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Breast Cancer and Other Neoplasias in Women with Neurofibromatosis Type 1: A Retrospective Review of Cases in the Detroit Metropolitan Area

X. Wang[1,*], **A. M. Levin**[2], **S. E. Smolinski**[3], **F. D. Vigneau**[4], **N. K. Levin**[5], and **M. A. Tainsky**[5]

[1]Department of Medical Genetics, Henry Ford Health System, Detroit, MI

[2]Department of Epidemiology and Biostatistics, Henry Ford Health System, Detroit, MI

[3]Wayne State University School of Medicine, Detroit, MI

[4]Epidemiology Unit Metropolitan Detroit Cancer Surveillance System, Surveillance, Epidemiology and End Results (SEER) Program, Wayne State University School of Medicine, Detroit, MI

[5]Program in Molecular Biology and Genetics, Karmanos Cancer Institute, Wayne State University School of Medicine, Department of Oncology, Detroit, MI

Abstract

Neurofibromatosis type 1 (NF1) is one of the most common cancer predisposing syndromes with an incidence of 1 in 3,500 worldwide. Certain neoplasias or malignancies are over-represented in individuals with NF1; however, an increased risk of breast cancer has not been widely recognized or accepted. We identified 76 women with NF1 seen in the Henry Ford Health System (HFHS) from 1990 to 2009, and linked them to the Surveillance Epidemiology and End Results (SEER) registry covering the Metropolitan Detroit Area. Fifty-one women (67%) were under age 50 years at the time of data analysis. Six women developed invasive breast cancer before age 50, and 3 developed invasive breast cancer after age 50. Using standardized incidence ratios (SIRs) calculated based on the SEER age-adjusted invasive breast cancer incidence rates, our findings demonstrated a statistically significant increase of breast cancer incidence occurring in NF1 women (SIR=5.2; 95%CI 2.4–9.8), and this relative increase was especially evident among those with breast cancer onset under age 50 (SIR=8.8; 95% CI 3.2–19.2). These data are consistent with other reports suggesting an increase in breast cancer risk among females with NF1, which suggests that breast cancer screening guidelines should be evaluated for this potentially high-risk group.

Keywords

breast cancer; neurofibromatosis 1; *NF1* gene; neurofibromin; hereditary cancer syndrome; hereditary cancer risk; Ras signaling

INTRODUCTION

Neurofibromatosis 1 (NF1) is one of the most common cancer predisposing syndromes. Besides neurofibromas, certain neoplasias are over-represented in individuals with NF1, including gliomas, malignant peripheral nerve sheath tumors (MPNST), gastrointestinal

Correspondence: Xia Wang, Department of Clinical Medical Genetics, Henry Ford Health Systems, 3031 West Grand Boulevard, Suite 700, Detroit, Michigan 48202. Telephone (313) 916-3188, Fax (313)916-1730, xwang1@hfhs.org.

stromal tumors (GIST), pheochromocytomas, juvenile myelocytic leukemia, and childhood rhabdomyosarcoma [Brems et al., 2009; Viskochil, 2005].

NF1 is generally caused by inactivating mutations in the *NF1* gene, which leads to upregulation of intracellular Ras signaling, and with somatic mutation leading to double inactivation of *NF1* results in neoplasias [Rebollo and Martinez-A, 1999]. Individuals with NF1 have significantly increased incidences of malignant neoplasms and shortened life spans, although common cancers in the general population, such as lung, colon, and prostate, are not more frequent in individuals with NF1 than those of the general population [Sørensen et al., 1986; Rasmussen et al., 2001; Walker et al., 2006]. One exception is the study done in the United Kingdom [Walker et al., 2006], which suggested an increased colorectal cancer risk for individuals younger than 50 years of age. Isolated case reports have suggested increased breast cancer risk in women with NF1 [Salemis et al., 2001; Safali et al., 2005]; however, a study with a small sample size [Zöller et al., 1997] and a study based on U.S. death certificate-derived Multiple-Cause Mortality Files [Rasmussen et al., 2001] failed to demonstrate an overall statistically significant increased risk of breast cancer. Walker and colleagues [2006] found an increased incidence of breast cancer in women younger than 50 years of age (standardized incidence ratio (SIR) 4.0 (1.1–10.3), $P = 0.037$). In Denmark, a 42-year follow-up study found 7 women who developed breast cancer among 212 males and females (the number of females was not given in this article) [Sørensen et al., 1986]. This cohort also had significantly worse survival rates compared to those of the general population. Unfortunately, neither the ages of cancer diagnosis nor the statistical analyses were provided. The most recent study [Sharif et al., 2007] based on 304 women from the NF1 registry covering the north-west of England described a 4.9-fold increase in breast cancer among women with NF1 under the age of 50 years. In spite of the results of these studies, increased breast cancer risks for individuals with NF1 have not been widely recognized or accepted.

MATERIALS AND METHODS

Study Subjects

To clarify the incidence of breast cancer in our subjects with NF1, we conducted a chart review in the Henry Ford Health System, Detroit, Michigan. Females with NF1 who were 20 years or older by March, 2009 were collected by searching the Department of Medical Genetics Clinic database, Medgis, and the Henry Ford Hospital (HFH) electronic medical records (EMR), CarePlus. Eighty-two individuals were identified in Medgis using a diagnosis of Neurofibromatosis, Neurofibromatosis 1, and/or ICD9 codes of 237.7 or 237.71. The Medgis search covered the period from its establishment in 1990 to 2009. Individuals with NF1 were first recorded in 1993. An additional 37 individuals were identified in the CarePlus using ICD9 codes of 237.7 or 237.71. The CarePlus record search covered the period from its establishment in 1990 to 2009. Five additional individuals of NF1 were identified through clinical encounters prior to 2009, although not identified by the Medgis search. Medical records were stored on microfiche, compact disc or in a digital form in the CarePlus EMR. Each record was individually reviewed. Women identified in CarePlus who did not have a genetic evaluation did not have pedigree or detailed family history information. After reviewing the medical records, individuals with segmental NF1 and Neurofibromatosis 2 (NF2) were excluded from our study. Other individuals were also excluded because of a lack of adequate medical records confirming a personal history NF, or erroneous coding due to family history of NF1 and/or suspicion of NF1. Forty-three of the 82 individuals from Medgis were excluded, which reflects a high rate of inaccurate coding or data input for this database. Five of the 37 individuals from CarePlus were excluded due to insufficient information to confirm a diagnosis of NF1. A woman and her daughter were excluded because they were initially referred for a diagnosis of breast cancer in the mother.

Subsequently, they were found to meet the NF1 diagnostic criteria. As a result, 76 individuals had sufficient documentation to fulfill the clinical diagnostic criteria of NF1 [Martuza & Eldridge, 1988]. To our knowledge, this NF1 population did not receive breast cancer surveillance above and beyond that of the general population.

Information about hereditary breast cancer is routinely recorded in the genetic clinical medical record, but not always recorded in the general hospital record. To our knowledge, none of the women has undergone *BRCA1/BRCA2* gene analysis.

In March, 2010, these 76 individuals were linked to the Metropolitan Detroit Cancer Surveillance System (MDCSS) Database, a participant in the National Surveillance Epidemiology and End Results (SEER) Registry, covering a population of approximately 4 million in Wayne, Oakland and Macomb counties (tri-county) in the Detroit Metropolitan Area. The occurrence of malignant neoplasms, malignant hematological proliferative disorders and brain tumors are consistently recorded in the registry. Benign neoplasms, such as neurofibromas, were recorded only when the brain or central nervous system were involved during the period from 2004 to the present. A diagnosis of NF1 was not recorded. The link of the NF1 cohort to MDCSS may fail to identify individuals who did not reside in the tri-county area at the time of their cancer diagnosis.

All protocols were approved by the Henry Ford Health System Institutional Review Board (IRB) and the Wayne State University Human Investigation Committee. A waiver of consent was obtained for the retrospective review of medical records.

Statistical Methods

The invasive breast cancer standardized incidence ratio (SIR) was calculated based on the ratio of the observed invasive cancers in this NF1 cohort and the expected number of incident cases. For the expected cases, we utilized the SEER five-year age-group specific incidence rates from 1973 to 2008 using the SEER*Stat [SEER*Stat version 7.0.5] software. For invasive breast cancer SIR calculations, age group rates were determined after removal of all in-situ cases, and the incidence rates were based on entire population (i.e., not ethnicity specific). Because rates were not available for 2009 and 2010, the 2008 rates were used as approximations. Person-years at risk started at the age of 20 or January 1, 1973, and continued until an initial diagnosis of invasive breast cancer, the date when SEER database was searched, or the date of death. Age-group specific person-year values were summed and multiplied by the corresponding incidence rate. The resulting age-group specific expected case values were then summed to provide the expected number of cases. All analyses were conducted using the R programming language (http://www.r-project.org/).

RESULTS

Among the 76 women in this cohort, 51 were under the age of 50 years and 25 were age 50 years or older by March 31, 2010. Only six women were older than 70 years. There were 48 Caucasians, 22 African Americans, four Asians, one Hispanic, and one with an unknown ethnic background. Based on the available family history, 19 women belong to 9 families within this cohort, 39 had family histories of NF1, five had family histories of breast cancer only, one had a family history of ovarian cancer only, one had family history of breast and ovarian cancer, 5 had family histories of other malignancies, but no breast or ovarian cancer, and two had family histories of breast cancer and other cancers.

Eleven women with histories of breast cancer have been identified by the SEER search. The identities of these women and their family histories were not available to us. However, during the record review, nine were identified with breast cancer and their family histories

were reviewed when available. Three of these nine women with breast cancer had family histories of other cancers. None of the women with breast cancer had family histories of breast cancer. These 9 women are not related.

Fifteen primary breast cancers of all types were found among 11 women, including invasive or *in situ* ductal carcinoma, and invasive or *in situ* lobular carcinoma. Eight of these women were Caucasian and three were African American. Two of these women had two primary invasive breast cancers. One woman had three isolated *in situ* breast cancers. Table I has illustrated all the malignant neoplasms identified by SEER registry search.

The observed number of initial invasive breast cancers among this cohort of 76 women was significantly higher than expected (Table II). Although a statistically significant difference in observed versus expected initial invasive breast cancers was found in this NF1 cohort, this appears to be principally driven by those individuals diagnosed under the age of 50 (SIR=8.8; 95%CI 3.2–19.2). In particular, the most extreme SIR value was observed among women with NF1 diagnosed with invasive breast cancer between the ages of 30 and 39.

In this cohort, eight women developed various malignant neoplasias, including MPNST, malignant peripheral neuroectodermal tumor, glioblastoma, astrocytoma, Waldenstrom macroglobinemia, rectal/sigmoid adenocarcinoma, and duodenum adenocarcinoma. Seven women had more than one primary malignancy (Table I).

DISCUSSION

In our study, the results are in agreement with those of the north-west England cohort [Sharif et al., 2007]. Our study shows a statistically significant overall invasive breast cancer SIR of 5.2, which is comparable to the 3.5 (95%CI: 1.9–5.9) found in the Sharif study [2007]. Among women under the age of 50, our significant SIR point estimate of 8.8 was also comparable to the estimate in the same age-group (SIR=4.9; 95%CI: 2.4–8.8) of Sharif et al. [2007]. In addition, four women (5%) in the present study developed invasive breast cancer before the age of 40 years, with the youngest occurring at 30 years old. In the Sharif report [2007], five women (1.64 %) developed invasive breast cancer under age 40 years, with the youngest occurring at 27 years old. These two studies demonstrate an increased occurrence of breast cancer in women with NF1, especially in younger women.

Limitations of the present study include its retrospective design and modest sample size, which both contribute to the wide confidence intervals for each SIR. From clinical experience, individuals with NF1 with subtle cutaneous signs or relatively good health are not likely to seek medical care, and are not likely to be ascertained in a retrospective study. Some individuals with NF1 are not designated as having the disorder during clinical encounter, whereas some are never given a diagnosis of NF1. Therefore, we are likely experiencing sampling bias because the individuals with more extensive cutaneous or internal tumor burden, malignancies, or severe co-morbidities are more likely to be ascertained in this study. In addition, the incidence for cancer may be underestimated because the cancer may be diagnosed outside the region of cancer registry.

Due to the small number of individuals, pathological features of the breast cancers (ie. Estrogen receptor positivity, lobular versus ductal, invasive versus *in situ*, lymph node invasion) in our cohort were not compared to the general population.

In this small cohort, 9.2% of the women developed multiple malignancies. These results support the previously reported estimate that 18% of the individuals with NF1 developed second tumors in the 42 years follow up study in Denmark [Sørensen et al., 1986]. In addition, there is no incidence of lung, uterine, cervical and skin cancers in our cohort. The

reasons may be that our sample size is small and the ages of the individuals are relatively young.

Attention should be given to the breast cancer risk in NF1, and a multi-institutional, long term, follow-up study with a larger cohort would better define the true risk of breast cancer in NF1. Until that is established, appropriate breast cancer screening in young women with NF1 is warranted. However, the age at which to begin breast cancer screening with imaging, and what type of imaging, cannot be determined with available data.

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Table I

Malignant Neoplasms in Women With NF1

Case ID	Ethnicity	Type of malignancy	Age at diagnosis
1	Caucasian	Malignant peripheral nerve sheath tumor	57
		Malignant peripheral nerve sheath tumor	65
2	Caucasian	Ductal carcinoma *in situ* of the breast	76
		Duodenal adenocarcinoma	82
3	African American	Malignant peripheral nerve sheath tumor	47
		Malignant peripheral nerve sheath tumor	52
		Waldenstrom macroglobinemia	61
4	African American	Invasive ductal carcinoma of the breast	39
5	Caucasian	Astrocytoma	52
6	Caucasian	Invasive ductal carcinoma of the breast	30
7	Caucasian	Invasive ductal carcinoma of the breast	56
		Invasive lobular carcinoma of the breast	67
8	Caucasian	Ductal carcinoma *in situ* of the breast left	40
		Ductal carcinoma *in situ* of the breast right	43
		Ductal carcinoma *in situ* of the breast left	44
		Glioblastoma	47
9	Caucasian	Invasive ductal carcinoma of the breast right	43
		Invasive ductal carcinoma of the breast left	47
10	Caucasian	Peripheral neuroectodermal tumor	24
11	Caucasian	Invasive ductal carcinoma of the breast	49
13	Caucasian	Invasive ductal carcinoma of the breast	67
		Recto-sigmoid adenocarcinoma	72
14	Caucasian	Malignant peripheral nerve sheath tumor	18
15	African American	Invasive ductal carcinoma of the breast	67
16	Caucasian	Invasive ductal carcinoma of the breast	39
17	African American	Invasive ductal carcinoma of the breast	31

Table II

Overall and Age-group Specific Standardized Incidence Ratios (SIRs) for a First Invasive Breast Cancer in Women With NF1

Age (years)	Observed cases	Expected cases	*SIR (95% CI)
All invasive cases	9	1.8	5.2 (2.4–9.8)
Age ≥ 50	3	1.1	2.8 (0.6–8.2)
Age < 50	6	0.7	8.8 (3.2–19.2)
40–49	2	0.5	4.4 (0.5–16.1)
30–39	4	0.2	19.5 (5.3–50.0)