Research Article

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Racial Differences in the Incidence of Mesenchymal Tumors Associated with *EWSR1* Translocation

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Abstract

Background: The incidence of Ewing sarcoma varies by race, with very low rates among persons of African and East Asian ancestry. The incidence by race of other mesenchymal tumors that also harbor *EWSR1* translocations has not been studied.

Methods: The SEER database was queried to find cases of mesenchymal tumors associated with *EWSR1* translocations: Ewing sarcoma; clear cell sarcoma; extraskeletal myxoid chondrosarcoma; myxoid liposarcoma; desmoplastic small round cell tumor; and myoepithelial tumor. Age-adjusted incidence rates were calculated for white, African American, and Asian/Native American populations and compared statistically.

Results: Ewing sarcoma was significantly less common in the African American and Asian/Native American populations compared with the white population, with incidence rate ratios of 0.12 (95% CI, 0.08–0.20; $P < 0.001$) and 0.54 (95% CI, 0.41–0.69; $P < 0.001$), respectively. Desmoplastic small round cell tumor was significantly more common in the African American population compared with the white population (incidence rate ratio = 3.0; 95% CI, 1.62–5.49; $P < 0.001$). Myxoid liposarcoma was significantly less common in the Asian/Native American population compared with the white population (incidence rate ratio = 0.72; 95% CI, 0.56–0.92; $P = 0.006$). The incidence rates for extraskeletal myxoid chondrosarcoma, myoepithelial tumors, and clear cell sarcoma did not differ significantly by race.

Conclusions: Tumors associated with EWSR1 translocation are not uniformly more common in people of European ancestry.

Impact: The relationship between race and *EWSR1* somatic translocation is complex. Future studies investigating the genetic epidemiology of *EWSR1* translocated tumors are required. *Cancer Epidemiol Biomarkers Prev; 20(3); 449–53. ©2011 AACR.*

Introduction

Ewing sarcoma (ES) is a malignant tumor of bone and soft tissue characterized by genetic translocations involving the Ewing sarcoma breakpoint region (*EWSR1*) in 95% of cases (1). Although *EWSR1* was initially identified in ES, a number of other mesenchymal tumors also harbor *EWSR1* gene translocations (2, 3). These tumors include clear cell sarcoma (CCS) with an *EWSR1/ATF1* frequency of 87% to 94% (4–6), extraskeletal myxoid chondrosarcoma (EMC) with an *EWSR1/CHN* frequency of 83% (7), myxoid liposarcoma (MLPS) with an *EWSR1/CHOP* frequency less than 5% (8, 9), desmoplastic small round cell tumor (DSRCT) with an *EWSR1/WT1* frequency of 96% to 97% (10, 11), and myoepithelial tumors (ME) with an *EWSR1* translocation frequency of 45% (3).

ES shows differential incidence according to race. People of European ancestry are much more frequently affected by this disease compared with people of African and East Asian ancestry (12, 13). In addition, differences in clinical presentation and outcome by race have been previously shown in this disease (14). The impact of race on the incidence of other mesenchymal tumors associated with *EWSR1* translocations has not been studied.

Given the difference in ES incidence between people of European, East Asian, and African ancestry, we hypothesized that race might also have an impact on the incidence of other mesenchymal tumors associated with *EWSR1* translocation. If the incidence of these other *EWSR1* tumors shows a similar racial distribution to ES, then the implication would be that the propensity for *EWSR1* to undergo genetic translocation varies in a uniform manner by race. To evaluate for incidence differences among patients diagnosed with mesenchymal tumors associated with *EWSR1* translocation, we carried out a

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secondary data analysis of all cases of these tumors registered on the Surveillance, Epidemiology, and End Results (SEER) public-access database collected from various geographic areas in the United States.

Methods

The SEER Program of the National Cancer Institute collects and publishes information on cancer incidence and survival in the United States (15). Currently, these data from 17 population-based cancer registries cover approximately 28% of the U.S. population from diverse geographic regions. The population covered by SEER is comparable to the general U.S. population with regard to measures of poverty and education, but tends to be somewhat more urban (15, 16). The proportion of foreign-born persons is higher than the general U.S. population (17). The percentages of the white, African American, Asian American, and Native American populations represented in the SEER registry are 25%, 26%, 54%, and 43%, respectively (18).

ICD-O-2 and ICD-O-3 diagnosis codes were used to identify patients diagnosed with ES (9260/3), CCS (9044/3), EMC (9231/3), and MLPS (8852/3) from 1973 to 2007 (19). The search for cases of DSRCT (8806/3) and ME tumors (8982/3) began in the year in which these entities were first described (1991 and 1997, respectively) and ended in 2007. Although angiomatoid fibrous histiocytoma (AFH) is also reported to harbor EWSR1 translocations (20, 21), cases of AFH were only rarely reported in SEER ($n = 4$) and therefore AFH was not further analyzed in this study. SEER classifies race into 28 mutually exclusive groups by using information from the medical record. SEER further classifies race into the major categories: "White," "Black," and "Others," with the latter group including people of American Indian/Alaskan native and Asian/Pacific Islander ancestry. An additional race category includes "other unspecified" cases.

The rate session feature of SEER*Stat version 6.6.2 was used to calculate age-adjusted annual incidences rates and incidence rate ratios according to the 3 major race categories (22). Age-adjusted rates are a weighted average of the crude rates, where the weights are the proportions of persons in the corresponding age groups of a standard population. Incidence rate ratios were calculated comparing age-adjusted incidence rates in either the SEER "Black" or "Other" (American Indian/Alaskan native and Asian/Pacific Islander) race categories compared with the "White" race category (reference group). These incidence rate ratios were expressed with 95% CI determined by SEER*Stat using the method described by Fay and Feuer (23).

Results

The search for mesenchymal tumors associated with *EWSR1* translocation in the SEER database identified a total of 2,893 cases. The number of cases for each tumor entity and the overall age-adjusted annual incidence rates are shown in Table 1.

Table 1. Age-adjusted annual incidence rate independent of race for mesenchymal tumors associated with *EWSR1* translocation

Histology[a]	Age-adjusted annual incidence rate (cases per 1,000,000)
Ewing sarcoma ($n = 1,185$)	1.4
Myxoid liposarcoma ($n = 1,236$)	1.6
Extraskeletal myxoid chondrosarcoma ($n = 214$)	0.3
Clear cell sarcoma ($n = 138$)	0.2
Myoepithelial tumor ($n = 59$)	0.2
Desmoplastic small round cell tumor ($n = 61$)	0.1

[a]Numbers reflect incident cases reported to SEER from 1973 to 2007, except for desmoplastic small round cell tumor (1991–2007) and myoepithelial tumors (1997–2007).

The age-adjusted annual incidence rates for several of these tumors differed according to race. Table 2 compares the incidence in the African American population with the incidence in the white population. As expected, the most striking difference in incidence between white and African American populations was noted in ES. The age-adjusted annual incidence of ES was 1.6 cases/1,000,000 in the white population compared with 0.2 cases/1,000,000 in the African American population, yielding an incidence rate ratio of 0.12 (95% CI, 0.08–0.20; $P < 0.001$). DSRCT showed the opposite pattern, with a higher age-adjusted annual incidence rate in the African American population (0.3 cases/1,000,000) compared with the white population (0.1 cases/1,000,000) yielding an incidence rate ratio of 3.0 (95% CI, 1.62–5.49; $P < 0.001$). MLPS was less common in the African American population (age-adjusted annual incidence rate of 1.4 cases/1,000,000) compared with the white population (age-adjusted annual incidence rate of 1.6 cases/1,000,000), though this difference was not statistically significant (incidence rate ratio = 0.83; 95% CI, 0.66–1.03; $P = 0.1$). EMC, CCS, and ME had comparable age-adjusted annual incidence rates that did not differ significantly between white and African American populations.

Differences in age-adjusted annual incidence rates were also observed between the white population compared with the "other" race category that includes the American Indian/Alaskan native and Asian/Pacific Islander populations (Table 2). ES showed clear differences in incidence between white and the "other" race

Table 2. Age-adjusted annual incidence rates for tumors associated with *EWSR1* translocations in white, African American, and Asian/Native American populations

Histology	*EWSR1* translocation		Age-adjusted annual incidence rate (cases per 1,000,000)			Rate ratio[a] (95% CI)	
	Most common fusion partner	*EWSR1* translocation frequency from literature (%)	White	African American	Asian/Native American	African American	Asian/Native American
Ewing sarcoma	*FLI1*	95	1.6	0.2	0.9	0.12 (0.08–0.2)	0.54 (0.41–0.69)
Myxoid liposarcoma	*CHOP*	<5	1.6	1.4	1.2	0.83 (0.66–1.03)	0.72 (0.56–0.92)
Extraskeletal myxoid chondrosarcoma	*CHN*	83	0.3	0.3	0.2	1.14 (0.67–1.82)	0.58 (0.27–1.1)
Clear cell sarcoma	*ATF1*	87–94	0.2	0.2	0.2	1.12 (0.59–2.07)	1.02 (0.52–1.84)
Myoepithelial tumor	*POU5F1*	45	0.2	0.3	0.3	1.46 (0.62–3.15)	1.75 (0.74–3.67)
Desmoplastic small round cell tumor	*WT1*	96–97	0.1	0.3	0.1	3.0 (1.62–5.49)	1.04 (0.36–2.6)

[a]Ratio of incidence rate in the African American or Asian/Native American population to incidence rate in the white population (reference).

category. The age-adjusted annual incidence of 0.9 cases/1,000,000 in the "other" race category was significantly less than 1.6 cases/1,000,000 in the white population, yielding an incidence rate ratio of 0.54 (95% CI, 0.41–0.69; $P < 0.001$). Interestingly, an incidence rate ratio of 0.72 (95% CI, 0.56–0.92; $P = 0.006$) for MLPS indicated that this tumor was also significantly less common among the American Indian/Alaskan Native/Asian and Pacific Islander population (age-adjusted annual incidence rate of 1.2 cases/1,000,000) compared with the white population (age-adjusted annual incidence rate of 1.6 cases/1,000,000). There were no differences in age-adjusted annual incidence for DSRCT, CCS, EMC, and ME between the white and "other" race categories.

Discussion

This is the first comprehensive analysis of racial differences in the incidence of mesenchymal tumors associated with *EWSR1* gene translocations. The results confirm previous reports of strong racial differences in the incidence of ES and provide the first description of significant racial differences in the incidence of both DSRCT and MLPS. Specifically, DSRCT was significantly more common in the African American population compared with the white population. In addition, MLPS had a lower incidence among the American Indian/Alaskan native and Asian/Pacific Islander population compared with the white population. These findings suggest that the relationship between *EWSR1* translocation and race is complex.

For various cancer histologies, race-related incidence differences have been shown (24–26). One of the few risk factors for ES is race, even among people that have emigrated from their continents of origin (12, 13). This finding suggests a genetic component of this disease. In addition, this pattern raises the possibility that people of European ancestry have an overall higher propensity to undergo somatic translocation at the *EWSR1* locus compared with people of African or Asian ancestry. The contrasting pattern of incidence by race between ES and DSRCT argues strongly against this possibility. Our analyses indicate that ES is 8 times more likely to occur in the white population compared with African Americans and 1.9 times more likely to occur in the white population compared with Asian Americans and Native Americans. The opposite was shown for DSRCT, which is 3 times more likely to occur among African Americans compared with whites. *EWSR1* translocations are present in a very high percentage of both of these tumors (1, 10). Nevertheless, these tumors show opposite incidence rate ratios between white and African American populations. The current findings suggest that differential propensity to translocation at the *EWSR1* locus may not be responsible for the differential incidence of these tumors between racial groups. However, it is important to note that the specific breakpoints in the *EWSR1* gene may differ between ES and DSRCT (1, 10). Even among tumors of the same histology, the specific breakpoints or fusion partners may differ by race, which could not be evaluated in this study. As such, it therefore remains possible that genetic differences at specific sites within the *EWSR1* gene may vary by race and mediate the differences observed in this study.

The main strength of the use of the SEER database is the high number of analyzed mesenchymal tumor

cases, which are rarely diagnosed. As with other retrospective population-based studies, this analysis comes with major limitations. First, race and tumor histology could not be independently confirmed. Second, data regarding potential environmental factors that might influence the observed differences are not available in SEER. Finally, information about genetic alterations of the tumor is not available in SEER. Instead, the tumor histology provided by SEER was viewed as a proxy for the presence of an *EWSR1* translocation. This assumption may be appropriate for tumors such as ES and DSRCT that show nearly universal *EWSR1* translocation (1, 10). In contrast, this assumption may be less appropriate for ME and particularly MLPS, which harbor *EWSR1* gene rearrangements in only in a minority of cases (2, 3, 8, 9). ME and MLPS were included in the current analysis to provide a complete evaluation of the role of race in tumors reported to be associated with *EWSR1* translocation. Despite the low frequency of *EWSR1* translocation in MLPS, our findings of differences in incidence according to race should prompt further investigations into their genetic epidemiology.

Despite these limitations, the significant differences in incidence rates according to race suggest that genetic differences may underlie the pathogenesis of these tumors. However, these tumors do not seem to share common racial differences in the propensity for *EWSR1* translocation. Additional study of the genetic epidemiology of these rare tumors will provide further insight into their pathogenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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