

Keywords: neurofibromatosis; breast cancer; malignant neoplasm; record linkage

Age-specific risk of breast cancer in women with neurofibromatosis type 1

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Background: Young women with neurofibromatosis type 1 (NF1) are reported to have a higher risk of breast cancer than others, and this might have implications for screening programmes. Our aim was to calculate this risk.

Methods: An all-England linked data set of hospital admissions and deaths was analysed to determine age-specific rates of breast cancer in women with NF1 and controls.

Results: The age-specific excess risk of breast cancer, comparing the NF1 cohort with the control cohort, was elevated 6.5-fold (95% confidence interval 2.6–13.5) in women aged 30–39 years. There was a 4.4 (2.5–7.0) times higher risk among women aged 40–49.

Conclusions: Women with NF1 develop breast cancer at younger ages than the general population.

We have previously reported on the risk of a wide range of cancer types in individuals with type 1 neurofibromatosis (NF1) in England (Seminog and Goldacre, 2013). Among other findings of elevated risks of site-specific cancers, the study demonstrated high risk of breast cancer among women with NF1. We sought to provide a more detailed breakdown of the results by age at which women with NF1 were diagnosed with breast cancer. This information could be used to guide the development of clinical recommendations about an appropriate age at which to start inviting women with NF1 for breast cancer screening.

MATERIALS AND METHODS

We analysed an all-England data set of linked Hospital Episode Statistics, which includes all hospital day cases and inpatient admissions in NHS hospitals in England, and mortality statistics, for 1999–2011. The risk of breast cancer in the cohort of women admitted to hospital with a diagnosis of NF1, ICD 10 code Q85.0, was compared with the risk in a control cohort. Inclusion and exclusion criteria for defining NF1, and the methods used in analysing the data set, are described in detail in our previous paper on NF1 and cancers (Seminog and Goldacre, 2013). We excluded women from the NF1 and the control cohort if they had a prior

record of breast cancer. We followed individuals in the NF1 cohort and the control cohort, through record linkage, for the development of subsequent breast cancer. The rate ratio (RR) of the risk of breast cancer was calculated on the basis of person-days at risk. We calculated the rate ratio using the formula $RR = (O^{NF}/E^{NF})/(O^{cont}/E^{cont})$, where the O's and E's are the observed and expected numbers of cases of breast cancer in the NF and control cohorts. The details of statistical analysis used here are described elsewhere (Seminog and Goldacre, 2013, Gold *et al.*, 2015). In the original study by Seminog and Goldacre (2013), the data were analysed by age at first recorded hospitalisation for NF1 or control condition. However, when considering screening programmes, age at cancer occurrence is the relevant age. Accordingly, here we calculated age-specific risks of breast cancer in women with NF1, and controls, on the basis of the women's age at first hospitalisation for breast cancer. The start date for follow-up of each individual in each age-specific analysis was the date of first hospital record for NF1, or first hospital record for the conditions in the control cohort, and the end date was the date of first hospital record for breast cancer, or death (regardless of cause of death), reaching the upper limit of the age range (for example, reaching 40 in the analysis of breast cancer in women aged 30–39), or the end of data collection (31 December 2011), whichever came first. The comparison between the NF1 cohort and the control cohort was standardised for age at

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Revised 12 January 2015; accepted 27 January 2015; published online 5 March 2015

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entry into the cohort in 5-year age groups, year of entry in single calendar years, region of residence and quintile of socioeconomic status according to the English Index of Multiple Deprivation. The age-specific rate ratios are summarised in 10-year age bands.

We do not have data about migration of the study population; accordingly, any estimate of absolute risk, undertaken wholly within our data set, would be imprecise. However, in addition to the estimates of relative risk within the data set, given as the rate ratios, we approximated the age-specific annual absolute risks in women with NF1, and compared them with women in the general population of the United Kingdom, as follows. We obtained the national annual age-specific rates of breast cancer in women in the United Kingdom from the Cancer Research UK website (CRUK, 2014). We applied the age-specific rate ratios (that is, the relative risks) for breast cancer associated with NF1 in our study to the annual absolute risks in the general population of women. Our RRs are based on small numbers and there is inevitable statistical uncertainty about them. Accordingly, as well as calculating the absolute risks on the basis of the point estimates of relative risks, we also calculated absolute risks on the basis of the lower and upper 95% confidence limits of relative risk.

RESULTS

In the total English population (~53 million people), we identified 58 cases of breast cancer during a period 1999–2011 among 3672 women hospitalised with NF1. Twenty-five cases of breast cancer were diagnosed among women aged below 50, the earliest age at which women in England are routinely invited for breast cancer screening, and 33 cases of cancer in women aged 50 years and over. We found one case of breast cancer in a woman with NF1 under 30 years of age; 7 in women aged 30–39 (RR 6.53, 95% confidence interval 2.6–13.5); 17 in women aged 40–49 (4.37, 2.5–7.0); 17 aged 50–59 (2.62, 1.5–4.2); 12 aged 60–69 (1.91, 1.0–3.3); 3 aged 70–79 (0.76, 0.2–2.2); and one aged 80+. Among women with NF1, the age-specific relative risks of breast cancer are higher in those aged 30–49 than in those aged 50 and over (Table 1).

Our estimates of absolute risks are shown in the Table 1. The annual absolute risk in women aged 30–39 in the NF cohort (1 in 359) is comparable to that in women aged 50–59 in the general population (1 in 363).

In our study there was only one man with NF1 and breast cancer (in a cohort of 3067 men with NF1).

DISCUSSION

We found that women with NF1 develop breast cancer at younger ages than the general female population.

These findings are consistent with reports published by other groups (Güran and Safali, 2005; Sharif *et al*, 2007; Madanikia *et al*, 2012; Patil and Chamberlain, 2012).

Researchers from John Hopkins Hospital, using information from the patient's charts of the women with NF1, estimated that the standardised incidence ratio (SIR) for breast cancer was 4.4 among women aged under 50 years old (Madanikia *et al*, 2012). Sharif *et al* (2007) found similarly elevated SIR of ~4.9 among young British women with NF1. Our estimates of the RR are very similar to these: for example, among women aged 40–49 in our study the RR was 4.4 (Table 1).

Women who develop breast cancer at a young age often have a family history of breast cancer. However, the BRCA mutations are detected only in 6–17% of women diagnosed with breast cancer before the age of 36 years (Peto *et al*, 1999; Bayraktar *et al*, 2014). Our study findings may help contribute to basic scientists' understanding of the pathophysiology of early-onset breast cancer, particularly among noncarriers of the BRCA mutations. It is also known that the *NF1* and *BRCA1* genes are located in close proximity to each other on the long arm of the chromosome 17; and it is therefore possible that, if mutations occur, they might affect both loci (Ceccaroni *et al*, 2002). NF1-associated gene mutations have themselves been suggested to have a role in the development of breast cancer (Ogata *et al*, 2001; Ceccaroni *et al*, 2002; Güran and Safali, 2005). These findings suggest that it might be reasonable to consider NF1 alongside other hereditary breast cancer syndromes. Thus, the NICE guidelines on early-onset breast cancer might need to be extended to include women with NF1. However, further evaluation would be needed to determine whether genetic counselling and screening programmes would actually benefit these women.

There is a published case report of breast cancer in a young male patient with NF1 (Wilson *et al*, 2004). Our data are insufficient to draw conclusions about the relationship between NF1 and breast cancer in men, since we found only one such case.

A strength of our study is that it was undertaken in a large defined population: given the rarity of the events described, especially when divided by age, this is important. We were not able to account for other risk factors associated with breast cancer, such as parity and other reproductive factors, use of hormone replacement therapy and other medication, or smoking. Another limitation is that our estimate of absolute risk of breast cancer is, as described above, a rather broad approximation.

To conclude, the findings of an excess risk of breast cancer in young women with NF1 might have implications for early breast cancer screening programmes. If surveillance of breast cancer in women with NF1 is considered, there may be a case for screening from 30 years of age. However, the benefits of a screening programme need to be carefully weighed against the risk of exposing young women with NF1, which is a tumour-suppressor syndrome, to radiation. Further study is needed to investigate

Table 1. Age-standardised^a risk (with 95% confidence interval) of breast cancer in women with NF1 and in the female population in the United Kingdom by age group

Age in years	No. of cases of breast cancer in the NF1 cohort	Relative risk (95% CI)	Absolute risk per year in women in the United Kingdom ^b	Estimated absolute risk per year in women with NF1 ^c
30–39	7	6.5 (2.6–13.5)	1 in 2337	1 in 359 (173, 899)
40–49	17	4.4 (2.5–7.0)	1 in 603	1 in 137 (86, 241)
50–59	17	2.6 (1.5–4.2)	1 in 363	1 in 140 (86, 242)
60–69	12	1.9 (1.0–3.3)	1 in 267	1 in 140 (81, 267)
70–79	3	0.8 (0.2–2.2)	1 in 285	1 in 356 (130, 1425)

Abbreviations: CI = confidence interval; NF1 = neurofibromatosis type 1.

^aStandardised for age in 5-year groups within each 10-year age group.

^bOn the basis of data from Cancer Research UK, 2014.

^cOn the basis of the point estimate, and limits of the confidence interval, in the third column in the table and the CRUK data in the fourth column.

whether young women with NF1 should be managed similarly to those with familial breast cancer. Acknowledging the limitations of epidemiological studies, a next step might be to design a clinical study of the prevalence of NF1-associated mutations among women diagnosed with breast cancer, or to investigate NF1 prevalence from one of the ongoing clinical trials of familial breast cancer. Finally, it is important to have more information about the prognosis of breast cancer in young women with NF1.

ACKNOWLEDGEMENTS

The construction of the record linkage data set was funded by the English National Institute for Health Research (RNC/035/002). MJG was partly funded by Public Health England. Ethical approval for a multi-purpose programme of work analysing of the record linkage study data was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLAIMER

The views expressed in this paper do not necessarily reflect those of the funding bodies.

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