Increased Risk of Breast Cancer at a Young Age in Women with Fibrous Dysplasia†

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Abstract

Background
Fibrous dysplasia is a rare bone disorder caused by mutations of the GNAS-gene, which are also identified in malignancies. We explored the potential relationship between breast cancer and fibrous dysplasia in two fibrous dysplasia cohorts from the Netherlands and the USA.

Patients and Methods
Data on fibrous dysplasia and breast cancer diagnosis were retrieved from hospital-records of 134 (Netherlands) and 121 (USA) female patients. Results were validated with breast cancer data of 645 female fibrous dysplasia patients from the Dutch Pathology Registry (PALGA). Standardized-morbidity-ratios for breast cancer were estimated with data from Dutch and US general population registries. GNAS-mutation was analyzed in 9 available breast cancer specimens.

Results
A combined total of 15 patients (6 polyostotic, 9 McCune-Albright-Syndrome) had breast cancer (87% thoracic localizations). In the Netherlands, a breast cancer incidence rate of 7.5% at median age of 46 years was validated in PALGA (6.5% at 51 years). Breast cancer risk was 3.4-fold increased (95%CI: 1.6-5.9) compared to the Dutch general population; 13.2-fold (95%CI: 6.2-22.8) in thoracic disease. In the USA cohort, breast cancer incidence rate was 4.5% at a median age of 36 years. Breast cancer risk was 3.9-fold increased (95%CI: 1.2-8.2) compared to the general population; 5.7-fold (95%CI: 1.4-13.0) in thoracic disease. GNAS-mutation was positive in four breast cancer specimens (44%).

Conclusion
Risk of breast cancer is increased at a younger age, particularly in polyostotic FD, suggesting that screening for breast cancer should be considered in this particular group at a younger age than currently advocated by national guidelines. This article is protected by copyright. All rights reserved

Keywords: Fibrous Dysplasia, McCune-Albright Syndrome, Breast Cancer, GNAS-mutation, G alpha
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Introduction

Fibrous dysplasia is a genetic but non-inherited rare bone disorder, in which normal bone is replaced by fibrous tissue of poor quality and structure, at one (monostotic) or multiple sites (polyostotic), associated with bone pain, deformities and increased fracture risk. In this disorder, somatic missense mutations of the \textit{GNAS}-gene on chromosome 20q13.3 have been identified not only in cells of the osteogenic lineage, but also in cells from tissues derived from any or all germ layers, including endocrine, skin or intramuscular mesenchymal cells. The post-zygotic and mosaic nature of the mutation and the various germ cells potentially carrying the mutation results in a broad clinical spectrum.\textsuperscript{(1,2)} The skeletal manifestations of fibrous dysplasia may thus be associated with extra-skeletal manifestations such as skin, endocrine or other manifestations in the McCune-Albright syndrome, and with intramuscular myxomas in Mazabraud’s syndrome.\textsuperscript{(3-5)} Outside the context of fibrous dysplasia, activating \textit{GNAS}-mutations have also been documented in various malignancies, such as thyroid carcinomas, pancreatic neoplasms and breast cancer.\textsuperscript{(5-9)} To our knowledge, only four case reports have so far documented an association between fibrous dysplasia and breast cancer, all four in patients with McCune-Albright syndrome.\textsuperscript{(10-13)}

In this study we explore the potential association between breast cancer and fibrous dysplasia by examining the prevalence of this malignancy in two relatively large cohorts of patients with fibrous dysplasia from the Netherlands and the United States, comparing breast cancer data with the general population.

Patients and Methods

Patients included in this study were part of two well-characterized cohorts of patients with all types of fibrous dysplasia from the Leiden University Medical Center (LUMC) in the
Netherlands and from the National Institutes of Health (NIH) in the USA (Figure 1). All patients were initially evaluated between 1990 and 2016. A diagnosis of fibrous dysplasia was established in both the Dutch and US cohorts on the basis of clinical and radiological and scintigraphic features, with histological and genetic confirmation of the presence of a GNAS-mutation occasionally required, mostly in case of monostotic lesions. Cases from the Dutch cohort with persistent uncertainty about the diagnosis were further discussed at meetings of the National Bone Tumor Committee of the Netherlands. For the LUMC cohort, data on the prevalence of breast cancer were validated using data from PALGA: the National Dutch Pathology Registry.(14)

Data on age at diagnosis, type of fibrous dysplasia, localization of lesions (specifically in the thoracic region) and where applicable age at diagnosis of breast cancer, and type and staging of the tumor were retrieved from patient’s medical records. Data on risk factors for breast cancer such as family history, radiation therapy, age at menarche, age at menopause, age at first pregnancy, family history, radiation exposure, lifestyle (diet, BMI, alcohol intake and smoking), the use of oral contraceptives and the use of hormone replacement therapy were also retrieved.(15) We also retrieved data on GH/IGF-1 excess. Data on tumor characteristics, TNM-classification, and therapeutic approaches used were documented. The respective medical ethical committees of the LUMC and NIH Centers approved the retrieval and analysis of the data. In the Netherlands, written informed consent was obtained to perform GNAS-mutation analysis on breast cancer specimens from patients who underwent surgery for breast cancer. Informed consent was also obtained from patients in the NIH natural history study (www.clinicaltrials.gov/NCT00001727).
**Histopathological and genetic characteristics of breast cancer**

Immunohistochemistry was performed on paraffin embedded pathological specimens of breast cancer tissue obtained from 10 LUMC patients in order to determine hormone and HER2 receptor status using previously described methods (supplemental file 1).(16,17) Next-generation sequencing (NGS) was carried out using the Ion PGM™ protocol and supplier’s materials, and libraries were generated using Life Technology’s Ion AmpliSeq™ Cancer Hotspot Panel v2 (supplemental file 1).(18) All sequences had a depth of over 100 reads and variances are reported with an allele frequency of 0.1 or more, ensuring a thorough analysis of possible mutations of the GNAS-gene.

**Epidemiology of Breast Cancer in the LUMC and NIH cohorts**

Standardized morbidity ratios (SMR) were calculated for both cohorts separately, as the ratio of observed versus expected morbidity, using age injunctions of five years (i.e. 0-4 years, 5-9 years etc.) by comparing the incidence rates of breast cancer for each cohort with the respective national incidence rate of breast cancer as retrieved from the Dutch Cancer Registry (IKNL) and the National Cancer Institute registry of the USA.(19,20) Follow-up time was measured from date of birth until time of death, outcome under study (breast cancer) or date of last follow-up.

In view of the potential association of fibrous dysplasia lesions with local development of soft tissue tumors (as observed in Mazabraud’s syndrome), we additionally estimated the SMR in patients with documented lesions of the thoracic region, including lesions in ribs, sternum and thoracic vertebrae. SMRs could not be calculated from the PALGA database as this database lacked information about age of first symptoms, localization or type of fibrous dysplasia.
Statistical Analysis

Statistical analysis was performed with the use of SPSS for Windows, Version 23.0 (SPSS, Inc., Chicago, IL, USA). Unless stated otherwise, results are presented as median (range) and as percentage in case of categorical data.

Results

Cohort characteristics (Table 1)

The Dutch cohort consisted of 254 patients including 134 women, 27 (20%) of whom had polyostotic disease and 11 (8%) had McCune-Albright syndrome. Median age was 25.5 years (range 0-70 years) at clinical presentation and 37 years (range 8-85 years) at last follow-up.

Data on 645 women with a registered histological diagnosis of fibrous dysplasia between 1992-2015 were retrieved from the PALGA database and examined for an associated diagnosis of breast cancer. The US cohort consisted of 226 patients: 121 women, 9 (7.4%) with polyostotic disease and 107 (88.4%) with McCune-Albright syndrome. Median age was 13.0 years (range 1-80 years) at clinical presentation and 19.0 years (range 5-100 years) at last follow-up.

Prevalence of breast cancer in fibrous dysplasia patients in the Dutch and US cohorts (Table 1)

In the Dutch cohort, breast cancer was diagnosed in 10 of 134 female patients (7.4%) at a median age of 46 years (range 32-54 years). The PALGA database revealed an additional histological diagnosis of breast cancer documented at a median age of 51 years (range 27-75 years) in 42 of 645 women with a histological diagnosis of fibrous dysplasia (6.5%). In the US cohort, breast cancer was diagnosed in 5 of 121 female patients (4.1 %) at a median age of 36 years (27-46 years). Median age at diagnosis of breast cancer was therefore considerably
lower compared to the national median age of 61 years in the Netherlands and 62 years in the US population.\(^{(19,20)}\)

**Standardized Morbidity Ratios**

In the Dutch cohort (5464 person-years), the SMR for the risk of developing breast cancer was 3.4 (95% CI: 1.6-5.9) compared to the general Dutch population.\(^{(19)}\) The SMR for breast cancer in patients with lesions localized in the thoracic region was even higher showing a 13.2-fold increased malignancy risk (95% CI: 6.2-22.8). Despite an overall lower incidence rate of breast cancer in the US cohort compared to the Dutch cohort (4.1% vs. 7.4%), the SMR was similarly increased in the US cohort (3053.5 person-years) showing a 3.9-fold increased risk for breast cancer (95% CI: 1.2-8.2) compared to the general US population, and a 5.7-fold increased risk (95% CI: 1.4-13.0) in the presence of thoracic lesions.\(^{(20)}\)

**Breast cancer characteristics in the combined Dutch and US cohorts (Table 2)**

A total of 15 patients were diagnosed with breast cancer in the combined cohorts, 10 with a ductal carcinoma in situ (DCIS) and 5 with an invasive adenocarcinoma, No Special Type, one of which had histological evidence for mucinous differentiation. In none of the 15 patients who developed breast cancer was this diagnosed by the physician who was treating their fibrous dysplasia. The diagnosis was based on the discovery of a painless swelling, which was further investigated by a general physician or by detection of features suspicious of malignancy on routine mammography performed in the context of a national screening program. All 15 patients had polyostotic fibrous dysplasia, and 9 had McCune-Albright syndrome, all with a history of precocious puberty and three with documented growth hormone (GH) excess. Thirteen of the 15 patients (87%) had lesions localized in the thoracic region: 11 (73%) in the ribs, 4 (27%) in the sternum and 9 (60%) in the thoracic vertebrae.
The thoracic lesions were ipsilateral to the breast cancer in 10 patients (77%), were located in the midline in one case and were contralateral in 2 cases. Traditional risk factors for breast cancer were assessed in 13 of the 15 patients and could not been documented in two patients who were lost to follow up. The most consistent risk factor for breast cancer was prolonged exposure to gonadal hormones because of precocious puberty in patients with McCune-Albright syndrome (n=9). One patient had a first degree relative (mother) with breast cancer diagnosed at the age of 84 years. Nine of eleven patients had positive expression of both estrogen (ER) and progesterone receptors (PR), and two patients with negative PR and ER had positive HER2-neu receptors. None of the 11 patients with receptor data had triple-negative receptor status. Survival was 100% and none of the patients had developed local recurrence or distant metastases after a median follow-up of 8.6 years (range 2-15 years).

**Mutation analysis**

Targeted next-generation-sequencing was performed to determine the presence of a GNAS-mutation in 8 of the 10 patients from the Dutch cohort using libraries of Life Technology’s Ion AmpliSeq™ Cancer Hotspot Panel v2 (supplemental file 1). Mutation analysis of one of the 5 patients from the US cohort was performed with Sanger sequencing (Table 2). NGS revealed a GNAS-mutation in three of 8 patients (38%) from the Dutch cohort in whom this could be evaluated. In two of these patients, the same GNAS-mutations were detected in fibrous dysplasia lesions, and in one patient the mutation was also detected in a myxoma (patient 7). Sanger sequencing revealed a GNAS-mutation in the pathological DCIS specimen of one US patient, resulting in a total prevalence of GNAS-mutations of 44% in the combined cohorts. PIK3CA mutations were additionally identified in most patients with NGS (n=6, 75%). All GNAS-positive tumors were ER and PR positive and HER2-Neu negative.
Discussion

In this study we demonstrate a more than three-fold increased risk for developing breast cancer at a younger age in women with the more severe forms of fibrous dysplasia compared to the general population.(19,20) Although an element of selection bias is inherent to the study of patients from cohorts from tertiary referral centers, we believe that combining the Dutch and US cohorts minimized this potential bias because of the different distribution of FD type and thus severity in the respective cohorts. In the Dutch cohort 72% of patients had monostotic fibrous dysplasia whereas in the US cohort 88% of patients had McCune-Albright syndrome. Standardized morbidity ratios for breast cancer were, however, very similar between cohorts: 3.4 (95% CI: 1.6-5.9) for the Dutch cohort and 3.9 (95% CI: 1.2-8.2) for the US cohort. In both cohorts, most recent data on national incidence ratio of breast cancer were used. The high incidence rate of breast cancer in women with FD and the young age at diagnosis of breast cancer were both confirmed in the national pathology registry of the Netherlands (PALGA), median age 51 years (range 27-75 years) and histological diagnosis of breast cancer (6.5%).

Patients with fibrous dysplasia were clearly younger than members of the general population at the time of diagnosis of breast cancer. While the median age at diagnosis of breast cancer was similarly above 60 years of age both for the Netherlands (61 years) and the United States (62 years), all patients in our combined cohort were younger than sixty years of age at the time of diagnosis of breast cancer, with a respective median age of 46 and 36 years for the Netherlands and the US. In addition to the median age, there is an increasing trend in breast cancer incidence in both countries in the past decades and both countries have their care similarly organized with national screening programs from the age of 50 years.(19,20)

Data on a possible association between breast cancer and fibrous dysplasia are scarce, restricted to 4 case reports which suggested the association to be potentially related to
hormonal disturbances commonly observed in McCune-Albright syndrome such as prolonged exposure to gonadal hormones associated with precocious puberty or GH-excess although the mechanism by which GH-excess may increase the risk of developing breast cancer remains speculative.(10-13) Whereas data from a large meta-analysis of epidemiological studies on the relevance of circulating IGF-1 for breast cancer risk suggests a potential role for IGF-1 in the development of breast cancer, a further study from Brazil showed no correlation between IGF-1 and risk for breast cancer development.(21,22) Breast cancer risk was also shown not to be increased in patients with true GH-excess in acromegaly(23,24). Notwithstanding, our finding of GH excess in 3 out of 15 patients with breast cancer suggests that perhaps we should not entirely exclude excess GH/IGF-1 as a potential risk factor for breast cancer in fibrous dysplasia. While endocrinopathies may be a potentially contributory factor, we did also observe a GNAS-positive cancer in a patient without endocrine disease.

We identified GNAS-mutations in pathological specimens of breast tumors in 4 out of 9 patients with fibrous dysplasia (44%), compared with less than 1% reported incidence of GNAS-positive breast cancer in the general population.(25-29) Since several other mutations, including the high prevalence of PIK3CA mutations, 75%, were detected, we do not feel that there was a technical or material quality issue explaining the lack of GNAS-mutations in the breast cancer tissue of 6 patients, especially since targeted next generation sequencing is very sensitive and has a detection limit of <1%. This might be due to intratumoral mosaicism of the GNAS-mutation in fibrous dysplasia, where a mixture of GNAS-mutated cells and wild type cells are needed to develop a neoplasm this has been described in other rare benign bone tumors, including enchondromas and osteochondromas, explaining the reported detection rates (range 36-82%) of GNAS-mutations in bone and in myxomas of
fibrous dysplasia patients and thus the detection rate for GNAS-mutations in the breast cancer tissue of our patients.(26,27) It might be also possible that GNAS-mutated cells are capable of creating an environment in which mutations occur more easily in wild type cells. The creation of an oncogenic niche by mesenchymal cells has been described in combination with the development of myelodysplastic syndrome and secondary leukemia as well as in the development of secondary peripheral chondrosarcoma from osteochondroma.(30,31) The prevalence of GNAS-mutations in the breast cancer tissue of fibrous dysplasia patients and the association between breast cancer and thoracic localization of FD lesions supports, in our view, a role for the GNAS-mutation in the pathophysiology of breast cancer in these patients. In addition to the increased prevalence of endocrinopathies, the increased prevalence of breast cancer provides further evidence that in fibrous dysplasia the role of GNAS-mutations extends beyond the scope of skeletal manifestations to a more systemic expression of the disease, including carcinogenesis.

Our findings from this study hold important implications for the follow up of FD patients. Although this is the first study addressing the prevalence of breast cancer in fibrous dysplasia, we believe our results to be substantial enough to enable us to recommend screening for breast cancer in women with fibrous dysplasia, especially those with thoracic lesions, at a younger age than currently advocated by national guidelines. Further research is required to unravel the exact mechanism by which a GNAS-mutation may be responsible or contribute to the development of breast cancer in patients with fibrous dysplasia.
Funding

This work was funded by a grant regarding research into fibrous dysplasia from the Bontius Foundation of the Leiden University Medical Center, and the Intramural Research Program of the National Institute of Dental and Craniofacial Research.

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Author Contributions

The study was designed by BCJM, PDSD, NATH and NMA-D. Acquisition of the data was performed by BCJM, AB and NMA-D. Analysis and interpretation of the data was performed by BCJM, AB, JB, VS, MTC, AMC, OMD, NATH, PDSD and NMA-D. Drafting of the manuscript, including critical revision was performed by all authors. All authors accept responsibility for the integrity of the data analysis.
References


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Figure Legends

Figure 1. Patient flow chart.
Table 1 Cohort Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LUMC</th>
<th>NIH</th>
<th>PALGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of female patients</td>
<td>134</td>
<td>121</td>
<td>645</td>
</tr>
<tr>
<td>Median age at diagnosis of FD</td>
<td>25.5 (0-70)</td>
<td>13.0 (1-80)</td>
<td>-</td>
</tr>
<tr>
<td>Median age at last follow-up (years)</td>
<td>40.5 (3-79)</td>
<td>19.0 (4-100)</td>
<td>-</td>
</tr>
<tr>
<td>Type FD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monostotic</td>
<td>94</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Polyostotic</td>
<td>27</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>McCune-Albright</td>
<td>13</td>
<td>107</td>
<td>-</td>
</tr>
<tr>
<td>Mazabraud’s Syndrome</td>
<td>9</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Thoracic FD Lesions</td>
<td>27 (20%)</td>
<td>70 (58%)</td>
<td>-</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>10 (7.4%)</td>
<td>5 (4.1%)</td>
<td>42 (6.5%)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>4</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>DCIS</td>
<td>5</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Both</td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>46.0</td>
<td>36.6</td>
<td>51.1</td>
</tr>
</tbody>
</table>

Table 1 Characteristics of the Dutch and US cohorts and of the PALGA cohort. FD = Fibrous Dysplasia, DCIS = ductal carcinoma in situ, NIH = National Institutes of Health, PALGA = Dutch National Pathology Registry.
<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age at diagnosis of FD (years)</th>
<th>Type of FD / MZB</th>
<th>Localization of FD lesions</th>
<th>Age at diagnosis of breast cancer (years)</th>
<th>Side of breast cancer</th>
<th>Type of breast cancer</th>
<th>Stage of breast cancer</th>
<th>Receptor status in breast cancer</th>
<th>Identified genes and type of mutation in breast cancer</th>
<th>Reads GNAS/ Frequency in breast cancer</th>
<th>GNAS mutation in bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>PFD</td>
<td>Skull, Humerus (R), Ulna (R), Ribs (L+R), Sternum, Pelvis (L+R), Femur (R), Tibia (R), Fibula (R), Metatarsal (R)</td>
<td>52</td>
<td>Right</td>
<td>Invasive Carcinoma NST</td>
<td>T3N1M0</td>
<td>ER/PR +; Her2/neu -</td>
<td>NA</td>
<td>R201H</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>PFD</td>
<td>Ribs (L+R), Thoracic and Lumbar Spine</td>
<td>52</td>
<td>Right</td>
<td>Invasive Carcinoma NST</td>
<td>T1N0M0</td>
<td>ER/PR +; Her2/neu +</td>
<td>PIK3CA: H1047A</td>
<td>11.356</td>
<td>0.243</td>
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<tr>
<td>3</td>
<td>58</td>
<td>PFD</td>
<td>Ribs (L), Sternum, Thoracic and Lumbar Spine, Pelvis (L), Femur (L), Tibia (L), Fibula (L)</td>
<td>50</td>
<td>Left</td>
<td>DCIS</td>
<td>DCIS gr III</td>
<td>ER/PR +; Her2/neu -</td>
<td>GNAS: R201C</td>
<td>1.416</td>
<td>0.210</td>
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<tr>
<td>4</td>
<td>24</td>
<td>PFD+ MZB</td>
<td>Skull, Sternum, Pelvis (R), Femur (R), Tibia (R), Fibula (R), Calcaneus (R), Metatarsal (R)</td>
<td>54</td>
<td>Left</td>
<td>DCIS</td>
<td>DCIS gr III</td>
<td>ER/PR -; Her2/neu +</td>
<td>PIK3CA: G545G</td>
<td>8.746</td>
<td>0.060</td>
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<tr>
<td>5</td>
<td>0</td>
<td>MAS+ MZB</td>
<td>Skull, Humerus (L+R), Radius (L+R), MCP (L+R), Ribs (R+L), Sternum, Thoracic and Lumbar Spine, Pelvis (L+R), Femur (L+R), Tibia (L+R), Metatarsal (L+R)</td>
<td>37</td>
<td>Right</td>
<td>DCIS</td>
<td>DCIS gr II</td>
<td>ER/PR +; Her2/neu -</td>
<td>GNAS: R201C; AKT1: G17L</td>
<td>7.610</td>
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<td>6</td>
<td>2</td>
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<td>Skull, Humerus (L+R), Ulna (L+R), Radius (L+R), Ribs (L+R), Sternum, Thoracic + Lumbar Spine, Pelvis (L+R), Femur (L+R), Tibia (L+R)</td>
<td>48</td>
<td>Left</td>
<td>Invasive Carcinoma NST</td>
<td>T2N1M0</td>
<td>ER/PR +; Her2/neu -</td>
<td>PIK3CA: G545L</td>
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<td>7</td>
<td>48</td>
<td>MAS+ MZB</td>
<td>Radius (R), Ribs (R), Pelvis (L), Femur (R), Tibia (R)</td>
<td>48</td>
<td>Right</td>
<td>Invasive Carcinoma NST</td>
<td>T2N1M0</td>
<td>ER/PR +; Her2/neu -</td>
<td>GNAS: R201H; PIK3CA: H1047A</td>
<td>12.013</td>
<td>0.348</td>
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<tr>
<td>8</td>
<td>3</td>
<td>PFD</td>
<td>Thoracic and Lumbar Spine, Femur (L)</td>
<td>37</td>
<td>Right</td>
<td>DCIS</td>
<td>DCIS gr III</td>
<td>ER/PR -; Her2/neu +</td>
<td>ERBB2: L755S; PIK3CA: H1047A; TP53: A240G</td>
<td>16.584</td>
<td>0.701</td>
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<tr>
<td>No.</td>
<td>Age</td>
<td>PFD</td>
<td>Lesion Extension</td>
<td>Tumor Type</td>
<td>Histopathology</td>
<td>Staging</td>
<td>ER/PR</td>
<td>Her2/neu</td>
<td>GNAS</td>
<td>Notes</td>
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<tr>
<td>9</td>
<td>56</td>
<td>PFD</td>
<td>Cervical Spine, Humerus (R)</td>
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<td>Left</td>
<td>Invasive Carcinoma NST</td>
<td>T2N1M0</td>
<td>ER/PR +;</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>MAS+ MZB</td>
<td>Skull, Cervical + Thoracic Spine, Rib (R), Humerus (R), Femur (R), Tibia (R)</td>
<td>32</td>
<td>Right</td>
<td>DCIS</td>
<td>DCIS</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>27</td>
<td>MAS</td>
<td>Skull, Rib (R), Cervical and Thoracic Spine, Tibia (L), Fibula (L)</td>
<td>41</td>
<td>Right</td>
<td>DCIS</td>
<td>DCIS</td>
<td>ER/PR +; Her2/neu -</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>MAS</td>
<td>Skull, Clavicle (L), Scapula (R), Humerus (L+R), Radius (L+R), Ulna (R), Rib (L), Pelvis (L+R), Femur (L+R), Tibia (R), Fibula (L+R)</td>
<td>27</td>
<td>Right</td>
<td>DCIS</td>
<td>DCIS</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>14</td>
<td>MAS</td>
<td>Skull, Pelvis (L+R)</td>
<td>40</td>
<td>Left</td>
<td>DCIS</td>
<td>DCIS</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>MAS</td>
<td>Skull, Clavicle (L), Scapula (R), Humerus (L+R), Radius (L+R), Hands (L+R), Sternum, Rib (L+R), Cervical, Thoracic and Lumbar Spine, Femur (L+R), Tibia (L), Fibula (R), Foot (L)</td>
<td>46</td>
<td>Right</td>
<td>DCIS</td>
<td>DCIS</td>
<td>NA</td>
<td>GNAS: R201H</td>
<td>NA</td>
<td></td>
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<tr>
<td>15</td>
<td>4</td>
<td>MAS</td>
<td>Skull, Humerus (L+R), Radius (L+R), Ulna (L+R), Hands (L+R), Thoracic Spine, Rib (L+R), Pelvis (L+R), Femur (L+R), Tibia (L+R), Fibula (L+R)</td>
<td>29</td>
<td>Left</td>
<td>DCIS</td>
<td>DCIS</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
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Figure 1. Patient flow chart

Dutch Cohort
n=254

Male
n=120

Female
n=134

Monostotic
n=94

Polyostotic
n=27

McCune-Albright
n=13

None

3 DCIS
3 Invasive breast cancer

2 DCIS
2 Invasive breast cancer

US Cohort
n=226

Male
n=105

Female
n=121

Monostotic
n=5

Polyostotic
n=9

McCune-Albright
n=107

None

None

5 DCIS