Health risks associated with the active use of tobacco have been documented extensively over many years. After the first Surgeon General’s report on smoking and health in 1964, the prevalence of cigarette smoking in the United States began a gradual decline (Department of Health and Human Services [DHHS] 2004), although the use of tobacco continues to be an important problem and remains the leading preventable cause of death and disability in the United States (DHHS 2004). In addition to mainstream smoke that is inhaled by the smoker, burning cigarettes also generate secondhand smoke (SHS; also sometimes referred to as environmental tobacco smoke [ETS]) that is formed from smoke exhaled into the environment from the smoldering tip of the cigarette, mixed with smoke exhaled by the smoker (National Research Council [NRC] 1986). Involuntary smoking results when nonsmokers are exposed to SHS, and health risks for nonsmokers posed by involuntary smoking were gradually realized. As early as 1972, the topic of SHS and the potential risk faced by nonsmokers exposed to SHS were noted in a Surgeon General’s report addressing the use of tobacco (DHHS 1972). An important further impetus for investigations regarding adverse health effects from SHS exposure resulted from the 1986 Surgeon General’s report (DHHS 1986), which for the first time focused on the health risks of SHS, and also from two influential reports by the National Research Council (NRC 1986) and the U.S. Environmental Protection Agency (U.S. EPA 1992). Both reports concluded that exposure to SHS causes lung cancer in nonsmokers and has other adverse effects in both adults and children. Several subsequent reports have confirmed and extended this link between SHS and adverse health effects (Jaakola and Samet 1999; National Cancer Institute 1999), which may include cancer, asthma, respiratory infections, decreased pulmonary function, and cardiovascular disease.

Despite the increasing awareness that SHS represents an important public health concern, the extent of the problem was initially difficult to measure because data on the exposure of nonsmokers were limited and often depended solely on self-reported exposure or on inferences, such as living with a smoker, rather than on direct measurements. However, objective biomarkers of exposure to tobacco have been identified and validated (Benowitz 1983, 1996; Jarvis et al. 1988), and an expert panel convened to review the prospects for biomarker measurements as an index of SHS exposure concluded that plasma cotinine was the marker of choice (Watts et al. 1990). Cotinine, the primary proximate metabolite of nicotine, is specific for exposure to tobacco, and it is preferred as a marker over nicotine because the half-life of cotinine in plasma is longer than that of nicotine. Serum cotinine can mark the exposure of an individual to tobacco only over the previous few days, and it is subject to interindividual variations in the metabolism of nicotine. However, these limitations are not substantial drawbacks when comparing mean values from groups of people, and in a review, Benowitz (1996) concluded that the evidence supports cotinine measurements providing “a valid and quantitative measure of average human ETS exposure over time.”

The first national survey of SHS exposure of the entire U.S. population based on serum cotinine measurements was conducted as part of the Third National Health and Nutrition Examination Survey (NHANES III) that covered the period of 1988–1994. NHANES III consisted of two phases, and we previously reported the results of cotinine measurements conducted with > 10,000 participants ≥ 4 years of age from phase 1, extending from 1988 through 1991 (Pirkle et al. 1996). Our results at that time indicated widespread exposure of the population to tobacco smoke. Overall, 88% of nonsmokers in the U.S. population in that study were found to have detectable levels (≥ 0.050 ng/mL) of cotinine in their blood, and certain groups of nonsmokers, including blacks, males, and children, were found to be at elevated risk of exposure based on their serum cotinine levels (Pirkle et al. 1996).

After phase 1, additional data were acquired during the continuation of NHANES III in phase 2, which extended from 1991 through 1994. No further studies were conducted during 1995–1998, but NHANES resumed in 1999 and has been continuous from that time onward, providing a new

Key words: biomarker, cotinine, environmental tobacco smoke, ETS, health and nutrition examination survey, NHANES, secondhand smoke, SHS, tandem mass spectrometry. Envir Health Perspect 114:853–858 (2006). doi:10.1289/ehp.8850 available via http://dx.doi.org/ [Online 2 February 2006]
sampling of the U.S. population every 2 years. Serum cotinine was measured in NHANES III (1988–1994), in NHANES 1999–2000, and NHANES 2001–2002. Thus, we now have acquired data from NHANES for >10 years that represent exposures after our initial report from the time period 1988–1991 (Pirkle et al. 1996). We report here the analysis of these data extending from 1988 through 2002, which indicates a decreasing trend in SHS exposure of nonsmokers in the United States, most likely reflecting extensive efforts made by the public health community during this time to reduce smoking in the home and the exposure of nonsmokers in public places. However, our results also indicate that two groups in the population, blacks and children, show relatively higher levels of SHS exposure during this time, suggesting that further work should provide special focus on these at-risk groups.

Materials and Methods

NHANES is a survey conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC), which is designed to examine a nationally representative sample of the U.S. civilian, noninstitutionalized population based on a complex, stratified, multistage probability cluster sampling design. The protocols included a home interview followed by a physical examination in a mobile examination center (MEC). These studies were approved by the National Center for Health Statistics Institutional Review Board, and all subjects (or their parent or guardian) provided informed consent before participation. During examination in the MEC, blood samples were drawn for serum cotinine analysis from all participants ≥4 years of age during NHANES III, and from participants ≥3 years of age in subsequent surveys. However, to maintain comparability among surveys in our present analyses, we have included only participants ≥4 years of age in each study interval.

NHANES III consisted of two phases, phase 1 extending from 1988 to 1991, and phase 2 from 1991 through 1994. In 1999, NHANES began operation on a continual basis, providing a new sampling of the U.S. population every 2 years. The data reported here were acquired during NHANES III, phases 1 and 2, and in NHANES 1999–2000 and NHANES 2001–2002. Thus, they cover four distinct intervals within an overall time period of 14 years, from 1988 through 2002.

Participants. Nonsmokers were defined in this study as persons whose serum cotinine concentration was ≤10 ng/mL. Previous comparisons in NHANES III demonstrated little difference when cutoffs of either 10 or 15 ng/mL were used (Pirkle et al. 1996). Race/ethnicity of the participants based on self-report was categorized as non-Hispanic white, non-Hispanic black, Mexican American, or other. The race/ethnicity category of “other” was included in mean and percentile estimates for the total population, but not in the regression models when race was included as a covariate. Age was the age in years at the time of interview. A total of 29,849 participants were included in this study.

Cotinine analysis. We measured serum cotinine by a high-performance liquid chromatography/atmospheric-pressure ionization tandem mass spectrometry (LC/MS/MS) method that has been described previously (Bernert et al. 1997, 2000). Briefly, serum samples were equilibrated with a trideuterated cotinine internal standard and then extracted using ChemElute columns (Varian, Harbor City, CA), concentrated, and analyzed by LC/MS/MS using atmospheric pressure chemical ionization. The limit of detection (LOD) for most of these analyses was 0.050 ng/mL in serum, and we periodically evaluated the results to assure that sensitivity at this level was maintained. However, as a result of continuing method improvements, including the introduction of a newer, more sensitive mass spectrometer, the LOD was lowered to 0.015 ng/mL during the analysis of samples from NHANES 2001–2002. Approximately 85% of the samples from 2001–2002 were analyzed using the newer, more sensitive LOD. For comparison, we also analyzed the 2001–2002 samples using an LOD of 0.050 ng/mL and found little difference in estimates for means and percentiles.

This LC/MS/MS method for serum cotinine has been continuously maintained in a single laboratory at the CDC and has analyzed NHANES samples collected since 1988. Both bench and blind serum pools are routinely included with each analytic run as part of the quality assurance program for this method, and additional pools spiked with known amounts of cotinine perchlorate are analyzed periodically to confirm both precision and accuracy of the assay. Because of ongoing improvements in the methodology and because of the potential for monitoring population trends in exposure, we have made a particular effort to assure continuity, stability, and uniformity in our analyses over an extended time period. As part of that effort, residual samples are retained from older serum quality control pools when new pools are prepared, and aliquots of the older pools are periodically reexamined to help confirm stability of the method. We have previously noted that serum cotinine is stable when stored at –60°C (Bernert et al. 2000). Three pools at levels of 0.268 ng/mL, 1.86 ng/mL, and 207 ng/mL have been measured periodically from 1990 through 2004 in this manner, and those data confirmed that no systematic drift has occurred in our measurement of serum cotinine during this time.

Statistical methods. All regression models were fitted using SUDAAN PROC REGRESS (Research Triangle Institute, Research Triangle Park, NC). All analyses incorporated sampling weights that adjusted for unequal probabilities of selection. The log of serum cotinine was used as the dependent variable because of the log-normal distribution of serum cotinine that has been previously described (Pirkle et al. 1996). Separate models were fitted for each time period. For each of the models, the following independent variables were used: sex (males, females), race/ethnicity (non-Hispanic whites, non-Hispanic blacks, Mexican Americans), and age group (4–11, 12–19 and ≥20 years). Initial models also included all possible two-way interactions. Geometric means computed for each age group, race/ethnicity, and sex were adjusted for all other variables in each model. Changes over time were evaluated by using a two-tailed t-test to compare model adjusted means of the log-transformed results for the periods 1988–1991 and 1999–2002. The degrees of freedom and SEs for these tests correspond to those associated with the model-adjusted means. In all cases, a null hypothesis probability level of ≤5% was taken to indicate statistical significance.

Results

Figure 1 shows the geometric mean (and 95% confidence interval [CI]) for serum cotinine concentrations in the U.S. population of nonsmokers of tobacco over the time period 1988–2002. The four time periods included in this and subsequent figures are 1988–1991, 1991–1994, 1999–2000, and 2001–2002; the data in Figure 1 are plotted at the approximate midpoint of each interval. These data demonstrate a consistent decrease over time, with a decline of approximately 70% observed between the first and last survey periods. In NHANES III, phase 1, nearly all nonsmokers (88%) had concentrations of cotinine
an exception, however, for which children’s values were not significantly higher than those of adults in any of the time intervals (Figure 2). Serum cotinine levels in NHANES also clearly differed by race/ethnicity. During each time period, the order for adjusted mean cotinine concentrations remained Mexican American < non-Hispanic white < non-Hispanic black, although the mean levels for Mexican-American and non-Hispanic white nonsmokers were not significantly different in the most recent (2001–2002) time period. Non-Hispanic blacks had mean cotinine concentrations significantly higher than those of either Mexican Americans or non-Hispanic whites during each time interval. The only exception was for non-Hispanic whites 4–11 years of age, for whom the difference from non-Hispanic blacks approached but did not achieve statistical significance (p = 0.059).

Figure 4 summarizes results by age and sex. A modest difference by sex was noted among adults ≥ 20 years of age, with men having significantly higher mean serum cotinine concentrations than did women in each time interval. Cotinine levels were also slightly higher in male adolescents (12–19 years of age) in every case, but those differences were not statistically significant. This pattern was reversed among the younger children in the 4–11 age group, with girls having consistently higher mean serum cotinine levels than did boys, although again, the differences were small and were not significant.

Percentiles for serum cotinine in nonsmokers in three main age groups are given in Table 1. Median concentrations tended to be higher among children and adolescents in each interval, with the greatest differences between adults ≥ 20 years of age versus younger participants. In addition, the decreases in concentrations from 1988 to 2002 were much less evident among individuals with the greatest exposure. Among adults, levels denoting the 95th percentile decreased only about 40% during this time, whereas the 95th percentile values among children and adolescents remained virtually unchanged throughout the entire period from 1988 through 2002. Similar results were seen for the most highly exposed individuals among non-Hispanic blacks, where again the 90th and 95th percentiles showed little decrease for the entire time period from 1988 to 2002 (Table 2).

Discussion
Comparison of nonsmoker serum cotinine concentrations acquired from NHANES over a period of 14 years clearly demonstrates a substantial decline, averaging approximately

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Figure 2. Serum cotinine adjusted geometric means (95% CI) by age and race/ethnicity—exposure of nonsmokers in the U.S. population to SHS, 1988–2002: (A) 4–11 years of age, (B) 12–19 years of age, and (C) ≥ 20 years of age. The data are plotted at the approximate midpoint for each of the four separate time intervals, with the individual race/ethnicity groups offset for clarity.

Figure 3. Serum cotinine adjusted geometric means (95% CI) by race/ethnicity and sex—exposure of nonsmokers in the U.S. population to SHS, 1988–2002: (A) non-Hispanic white, (B) non-Hispanic black, and (C) Mexican American. The data are plotted at the approximate midpoint for each of the four separate time intervals, with the two sex groups offset for clarity.

Figure 4. Serum cotinine adjusted geometric means (95% CI) by age and sex—exposure of nonsmokers in the U.S. population to SHS, 1988–2002: (A) 4–11 years of age, (B) 12–19 years of age, and (C) ≥ 20 years of age. The data are plotted at the approximate midpoint for each of the four separate time intervals, with the two sex groups offset for clarity.
Table 1. Percentile points for serum cotinine in nonsmokers by age.

| Age group                  | Selected percentile (95% CI) |
|----------------------------|-----------------------------|
|                             | 1988–1991       | 1991–1994       | 1999–2000       | 2001–2002       |
| Children (4–11 years of age) |                             |                 |                 |                 |
| 50th percentile             | 0.262 (0.194–0.401)       | 0.211 (0.167–0.254) | 0.110 (0.062–0.173) | 0.067 (0.038–0.118) |
| 75th percentile             | 1.010 (0.791–1.29)        | 0.935 (0.769–1.10) | 0.489 (0.264–1.06) | 0.495 (0.275–0.934) |
| 90th percentile             | 2.162 (1.72–2.75)         | 2.40 (2.04–2.85)  | 1.82 (0.91–3.47)  | 2.03 (1.42–2.53)  |
| 95th percentile             | 3.330 (2.62–3.82)         | 3.58 (2.95–4.49)  | 3.44 (1.34–4.79)  | 3.05 (2.44–3.37)  |
| No.                         | 1.839               | 2.080           | 1.065           | 1.278           |
| Adolescents (12–19 years of age) |                             |                 |                 |                 |
| 50th percentile             | 0.247 (0.204–0.340)       | 0.208 (0.152–0.250) | 0.107 (0.080–0.160) | 0.051 (0.032–0.109) |
| 75th percentile             | 0.848 (0.672–1.17)       | 0.658 (0.530–0.999) | 0.540 (0.428–0.660) | 0.352 (0.189–0.580) |
| 90th percentile             | 2.140 (1.66–2.62)        | 1.92 (1.75–2.34)  | 1.65 (1.48–1.92)  | 1.53 (1.09–1.21)  |
| 95th percentile             | 3.180 (2.48–3.23)        | 3.06 (2.49–3.29)  | 2.56 (2.09–3.39)  | 3.12 (2.47–3.99)  |
| No.                         | 1.094               | 1.418           | 1.773           | 1.902           |
| Adults (≥20 years of age)   |                             |                 |                 |                 |
| 50th percentile             | 0.204 (0.178–0.233)       | 0.128 (0.111–0.151) | 0.035 (0.036–0.066) | 0.034 (0.024–0.038) |
| 75th percentile             | 0.522 (0.463–0.613)       | 0.353 (0.308–0.417) | 0.167 (0.140–0.193) | 0.113 (0.090–0.150) |
| 90th percentile             | 1.350 (1.11–1.61)        | 0.948 (0.822–1.18) | 0.630 (0.530–0.810) | 0.623 (0.485–0.770) |
| 95th percentile             | 2.370 (1.93–2.80)        | 1.73 (1.45–2.18)  | 1.48 (1.28–1.66)  | 1.38 (1.11–1.84)  |
| No.                         | 5.157               | 5.684           | 3.052           | 3.407           |

Table 2. Percentile points for serum cotinine in nonsmokers by race/ethnicity.

| Race/ethnicity          | Selected percentile (95% CI) |
|-------------------------|-----------------------------|
|                         | 1988–1991       | 1991–1994       | 1999–2000       | 2001–2002       |
| Non-Hispanic white     |                             |                 |                 |                 |
| 50th percentile         | 0.199 (0.172–0.234)       | 0.129 (0.109–0.158) | 0.050 (0.035–0.070) | 0.035 (0.022–0.042) |
| 75th percentile         | 0.573 (0.467–0.698)       | 0.384 (0.305–0.493) | 0.210 (0.150–0.308) | 0.115 (0.084–0.174) |
| 90th percentile         | 1.480 (1.17–1.86)        | 1.30 (0.97–1.61)  | 0.916 (0.621–1.29) | 0.705 (0.533–1.06)  |
| 95th percentile         | 2.500 (2.00–2.97)        | 2.30 (1.92–2.66)  | 1.85 (1.35–2.74)  | 1.81 (1.14–2.23)  |
| No.                     | 3.150               | 3.023           | 2.926           | 2.798           |
| Non-Hispanic black      |                             |                 |                 |                 |
| 50th percentile         | 0.458 (0.326–0.608)       | 0.338 (0.236–0.394) | 0.130 (0.110–0.144) | 0.130 (0.105–0.159) |
| 75th percentile         | 1.160 (0.943–1.444)       | 0.942 (0.825–1.06) | 0.493 (0.350–0.599) | 0.556 (0.436–0.749) |
| 90th percentile         | 2.430 (2.05–2.84)        | 2.06 (1.87–2.29)  | 1.39 (1.14–1.66)  | 1.74 (1.54–1.98)  |
| 95th percentile         | 3.460 (3.14–4.04)        | 3.08 (2.78–3.46)  | 2.26 (1.78–3.19)  | 3.01 (2.42–3.78)  |
| No.                     | 1.850               | 2.871           | 1.303           | 1.557           |
| Mexican American        |                             |                 |                 |                 |
| 50th percentile         | 0.173 (0.136–0.221)       | 0.101 (0.080–0.125) | —               | 0.036 (0.025–0.060) |
| 75th percentile         | 0.437 (0.327–0.559)       | 0.314 (0.246–0.380) | 0.136 (0.110–0.170) | 0.157 (0.080–0.308) |
| 90th percentile         | 1.130 (0.974–1.252)       | 0.904 (0.890–1.14) | 0.506 (0.372–0.738) | 0.670 (0.418–1.19)  |
| 95th percentile         | 2.330 (1.49–3.56)        | 1.89 (1.42–2.47)  | 1.24 (0.90–1.71)  | 2.35 (1.14–2.98)  |
| No.                     | 2.807               | 2.794           | 2.196           | 1.843           |
that the difference in serum cotinine did not persist after adjustment for self-reported exposure to SHS. Sexton et al. (2004) also found that questionnaires, time-activity data, and cotinine measurements all indicated higher SHS exposure among African-American children. Thus, the consistently higher serum cotinine levels for black nonsmokers in NHANES appear to reflect higher SHS exposure, although the extent to which differences in metabolism may confound these estimates remains uncertain.

Exposure of nonsmokers to SHS also appears to have declined in other countries besides the United States during this time period, at least based on self-report. For example, Borland et al. (1999) described annual surveys of approximately 2,500 adults conducted in Victoria, Australia, from 1989 to 1997. The percentage of respondents reporting that they did not smoke in the presence of children and that visitors were discouraged from smoking in the home both approximately doubled during this time. In addition, the percentage of indoor workers in Victoria protected by restrictions on smoking in the workplace increased from 17% to 66% between 1988 and 1995. Within 1 year after Finland passed its Tobacco Control Act in 1995 prohibiting smoking in the workplace in all joint and public premises, workers reporting no ETS exposure in the workplace increased almost 3-fold, from 19.2% to 54.2% (Heloma et al. 2001).

Most studies finding decreased exposure to SHS over time have relied on self-reports. However, Jarvis et al. (2000) have reported a substantial decrease during the 1990s in the exposure of British school children to SHS as assessed by salivary cotinine measurements. They monitored secondary school children 11–15 years of age from 1988 through 1996 and found that their salivary cotinine levels decreased by almost 50% during that time. They attributed the decline to both the decrease in prevalence of smoking among young adults with children and the increased restrictions in Great Britain on smoking in public places. However, Jarvis et al. (2000) found only small declines among children whose parents smoked, suggesting that cessation rather than smokers simply avoiding exposure of children in the home was the primary factor driving the decline.

Our study has several strengths and some limitations. The data were taken from several large surveys conducted over a period of 14 years, evaluating national samples of individuals who were representative of the entire U.S. civilian, noninstitutionalized population, and included a total of nearly 30,000 nonsmokers. We used a sensitive and specific method for serum cotinine analysis, and all assays were conducted under uniform and rigorously controlled conditions. Repetitive analyses of common samples over time confirmed the absence of any unusual variations or drift in the analytic method. Thus, the substantial decreases in serum cotinine we observed over time most likely reflect corresponding decreases in exposure of nonsmokers to SHS. Nevertheless, serum cotinine has limitations as an exposure marker because it can monitor exposures only over the previous few days, and because nicotine metabolite differences among groups may influence the concentrations observed. However, despite the relatively short half-life of cotinine, measures of central tendency among groups based on large numbers of individuals should provide reasonable estimates of group steady-state levels. Although the differences we observed among ethnic/racial groups most likely reflect differences in exposure, metabolic influences cannot be excluded, and additional work is needed to evaluate the relative contributions of exposure and metabolism. Finally, a few occasional smokers could possibly have been included inadvertently among the more highly exposed participants in our study, because some infrequent smokers may have serum cotinine levels < 10 ng/mL. This factor is unlikely to have been significant among adults, and it is even less likely to have been influential among young children because few children in the 4–11 age group are active smokers.

Conclusion

Serum cotinine concentrations among nonsmokers in the U.S. population declined significantly during the 1990s. This decrease was found in all groups within the population and probably reflects the substantial progress made in reducing the exposure of nonsmokers to SHS during this time. Nevertheless, children and non-Hispanic blacks continue to show relatively higher serum cotinine concentrations, suggesting that these two groups in particular should be the focus of increased intervention efforts, and that additional work is needed to further encourage restrictions on smoking in the home, automobiles, and other locations when children are present.

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