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RISK OF BREAST CANCER NOT INCREASED IN TRANSLOCATION 11;22 CARRIERS: ANALYSIS OF 80 PEDIGREES

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TO THE EDITOR:

The t(11;22)(q23.3;q11.2) is the most common recurrent reciprocal translocation in humans [Zackai and Emanuel, 1980]. Carriers of this translocation are phenotypically normal, so are usually ascertained following investigation for multiple miscarriages, infertility, or after the birth of a child with supernumerary derivative 22 syndrome (also known as Emanuel syndrome), which results from 3:1 malsegregation of the parental derivative 22 [Fraccaro et al., 1980; Zackai and Emanuel, 1980; Carter et al., 2009]. A small number of reports have suggested an association between the 11;22 translocation and an increased risk of breast cancer in carrier women. Lindblom et al. [1994] reported on five women from eight families (22 translocation carriers, 17 female) with breast cancer. The observed number of breast cancer cases was significantly increased over the expected number based on age-specific incidences of breast cancer reported by the Swedish Cancer Registry. Kurahashi et al. [2000], in their study of 40 unrelated translocation carriers for fine mapping of the translocation breakpoints, noted that one female t(11;22) carrier had bilateral breast malignancies diagnosed at ages 39 and 59. Jobanputra [2005] reported on a single family ascertained because of a prenatally diagnosed tertiary monosomy in the fetus. The mother had the t(11;22) translocation and a family history of breast cancer; five relatives affected with breast cancer carried the familial translocation. Finally, Wieland et al. [2006] reported on a family with breast cancer in seven individuals in three generations, four of whom were available for testing and carried the 11;22 translocation. Two of these reports recommended increased screening for breast cancer in female translocation carriers [Lindblom et al., 1994; Jobanputra et al., 2005].

As part of a study to delineate the clinical features and natural history of Emanuel syndrome [Carter et al., 2009], we collected family history information from 80 pedigrees in which at

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least one individual was known to carry the 11;22 translocation. The families were ascertained from an online support group for parents of children with chromosome 22 disorders (www.c22c.org). Questionnaires were distributed to known carriers of the 11;22 translocation. We elicited family history information including identification of known translocation carriers in the family and their general health history. Because of the reported association with breast cancer, we asked specifically about breast and other types of cancer in our questionnaire.

Of 130 questionnaires distributed, 85 were returned completed. A total of 80 pedigrees were constructed from the family history questionnaires received; some were from members of the same family, so those pedigrees were merged. We had data on 103 female and 49 male carriers over the age of 25 years. Of the 103 female carriers, there were two unrelated individuals with a history of breast cancer; ages at diagnosis were 39 and 42 years. One of the women had a second breast cancer in the contralateral breast at age 59 (incidentally, this is the same woman reported on in Kurahashi et al., 2000). Neither woman had a family history of breast or ovarian cancer. One had a first degree relative with colon cancer and another with melanoma. Other types of cancers reported in identified translocation carriers are shown in Table I. U.S. age-specific female breast cancer incidence rates [United States Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, 2008] were used to compute an expected incidence of breast cancer of 3.34 in this group of women (based on age). The observed incidence of breast cancer in this group was 2 out of 103. A mid-P exact test [Rothman and Boice, 1979] gave a two-sided p-value of 0.51. The standardized incidence ratio was 0.60 (95% confidence interval 0.10 to 1.98 computed using the mid-P method).

We performed the same analyses for all cancer types reported in carriers, and found that melanoma and esophageal cancer were more frequent in our sample of carriers than in the general population. There were three reported cases of melanoma in the carriers (one male and 2 female); the expected incidence of melanoma in this group was 0.63 (mid-P exact test two-sided p-value of 0.03). The standardized incidence ratio was 4.78 (95% confidence interval 1.22 to 13.00). Esophageal cancer was also reported in two male carriers; the expected incidence in our sample is 0.13 (mid-P exact test two-sided p-value of 0.008) (Table I). The standardized incidence ratio was 15.38 (95% confidence interval 2.58 to 50.83).

Our results suggest that the incidence of breast cancer is not increased in 11;22 translocation carriers over that which is expected in the general population. This is in contrast to the results of Lindblom et al. [1994], the Swedish study in which the observed number of breast cancer cases in carriers (5 out of 11 women over the age of 40) was significantly increased over the expected number based on age-specific breast cancer incidence. In each of the five pedigrees they reported, there is only a single individual with breast cancer - a common malignancy in the general population. Thus, the numbers are not large enough to convincingly rule out random chance as an explanation for the apparent excess of breast cancer in their study group. Jobanputra et al. [2005] and Wieland et al. [2006] each report only a single multi-generation family in which there are several women with breast cancer who also happen to be carriers of t(11;22). Close examination of these reports reveals that in the family reported by Wieland et al. [2006], three out of seven women with breast cancer were not available for chromosome analysis, and while Jobanputra et al. [2005] identified five out of six women with breast cancer to also be translocation carriers, they did not provide a pedigree to provide carrier status and health information on other female members of this family. Therefore, the apparent association between carrier status and breast cancer in these two families may also be a chance event, and perhaps subject to reporting bias based on the pre-existing literature which suggested that carriers of this translocation are at high

risk for the development of breast cancer. Our study examined the breast cancer incidence in 80 unrelated pedigrees; importantly, these families were not ascertained due to a family history of cancer, but because of abnormal reproductive outcomes. While we did not verify the breast cancer diagnoses in these families with pathology reports, previous studies have reported that the accuracy of reporting of breast cancer within families is reliable [Sijmons et al., 2000; Murff et al., 2004].

The significance of the increased incidence of melanoma and esophageal cancer in our sample of t(11;22) carriers is unclear and may reflect the relatively small sample size. We did not collect information on the affected individuals' other cancer risk factors, such as smoking or sun exposure; therefore, we cannot comment about the impact of environmental exposures for these particular individuals. Melanoma has been shown to be over-reported by relatives (ie, mistakenly reported as melanoma when another type of skin cancer was the true diagnosis) [Aitken et al., 1996]. Interestingly, the proband reported by Jobanputra et al. [2005] had a personal history of melanoma diagnosed at age 30 years. Disruption of the expression of tumor suppression genes, either by direct gene disruption or loss of heterozygosity (LOH), is a frequent mechanism leading to tumor progression. The t(11;22) chromosome 11 breakpoint lies within 11q23 [Kurahashi et al., 2000], a region that has been associated with LOH in a number of human cancers, including breast [Negrini et al., 1995], colorectal [Gustafson et al., 1994], and lung [Rasio et al., 1995] and a number of putative tumor suppressor genes have been mapped to 11q23 [Wang et al., 1998; Gentile et al., 2001; Martin et al., 2003]. There are no reports of LOH at 11q23 associated with esophageal cancer to our knowledge. However, progression of cutaneous melanoma has been associated with LOH at 11q23 [Herbst et al., 1995] and the MCAM/MUC18 gene, which encodes a cell adhesion molecule that is ectopically expressed by some malignant melanomas, maps to 11q23.3 [Kuske and Johnson, 1999; Johnson et al., 1996]. Whether translocation of this gene to chromosome 22 causes its ectopic expression is unknown. Given the above, an increased risk for esophageal cancer and melanoma in carriers of the 11;22 translocation cannot be excluded; larger studies are needed to clarify the issue.

Our study of 80 pedigrees, the largest to date, demonstrates that constitutional t(11;22)(q23.3;q11.2) is not associated with an increased incidence of breast cancer. Recommendations for breast cancer screening in female carriers of this translocation have not been clear; increased surveillance has been suggested based on small studies [Lindblom et al., 1994; Jobanputra et al., 2005]. The results of the present study suggest that enhanced screening in these women is not indicated unless there is a family history of breast cancer; in that situation the existing general population guidelines for screening based on family history should be followed. Whether there is a true increased risk of melanoma and/or esophageal cancer in carrier men and women is still unclear. We recommend, as a precaution, increased vigilance with respect to sun protection and investigation of skin lesions in t(11;22) carriers, and close attention to possible cancer symptoms as per the general population.

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Table I

Summary of Cancer Types Reported in t(11;22) Carriers

Type of Cancer	Number of Reported Male Carriers (average age at diagnosis)	Expected (male)	p-value (male)	Number of Reported Female Carriers (average age at diagnosis)	Expected (female)	p-value (female)	Expected (male + female)	p-value
Breast	0	0.013	1	2 (40.5)	3.34	0.51	-	-
Prostate	2 (70)	1.59	0.69	n/a	n/a	n/a	n/a	n/a
Colorectal	0	-	-	2 (82.5)	-	-	1.28	0.50
Esophageal	2 (72)	-	-	0	-	-	0.13	*0.008*
Renal	1 (48)	-	-	0	-	-	0.42	0.41
Uterine	n/a	n/a	n/a	1 (45)	0.45	0.44	n/a	n/a
Ovarian	n/a	n/a	n/a	1 (55)	0.28	0.28	n/a	n/a
Cervical	n/a	n/a	n/a	1 (73)	0.28	0.28	n/a	n/a
Leukemia	0	-	-	1 (16)	-	-	0.48	0.47
Melanoma	1 (72)	-	-	2 (42.5)	-	-	0.63	*0.03*

U.S. age- and gender-specific cancer incidence rates [United States Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, 2008] were used to compute an expected incidence for each cancer type. The expected and observed numbers of each cancer type were compared and a mid-P exact test [Rothman and Boice, 1979] was used to generate p-values. P-values that reached statistical significance are italicized. n/a= not applicable.