

Risks of Selected Congenital Malformations among Offspring of Mixed Race-Ethnicity

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BACKGROUND: Little is known about the occurrence of specific congenital malformations among offspring of mixed race-ethnicity. **METHODS:** Using data from a population-based registry, we explored the occurrence of selected malformation phenotypes in offspring to parents who were of different race-ethnicity. Data were derived from the California Birth Defects Monitoring Program, a population-based active surveillance system for collecting information on infants and fetuses with congenital malformations using multiple source ascertainment. Approximately 2.6 million live births and stillbirths occurred during 1989–2000. Information on parental race-ethnicity (non-Hispanic white, Hispanic, black, and Asian) was obtained from birth certificates and fetal death files. Malformation phenotypes studied were spina bifida, anencephaly, cleft lip, cleft palate, tetralogy of Fallot, d-transposition of great arteries, hypospadias, small intestinal atresia, preaxial polydactyly, microtia, and hypertrophic pyloric stenosis. **RESULTS:** A total of 11.2% of births were to parents of mixed race-ethnicity. Compared to births of parents who were both white, moderately increased risks (risk ratio ≥ 1.7) of anencephaly, polydactyly, and microtia, and decreased risks (risk ratio ≤ 0.6) of hypospadias and hypertrophic pyloric stenosis were observed among births of several mixed race-ethnicity groups. For anencephaly, polydactyly, and microtia, but not other phenotypes, the risks were different depending on whether maternal versus paternal race-ethnicity was considered. Risks observed between births of a nonwhite parent and a white parent and births of parents who were both nonwhite were similar for most malformation phenotypes. **CONCLUSIONS:** Some malformation phenotypes appear to vary in their risk based on mixed racial-ethnic groupings. *Birth Defects Research (Part A) 70:820–824, 2004.* © 2004 Wiley-Liss, Inc.

Key words: congenital malformations; mixed race-ethnicity; pregnancy

INTRODUCTION

Racial-ethnic differences in occurrence of congenital malformations have been observed, though results are inconsistent and remain unexplained (Khoury et al., 1983; Chavez et al., 1988; Anonymous, 1992, 1994; Shaw et al., 1994; Harris et al., 1995; Harris et al., 1996; Williams, 1996; Shaw et al., 1997; Croen et al., 1998; Kirby et al., 2000; Sondik et al., 2000; Botto et al., 2001; Shaw et al., 2002; Botto and Correa, 2003). Environmental risk factors (including socioeconomic, cultural, nutritional, and behavioral factors), genetic susceptibilities, or the combinations between them have been postulated as contributors to the differences (Croen et al., 1998; Shaw et al., 2002). Most previous studies investigated congenital malformation occurrence by maternal race-ethnicity only. Few studies have investigated malformation occurrence among births of mixed racial-ethnic parentage. Four studies that have explored the occurrence of congenital malformations among mixed racial-ethnic births found provocative results. In the first

study, births of white mothers and Mexico-born Mexican fathers, but not births of Mexico-born Mexican mothers and white fathers, had an increased risk of neural tube defects compared to births of white mothers and white fathers, with odds ratios (ORs) and 95% confidence intervals (CIs) of 1.7 (0.6–4.6) and 1.0 (0.2–4.4), respectively (Shaw et al., 1997). In the second study, the prevalence of cleft lip among births of white mothers and black fathers was higher (5.8 per 1000) than the prevalence among births

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of black mothers and black fathers (2.6 per 1000), but lower than that of births of white mothers and white fathers (6.8 per 1000) (Khoury et al., 1983). The third and fourth studies found that malformations were associated with ethnicity of both parents but not that of the mother alone (Chung et al., 1987; Leck and Lancashire 1995).

Births of mixed race-ethnicity are likely to be demographically different from those births whose parents are of the same race-ethnicity. For example, infants born to black mothers and white fathers were more likely to have higher maternal education attainment (>12 years) than infants born to parents who were both white (OR, 0.7; 95% CI, 0.5–0.8) (Collins and David, 1993). Fewer children of parents who were both white (22.7%), but more children of parents who were both black (57.9%) lived in a lower income household than children of parents who were black and white (48.8%) (Parker and Lucas, 2000). The proportion of births from mixed racial-ethnic parentage tripled over the past three decades, from 1.4% in the early 1970s to 4.3% in 1998 (Parker and Madans, 2002). Multiple-race reporting is now a component of birth registration in the United States (Office of Management and Budget, 1997). Further study of congenital malformations among births of mixed race-ethnicity would serve as a potential source of clues for the occurrence of selected congenital malformations. Using data from a large population-based registry in California, our study investigated occurrences of selected major congenital malformations among subgroups of mixed racial-ethnic births compared to births among parents who were both white.

MATERIALS AND METHODS

Data were derived from the California Birth Defects Monitoring Program (CBDMP), a population-based active surveillance system that collects information on infants and fetuses with congenital malformations born to women who reside in California. Diagnostic and demographic information was collected by program staff from multiple sources of medical records for all live births and stillbirths (defined as fetuses ≥ 20 weeks gestation) diagnosed with congenital malformations by one year of age (Croen et al., 1991). Nearly all structural anomalies diagnosed within one year of delivery were ascertained, with ascertainment estimated to be 97% complete (Schulman and Hahn 1993).

Information on parental race-ethnicity was obtained from California birth and death certificate files. We categorized self-reported race-ethnicity of the parents as non-Hispanic white, Hispanic, black, and Asian. Offspring of mixed race-ethnicity couples were categorized based on the combination of maternal and paternal race-ethnicities.

We examined distributions of spina bifida, anencephaly, cleft lip, cleft palate, tetralogy of Fallot (TOF), d-transposition of great arteries (dTGA), hypospadias, small intestinal atresia, preaxial polydactyly, microtia, and hypertrophic pyloric stenosis among births of mixed race-ethnicity in comparison to births of same race-ethnicity. These phenotypes were identified from 2,615,197 births during 1989–2000. Births with small intestinal atresia, polydactyly, microtia, and hypertrophic pyloric stenosis were identified from 2,420,324 births owing to a geographic monitoring coverage change during the study period. Infants with hypospadias were derived from 1,237,378 male births only. Poisson regression models were constructed to estimate risk ratios (RRs) and their 95% CIs for each grouped anom-

Table 1
Proportion Distribution of Births from Parents of Mixed Race-Ethnicity, California Births, 1989–2000*

Maternal race-ethnicity	Paternal race-ethnicity	No. of deliveries	%
Total		293,427	100.0
White	Hispanic	81,887	27.9
White	Black	17,465	6.0
White	Asian	7,378	2.5
White	Other	12,665	4.3
Hispanic	White	71,540	24.4
Hispanic	Black	15,919	5.4
Hispanic	Asian	4,124	1.4
Hispanic	Other	10,457	3.6
Black	White	5,674	1.9
Black	Hispanic	6,296	2.1
Black	Asian	385	0.1
Black	Other	1,308	0.4
Asian	White	15,913	5.4
Asian	Hispanic	3,871	1.3
Asian	Black	1,469	0.5
Asian	Other	2,085	0.7
Other	White	16,093	5.5
Other	Hispanic	11,589	3.9
Other	Black	4,495	1.5
Other	Asian	2,814	1.0

*Among 2,615,197 livebirths and stillbirths studied, 21.7% (568,839), 46.4% (1,214,282), 6.9% (180,123), 6.3% (164,686), and 2.9% (75,667) were born to parents who were both white, Hispanic, Asian, and other race-ethnicity, respectively. A total of 118,173 (4.5%) births had either maternal or paternal race-ethnicity unknown.

aly, using SAS software GENMOD (SAS Institute, 2001). We did not estimate RRs and 95% CIs for mixed racial-ethnic groups with case numbers fewer than five. Births to parents who were both white were the reference group. RRs were adjusted by maternal age (25, 25–34, ≥ 35 years), education (<12, 12, >12 years), and parity (0, ≥ 1).

RESULTS

Births of mixed race-ethnicity represented 11.2% (293,427 of 2,615,197) of all births. Most (77.9%) had one parent who was white. The most frequent birth groups of mixed race-ethnicity were births of white mothers and Hispanic fathers (27.9%) and births of Hispanic mothers and white fathers (24.4%) (Table 1). Risks of congenital malformations were estimated only among births of mixed race-ethnicity with one parent who was white, owing to the limited sample size of other subgroups. Table 2 shows numbers of infants with malformations among mixed and same race-ethnicity births.

Table 3 shows RRs of selected congenital malformations among births from mixed racial-ethnic parents compared to births from parents who were both white, adjusted by maternal age, education, and parity. Moderately increased risks (RR ≥ 1.7) of anencephaly, polydactyly, and microtia and decreased risks (RR ≤ 0.6) of hypospadias and hypertrophic pyloric stenosis were observed among births of several mixed race-ethnicity groups. We did not find substantial differences (i.e., RRs ≤ 0.6 or RRs ≥ 1.7) in occurrences of spina bifida, cleft lip, cleft palate, TOF, dTGA, and small intestinal atresia among births of mixed race-ethnicity.

Table 2
Case Numbers of Congenital Malformation Phenotypes among Mixed and Same Racial-Ethnic Groups,
California Births, 1989–2000

Malformation group	Births of mixed race-ethnicity						Births of same race-ethnicity			
	White-Hispanic ^a	Hispanic-White	White-Black	Black-White	White-Asian	Asian-White	White-White	Hispanic-Hispanic	Black-Black	Asian-Asian
Spina bifida	58	46	9	1	1	5	332	1148	85	44
Anencephaly	11	29	5	0	1	5	94	391	32	54
Cleft lip	79	43	16	7	6	16	535	886	114	161
Cleft palate	197	121	33	12	16	29	1310	2721	283	385
TOF	23	34	5	0	3	10	239	415	68	78
dTGA	25	23	2	2	1	4	143	304	41	41
Hypospadias	102	93	29	14	7	14	1238	1018	236	178
Small Intestinal atresia	44	27	6	4	1	5	249	440	95	61
Polydactyly	29	18	8	5	2	4	164	299	68	139
Microtia	21	12	3	0	0	4	82	424	20	38
Hypertrophic pyloric stenosis	175	124	34	5	8	12	1080	1929	121	76

^aWhite-Hispanic represents that maternal race-ethnicity is white and paternal race-ethnicity is Hispanic, the same maternal-paternal racial-ethnic ordering applies to other groups.

For those mixed racial-ethnic groups having moderately increased or decreased risk for a specific malformation, we compared the occurrence of congenital malformation between births of a white mother and a nonwhite father and births of a corresponding nonwhite mother and a white father (Table 3). We observed comparable lowered risk of hypospadias between births of white mothers and Hispanic fathers (RR, 0.6; 95% CI, 0.5–0.7) and births of Hispanic mothers and white fathers (RR, 0.6; 95% CI, 0.5–0.8) relative to births of parents who were both white. A similar pattern of lowered risk was observed for the risks of hypospadias and hypertrophic pyloric stenosis between mixed racial-ethnic birth pairs with one Asian parent and one white parent. In contrast, mixed racial-ethnic birth pairs with one Hispanic parent had different risks for anencephaly and microtia, as did birth pairs with one black parent for polydactyly and hypertrophic pyloric stenosis.

Table 3 also reveals similar RRs among births of parents who were both nonwhite and births of mixed race-ethnicity with only one nonwhite parent for most malformation phenotypes. For example, we found moderately elevated risks (RR \geq 1.7) of anencephaly and microtia and reduced risks (RR \leq 0.6) of hypospadias and hypertrophic pyloric stenosis among most births of parents who were both nonwhite, as well as for births of mixed race-ethnicity. Some exceptions include considerably increased risk of spina bifida among births whose parents were both Hispanic (RR, 1.5; 95% CI, 1.3–1.7) but not among births with only one Hispanic parent and decreased risk of cleft palate (RR, 0.7; 95% CI, 0.6–0.9) among births whose parents were both black but a slightly increased risk (RR, 1.4; 95% CI, 0.6–2.8) among births of black mothers and white fathers.

DISCUSSION

Our study revealed moderately increased or decreased risks of several congenital malformations among births of mixed race-ethnicity relative to births of two white parents. Our finding of an increased risk of polydactyly and decreased risk of cleft lip among births for which either one

or two parents were black agree with the findings of Khoury et al. (1983). Another study of California data (Shaw et al., 1997) also found an increased risk (OR, 1.7; 95% CI, 0.6–4.6) of neural tube defects among births of white mothers and Mexico-born Mexican fathers but not among births of Mexico-born Mexican mothers and white fathers (OR, 1.0; 95% CI, 0.2–4.4), relative to births of parents who were both white. Our study examined spina bifida and anencephaly separately and found an increased risk among births of Hispanic mothers and white fathers (RR, 2.4; 95% CI, 1.6–3.8) and a slightly decreased risk among births of white mothers and Hispanic fathers (RR, 0.7; 95% CI, 0.3–1.3) only for anencephaly. We were unable to identify previous studies that estimated occurrences of the other phenotypes included in our analysis.

Our results revealed different RRs for anencephaly, polydactyly, and microtia and comparable RRs for hypospadias and hypertrophic pyloric stenosis between pairs of mixed racial-ethnic births, in which race-ethnicity of the mother and the father were interchanged. This has not been systematically examined before among subgroups of mixed race-ethnicity. Our findings, if not due to random fluctuation, indicate that maternal and paternal race-ethnicity may represent different risk factors for specific congenital malformations.

Environmental exposures, genetic susceptibilities, or the potential interactions between them have been hypothesized to contribute to racial-ethnic disparities of congenital malformations in previous studies (Khoury et al., 1983; Shaw et al., 1997; Croen et al., 1998). In general, we observed similar RRs of malformations between births of a white and a nonwhite parent and births of parents who were both nonwhite relative to births of parents who were both white. Our study cannot disentangle whether the similar RRs between births of mixed race-ethnicity and births of same race-ethnicity are indicative of shared risk backgrounds or are indicative of the imprecision associated with classification of race-ethnicity and therefore true difference have been masked.

Table 3
Adjusted Risk Ratios of Congenital Malformation Phenotypes among Births of Mixed and Same Race-Ethnicity, in Reference to Births of White Mother and White Father, California Births, 1989–2000*

Malformation group	White-Hispanic ^a		Hispanic-white		Hispanic-Hispanic		White-black		Black-white		Black-black		White-Asian		Asian-white		Asian-Asian	
	RR ^b	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Spina bifida	1.1	0.9–1.5	1.1	0.8–1.5	1.5	1.3–1.7	0.8	0.4–1.5	— ^c	—	0.8	0.6–1.0	—	—	0.7	0.3–1.7	0.5	0.3–0.6
Anencephaly	0.7	0.3–1.3	2.4	1.6–3.8	1.5	1.2–2.0	1.5	0.5–4.0	—	—	0.8	0.5–1.3	—	—	2.6	0.9–7.2	1.8	1.2–2.6
Cleft lip	1.0	0.8–1.3	0.8	0.6–1.0	1.0	0.9–1.1	0.7	0.4–1.1	0.7	0.3–1.6	0.7	0.6–0.8	1.0	0.5–1.9	0.6	0.4–1.1	1.0	0.8–1.1
Cleft palate	1.0	0.8–1.3	0.7	0.5–0.9	0.8	0.7–0.9	1.0	0.6–1.7	1.4	0.6–2.8	0.7	0.6–0.9	0.9	0.4–2.0	1.1	0.7–1.8	1.0	0.9–1.2
TOF	0.7	0.4–1.1	1.2	0.8–1.7	0.9	0.7–1.0	0.7	0.3–1.7	—	—	1.0	0.7–1.3	—	—	1.4	0.7–2.6	1.1	0.8–1.4
dTGA	1.2	0.8–1.8	1.3	0.8–2.0	1.0	0.8–1.3	—	—	—	—	0.9	0.6–1.3	—	—	1.1	0.4–2.9	1.0	0.7–1.4
Hypospadias	0.6	0.5–0.7	0.6	0.5–0.8	0.4	0.3–0.5	0.8	0.6–1.2	1.2	0.7–2.0	0.7	0.6–0.8	0.4	0.2–0.9	0.4	0.2–0.7	0.5	0.4–0.6
Small intestinal atresia	1.2	0.8–1.6	0.8	0.6–1.3	0.8	0.6–0.9	0.7	0.3–1.7	—	—	1.2	0.9–1.5	—	—	0.8	0.3–1.9	0.8	0.6–1.1
Polydactyly	1.2	0.8–1.7	0.9	0.5–1.4	0.9	0.7–1.1	1.6	0.8–3.2	3.1	1.3–7.6	1.4	1.0–1.8	—	—	—	—	3.1	2.4–3.9
Microtia	1.8	1.1–3.0	1.0	0.5–1.9	2.5	1.9–3.2	—	—	—	—	0.8	0.5–1.3	—	—	—	—	1.6	1.1–2.4
Hypertrophic pyloric stenosis	1.1	0.9–1.2	0.9	0.7–1.1	0.8	0.7–0.9	1.0	0.7–1.4	0.5	0.2–1.1	0.3	0.2–0.4	0.6	0.3–1.2	0.5	0.3–0.8	0.3	0.2–0.5

*Adjusted by maternal age (<25, 25–34, ≥35 years), education (<12, 12, >12 years), and parity (0, ≥1).
^aWhite-Hispanic represents that maternal race-ethnicity is white and paternal race-ethnicity is Hispanic, the same maternal-paternal racial-ethnic ordering applies to the others.
^bRR for births of white mother and Hispanic father is the prevalence of a given birth defect among this group divided by prevalence of given birth defect among births of white mother and white father. Births of white mother and white father were also the reference group for other RRs.
^cRRs and 95% CIs were not calculated due to case numbers <5.

The strengths of this study include its large sample size, its population-based data collection, detailed groupings of parental race-ethnicity, and adjustment for potential covariates. However, several limitations of these data should be noted. First, the ascertainment of congenital malformations by the CBDMP relies on the completeness and accuracy of medical records. If the diagnoses were made or identified either less or more commonly in births with at least one nonwhite parent, the observed findings could have been biased due to differential diagnoses. However, this is unlikely given the severe nature of most studied defects. Second, we excluded 4.5% of all births with missing values of either paternal or maternal race-ethnicity; most of them (92.0%) had only paternal race-ethnicity unknown. The observed findings among mixed racial-ethnic births could be biased if more births to parents of mixed race-ethnicity failed to report paternal racial-ethnic background. The influence, although its extent is unknown, may not be trivial given that only 11.2% of all births were to parents of mixed race-ethnicity. Third, even though our observations derived from a population base of over two million births, for some comparisons, mixed racial-ethnic group sample sizes were small, resulting in limited precision in risk ratio estimation. Fourth, race-ethnicity from vital records is based on parental self-reporting. Parents themselves may be of mixed race-ethnicity but self-identify as a single race-ethnicity. Thus, the studied racial-ethnic groups are likely to be less discrete than we have presented. Fifth, this study did not include ascertainment of malformations among electively terminated fetuses. If diagnoses of or decisions to electively terminate malformed fetuses differed substantially among the population groups studied, one could expect to observe artificial increased or decreased risks. The extent of this potential bias to our results is unknown. Lastly, the CBDMP registry program obtains information from birth and death certificates. We do not have information about some potentially important periconceptional exposures, e.g., vitamin use, that would permit better risk estimation.

Our observation that some congenital malformations vary in risk based on mixed racial-ethnic groupings may offer some clues to racial-ethnic differences in occurrence of congenital malformations. These clues, albeit nonspecific, need to be further investigated to better characterize whether the observed results among births of mixed race-ethnicity are related to environmental exposures, to potential genetic susceptibilities, or to both.

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