

Incidence of Cleft Lip, Cleft Palate, and Cleft Lip and Palate Among Races: A Review

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A review of the literature pertaining to the incidence of cleft lip, cleft palate, and cleft lip and palate in different races is presented. The studies have been evaluated according to the method used to record the incidence rate. Half of the studies include in their base population livebirths, stillbirths, and abortions, or livebirths and stillbirths to record the incidence rate. In addition, in most of the studies, clefts with associated malformations and possible syndromes are included in the reported incidence. There is evidence, however, to suggest that the risk of developing clefts in stillbirths and abortions is three times as frequent as in livebirths and that clefts with associated malformations behave differently epidemiologically from clefts without associated malformations. It is suggested, therefore, that the incidence of cleft lip, cleft palate, and cleft lip and palate should be studied separately for each group, namely for livebirths, stillbirths, and abortions and should be reported separately for clefts without associated malformations, clefts with associated malformations, and syndromes. More research is needed to study the risk of developing clefts among the various groups that exhibit different epidemiologic behavior for each race.

Many epidemiologic studies have been conducted on the incidence of cleft lip, cleft palate, and cleft lip and palate in the United States and in other countries. Their results show a wide variation in the risk of developing clefts within and among races. The majority of the studies include in the base population groups of subjects that differ in risk of developing orofacial clefts. In addition, in most of the studies, the reported incidence includes clefts with associated malformations and possible syndromes that behave differently epidemiologically from clefts without associated malformations.

The purpose of this paper is to review the epidemiologic studies conducted in different races on the incidence of cleft lip, cleft palate, and cleft lip and palate and to provide a critical evaluation of the methods used to record the incidence rate.

REVIEW OF LITERATURE

Studies published in English are reviewed in this section. They are classified in studies on whites, blacks, and orientals. Studies in which

the race was not clearly defined were excluded. Those conducted on Orientals are further classified in studies on American Indians, Chinese, and Japanese. Most of the relevant information provided by each study is summarized in Tables. Thus, Tables 1,2,3,4, and 5 include the investigator, time period in which the investigation was undertaken, location, source of information, number of births and clefts, base population, and the incidence rate per 1,000 for each study.

A small number of studies have been conducted on mixed races. Thus, Stevenson et al (1966), in a World Health Organization survey, reported that the overall incidence rate of cleft lip, cleft palate, and cleft lip and palate in Filipinos, in Manila, was 1.52 per 1,000. The same survey revealed that in Mexico City the incidence was 0.93 per 1,000 in one hospital and 0.42 per 1,000 in another. Ching and Chung (1974) examined 20,320 Filipino births in Hawaii and found that the incidence rate of cleft lip, cleft palate, and cleft lip and palate was 2.45 per 1,000 livebirths. In another Mexican study, Armendares and Lisker (1974) reported the incidence rate to be 1.03 per 1,000 livebirths. Oliver-Padilla and Martinez-Gonzalez (1986) examined the births registered in a cleft palate clinic in Puerto Rico and found an increase of 2.10 per 100,000 live-

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TABLE 1 Studies on the Incidence of Cleft Lip, Cleft Palate, and Cleft Lip and Palate in White Subjects

Investigator	Period (yr)	Location	Source	Births (N)	Clefts (N)	Base Population* 1,000	Clefts per 1,000
Davis (1924)	-	Baltimore	Deliveries	15,565	17	L,S	1.09
Grace (1943)	1942	Pennsylvania	Birth records	191,161	241	-	1.26
Hixon (1951)	1943-49	Ontario Canada	Surgical records	655,322	695	L	1.06
MacMahon & Mckeown (1952)	1940-50	Birmingham England	Multiple sources	218,693	285	L,S	1.30
Lutz & Moor (1955)	1936-57	Los-Angeles	Hospital records	29,000	29	L,S	1.00
Rank & Thomson (1960)	1945-57	Tasmania Australia	Multiple sources	96,510	160	L,S	1.66
Fogh-Andersen (1961)	1938-57	Denmark	Surgical records	1,631,376	2,355	L	1.44
Loretz et al (1961)	1955	California	Birth certificates	282,812	341	L	1.20
Knox & Braithwaite (1962)	1949-58	England	Multiple sources	404,124	574	L	1.42
Ivy (1962)	1961	State of Pennsylvania Philadelphia County	Birth certificates	213,778	284	L	1.32
Woolf et al (1963)	1951-61	Utah	Nursery records	28,350	27	L	0.95
Moller (1965)	1956-62	Iceland	Multiple sources	59,650	90	L	1.51
Conway & Wagner (1966)	1952-62	New York City	Birth certificate	32,979	64	L	1.94
Gilmore & Hofman (1966)	1943-62	Wisconsin	Multiple sources	1,478,315	1,457	L	0.98
Leck (1969)	1943-62	England	Multiple sources	1,670,400	1,740	L	1.04
Chung & Myrianthopoulos (1967)	1950-59	England	Multiple sources	186,046	354	L,S	1.90
Chi & Godfrey (1970)	-	in the U.S.A.	Follow-up pregnancies	16,385	15	L,S,A	1.82
Hay (1971)	1964-66	South Wales Australia	Hospital records	143,948	174	L	1.21
Czeizel & Tusnadi (1971)	1963	Iowa	Multiple sources	58,686	130	L,S	2.22
Emanuel et al (1973)	1962-67	Hungary	Multiple sources	110,299	144	L,S	1.30
Myrianthopoulos & Chung (1974)	1956-85	Washington	Multiple sources	189,096	311	L	1.75
Brogan & Woodings (1974)	1973-74	Twelve Institutions in the U.S.A.	Follow-up pregnancies	24,153	65	L	2.69
Ching & Chung (1974)	1963-72	Australia	Multiple sources	193,520	332	L	1.73
Saxen & Lahti (1974)	1948-86	Hawaii	Multiple sources	77,013	123	L	1.55
Tal et al (1974)	1967-71	Finland	Multiple sources	347,316	599	L	1.72
Spry & Nugent (1975)	1961-71	Israel	Multiple sources	-	175	L	0.80
Saxen (1975)	1949-68	South Australia	Hospital records	392,228	559	L	1.41
Lowry & Trimble (1977)	1972-73	Finland	Multiple sources	116,407	190	L	1.63
Owens et al (1985)	1952-71	British Columbia Canada	Multiple sources	713,316	1,409	L	1.97
	1960-82	England	Multiple sources	325,727	456	L,S	1.40

* L = livebirths; S = stillbirths; A = abortions

births in the prevalence rate of cleft lip, cleft palate, and cleft lip and palate between 1952 and 1979. Chapman (1983) reported the incidence rate of facial clefts in New Zealand Maoris to be 2.27 per 1,000 births.

ANALYSIS OF THE RESULTS

Whites

The overall incidence rate of cleft lip, cleft palate, and cleft lip and palate for whites ranged from 0.91 to 2.69 per 1,000 (Table 1). Nine of the studies were conducted in Europe and reported a range between 1.30 and 1.94 per 1,000. In four of these studies, livebirths and stillbirths (late fetal deaths of 28 or more weeks of gestation) were included in the base population (Table 1), while in five of them (MacMahon and Mckeown, 1952; Knox and Braithwaite, 1962; Moller, 1965; Leck, 1969; Czeizel and Tusnadi, 1971) clefts with associated malformations and possible syndromes were included in the incidence rate. Two studies were conducted in Canada (Hixon, 1951; Lowry and Trimble, 1977) and the reported incidence rate was 1.06 and 1.97 per 1,000 livebirths. In both studies clefts with associated malformations and possi-

ble syndromes were included in the incidence rate. Another four studies were conducted in Australia, and the reported incidence rate ranged from 1.21 to 1.73 per 1,000. Three studies (Rank and Thomson, 1960; Chi and Godfrey, 1970; Brogan and Woodings, 1984) included clefts with associated malformations and possible syndromes in the reported incidence. In one of them (Rank and Thomson, 1960), livebirths and stillbirths were included in the sample, but in the others only livebirths were examined. One study was conducted in Israel and the incidence was found to be 0.80 per 1,000 livebirths.

The remaining thirteen studies were conducted in different places in the United States (Table 1) and showed a range from 0.95 to 2.69 per 1,000. One of these studies (Chung and Myrianthopoulos, 1967) included in the sample livebirths, stillbirths, and abortions¹, while another three (Davis, 1924; Lutz and Moor, 1955; Hay, 1971) livebirths and stillbirths. In the reported incidence, eleven studies (Davis, 1924; Ivy, 1962; Woolf et al, 1963; Conway and Wagner, 1966; Gilmore and Hofman, 1966; Chung and

¹ Throughout the paper abortion referred to is spontaneous abortion, which is defined as the involuntary termination of pregnancy.

Myriantopoulos, 1967; Emanuel et al, 1973; Myriantopoulos and Chung, 1974; Ching and Chung, 1974; Lutz and Moor, 1955; Loretz et al, 1961) included clefts with associated malformations and possible syndromes; in only one of them (Ching and Chung, 1974) exclusion of the syndromes was mentioned. In addition, two studies (Chung and Myriantopoulos, 1967; Myriantopoulos and Chung, 1974) were longitudinal; the others were retrospective.

The values of the incidence of cleft lip alone in whites ranged from 0.29 to 0.45 per 1,000. The lowest value was reported in Canada (Hixon, 1951) and the highest in Canada (Lowry and Trimble, 1977) and England (Knox and Braithwaite, 1962). The incidence rate of cleft lip with cleft palate ranged from 0.36 to 0.83 per 1,000. The two extreme values were reported in the United States (Woolf et al, 1963; Conway and Wagner, 1966). Three studies conducted in the United States (Chung and Myriantopoulos, 1967; Hay, 1971; Emanuel et al, 1973) reported the incidence rate of cleft lip with and without cleft palate together and the values ranged from 0.71 to 1.29 per 1,000. The values of cleft lip with cleft palate were greater than those of cleft lip alone. The incidence of the isolated cleft palate ranged from 0.19 to 0.83 per 1,000. The lowest value was reported in Canada (Hixon, 1951) and the highest in Finland (Saxen and Lahti, 1974). Only two studies (Hixon, 1951; Woolf et al, 1963) showed the incidence of isolated cleft palate to be lower than that of cleft lip alone. Four studies (MacMahon and Mckeown, 1952; Brogan and Woodings, 1974; Saxen and Lahti, 1974; Saxen, 1975) reported the incidence of isolated cleft palate to be greater than that of cleft lip with cleft palate. On the

basis of the reviewed studies, the incidence rate of cleft lip with cleft palate is highest, followed by the incidence of isolated cleft palate and then by cleft lip alone.

With respect to the sex ratio by cleft type, fourteen studies (Hixon, 1951; Mazaheri, 1958; Rank and Thomson, 1960; Knox and Braithwaite, 1962; Moller, 1965; Conway and Wagner, 1966; Meskin et al, 1968; Chi and Godfrey, 1970; Saxen and Lahti, 1974; Brogan and Woodings, 1974; Tal et al, 1974; Saxen, 1975; Spry and Nugent, 1975; Owens et al, 1985), which included 6,583 individuals with cleft lip, cleft palate, and cleft lip and palate, showed that males outnumbered females in both cleft lip and cleft lip with cleft palate. One study (MacMahon and Mckeown, 1952) reported the opposite trend for cleft lip with cleft palate. One study (Owens et al, 1985) reported equal sex distribution for cleft palate, and three studies (MacMahon and Mckeown, 1952; Brogan and Woodings, 1974; Tal et al, 1974) reported that males outnumbered females; females outnumbered males in the rest of the studies.

Blacks

The incidence rate of cleft lip, cleft palate, and cleft lip and palate in blacks ranged from 0.18 to 1.67 per 1,000 (Table 2). One of the studies was conducted in Nigeria (Iregbulem, 1982), and the rest of the studies were done in the United States. Two studies (Davis, 1924; Lutz and Moor, 1955) included livebirths and stillbirths in the base population, and one study (Chung and Myriantopoulos, 1967) included livebirths, stillbirths, and abortions. The sample of the other studies consisted only of livebirths. In eight

TABLE 2 Studies on the Incidence of Cleft Lip, Cleft Palate, and Cleft Lip and Palate in Black Subjects

Investigator	Period (yr)	Location	Source	Births (N)	Clefts (N)	Base Population*	Clefts per 1,000
Davis (1924)	-	Baltimore	Deliveries	12,520	7	L,S	0.56
Grace (1943)	1942	Pennsylvania	Birth records	11,340	9	-	0.23
Lutz & Moor (1955)	1936-51	Los Angeles	Hospital records	-	12	L,S	0.71
Loretz et al (1961)	1955	California	Birth records	21,532	13	L	0.60
Ivy (1962)	1961	State of PA	Birth certificates	26,367	6	L	0.23
		Philadelphia County		16,665	5	-	0.30
Altemus (1966)	1952-6	Washington D.C.	Hospital records	26,131	8	-	0.30
				53,711	36	-	0.67
Gilmore & Hofman (1966)	1943-62	Wisconsin	Birth records	33,642	6	L	0.18
Chung & Myriantopoulos (1967)	-	14 Institutions in the U.S.A.	Follow-up pregnancies	16,959	8	L,S,A	0.82
Emanuel et al (1973)	1956-65	Washington D.C.	Multiple sources	8,708	11	L	1.26
Myriantopoulos & Chung (1974)	1973-74	12 Institutions in the U.S.A.	Follow-up pregnancies	25,126	42	L	1.67
Iregbulem (1982)	1976-80	Nigeria	Clinical examination at birth	21,624	8	L	0.37

* L = livebirths; S = stillbirths; A = abortions

studies (Davis, 1924; Lutz and Moor, 1955; Ivy, 1962; Gilmore and Hofman, 1966; Chung and Myriantopoulos, 1967; Emanuel et al, 1973; Myriantopoulos and Chung, 1974; Iregbulem, 1982) clefts with associated malformations and possible syndromes were included in the reported incidence rate; in one (Altemus, 1966) it is not clear whether they were accounted for. Two studies were longitudinal (Chung and Myriantopoulos, 1967; Myriantopoulos and Chung, 1974); the others were retrospective.

A breakdown of the incidence of oral clefts by cleft type in blacks showed that the incidence rate of cleft lip alone ranged from 0.038 to 0.20 per 1,000, with the highest value reported in Nigeria (Iregbulem, 1982). The incidence of cleft lip with cleft palate ranged from 0.076 to 0.26 per 1,000, with the lowest value reported in Nigeria (Iregbulem, 1982). Three studies (Chung and Myriantopoulos, 1967; Emanuel et al, 1973; Myriantopoulos and Chung, 1974) reported the incidence of cleft lip with and without cleft palate together and the values ranged from 0.43 to 0.80 per 1,000. Only one study (Iregbulem, 1982) showed the incidence of cleft lip alone to be higher than that of cleft lip and palate. The incidence of the isolated cleft palate ranged from 0.05 to 0.96 per 1,000, with the lowest value reported in Nigeria (Iregbulem, 1982). However, the number of oral clefts examined was small in all studies.

Although the sex ratio of cleft lip, cleft palate, and cleft lip and palate has not been studied adequately in blacks, two of the existing studies (Altemus, 1966; Myriantopoulos and Chung, 1974) conducted in the United States reported that males outnumbered females for all types of clefts; the Nigerian study (Iregbulem, 1982) showed slight differences between male and female only for cleft lip alone.

American Indians

The reported incidence of cleft lip, cleft palate, and cleft lip and palate for American Indi-

ans ranged from 0.79 to 3.74 per 1,000 (Table 3). Five studies were conducted in the United States and reported the incidence rate to range from 0.79 to 3.62 per 1,000 livebirths; one study (Lowry and Trimble, 1977) conducted in Canada reported the incidence rate to be 3.74 per 1,000 livebirths. All studies included only livebirths in the base population.

The reported incidence of cleft lip with cleft palate was greater than those of cleft lip alone and isolated cleft palate. However, the number of cases examined was small in all studies. With respect to the sex ratio by cleft type, one study (Tretsven, 1963) reported equal sex ratio for cleft lip alone, and males outnumbered females in both cleft lip with palate and isolated cleft palate.

Chinese

Table 4 shows the incidence of cleft lip, cleft palate, and cleft lip and palate for Chinese. Three of the studies included livebirths and stillbirths in the base population; the other two considered only livebirths. Two studies (Stevenson et al, 1966; Emanuel et al, 1972) reported the incidence without associated malformations and three studies (Wei and Chen, 1965; Emanuel et al, 1973; Lowry and Trimble, 1977) recorded the incidence with associated malformations. One study (Stevenson et al, 1966) was conducted in three different places, Hong Kong, Kuala Lumpur, and Singapore; one was conducted in Taiwan (Emanuel et al, 1972), one in the United States (Emanuel et al, 1973), and one in Canada (Lowry and Trimble, 1977). The highest incidence was reported to occur in the United States, but the sample was small. One study (Stevenson et al, 1966) was prospective while the others retrospective. With respect to the incidence by cleft type, two studies (Stevenson et al, 1966; Emanuel et al, 1972) showed that the incidence of cleft lip with cleft palate was greater than that of cleft lip alone and isolated cleft palate, one study (Lowry and Trimble, 1977) reported the incidence of cleft lip and palate to

TABLE 3 Studies on the Incidence of Cleft Lip, Cleft Palate, and Cleft Lip and Palate in American Indians

Investigator	Period (yr)	Location	Source	Births (N)	Clefts (N)	Base Population *	Clefts per 1,000
Tretsven (1963)	1955-61	Modana	Birth records	7,461	27	L	3.62
Gilmore & Hofman (1966)	1943-62	Wisconsin	Multiple sources	10,120	8	L	0.79
Niswander & Adams (1967)	1963-68	U.S.A.	Hospital records	25,341	50	L	1.97
Emanuel et al (1973)	1956-65	Washington D.C.	Multiple sources	1,764	6	L	3.40
Niswander et al (1975)	1964-69	U.S.A.	Multiple sources	43,409	100	L	2.30
Lowry & Trimble (1977)	1952-71	British Columbia	Multiple sources	30,532	114	L	3.74

* L = livebirths

TABLE 4 Studies on the Incidence of Cleft Lip, Cleft Palate, and Cleft lip and Palate in Chinese Subjects

Investigator	Period (yr)	Location	Source	Births (N)	Clefts (N)	Base Population*	Clefts per 1,000
Wei and Chen (1965)	1955-62	Taiwan	Hospital births	14,834	28	L,S	1.92
Stevenson et al (1966)	-	Hong Kong	Hospital births	9,876	16	L,S	1.62
Stevenson et al (1966)	-	Kuala Lumpur	Hospital births	16,025	25	L,S	1.56
Stevenson et al (1966)	-	Singapore	Hospital births	39,665	69	L,S	1.74
Emanuel et al (1972)	1965-68	Taiwan	Hospital births	25,517	37	L,S	1.45
Emanuel et al (1973)	1956-65	Washington	Multiple sources	1,239	5	L	4.04
Lowry & Trimble (1977)	1952-71	British Columbia	Multiple sources	12,430	22	L	1.76

* L = livebirths; S = stillbirths

be greater than that of cleft lip alone but equal to that of isolated cleft palate.

The sex ratio has not been studied adequately. One study (Stevenson et al, 1966) conducted in three different places, Hong Kong, Kuala Lumpur, and Singapore, showed that males outnumbered females for cleft lip alone in two places (Hong Kong and Singapore), but females outnumbered males in Kuala Lumpur; the same trend was observed for cleft lip and palate. The incidence of isolated cleft palate in two places (Hong Kong and Kuala Lumpur) showed an equal ratio, and in Singapore, the incidence for females outnumbered that for males. However, the number of cases studied was small.

Japanese

A wide variation in the incidence of cleft lip, cleft palate, and cleft lip and palate was reported for Japanese (Table 5). Twelve studies conducted in different places in Japan reported the incidence to range from 0.85 to 2.68 per 1,000.

In only one study (Moriyama, 1963), which reported the lowest incidence, clefts with associated malformations and syndromes were excluded. Ten studies included livebirths, stillbirths, and abortions in the base population and two studies only livebirths (Table 5). Three more studies (Emanuel et al, 1973; Ching and Chung, 1974; Tyan, 1982) were conducted with Japanese who migrated to different places in the United States, and one study (Lowry and Trimble, 1977) was conducted in Canada. The base population of these studies consisted of livebirths; the incidence in two of them (Emanuel et al, 1973, Lowry and Trimble, 1977) included clefts with associated malformations and syndromes; in the other one (Ching and Chung, 1974) syndromes were excluded. It is not clear whether the incidence reported by the fourth study included clefts with associated malformations and syndromes. The highest incidence of cleft among all studies for Japanese was reported in Canada, and the lowest incidence was in California.

TABLE 5 Studies on the Incidence of Cleft Lip, Cleft Palate, and Cleft Lip and Palate in Japanese Subjects

Investigator	Period (yr)	Location	Source	Births (N)	Clefts (N)	Base Population*	Clefts per 1,000
Tsutsui (1951)	-	Osaka	Hospital birth records	10,361	25	L,S,A	2.41
Hikita (1953)	1948-52	Nagasaki	Survey of ABCC**	27,020	67	L,S,A	2.48
Saburi (1954)	-	Tokyo	Hospital birth records	16,885	35	L,S,A	2.07
Mitani (1954)	1922-52	Tokyo	Hospital birth records	80,435	152	L,S,A	1.89
Tsukamoto (1956)	1922-55	Whole country	Questionnaire to Hospitals	105,730	217	L,S,A	2.05
Neel (1958)	1948-54	Hiroshima, Nagasaki	Survey of ABCC**	63,796	171	L,S,A	2.68
Kobayasi (1958)	1940-56	Tokyo	Hospital birth records	46,651	97	L	2.08
Kurozumi (1963)	1953-60	Okayama	Hospital birth records	35,463	58	L,S,A	1.64
Moriyama (1963)	1957-61	Whole country	Questionnaire to Hospitals	334,529	286	L,S,A	0.85
Kaminura et al (1965)	1958-63	Niigata	Questionnaire to Hospitals	48,015	93	L,S,A	1.94
Sato (1966)	1957-61	Whole country	Questionnaire to Hospitals	280,828	462	L,S,A	1.65
Tanaka (1972)	1965-67	Hokkaido	Questionnaire to Hospitals	105,462	189	L	1.79
Emanuel et al (1973)	1956-65	Washington, D.C.	Multiple sources	106,854	197	L,S,A	1.84
Ching & Chung	1948-66	Hawaii	Multiple sources	2,538	5	L	1.97
Lowry & Trimble (1977)	1952-71	British Columbia	Multiple sources	67,068	178	L	2.65
Tyan (1982)	1974-77	Hawaii	Multiple sources	3,569	12	L	3.36
		California	Birth records	4,650	7	L	2.41
				5,483	3	L	0.82

* L = livebirths; S = stillbirths; A = abortions

** ABCC: Atomic Bomb Casualty Committee

Source: The data for the first twelve studies were taken from Koguchi (1980).

With respect to the incidence by cleft type for Japanese, three studies (Saburi, 1954; Moriyama, 1963; Kaminura et al, 1965) showed that the incidence for cleft lip alone was greater than that for cleft lip with cleft palate; one study (Lowry and Trimble, 1977) showed the values for the incidence of cleft lip alone and cleft lip with cleft palate to be equal; the remaining studies found the incidence of cleft lip alone to be lower than that of cleft lip with cleft palate. All studies but one (Emanuel et al, 1973) reported the incidence of isolated cleft palate to be lower than that of cleft lip with cleft palate. In only one study (Ching and Chung, 1974), the incidence of isolated cleft palate was greater than that of cleft lip alone. On the basis of this review, the incidence of cleft lip with cleft palate shows the highest incidence, followed by cleft lip alone and then by isolated cleft palate.

Two studies (Tsutsui, 1951; Tanaka, 1972) showed that males with cleft lip alone outnumbered females, but the other studies revealed the opposite trend. All studies found that males with cleft lip and cleft palate outnumbered females, although females with isolated cleft palate outnumbered males.

DISCUSSION

The reviewed studies suggest that differences exist in the incidence of cleft lip, cleft palate, and cleft lip and palate among races. The American Indians showed the highest values followed by the Japanese, the Maoris, and the Chinese. The whites showed lower values, and the blacks the lowest values. Four studies (Stevenson et al, 1966; Ching and Chung 1974; Armendares and Lisker, 1974; Oliver-Padilla and Martinez-Gonzalez, 1986) conducted in mixed races reported a wide variation of the incidence ranging from as low as 0.43 per 1,000 to as high as 2.45 per 1,000. This range reflects the range of incidence of the other races.

The incidence of cleft lip, cleft palate, and cleft lip and palate reported to occur among races is

a gross estimate based on different sources of information, sample size, time of diagnosis, classification of the clefts, degree of clinical delineation, inclusion of stillbirths and abortions in the base population, and inclusion of clefts with associated malformations and syndromes in the reported rates. In view of these differences, the results of the studies are not comparable. Also, these factors might explain the great discrepancies in incidence reported by some studies.

Hay (1967) studied parental age after separating clefts into those with and without associated malformations and found an increased occurrence of cleft lip, cleft lip with cleft palate, and isolated cleft palate with other malformations at late maternal ages. Only cleft lip with cleft palate and isolated cleft palate showed a relation to maternal age when reported as a sole defect. Hay concluded that some clefts, particularly those involving the lip and occurring as a single malformation, may have a different etiology from those occurring with other malformations. Emanuel et al (1973) found that clefts with associated malformations are different epidemiologic entities from clefts without associated malformations with respect to sex ratio, maternal age, birth weight, and infant mortality. Similar epidemiologic differences between clefts without associated malformations and clefts with associated malformations were reported by Czeizel and Tusnadi (1971). In clinical studies, Rollnick and Pruzansky (1981) and Shprintzen et al (1985) found 44 percent of 2,512 cases and 63.4 percent of 1,000 cases of clefts with associated anomalies respectively. They concluded that orofacial clefts present etiologic heterogeneity and stressed the importance of separating isolated orofacial clefts from those with associated malformations or identifiable syndromes in studying populations of subjects with clefts.

Krause et al (1963) found in 3,186 human embryos and fetuses that the risk of developing clefts with associated malformations was 11.61 per 1,000 and the risk of developing clefts

TABLE 6 Incidence of Cleft Lip, Cleft Palate, and Cleft Lip and Palate in Livebirths and Stillbirths

Investigator	Race	Livebirths			Stillbirths		
		N	Affected	per 1,000	N	Affected	per 1,000
Lutz & Moor (1955)	Whites	69,901	64	.91	2,206	6	2.72*
	Blacks						
	Mexicans						
Chi & Godfrey (1970)	Whites	143,948	174	1.21	3,094**	18	5.81*
Hay (1971)	Whites	57,909	125	2.16	777	5	6.43*
Tanaka (1972)	Japanese	105,462	189	1.79	1,392†	8	5.75

* Calculated from the original data

** Includes stillbirths and neonatal deaths

† Includes stillbirths and abortions

without associated malformations was 7.22 per 1,000. Iizuka (1973) found in 5,117 voluntarily aborted human embryos the incidence of cleft lip to be 4.3 per 1,000, whereas the incidence of cleft lip with cleft palate and cleft palate in 615 fetuses was 8.10 and 3.2 per 1,000 respectively. Nishimura et al (1966) reported the frequency of cleft lip in 1,213 voluntarily aborted human embryos to be 14.70 per 1,000.

Table 6 presents the incidence of cleft lip, cleft palate, and cleft lip and palate between livebirths and stillbirths (late fetal deaths of 28 or more weeks of gestation). The risk of developing a cleft in the stillbirths group ranges from 2.72 to 6.43 per 1,000, whereas in the livebirths group, the range is 0.96 to 2.72 per 1,000. The risk is three times greater in the stillbirths group than that in the livebirths group. The incidence of clefts for whites in the stillbirths (Hay, 1971; Chi and Godfrey, 1970) is greater than that for Japanese (Tanaka, 1972). In the Japanese study, stillbirths and abortions were included in the sample, whereas in one study of whites (Chi and Godfrey, 1970), stillbirths and neonatal deaths (deaths within the first 4 weeks of life) were included. There is evidence, therefore, to suggest that clefts with associated malformations behave differently epidemiologically from clefts without associated malformations, and the risk of developing clefts in stillbirths is three times greater than that in livebirths.

However, eleven of the reviewed studies (Tsutsui, 1951; Hikita, 1953; Saburi, 1954; Mitani, 1954; Tsukamoto, 1956; Neel, 1958; Kurozumi et al, 1963; Kaminura et al, 1965; Sato, 1966; Chung and Myrianthopoulos, 1967; Tanaka, 1972) included livebirths, stillbirths, and abortions in the base population and also clefts with associated malformations in the reported incidence. Twenty-two studies (Hixon, 1951; Kobayasi, 1958; Fogh-Andersen, 1961; Loretz et al, 1961; Ivy, 1962; Knox and Braithwaite, 1962; Tretsvan, 1963; Woolf et al, 1963; Moller, 1965; Gilmore and Hofman, 1966; Conway and Wagner, 1966; Niswander and Adams, 1967; Chi and Godfrey, 1970; Emanuel et al, 1973; Ching and Chung, 1974; Brogan and Woodings, 1974; Myrianthopoulos and Chung, 1974; Spry and Nugent, 1975; Niswander et al, 1975; Lowry and Trimble, 1977; Iregbulem, 1982) included only livebirths in the base population and clefts with associated malformations in the reported incidence. Eight studies (Davis, 1924; Lutz and Moor, 1955; MacMahon and Mckeown, 1952; Rank and Thomson, 1960; Wei and Chen, 1965; Leck, 1969; Hay, 1971; Czeizel and Tusnadi, 1971) included livebirths and stillbirths in the base population and clefts with as-

sociated malformations in the incidence rate. Four studies (Moriyama, 1963; Stevenson et al, 1966; Emanuel et al, 1972; Owens et al, 1985) included livebirths and stillbirths in the base population and reported the incidence without associated malformations. Two studies (Saxen and Lahti, 1974; Saxen, 1975) included livebirths in the base population and reported the incidence without associated malformations. Two studies (Grace, 1943; Altemus, 1966) did not report the base population or whether clefts with associated malformations were included in the incidence. Three studies (Stevenson et al, 1966; Emanuel et al, 1972; Ching and Chung, 1974) did not include syndromes in the reported incidence rate. In sixteen studies (Tsutsui, 1951; Hikita, 1953; Saburi, 1954; Mitani, 1954; Tsukamoto, 1956; Neel, 1958; Kobayasi, 1958; Ivy, 1962; Kurozumi et al, 1963; Kaminura et al, 1965; Sato, 1966; Conway and Wagner, 1966; Gilmore and Hofman, 1966; Hay, 1971; Emanuel et al, 1973; Spry and Nugent, 1975), syndromes were included. Although not explicitly reported, it is likely that in the remaining studies syndromes were also included in the incidence rate.

If the risk of developing a cleft in stillbirths and abortions is three times greater than that in livebirths, then the actual values of the incidence rate reported by studies including livebirths, stillbirths, and abortions in the base population must be higher than the values reported by studies which included only livebirths. Therefore, it is expected that the rate of incidence varies proportionately with the number of stillbirths and abortions included in the base population. Moreover, the inclusion or exclusion of clefts with associated malformations and syndromes may account for a certain degree of variability among all studies.

It is believed that studies that include livebirths, stillbirths, and abortions in the base population come closer to fulfilling the definition of incidence rate, whereas those that include only livebirths are closer to the definition of prevalence rate. Although the use of the terms incidence and prevalence in congenital malformations is complex, this study provides evidence that stillbirths and abortions are epidemiologically different groups from livebirths with respect to the risk of developing clefts and should be studied separately. Therefore, the studies that included livebirths, stillbirths, and abortions in the base population did not report the true incidence, because two groups with different risk of developing clefts were examined together. Since this distinction eliminates the ascertainment of fetal loss in the livebirths, it is suggested the term incidence be used in report-

ing frequency of clefts in livebirths. Also, the same term seems appropriate for stillbirths and abortions.

In the literature, the variability of the incidence of cleft malformations among races has been attributed mainly to the following factors: differences in the environment (Morton, 1962; Tyan, 1982), differences in the frequency of particular combinations of the genes in a population (Neel, 1958; Emanuel et al, 1973) or to the combination of both factors (Leck, 1969). Therefore, accounting for the differences mentioned previously in the base population and the different numbers of clefts with associated malformations and syndromes included, the reported incidence may shed more light on the particular factors that contribute to the observed variability.

The existing evidence suggests that clefts with associated malformations and syndromes behave differently epidemiologically from clefts without associated malformations and their inclusion in the incidence rates, therefore, may complicate the research of etiology of oral clefts and consequently the genetic counseling. In addition, the inclusion of these clefts whose mortality rate is higher than that in clefts without associated malformations in the incidence rate does not help when planning health services for treatment and habilitation of patients with clefts.

The multifactorial two-threshold model has been employed (Niswander et al, 1972; Dronamraju et al, 1982) to explain the sex differences in the incidence of oral clefts. According to this model, a lower threshold level of liability results in cleft formation, whereas a higher level of liability causes fetal death. Three classes of individuals were hypothesized to be associated with cleft lip, cleft palate, and cleft lip and palate liability: (1) normal infants, (2) livebirths with clefts, and (3) early abortuses (Niswander et al, 1972). However, the existing evidence to support this hypothesis is not adequate, and data on the sex and cleft type in abortuses are not available. In addition, no distinction has been made among the different categories of clefts, namely clefts without associated malformations, clefts with associated malformations, and clefts with syndromes, and if clefts with associated malformations behave differently epidemiologically from clefts without associated malformations with respect to sex ratio (Emanuel et al, 1973) it is unlikely that this hypothesis can increase our understanding of the etiology of oral clefts.

In summary, clues to etiology, genetic or otherwise, in clefting have been sought in the variations by race, sex, and geographic area. Based on the existing evidence that the incidence of cleft lip, cleft palate, and cleft lip and palate

is three times as frequent in stillbirths and abortions as in livebirths and that clefts with associated malformations and syndromes are different epidemiologic entities from clefts without associated malformations, it is likely that most of the reviewed studies did not measure either the true cleft lip, cleft palate, and cleft lip and palate incidence or the true sex ratio within a race. This may explain the futility of sophisticated mathematical analytic approaches applied to investigate the etiology of orofacial clefts. It is suggested, therefore, that the incidence of cleft lip, cleft palate, and cleft lip and palate should be studied separately for each group, namely livebirths, stillbirths, and abortions and should be reported separately for clefts without associated malformations, clefts with associated malformations, and clefts with syndromes.

CONCLUSIONS

Based on the review of the literature, it can be concluded that:

1. Half of the reviewed studies recorded the risk of developing cleft lip, cleft palate, and cleft lip and palate among livebirths, stillbirths, and abortions or livebirths and stillbirths.
2. Most of the studies reported the incidence rate including clefts with associated malformations and possible syndromes.
3. There is evidence to suggest that clefts with associated malformations are different epidemiologic entities from clefts without associated malformations.
4. The risk of developing cleft lip, cleft palate, and cleft lip and palate in stillbirths, or in stillbirths and abortions, is three times as frequent as in livebirths.
5. The incidence of cleft lip, cleft palate, and cleft lip and palate should be studied separately for each group (i.e., livebirths, stillbirths and abortions) and should be reported separately for clefts without associated malformations, clefts with associated malformations, and clefts with syndromes.
6. The term incidence should be used to report the frequency of orofacial clefts for the previously mentioned groups.
7. More research is needed to study the risk of developing clefts among the various groups that exhibit different epidemiologic behavior for each race.

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