Decline in the Prevalence of Spina Bifida and Anencephaly by Race/Ethnicity: 1995–2002

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Decline in the Prevalence of Spina Bifida and Anencephaly by Race/Ethnicity: 1995–2002

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ABSTRACT. *Objective.* **In an effort to reduce the occurrence of neural tube defects (NTDs), folic acid fortification of US enriched grain products was authorized by the Food and Drug Administration in March 1996 and required by January 1998. Fortification has been shown to result in an important decline in the prevalence of spina bifida and anencephaly in the general US population; however, fortification's impact on specific racial/ethnic groups has not been well described. We sought to characterize the decline in the prevalence of spina bifida and anencephaly among specific racial/ethnic groups during the transition to mandatory folic acid fortification in the United States.**

Methods. **Data from 21 population-based birth defects surveillance systems were used to examine trends in prevalence of spina bifida and anencephaly for specific racial/ethnic groups for the years 1995–2002. These years were divided into 3 periods: prefortification, optional fortification, and mandatory fortification. Race/ethnicity was defined as Hispanic, non-Hispanic white, and non-Hispanic black. Prevalence ratios were calculated for each racial/ethnic group by dividing the prevalence from the mandatory fortification period by the prevalence in the prefortification period.**

Results. **The study included data on 4468 cases of spina bifida and 2625 cases of anencephaly. The prevalence of spina bifida and anencephaly was highest among Hispanic births, followed by non-Hispanic white births, with the lowest prevalence among non-Hispanic black births. Significant declines in spina bifida and anencephaly were observed among Hispanic births and non-Hispanic white births. The prevalence ratio for non-Hispanic black births was of borderline significance for spina bifida and was not significant for anencephaly.**

Conclusions. **The results of this study suggest that folic acid fortification is associated with significant decreases in the prevalence of spina bifida and anencephaly among non-Hispanic white and Hispanic births. The magnitude of the reduction was similar between these 2 groups and was more pronounced for spina bifida than for anencephaly. The decline in the prevalence of spina bifida and anencephaly among non-Hispanic black births did not reach statistical significance. Efforts to increase folic acid consumption for the prevention of NTDs in pregnancies among women of all races/ethnicities should be continued, and studies to identify and elucidate other risk factors for NTDs are warranted.** *Pediatrics* **2005;116:580–586;** ***spina bifida, anencephaly, folic acid, fortification, race-ethnicity, neural tube defects.***

ABBREVIATIONS. NTD, neural tube defect; FDA, Food and Drug Administration; PR, prevalence ratio; CI, confidence interval; MTHFR, methylenetetrahydrofolate reductase.

Spina bifida and anencephaly, the 2 most common types of neural tube defects (NTDs), are estimated to affect ~3000 pregnancies each year in the United States.[1] The prevalence of NTDs has been shown to vary by race/ethnicity,[2–12] with the highest rates among women of Hispanic ethnicity and the lowest rates among black and Asian women.

Several studies, including 2 randomized, controlled trials[13,14] and a community intervention project,[15] have shown that periconceptional consumption of folic acid, a B vitamin, can reduce a woman's risk for having an infant with an NTD by 50% to 70%. In 1996, to increase folic acid consumption among women of childbearing age, the US Food and Drug Administration (FDA) mandated the fortification of enriched grain products with folic acid; compliance was mandatory by January 1998.[16] The impact of US folic acid fortification on the prevalence of NTDs was evaluated in 2 previous studies, which demonstrated a significant decrease in the prevalence of spina bifida, although the impact on anencephaly was less clear.[17,18] It has been estimated that ~4000 pregnancies in the United States were affected by NTDs annually before folic acid fortification. Recent estimates suggest that since folic acid fortification, 1000 fewer NTD-affected pregnancies occur in the United States each year.[1]

Because of the observed higher rates of NTD-affected pregnancies among Hispanic women, it was essential to determine whether the benefits of folic acid fortification varied by racial/ethnic group. This study used data from 21 population-based birth defects surveillance systems, collected as part of an NTD ascertainment project established by the National Birth Defects Prevention Network, to characterize the trends in prevalence of spina bifida and anencephaly among Hispanic, non-Hispanic white, and non-Hispanic black births during the transition to mandatory folic acid fortification in the United States.

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METHODS

The National Birth Defects Prevention Network's Neural Tube Defect Surveillance/Folic Acid Education Committee, with assistance from the Centers for Disease Control and Prevention, established an NTD Ascertainment Project to monitor trends in the prevalence of NTDs in the United States before and after folic acid fortification.[17] Population-based birth defects surveillance systems were eligible to participate in this study when they met the following criteria:

1. The program's surveillance method identified cases from sources other than birth certificates.
2. The program was able to report cases of anencephaly (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes 740.0–740.1) and spina bifida (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes 741.0 and 741.9 without 740.0–740.1) by quarter of birth year from 1995 to 2002 (first quarter: January to March; second quarter: April to June; third quarter: July to September; fourth quarter: October to December).
3. Cases and denominator data could be stratified into the following racial/ethnic categories: Hispanic, non-Hispanic white, and non-Hispanic black.

Programs were asked to adjust fetal deaths and elective pregnancy terminations to the expected date of delivery. Twenty-one birth defects surveillance systems (Arkansas, California, Colorado, Delaware, Georgia, Hawaii, Illinois, Iowa, Kentucky, Maryland, Missouri, New Jersey, New York, North Carolina, Oklahoma, Puerto Rico, South Carolina, Texas, Utah, West Virginia, and Wisconsin) met the eligibility criteria for participation in this study. Of these, 9 ascertained prenatally diagnosed NTD cases as part of their surveillance program.[17]

The addition of folic acid to fortified grain products was authorized by the FDA in March 1996 and required by January 1998. Because women need elevated levels of folic acid periconceptionally to prevent the occurrence of NTDs, data were stratified into 3 temporally defined groups that reflect pregnancies that are exposed to folic acid fortification during the fourth week of gestation, the critical time of neural tube closure.[19] Births from January 1995 through December 1996, whose mothers would not have been exposed to folic acid through fortification, were considered in the "prefortification period." Births from January 1997 through September 1998 were classified as the "optional fortification period" because, at the time of neural tube closure, folic acid fortification was voluntary but not required. October 1998 through December 2002 was classified as the "mandatory fortification period," when all women would have been consuming folic acid–fortified foods during their entire pregnancy.

Prevalence ratios (PRs) were calculated by dividing the birth prevalence during the mandatory fortification period by the birth prevalence during the prefortification period. The Taylor Series method was used to calculate 95% confidence intervals (CIs) for the PRs. Data were analyzed using the Statistical Analysis Battery for Epidemiologic Research.[20]

RESULTS

From 1995 through 2002, the NTD Ascertainment Project covered 2.7 million Hispanic births, 6.7 million non-Hispanic white births, and 1.7 million non-Hispanic black births, representing between 35% and 41% of all births in these racial/ethnic categories in the United States and Puerto Rico (Table 1). The study included 4468 cases of spina bifida and 2625 cases of anencephaly.

Table 2 shows the prevalence of spina bifida, stratified by racial/ethnic category, in the pre–, optional, and mandatory folic acid fortification time periods. The highest prevalence of spina bifida was observed among Hispanic births, and the lowest was among non-Hispanic black births. The prevalence of spina bifida decreased 36% among Hispanic births from the prefortification to the mandatory fortification period (PR: 0.64; 95% CI: 0.56–0.74) and 34% among non-Hispanic white births (PR: 0.66; 95% CI: 0.60–0.72). The magnitude of the decline among black births was borderline statistically significant (PR: 0.81; 95% CI: 0.67–1.00). The three-quarter moving average of the prevalence of spina bifida by racial/ethnic category is shown in Fig 1.

As with spina bifida, the highest prevalence of anencephaly in this study was observed among Hispanic births. This was followed by non-Hispanic white births and non-Hispanic black births (Table 3). The decline in the prevalence of anencephaly was similar among Hispanic births (PR: 0.74; 95% CI: 0.62–0.88) and non-Hispanic white births (PR: 0.71; 95% CI: 0.63–0.80). No significant decline was observed among non-Hispanic black births. Figure 2 shows the 3-quarter moving average of the prevalence of anencephaly by racial/ethnic category.

DISCUSSION

Studies that have investigated trends in the prevalence of NTDs during the transition to folic acid fortification have reported declines in spina bifida and anencephaly,[17,18] but trends by racial/ethnic category during the time of fortification have not previously been examined. The results of this study show statistically significant decreases in the prevalence during the mandatory fortification period of spina bifida and anencephaly among Hispanic and non-Hispanic white births but not among non-Hispanic black births.

The findings of our study were consistent with previous reports showing lower rates of NTD-affected pregnancies among women of non-Hispanic black race and higher rates of NTD-affected pregnancies among Hispanic women.[2–12] The reasons for the disparity in the rate of NTDs by race/ethnicity are unknown. In addition, the reasons for the disparity in declines in the prevalence of NTDs since folic acid fortification are unknown.

Eating habits and supplement-taking practices have been shown to differ among racial/ethnic groups[21–25] and could explain some of the differences in NTD risk. One study showed that Hispanic women had lower levels of folic acid awareness than non-Hispanic women.[26] In a study of women of all

TABLE 1. Percentage of All Births in the United States and Puerto Rico Covered by the NTD Ascertainment Project According to Race/Ethnicity: 1995–2002

Racial/Ethnic Category	No. of Births Covered	% of Total Births in United States and Puerto Rico
Hispanic	2 653 365	40.49
Non-Hispanic white	6 694 699	35.67
Non-Hispanic black	1 730 343	36.80

TABLE 2. Prevalence of Spina Bifida According to Race/Ethnicity Before and After Folic Acid Fortification

Racial/Ethnic Category	Prefortification (January 1995–December 1996)		Optional Fortification (January 1997–September 1998)		Mandatory Fortification (October 1998–December 2002)		PR (Mandatory/Prefortification)	95% CI
	No. of Cases	Prevalence (per 10 000)	No. of Cases	Prevalence (per 10 000)	No. of Cases	Prevalence (per 10 000)		
Hispanic	280	6.49	297	5.52	704	4.18	0.64	0.56–0.74
Non-Hispanic white	790	5.13	633	4.37	1249	3.37	0.66	0.60–0.72
Non-Hispanic black	142	3.57	92	2.53	281	2.90	0.81	0.67–1.00

ages from the 1994 to 1996 Continuing Survey of Food Intake by Individuals,[22] supplement use was significantly less likely to be reported among Hispanic women (45%) than among white women (57%), even after controlling for age, education, and household income. A study of pregnant patients who sought outpatient perinatal care[27] showed that Spanish-speaking women were significantly less likely to report preconceptional use of a multivitamin (3.8%) when compared with English-speaking women (22.4%). Food choices also differ by racial/ethnic group. Hispanic women are less likely to consume breakfast cereals, which can provide an important source of folic acid.[28] They also are more likely to use corn flour instead of wheat flour in cooking. In the United States, only companies that manufacture corn flour with an "enriched" label are required to fortify their product. In addition, some Hispanic women still purchase imported corn flour, which may or may not be fortified. Although many Latin American countries have fortified wheat flour with folic acid, efforts to standardize fortification of corn flour are still under way.[29]

Differences in folic acid consumption through diet and supplement use are unlikely to be the cause of the observed higher rate of NTD-affected pregnancies among Hispanic women and lower rates among non-Hispanic black women for several reasons. First, rates of folic acid consumption through supplements among black women are even lower than those among Hispanic women.[22] Second, data from the Third National Health and Nutrition Examination Survey report show that black women had lower dietary folate intake than either Mexican-American women or white women.[23] Finally, serum folate levels have been shown to be similar in Hispanic and non-Hispanic black women of childbearing age, both before and after fortification.[30] Thus, it is likely that other factors also contribute to the differences in NTD rates observed between these 2 populations.

Some of the observed disparity may reflect differences in genetic factors, such as in the genes associated with folate metabolism. One of these genes, methylenetetrahydrofolate reductase (*MTHFR*), encodes an enzyme that converts 5-methylenetetrahydrofolate into 5-methyltetrahydrofolate, the major circulating form of folate.[31] Two major polymorphisms in the *MTHFR* gene have been studied among different racial/ethnic groups, C677T and A1298C, and have been shown to reduce MTHFR activity. The presence of the C677T allele has been shown to increase the risk for NTDs in most populations; in a meta-analysis, the risk for spina bifida was increased both in infants (pooled odds ratio: 1.8; 95% CI: 1.4–2.2) and in mothers (pooled odds ratio: 2.0; 95% CI: 1.5–2.8) with C677T homozygosity.[32] Several studies have shown a higher frequency of this polymorphism among people of Hispanic ethnicity compared with white people, who have an intermediate frequency, and black people, in whom the frequency is the lowest,[32,33] consistent with the variation in NTD prevalence in these 3 groups. However, the frequency of this allele does not explain the differences in NTD rates in all populations. Two

Fig 1. Three-quarter moving average of the birth prevalence (per 10 000 live births) of spina bifida according to race/ethnicity for 21 birth defects surveillance programs, 1995–2002.

regions with a very high frequency of the TT genotype, Mexico and northern China, also have high rates of NTDs. However, the TT genotype is common in southern Italy, despite that the NTD rate in this region is not high.[33] The A1298C polymorphism in *MTHFR* is most common among non-Hispanic white women[32] and thus does not correlate well with the variation in NTD risk among racial/ethnic groups. This suggests that other genes or environmental factors are likely to be important in NTD risk. The associations between NTD risk and several other genes have been studied,[34–38] but none has been shown to explain the observed differences in NTD risk associated with race/ethnicity.

Other factors associated with NTD risk, such as maternal diabetes[39] and obesity[40] or intake of other nutrients, such as vitamin B_{12},[41,42] vary by racial and ethnic groups and could explain some of the observed differences. Information on these factors was not available for this analysis. However, studies of the frequency of overweight and obesity among women aged 20 to 39 years show the highest prevalence among non-Hispanic black women, the lowest among non-Hispanic white women, and intermediate prevalence in Mexican American women.[43] A study of obesity and diabetes prevalence using 2001 data from the Behavioral Risk Factor Surveillance System showed similar results,[44] with the highest prevalence of both conditions among black women, intermediate among Hispanic women, and lowest among white women.

Intake of other nutrients may be an important factor in the causation of NTDs; for example, several studies have suggested that low vitamin B_{12} levels may be associated with an increased risk for NTDs.[41,42] Vitamin B_{12} levels vary by race/ethnicity, with non-Hispanic white people having the lowest concentrations, black people having the highest levels, and Mexican American people having intermediate values.[45] Thus, distribution of these risk factors varies by race/ethnicity, but the variation does not explain the prevalence of NTDs by race/ethnicity.

To our knowledge, studies assessing the impact of folic acid consumption on the rate of NTD-affected pregnancies among women of African descent have not been published. The initial randomized, controlled trials that reported decreased risk for NTDs with increased folic acid intake were conducted primarily among non-Hispanic white women. Thus, it is possible that the remaining NTD-affected pregnancies among black women are not folic acid sensitive. It also may be possible that higher levels of folic acid consumption would be required to prevent NTD cases in this population.

The observed decrease associated with fortification among certain Hispanic groups conflicts with the results of some previous studies that questioned the effectiveness of folic acid supplementation for the prevention of NTDs among women of Mexican descent[46,47]; these studies were limited by small sample size and low rates of consumption of folic acid–containing supplements. However, 3 studies that in-

TABLE 3. Prevalence of Anencephaly According to Race/Ethnicity Before and After Folic Acid Fortification

Racial/Ethnic Category	Prefortification (January 1995–December 1996)		Optional Fortification (January 1997–September 1998)		Mandatory Fortification (October 1998–December 2002)		PR (Mandatory/Prefortification)	95% CI
	No. of Cases	Prevalence (per 10 000)	No. of Cases	Prevalence (per 10 000)	No. of Cases	Prevalence (per 10 000)		
Hispanic	166	3.85	191	3.55	478	2.84	0.74	0.62–0.88
Non-Hispanic white	429	2.79	307	2.12	735	1.98	0.71	0.63–0.80
Non-Hispanic black	79	1.98	66	1.82	174	1.80	0.91	0.70–1.19

vestigated the impact of folic acid consumption on the prevalence of NTDs in Chile, Mexico, and Costa Rica found significant decreases in prevalence after increased consumption was implemented. In Chile, folic acid fortification of wheat flour was mandated at a level estimated to provide an additional 400 μg of folic acid per day to women of childbearing age. A pilot surveillance system that was set up to monitor rates of NTDs found that the prevalence of NTDs decreased 40% after fortification was established.[48] In Mexico, women were provided with free 5-mg folic acid supplements and were encouraged to take a supplement once per week. The study reported a 43% decline in the prevalence of NTDs over the course of the intervention.[49] In Costa Rica, programs to fortify wheat flour and corn flour were initiated in 1997 and 1999, respectively. A 74% decline in the prevalence of spina bifida at birth was noted after fortification.[50]

The primary strength of this study is that it provides population-based data from 21 birth defects surveillance systems, covering 35% to 40% of births in the 3 racial/ethnic groups studied and that it covers several years, spanning the pre- and postfortification period. However, the study has several limitations. Data were pooled from 21 different birth defects surveillance systems, with varying birth defects surveillance methods. Only 9 of the 21 participating surveillance systems were able to ascertain prenatally diagnosed cases. Some of the observed differences in rates among different racial/ethnic groups could be attributable to differences in the use of prenatal diagnostic techniques or in the frequency of elective termination after identification of an affected pregnancy, which have been shown to vary by race/ethnicity.[51–53] When data from our study were analyzed only among programs that conduct prenatal surveillance, the prevalence of NTDs among Hispanic births was 10% (PR: 1.10; 95% CI: 1.00–1.21) higher than the prevalence of NTDs among non-Hispanic white births, although this was of borderline significance. Among programs that do not conduct prenatal surveillance, the difference in the prevalence of NTDs between Hispanic and non-Hispanic white births was 42% (PR: 1.42; 95% CI: 1.33–1.52). This suggests that, in this study, at least some of the disparity in the prevalence of NTDs by race/ethnicity may be attributable to differences in prenatal testing and pregnancy outcome. However, the declines in the prevalence of NTDs during folic acid fortification among programs that conduct prenatal surveillance in each racial/ethnic group were consistent with results from all programs combined (results not shown). Another limitation is that we were unable to subdivide racial/ethnic groups into more meaningful subpopulations. The term "Hispanic" refers to a diverse group of populations with different culture, socioeconomic status, and country of origin[9] and, thus, varying genetic background and dietary and other risk factors for NTDs. In a study by Tumiel et al,[54] risks for preterm birth and low birth weight were shown to differ among Hispanic ethnic subgroups, supporting the need to separate these subgroups, when possible. Finally, we were unable to

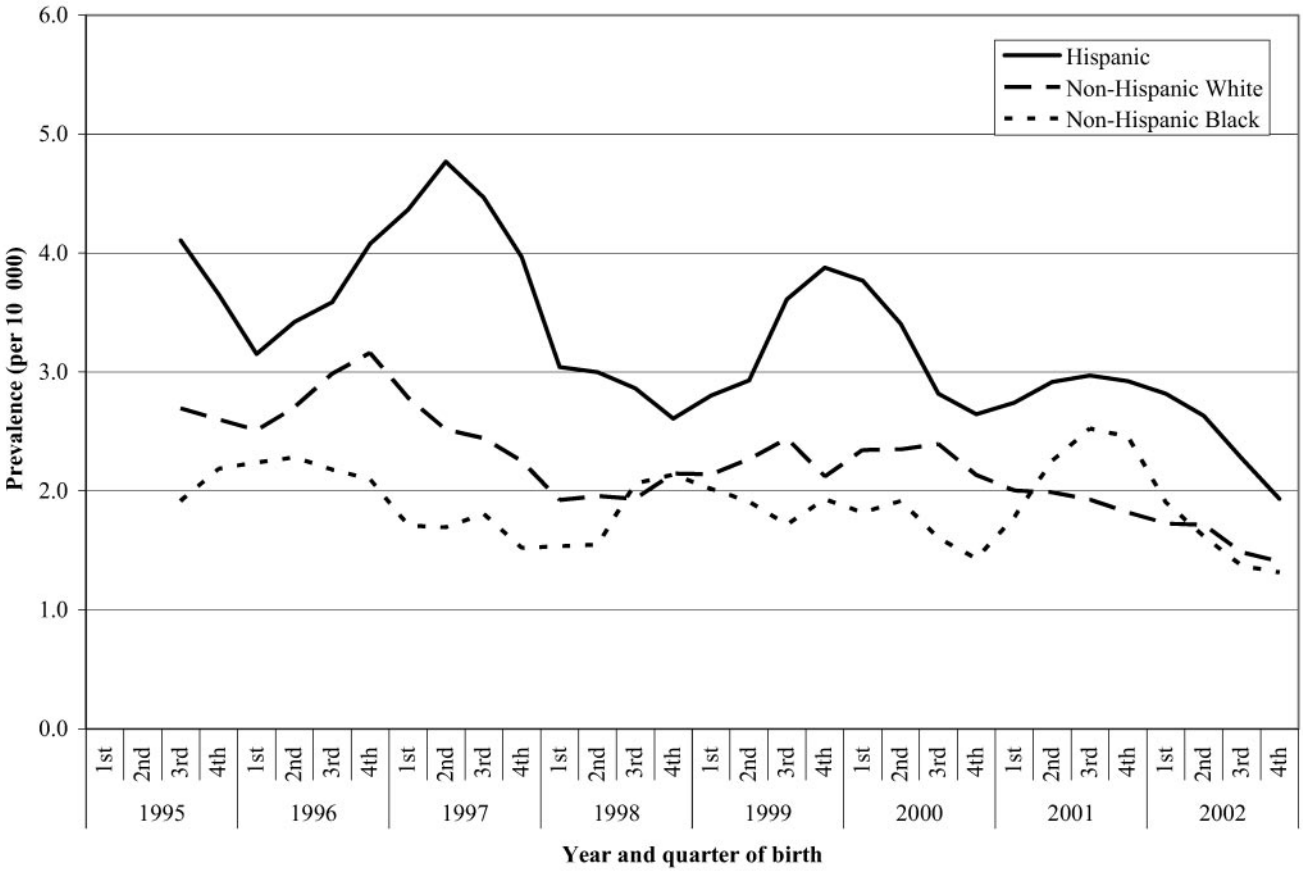

Fig 2. Three-quarter moving average of the birth prevalence (per 10 000 live births) of anencephaly according to race/ethnicity for 21 birth defects surveillance programs, 1995–2002.

control for other potentially confounding factors, such as maternal diabetes or obesity, which are known to be related to NTD risk.

CONCLUSIONS

The prevalence of NTD-affected pregnancies declined significantly among Hispanic women and non-Hispanic white women after folic acid fortification. The prevalence of NTDs among non-Hispanic black births did not decrease significantly. Educational efforts regarding the importance of consumption of folic acid–containing supplements and foods high in folic acid and natural folate among women of all racial/ethnic groups should be continued. However, it is likely that a combination of genetic and environmental factors are responsible for the differences in NTD risk observed among racial/ethnic groups. Future studies with the ability to study genetic and environmental risk factors as well as gene–environment interaction, such as the National Birth Defects Prevention Study,[55] will be crucial to explaining the differences in NTD risk by race/ethnicity observed in this study. In addition, trends in the prevalence of NTDs by racial/ethnic group in the United States should continue to be monitored.

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