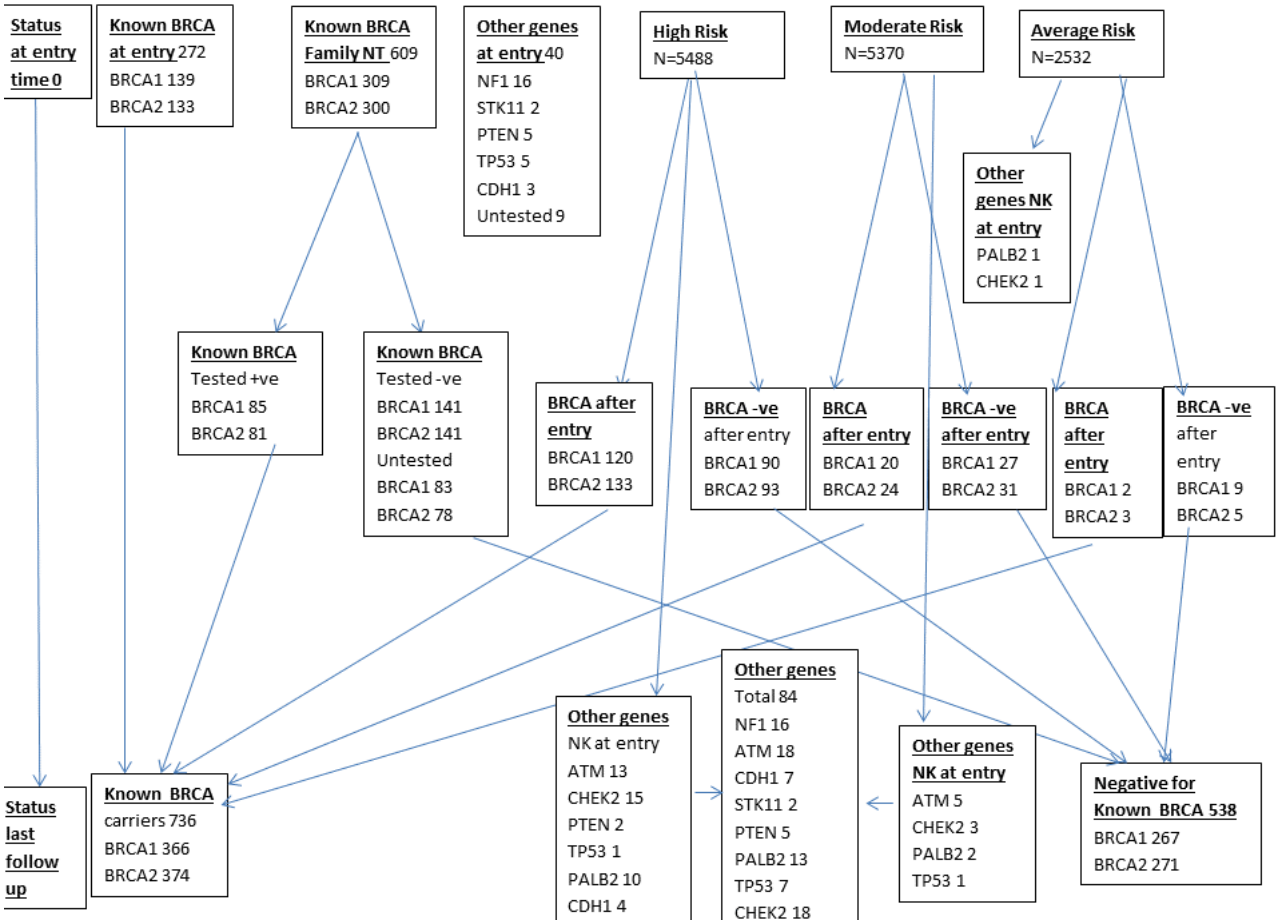

Figure 1

Flow diagram of Gene status and risk at entry and later Foot notes: NT-not tested; NK-not known; BRCA -ve negative for known BRCA PV in family; BRCA +ve positive for known BRCA PV in family

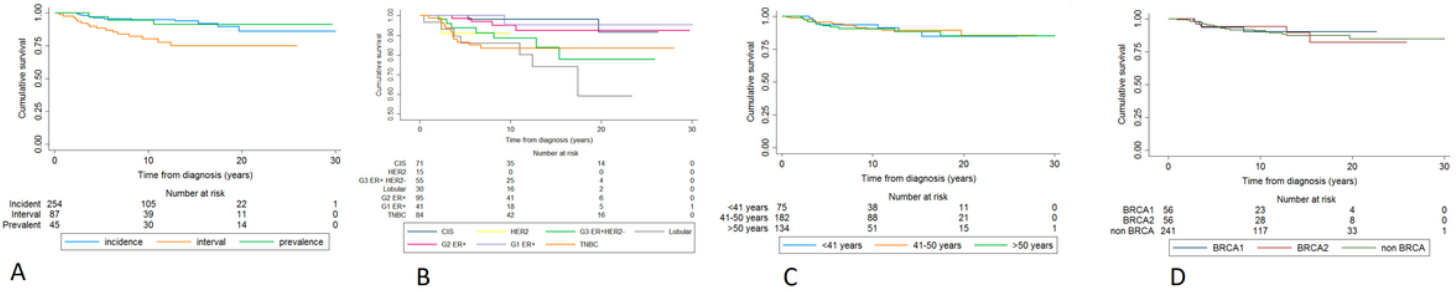

Figure 2

a: Survival by presentation (interval, incident, prevalent) – breast cancer deaths Incidence vs interval (p<0.001), prevalence vs incidence (p=0.052) b: Survival by pathology type – breast cancer deaths TNBC vs G1 ER+ (p=0.04), G2 ER+ (, p=0.03), CIS (p=0.01); G1 ER+ vs lobular (p=0.015); G2 ER+ vs lobular (p=0.006); lobular vs CIS (p<0.001); G3 ER+ HER2- vs CIS (p=0.019) TNBC – triple negative breast cancer, CIS – carcinoma in situ, G – grade, ER – estrogen receptor, HER2 - human epidermal growth factor receptor 2 c: Survival by age group – breast cancer deaths d: Kaplan Meier breast cancer specific survival curves comparing BRCA1, BRCA2, and non-BRCA affected women

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx