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Running title: NICE criteria for stratifying breast cancer risk

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Abstract

Breast cancer risk is a common indication for referral to clinical genetics services. UK National Institute of Health and Care Excellence (NICE) guidelines use family history (FH) to stratify by 10-year risk of breast cancer from age 40. Patients are stratified into population risk (PR, 10-year risk <3%), moderate (MR, 3-8%) and high risk (HR, >8%). Women at increased risk are offered screening at or prior to age 40. To assess the clinical effectiveness of current risk stratification, FH data was obtained for all unaffected women with a FH of breast cancer aged <50, referred to cancer genetics from 2000-2010. Patients were risk stratified by NICE criteria, identifying patients who subsequently developed breast cancer. 1,409 women had 15,414 patient-years of follow up. 30 invasive breast cancers developed, 13 in MR and 13 in HR women. Kaplan-Meier analysis demonstrated no significant difference in rate of breast cancer development between PR and MR women from ages 40-49 (Log rank p=0.431). There was a significant difference between ages 40-49 years between PR and HR women (p=0.036), but not on exclusion of BRCA mutation carriers (p=0.136). NICE absolute 10-year risk thresholds between ages 40-49 were not met in any risk group, when risk was estimated using the guidelines (PR=0.82%, MR=1.68%, HR=3.56%). Our data suggests that improved criteria are required for risk assessment prior to age 50 and screening resources may be best focussed on those with highly penetrant mutations in cancer risk genes.

Key words: *breast;cancer;risk;hereditary;familial;screening*

Introduction

Familial clustering of breast cancer is a common indication for referral to clinical genetics services. Whilst shared environmental factors contribute, they do not fully explain the risk, and genetic predisposition is thought to be a major factor. This can be due to rare, highly penetrant mutations, or multiple low penetrance variants (1,2). Risk assessment includes variant analysis for known cancer risk genes where appropriate, or assessment by family history (FH). The UK National Institute of Health and Care Excellence (NICE) provide guidance for classification and management of people with a FH of breast cancer (CG164) (3). Patients are stratified according to FH into near population risk (PR), moderate risk (MR) and high risk (HR) based on percentage lifetime risk and 10-year risk from age 40. Risk stratification uses empirical criteria provided (shown in *Table 1*), or other models such as the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), a computer program that is used to calculate the risks of breast and ovarian cancer in women based on their family history (4). NICE recommends additional screening for women at MR and HR, as seen in *Table 1*, in the form of mammograms or MRI. This is of relevance for younger women who are not yet enrolled in the UK National Breast Screening Programme (NBSP), which offers 3-yearly mammograms to all women aged 50-70. To our knowledge, there has been no attempt to validate the empirical NICE criteria in women attending clinical genetics services regarding their breast cancer risk.

Subjects and Methods

Female patients referred to clinical genetics services for breast cancer risk from 2000-2010 were included in the study. Patients were aged under 50 at initial consultation, with no personal history of breast and/or ovarian cancer. FH information was collected from clinical genetics services

records. BRCA (referring to both *BRCA1* and *BRCA2*) mutation carriers were identified through the national BRCA testing service. Women who went on to develop breast cancer were identified by linkage to pathology records.

All women were risk categorised into PR, MR and HR as outlined in the NICE guidelines (3). NICE guidelines do not state that affected relatives must be from the same side of the family. However, it is acknowledged that many clinicians interpret the guidelines this way. Therefore, all analyses were performed based on a risk categorisation which 1) did not assume and 2) assumed same-side FH as necessary to meet risk criteria. The result of BRCA testing was also considered for appropriate risk categorisation. This was time intensive with each case taking between 5-15 minutes for risk assignment. As this was done retrospectively using clinical notes, time taken for clinical consultation and confirmation of diagnoses of affected family members is not included.

Percentage 10-year risk was calculated for each risk category and for BRCA mutation carriers, for ages 40-49 and ages 50-59 years inclusive. Incidence of breast cancer per patient year of follow up within each group was calculated, and extrapolated to give the 10-year absolute breast cancer risk. Kaplan-Meier Survival Analysis (KMSA) was used to assess the rate of breast cancer development across different risk categories and age ranges. Patients were censored at completed time of follow up or at breast cancer diagnosis. The HR group was analysed both including and excluding BRCA carriers.

Results

In total, 1,409 patients were eligible for inclusion with a total of 15,414 patient years of follow up. Using both sides of the FH to calculate risk, 505 women were PR (35.8%), 522 MR (37%) and 382 HR (27.1%), including 12 *BRCA1* and 10 *BRCA2* carriers. Using only a same-side FH, there were 554 (39.3%) PR, 490 (34.8%) MR and 365 (25.9%) HR women.

30 women developed an invasive cancer prior to May 2016. The frequency and percentage 10-year absolute risk are shown in *Table 2*. Not assuming a same-side FH, the highest absolute risk between the ages of 40-49 was in the HR group, both including (3.56% (3.34-3.80%) and excluding BRCA carriers (2.49% (2.28-2.70%). From ages 50-59, the MR group had the highest percentage absolute risk, at 7.05% (6.78-7.31%).

Between ages 40-49, none of the groups met the 10-year risk suggested by NICE guidelines. Assuming a same-side FH, a similar pattern of absolute risk is seen, with no group reaching the screening threshold suggested by NICE.

Table 3 shows the results of KMSA. Not assuming same-side FH there is no significant difference in rate of breast cancer development between PR and MR group from 40-49 (p=0.431). A risk difference between these two groups emerges after the age of 50 (p=0.037). When same-side FH is assumed, there is no significant difference in breast cancer rates between PR and MR group overall (p=0.134) or across any age range (<39 years p=0.283, 40-49 years p=0.791, 50-59 years p=0.11).

Both not assuming, and assuming same-side FH, there is a difference in breast cancer rates between the PR and HR women from 40-49 (p=0.036 and p=0.042 respectively) However, this significance is lost on exclusion of BRCA carriers (p=0.136 and p=0.171 respectively). There is no significant difference in rate of breast cancer between these groups from the ages of 50-59 not assuming or assuming same-side FH (p=0.149 and p=0.063).

The MR and HR group combined were compared with the PR group to try and detect a significantly increased rate of breast cancer in women deemed at any increased risk. Not assuming same-side FH, the MR/HR group (excluding BRCA carriers) had a significantly increased rate of

breast cancer from 50-59 years (p=0.049). There was no detectable difference in breast cancer rates between MR and HR women at any time.

Discussion

Before the age of 50, neither the MR or HR groups have a risk that reached the suggested NICE 10-year threshold. KMSA showed the rate of breast cancer development under the age of 50 to be significantly greater for those with a BRCA mutation but, crucially, not for other MR or HR women in the cohort compared to the PR group.

Our study has used a real clinical cohort, based on routine clinical practice for patients referred over a 10-year period. In this context, empirical NICE risk criteria do not appear to achieve effective risk stratification of those without a highly penetrant mutation before the age of 50. In the MR group, there was a detectable increase in cancer risk after the age of 50, however, additional screening is not mandated for this group. When interpreted as requiring a same-sided FH, empirical criteria fail to detect this difference.

It is recognised that the moderately increased risk of breast cancer observed in some families may be due to a multifactorial, polygenic risk model. The greater ability of the guidance to identify at-risk women when both sides of a FH are used in risk estimation, may reflect this model of inheritance, with risk alleles being transmitted from both sides of the family. Future routine clinical practice is likely to require the analysis of genetic variants contributing to polygenic risk to achieve better performing risk estimation models. This is currently under investigation (5, 6).

NICE guidelines do suggest use of other methods of risk stratification, specifically BOADICEA (3). There is evidence that other methods such as BOADICEA may be effective in

risk stratification (7), although there is no direct published comparison with NICE empirical criteria.

This study has used a simple methodology to assess current clinical practice in UK cancer genetics. Of 1,409 patients being screening over a 16-year period, 30 developed invasive breast cancer. In this cohort, the ability of the current guidance to identify at risk women, once highly penetrant mutations are excluded, is poor. Though we have a moderate cohort size, we feel that these results are important and should encourage further investigation of the effectiveness of these national guidelines. It would appear beneficial to refine risk stratification methods to focus resources on women who will benefit most from early screening.

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Conflict of Interest

No conflict of interest to declare

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Table 1. NICE risk criteria and interventions

	Moderate Risk	High Risk (including *BRCA* mutation carriers)
NICE criteria	- One FDR diagnosed with breast cancer at younger than age 40 years or - Two first-degree or SDRs diagnosed with breast cancer at an average age of older than 50 years or - Three first-degree or SDRs diagnosed with breast cancer at an average age of older than 60 years	*At least the following female breast cancers only in the family:* - Two first-degree or SDRs diagnosed with breast cancer at younger than an average age of 50 years (at least one must be a FDR) or - Three first-degree or SDRs diagnosed with breast cancer at younger than an average age of 60 years (at least one must be a FDR) or - Four relatives diagnosed with breast cancer at any age (at least one must be a FDR) or *Families containing one relative with ovarian cancer at any age and, on the same side of the family:* - One FDR (including the relative with ovarian cancer) or SDR diagnosed with breast cancer at younger than age 50 years. or - Two first-degree or SDRs diagnosed with breast cancer at younger than an average age of 60 years. or - Another ovarian cancer at any age. or *Families affected by bilateral cancer (each breast cancer has the same count value as one relative):* - One FDR with cancer diagnosed in both breasts at younger than an average age 50 years. or - One first-degree or SDR diagnosed with bilateral cancer and one first or SDR diagnosed with breast cancer at younger than an average age 60 years. or *Families containing male breast cancer at any age and, on the same side of the family, at least:* - One first-degree or SDR diagnosed with breast cancer at younger than age 50 years. or - Two first-degree or SDRs diagnosed with breast cancer at younger than an average age of 60 years.
Mammographic Surveillance	Offer annually to women: - aged 40–49 years Consider annually for women: -aged 50-59 years	*Offer annually to women:* - Aged 40–59 years at high risk of breast cancer but with a 30% or lower probability of being a *BRCA* or *TP53* carrier - Aged 40–59 years who have not had genetic testing but have a greater than 30% probability of being a *BRCA* carrier - Aged 40–69 years with a known *BRCA1* or *BRCA2* mutation *Offer as part of the population screening programme to women:* - Aged 70 years and over with a known *BRCA1* or *BRCA2* mutation *Consider annually for women:* - Aged 30–39 years at high risk of breast cancer but with a 30% or lower probability of being a *BRCA* carrier - Aged 30–39 years who have not had genetic testing but have a greater than 30% probability of being a *BRCA* carrier - Aged 30–39 years with a known *BRCA1* or *BRCA2* mutation
MRI surveillance	Do not offer at any age	Offer annually to women: - Aged 30–49 years who have not had genetic testing but have a greater than 30% probability of being a *BRCA* carrier - Aged 30–49 years with a known *BRCA1* or *BRCA2* mutation
Risk-reducing mastectomy	Do not offer	-Should be raised as a risk-reducing strategy option with all women at high risk -Women considering this Should have specialist genetic counselling
Risk-reducing oopherectomy	Do not offer	Information should be provided

Table 2. Frequency and absolute risk of breast cancer by NICE risk category

	Risk categorised using both sides of FH		Risk categorised using only one side of FH	
	Number of invasive cancers		Number of invasive cancers	
	% 10-year absolute risk (95% CI)		% 10-year absolute risk (95% CI)	
	40-49 years	50-59 years	40-49 years	50-59 years
Population risk	2	2	3	3
	0.82% (0.72-0.94%)	1.61% (1.42-1.83%)	1.11% (0.10-1.23%)	2.23% (2.02-2.47%)
Moderate Risk	4	8	3	7
	1.68% (1.53-1.83%)	7.05% (6.78-7.31%)	1.37% (1.23-1.52%)	6.47% (6.19-6.75%)
High Risk (excluding *BRCA* carriers)	4	4	4	4
	2.49% (2.28-2.70%)	5.28% (4.93-5.64%)	2.62% (2.40-2.84%)	5.62% (5.26-5.99%)
BRCA carriers	2	1	2	1
	26.67% (17.98-37.63%)	52.63% (31.71-72.67%)	26.67% (17.98-37.63%)	52.63% (31.71-72.67%)
High Risk (including *BRCA* carriers)	6	5	6	5
	3.56% (3.34-3.80%)	6.44% (6.10-6.78%)	3.74% (3.51-3.98%)	6.84% (6.50-7.18%)

Table 3. Kaplan-Meier analysis of rate of breast cancer diagnosis comparing NICE risk categories by age range

	Same-side FH not assumed				Same-side FH assumed			
	KM Log-Rank (*p* -value)				KM Log-Rank (*p* -value)			
	Total follow up time	<39 years	40-49 years	50-59 years	Total follow up time	<39 years	40-49 years	50-59 years
Population & moderate	**0.048**	0.341	0.431	**0.037**	0.134	0.283	0.791	0.11
Population & high	**0.003**	0.091	**0.036**	0.149	**0.005**	0.328	**0.042**	0.063
Population & high (*BRCA* carriers excluded)	**0.019**	0.085	0.136	0.145	**0.027**	0.317	0.171	0.131
Moderate & high	0.274	0.328	0.183	0.581	0.218	0.995	0.111	0.795
Moderate & high (*BRCA* carriers excluded)	0.644	0.299	0.499	0.598	0.505	0.963	0.334	0.942
Population & moderate/high	**0.011**	0.216	0.134	0.05	**0.022**	0.298	0.206	0.069
Population & moderate/high (*BRCA* carriers excluded)	**0.024**	0.217	0.241	**0.049**	**0.049**	0.292	0.383	0.093