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ORIGINAL ARTICLE

Defining clinicopathological and radiological features of breast cancer in women under the age of 35: an epidemiological study

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Abstract

Introduction Breast cancer is the most commonly diagnosed female cancer. Diagnosis in younger women (under 35 years) is different to their older counterparts, and mammography is not considered as sensitive in this cohort. Consequentially, younger patients may present later with more advanced disease.

Methods This is a retrospective analysis of a prospectively updated database containing consecutive patients who presented to the symptomatic breast unit of Galway University Hospital between 2009 and 2015. Patient clinicopathologic factors, clinical examination features, diagnostic radiological modalities and Bi-RADS score were all assessed. Data was analysed using Statistical Package for the Social Sciences version 25.

Results One thousand eight hundred thirty-six patients were diagnosed with breast cancer, and of these, 51 (2.8%) patients were < 35 years. Invasive ductal carcinoma made up 90% of diagnosis, and 42% had an associated ductal carcinoma in situ. Fifty-four percent were high-grade tumours and 52% presented with stage III disease or greater. The main radiological tool used was ultrasound, which had a sensitivity of 87.50% (95% confidence interval [CI] 74.75 to 95.27%). Mammogram sensitivity was 86.84% (95% CI 71.91 to 95.59%). Magnetic resonance imaging was used in 29% of cases, with a sensitivity of 100.00% (95% CI 78.20 to 100.00%).

Conclusion Females under 35 tend to be diagnosed with aggressive, advanced stage tumours. Ultrasound remains the radiological test of choice, although diagnosis using mammography demonstrated a relatively high sensitivity compared with previous reports. This study emphasises the varying epidemiology of breast cancer in younger patients and the potential role of mammography in making radiological diagnosis in those who are symptomatic.

Keywords Breast cancer · Diagnostic imaging · Under 35 · Women's health

Introduction

Breast cancer (BC) is the most prevalent cancer among women worldwide, and is the second leading cause of female cancer death [1, 2]. Currently, one in eight Irish women will be diagnosed with BC, and diagnosis tends to be made in older, post-menopausal patients [3]. Only 2.5% of BC diagnoses occur in patients less than 35 years old, while only 5–7% occur in women less than 40 years old [4, 5]. Despite the low prevalence in young patients, BC is still the most common solid tumour malignancy diagnosed in women aged 15–35 years and its incidence is on the rise [6].

Aggressive tumour biology, higher grade and advanced tumour staging at the time of diagnosis are considered to contribute to poorer outcomes in BC patients [7]. Hormone receptor positive BCs are the most common molecular subtype of BC overall (~ 70%); however, these cancers occur less frequently in younger patients. The more aggressive triple negative (TNBC) and human epidermal growth factor receptor-2 positive (HER2) BC subtypes are overrepresented in younger BC patients versus their older counterparts [7, 8].

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Consequently, there is a disproportional incidence of BC-related mortality in this cohort compared with older populations, despite younger patients generally having higher functional status prior to BC diagnosis [9]. This increased incidence of hormone receptor negative BC also makes younger patients less likely to be indicated for adjuvant endocrine therapies, which are proven to enhance oncological outcome in hormone receptor positive cancers [10]. As a result, young women with TNBC are often indicated to receive treatment in the form neo-adjuvant or adjuvant chemotherapy prescription, and are exposed to its toxic adverse effects [11].

Diagnostic accuracy of the various screening strategies depends on a number of patient, tumour and economic factors [12]. Optimal outcomes in BC management require early tumour detection [13] and mammography-based breast screening programmes such as the Health Service Executive's *Breast Check* have been validated in identifying breast pathology at a stage prior to the patient becoming initially symptomatic [14, 15]. Healthcare economic and cost-effectiveness implications of screening programmes mean that screening is only currently offered only to patients between 50 and 70 years in Ireland [16]. Younger patients are typically excluded from this programme on account of a lower incidence of disease in younger patients, and only indicated for screening if considered to be high risk [17, 18]. Furthermore, radiological analysis of younger breast tissue is much more challenging, making radiological diagnosis less effective in these patients [19]. Further assessment of radiological diagnostic modalities within this group is paramount to ensure the best oncological outcomes, particularly considering the more aggressive tumour biology of BC in younger women [20].

Suspicious breast lesions in younger patients are best evaluated using ultrasound (US) scanning to inform diagnosis [21]. Mammography is the radiological tool of choice in older women, however is considered to be of less diagnostic value in younger patients on account of the more dense nature of breast tissue in younger women [21]. Consequently, diagnostic interpretation and image quality of the mammography is more challenging for the radiologist. Diagnostic sensitivity in patients under the age of 35 is reported at approximately 84% [22]; in clinical practice this means 3 of every 20 young women will have a breast tumour missed on mammographic examination. For these reasons, regular mammography screening (as per *Breast Check)* in this patient group may be considered inappropriate to yield high diagnostic accuracy [23].

Radiological assessment of the breast parenchyma is more challenging in younger patients. As a result of this, BC diagnosis may be made later when the disease has progressed to an advanced stage. The aim of this study is to establish the clinical, pathological and radiological features of BC diagnosed in patients under the age of 35 that were diagnosed and managed in a publicly funded, tertiary referral centre over a 7-year period.

Aim and methodology

This was a retrospective analysis of a prospectively updated clinical database of patients who presented symptomatically to the symptomatic breast unit of Galway University Hospitals (GUH), Ireland. Inclusion criteria for the study were consecutive patients under the age of 35 years, diagnosed and treated for breast lesions between 2009 and 2015. Clinical, radiological and histopathological features were evaluated. Patients were categorized into three separate age categories: 21–25, 26–30 and 31–35 years respectively. Time from onset symptoms to clinical review was recorded. Information detailing genetic testing and specific patient family history of breast cancer were recorded, those with no relative diagnosed with BC were considered to have no significant family history, those with one first degree relative were considered to be at increased risk, and those with two or more first degree relatives were considered to be at a very high risk of BC.

Clinical details noted included clinical examination scores (S scores), a clinical measurement recorded by the consultant breast and endocrine surgeon at the time of triple assessment. Histopathological data was obtained from pathological evaluation conducted by the Department of Histopathology at the tertiary referral centre. All histopathological evaluation was conducted by a consultant histopathologist with a special interest in breast pathology. Grading was assessed according to the Elston and Ellis grading system [24]. All red scoring was used to define the histopathological oestrogen and progesterone receptor status of each tumour [25]. Human epidermal growth factor receptor-2 (HER2) status was assessed using immunohistochemical techniques, and patients with scores of 2 + were submitted for fluorescence in situ hybridisation (FISH) for confirmation of HER2 tumour status. Tumour lymphatic invasion was evaluated using IHC staining with D2-40 and vascular invasion using CD34 [26–28]. Tumour stage was calculated using the tumour nodes metastasis system of staging as per American Joint Committee on Cancer version 8 guidelines [29].

Radiological data were obtained from the hospital database, following reporting from a consultant radiology consultant with a specialised interest in breast disease imaging. Mammography, US scanning and magnetic resonance imaging (MRI) results were classified using breast imaging reporting and data system (BI-RADS) scores [30]. Categories 1–3 were considered a false negative. Categories 4–5 were considered positive breast cancer diagnoses.

Data collected was analysed using Statistical Package for the Social Sciences (SPSS) version 26. Significance threshold was set at $p < 0.05$. Sensitivity and specificity of mammographic and US imaging were expressed as percentages. The number of true-positive, false-positive, true-negative and false-negative test results was calculated for each imaging modality. Using these results, sensitivity and specificity with

confidence intervals (CI 95%) were calculated for each test. Accuracy was calculated as the proportion of true results (both true positives and true negatives) among the total number of cases examined. Confidence intervals are 'exact' Clopper-Pearson confidence intervals [31–33]. Student independent *t* test was used to determine correlation between histopathological tumour features. For all tests two-tailed *p* value of less than 0.05 indicated statistical significance.

Results

Between 2009 and 2015, 1836 patients were diagnosed with BC in our tertiary referral centre. Fifty-one of these patients (2.8%) were diagnosed at 35 years old or younger. The mean age at the time of diagnosis was 30 years ± 3.10 (range; 21–34 years) and the majority of patients were aged 31–35 years (36 of 51, 70.59%) (Fig. 1). The time taken from onset of symptoms to contacting a healthcare provider were recorded; 10 patients (19.61%) were seen in 30 days or less, 18 patients were seen between 31 and 60 days (35.29%), 14 patients were seen between 61 and 90 days (27.45%) and 9 patients were not seen until more than 90 days post-developing symptoms (17.65%). Details of family history were available for 32 of 51 patients (62.75%). The majority of patients had no significant family history of BC (28 of 32, 87.50%), 9.38% (3 of 32) were at an increased risk of BC due to family history and 3.13% (1 patient) was found to have a high-risk family history for BC. No patients in this study had undergone BRCA genetic testing.

S scores were available for 50 of 51 cases (98.04%). Of these, 18.00% (9 of 50 cases) were given a score of 1 or 2 indicating normal or benign breast on examination, 44.00% (22 of 50 cases) were given a score of 3, indicating benign feeling lump and 38.00% (19 of 50) were given a score of 4–5, suspicious lesion. As such, a false-negative rate of clinical examination was 56.00% in this age group.

The vast majority of patients (48 of 51, 94.11%) underwent diagnostic mammography. In the remaining 3 cases, the women were pregnant at time of diagnosis and therefore were not subject mammography. Of these, full data was available for 38 of the 48 cases. Mammography was diagnostically successful in diagnosing a breast tumour in 33 of the 38 mammograms. Mammogram sensitivity in this cohort of patients was 86.84% (95% CI 71.91 to 95.59%). A total of 10.52% (4 out of 38) were classified as BI-RADS categories 1–3, which was consequentially considered to be false negative for BC diagnosis. Only one case (2.63%) was categorised as BI-RADS 1, 5.26% (2 out of 38) were categorised as BI-RADS 2, while 2.63% (1 out of 38) was categorised as category 3. Thirty-four percent of patients (13 out of 38) were categorised as suspicious (category 4), and a majority of 52.63% (20 of 38) were categorised as highly suspicious (category 5) (Fig. 2). Microcalcifications were reported in 31% of mammograms, yet microcalcifications were noted on histopathology in 44.73% of cases (17 out of 38). The presence of microcalcifications on mammography was compared with tumour subtype, but failed to reach a significant association.

All patients underwent US scanning of the breast. Full data was available for 42 patients (82.35%). US sensitivity was 87.50% (95% CI 74.75 to 95.27%). False negatives were reported in 12.50% of cases (6 out of 48). Lesions seen on US were then classified as highly suspicious BI-RADS 5 (20 of 42 cases, 47.62%), suspicious BI-RADS 4 (17 of 42 cases, 40.48% of cases), probably benign BI-RADS 3 (3 of 42 cases, 7.14%) and benign BI-RADS 2 (2 of 42 cases, 4.76%).

Twenty-nine percent of patients (15 of 51 cases) underwent MRI of their breast tissue. Of these, 20.00% (3 of 15) were classified as category 4, 53.33% (8 of 15) was classed as category 5 and 26.66% (4 of 15) were classed category 6.

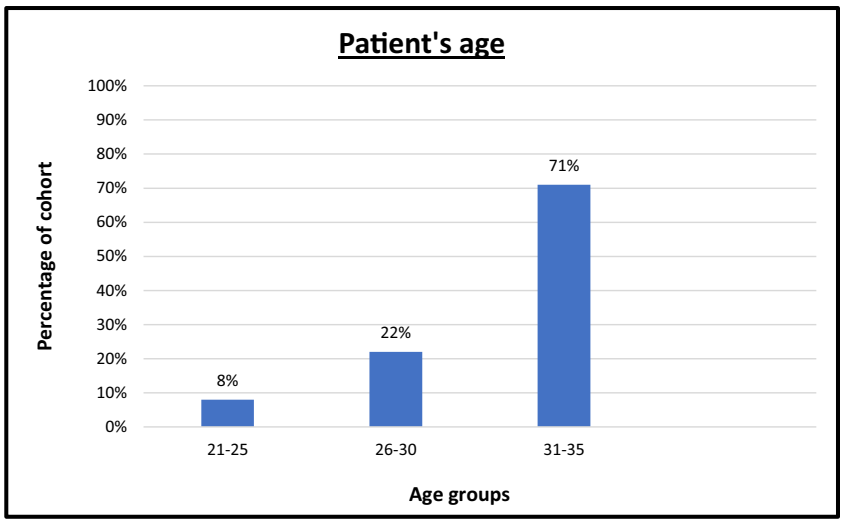

Fig. 1 Patient's age categories

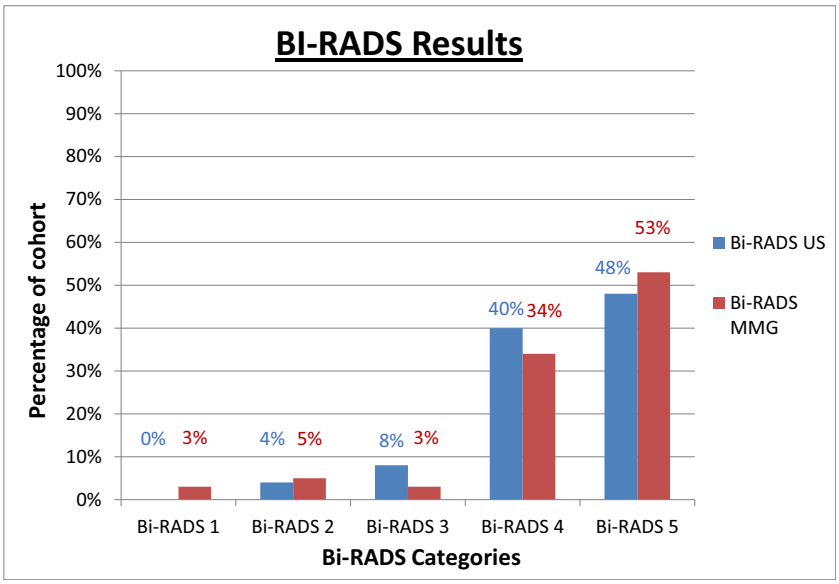

Fig. 2 Bi-RADS score by percentage

Magnetic resonance imaging sensitivity was 100.00% (95% CI 78.20 to 100.00%).

The mean tumour size was 43 mm ± 28.31 mm, while the median tumour size was 30.00 mm (range 7 –105 mm) (Fig. 3). Four different histopathological BC subtypes were seen in our patients; 47.06% of tumours (24 of 51) were classified as invasive ductal carcinomas (IDC), 7.84% of tumours (4 of 51) were classified as being ductal carcinoma in situ (DCIS), 43.14% (22 of 51 tumours) were classified as having IDC with DCIS component to the tumour specimen and 1 patient was diagnosed a malignant phyllodes tumour (1.96%). Twenty-eight of patients had high-grade tumours (54.90%) (Fig. 4). Twenty-seven patients (27 of 46 patients, 58.70%) had advanced stage disease (stage 3 or 4) (Fig. 5). Lymphovascular invasion (LVI) was present in 34.78% (16 of 46 tumours), and 30.43% (14 of 46 tumours) had positive axillary lymph nodes following sentinel lymph node biopsy or axillary clearance. With regard to the molecular

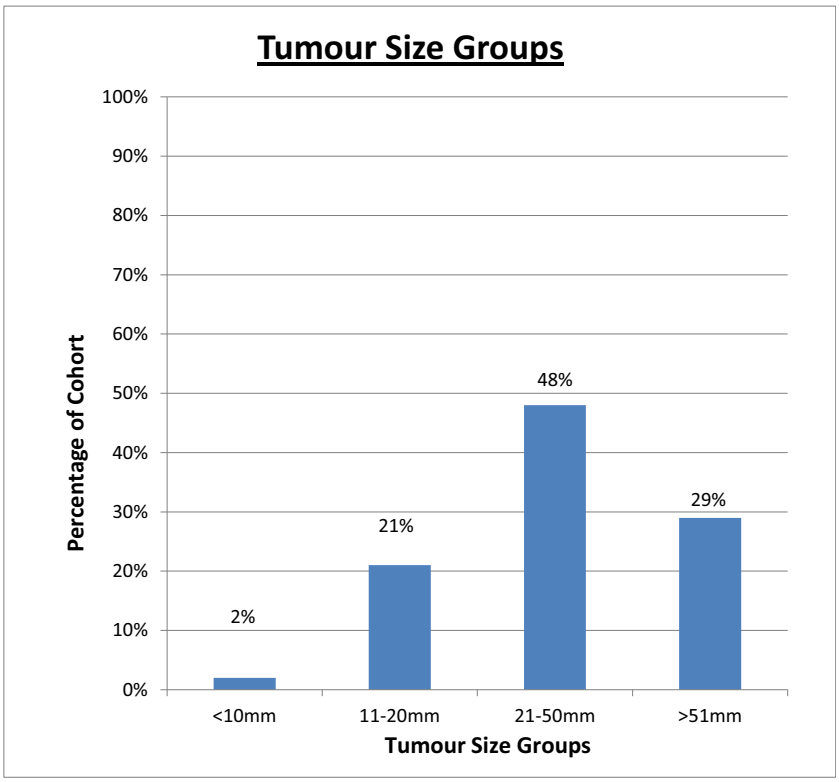

Fig. 3 Tumour size groups (including invasive tumour and in situ components)

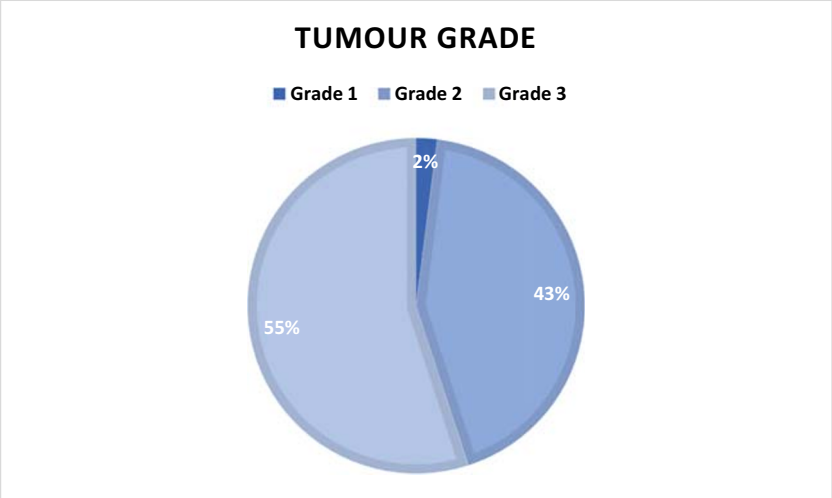

Fig. 4 Patients categorised according to tumour grade

classification of the tumour specimens, 50.00% (23 of 46 tumours) of tumours were classified as luminal A BCs, 8.70% (4 of 46 tumours) were luminal B BCs, 13.04% (6 of 46 tumours) were HER2+ BCs and 28.26% (13 of 46 tumours) were TNBC (Fig. 6). LVI and positive axillary lymph nodes demonstrated a significant correlation ($p = 0.043$).

Discussion

The main finding of the present study is that the majority of young BC patients diagnosed in our symptomatic breast clinic were found to have aggressive pathological tumours. Approximately 90% patients exhibited an invasive component to their disease and high-grade invasive breast carcinoma was found in the majority of this cohort. Moreover, a large proportion had an advanced stage at the time of diagnosis (52% of patients had a pathological stage of 3 or greater). Our patients demonstrated a high rate of LVI, with almost one-third of patients demonstrating this poor prognostic histopathological finding, and over 25% of patients harbouring positive axillary lymph node biopsies. This is similar to previous literature within young patients, as this cohort is classically known to develop more aggressive histopathological disease [7]. Our study results regarding molecular tumour subtypes also mirrored the published literature, with a 30% rate of TNBC, further highlighting the aggressive nature of BCs affecting patients in this age group [7, 8]. Despite this incidence of TNBC, none of the patients in this series were previously indicated for BRCA1 or BRCA2 mutation testing, a finding often associated with TNBC in young women [34]. Other clinicopathological findings are predominantly expected within this young cohort of breast carcinoma patients; however, none were diagnosed with an invasive lobular carcinoma. This finding is somewhat inconsistent with previously published literature, where 8% of cases in young BC patients harbour this histopathological diagnosis [35]. Drawing the conclusion that women under 35 rarely face this diagnosis

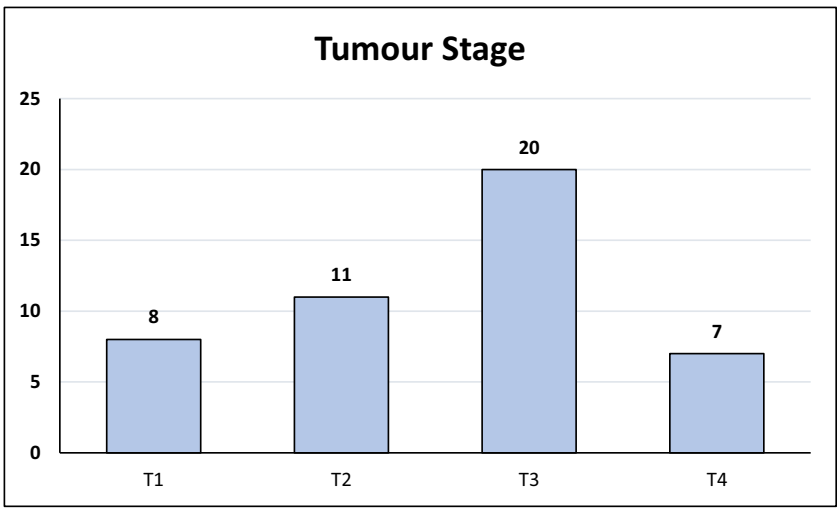

Fig. 5 Tumour staging for our patients

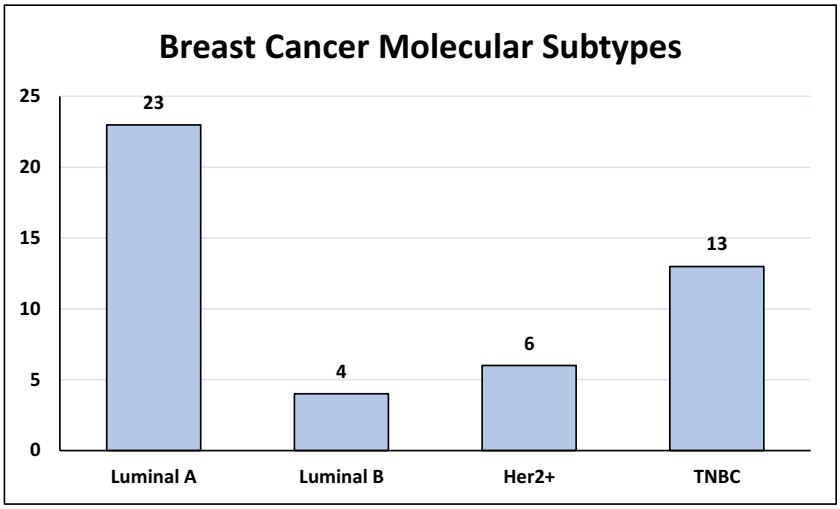

Fig. 6 Breast cancer molcular subtypes

would be somewhat naïve, given the small number of patients powering this study. Furthermore, one must consider the occult nature of lobular BC subtype on radiological imaging [36, 37], as it often relies upon MRI alone to inform diagnosis [38]. Our study illustrates 100% sensitivity with regard to MRI in breast cancer workup in women under 35, which is an extremely reassuring result irrespective of the absence of lobular cancers in this study.

Breast US has been described as significantly more accurate than mammography in detecting breast cancer with respect to tumour size, tissue density and patient age. [20]. US imaging typically demonstrates a difference range of only ± 2 mm when compared with post-operative pathological tumour size measurement, illustrating concise accuracy for triple assessment radiological evaluation [39]. However, our study noted mammographic sensitivity of 86%, results equivocal to that of breast US in terms of accuracy irrespective of tumour size. This sensitivity is satisfactory compared with previously published literature, which reports mammogram sensitivity ranging between 68 and 85% [40]. It is relatively plausible that our reported sensitivity is perhaps due to some of these patients proceeding to mammography post-diagnostic US, which may directly influence our reported sensitivity. This unfortunately could not have been avoided as carcinoma diagnosis should always remain the priority. Radiological detection of microcalcifications in our series was approximately 30% which is directly consistent with previously published in the literature (~28%) [41]. However, this was less than the 45% reported incidence (17 of 38 tumours) of microcalcifications on histopathological assessment. A retrospective review by a breast specialist consultant radiologist was performed on mammographic imaging confirming the radiological rate and also that up to 14% of microcalcifications may not be radiologically visible on mammography in young women with breast cancer. Perhaps, caution should be taken by physicians when relying upon these radiological modalities to detect calcification in clinical practice.

The high percentage of patients presenting with advanced stage BC in this cohort is perhaps due to the absence of screening service for patients under the age of 50 years in the Republic of Ireland, leaving the obligation upon the patient themselves to conduct routine self-examination of their breasts. We appreciate the Junger and Wilson criteria for screening and appreciate that given the natural history of BC disease, there is no justifiable role for women under 35 to undergo screening [42]. Moreover, up to 80% of cancers in this group were self-detected, meaning perhaps redeployment of funding for education of women from a school age may provide a more cost-effective and effective means of early detection. On the contrary, 18% of women waited over 90 days following symptom discovery before they consulted a healthcare provider, and in the context of these advanced staged tumours, this is a concerning statistic. This highlights the need for patients themselves to activate the urgent referral pathway for self-detected lesions, and reiterates value patient education in secondary level schools in order to counteract these delayed presentations. Herein, we appreciate that the vast majority of young patients seen in symptomatic breast clinics have no abnormality or a benign diagnosis. Of those who present with disease, we respect that more than half such patients may have a false-negative clinical examination, with 18% in the present study having no palpable abnormality, and 38% considered to have a 'benign-feeling' lesion. These findings indicate the complexity associated with BC diagnosis in young women, and illustrate the difficulty appreciating these cancers clinically, as merit of triple assessment for accurate diagnosis. This subtle clinical nature of some BCs in younger people also provides rationale as to why patients present at late stages. Perhaps general practitioners and other healthcare

providers should have a lower threshold to refer young symptomatic patients for triple assessment, although we further the knowledge that a large volume of young patients in the breast clinic will ultimately have no malignant pathology. These results emphasise the significance of prompt presentation and thorough triple assessment of breast lumps in this group and the consideration that these are high risk until malignancy is ruled out objectively.

This study is susceptible to limitations associated with being conducted in a single centre. The retrospective nature of the study increases the risk of ascertainment and confounding bias. Patient sample sizes were small which ultimately has influenced the results derived from this study; sample sizes in the disease positive and disease negative groups do not reflect the real prevalence of the disease. Specificity, positive and negative predicted values and accuracy of the imaging modalities could not be estimated which limited our evaluation of radiological modalities. Moreover, anonymisation of the data in in an effort to comply with the original advice from the Department of Health and the Health Service Executive regarding retrospective chart review in the context of the General Data Protection Regulation (EU-GDPR) meant that no follow-up data could be collated for the involved patient cohort. Nevertheless, this study further confirms that breast cancer often presents aggressively and less differentiated in younger women. US was the radiological test of choice in our patients, and mammogram demonstrated a relatively high sensitivity. Triple assessment of all lumps and asymmetrical nodularity is critical in order not to miss or delay a cancer diagnosis in this age group. Given the high false-negative rate of clinical examination, we would urge clinicians not to overlook the possibility of malignancy in women under 35 in the breast clinic, particularly when considering the aggressive epidemiology of BC disease for these patients.

To conclude, females under 35 tend to be diagnosed with aggressive cancers that are typically advanced stage. US remains the radiological test of choice for this cohort of patients, although the utilisation of mammography demonstrated a high sensitivity for breast tumour diagnosis compared with previous reports. Our study demonstrates the epidemiology of breast cancer in younger patients and the value of conducting multimodal radiological assessment in cases of uncertainty to inform diagnosis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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