RESEARCH LETTER

Scientific Publications on Firearms in Youth Before and After Congressional Action Prohibiting Federal Research Funding

In January 1996, Congress passed an appropriations bill amendment prohibiting the US Centers for Disease Control and Prevention (CDC) from using “funds made available for injury prevention . . . to advocate or promote gun control.” This provision was triggered by evidence linking gun ownership to health harms, created uncertainty among CDC officials and researchers about what could be studied, and led to significant declines in funding. We evaluated the change in the number of publications on firearms in youth compared with research on other leading causes of death before and after the Congressional action. We focused on children and adolescents because they disproportionately experience gun violence and injury.

Methods | We identified 10 leading causes of death among children and adolescents aged 1 to 17 years using CDC data on mortality between 1991 and 2010. Each cause was then matched to a Medical Subject Heading, and PubMed was searched from 1991-2010 using causes of death and child or adolescent to determine the annual number of publications. Publications of all types and on all outcomes were included for each cause. To explore funding trends, we identified federal and private or nonfederal funding sources for firearms studies as reported by PubMed.

To quantify the change in annual publications, we used a quasi-experimental differences-in-differences design implemented with log-linear regression models. This approach assessed change in the volume of firearms publications before and after a year, relative to the change in volume of publications on other causes before and after the same cut-point year. The null hypothesis was that the percentage change in volume of firearms publications would have been the same as the percentage change in volume of nonfirearms publications despite the events of 1996.

Because the Congressional action may have had a delayed effect on publications, we allowed for a lag between the amendment and changes in annual firearms publications of 1 to 6 years. For each year, our model was specified as: publication volume = f(causes of death, firearms, post–cut-point year, firearms × post–cut-point year), in which post–cut-point year is an indicator variable for whether the data were drawn from before or after the year in question. The interaction term coefficient was the parameter of interest. Funding trends were categorized into prelag, perilag, and postlag periods.

Analyses were conducted using Stata version 12.0 (StataCorp Inc). Two-tailed P value of less than .05 was considered significant.

Results | Between 1991 and 2010, there were 310,203 deaths among youth from the 10 leading causes and 301,475 publications. Firearms accounted for 12.6% of deaths, but less than 0.3% of publications. There were 25 publications on firearms in 1991, 43 in 1993, 38 in 1994, 49 in 1995, 49 in 1996, 48 in 1997, 54 in 1998, 61 in 1999, and 33 in 2009 (Figure). In contrast, publications on neoplasms, which are responsible for approximately the same number of deaths, increased from 5,519 to 9,707. Using the differences-in-differences model and 1999 as the cut point, the volume of publications on firearms was 24.5% (P = .001) lower than it may have otherwise been compared with publications not on firearms (Table). Using different lag times did not significantly alter the results. The estimate was...
similar when considering only publications associated with a single cause of death (87%; differences-in-differences estimate, −19.9%; \( P = .03 \)). In 1991-1996, 1997-2002, and 2003-2010, 33, 43, and 41 firearms publications reported federal funding, respectively; 25, 63, and 86 reported private or nonfederal funding.

Discussion | We only found modest increases in the number of scientific publications on firearms between 1991 and 2010, in contrast to other leading causes of death in youth. The change in number of publications on firearms was lower than anticipated compared with publications not on firearms. There was not a discrete point identified at which the pattern of publications changed. Therefore, whether the Congressional action or other events were responsible is unclear. Important limitations include use of a single database (PubMed) and lack of information on study inception. The effect on publications after President Obama’s January 2013 memorandum directing the CDC to conduct or support research on the causes of gun violence and approaches to prevent it should be evaluated.

Table. Average and Percentage Change in Annual Volume of Firearms Publications

<table>
<thead>
<tr>
<th>Model(^a); Cut-Point Year(^b)</th>
<th>Publication Topic</th>
<th>No. of Publications by Publication Year</th>
<th>Regression Model Estimates for Annual Volume of Publications(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1991</td>
<td>1995</td>
</tr>
<tr>
<td>1; 1997 Firearms</td>
<td></td>
<td>25</td>
<td>49</td>
</tr>
<tr>
<td>2; 1998 Firearms</td>
<td></td>
<td>40</td>
<td>44</td>
</tr>
<tr>
<td>3; 1999 Firearms</td>
<td></td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>4; 2000 Firearms</td>
<td></td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>5; 2001 Firearms</td>
<td></td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>6; 2002 Firearms</td>
<td></td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>3; 1999 Unintentional injury</td>
<td></td>
<td>310</td>
<td>374</td>
</tr>
<tr>
<td>3; 1999 Neoplasms</td>
<td></td>
<td>5519</td>
<td>6320</td>
</tr>
<tr>
<td>3; 1999 Homicide</td>
<td></td>
<td>88</td>
<td>106</td>
</tr>
<tr>
<td>3; 1999 Suicide</td>
<td></td>
<td>286</td>
<td>341</td>
</tr>
<tr>
<td>3; 1999 Congenital anomalies</td>
<td></td>
<td>2701</td>
<td>2916</td>
</tr>
<tr>
<td>3; 1999 Heart disease</td>
<td></td>
<td>1930</td>
<td>2046</td>
</tr>
<tr>
<td>3; 1999 Influenza or pneumonia</td>
<td></td>
<td>370</td>
<td>361</td>
</tr>
<tr>
<td>3; 1999 Chronic lower respiratory disease</td>
<td></td>
<td>623</td>
<td>879</td>
</tr>
<tr>
<td>3; 1999 Septicemia</td>
<td></td>
<td>236</td>
<td>390</td>
</tr>
<tr>
<td>3; 1999 Cerebrovascular disease</td>
<td></td>
<td>482</td>
<td>592</td>
</tr>
</tbody>
</table>

\(a\) Model 3 uses a cut-point year of 1999 (the approximate midpoint of a period at which the US Centers for Disease Control and Prevention funding for firearms research decreased sharply) and is the primary model. Models using other cut-point years (models 1-6) are presented for comparison.

\(b\) The cut-point year separates the before and after periods, taking into account other cut-point years (models 1-6) are presented for comparison.

\(c\) This represents the average annual change in publications comparing the period before the cut-point year with the period after the cut-point year.

\(d\) This represents the average annual change in firearms publications after the cut-point year, relative to the average annual change in publications not on firearms during the same period. It assumes that the change in firearms publications would have been the same as the change in publications not on firearms during the same period, despite the events of 1996.

\(e\) Models used a log-linear differences-in-differences design with cause-of-death fixed effects.

Joseph A. Ladapo, MD, PhD
Benjamin A. Rodwin, BS
Andrew M. Ryan, PhD
Leonardo Trasande, MD, MPP
Jan Blustein, MD, PhD

Author Affiliations: Department of Population Health, New York University School of Medicine, New York, New York (Ladapo); Department of Medicine, New York University School of Medicine, New York, New York (Rodwin); Division of Outcomes and Effectiveness Research, Weill Cornell Medical College, New York, New York (Ryan); Department of Pediatrics, New York University School of Medicine, New York, New York (Trasande); Wagner School of Public Service, New York University, New York, New York (Blustein).

Corresponding Author: Joseph A. Ladapo, MD, PhD, New York University School of Medicine, 550 First Ave, VZ30 Sixth Floor, 614, New York, NY 10016 (joseph.ladapo@nyumc.org).

Author Contributions: Dr Ladapo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ladapo, Rodwin.
Acquisition of data: Ladapo, Rodwin.
Analysis and interpretation of data: Ladapo, Ryan, Trasande, Blustein.
Drafting of the manuscript: Ladapo, Blustein.
BRAF V600E Mutation and Papillary Thyroid Cancer

To the Editor The study by Dr Xing and colleagues explored the association between the BRAF V600E mutation and mortality in patients with papillary thyroid cancer (PTC) in a large retrospective cohort of 1849 patients from 13 centers worldwide. The authors concluded that the BRAF mutation was significantly associated with cancer-related mortality.

However, this work actually demonstrates that the BRAF mutation is just a marker of aggressiveness and not a true prognostic factor because it was significantly associated with aggressive features and mortality in the bivariable analysis. When other clinical variables were entered in the analysis, the correlation disappeared. Therefore, the way the data were described and the conclusion may be misleading.

The conclusion that the BRAF mutation does not predict negative outcomes emerged from a recent study, in which the BRAF mutation was analyzed in a sample of 47 patients with PTC with distant metastases, 26 of whom died because of the tumor. The BRAF V600E was not predictive of distant metastases or higher mortality because the frequency of this mutation was lower in the distantly metastatic group and within the subgroup of patients who died than in the control group (75 PTCs without distant metastases on a minimum follow-up of 7 years). This evidence extends and confirms the results from the study by Xing et al that the BRAF mutation is not a determinant of the metastatic potential of PTC.

Papillary thyroid cancers are generally nonaggressive tumors with low occurrence of metastases and death. This is a limitation for correlational prognostic studies. The series of PTC with distant metastases and the sample described by Xing et al are the largest ever analyzed. Xing et al suggested that further studies are needed to determine the most appropriate use of the BRAF mutation as a clinical marker, whereas we believe that it is time to move forward and look for novel molecular determinants that may perform better in predicting outcome of patients with PTC.

Alessia Ciarrocchi, PhD
Silvio Cavuto, MSc
Simonetta Piana, MD

Author Affiliations: Laboratory of Molecular Biology, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy (Ciarrocchi); Scientific Directorate, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy (Cavuto); Pathology Unit, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy (Piana).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.


In Reply I disagree with Dr Ciarrocchi and colleagues that BRAF V600E has no role in the aggressiveness of PTC because of its dependence on tumor behaviors, including local and distant metastases and invasion. It is clear that PTC would not cause patient death without aggressive tumor behaviors.

Our study demonstrated a strong synergism between BRAF V600E and aggressive clinicopathological behaviors, as reflected by the strong synergy indices and the fact that the association of mortality with BRAF V600E or clinicopathological behavior alone was only moderate but increased when the 2 were considered jointly. Thus, BRAF V600E does have a significant association with mortality, which likely occurs through promoting aggressive tumor behaviors and would be misleadingly lost using conventional multivariable models. Further efforts are needed to define how to specifically use the prognostic value of BRAF V600E clinically.

Some studies have not shown an association of BRAF V600E with aggressive behaviors of PTC. However, most have, as shown in large meta-analyses. Many factors could bias the conclusion about the prognostic value of BRAF V600E. For example, in a large study of 631 patients with PTC that failed to show an association of aggressiveness of PTC with BRAF V600E, many patients (41.5%) had only partial thyroidectomy, making thorough pathological characterization difficult. In addition, the majority of the patients in this study did not receive radioiodine ablation, potentially masking an effect of BRAF V600E on clinical outcomes given that BRAF mutation–negative PTC is more sensitive to radioiodine ablation.

Ciarrocchi and colleagues’ statement that a previous study showing no aggressive role of BRAF V600E in PTC confirms our study is incorrect. However, the 2 studies are not comparable; the former was a single institution study focused on a small number of highly selected cases and the latter was a large multicenter study of consecutive cases.

The study by Sancisi et al selected patients with distant metastases who only had well-differentiated primary cancer.

COMMENT & RESPONSE

BRAF V600E Mutation and Papillary Thyroid Cancer

To the Editor The study by Dr Xing and colleagues explored the association between the BRAF V600E mutation and mortality in patients with papillary thyroid cancer (PTC) in a large retrospective cohort of 1849 patients from 13 centers worldwide. The authors concluded that the BRAF mutation was significantly associated with cancer-related mortality.

However, this work actually demonstrates that the BRAF mutation is just a marker of aggressiveness and not a true prognostic factor because it was significantly associated with aggressive features and mortality in the bivariable analysis. When other clinical variables were entered in the analysis, the correlation disappeared. Therefore, the way the data were described and the conclusion may be misleading.

The conclusion that the BRAF mutation does not predict negative outcomes emerged from a recent study, in which the BRAF mutation was analyzed in a sample of 47 patients with PTC with distant metastases, 26 of whom died because of the tumor. The BRAF V600E was not predictive of distant metastases or higher mortality because the frequency of this mutation was lower in the distantly metastatic group and within the subgroup of patients who died than in the control group (75 PTCs without distant metastases on a minimum follow-up of 7 years). This evidence extends and confirms the results from the study by Xing et al that the BRAF mutation is not a determinant of the metastatic potential of PTC.

Papillary thyroid cancers are generally nonaggressive tumors with low occurrence of metastases and death. This is a limitation for correlational prognostic studies. The series of PTC with distant metastases and the sample described by Xing et al are the largest ever analyzed. Xing et al suggested that further studies are needed to determine the most appropriate use of the BRAF mutation as a clinical marker, whereas we believe that it is time to move forward and look for novel molecular determinants that may perform better in predicting outcome of patients with PTC.

Alessia Ciarrocchi, PhD
Silvio Cavuto, MSc
Simonetta Piana, MD

Author Affiliations: Laboratory of Molecular Biology, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy (Ciarrocchi); Scientific Directorate, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy (Cavuto); Pathology Unit, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy (Piana).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.


In Reply I disagree with Dr Ciarrocchi and colleagues that BRAF V600E has no role in the aggressiveness of PTC because of its dependence on tumor behaviors, including local and distant metastases and invasion. It is clear that PTC would not cause patient death without aggressive tumor behaviors.

Our study demonstrated a strong synergism between BRAF V600E and aggressive clinicopathological behaviors, as reflected by the strong synergy indices and the fact that the association of mortality with BRAF V600E or clinicopathological behavior alone was only moderate but increased when the 2 were considered jointly. Thus, BRAF V600E does have a significant association with mortality, which likely occurs through promoting aggressive tumor behaviors and would be misleadingly lost using conventional multivariable models. Further efforts are needed to define how to specifically use the prognostic value of BRAF V600E clinically.

Some studies have not shown an association of BRAF V600E with aggressive behaviors of PTC. However, most have, as shown in large meta-analyses. Many factors could bias the conclusion about the prognostic value of BRAF V600E. For example, in a large study of 631 patients with PTC that failed to show an association of aggressiveness of PTC with BRAF V600E, many patients (41.5%) had only partial thyroidectomy, making thorough pathological characterization difficult. In addition, the majority of the patients in this study did not receive radioiodine ablation, potentially masking an effect of BRAF V600E on clinical outcomes given that BRAF mutation–negative PTC is more sensitive to radioiodine ablation.

Ciarrocchi and colleagues’ statement that a previous study showing no aggressive role of BRAF V600E in PTC confirms our study is incorrect. However, the 2 studies are not comparable; the former was a single institution study focused on a small number of highly selected cases and the latter was a large multicenter study of consecutive cases.

The study by Sancisi et al selected patients with distant metastases who only had well-differentiated primary cancer;