INVESTIGATION OF POSSIBLE CAUSES OF THE CHANGE IN THE SEX RATIO OF LIVE BIRTHS IN JAPAN: PUTATIVE RELATION TO DIOXIN BODY BURDENS

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Introduction

Sex ratio which is the ratio of male to female, of live births in Japan shows a characteristic trend in Japan, i.e., an increase from 1950 to 1969, and a decrease from 1970 to present. A trend of decreasing sex ratios has been reported from several developed countries[1]. We investigated possible causes of the sex ratio changes in Japan, and also analyzed if the change has something to do with the body burden of dixoins in Japanese people.

Methods

Data from the annual vital statistics of Japan are used for analysis. The benchmark dose for sex ratio bias was estimated from Seveso report data[2,3] using benchmark dose software (BMDS) of the US EPA.

Results and Discussion

(1) Sex ratio change of live births in Japan

Sex ratios of live births in Japan steadily changed from 1.049 in 1951 to 1.072 in 1969 (increase by 2.2%), and started decline sharply until early 1980's and slowly thereafter to 1.052 in 1995 (decrease by 1.9%) (Figure). These changes are rather conspicuous compared to reports of declines in the sex ratio from Canada, USA, Denmark and the Netherlands[1] showing decrease by only 0.1-0.3% in these 20-44 years.

As in many developed countries, bearing the first child becomes later in ages of mothers in Japan, such as, 24.4, 25.6, and 29.4 years old in 1950, 1970 and 1998, respectively. Numbers of children born to a mother have been decreased after the world war, such as 4.54, 2.13 and 1.38 in 1947, 1970 and 1998, respectively. To examine the effects of the ages of mother, sex ratio of the live births from different age groups of mother was compared from the data of 1998 (data not shown). Except the age group of 15-19 which produces only 1.5% of the total births, aging of mothers does not seem to lower the sex ratio. The sex ratio of the first born children is somewhat lower than the others, means need for more in-depth study.

Ratio of live births with body weights under 2.5 kg shows opposite pattern to the sex ratio, i.e., high (6.4 and 8.3% for males and females in 1951), low (5.2 and 6.1 for males and females in 1970), high (7.3 and 9.0 for males and females in 1998) again (data not shown). It is conceivable that the sex ratios are lower with the lower body weights in live births through the period of 1951-1998 (0.79-0.89 for 2.0-2.5 kg group, and 0.83-0.86 for 2.5-3.0 kg group). In 1970, 2.5-3.0 kg births comprised 26.8 and 33.7% of total births for males and females, but in 1998 they comprised 37.6 and 46.4% of total births for males and females.

(2) Benchmark dose estimation for sex ratio change in Seveso case

Mocarelli's group reported that there was a dramatic change in sex ratio for increase of female births after exposure to high concentrations of dioxins in Seveso in 1976 [2]. They reported later that the effect seems to be related to the high blood levels of dioxins in exposed fathers [3]. We analyzed the case using BMDS to estimate the benchmark dose for occurrence of this phenomena at 2, 5 and 10% level. Since the original data are limited in the number of cases especially with respect to the background level, putative background data are used for the purpose of the analysis assuming the present background level of exposures in Japan and other developed countries (Table).

Benchmark dose (BMD) and its 95% confidence limit (BMDL) vary with the background data, but BMD and BMDL for 2% or 5% of occurrence, at ca. 80 ppt (fat basis, serum level), and 22-26 ppt may be the approximate estimates. This means the phenomena, if related to body burden of dioxins, and does not depend to dioxin species, the probability of 2% or 5% occurrence of female predominance can be seen at the 4 times present background blood levels of many developed countries including Japan.

Furthermore, we assumed that the Seveso data represent completely statistically binary phenomena that every female or male could have been opposite sex. Estimated value of BMD and BMDL varied with various assumptions. If sex of children of fathers with lower blood levels is changed to opposite one, not much change in BMD or BMDL was seen. However, if we assumed change with the female who is the child of the father at the lowest blood level with the bias to female, there was an shift of BMD and BMDL to higher levels (data not shown).

It might be the case that some environmental agents effect to the selection of sex in live births. We are currently analyzing whether there is any correlation between dioxin body burden in Japan and sex ratio change, because our analysis showed 95% confidence limit of BMD for sex ratio change based on Seveso data is close to current blood level of dioxins among Japanese people.

(3) Sex ratio in stillbirths

Mizuno reported that sex ratio in fetal deaths in Japan has been increasing snce 1970's, and suggested that this may explain decrease of sex ratio decrease in live births[4]. We analyzed the sex ratio changes in still births by the week of gestation, and found very dramatic change occurring only during the gestation week of 12-15. However, the statistics reports that there are many still births with sex unknown in those weeks, which may compensate the difference in numbers of fetal deaths between male and female. Although she neglected the effects of births order or ages of mothers who gave births, our preliminary analysis shown above warrants needs of further analysis. We are investigating in details these and other potential causes to explain this conspicuous effects happening in the real world of human being in clear manner in Japan, that is increase of sex ratio in still births and decrease in live births.

Acknowledgements

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References

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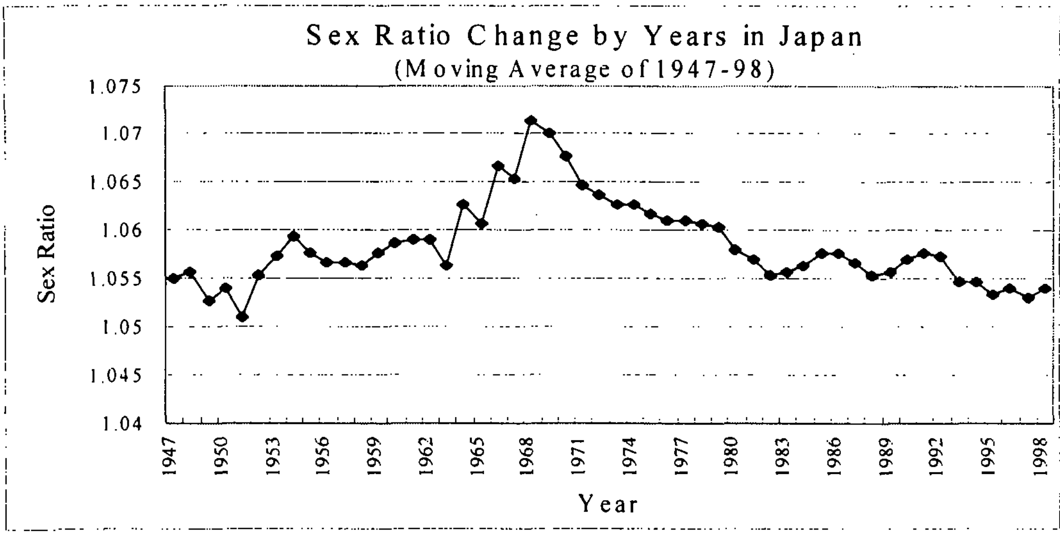

Benchmark Dose and Benchmark Dose Lower Limit Values with Several Putative Background Populations

Dataset	Background population	BMD Level	BMD (ppt)	BMDL (ppt)
Sevesofather3	20ppt (513 males/487 females)	BMD2	79.6	21.5
		BMD5	80.6	26.2
Sevesofather2	14-24 ppt	BMD2	76.9	18.3
	(mix of 3 female and 3 males)	BMD5	77.6	26
		BMD10	78.2	44.3
Sevesofather	20 ppt (51males/49 females)	BMD2	91.6	46.9
		BMD5	92.1	47.5
		BMD10	92.6	47.9
Sevesomother	14-24 ppt (6 damy)	BMD10	59.6	9.9

Extra risk was estimated with 95% confidence limit using log-logistic model
BMD : Benchmark Dose BMDL: Benchmark Dose Lower Limit
BMDx: Benchmark level of an effect at x% increase
Sevesofather3, sevesofather2 and sevesofather : father's serum blood data used.
Sevesomother : data of mother's serum blood data used