ORIGINAL ARTICLE

Women with neurofibromatosis 1 are at a moderately increased risk of developing breast cancer and should be considered for early screening

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Background: Malignancy risks in patients with neurofibromatosis 1 (NF1) are increased, but those occurring outside of the nervous system have not been clearly defined.
Aim: To evaluate the risk of breast cancer in women with NF1 in a population-based study.
Methods: The risk of breast cancer in a cohort of 304 women with NF1 aged ⩾20 years was assessed and compared with population risks over the period 1975–2005 using a person-years-at-risk analysis.
Results: There were 14 cases of breast cancers in the follow-up period, yielding a standardised incidence ratio (SIR) of 3.5 (95% CI 1.9 to 5.9). However, six breast cancers occurred in women in their 40s, and the SIR of breast cancer in women aged <50 years was 4.9 (95% CI 2.4 to 8.8).
Interpretation: Women with NF1 aged <50 years have a fivefold risk of breast cancer, are in the moderate risk category and should be considered for mammography from 40 years of age.

Neurofibromatosis 1 (NF1; MIM 162200) is a common autosomal dominant genetic disorder with an estimated birth incidence of 1 in 2500 and a prevalence of 1 in 5000.[1] NF1 is a fully penetrant condition, with all patients manifesting signs of the disease by the age of 5 years. However, many de novo cases remain undiagnosed well into adult life. All affected individuals will develop at least some of the neurocutaneous features, none of which are life threatening; these include the pigmentary changes (café au lait spots, skin fold freckling and Lisch nodules) and neurofibromas (although these may not be numerous). It is the occurrence of disease complications that causes most of the associated morbidity and mortality. A third of affected individuals will develop at least one of the more severe disease complications in their lifetime; the occurrence of complications cannot be predicted even within families.[2] The disease is extremely variable, and the individual gene fault is unlikely to determine the total course of the condition.

The NF1 gene is a tumour suppressor gene and those with the mutation are at a fourfold increased risk of cancer compared with the general population.[3–5] The gene product neurofibromin is thought to deliver much of its function through down-regulating the oncogene ras. Patients with NF1 have a greatly increased relative risk of developing gliomas, malignant peripheral nerve sheath tumours, juvenile chronic myelomonocytic leukaemia, rhabdomyosarcoma and phaeochromocytoma; such tumours may have a different natural history from those occurring sporadically, and require a specific approach to their detection and management.

Until now no one has reported an overall significantly increased risk of any commonly occurring cancers in patients with NF1, although a recent paper did find a significantly increased risk in women aged <50 years—this was not significant overall.[6] The fact that several patients develop breast cancer before 50 years of age prompted us to look systematically for an increased risk of breast cancer.

METHODS

The Regional Genetic Service in Manchester covers the north-west of England (excluding Merseyside)—a population of about 4.1 million. Patients with NF1 are referred from all healthcare sectors and lay groups; they are also identified via known families who are followed up over generations as part of the genetic register service. A genetic register for patients with NF1 has been in existence since 1989, and patients consent to regular contact, research and data collection. All patients and any deceased affected relatives are entered onto a comprehensive clinical database with information on clinical features and date of last assessment. Other major health problems, including tumours, are recorded. A clinical geneticist confirms all the diagnoses of NF1. The register cohort is therefore a relatively unbiased population-based group of patients.

The database (as of 1 July 2005) was searched for the diagnosis of breast cancer, and the NF1 dataset was also checked against the North Western Cancer Registry (NWCR) database to obtain as complete case ascertainment as possible. It is important to note that the study started with known patients having NF1, and did not select patients on the basis of their breast cancer status.

The standardised incidence ratio (SIR) of invasive breast cancer was estimated by calculating the ratio of observed to expected numbers of cases. Expected numbers were calculated using incidence rates for the period 1 January 1975 to 31 June 2005 for the population covered by the NWCR (although the NWCR started collecting data in 1962, its rates were not robust until 1975). As incidence rates for 2004 and 2005 were not available, 2003 rates were used for each of these years. Age group-, sex- and calendar-period-specific person-years at risk were multiplied by the corresponding incidence rates to produce the number of expected cases.

Abbreviations: NF1, neurofibromatosis 1; NWCR, North Western Cancer Registry

Follow-up of women was started on 1 January 1975 or on their 20th birthday, whichever was the later. Patients were censored at the date of diagnosis of their breast cancer, last follow-up or date of death, whichever was the earliest.

The cumulative risk of breast cancer to age 50 years was calculated by adding the age-specific rates for each 5-year age group from 20–24 to 45–49, followed by application of the formula: cumulate risk $= 100 \times [1 - \exp(-\text{cum rate}/100)]$.

RESULTS

On 1st July 2005, 848 patients with NF1 were on the NF1 database, of which 418 were women. Eight were excluded because of insufficient data, and five died before 1975. Of the remaining 405, 304 were aged ⩾20 years during at least part of the follow-up period and were considered to be at risk of developing breast cancer. The total person-years at risk were 5411 (median 17.8 years). A total of 788 living patients with NFI is equivalent to a population prevalence of 1 in 5200.

Of the 304 women, 14 were identified as having had invasive breast cancer; 3 had at least two separate primary breast cancers, but only the first tumour was included in the SIR analysis. Table 1 shows the observed and expected number of cases of breast cancer.

The SIR of developing breast cancer was 3.5 (95% CI 1.9 to 5.9). The earlier average age of onset is reflected by the increased SIR of 4.9 (95% CI 2.4 to 8.8) up to age 50 years. The cumulative risk of developing breast cancer to age 50 years in women in the general population was 2%,[7] and that of the women with NF1 was 8.4%. Six women developed their first breast cancer between 40 and 49 years of age, resulting in a risk of 5.8% during that decade. The age of diagnosis of NF1 ranged from 0 to 54 years for the total population with NF1 and from 5 to 39 years in the 14 women with breast cancer. Median age at diagnosis of NF1 was 4 years for the total population, compared with 20 years for women with breast cancer (table 2).

All 304 women had café au lait spots, 219 (72%) had skin fold freckling, 195 (64%) had neurofibromas and 167 (55%) had Lisch nodules. These women had an early age of onset of breast cancer, with a median (range) age of diagnosis of 44 (27–64) years, although all had a prior diagnosis of NF1 (table 2). Histology was available for all women, including further primaries: 14 women had infiltrating ductal carcinoma, 3 had infiltrating lobular carcinoma and 1 had contralateral ductal carcinoma in situ (table 2). Only 1 of the 14 women was known to carry a *BRCA1* (2190 delA) mutation. None of the other families fulfilled the criteria for mutational analysis.[7] Of the 14 women, 5 died from metastatic breast cancer, 2 from a primary cancer at another site (lung, fallopian tube) and 1 from myocardial infarction. The details of death entered on the cancer registry from death certification made no reference to the diagnosis of NF1 in any of these women. The six remaining patients were alive at the last follow-up. In view of the reported reduced genetic fitness in NF1, we analysed the possible effect of late first pregnancy or nulliparity on the breast cancer cases. Of the 14 women, 3 were nulliparous. Of the 11 parous women, 9 had had their first pregnancy before the age of 30 years (mean age 25.5 years; median 25; range 19–35). Therefore, 9 of 14 women should have had protective reproductive risk factors for breast cancer.

Table 1 Standard incidence rate of developing breast cancer in women with neurofibromatosis, with 95% CI*

	Women with NF1	Women with NF1 until age 50 years
Observed	14	11
Expected	4.0	2.2
SIR (95% CI)	3.5 (1.9 to 5.9)	4.9 (2.4 to 8.8)

NF1, neurofibromatosis; SIR, standardised incidence ratio.
*Observed and expected cases of breast cancer in the NF1 dataset, together with SIRs and 95% CI, with follow-up assumed to end on 31 June 2005 (unless the patient died or was diagnosed with breast cancer before this date).

DISCUSSION

Although a recent cohort study showed an increased risk of breast cancer in women aged <50 years,[6] this was based on small numbers, and the overall significance was not obtained. The present study is the first to report a significantly increased risk of a common cancer across all age groups in NF1. Our results show that women with NF1 have an overall SIR of breast cancer of 3.5 and a 4.9-fold risk of developing breast cancer to age 50 years, compared with women in the general population. Their risk of developing breast cancer by the 50th birthday is 8.4%.

Although it is possible that we underascertained patients with NF1 for our region, the prevalence of 1 in 5200 in our study is very similar to that for other highly ascertained population studies.[8] Although we could have missed milder patients with NF1 who may have had a lower risk, our analysis almost certainly reflects the risks to a woman significantly affected enough to get a clinical diagnosis. Cases of breast cancer were also obtained from two independent sources, so that we would have been unlikely to miss any case of breast cancer in our families with NF1. It is possible that patients with both breast cancer and NF1 may have been diagnosed between 1975 and 1989 and so had not come to our attention because they died from the disease, but including such cases would actually have increased the SIR. A bias would have occurred if women with NF1 and breast cancer were more likely to be included in the study than those with only NF1. As NF1 was diagnosed first in all 14 women, the extra medical attention after a diagnosis of breast cancer could not have led to a diagnosis of NF1 in these women. As no relationship had been reported until recently between NF1 and breast cancer, it is unlikely that a diagnosis of NF1 would have brought forward a diagnosis of breast cancer. Even with mammography screening under 50 years, the lead time is only 18 months, and these women were not undergoing surveillance. Although the age at diagnosis of NF1 was older in our women with breast cancer, this is likely to reflect increasing awareness of the condition in recent years rather than a different mechanism. In particular, our NF1 register since 1989 has diagnosed many offspring of patients with NF1 in the first year of life, bringing the overall age at diagnosis down to a much younger age. Even today de novo patients with NF1 are often not diagnosed until their 30s or 40s. Another potential criticism of our study is the semiretrospective aspect. We started follow-up in 1975 to increase the power of the study. In fact, only 2 of 14 breast cancer cases first occurred before 1989, and exclusion of the extra 14 years would, if anything, have increased the SIR. Another possible explanation for an increased risk would have been reduced genetic fitness and therefore nulliparity. This was not supported as a plausible explanation for the increased risk seen.

Our findings, if confirmed by other groups, have major implications for patients with NF1, as regards the early diagnosis of breast cancers. The 2004 National Institute for Health and Clinical Excellence guidelines define the risk of developing breast cancer as 1.5% in women aged 40–49 years in the UK population.[7] Those with a 3–8% risk are considered to be at moderately increased risk; such individuals are deemed suitable for breast cancer screening from 40 years of age, unlike women in the UK general population. Women with NF1 are the

Table 2 Breast cancer diagnoses and follow-up in 14 women with invasive breast cancer

Patient	Age at diagnosis of NF1 (years)	Age at diagnosis of breast cancer (years)	Breast cancer histology (ICD 01 classification)	Other tumour diagnosis* (years)	Follow-up from breast cancer diagnosis (months)
1	30	38.5 (1982)	IDC	No	104 died†
2	6	43.7 (1996)	IDC	OPG 6‡	52 died
3	21	44.5 (2005)	Lobular grade 2	No	12
4	5	43.3 (1990)	IDC	No	21 died†
5	33	35.7 (1998)	IDC	Lung 39	51 died
6	39	64.1 (1997)	IDC grade 3	No	84
7	5	35.9 (1993)	IDC	No	21 died†
8	25	51.4 (1995)	IDC	No	116
9	19	51.0 (1994)	Lobular	No	10 died†
10	5	48.8 (1999)	IDC grade 2	No	61
11	30	47.7 and 53.2§ (1987)	IDC IDC	No	67 died†
12	5	27 (2005)	Lobular grade 2	No	14
13	5	34.4 and 36.4§ 44.2 (1989)	IDC grade 3 IDC grade 3 IDC grade 3	Ovarian cancer 47	204 died
14	33	42.4 and 42.4 (2002)	IDC DCIS	No	39

DCIS, ductal carcinoma in situ; ICD, international classification of diseases; IDC, invasive ductal carcinoma; OPG, optic pathway glioma; NF1, neurofibromatosis 1.
*Excludes neurofibroma.
†Death from breast cancer.
§Contralateral breast cancer.
‡At 4 years had decreased vision on the left eye, at 7 years investigated for optic atrophy and blind left eye when café au lait spots noted, surgery to remove part of left optic nerve. No radiotherapy.

first group of patients at increased genetic risk of breast cancer, which is easily identified on routine examination by any physician.[7] It is important that patients and physicians are aware of the increased risk and that steps are taken to ensure early diagnosis of palpable tumours. The use of radiotherapy in NF1 will need to be a particular area of focus. There are increasing concerns of an increased risk of further malignancies after radiation therapy in tumour-prone disorders,[9–17] which is particularly true for children with NF1.[18] However, there is no evidence to suggest that the small doses associated with mammography would be sufficient to increase the risk, although this may need addressing further before widespread implementation of extra screening.

This study reports a relationship between NF1 and breast cancer. Not all of this increased risk may be due to the presence of NF1. Further studies are needed to compare the risk profiles for breast cancer in those with and without NF1, and to determine whether any factors that are more common in those with NF1 are simply associations or part of a causal mechanism by which NF1 increases the risk of breast cancer.

Recent scientific data support a possible association between breast cancer and NF1. It has been suggested that there may be genes that could interact with the NF1 gene, particularly in relation to the *BRCA1* subset. They could share a common gene location (both NF1 and BRCA1 are on human chromosome 17q),[19] which has been conserved between man and mouse,[20] or another breast cancer gene may also interact.[21] Ceccaroni *et al*[19] showed the inheritance of a common haplotype including both the *NF1* and the *BRCA1* genes in relatives of patients with NF1 and breast cancer, and a mutation in the *BRCA1* gene was also detected in the patients. Altered expression of the NF1 protein neurofibromin in breast cell lines with upregulation of Ras[22] has been seen and could suggest an overlapping aetiology. However, it is not known whether the lack of neurofibromin is a primary or a secondary event in this sequence. Guran and Safali[23] have shown loss of heterozygosity for *NF1* in breast tumours from a woman with NF1, but loss of the long arm of chromosome 17 is common in breast cancers. No germline *NF1*, *BRCA1* or *BRCA2* mutation was identified in the proband in this report. Nonetheless, they suggested a role of the *NF1* gene in the progression of tumour. The progression of cancer diagnoses in our patient (table 2, patient 13) with a concomitant *BRCA1* mutation is severe even for *BRCA1*. An argument could be made to exclude the BRCA1 case from the analysis. This would have reduced the SIRs to 3.25 overall, and to 4.5 for those aged $<$50 years. However, in any population large enough to carry other gene mutations, these will occur as they will in any comparison with the general population. One *BRCA1/2* carrier would have been expected among over 300 women, with a combined population frequency of 1 in 4–500.[6] The tumour distribution and histology excluding the BRCA1 case was not consistent with a predominantly basal phenotype, as would be expected with BRCA1-related breast cancers (table 2).

An obvious question arising from our data is why this association has not been reported before. The increased risk of malignancy in NF1 has been known for some time, the SIR for all tumour types being up to four times that seen in the general population.[4 5] Certain tumours are seen more commonly at particular ages, and there is also an increased risk of developing second tumours.[1 4 5 24–31]

Several groups have reviewed the types and incidence of malignancies in patients with NF1.[1 4 5 25–27] The majority of these studies were too small to identify significant cancer excess outside the known extremely high relative incidence of malignant peripheral nerve sheath tumour, rhabdomyosarcoma, glioma and juvenile chronic myelomonocytic leukaemia. It is interesting to note that in previous studies breast cancer has been reported in women with NF1,[4 5 27] but no specific attempt has been made to determine whether this was at a greater than expected frequency.

Although a death certificate study in North America was potentially large enough to provide a robust estimate of the risk of breast cancer, the analysis is flawed by the necessity of NF1 to be stated on the death certificate as a secondary feature.[32] As breast cancer has not previously been reported as related to NF1, it is doubtful whether clinicians would have recorded the diagnosis of NF1 on the death certificate. It is of note that none of our five cases of deaths from breast cancer had the NF1

diagnosis on the death certificate. Also, as breast cancer is often cured, many women with breast cancer would have been excluded from the study.

Several authors have tried to overcome the above biases by identifying a live group of patients based either on NF1 status[1 4] or on a diagnosis of cancer.[26] However, many of these studies have other biases. Cross-sectional studies such as the Welsh study[1] will not give accurate risks as they exclude deceased cases, and a longitudinal component is needed as the median age for a diagnosis of breast cancer is much older than for NF1. Studies that identified subjects on the basis of their cancer status may miss mildly affected individuals with NF1 who have not been diagnosed or known to clinics performing these analyses, and would have difficulty calculating a robust estimate of the number of expected cases of NF1.

Identifying a population-based cohort of patients with NF1 who are followed over time to determine the number who develop breast cancer is the only way to provide an unbiased estimate of relative risk. The most recent study of this type included 448 individuals (227 women, 40% of whom were <20 years at the start of follow-up) ascertained through the UK Neurofibromatosis Association.[6] They showed a marginally significantly increased risk of breast cancer of fourfold (95% CI 1.09 to 10.3) in women aged <50 years. However, the overall breast cancer incidence was not significantly increased, so they did not highlight this finding. Our study included considerably more follow-up years for adult women (about three fold), and so has the power to provide a better estimate of risk. The Walker *et al*[6] study was not strictly population based but did follow a defined cohort. The results from both our own and the Walker *et al*[6] study show a significantly raised SIR for breast cancer in those aged <50 years, suggesting that the increased risk is concentrated before the age of 50 years.

Thus, we have shown that breast cancer should be considered as a common association in NF1, and that affected women will require screening for this from the age of 40 years. We need to clarify further the exact incidence of breast cancer in these patients, understand the aetiology and natural history of these tumours, and determine the best way of managing such patients. This report will help to raise awareness and in turn enable further studies to define this recent association with NF1.

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