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Original article

A comparison of clinical–pathological characteristics between symptomatic and interval breast cancer

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ABSTRACT

Background: An association between interval breast cancers (cancer detected after a normal mammogram and before the next scheduled mammogram) and tumour aggressiveness has been postulated which may reflect their relatively poor overall prognosis. The aim of this study was to evaluate known prognostic features of screen detected breast cancers compared to interval breast cancers.

Methods: Patients diagnosed with breast cancer between January 2010 and 2013 at a single unit of the National Breast Screening Program (NBSP) in Ireland and those between the ages of 50 and 65 diagnosed at a symptomatic breast clinic were included in the study. Patients who had not had a screening mammogram within the proceeding two years or had a previous history of breast cancer were excluded. Data were retrospectively collected on patient demographics, tumour type, grade, hormone receptor status and stage of disease at presentation.

Results: There were 915 patients included in the study, with 92% (n = 844) diagnosed through the NBSP. Ductal carcinoma *in-situ* accounted for 19% (n = 160) of screen-detected breast cancers but only 2.8% of interval cancers ($p < 0.05$). The most common type of invasive cancer was invasive ductal carcinoma. Tumour grade was significantly higher in interval breast cancers ($p < 0.05$). Interval cancers were identified at a significantly higher stage (Stage 1 versus 2; $p < 0.001$) than screen-detected cancers. Interval breast cancers were less likely to be ER positive (76% versus 81%; $p < 0.05$) and significantly more likely to over-express HER2 (20% vs 10%, $p < 0.05$) than screen-detected cancers.

Conclusion: This study highlights the fact that interval cancers appear to have a number of adverse prognostic markers for overall breast cancer survival when compared to women with screen-detected breast cancers. Interval cancers were more likely to be invasive, of a higher grade and stage and with a greater predominance of HER2 and triple negative molecular subtypes. Therefore this heterogeneous group of tumours may be biologically more aggressive and account disproportionately to overall breast cancer mortality.

Introduction

Breast cancer remains the most common female malignancy in Ireland with over 2700 new cases diagnosed per year and while the incidence continues to increase the overall mortality has seen a gradual decline [1]. This has been attributed, at least in part, to the introduction of a structured nationwide screening program since the year 2000 of women aged 50–65 years biennially in Ireland. Screen-detected cancers are often of lower stage at presentation than symptomatically detected breast cancers which may translate into better overall survival [2]. While screening intrinsically infers a degree of lead and length time bias, there appears to be a survival benefit beyond stage shift for patients with screen detected breast cancers [2–7].

Interval breast cancers are defined as in-situ or invasive breast cancers diagnosed following a negative mammographic screening examination and prior to the next recommended routine screening mammogram [8–16]. A number of recent studies have postulated

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that tumours which arise between screening examinations may be more aggressive biologically and contribute disproportionately to overall breast cancer mortality [15,17–20]. It has also been hypothesized that interval breast cancers are more likely to be either triple negative or HER2 positive molecular subtypes, traditionally associated with a comparably worse prognosis [21–24]. These studies have been limited by both study and screening heterogeneity and therefore firm conclusions are difficult to draw. The aim of this study was to evaluate known clinical and pathological characteristics of a cohort of screen-detected breast carcinomas and compared them to identified interval breast cancers within a symptomatic cohort of patients.

Methods

A retrospective single centre study comparing clinical and pathological prognostic features between a cohort of screen-detected breast cancers and a cohort of interval breast cancers from January 2010 to January 2013 was performed.

Patient selection

St Vincent's University Hospital (SVUH) is one of eight national breast cancer treatment centres in Ireland and is associated with a National Breast Screening Program (NBSP) centre. Prospective databases are maintained for both screen-detected and symptomatic breast cancer patients. All patients with screen-detected breast cancers and patients within the screening age (50–65 years) who were diagnosed with breast cancer in the symptomatic clinic were identified. Women who had not had a screening mammogram within the preceding two years or had a previous history of breast cancer were excluded (Fig. 1). The remaining breast cancers were considered interval breast cancers.

Data collection

Patient demographics, the date of last screening mammogram and known prognostic indicators including tumour type and grade, nodal status, hormone receptor status and the American Joint Committee on Cancer (AJCC) stage at presentation were collected.

Tumour type was recorded according to the WHO classification of breast tumours [25]. For the purposes of the study tumours were grouped as follows: ductal carcinoma in situ (DCIS), invasive ducal carcinoma (IDC), invasive lobular carcinoma (ILC) and 'others' (special types apart from invasive lobular carcinoma and tumours showing mixed features. Histological grade was assessed using the modified Bloom and Richardson classification [26].

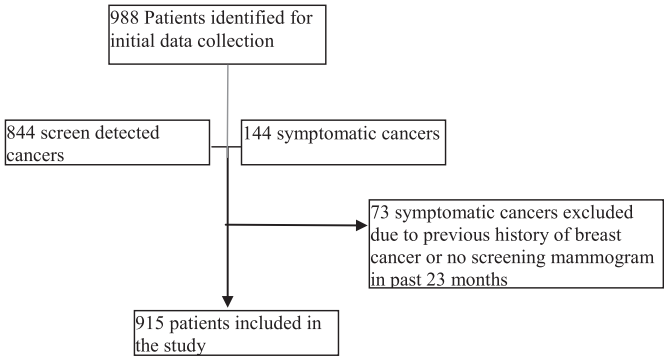

Fig. 1. Consort diagram of patient cohort.

Oestrogen and progesterone receptor status (ER and PR) were determined using immunohistochemistry (IHC). Initial assessment of Human Epidermal growth factor Receptor 2 status (HER2) was also performed using IHC, where strong circumferential membranous staining in >30% of invasive carcinoma cells was scored as 3+; moderate circumferential membranous staining in >10% of invasive carcinoma cells was scored as 2+; weak and incomplete membranous staining in >10% of invasive tumour cells was scored as 1+ and no staining was scored as 0. Tumours with 0 and 1+ staining were considered negative. Cases with 3+ were considered positive. Tumours scored as 2+ were considered equivocal and HER2 status was determined using fluorescence *in situ* hybridization (FISH). Using the receptor status of the invasive tumours, the molecular subtype was estimated as follows: Luminal A (ER and/or PR positive, HER2 negative), Luminal B (ER and/or PR positive, HER2 Positive), Triple negative (ER negative, PR negative and HER2 negative), HER2 type (ER negative, PR negative, HER2 positive).

Nodal status was evaluated pre-operatively with an ultrasound (USS) and where nodes appeared abnormal a fine needle aspiration biopsy (FNAC) was performed. Patients with a negative FNAC or normal appearing nodes on ultrasound proceed to a sentinel lymph node biopsy (SNB). Single modality (radio-isotope) mapping was utilised except where patients had a negative scintigram when dual modality was used. Patients with a positive FNAC underwent an axillary clearance

Statistical analysis

Data were analysed using Stata version 13. Two sample t-test was used for comparison of mean ages in the two groups. Univariate analysis of individual clinical and pathological features was performed using Chi-squared test with $p < 0.05$ considered statistically significant.

Results

A total of 988 patients, 844 screen-detected and 144 symptomatic breast cancers, were identified. Seventy three of the symptomatic patients were excluded as they had not undergone a screening mammogram in the 23 months preceding their diagnosis or had a previous history of breast cancer (Fig. 1). A total of 915 patients were included in the final analysis. The mean age of the screen detected cohort was 57 years compared to 58 years for the interval breast cancers ($p = 0.95$).

Ductal carcinoma *in-situ* accounted for 19% ($n = 160$) of screen-detected breast cancers but only 3% ($n = 2$) of interval cancers, a difference which was statistically significant ($p < 0.05$). Invasive ductal carcinoma (IDC) was the commonest tumour type in both groups, accounting for 72% of interval breast cancers and 61% of screen detected cancers ($p = 0.097$). Invasive lobular carcinoma was more commonly found in interval cancers compared to screen-detected patients (21% versus 11%; $p < 0.05$) (Table 1).

Interval breast cancers were of a higher grade than screen-detected carcinomas. Of the interval cancers 7% were grade 1, 51% grade 2 and 38% grade 3 compared to screen-detected cancers of which 19% were grade 1, 39% grade 2 and 24% grade 3 ($p < 0.05$) (Table 1). DCIS accounted for 3% of interval cancers compared with 19% of screen detected cancers. Interval detected cancers were node positive in 39% ($n = 28$) of patients compared to 24% ($n = 204$) of patients with a screen-detected cancer which was statistically significant ($p < 0.05$). A similar trend was seen in tumour stage between the two groups with interval cancers more frequently presenting at a later stage. Screen-detected tumours were detected at stage one in over 62% of cases, whereas interval cancers were at stage one in only 33% of cases ($p < 0.05$). 41% of interval cancers