Lack of Regional Variation in IDDM Risk in Japan

JAPAN IDDM EPIDEMIOLOGY STUDY GROUP

OBJECTIVE — To examine the intracountry variation of IDDM incidence in Japan and compare it with data from the British Isles and the U.S.

RESEARCH DESIGN AND METHODS — IDDM incidence was determined with a standardized registry approach in five geographically different areas in Japan (Hokkaido, Tokyo, Yokohama, Osaka, and Kagoshima) with a total at-risk population <15 yr of age of 4.4 million. Data collection was completed under the guidelines of the World Health Organization DiaMond project.

RESULTS — The incidence and patterns of disease were remarkably similar across the five environmentally different areas. Incidence rates per 100,000 were very low and almost identical from northern to southern Japan (Hokkaido, 2.07; Tokyo, 1.65; Yokohama, 1.66; Osaka, 1.78; and Kagoshima, 1.93). This remarkably low intracountry variation of 0.4/100,000 stands in sharp contrast with the 13.0/100,000 regional variation in the British Isles and the 10.6/100,000 variation in the U.S.

CONCLUSIONS — The results suggest that the remarkable genetic homogeneity in Japan may produce uniformity of incidence.

The risk for individuals of developing IDDM varies remarkably based on the country of residence and race, with Asians having a lower incidence than Europoids (1,2). Recent studies suggest that a potent determinant of this difference may be genetic background (3,4). Although the number of papers assessing intercountry variation in incidence rates has increased over the last few years, (2,5,6), intracountry differences have been infrequently examined. To our knowledge, no study has examined both inter and intracountry variation in the incidence of IDDM.

This is important because we might predict that, as with intercountry differences, the intracountry variation in incidence may be determined at least partially by genetic diversity. Areas with considerable genetic heterogeneity may have a large variation in incidence rates, and areas where the genetic diversity is constrained would have a limited variability of incidence. In this paper, we compared the intercountry variability in IDDM incidence rate in Japan with variability in the British Isles (7) and the U.S. (2), which are melting pots with markedly different ethnic and racial distributions across regions. We would predict that in Japan, whose population is genetically homogenous, both absolute and relative incidence variation will be less than that seen in the British Isles and the U.S., despite the enormous environmental variation seen across Japan. A brief review of the history of Japan reveals why our country is so genetically homogenous.

Immigration of people to the island of Japan began ~30,000 yr ago. They were old Mongoloids living in the southern part of China and came through a southern route. A second wave of new Mongoloids, who originated in the northern part of China and whose technologies were more sophisticated, migrated from the Korean peninsula ~20,000 yr ago and governed most of ancient Japan (8). The mixture of these two types of Mongoloids created the original Japanese. Figure 1 demonstrates the facial variation of the old, new, and mixed groups (8). Closure of the country for ~300 yr during the 17th–19th centuries apparently made the Japanese race very homogeneous. Classic work by Matsumoto has shown no evidence of genetic heterogeneity, using genetic markers of human immunoglobulin, except for a very small population of Ainus in Hokkaido and people living in the isolated island near Okinawa, who likely belong to old Mongoloids (9,10). Because both of these populations are quite small, Japan's population of 120 million represents one of the few very large countries in the world with an extremely low degree of genetic variation across its population.

In contrast to the genetic homogeneity, considerable environmental variation exists within the country (Fig. 2), especially in climatic factors such as land height from sea level, mean annual precipitation, and temperature (11). All

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RECEIVED FOR PUBLICATION 28 AUGUST 1992 AND ACCEPTED IN REVISED FORM 7 JANUARY 1993.

IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; WHO, WORLD HEALTH ORGANIZATION; CI, CONFIDENCE INTERVAL; CV, COEFFICIENT OF VARIATION.

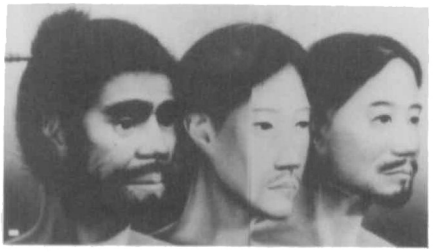

Figure 1—*Faces of Mongoloids. Picture shows difference in appearance of (from left) old Mongoloid, new Mongoloid, and original Japanese suggested by research on structure of skull. Ainus in Hokkaido and limited number of people in southern part of Japan resemble old Mongoloids. Original Japanese look similar to new Mongoloid with some influence of old Mongoloid. From Baba (8).*

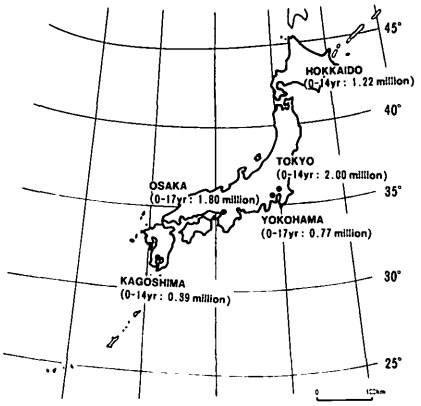

Figure 3—*Location and total population examined for 5 centers. These 5 areas were selected for their high case ascertainment and geographical distribution. Total at-risk population is ~4.4 million.*

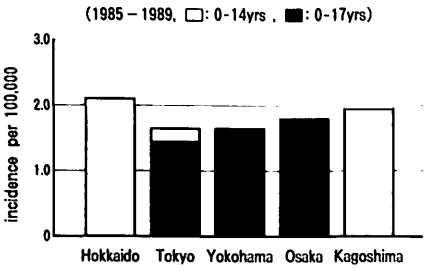

Figure 4—*Overall IDDM incidence for ages 0–14 yr (□) and 0–17 yr (■) for 1985–1989 in 5 areas in Japan from north (left) to south (right).*

of these factors have been strongly associated with the risk of communicable diseases and, in some cases, noncommunicable diseases as well. Sociological factors including annual income (12), medical infrastructure (13), and population density (11) are quite different. Non–diabetes-related diseases vary dramatically across these areas, with >10-fold variation in the incidence rates for measles and influenza (14) and 2-fold variations in mortality rates for ischemic heart disease and cerebral infarction (15). We thus have an interesting natural experiment in that there is homogeneity in genetic background but considerable heterogeneity of environmental factors and heterogeneity of both communicable and noncommunicable diseases across the areas.

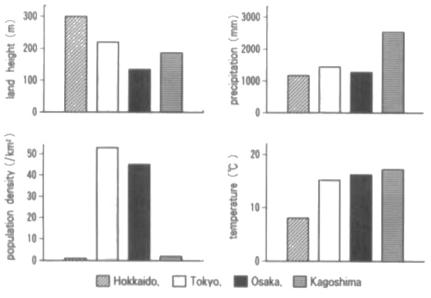

Figure 2—*Environmental differences within Japan.*

RESEARCH DESIGN AND METHODS

— In Japan, two major population-based systems were developed to detect childhood diabetes during the mid-1970s. One is the Central Registry for free medical care for diabetic people <18 yr of age, and the other is urine glucose screening tests for schoolchildren (16). The establishment of these systems made it possible to accumulate accurate IDDM incidence data rather rapidly within the past 5 yr in the various parts of Japan. To develop registries of childhood-onset diabetes, the investigators used hospital records and Central Registry data as the primary sources, with varied secondary sources for external validation. These secondary sources included the urine screening test for schoolchildren, a list of diabetes summer-camp attendees, and files from school nurses. The cohorts included in these analyses were, from the north, Hokkaido (17,18), Tokyo (19), Yokohama (20,21), Osaka (22), and Kagoshima (23) (Fig. 3) with a total population of 4.4 million according to 1985 Japan Census Bureau data. Case ascertainment is well over 95% in each registry.

The variation in incidence in Japan is contrasted with Metcalfe and Baum's recent report from the British Isles (7) and that of the Diabetes Epidemiology Research International Group evaluating the incidence data in the U.S. (2). All registries in Japan, the British Isles, and the U.S. were developed in a comparable manner, as advocated by the WHO DiaMond project (24). The 95% CIs of incidence rates were determined using the Poisson distribution (25).

RESULTS

Overall and age-specific IDDM incidence

The overall incidence rates by area in Japan for 1985–1989 for children 0–14 yr of age at diagnosis were ~2/100,000, ranging from 1.65 to 2.07 with no discernible pattern (Fig. 4). These rates are quite low and practically identical across these very diverse areas. The age-specific incidence rates were also quite similar across different areas (Table 1). What is of particular importance is the extremely low variation in the incidence rates and the tight 95% CI surrounding the variation (mean ± SD, 1.82 ± 0.16; variance, 0.03; 95% CI, 0.01–0.27; 26).

Table 1—*Annual IDDM incidence rates per 100,000 and 95% CI*

AGE-GROUP	HOKKAIDO	TOKYO	KAGOSHIMA
0–4 YR	0.74 (0.39–1.26)	1.16 (0.72–1.78)	1.48 (0.88–2.33)
5–9 YR	1.43 (0.96–2.06)	1.68 (1.14–2.37)	1.76 (1.11–2.63)
10–14 YR	3.65 (3.29–4.56)	2.01 (1.46–2.67)	2.07 (1.39–2.98)
0–14 YR	2.07 (1.73–2.48)	1.65 (1.35–2.01)	1.78 (1.40–2.26)

Dates of study in Kagoshima was 1980–1989.

Intraregion variation comparing Japan with the British Isles and the U.S.

Table 2 presents the inter- and intraregion variation for 18 centers in the British Isles, 6 centers in the U.S., and 5 centers in Japan and its statistics. The average incidence is much lower in Japan than in the two other areas. What is most interesting is the extremely low intracountry variation in the incidence rates in Japan, in contrast with the British Isles and the U.S. The overall range as well as semi-interquartile range (P_{75}–P_{25}) in incidence rates for various parts of the British Isles and overall in the U.S. were 25 and 24 times as greater, respectively, than that seen in Japan (Table 2).

Of the within-country variability, ~40% could be attributable to racial mix, because semi-interquartile range for U.S. whites was much less than the U.S. total (3.00 vs. 5.95). Secondly, the 95% CI surrounding the variance estimates (26) completely overlapped between the U.S. (variance, 17.53; 95% CI, 6.83–105.43) and the British Isles (variance, 10.16; 95% CI, 5.72–22.84), but noticeably did not overlap with the tight CIs seen in Japan (variance, 0.03; 95% CI, 0.01–0.27). Furthermore, it was not only the absolute variation that was much smaller in Japan, but also the relative variation. The ratio of the highest to the lowest incidence rates in the British Isles (2.90) and the U.S. (2.13) were almost twice as great as that in Japan (1.25). The CV in Japan was <33% that seen in the British Isles and the U.S.

CONCLUSIONS— The IDDM incidence rate in Japan reveals very consistent patterns in environmentally diverse areas. Overall, the average incidence in Japan is much lower than that seen in Europoid populations. We recognize that some of the variation in the regions in the British Isles and the U.S. may be attributable to variation in the level of ascertainment or variability of the time periods under investigation. However, the magnitude of differences between Japan, the U.S., and the British Isles surely cannot explain all the enormous intracountry variation differences. It was interesting, also, that when the incidence rates were examined for whites only in the U.S., the variation in the incidence rates was still considerably greater than in Japan. This may reflect the large ethnic variation among Europoids in the U.S., with Minnesota, for example, having its parent population from Scandinavia, a high-risk area of Europe, and Allegheny County, Pennsylvania, having as its parent population the low-risk area of Eastern Europe. It is likely that much of the inter- and intracountry variation results from genetic factors.

The low incidence rates in Japan in contrast to Europoid populations imply that Asians are genetically protected against IDDM compared with people of European origin. Moreover, because of the homogeneity of genetic background across Japan, a remarkable homogeneity in IDDM incidence rates was seen despite marked environmental and social differences, in contrast with the hetero-

Table 2—*Range and semi-interquartile range in incidence rates for various parts of the British Isles, U.S., and Japan*

	BRITISH ISLES	U.S. (TOTAL)	U.S. (WHITE)	JAPAN
	19.80	20.00	20.60	2.07
	17.70	17.80	20.30	1.93
	17.10	15.10	16.90	1.78
	15.80	13.40	16.40	1.66
	15.80	11.40	16.20	1.65
	15.20	9.40	13.80	
	14.90			
	14.60			
	13.50			
	13.40			
	13.30			
	13.10			
	12.80			
	12.40			
	11.80			
	10.90			
	8.00			
	6.80			
MEAN ± SD	13.72 ± 3.11	14.65 ± 4.19	17.37 ± 2.62	1.82 ± 0.16
RANGE	(13.00)	(10.60)	(6.80)	(0.42)
Q_3–Q_1	3.65	5.95	3.00	0.25
P_{50} CV	0.23	0.29	0.15	0.09

Q_3–Q_1, semi-interquartile range.

genous genetic pool and incidence in the British Isles and U.S.

The exact nature of the genetic and environmental contributions to the onset of IDDM, though, remains unknown. Therefore, three possible approaches could be considered to shed additional light on the interaction of genetic and environmental factors in the occurrence of IDDM. The first is an evaluation of IDDM incidence rates in other large populations with limited genetic variability, such as the Han Nationality in China. The Han are the largest group among >50 ethnic groups in China, and its members live in a geographically and culturally diverse area (27). Based on our data, we would predict little to no geographic variation in IDDM incidence among Hans. It would also be important to compare the incidence across regions and ethnic groups in China. We are currently collaborating with the Chinese Academy of Preventive Medicine to establish IDDM registries from a population base of 30,000,000 children throughout China to test this hypothesis as part of our WHO DiaMond project (24).

The second approach would be a multinational case-control study of host susceptibility. A project of this type based on IDDM registries has just begun as one component of the WHO DiaMond project (24), developed by Dr. Dorman. This should be expanded to several areas in Japan and Asia.

The third approach would be a migrant study. Migrant studies are one of the best approaches for evaluating the effect of environmental factors on the occurrence of IDDM. A recent report demonstrated that the British Isles appears to be diabetogenic for its Asian minorities (28). We might expect a similar finding if we examined Asian migrants to the U.S. We are, therefore, planning a low incidence migrant epidemiology study including both Japanese and Chinese heritage populations. It is important to determine whether the rate among Asian migrants in high-risk areas such as Hawaii or California is increased.

Our results point out the importance of evaluating both the inter- and intrapopulation incidence variation. Clearly, almost no variation exists in Japan, in contrast to the British Isles or the U.S. Now we need to find out why the global inter- and intracountry variation in the incidence rates is so diverse. We believe that most of the inter- and intracountry variation has to be explained by genetic differences in the populations at risk. Future studies, such as those underway in the WHO DiaMond project, are needed to elucidate the host-environment interaction in IDDM.

Acknowledgments— We express our sincere appreciation to Drs. S. Baba and Y. Kanazawa for valuable comments on preparing manuscripts.

This paper was presented at the Satellite Symposium of Epidemiology of Diabetes and its Complications at the 14th International Diabetes Foundation Congress, Williamsburg, Virginia, 29 June–1 July 1991.

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