7 **Rapid #: -4236676**

Ariel IP: 129.252.80.49

Status	Rapid Code	Branch Name	Start Date
Pending	MYG	Main Library	3/14/2011 6:40:16 AM

CALL #: **QH.R127**

LOCATION: **MYG :: Main Library :: Science Library Journal Collection**

TYPE: Article CC:CCL

JOURNAL TITLE: Radiation research

USER JOURNAL TITLE: Radiation Research

MYG CATALOG TITLE: Radiation research.

ARTICLE TITLE: Genetic monitoring of the human population from high-level natural radiation areas of Kerala on the

ARTICLE AUTHOR:

VOLUME: 152

ISSUE: 6

MONTH:

YEAR: 1999

PAGES: S149-53

ISSN: 0033-7587

OCLC #: MYG OCLC #: 1763361

CROSS REFERENCE ID: [TN:919285][ODYSSEY:129.252.106.237/COLUM]

VERIFIED:

BORROWER: **SUC :: Main Library**

PATRON: **Tim Mousseau**

PATRON ID: mousseau

PATRON ADDRESS:

PATRON PHONE:

PATRON FAX:

PATRON E-MAIL:

PATRON DEPT:

PATRON STATUS:

PATRON NOTES:

System Date/Time: 3/14/2011 7:08:15 AM MST

RADIATION RESEARCH 152, S149–S153 (1999)
0033-7587/99 $5.00

Genetic Monitoring of the Human Population from High-Level Natural Radiation Areas of Kerala on the Southwest Coast of India. I. Prevalence of Congenital Malformations in Newborns[1]

G. Jaikrishan,[a] V. J. Andrews,[a] M. V. Thampi,[a] P. K. M. Koya,[a] V. K. Rajan[b] and P. S. Chauhan[a,2]

[a]*Monazite Survey Project, Cell Biology Division, Bhabha Atomic Research Centre, Trombay, Mumbai—400 085, India; and*
[b]*Directorate of Health Services, Government of Kerala, Thiruvananthapuram—695 037, India*

Jaikrishan, G., Andrews, V. J., Thampi, M. V., Koya, P. K. M., Rajan, V. K. and Chauhan, P. S. Genetic Monitoring of the Human Population from High-Level Natural Radiation Areas of Kerala on the Southwest Coast of India. I. Prevalence of Congenital Malformations in Newborns. *Radiat. Res.* 152, S149–S153 (1999).

In the densely populated monazite-bearing sands of Kerala, on the southwest coast of India, natural radiation dose rates range from 1.0 to over 35.0 mGy per year in certain well-defined high-level natural radiation areas. As a part of the program to assess the health effects of this naturally occurring high-level natural radiation on human populations, monitoring of newborns is being undertaken to determine the incidence of congenital malformations. From August 1995 to December 1998, a total of 36,805 newborns were screened, including 212 (0.58%) stillbirths. There were 36,263 singletons, 536 (1.45%) twins, and 6 born as triplets. The overall incidence of malformations was 1.46% and was dependent on maternal age. The stillborns exhibited a very high malformation rate of 20.75% compared to 1.35% among the live births. Likewise, twins also had a higher malformation rate (2.99%) compared to singletons (1.44%). About 3.5% of the newborns originated from consanguineous marriages. Consanguinity also led to a relatively higher rate of malformations (1.97%) as well as of stillbirths (1.18%). About 92% of the deliveries took place by the maternal age of 29 years and only 1.2% among women above 34 years old. The stratification of newborns with malformations, stillbirths or twinning showed no correlation with the natural radiation levels in the different areas. Thus no significant differences were observed in any of the reproductive parameters between the two population groups based on the monitoring of 26,151 newborns from high-level natural radiation and 10,654 from normal-level natural radiation (dose rate ≤1.5 mGy/year) areas of the Kerala coast.

INTRODUCTION

The biological and health effects of low-level radiation doses continue to be debated, while those of higher doses are well documented (*1*). The estimates of genetic risk in humans exposed to low-dose radiation are based on linear extrapolation to zero dose from the well-documented effects observed at high doses, largely delivered at high dose rates in laboratory models or during accidental exposures. However, there is growing interest as well as controversy over the relationship between the effects of high- and low-dose ionizing radiation due to uncertainties in the assumptions made in the process of extrapolation. The recent evidence of radioadaptive responses and the diversity of radiation effects observed after exposures to extremely low and high doses further contribute to the complex problem of the relationship between high- and low-dose exposures. Therefore, direct studies of humans after low-dose and low-dose-rate exposures assume profound significance. These are also more appropriate for consideration of assessment of risk to occupational workers and radiation protection practices.

The monazite-bearing high-level natural radiation areas of Kerala on the southwest coast of India provide unique opportunities to investigate health effects of low-level chronic radiation exposure directly in humans. The average per capita dose received by the population of this area is about four times the normal background radiation level (*2, 3*). However, the background levels in the region range from ≤1.0 mGy to over 35.0 mGy per year. The radioactivity in this area (a belt about 55 km long and 0.5 km wide) is primarily due to levels of thorium and its decay products ranging from 8–10% in the monazite, which is 1% of the sand and is the highest recorded anywhere. The high-level natural radiation area has distinctive geographical features with backwaters separating the coastal strip from the mainland, and the population is also one of the largest found in high-level natural radiation areas. Humans have been living in this area for over 1,000 years. This provides a unique and perhaps the most appropriate source of material to discern the effects of continuous radiation exposure

[1] Please address correspondence to Dr. M. Sheshadri, Project Manager, Monazite Survey Project, Bhabha Atomic Research Centre, Trombay Mumbai—400 085, India.

[2] Current address: EHS Centre, E1/12/A3, Sector 2, Nerul, Navi Mumbai 400 706, India.

TABLE 1
Congenital Malformations in the Newborns from High-Level Natural Radiation Areas of the Kerala Coast: Single, Twin and Multiple Births

Newborns	Normal	Malformed	Total	Percentage malformed
Total newborns	36,267	538	36,805	1.46
Live births	36,099	494	36,593	1.35
Stillbirths	168	44	212 (0.58)	20.75
Singletons	35,741	522	36,263	1.44
Live births	35,591	482	36,073	1.34
Stillbirths	150	40	190 (0.52)	21.05
Twins	520	16	536 (1.45)	2.99
Live births	504	12	516	2.33
Stillbirths	16	4	20 (3.73)	20.00
Multiple (triplets)	6	—	6 (0.02)	—
Live births	4	—	4	—
Stillbirths	2	—	2 (33.3)	—

Note. Figures in parentheses denote the percentage of the respective event.

during all the stages of human development for many generations.

Studies undertaken in the past (*3, 4*) include dosimetric measurements of radiation levels in the area (*2, 3, 5*), cytogenetic studies of native plants belonging to different genera and species (*6, 7*), and genetic studies in wild rats based on skeletal and dental variants (*8, 9*). In humans, a demographic study in a population of 70,000 individuals showed no significant differences in reproductive parameters, infant mortality, etc. between the high- and normal-level radiation areas (*10*). However, a higher prevalence of Down syndrome among the population from the high-level natural radiation area was reported by Kochupillai *et al.* (*11*), with no case of Down syndrome recorded in the control population. The Department of Atomic Energy (BARC) established a field laboratory in the area to study in depth the biological and health effects of the high-level radiation on the human population, with major emphasis on the genetic effects. This program includes monitoring of newborns for congenital malformations and chromosomal anomalies as well as a demographic health survey and cytogenetic studies among the adult population. The reproductive outcome and the incidence of malformations among the newborns delivered in the hospitals of the study area between August 1995 and December 1998 are summarized in this paper.

MATERIALS AND METHODS

In four state government hospitals catering to the study population, all newborns are monitored for congenital malformations that are identifiable at birth. Two of these hospitals are on the periphery and two are in the midst of high-level natural radiation areas. The studies are being carried out in collaboration with the Department of Health, Government of Kerala, which is responsible for public health in the State. Data pertaining to socio-demographic profile, pregnancy history, lifestyle, occupation, consanguinity, place(s) at which both parents stayed prior to, during and after conception, etc. are elucidated from the family and recorded in proformae designed under the WHO guidelines. The completeness and consistency of information are ascertained at different levels and verified further prior to inclusion in the computer database. The average radiation levels for the family are incorporated for each newborn. The data entry is verified and validated for internal consistency.

The average radiation dose in control areas of Quilon district is 1.2 mGy per year with a range of <1.0 to 1.5 mGy per year. Hence areas with an exposure above 1.5 mGy per year are considered as high-level natural radiation areas and those with less than 1.5 mGy/year as normal-level natural radiation areas. The classification of high-level and normal-level natural radiation is based on the level prevailing at the residence of the mother and provides the opportunity to have built-in controls. Though the mobility of the population is an important factor, a high correlation of the average dose rates in air from terrestrial γ radiation in the outdoors and indoors in the study area (*3*) lends support to the classification.

The proportion of newborns with congenital anomalies across various subgroups was compared using the χ^2 test. The comparison of the prevalence in high-level and normal-level natural radiation areas was made using the relative risk (relative frequency) approach. The significance of the observed relative frequency was judged from the confidence interval (CI). Relative frequency is statistically significant if the CI does not include 1, which is the value of relative frequency under the null hypothesis of no difference between high-level and normal-level natural radiation areas (*12*). To eliminate the possible effects of confounding factors, a stratified analysis was also carried out.

RESULTS AND DISCUSSION

During these studies, from a total of 36,805 newborns examined in the four hospitals, 538 newborns were identified with malformations, an incidence of 1.46% at birth. The prevalence of malformations among 212 stillborns (0.58%) was almost 15-fold higher at 20.8%. The twins also exhibited relatively higher malformation rates (Table 1). Consanguinity resulted in a higher risk of malformations as well as stillbirths. The incidence of malformations was associated with maternal age. An increased prevalence of 2.09% was also seen for gravida four (or more) compared to 1.5, 1.48 and 1.01% for primi, second and third gravida, respectively (data not shown). Males were at a significantly higher risk for malformations compared to females (1.66%

TABLE 2
Congenital Malformations and Stillbirths in the Newborns from High-Level Natural Radiation Areas of the Kerala Coast: Association with Consanguinity, Maternal Age, and Other Characteristics

	Total births		Malformations		Stillbirths[a]	
Characteristics	No.	(%)	No.	(%)	No.	(%)
Total consanguinity	36,805	(100)	538	1.46	212	0.58
Absent	35,535	(96.5)	513	1.44	197	0.55
Present	1,270	(3.5)	25	1.97	15	1.18
Gender						
Male	18,905	(51.4)	313	1.66	155	0.61
Female	17,898	(48.6)	223	1.25	97	0.54
Religion						
Hindu	25,200	(68.5)	365	1.45	141	0.56
Christian	4,382	(11.9)	49	1.12	25	0.57
Muslim	7,223	(19.6)	124	1.72	46	0.64
Maternal age						
15–19	2,584	(7.0)	35	1.35	22	0.85
20–24	18,970	(51.5)	286	1.51	97	0.51
25–29	12,305	(33.4)	155	1.26	66	0.54
30–34	2,505	(6.8)	53	2.12	22	0.88
≥35	441	(1.2)	9	2.04	5	1.13
Radiation area						
High-level	26,151	(71.1)	391	1.50	160	0.61
Normal-level	10,654	(28.9)	147	1.38	52	0.49

[a] Stillbirths include intrauterine deaths, stillbirths and newborns who died immediately after birth.

compared to 1.25%, $P < 0.05$), mainly due to anomalies of the male urogenital system, such as cryptorchidism and hypospadias. As many as 92% of the babies were born to mothers under the age of 30, and only 1.2% to mothers over 34 (Table 2). The major religious groups in the study population are Hindus (68.5%), followed by Muslims (19.6%) and Christians (11.9%). The incidence of malformations among the Hindu subjects varied from 1.30% among Nairs to 2.4% among Arayas, with an overall frequency of 1.45%. It is noteworthy that the Araya ethnic group (1.5% of the total population) also exhibited the highest rate of consanguineous marriages (6.6%). The Arayas, who have traditionally engaged in fishing, are generally concentrated in the coastal area, where the natural background radiation is also relatively quite high (about 68% are exposed to a dose rate of more than 6 mGy per year). The lowest incidence of malformations was among the Christians, which is also the group with the lowest proportion of consanguineous marriages (0.96%). The incidence of malformations showed no association with various radiation levels (Table 3) and was comparable between high-level and normal-level natural radiation areas (1.5% compared to 1.38%; relative frequency of 1.08, 95% CI: 0.90–1.31). Defects of the musculoskeletal system were the most frequent malformations. Twenty-five cases of Down syndrome were identified, with an incidence of 1 in 1472 births. The incidence increased with maternal age, the frequency being 1 Down syndrome case in 2584, 3162, 1538, 358 and 147 births, respectively, in the maternal age groups of 15–19, 20–24, 25–29, 30–34 and ≥35 years (trend χ^2 24.6, $P < 0.001$).

Unlike the other parts of India, the population in the study area is generally literate and health conscious and

TABLE 3
Congenital Malformations in the Newborns from Different High-Level Natural Radiation Areas of the Kerala Coast: Dose Rate and Malformations

Dose (mGy/year) (average)[a]	Total newborns	Newborns with malformations		Relative frequency (95% CI)[b]
		No.	%	
≤1.50 (1.20)	10,654	147	1.38	1.00
1.51–3.0 (1.81)	22,599	337	1.49	1.08 (0.89–1.31)
3.01–6.0 (4.08)	2195	30	1.37	0.99 (0.67–1.46)
6.01–18.0 (13.47)	975	18	1.85	1.34 (0.82–2.17)
≥18.0 (29.53)	382	6	1.57	1.14 (0.51–2.56)
Total	36,805	538	1.46	

[a] Average radiation levels in the respective group: The lowest and highest dose rates recorded in the area were 0.70 and 48.18 mGy per year.

[b] CI denotes lowest and highest 95% confidence intervals. The group (dose rate 6.01–18.0 mGy/year) showing 1.85% malformations had a large proportion of Arayas population, the ethnic group which had the highest consanguineous marriages.

practices a small family norm. The mean maternal age of 24.2 years at delivery was low, with only 8% of the deliveries occurring after the age of 29 years. Primi together with second gravida constituted 90% of the births. The rate of stillbirths was also comparatively lower than in the rest of the country at 0.58%, as was the rate of low-birth weight babies (<2500 g) at 7.5%. The sex ratio among twin births was 1000:1110 compared to 1000:945 among singleton deliveries, probably supporting the hypothesis of the role of X inactivation in the process of twinning of female zygotes (*13*) and consequent preponderance of female monozygotic twins. As expected, the incidence of Down syndrome showed an increase that was dependent on maternal age, with an overall frequency of 1 Down syndrome case in 1472 births. The relatively lower incidence is compatible with the younger maternal age, as reported recently (*15, 16*). At present the 25 cases of Down syndrome are too few to draw a dose response, especially when the radiation levels vary so widely. However, based on the limited data, the incidence of Down syndrome showed no significant differences between high-level and normal-level natural radiation areas, nor there was any association with different radiation levels. These observations are in contrast to the report of Kochupillai *et al.* (*11*), which was based on a population prevalence study and not on newborns. The conclusion drawn by these investigators was beset with the problem of the absence of any Down syndrome case in the normal radiation (control) areas. Surprisingly, there was no maternal age dependence; in fact, the frequency of Down syndrome was much lower above a maternal age of 35 years. Kochupillai *et al.* reported 12 Down syndrome cases in the high-level natural radiation area of the Kerala coast among the study population of 13,000, a frequency of 0.9 Down syndrome cases per 1000. In a recently concluded multicentric study of over 95,000 newborns at three centers in New Delhi, Mumbai and Baroda, the overall frequency of Down syndrome was found to be 1 in 1139 births with clear maternal age dependence (Project Report submitted by Verma, Anand, Modi and Bharucha to BRNS, DAE, 1999). The incidence of Down syndrome in the comparative maternal age group was comparable to that in our present studies. The multicentric study, however, had a higher number of deliveries above the maternal age of 35 years compared to our population. Thus the incidence of Down syndrome in Indian populations from control (normal-level natural radiation) areas further highlights the weakness of the conclusions of Kochupillai *et al.* as discussed by others (see ref. *4*).

It must be pointed out that the incidence of congenital malformations at the various radiation dose rates are based on limited data, especially at the higher radiation levels, and only a large sample size with adequate numbers would provide reliable conclusions. However, the findings are in agreement with other reports (*16, 18*). The genetic studies in the analysis of the data for the children of parents exposed during the Hiroshima and Nagasaki atomic bombing also showed no statistically significant differences compared to the control population (*16*). It is also pertinent to add that in the high-level natural radiation areas of the study population, the age-standardized cancer rate involving a large population group also has not shown any association with radiation background levels (*17*), and the overall prevalence of cancer was comparable to that in the rest of the Kerala state. The Chinese studies in high-level natural radiation areas, based on 32 disorders, have also shown no increase in the congenital malformations associated with radiation levels (*18*). To discern the roles of high-level natural radiation and various socio-genetic factors in the etiology of congenital malformations, a larger sample is required, and efforts continue to achieve these objectives.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the help and unfailing support of the Department of Health of Kerala State, particularly the collaborating medical and paramedical staff of the four hospitals catering to the study area. But for their dedication and hard work, these investigations would not have been possible. The assistance rendered by Mr. P. N. Panicker and other technical staff of our laboratory who have contributed to these studies is also gratefully acknowledged.

REFERENCES

1. United Nations Scientific Committee on the Effects of Atomic Radiation, *Sources, Effects and Risks of Ionizing Radiation*, 1993 Report to the General Assembly. United Nations, New York, 1993.
2. D. S. Bharatwal and G. H. Vaze, Radiation dose measurements in the monazite areas of Kerala State in India. In *Proceedings of the 2nd UN International Conference on Peaceful Uses of Atomic Energy*, Vol. 23, p. 156. United Nations, New York, 1958.
3. C. M. Sunta, A review of the studies of high background areas of the S-W coast of India. In *Proceedings of the International Conference on High Levels of Natural Radiation* (M. Sohrabi, J. U. Ahmed and S. A. Durani, Eds.). Atomic Energy Organization of Iran, Tehran, 1993.
4. K. S. B. Rose, Review of health studies in Kerala. *Nucl. Energy* **21**, 399–408 (1982).
5. K. B. Mistry, K. G. Bhathran and A. R. Gopal-Ayengar, Radioactivity in the diet of population of Kerala coast including monazite bearing high radiation areas. *Health Phys.* **19**, 535–542 (1970).
6. A. R. Gopal-Ayengar, G. G. Nayar, K. P. George and K. B. Mistry, Biological effects of high background radioactivity: studies on plants growing on the monazite-bearing areas of Kerala coast and adjoining regions. *Indian J. Exp. Biol.* **8**, 313–318 (1970).
7. G. G. Nayar, K. P. George and A. R. Gopal Ayengar, On the biological effects of high background radioactivity: Studies on Tradescantia grown in radioactive monazite sand. *Radiat. Bot.* **10**, 287–292 (1970).
8. H. Gruneberg, Genetical research in an area of high natural radioactivity in South India. *Nature* **204**, 222–224 (1964).
9. H. Gruneberg, G. S. Bains, R. J. Berry, L. Riles, C. A. B. Smith and R. A. Weiss, *A Search for Genetic Effects of High Natural Radioactivity in South India.* Report SRS 307, Medical Research Council, Her Majesty's Stationary Office, London, 1966.
10. A. R. Gopal-Ayengar, K. Sundaram, K. B. Mistry, C. M. Suntha, K. S. V. Nambi, S. P. Kaithuria, A. S. Basu and M. David, Evaluation of the long term effects of high background radiation on selected population groups of Kerala coasts. In *Proceedings of the IV International Conference on Peaceful Uses of Atomic Energy*, Vol. II, pp. 31–61. United Nations, New York, 1971.

11. N. Kochupillai, I. C. Verma, M. S. Grewal and V. Ramalingaswamy, Down syndrome and related abnormalities in an area of high background radiation in coastal Kerala. *Nature* **262**, 60–61 (1976).

12. H. A. Khan and C. T. Sempos, *Statistical Methods in Epidemiology*. Oxford University Press, Oxford, 1989.

13. M. C. Phelan, Twins. In *Human Malformations and Related Anomalies*, Vol. II (R. E. Stevenson, J. G. Hall and R. M. Goodman, Eds.). Oxford University Press, Oxford, 1993.

14. C. A. Hecht and E. B. Hook, Rates of Down syndrome at live birth by one-year maternal age intervals in studies with apparent close to complete ascertainment in populations of European origin: A proposed revised rate schedule for use in genetic and prenatal screening. *Am. J. Med. Genet.* **62**, 376–385 (1996).

15. A. D. Carothers, E. Boyd, G. Lowther, P. M. Ellis, D. A. Couzin, M. J. W. Faed and A. Robb, Trends in prenatal diagnosis of Down syndrome and other autosomal trisomies in Scotland 1990 to 1994, with associated cytogenetic and epidemiological findings. *Genet. Epidemiol.* **16**, 179–190 (1999).

16. J. V. Neel, W. J. Schull, A. A. Awa, C. Satoh, H. Kato, M. Otake and Y. Yoshimoto, The children of parents exposed to atomic bombs: Estimates of the genetic doubling dose of radiation for humans. *Am. J. Hum. Genet.* **46**, 1053–1072 (1990).

17. M. Krishnan Nair, N. Sreedevi Amma, P. Gangadharan, V. Padmanabhan, C. Varghese, P. Jayalekshmy, S. Jayadevan and K. S. Mani, Epidemiologic study of cancer in the high background radiation area in Kerala. In *High Levels of Natural Radiation 1996, Radiation Dose and Health Effects* (W. Luxin, T. Sugahara and Z. Tao, Eds.), pp. 271–276. Elsevier Science, Amsterdam, 1997.

18. L. Wei, Y. Zha, Z. Tao, W. He, D. Chen and Y. Yuan, Epidemiological investigations of radiological effects in high background radiation areas of Yangjiang, China. *J. Radiat. Res.* **31**, 119–136 (1990).