Aryl Hydrocarbon Receptor Expression Is Associated with a Family History of Upper Gastrointestinal Tract Cancer in a High-Risk Population Exposed to Aromatic Hydrocarbons

Mark J. Roth,1 Wen-Qiang Wei,3 Jessica Baer,6 Christian C. Abnet,1 Guo-Qing Wang,4 Lawrence R. Sternberg,7 Andrew C. Warner,7 Laura Lee Johnson,2 Ning Lu,5 Carol A. Giffen,8 Sanford M. Dawsey,1 You-Lin Qiao,3 and James Cherry6

1Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute; 2National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, Maryland; 3Departments of Cancer Epidemiology, Endoscopy, and Pathology, Cancer Institute, Chinese Academy of Medical Sciences, Beijing, People’s Republic of China; 4Laboratory of Molecular Technology and Pathology and Histotechnology Laboratory, Science Applications International Corporation-Frederick, Inc., National Cancer Institute-Frederick, Frederick, Maryland; and 5Information Management Services, Silver Spring, Maryland

Abstract

Background: Polycyclic aromatic hydrocarbon (PAH) exposure is a risk factor for esophageal squamous cell carcinoma, and PAHs are ligands of the aryl hydrocarbon receptor (AhR). This study measured the expression of AhR and related genes in frozen esophageal cell samples from patients exposed to different levels of indoor air pollution, who did or did not have high-grade squamous dysplasia and who did or did not have a family history of upper gastrointestinal tract (UGI) cancer.

Methods: 147 samples were evaluated, including 23 (16%) from patients with high-grade dysplasia and 48 (33%) from patients without dysplasia who heated their homes with coal, without a chimney (a "high" indoor air pollution group), and 27 (18%) from patients with high-grade dysplasia and 49 (33%) from patients without dysplasia who did not heat their homes at all (a "low" indoor air pollution group). Sixty-four (44%) had a family history of UGI cancer. RNA was extracted and quantitative PCR analysis was done.

Results: AhR gene expression was detectable in 85 (58%) of the samples and was >9-fold higher in those with a family history of UGI cancer (median expression, interquartile range), −1,964 (−18,000, −610) versus −18,000 (−18,000, −1036); P = 0.02, Wilcoxon rank-sum test). Heating status, dysplasia category, age, gender, and smoking were not associated with AhR expression (linear regression; all P values ≥ 0.1).

Conclusion: AhR expression was higher in patients with a family history of UGI cancer. Such individuals may be more susceptible to the deleterious effects of PAH exposure, including PAH-induced cancer. (Cancer Epidemiol Biomarkers Prev 2009;18(9):2391–6)

Introduction

Esophageal cancer is the sixth leading cause of cancer death worldwide and is the leading cause of cancer death in Linxian, China, where mortality rates from this disease are ∼100/100,000 person-years for both sexes (1). These are some of the highest mortality rates for any single cancer found anywhere. In high-risk populations throughout the world, esophageal squamous cell carcinoma (ESCC) is the predominant histologic type of esophageal cancer. The primary prevention of ESCC within high-risk groups continues to be limited by our inability to identify specific risk factors and etiologic agents.

Having a positive family history of cancer is known to be associated with an increased risk for several cancers (2-4). In Linxian, China, a recent prospective study with 15 years of follow-up and >3,400 incident upper gastrointestinal tract (UGI) cancers, including >1,900 ESCC, 1,000 gastric cardia cancers, and 300 gastric noncardia cancers, found positive family history of esophageal or gastric cardia cancer to be significantly associated with increased risk of cancer at all of these sites (5). A separate case-control study of esophageal squamous dysplasia, the precursor lesion of ESCC, conducted in the same region, confirmed an association between family history of esophageal or gastric cancer and risk of dysplasia (6). Similar associations have also been reported in other high-risk regions of China (7-9). These include not only associations between family history of UGI cancer and esophageal cancer risk but also associations between family history of these cancers and chromosomal aberrations (frequency of allelic loss; refs. 10, 11) or gene-environment interactions (7).
High-grade (moderate or severe) esophageal squamous dysplasia is also known to be associated with an increased risk of ESCC. In a 13-year follow-up study of a cohort of 682 endoscoped patients in Linxian, those who began with moderate dysplasia were ~10 times as likely and those with severe dysplasia were ~30 times as likely to develop ESCC as those who began with normal esophageal mucosa (12).

Polycyclic aromatic hydrocarbons (PAH), such as benzo[a]pyrene, are likely to play an etiologic role in ESCC. In low-risk areas, exposure to PAHs comes primarily from tobacco smoke, but exposure from non-tobacco sources may be more important in high-risk areas. Evidence that supports the role of PAHs in the high-risk areas of China includes a high prevalence of anthracotic periesophageal lymph nodes in squamous cell carcinoma resections (13), high levels of benzo[a]pyrene in uncooked and cooked staple food samples (14), and high concentrations of urine 1-hydroxypyrene glucuronide, a PAH metabolite and biomarker of recent exposure (15). This exposure may come from indoor air pollution caused by burning soft coal in unventilated rooms, and such coal burning was recently shown to be associated with a 2-fold increased risk for esophageal squamous dysplasia (6), the histologic precursor lesion of ESCC. In other high-risk areas for ESCC, such as southern Brazil and northeastern Iran, high levels of urine 1-hydroxypyrene glucuronide have also been detected (16, 17).

PAHs are ligands for the aryl hydrocarbon receptor (AhR). On binding, the AhR is translocated to the nucleus and binds the AhR nuclear translocator, resulting in the increased expression of the cytochrome P450 metabolism genes CYP1a1 and CYP1b1 (18-22), among others. This interrelationship represents part of the AhR/dioxin response element paradigm (19, 23). Studies find higher tissue expression of AhR in response to PAH exposure (22, 24-26), and tissue-specific metabolic activation or accumulation of PAHs increases DNA adduct formation and mutagenesis (27-29). Variability in gene induction along this pathway may be related to both ligand exposure and cancer risk (21, 23, 26, 30); for example, tobacco exposure can induce AhR and can increase lung cancer risk (31), and tobacco smoke can induce CYP1b1 in the gastrointestinal tract (32).

The current cross-sectional study measured gene expression of AhR, AhR repressor (AhRR), CYP1a1, and CYP1b1 in esophageal cell samples from adults living in the high ESCC risk region of Linxian, China. These participants and their samples were a subset of a recent cross-sectional esophageal screening study to detect squamous dysplasia or ESCC (33). All of these subjects completed a structured questionnaire that included information about home heating and family history of UGI cancer, and they all underwent esophageal cytology examination followed by chromoendoscopy with Lugol’s iodine staining and biopsy. Gene expression was compared between individuals who heated their homes without a chimney (a “high” indoor air pollution group) and those who did not heat their homes at all (a “low” indoor air pollution group) to assess the effect of this exposure on the AhR pathway. Expression of these genes was also compared between individuals with biopsy-proven high-grade esophageal squamous dysplasia and those with no histologic evidence of dysplasia to evaluate the association between these genes and the precursor lesions of ESCC and between those with and without a family history of UGI cancer.

Materials and Methods

Study Subjects and Procedures. The subjects in this study were a subset of the subjects who participated in the Cytology Sampling Study 2, a cross-sectional esophageal balloon cytology screening study in Linxian, which has been described previously in detail (6, 33). The Cytology Sampling Study 2 included 40- to 65-year-old volunteers who were apparently healthy and had no contraindications for balloon cytology or UGI endoscopy.

All subjects in the Cytology Sampling Study 2 completed a structured questionnaire based on information previously found or suspected to be associated with ESCC in this population, including family history of UGI cancer and living conditions such as the use of home heating, with or without a chimney. Each subject then underwent an esophageal balloon cytology examination followed by chromoendoscopy with Lugol’s iodine staining and biopsy. The cytologic sampler was either a mechanical balloon (Cytomesh Esophageal Cytology Device; Wilson-Cook Medical) or a traditional Chinese inflatable balloon (Cancer Institute of the Chinese Academy of Medical Sciences). All subjects gave written informed consent, and this study was approved by the institutional review boards of the Cancer Institute of the Chinese Academy of Medical Sciences and the U.S. National Cancer Institute.

After esophageal sampling, the balloon was placed in 40 mL saline in a 50 mL centrifuge tube, cut from its catheter, shaken, and transferred on ice to a central laboratory at the Cancer Institute of the Chinese Academy of Medical Sciences field station in Yaocun Commune, Linxian.

At the central laboratory, each sample was vortexed for 30 s to remove adherent cells from the balloon, the balloon was removed from the tube, and the remaining cell suspension was centrifuged at 1,500 rpm for 5 min. The excess supernatant was discarded and the cell pellet was resuspended in supernatant to ~1.0 mL final volume. Half of this concentrated cell solution was transferred to a 1.25 mL Eppendorf tube (Sarstedt) and snap-frozen in liquid nitrogen. The frozen samples were transported from the field laboratory on dry ice and stored at ~80°C until RNA extraction.

The subjects underwent endoscopy at the Cancer Institute of the Chinese Academy of Medical Sciences field station within 2 weeks after their cytology examinations. Endoscopy with Lugol’s iodine staining, with targeted biopsies of all unstained lesions and standard biopsies of normal-appearing mucosal sites, was done as described previously (33). The endoscopic biopsy slides were read separately by two pathologists (N.L. and S.M.D.) using criteria described previously (34). Discrepant results were adjudicated by joint review. Each subject’s esophageal disease status was categorized by his or her worst squamous endoscopic biopsy diagnosis. For this analysis, subjects with biopsy-proven moderate or severe squamous dysplasia were classified as having high-grade dysplasia, and subjects with biopsies showing only normal mucosa or esophagitis were classified as having no dysplasia.

Sample Selection. For the current study, the Cytology Sampling Study 2 subjects were selected in two ways: by...
their questionnaire responses related to indoor air pollution and by their histologic evidence of high-grade squamous dysplasia.

From the 720 Cytology Sampling Study 2 subjects with frozen esophageal cytology samples, 572 (79%) had frozen esophageal cytology samples available in our repository. Of these subjects, 344 (60%) could be stratified into either a “high” indoor air pollution group (n = 94, 16%) that heated their homes without a chimney or a “low” indoor air pollution group (n = 250, 44%) that did not heat their homes at all. The remaining 228 (40%) with available biologic samples used other methods to heat their homes, and they were not included in this analysis.

Of the 344 subjects in the two indoor air pollution groups, 51 (15%) had high-grade dysplasia and 234 (68%) had no evidence of dysplasia. The remaining 59 (17%) samples had other histologic diagnoses and thus were not included in this analysis.

All 51 subjects with high-grade dysplasia were included, with 23 (45%) representing the “high” indoor air pollution group and 28 (55%) the “low” indoor air pollution group. Similarly, all 49 (7%) subjects without dysplasia who were in the “high” indoor pollution group were selected for inclusion. A random subset of equal size (49 patients) and gender proportions (51% male) was selected from the 185 available subjects without dysplasia who were in the “low” indoor air pollution group.

Thus, 149 participants were selected based on sample availability, biopsy diagnosis, and questionnaire data including 23 with high-grade dysplasia and 49 without dysplasia who heated their homes without a chimney (the “high” indoor air pollution group) and 28 with high-grade dysplasia and 49 without dysplasia who did not heat their homes (the “low” indoor air pollution group).

Sixty-four (44%) of these subjects had a family history of UGI cancer (Table 1).

### RNA Extraction
A 50 μL aliquot of each frozen esophageal cell sample was thawed by the addition of 10 μL Arcturus Picopure extraction buffer under RNase-free conditions (Picopure Isolation Kit; Arcturus). RNA isolation included on-column DNase treatment of all samples. The RNA was then eluted into 30 μL of the provided Arcturus elution solution. Quantitation and purity check was done on 2 μL of each sample by spectrophotometer (NanoDrop). A260/280 quality analysis was done on 1 μL of each sample by Agilent Bioanalyzer (picochip) and reported as a RNA integrity number on a scale of 1 to 10, with 10 representing maximum quality. Samples were run in duplicate.

The mean (SD) RNA yield per sample was 300.1 (581.1) ng, and the mean (SD) RNA concentration per sample was 15.0 (29.0) ng/μL. Post-extraction RNA quality for all the samples, as determined by the RNA integrity number, had a mean (SD) of 2.9 (1.5). Both RNA concentration and quality were deemed suitable for quantitative reverse transcription-PCR expression analysis, because they were similar to the values obtained from a set of successfully amplified pilot samples (data not shown).

### Quantitative Reverse Transcription-PCR First-Strand cDNA Synthesis
The SuperScript III First-Strand Synthesis System for reverse transcription-PCR (Invitrogen) was used to synthesize cDNA from total RNA in a 96-well microtiter plate format. A minimum of 1 ng total RNA served as the template for first-strand cDNA synthesis and RNase OUT (Invitrogen) was included in the reaction to prevent degradation of the target RNA by contaminating ribonucleases. Incubations were carried out in a thermocycler at the following conditions: 50°C for 50 min, followed by 85°C for 5 min followed by the addition of RNase H, with a continued incubation for 20 min at 37°C.

### Analysis of Gene Expression by Quantitative PCR
Quantitative PCR analysis was done using TaqMan probes (Applied Biosystems) according to the manufacturer’s instructions in 10 μL final volumes in 384-well microtiter plates. Thermocycling conditions, using an Applied Biosystems ABI-7900 SDS, were as follows: 50°C for 2 min, 95°C for 10 min, 95°C for 40 cycles of 15 s, and 60°C for 1 min. The primers for the genes of interest, AhR, AhRR, Cyp1a1, and Cyp1b1, and an 18S endogenous control gene were purchased using the Applied Biosystems Assay-on-Demand program; the sequences of these genes/probes are proprietary in nature (Applied Biosystems). Raw data from the quantitative PCR run were exported into a comparative Ct analysis workbook. In our criterion for selecting real target amplification, the Ct value (signal above cycle threshold) had to be ≥33 Ct values and had to be detected 3 Ct values earlier than the negative controls. Quantification of mRNA was done using a ΔΔCT log2 transformation approach. The mRNA expression of each target gene was normalized to the expression of the 18S control gene and then it was compared with the Universal Human Reference RNA sample (Stratagene) to yield a relative mRNA expression value (relative to the reference sample). This ΔΔCT sample value (ΔΔCT = ΔCT-sample – ΔCT-reference) was then modified as follows: if 2

### Table 1. Demographic and lifestyle factors

<table>
<thead>
<tr>
<th>Total</th>
<th>Indoor air pollution</th>
<th>Worst histologic diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Samples</td>
<td>147</td>
<td>71</td>
</tr>
<tr>
<td>Mean (SD) age</td>
<td>54 (5.0)</td>
<td>54 (5.1)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>74 (50)</td>
<td>38 (54)</td>
</tr>
<tr>
<td>Smoking, * yes (%)</td>
<td>48 (33)</td>
<td>24 (34)</td>
</tr>
<tr>
<td>Family history, † yes (%)</td>
<td>64 (44)</td>
<td>35 (49)</td>
</tr>
</tbody>
</table>

*Smoking: high versus low indoor air pollution, Pearson's χ2 test P = 0.77 and with versus without dysplasia, P = 0.32.
†Family history of cancer: high versus low indoor air pollution P = 0.17 and with versus without dysplasia P = 0.03.
‡UGI cancer in one or more first-degree relatives (father, mother, siblings, or children).
AhR and Family History of UGI Cancer

NOTE: Pearson’s χ² test AhR P = 0.02; P > 0.2 for all other genes.

### Results

Table 2 shows the distribution of selected demographic and lifestyle factors in all subjects, in those with high and low exposure to indoor air pollution, and in those with and without high-grade esophageal squamous dysplasia. The analytical cohort consisted of 147 subjects with an average age of 54 years, with nearly equal representation of men and women across the heating and dysplasia categories. Slightly more of the subjects with high indoor pollution and high-grade dysplasia were smokers, and significantly more of those with high-grade dysplasia had a family history of cancer (P = 0.03, Pearson’s χ² test).

The expression of each transcript was evaluated in duplicate in neighboring wells. The coefficient of variation of these duplicates was <2.4% for all genes. Expression of the 18S housekeeping gene was measurable in all 147 samples. AhR gene expression was measurable in 85 (58%) of the 147 samples, but AhRR, CYP1a1, and CYP1b1 gene expression was measurable in only 25 (17%), 13 (9%), and 14 (10%) of the samples, respectively.

Table 3. AhR relative gene expression, by family history of UGI cancer, dysplasia, and indoor air pollution exposure status

<table>
<thead>
<tr>
<th>Category</th>
<th>No. subjects</th>
<th>Fold change in AhR gene expression (interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without a family history of UGI cancer</td>
<td>83</td>
<td>1.0 [-18,000 (-18,000, -1,036)]</td>
</tr>
<tr>
<td>With a family history of UGI cancer</td>
<td>64</td>
<td>9.2 [-1,964 (-18,000, -610)]</td>
</tr>
<tr>
<td>Without esophageal dysplasia (reference)</td>
<td>97</td>
<td>1.0 [-2,434 (-18,000, -711)]</td>
</tr>
<tr>
<td>With high-grade esophageal dysplasia</td>
<td>50</td>
<td>0.1 [-18,000 (-18,000, -847)]</td>
</tr>
<tr>
<td>Indoor air pollution with low exposure</td>
<td>76</td>
<td>1.0 [-3,714 (-18,000, -1,010)]</td>
</tr>
<tr>
<td>Indoor air pollution with high exposure</td>
<td>71</td>
<td>1.2 [-3,015 (-18,000, -623)]</td>
</tr>
<tr>
<td>Nonsmoker (reference)</td>
<td>99</td>
<td>1.0 [-4,904 (-18,000, -623)]</td>
</tr>
<tr>
<td>Smoker</td>
<td>48</td>
<td>2.0 [-2,386 (-18,000, -1,026)]</td>
</tr>
<tr>
<td>Male (reference)</td>
<td>74</td>
<td>1.0 [-3,906 (-18,000, -1,351)]</td>
</tr>
<tr>
<td>Female</td>
<td>73</td>
<td>1.4 [-2,668 (-18,000, -533)]</td>
</tr>
</tbody>
</table>

NOTE: Wilcoxon rank-sum and linear regression tests: family history of cancer P = 0.02 and P = 0.02, esophageal dysplasia P = 0.3 and P = 0.1, indoor air pollution P = 0.6 and P = 0.6, smoking status P = 0.4 and P = 0.4, and gender P = 0.04 and P = 0.2.

log_{2} ΔACT sample value.

### Discussion

The low expression of AhR, CYP1a1, and CYP1b1 prevented detailed comparisons, but expression of CYP1a1 tended to be more common among those with a family history of cancer (12.5% versus 6%; Table 2).

Subjects with a family history of UGI cancer had a relative AhR expression >9-fold higher than those with a negative family history of these cancers (P = 0.02, Wilcoxon rank-sum test; Table 3). This association was also positive when tested by univariate linear regression using a family history of UGI cancer as a dichotomous variable to predict AhR expression (P = 0.02). Because more of the subjects with a positive family history had high-grade dysplasia than those with a negative family history (56% versus 44%, respectively; P = 0.03, Pearson’s χ² test) and those with a positive family history of UGI cancer tended to have higher RNA concentrations than those with a negative family history [median (interquartile range), 8.7 (1.9-19) versus 3.4 (1.0-12) ng/μL, respectively; P = 0.05], the association between family history and AhR expression was tested and persisted after adjusting for dysplasia status and sample RNA concentration (P = 0.02). It was also unaltered by the inclusion of variables for indoor air pollution category or smoking status.

Exposure to high levels of indoor air pollution, the presence of high-grade squamous dysplasia, and other covariates of potential interest, including age, gender, and smoking, were not associated with AhR expression in linear regression models (P ≥ 0.14).

PAHs are formed during the incomplete combustion of carbon, and several are classified as human carcinogens by
IARC and the U.S. National Toxicology Program (35, 36). Urine 1-hydroxypyrene glucuronide reflects recent PAH exposure, and using this marker, we have shown that several populations at high risk for ESCC in China, Iran, and Brazil are highly exposed to PAHs (15-17). Consequently, studies on the biological effects of this exposure in high-risk populations and its potential relationship with precursor lesions and invasive cancers are needed to further elucidate the association between PAH exposure and ESCC.

The observation that a positive family history of cancer is associated with increased cancer risk is well accepted, and it is particularly evident in gastrointestinal, genitourinary, and gynecologic cancers (2-4). This predisposition may be attributable to an inherited genetic susceptibility that, in some instances, is modified by the environment, that is, a gene-environment interaction (4). One such example is the association between tobacco use and specific cytochrome P450–related enzyme genotypes that predispose the esophagus of smokers to an even higher risk for DNA damage or cancer (37, 38). A recent 15-year prospective study in Linxian has shown a significant association between a positive family history of UGI cancer and an increased risk of both esophageal and gastric cancer (5), and a separate case-control study showed an association between family history of these cancers and risk of esophageal squamous dysplasia (6).

The current study evaluated the expression of genes coding for proteins that are related to the carcinogenic effect of PAH exposure, including AhR, CYP1a1, CYP1b1, and AhRR, which acts as an AhR antagonist (18). The expression of these genes was evaluated in epithelial cell samples from the esophagus, the target organ of interest in the Linxian population, which has known environmental PAH exposure and high rates of ESCC. Our data showed that median AhR expression was significantly higher in individuals with a positive family history of UGI cancer but was not associated with apparently higher levels of PAH exposure or the presence of high-grade esophageal squamous dysplasia, the precursor lesion of ESCC. Expression levels of AhRR, CYP1a1, and CYP1b1 were all low. These results suggest that individuals in this population with a family history of UGI cancer may be more susceptible to the detrimental effects of PAH exposure, including PAH-induced cancer.

Median AhR expression was not higher among individuals who heated their homes without a chimney or among tobacco smokers, groups that appeared to be exposed to more PAHs. However, our assessments of these exposures were relatively simple and a more accurate measurement of environmental PAH exposure at the time of sample collection may be needed to test this association more completely. Median AhR expression was also not higher among subjects with high-grade squamous dysplasia possibly because the esophageal balloons sample the entire esophageal epithelium and may not accurately detect increased expression that is found only in focal mucosal lesions. In contrast, differences in AhR expression related to familial predisposition would be expected to be present in all cells, so it should be more easily seen in balloon samples.

The current study was limited by the number of samples with expression below our limit of detection. This was most significant for AhRR and the cytochrome P450 genes. The lack of detectable expression for these genes of interest in the setting of detectable levels of a housekeeping gene is indicative of minimal to no expression (39) and is consistent with previous reports that these genes are variably expressed in the esophagus (40, 41). The interpretation that this is a real finding is supported by the fact that the efficiency of our short quantitative reverse transcription-PCR products should be relatively ‘independent’ of RNA quality (39), and any potential effect of suboptimal RNA quality would have been minimized after normalization of the target gene expression results to the 18S endogenous control and the Universal Human Reference sample. Finally, the positive association, which we found between AhR expression and family history of cancer, persisted with a variety of statistical approaches.

Advantageous aspects of our cell sampling method also deserve mention. This minimally invasive approach samples the entire mucosal epithelium of the target organ of interest and theoretically provides an integrated assessment of its exposure and biological potential. Sampling the target organ of interest is important because induction of gene expression is frequently cell and tissue-specific (42, 43). Our cell sampling method also avoids problems that may occur when sampling is limited to neoplastic tissue, such as the inhibition of cytochrome P450 enzyme expression by inflammatory cytokines associated with such lesional tissue (44) and the fact that PAHs may induce xenobiotic-metabolizing enzymes more potently in normal squamous cells than in premalignant or tumor cells (45). The cell sampling method used in our study avoids these potential pitfalls and may be suitable for inclusion in other epidemiologic studies, especially those looking for variation in constitutive traits.

In summary, we measured gene expression of AhR and related genes in esophageal epithelial cell samples from subjects in a Chinese population at high risk for ESCC, and we compared expression levels in subjects who differed by apparent PAH exposure, by the presence or absence of esophageal squamous dysplasia, the precursor lesion of ESCC, and by family history of UGI cancer. We found significantly higher AhR expression in subjects with a family history of UGI cancer but no difference in this expression between subjects with different levels of indoor air pollution or the presence or absence of esophageal squamous dysplasia. This is the first report of an association between AhR expression and family history of cancer in humans, and it supports the idea of a familial predisposition to the deleterious effects of PAH exposure in this high-risk population.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Acknowledgement
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