INTRODUCTION

Cancer remains the leading cause of disease-related death among children in the United States despite progress in clinical trials and significant improvements in survival rates [1]. Over the past 20 years in the United States, increases in the incidence of childhood cancer have also been observed from 11.5 cases per 100,000 children in 1975 to 14.8 per 100,000 children in 2004 [2]. In 2009, approximately 10,730 children under the age of 15 will be diagnosed with cancer and about 1,480 are projected to die from the disease [3].

Despite the burden of childhood cancer and the many years of epidemiologic investigations, its causes remain largely unknown but have been linked in small percentages to certain genetic predispositions and exposures to chemotherapy agents and ionizing radiation [4–7]. A number of studies continue to examine the complexities of other possible risk factors for childhood cancers [8–11]. These include early-life exposures to infectious agents; parental, fetal, or childhood exposures to environmental toxins; maternal diet during pregnancy; early postnatal feeding patterns and diet; and maternal reproductive history [12–24]. Environmental factors may play an important etiologic role in childhood malignancies and can be evidenced by excessive numbers of cases in a defined geographic area relative to other areas, termed clusters.

A cancer cluster can be defined as the occurrence of a greater than expected number of cases of a malignancy within a group of people, a geographic area, or a period of time. There exist various definitions of the terms “cluster” and “clustering” in the context of spatial epidemiology and cancer research, respectively [25,26]. Identification of space–time variations in incidence rate patterns can provide important clues for further in-depth studies into the etiology and control of cancer [27]. Spatial clustering is defined as a general irregular spatial distribution of cases that is not confined to one particular small area. Space–time cancer clustering is observed when an excess number of cases occur within a geographical location over very limited periods of time and cannot be explained in terms of general excesses in these locations or time frames. Regional, national, and international registries have been utilized to investigate possible spatial and space–time clustering and any associated risks of cancer predisposition [21–24,28–31].

In Florida, overall cancer statistics are similar to the rest of the United States. From 1981 to 2000, 10,238 new cases of cancer were diagnosed among Florida children and adolescents, representing 0.7% of all cancer cases diagnosed in the state [28]. The Florida Association of Pediatric Tumor Programs (FAPTP) was founded in 1970 as a statewide network of children’s cancer programs under the auspices of the Florida Regional Medical Program (FRMP). The Florida legislature established a pediatric hematology/oncology program within Children’s Medical Services (CMS) and FAPTP that was given the responsibility and authority to monitor and evaluate pediatric cancer care statewide. This reporting system provides the state and the public with data on cancer incidence, clinical trial participation, and survivorship. The Statewide Patient Information Recording System (SPIRS) registers patients from the 16 pediatric hematology/oncology centers statewide. In addition, the Florida Cancer Data System (FCDS) captures the data from patients treated outside the FAPTP system and can be linked with SPIRS data to study the larger patient data base.

**Key words:** cancer cluster; childhood neoplasm; cluster analysis; epidemiology; Florida
The recently founded Nemours Center for Childhood Cancer Research (NCCCR) has three of its oncology clinics in Jacksonville, Orlando, and Pensacola, Florida as well as one in Wilmington, Delaware. One of the initial goals of this center was to evaluate pediatric cancer epidemiology data in the states of Florida and Delaware. In 2008, the Delaware childhood cancer rates were evaluated by NCCCR in collaboration with Delaware Department of Health and Social Services for possible childhood cancer clusters. This assessment failed to confirm clusters probably due to small number of cases as well as absence of clusters. The current study was initiated about 2 years ago in collaboration with the University of West Florida. We sought to identify and confirm overall childhood cancer clusters as well as to determine whether or not clusters could be confirmed by cancer subtypes. We utilized the data from FAPTP and modeled our analysis using SaTScan™ to test the following null hypotheses: (1) The pediatric cancer rate of all cancer types is randomly distributed over space in Florida from 2000 to 2007, (2) The pediatric cancer rate of all cancer types is randomly distributed over time and space in Florida from 2000 to 2007, (3) The rates for specific pediatric cancer types are randomly distributed over space in Florida from 2000 to 2007, and (4) The rates for specific pediatric cancer types are randomly distributed over time and space in Florida from 2000 to 2007.

MATERIALS AND METHODS

We conducted purely spatial and space–time analyzes to assess the evidence of childhood cancer clusters in the state of Florida using SaTScan™.

Study Area and Population

We identified 67 counties and 972 zip code areas in Florida in the year 2000. While the clustering evaluations could have been based on Florida counties, we decided to obtain more detailed information by using the zip code areas. The statistical analysis used in this study requires that the geographic information for each zip code area be represented by some form of a centroid. To obtain the geographical centroid of each zip code area and to create maps with information on the cancer clusters, the geographical information system ArcGIS was utilized. We used consistent geographical data for zip code areas, Zip Code Tabulation Area (ZCTA), from the year 2000 from the Florida Geographic Data Library (FGDL). For zip code areas that were created after 2000 with an identified cancer case, we manually assigned in the software package ArcGIS a zip code based on its position in the 2000 geographical data set. A marginal number of cases for which we could not determine their position relative to the 2000 zip code area file were discarded. The study population included the entire population of children 0–19 years of age in the state of Florida during the time period 2000–2007. These included children with and without the diagnosis of a childhood cancer. During this time, there were 4,591 cases of pediatric cancer diagnosed, of which 1,254 (27%) had leukemia, 839 (18%) had brain/central nervous system (CNS) cancer, and 252 (5.5%) had lymphoma.

Data Sources

The data for this study were available from FAPTP, an existing de-identified dataset, that is, publicly available. FAPTP has been shown to be a valid and reliable source for pediatric cancer incidence data in Florida [28,32,33]. The dataset included information on cancer cases such as the diagnosis code for the study period 2000–2007 designated by the International Classification for Childhood Cancer (ICCC) [34], incorporating the new codes introduced in ICD-O-2 and the updated ICD-O-3. Demographic information was also included, such as date of birth, age at cancer diagnosis, sex, and zip code of residence. This study involved age-adjusted data. We obtained Florida demographic population data such as age and race/ethnicity from the 2000 census. For each ZCTA, we obtained the total population at risk, stratified by age, sex, and race/ethnicity.

Data Analyzes

Clusters have been analyzed previously using several statistical and epidemiologic approaches [35]. In this study, we used SaTScan™. The software package SaTScan™ [26] uses spatial scan statistics to identify and test for the significance of cancer clusters. The incidence counts in each zip code area are used either in two dimensions for a purely spatial analysis or in a three-dimensional setting for a space–time analysis with the additional dimension representing time. We assumed that the incidence of cancer in each zip code area is distributed according to a Poisson model [36,37]. This method tests the null hypothesis that the age-adjusted risk of cancer incidence is the same for all zip code areas. With the covariates included in the model, we tested the null hypothesis that within any age group, the risk of cancer incidence is the same for the entire area covered in this study [37]. To include the effect of urbanicity in our analysis, we used the population density information for postal code level [37] that is available through the Florida Geographic Data Library (FGDL). Possible associations to socioeconomic status (SES) were investigated by using the economics wealth index by Woods & Poole Economics Inc., which we obtained from the HAAS Business Center at the University of West Florida [38]. Since neither of these two covariates resulted in any changes in the SaTScan™ computations, results on population density or the socioeconomic status are not presented.

The spatial scan statistics in SaTScan™ identifies clusters by imposing a window that moves over a map, including different sets of neighboring zip code areas represented by their corresponding centroids [29]. If the window includes the centroid of a specific zip code area, then this zip code area is included in the window. As suggested by Kulldorff et al. [29], the center of the window is positioned only at the 972 zip code centroids. For each window, the spatial scan statistic tests the null hypothesis of equal risk of childhood cancer incidence for all zip code areas against the alternative hypothesis that there exists an elevated risk of childhood cancer incidence within the scan window when compared with areas outside the window. The likelihood function for the Poisson model can be shown to be proportional to

\[
\frac{(n/E)^n}{N^n (N-n)^{N-n}} I(n > E)
\]

where \(n\) is the number of cancer incidences within the scan window, \(N\) is the total number of incidences in Florida, and \(E\) is the expected number of cancer incidences under the null hypothesis [29,37]. Since we are using a one-tailed test that rejects the null hypothesis if there exists elevated cancer risk, an indicator function \(I\) is used such that \(I = 1\) when the scan window has a larger number of cancer incidences than expected if the null hypothesis were true, and zero
otherwise. It can be shown that for a given \( N \) and \( E \), the likelihood increases as the number of incidences, \( n \), increase in the scan window. How the spatial scan statistic within SaTScan™ actually identifies cancer clusters is described elsewhere in detail [37]. By a Monte Carlo simulation, we generated 999 random replications of the data set to obtain the statistical stability for the identified cancer clusters in the program SaTScan™. The Monte Carlo’s test also allows for the simultaneous controlling of multiple confounders such as age, sex, race, income level, etc. The identified cancer clusters are listed by SaTScan™ in order of significance such that the \( P \)-value for each cluster is compared with a pre-set significance level of 0.05.

There exist different types of the spatial scan statistics. Circular or elliptical windows can be used to identify circular clusters and elliptical shaped clusters, respectively. Both approaches were used, and we arrived at virtually identical cluster results. In this study, we present only the cancer clusters identified by circular windows. While the spatial scan statistic requires specification of the underlying distribution of the data used in SaTScan™, making it a parametric statistical method, a non-parametric smoothing method was also used to check whether similar or identical cluster results would be obtained. In particular, we used a weighted Head Banging algorithm based on median smoothing which removes the background noise of random variability so that the underlying spatial pattern becomes more clear [39–41]. Both parametric and non-parametric methods were used for the purpose of results validation. In this study, Head Bang was used to statistically double check the results from SaTScan™ by removing local variations in cancer incidence age-adjusted rates for the 972 zip code areas. This particular smoother retains the important features, such as edges, but smoothes out unreliable data points and spikes for low population areas based on the chosen weights in the algorithm. To ensure adequate statistical power, all cancer cases for the period 2000–2007 were used to perform a purely spatial analysis. For the space–time analysis, which is a temporal extension of the spatial analysis, the algorithm searches within 2000–2007 for time periods in which clusters appear.

RESULTS

The SaTScan™ purely spatial analysis of the FAPTP data revealed two significant clusters in the state, one in southern Florida and the other in northeastern Florida (NEF). The south Florida (SF) cluster encompasses the southwest, south central and southeast regions. The NEF cluster incorporates areas of the northeast and north central regions. After adjusting for age, sex, and race as covariates, a total of 4,181 cases were identified with a corresponding incidence rate of 14.4 average annual cases per 100,000. In SF, there were 465 observed cases and 352 expected cases, with a relative risk of 1.36, implying that compared with the state, there is a statistically significant 36% increase risk of childhood cancer (\( P = 0.001 \)). In the NEF cluster, there were 466 and 375 observed and expected cases, respectively. This region appears to be smaller in size, although it may represent a more densely populated area. A similar increase in the rates of childhood cancer was identified with a RR = 1.30 (\( P = 0.01 \)). In addition, a third overall childhood cancer cluster was identified in a small area of central Florida in which the observed number of cases was 31 as compared to 11 expected cases. The rates were statistically significantly higher in this area relative to the state with a RR = 2.82 (\( P = 0.008 \)), which implies that compared with the state of Florida, those in this area are almost three times as likely to be diagnosed with childhood cancer (Fig. 1).

Since a purely spatial analysis for the period 2000–2007 does not indicate when the cluster appeared, a space–time analysis was performed, assessing these clusters using the Poisson model within SaTScan™. We observed that the spatial dimensions of the clusters persisted during these periods. SF emerged as the most likely temporal cluster with elevated risk during 2006–2007 (Fig. 2). Whereas the observed cases were 403, the expected were 274, RR = 1.52, \( P = 0.001 \), implying a significant 52% increase in childhood cancer rate in SF compared with the state of Florida. Similarly, the NEF emerged as a secondary temporal cluster for 2001–2004, with the observed and expected cases as 136 and 87 respectively, RR = 1.59, \( P = 0.06 \). This suggested a 59% increase in the rate of overall childhood cancer in NEF relative to the state, but the increase was not statistically significant.

To confirm the clusters, we compared cancer rates within SF to the state. The cancer rates of the state for this time period was 14.1 per 100,000 in 2005 and increased slightly to 16.4 per 100,000 and 15.7 per 100,000 for 2006 and 2007, respectively. By contrast, from 2000 to 2007, the SF cancer rates have been consistently higher than the corresponding Florida rates. In particular, the rates computed for 2006 and 2007 increased significantly from 13.8 per 100,000 in 2005 to 23.9 and 21.1 per 100,000, in 2006 and 2007, respectively.
However, when we excluded the SF cases from the overall Florida cancer cases, the rates in Florida significantly decreased (Table I, Fig. 3).

Table I. Childhood Age and Sex Adjusted Cancer Incidence Rates for Florida, SF Cluster, and Florida Without SF Cluster

<table>
<thead>
<tr>
<th>Area</th>
<th>Year</th>
<th>Rate</th>
<th>95% CI</th>
<th>Rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL</td>
<td>2006</td>
<td>16.4</td>
<td>15.1, 17.6</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>2007</td>
<td>15.7</td>
<td>14.5, 16.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Aggregate</td>
<td></td>
<td>16.05</td>
<td>14.8, 17.3</td>
<td>1.0</td>
</tr>
<tr>
<td>FL w/o SF</td>
<td>2006</td>
<td>14.8</td>
<td>13.5, 16.1</td>
<td>0.9024</td>
</tr>
<tr>
<td></td>
<td>2007</td>
<td>14.5</td>
<td>13.2, 15.8</td>
<td>0.9236</td>
</tr>
<tr>
<td>Aggregate</td>
<td></td>
<td>14.65</td>
<td>13.2, 15.7</td>
<td>0.9128</td>
</tr>
<tr>
<td>SF</td>
<td>2006</td>
<td>23.9</td>
<td>20.3, 27.5</td>
<td>1.4573</td>
</tr>
<tr>
<td></td>
<td>2007</td>
<td>21.1</td>
<td>17.7, 24.4</td>
<td>1.3439</td>
</tr>
<tr>
<td>Aggregate</td>
<td></td>
<td>22.5</td>
<td>19.2, 26.1</td>
<td>1.4019</td>
</tr>
</tbody>
</table>

Incidence counts were utilized directly to compute incidence rates using the FAPTP Dataset for 2000–2007 and Florida population statistics for 2000. Confidence intervals are provided, as uncertainty still exists within ideal registry datasets and computed cancer statistics (United States Cancer Statistics: 1999 incidence). Aggregate refers to the rates for 2006 and 2007 combined. The state of Florida is the reference group, hence the ratio is 1.0 for FL, Florida. SF is the southern Florida cluster. The time frame for the SF cluster was noted to be January 1, 2006 to December 31, 2007. CI, Confidence intervals.

Fig. 2. Space–time analysis of FAPTP database for all cancer types 2000–2007. Clustering representation of SaTScan™ space–time analysis is illustrated utilizing zip code data with age, sex, and race as covariates. Clusters are represented in colors. Spatial representations were not affected significantly however time frame results for the Southern Florida (SF) cluster (2006–2007) are noted to be representative of a recent surge in incidence rates. The red area represents the South Florida cluster. SaTScan™ computed results include: Coordinates/radius = (26.0N, 81.4W)/121.1 km, Time frame = January 1, 2006 to December 31, 2007, Population 963,643, Observed cases = 403, Expected cases = 274. The orange area represents the North Central Florida cluster. SaTScan™ computed results include: Coordinates/radius = (29.5N, 82.0W)/65.9 km, Time frame = January 1, 2001 to December 31, 2004, Population 155,681, Observed cases = 136, Expected cases = 87.

Fig. 3. Age-adjusted pediatric cancer incidence rates 2000–2007. Incidence counts were utilized directly to compute incidence rates using FAPTP Dataset for 2000–2007 and Florida population statistics for 2000. Southern Florida cluster (SF) is shown in comparison to the rates for the entire state of Florida and to rates for the state of Florida excluding the influence of the SF. Differences between these rates during 2006 and 2007 suggest that the rise in Florida rates during this period was influenced by the surge in incidence rates in the SF cluster.

A purely spatial analysis of leukemia rates identified two regions of Florida (during the period of 2000–2007) similar to the cluster areas identified when all cancer types were combined. A total of 1,254 leukemia cases in the state were identified and utilized in this analysis. There was a statistically significant cluster in SF (RR = 1.53, P = 0.001) (Fig. 4). A second cluster was identified in the north central region of the state, shifting somewhat from the NEF cluster and was statistically significant as well, RR = 1.45, P = 0.03. Likewise, in the space–time analysis of leukemia cases, there was a statistically significant cluster in SF (RR = 1.74, P = 0.05) (Fig. 5). The time period identified for the peak rate of the cluster was 2000–2002. During this time period, the number of observed cancer cases was 105 while the expected number of cases was 63. While the space–time analysis points to 2000–2002 as the time of the peak in leukemia rates, the purely spatial analysis indicated that leukemia rates in the SF cluster area remained elevated throughout the entire period (2000–2007), when compared to the state.

A purely spatial analysis of brain/CNS cancer identified one area in southern Florida. Of the 839 cases identified in the state, there were 60 observed and 33 expected cases in this region. The relative risk comparing Florida to SF was not statistically significant, RR = 1.86, P = 0.07 (Fig. 6). A space–time analysis (52 observed cases and 24 expected cases) for the brain/CNS cancer identified a cluster corresponding to the SF cluster, with a statistically significant increased incidence rate RR = 2.25, P = 0.02, implying that children in SF were two times as likely to develop brain/CNS cancer when compared with children in the state of Florida. The time period identified for this cluster was 2006–2007 (Fig. 7). In contrast, lymphoma rates were not statistically significant probably due to small numbers.
DISCUSSION

These purely spatial and space–time clustering studies of childhood cancer in Florida were conducted using data from FAPTP and the Census data of 2000. The accuracy of case ascertainment is high with FAPTP and has been described and validated elsewhere [28,32,33]. This epidemiologic mapping study of Florida reveals three major findings. First, childhood cancer clusters were identified in SF and NEF. Second, the childhood cancer clusters persisted after controlling for age, sex, and race/ethnicity. Third, whereas significant increase in cancer rates was observed in leukemia and brain/CNS cancer, there was no significant increase in the lymphoma rate among children in SF and NEF.

There are several methodologic issues in identification and confirmation of childhood cancer clusters, especially leukemia [42]. In general, these studies are limited by low statistical power [43]. Therefore, the identification of cancer clusters may be driven by bias such as the practice of defining geographical boundaries of the cluster and improved case ascertainment in the areas suspected of having clusters, as well as error, namely, random variation [44]. Cancer cluster studies utilizing multiple comparisons over a small period of time or different methods have shown false positive results [45]. Further, population density, age, migration, sex, and race/ethnicity are potential confounding elements affecting childhood cancer cluster confirmation [46,47].

This study utilized statistical software (SaTScan™) that is reliable in the assessment of cancer clusters, as well as other disease clusters, in the human population [29–31,35,36]. By utilizing the data from FAPTP, we ensured the accuracy and reliability of the data used. FAPTP routinely reviews the cancer data for discrepancies including duplications and provides the most comprehensive incidence data of childhood cancer in Florida. Thus, FAPTP facilitates assessment of patterns of cancer rates and geographical trends within the state of Florida. Whereas the limitations addressed in previous studies on clusters could not be avoided completely, our chances of repeating similar methodologic issues were substantially minimized as described below.

The large sample of cases with overall childhood cancer as well as significant cases in cancer subtypes should ensure a sufficiently high statistical power. It has been shown in a simple power study [36] for the likelihood ratio test used in SaTScan™ that a relative risk of 1.35 can result in an estimated power (1 − β > 0.80) to detect the differences in cancer cases between the clusters and non-cluster areas (in the state of Florida), if one does exist. For example, from 2006 to 2007, the observed cases were 403 in SF, which is a large sample for comparison between areas with and without clusters (Fig. 2). Because we used cancer data from a highly reliable source (FAPTP), both selection and misclassification biases were dramatically minimized in our study. The observed clusters in SF and NEF are not driven by improved case ascertainment following the increased childhood cancers in certain geographic areas in Florida. In addition, because this study started 2 years ago, it is highly unlikely that our findings are influenced by other recent studies on Florida clusters.
To better understand the increased cancer rates in SF, it is important to consider changes in the population for that region as well. Otherwise, the possible environmental factors affecting cancer rates could be confounded with population migrations and increases. While estimates for the pediatric population counts for all ages in each of the Florida zip code areas were not available for the period 2001–2007, we utilized population estimates for the pediatric population by county for 2001 and 2007 from the Florida Legislature [48] and the estimates of the pediatric population for a 3-year-period 2005–2007 from the American Community Survey of the Census Bureau [49]. Considering the relative annual population increase, defined by the ratio \( r \) as follows:

\[
r = \frac{\text{pediatric pop 2007} - \text{pediatric pop 2000}}{\text{pediatric pop 2000}}
\]

where the change in the pediatric population count in 2007 is obtained relative to the pediatric population count in 2000, we compared the average values for the ratio \( r \) for the SF area with the corresponding annual relative population increase for the rest of Florida. Similarly, we also obtained a ratio based on the 2005–2007 estimates. Our results indicated that relative population increases in the SF cluster area are not significantly different from the rest of the state. It is also possible that zip code population shifts over time could have altered the results between 2000 and 2007. Such shifts could result in an apparently elevated cancer rate when using 2000 as the population standard. Using population estimates for larger areas such as counties would limit the effects of such small-area migrations on the cancer rates. Florida county population estimates between 2005 and 2007 were available for 53 counties in Florida with populations greater than 20,000. We analyzed purely spatial and space–time SaTScan™ results for these 53 counties from 2000 to 2007 and found that the brain tumor cluster persisted. Analysis of leukemia clusters persisted during the space–time analysis but not for the purely spatial analysis. While our initial analysis was based on zip codes, limited analysis based on counties indirectly suggests that population shifts did not play a significant role in altering the cancer clusters. Thus, it is highly unlikely that our findings of childhood cancer clusters are driven primarily by migration since population changes in these geographic areas were non-differential, thus minimizing any misclassification bias and confounding from the observed clusters.

In this study, we have shown that there is a relative increase in childhood cancer crude incidence rate in SF and NEF during the years 2000–2007. Since this finding might have been influenced by potential confounders of childhood cancer [44], we adjusted for age at diagnosis, sex, and race/ethnicity and still observed a statistically significant relative increase in SF and NEF compared with the state of Florida. Therefore, given these adjustments, it is possible to suspect geographic variation as the potential risk variable for the clusters. Although the cluster areas identified are quite large geographically, it is possible that localized environmental factors or person-to-person spread of viral or bacterial pathogen [12,13,21–24], may be involved in these suspected...
geographic areas. Finally, despite these adjustments, we cannot rule out unmeasured confounding elements as a possible explanation of the observed clusters. Furthermore, residual confounding elements may influence this confirmation especially by race/ethnicity, since this information may have suffered from misclassification bias. Therefore, statistical modeling cannot completely remove the effect of confounding [27,50].

Our study found the crude incidence rate of childhood leukemia and brain/CNS cancers to be significantly higher in the SF and NEF clusters when compared with the state of Florida. As described earlier, these findings are unlikely to be driven by non-factual attributes of cancer clusters but are suggestive of environmental factors or common risk factors in the areas. Consequently, these findings could be etiologically driven, indicating the need for further investigation to identify the potential risk factors in the observed leukemia and brain/CNS cancer clusters in these areas. We did not find spatial or space–time clustering with lymphoma in the adjusted models. The negative finding with lymphoma may be due to the small number of cases in this subset, which limits the statistical power to detect significant clusters with these data [47] or due to the lack of a lymphoma cluster.

Despite the strengths of this article, there are also some limitations. First, we used a preexisting dataset that may be associated with information and selection bias, thus influencing the validity of our findings. However, since the FAPTP data are highly reliable, it is unlikely that our confirmation of cancer clusters in SF is driven solely by information or selection bias. Second, confounding elements such as race/ethnicity and age may very well influence our results. But this is unlikely since we focused on childhood malignancy with no reference to adult tumors. Finally, as with all epidemiologic studies, unmeasured and residual confounding elements may also partly influence the findings reported.

In summary, we found evidence of spatial and space–time childhood cancer clustering in SF and NEF. Statistically significant cancer subtype clustering was found for leukemia and brain/CNS cancer but not for lymphomas, which may be due to low statistical power of our study to detect smaller clusters. This evidence is suggestive of the presence of some environmental and possibly social conditions that may act individually or collectively to predispose children in these cluster regions to increased risk of childhood cancer. Further study is needed to investigate the possible predisposing factors in the elevated childhood cancer rates in SF and NEF.

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