

Malignancy in Neurofibromatosis Type 1 (NF1)

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Background to NF1

A case study was presented to illustrate the difficulty NF1 presents in the genetics clinic due to its variable severity and symptoms. These can be grouped into 4 main areas – ophthalmological, cardiovascular, musculoskeletal and neurological. NF1 is an autosomal dominant condition affecting 1 in 3000 live births. Mutation analysis has recently become available but is not commonly undertaken as it does not at present affect clinical management of the condition.

Previous papers on malignancy in NF1

The 4 main papers that provided information about malignancy in NF1 before this study were outlined:

- a) Sorensen *et al* (NEJM 1986) – malignancy rate of 26% but the study occurred before the separation of NF1 and NF2.
- b) Zoller *et al* (Cancer 1997) – 15% malignancy rate during the follow up period.

The following 2 papers were population based studies:

- c) Huson *et al* (Brain 1988, J Med Genet 1989) – overall malignancy rate of 7%.
- d) Friedman and Birch (Am J Med Genet 1997) – overall malignancy rate of 4.6%.

Study into malignancy in NF1

This study began in 1987 and was set up to record demographic and diagnostic details of NF1 patients within the UK. Diagnoses of cancer and deaths (and causes of death) among NF1 patients were obtained from the Office of National Statistics. In the total cohort there were 464 NF1 patients from 299 families. The median age of entry was 26, and approximately 40% of people were below the age of 20.

Individuals who had been diagnosed with cancer before they were recruited to the study were excluded, making this the first prospective study of its kind. Follow up was stopped either at death, on an individual's 80th birthday or on 1st April 2004 (whichever came first). Only the first malignant cancer, as recorded by the cancer registries, was included.

The cancer incidence in the NF1 cohort compared to that in the general population was analysed using Standardised Incidence Ratios (SIR). The expected number of cancers in each individual was estimated using sex, age and calendar period SIRs.

7.8% of the cohort had a malignancy (35 individuals, compared to the 13 expected). The cumulative risk of a malignancy by the age of 70 is 35%, compared to 18% in the general population. This represents a RR of approximately 2.7. A range of cancer types were present although half the tumours were connective tissue (7) or (11) brain tumours.

The overall cancer risk was significantly increased in patients under 50. In particular there was a 4-fold increase in risk of breast cancer in this age group (5 cases). Overall cancer risk in those over 50 was not significantly increased. The greatest increased risk was in children: below the age of 20, six individuals had cancer (4 brain and 2 other CNS). This represents a 7% (1/14) risk by the age of 20 – in the general population the risk in this age group is 1/380.

Potential link between breast cancer and NF1

Limited data is available at present to establish whether there is a link between breast cancer and NF1. In this study 4 of the 5 women with breast cancer were diagnosed under the age of 50 (equates to a RR of 4). Other unpublished data gives a RR of approximately 5 although both these studies involve very small numbers. Further work is needed to accurately delineate these risks and establish if there is a need for screening within the NF1 population. A larger collaborative prospective study combining several cohorts is proposed and will allow a more accurate estimation of breast cancer risk. There is also interest in examining risk of malignancy of other tumour types in NF1.