Fibrous dysplasia

Majoor, B.C.J.

Author: Majoor, Bas
Title: Fibrous dysplasia
Date: 2018-04-25

Chapter 6

Increased risk of breast cancer at a young age in women with fibrous dysplasia

B.C.J. Majoor, A.M. Boyce, J.V.M.G. Bovée, V.T.H.B.M. Smit,
M.T. Collins, A.M. Cleton-Jansen, O.M. Dekkers, N.A.T. Hamdy,
S.P.D. Dijkstra, N.M. Appelman-Dijkstra

J Bone Miner Res. 2018;33(1):84-90

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.

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 *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.[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.[3-5] Outside the context of fibrous dysplasia, activating *GNAS*-mutations have also been documented in various malignancies, such as thyroid carcinomas, pancreatic neoplasms and breast cancer.[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.[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 6.1). 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]

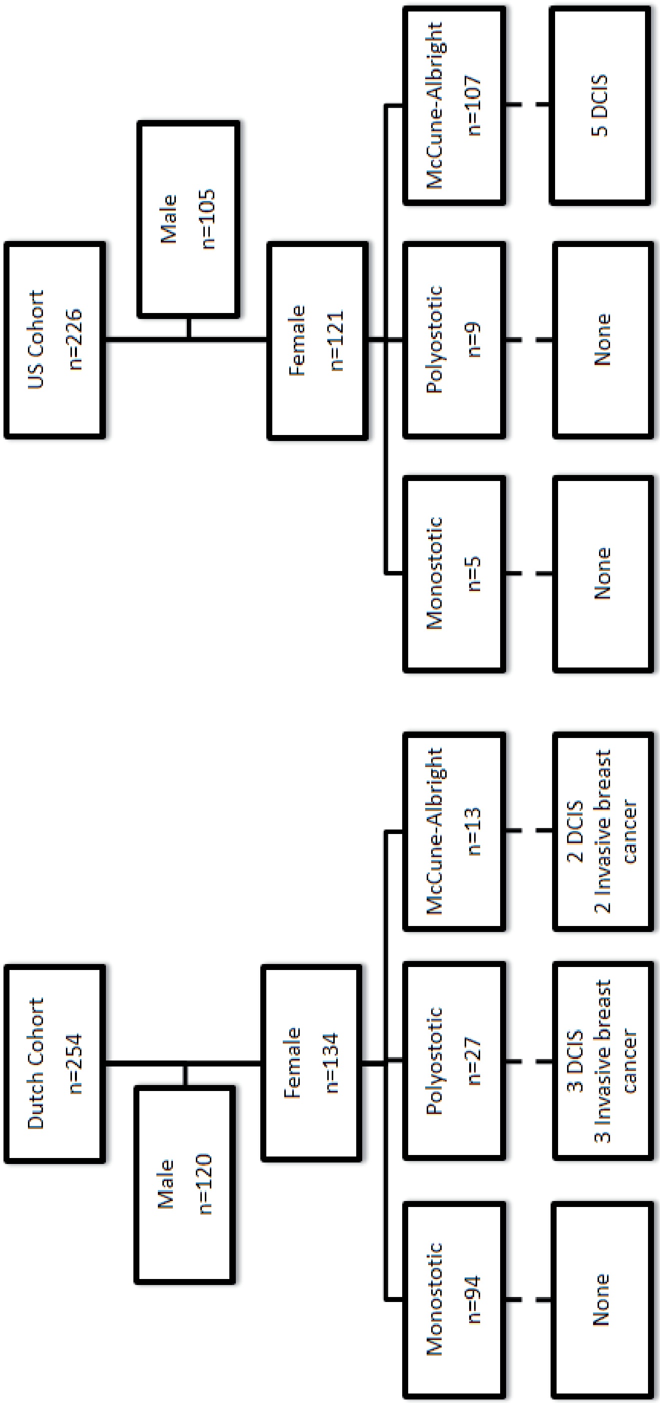

Fig. 6.1 Patient flow chart.

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 data).[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 data).[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 6.1)

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 6.1)

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

Table 6.1 Cohort characteristics

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

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.

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 6.2)

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

Table 6.2 Patient and tumor characteristics

Patient ID	Age at diagnosis of FD	FD type[A]/ MZB	Localization of FD lesions[B]	Age at diagnosis of breast cancer	Side of breast cancer	Type of breast cancer[C]	Stage of breast cancer	Receptor status in breast cancer[D]	Identified genes and type of mutation in breast cancer[E]	Reads GNAS/ frequency in breast cancer	GNAS mutation in bone
1	16	PFD	Skull, Humerus (R), Ulna (R), Ribs (L+R), Sternum, Pelvis (L+R), Femur (R), Tibia (R), Fibula (R) Metatarsal (R)	52	Right	Invasive Carcinoma NST Mucinous diff + DCIS gr III[F]	T3N1M0	ER/PR + Her2/ neu -	NA		R201H
2	49	PFD	Ribs (L+R), Thoracic and Lumbar Spine	52	Right	Invasive Carcinoma NST	T1N0M0	ER/PR + Her2/ neu +	PIK3CA: H1047A	11.356 0.243	NA
3	58	PFD	Ribs (L), Sternum, Thoracic and Lumbar Spine, Pelvis (L), Femur (L), Tibia (L), Fibula (L)	50	Left	DCIS	DCIS gr III	ER/PR + Her2/ neu -	**GNAS**: R201C	1.416 0.210	R201C
4	24	PFD+ MZB	Skull, Sternum, Pelvis (R), Femur (R), Tibia (R), Fibula (R), Calcaneus (R), Metatarsal (R)	54	Left	DCIS	DCIS gr III	ER/PR - Her2/ neu +	PIK3CA: G545G	8.746 0.060	R201H
5	0	MAS+MZB	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)	37	Right	DCIS	DCIS gr II	ER/PR + Her2/ neu -	**GNAS**: R201C AKT1: G17L	7.610 0.347 0.499	R201C

Table 6.2 *Continued*

Patient ID	Age at diagnosis of FD	FD type[A]/ MZB	Localization of FD lesions[B]	Age at diagnosis of breast cancer	Side of breast cancer	Type of breast cancer[C]	Stage of breast cancer	Receptor status in breast cancer[D]	Identified genes and type of mutation in breast cancer[E]	Reads GNAS/ frequency in breast cancer	GNAS mutation in bone
6	2	MAS	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)	48	Left	Invasive Carcinoma NST	T2N1M0	ER/PR +; Her2/ neu -	PIK3CA: G545L	7.882 0.257	R201C
7	48	MAS+ MZB	Radius (R), Ribs (R), Pelvis (L), Femur (R), Tibia (R)	48	Right	Invasive Carcinoma NST	T2N1M0	ER/PR +; Her2/ neu -	**GNAS**: R201H PIK3CA: H1047A	12.013 0.348 0.030	NA
8	3	PFD	Thoracic and Lumbar Spine, Femur (L)	37	Right	DCIS	DCIS gr III	ER/PR -; Her2/ neu +	ERBB2: L755S PIK3CA: H1047A TP53: A248G	16.584 0.701 0.258 0.547	NA
9	56	PFD	Cervical Spine, Humerus (R)	50	Left	Invasive Carcinoma NST	T2N1M0	ER/PR +;	-		NA
10	0	MAS+MZB	Skull, Cervical + Thoracic Spine, Ribs (R), Humerus (R), Femur (R), Tibia (R)	32	Right	DCIS	DCIS	NA	NA	NA	NA
11	27	MAS	Skull, Ribs (R), Cervical and Thoracic Spine, Tibia (L), Fibula (L)	41	Right	DCIS	DCIS	ER/PR +; Her2/ neu -	NA	NA	NA

Table 6.2 continues on next page

Table 6.2 *Continued*

Patient ID	Age at diagnosis of FD	FD type[A]/ MZB	Localization of FD lesions[B]	Age at diagnosis of breast cancer	Side of breast cancer	Type of breast cancer[C]	Stage of breast cancer	Receptor status in breast cancer[D]	Identified genes and type of mutation in breast cancer[E]	Reads GNAS/ frequency in breast cancer	GNAS mutation in bone
12	3	MAS	Skull, Clacicle (L), Scapula (R), Humerus (L+R), Radius (L+R), Ulna (R), Ribs (L), Pelvis (L+R), Femur (L+R), Tibia (R), Fibula (L+R)	27	Right	DCIS	DCIS	ER/PR +;	NA	NA	NA
13	14	MAS	Skull, Pelvis (L+R)	40	Left	DCIS	DCIS	NA	NA	NA	NA
14	2	MAS	Skull, Scapula (R), Humerus (L+R), Radius (L+R), Hands (L+R), Sternum, Ribs (L+R), Cervical, Thoracic and Lumbar Spine, Femur (L+R), Tibia (L), Fibula (R), Foot (L)	46	Right	DCIS	DCIS	NA	**GNAS:** R201H	NA	NA
15	4	MAS	Skull, Humerus (L+R), Radius (L+R), Ulna (L+R), Hands (L+R), Thoracic Spine, Ribs (L+R), Pelvis (L+R), Femur (L+R), Tibia (L+R), Fibula (L+R)	29	Left	DCIS	DCIS	NA	NA	NA	NA

Characteristics of patients with breast cancer
[A] PFD = polyostotic fibrous dysplasia; MAS = McCune-Albright syndrome; MZB = Mazabraud syndrome.
[B] R = right; L = left.
[C] DCIS = Ductal carcinoma in situ; NST = no special type.
[D] ER = estrogen receptor; PR = progesterone receptor.
[E] NA = Not Available.
[F] Patient has two breast tumours (bilateral).

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 data). Mutation analysis of one of the 5 patients from the US cohort was performed with Sanger sequencing (Table 6.2). 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 intra-tumoral 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.

Acknowledgements
We like to thank Brendy van den Akker for her much appreciated help with mutation analysis and immunohistochemistry of the samples used. We would also like to thank Dina Ruano Neto, Ronald van Eijk and Tom van Wezel for developing the targeted NGS-protocol. Lastly, we would like to thank Jan Schoones for his help in evaluating the literature.

REFERENCES

1. Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. *The New England journal of medicine*. Dec 12 1991;325(24):1688-1695.
2. Bianco P, Riminucci M, Majolagbe A, et al. Mutations of the GNAS1 gene, stromal cell dysfunction, and osteomalacic changes in non-McCune-Albright fibrous dysplasia of bone. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. Jan 2000;15(1):120-128.
3. Landis CA, Masters SB, Spada A, Pace AM, Bourne HR, Vallar L. GTPase inhibiting mutations activate the alpha chain of Gs and stimulate adenylyl cyclase in human pituitary tumours. *Nature*. Aug 31 1989;340(6236):692-696.
4. Yoshimoto K, Iwahana H, Fukuda A, Sano T, Itakura M. Rare mutations of the Gs alpha subunit gene in human endocrine tumors. Mutation detection by polymerase chain reaction-primer-introduced restriction analysis. *Cancer*. Aug 15 1993;72(4):1386-1393.
5. Turan S, Bastepe M. GNAS Spectrum of Disorders. *Current osteoporosis reports*. Jun 2015;13(3):146-158.
6. Kalfa N, Lumbroso S, Boulle N, et al. Activating mutations of Gsalpha in kidney cancer. *The Journal of urology*. Sep 2006;176(3):891-895.
7. Collins MT, Sarlis NJ, Merino MJ, et al. Thyroid carcinoma in the McCune-Albright syndrome: contributory role of activating Gs alpha mutations. *The Journal of clinical endocrinology and metabolism*. Sep 2003;88(9):4413-4417.
8. Fecteau RE, Lutterbaugh J, Markowitz SD, Willis J, Guda K. GNAS mutations identify a set of right-sided, RAS mutant, villous colon cancers. *PloS one*. 2014;9(1):e87966.
9. Gaujoux S, Salenave S, Ronot M, et al. Hepatobiliary and Pancreatic neoplasms in patients with McCune-Albright syndrome. *The Journal of clinical endocrinology and metabolism*. Jan 2014;99(1):E97-101.
10. Tanabeu Y, Nakahara S, Mitsuyama S, Ono M, Toyoshima S. Breast Cancer in a Patient with McCune-Albright Syndrome. *Breast cancer*. Apr 25 1998;5(2):175-178.
11. Scanlon EF. Breast carcinoma in an 11-year-old girl with Albright's syndrome. *Breast*. 1980;6:6 - 9.
12. Collins MT, Singer FR, Eugster E. McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia. *Orphanet journal of rare diseases*. May 24 2012;7 Suppl 1:S4.
13. Huston TL, Simmons RM. Ductal carcinoma in situ in a 27-year-old woman with McCune-Albright syndrome. *The breast journal*. Sep-Oct 2004;10(5):440-442.
14. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Cellular oncology : the official journal of the International Society for Cellular Oncology*. 2007;29(1):19-24.
15. McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. *Bmj*. Sep 9 2000;321(7261):624-628.
16. Press M, Spaulding B, Groshen S, et al. Comparison of different antibodies for detection of progesterone receptor in breast cancer. *Steroids*. Aug 2002;67(9):799-813.
17. Elledge RM, Fuqua SAW. Estrogen and Progesterone Receptors. In: Wilkins LW, ed. *Diseases of the breast*. Philadelphia: Lippincott Williams & Wilkins 2000:471-485.
18. Thorvaldsdottir H, Robinson JT, Mesirov JP. Integrative Genomics Viewer (IGV): high-performance genomics data visualization and exploration. *Briefings in bioinformatics*. Mar 2013;14(2):178-192.
19. Demographics on cancer by the Dutch National Cancer Organisation (IKNL); Numbers on breast cancer. (Accessed august 8th, 2015 at http://www.cijfersoverkanker.nl).
20. NIH, National Cancer Institute, demographics on breast cancer (accessed at oktober 10th 2016 at http://www.cancer.gov).