REVIEW Jpn. J. Cancer Res. 87, 221–226, March 1996

The U.S.-Japan Cooperative Cancer Research Program: Some Highlights of Seminars, Interdisciplinary Program Area, 1981–1996*

Robert W. Miller

Scientist Emeritus, Genetic Epidemiology Branch, National Cancer Institute, EPN-400, Bethesda, MD 20892–7360, USA

Thirty-one seminars have been held in the 16 years since 1981. A principal interest from the beginning was the genetics of cancer, well before this subject became widely popular. This interest arose in part because of marked binational differences in type-specific cancer rates, such as the very low rates among Japanese for Hodgkin's disease in the young, testicular cancer, Ewing's sarcoma, superficial spreading melanoma, chronic lymphocytic leukemia, and Wilms' tumor (half the U.S. frequency). Three seminars were devoted to the seeming reciprocal relationship between B-cell lymphoma (low in Japan) and certain autoimmune diseases (high in Japan), which is perhaps similar in origin to the male/female differences in the rates for these diseases. A seminar on Li-Fraumeni syndrome led to the recognition of cases among Japanese pedigrees brought to the meeting, and generated a study of its occurrence in Japanese families with adrenocortical carcinoma in a child. Another seminar revealed a marked clustering of rare cancers in Werner's (premature aging) syndrome in Japan, and led to a binational study and analysis of case-reports worldwide. Three seminars on pathology heightened appreciation of the importance of subclassifying cancer by subsite and subtype for racial and other comparisons. Four seminars on biostatistics in cancer research generated a substantial exchange of specialists and trainees in this field.

Key words: Cancer — Genetics — Neoplastic syndromes — Demography — Racial stock

In 1974, representatives of the National Cancer Institute (NCI) and the Japan Society for the Promotion of Science signed a five-year agreement for a Cooperative Cancer Research Program to exchange a) information at seminars, b) brief visits by scientists, and c) resources. When the agreement was extended in 1979, the original 11 areas of interest were combined into four program areas: Etiology; Biology and Diagnosis; Treatment; and Interdisciplinary. Reviewed here are highlights from the seminars of the Interdisciplinary Program Area (two a year for 16 years, six or seven participants from each side). This Program Area, which covers epidemiology, geographic pathology, clinical cancer genetics and biostatistics in particular, has been coordinated throughout by Robert W. Miller of NCI and Haruo Sugano of the Cancer Institute. One or both of them played a role in almost all of the 31 seminars, although 14 were organized by others (Table I).

The seminars have been on a wide variety of subjects, which have featured marked binational differences in cancer experience. They have the advantage of continuity in the approach, and the ability to follow up ideas generated — by convening a related seminar or by the short-term exchange of scientists to implement a study. They are interdisciplinary with regard to scientific specialityand in linking clinical, laboratory and epidemiologic observations.

Lymphoproliferative and autoimmune diseases The first seminar, in 1981, concerned the question: is there a reciprocal relationship between the low rates of lymphoproliferative diseases in Japan and the high rates of certain autoimmune diseases, as compared with the United States. (There is an inverse relationship between these diseases in males and females everywhere.[1]) The neoplasms with low rates in Japan are chronic lymphocytic leukemia, B-cell lymphoma and Hodgkin's disease under 30 years of age. Among the autoimmune diseases with rates 2–3 times higher in Japan than in the U.S., are systemic lupus erythematosus, Hashimoto's thyroiditis and Takayasu's aortitis.[2] Several rare lymphadenopathies also are unique to or more frequent in Japan than elsewhere (Kawasaki's disease, Takatsuki's plasma cell dyscrasia; Kimura's T-cell lymphadenopathy with peripheral blood eosinophilia, adult T-cell leukemia and necrotizing lymphadenitis, especially among women 20–34 years old in Hokkaido). A second seminar on this subject was held in Seattle 18 months later to describe in greater detail the clinical, immunological and pathological features of these unusual diseases.[3]

Individual presentations were given on this subject at intervals during the next ten years. Then, a coincidence of presentations in 1994 led to a reconsideration of the

* In honor of Haruo Sugano, M.D., on his 70th birthday.

Table I. Seminars of the Interdisciplinary Program Area, U.S.-Japan Cooperative Cancer Research Program, 1981–1996

	Title	Date/Organizers
1.	Lymphocytic Diseases in the US and Japan	March 11–12, 1981 R. Miller/H. Sugano/P. Gilman
2.	Neural Crest Tumors	March 1–2, 1982 R. Miller/H. Sugano
3.	T-cell Leukemia/Lymphoma — Role of Human Type C Retrovirus	March 10–11, 1982 G. O'Conor/H. Sugano
4.	Lymphoproliferative Diseases	September 6–7, 1982 M. Kadin/H. Sugano
5.	Human Hepatocarcinogenesis	January 20–22, 1983 W. Mori/H. Popper
6.	Statistical Methods in Cancer Epidemiology	March 1–2, 1984 W. Blot/T. Hirayama/D. Hoel
7.	Role of Pathologists in Cancer Epidemiology	March 10–11, 1984 H. Sugano/R. Miller
8.	Etiologic Importance of Cancer Subtypes and Subsites	October 16–17, 1984 H. Sugano/R. Miller
9.	Adult-type Cancer under Age 30	March 11–13, 1985 H. Sugano/R. Miller
10.	Cancer Epidemiology in SE Asia	December 12–13, 1985 H. Sugano/K. Aoki/R. Miller
11.	Bladder Cancer	March 24–25, 1986 S. Cohen/N. Ito
12.	Hepatitis B in Hepatocellular Carcinoma	January 29–30, 1987 T. London/T. Kitagawa
13.	Genetics of Human Cancer	March 23–25, 1987 F. Li/H. Takebe
14.	Melanoma	November 13–15, 1987 T. Fitzpatrick/K. Jimbow
15.	Li-Fraumeni Syndrome	March 21–23, 1988 R. Miller/F. Li/H. Sugano
16.	Biostatistics	November 11–13, 1988 D. Hoel/T. Yanagawa
17.	Cancer Registries in Japan and in the American Association Central Cancer Registries	March 9–10, 1989 K. Aoki/B. Hankey
18.	Gastrointestinal Cancer: Ethnicity and Some Other High-Risk Groups	March 10–11, 1990 R. Miller/H. Sugano
19.	Genes Controlling Breast Cancer Behaviour	March 26–28, 1990 K. Matsumoto/W. McGuire
20.	Transplacental & Transgenerational Carcinogenesis	November 13–14, 1990 J. Rice/T. Nomura
21.	Cancers of the Kidney	February 18–19, 1991 H. Sugano/R. Miller
22.	Genetic Analysis of Hepatocarcinogenesis	February 8–9, 1992 T. Kitagawa/N. Drinkwater
23.	US-Japan Differences in Cancer Experience	March 12–13, 1992 R. Miller/H. Sugano
24.	Biostatistics	November 9–11, 1992 D. Hoel/T. Yanagawa
25.	Retrovirus and Cancer: US-Japan Clinical Epidemiological Studies	January 6–8, 1993 W. Blattner/S. Hino
26.	Ethnic Differences in Cancer Occurrence	March 24–25, 1994 R. Miller/K. Aoki
27.	Cancer Clusters	February 14–15, 1994 R. Miller/H. Sugano
28.	Genetic Syndromes with High Risk of Cancer	February 6–7, 1995 R. Miller/H. Sugano
29.	Lymphoma & Autoimmune Diseases: A Reciprocal Relationship	February 9–10,1995 R. Miller/S. Sonoda/H. Sugano
30.	Molecular Pathology	February 12–13, 1996 Y. Nakamura/W. Nelson
31.	Cancer in Werner Syndrome	February 15–17, 1996 M. Goto/G. Martin/R. Miller/H. Sugano

seeming reciprocal relationship. At a seminar on cancer clusters, Shunro Sonoda (Kagoshima University) spoke on marked differences in HLA haplotypes in patients with human T-cell leukemia virus (HTLV)-I lymphoproliferative disease as contrasted with HTLV-I-associated myelopathy, an autoimmune disease. Other autoimmune diseases associated with HTLV-I are uveitis, Grave's disease, Sjögren's disease, and rheumatoid arthritis. At the next seminar, in which the U.S.-Japan differences in rates of lymphoma and autoimmune diseases were updated in detail by Stuart C. Finch (Robert Wood Johnson Medical School, New Jersey), the idea arose that further understanding might be sought using the model set by HTLV-I, with its different manifestations related to HLA haplotypes. At a seminar in 1995, specialists in lymphoma or autoimmune diseases discussed this question. It was noted that in Japan about one-third of various autoimmune diseases have high rates, one-third have low rates and one-third have rates similar to those in the U.S. Lymphoma occurs late in at least one autoimmune disorder, Sjögren's disease, after gammaglobulin levels, typically high, fall to abnormally low levels. In general, this immunologic change does not occur in autoimmune disorders that have no excess of lymphoma. Lymphoma rates are high in immunodeficiency disorders, either inborn (as in ataxia-telangiectasia) or acquired (as from immunosuppressive drugs for organ transplantation.[4]) Ikehara and his associates (Kansai University) have demonstrated that autoimmune diseases can be induced in mice by transplantation of marrow stem-cell concentrates from mice with diabetes mellitus (insulin-dependent or not), immune thrombocytopenia, segmental glomerulonephritis or systemic lupus erythematosus.[5] Several human bone-marrow recipients have developed autoimmune disease from affected donors.[5] Thus, the origin of autoimmune diseases, either organ-specific or systemic, is attributable to defects in hematopoietic stem cells, which produce polyclonal abnormal proliferations. The reciprocal relationship between B cell lymphoma and certain autoimmune diseases, then, may be coincidental and not explained by a pathogenesis in common. Much of the information exchanged was new to the seminar participants, because their disciplines seldom cross at meetings.

Genetics of cancer In the early years of the program, the genetics of cancer was not a popular subject in either country, but about half of the seminars focused on it, beginning with the first in this series (Table I). Racial differences in cancer occurrence, presumably genetic in origin, were a recurrent theme initially explored for an array of diseases in 1987 at a seminar on adult-type cancer under age 30.[6] Among the findings reported were very low rates in Japan for Ewing's sarcoma, Hodgkin's disease, B-cell lymphoma, testicular cancer, melanoma and breast cancer; and the rate for Wilms' tumor is about half that in the U.S. In the U.S. among persons 15–29 years of age, these malignancies account for 58% of all cancers in males and 40% of those in females. Cancer clinics in Japan have a fortunate deficiency of cases in this age-range as compared with the U.S.

Among young Japanese, several cancers have high rates. Stomach carcinoma, so common in Japanese adults, begins its rise before the age of 30 (an average of 550 deaths annually), and diffuse carcinoma predominates, as contrasted with the intestinal type later in life. Some studies indicate that in Kyushu the rate of pineal tumors in childhood is 12 times greater than that in other countries. Another rarity, more common in Japan than in the U.S., is maxillary sinus cancer, which causes an average of 17 deaths annually under age 30.

Interest in the research implications of these binational differences has increased with advances in molecular biology. A volume on racial differences in cancer occurrence is being planned for publication in Japan.

Li-Fraumeni syndrome (LFS) was the subject of a seminar in 1988.[7] The syndrome was first described in the U.S. in 1969 and pedigrees have since revealed the mode of genetic transmission and the array of cancers that aggregate in the families or as multiple primary cancers in individuals. Efforts to locate the gene had been unsuccessful. The seminar brought the syndrome to the attention of the Japanese, who presented family case-histories involving individual neoplasms in the syndrome: breast cancer, osteosarcoma, soft-tissue sarcoma, brain tumors, leukemia and adrenocortical carcinoma (ACC). Some of the family histories or multiple primary cancers in Japanese were thought to be possible LFS. The most promising in this regard were families with childhood ACC, a very rare neoplasm. It was suggested that a study be made of cancer in families in which the index case was a child with ACC. Yukiko Tsunematsu (National Children's Hospital) spent a month in the U.S. learning more about the syndrome and pedigree analysis under the guidance of Louise C. Strong (Anderson Hospital, Texas) and Anna Meadows (Children's Hospital of Philadelphia). The study revealed that among the families of 47 children with ACC, one fulfilled all the criteria for LFS, and three others almost did; e.g., a child with ACC, whose brother died of a brain tumor and whose mother, maternal grandmother and maternal great-grandmother had developed breast cancer.[8]

Neural crest tumors In 1982, before much thought was being given to the interrelations of neural crest tumors, a seminar was held on this subject. The presentations revealed the array to include melanoma, neuroblastoma, pheochromocytoma, meningioma, multiple endocrine neoplasia (MEN) syndromes types II and III, and the neurofibromatoses (NF). The participants synthesized

the information into a schematic diagram to show that a gene acting on the "trunk line" early in embryogenesis could explain the syndromes (MEN and NF), while genes acting later could account for the familial tumors that occur in pairs or individually.

Prince Masahito spoke of the high frequency of melanoma in Japanese carp at about 12 years of age. The lesions are red, black or iridescent, depending on the color of the scales at the site affected. Ten years later at a seminar on renal cancer he reported that one percent of farm-raised eels developed Wilms' tumor, which is perhaps related to a carcinogen that develops in the overpopulated tanks in which the eels were raised.

Melanoma A seminar on superficial spreading melanoma in 1987 focused attention on its very low rate among Japanese as compared with Caucasians, whose frequency of the disease is related to exposure to sunlight. Japanese were thought to be protected by their skin pigmentation. More likely explanations may be their avoidance of sun exposure and a diminished genetic susceptibility as evidenced by a low frequency of the dysplastic nevus syndrome, which predisposes to superficial spreading melanoma and is found in about 33% of U.S. cases.[9] Acral lentiginous melanoma, which occurs on the palms, soles and mucous membranes, apparently has the same frequency in Japan as elsewhere, 0.16 new cases per 100,000 per year.[10] In Japanese under 30 year of age, a high frequency of meningeal melanoma has been reported — 23% of all melanoma in this age-range. This information was extracted from the Annual Review of Pathological Autopsy Cases in Japan, 1958–82. The proceedings of the meeting were published.[11]

Pathology, subtypes/subsites and epidemiology In March 1984 a seminar on the role of pathologists in epidemiology enhanced our appreciation of the importance of subtypes and subsites in the classification of cancer. For example, morphologic sub-classification of Wilms' tumor uncovered rhabdoid tumor of the kidney and clear-cell sarcoma of the kidney as entities that have different natural histories and a less favorable response to therapy than Wilms' tumor does. The excess of gastric carcinoma in Japan as compared with the U.S. is greatest in the pyloric antrum, not the stomach in general. Distribution by cell types may differ from usual when the neoplasm is environmentally induced. The seminar served as a prologue to the next one, which considered further the importance of sub-classifying cancers. Subtypes and subsites may be clinically determined — by syndromes, for example, as in a family cluster of renal cell carcinoma associated with a chromosome 3:8 translocation, or in family aggregation of certain dissimilar tumors (that later became known as the LFS). Subclassification then could be by gross anatomy, natural history, metastatic patterns, cytohistology, histochemistry, cell surface markers and other antigen identification, ultrastructure, cell products and chemical receptors, chromosomal and DNA abnormalities, familial vs sporadic occurrence, demography, response to therapy, and host susceptibility, including racial differences. In 1990 a seminar was held on subsites at high risk in aerodigestive cancer with regard to race and other factors. It was noted that each of 5 major racial groups had small areas of the aerodigestive tract at very high risk of cancer: the nasopharynx of Chinese, the mid-esophagus of U.S. Blacks (squamous cell carcinoma), the lower esophagus of U.S. White males (adenocarcinoma, Barrett's esophagus); the pyloric antrum of Japanese, and the gall bladder of American Indians.

Biostatistics in cancer research Although Japan has a 2000-year history of mathematics, not much attention had been given to biostatistics. A seminar organized by William J. Blot (NCI) and Akio Kudo (Kyushu University) in Hiroshima in 1978 (under the earlier binational program) brought Americans and Japanese together for the first time to discuss statistical and methodological issues in cancer epidemiology. Additional seminars in 1983, 1988 and 1992 furthered these discussions. Proceedings from the first and third seminars were published in Environmental Health Perspectives[12, 13]; and the second was published as a separate volume.[14] The first three meetings were held in Hiroshima because of the concentration of biostatistical talent there at the Radiation Effects Research Foundation (RERF) and Hiroshima University. David G. Hoel (National Institute of Environmental Health Sciences), introduced by the seminar to RERF, returned to serve two terms as the Chief of Biostatistics there, organized the third and fourth seminars, and invited a series of Japanese mathematicians to the U.S. as Fellows in biostatistics. Takeshi Yanagawa (Kyushu University), the Japanese organizer for all but the first seminar, has stated that these meetings and their proceedings introduced to Japan novel statistical methods in cancer epidemiology such as proportional hazard models, relative risk regression models and geographic clustering on cancer maps. The seminars played a role in raising the frequency of case-control studies reported at the annual meeting of the Japan Epidemiological Association from zero to about 20% of all presentations in 1992.

Transgenerational carcinogenesis In 1990, Gardner *et al.*,[15] reported a small cluster of leukemia among persons under the age of 25 whose fathers were exposed to low doses of ionizing radiation at the Sellafield nuclear power plant (U.K.) in the 6 months before conception of the affected child. A seminar was held in 1990 to assess current evidence for preconceptional or intrauterine exposures as possible causes of human cancer. Since 1950, according to Lucy M. Anderson (NCI), 29 reports and 2

abstracts had been published which found transgenerational carcinogenesis in rats or mice treated with 6 different chemical carcinogens or X-rays. The study of X-rays was by Taisei Nomura (Osaka University). Five papers described negative results. The mode of genetic transmission could be through a heritable structural gene change or through epigenetic cellular imprinting of the gametes. The classical geneticists present regarded the hypothesis that a genetic mutation was responsible as untenable, because extensive evaluation of numerous measures of genetic effects of radiation had been made of atomic-bomb survivors, and none showed a statistically significant increase. In particular, no increase has been observed in the frequency of known heritable disorders, such as retinoblastoma. It is strange, they said, that leukemia, not known to be due to germ-cell mutation in humans, would be transmitted genetically after preconception radiation exposure. The possibility of genetic imprinting could not be discounted by the classical geneticists. The Sellafield leukemia cluster was found in persons under 25 years of age, an unusual cut-off age that includes children, adolescents and young adults. This cluster of leukemia has since been judged not to be due to radiation.[16] Many geographic clusters of leukemia occur by chance.[17] Animal experiments that show transgenerational carcinogenesis have been reported from Japan, France, Italy, Russia and the U.S.,[18] but remain unexplained.

Hepatic carcinoma Three seminars were held on hepatocarcinogenesis. In one, Masamichi Kojiro[19] (Kurume) described studies, perhaps possible only in Japan, in which hepatitis B infection (HBV) was found in 26% of patients with *Schistosoma japonica* and primary hepatic carcinoma (PHC) as compared with 8.5% of patients with PHC without *S. japonica.* Thorotrast-associated malignancies showed no association with HBV. Other influences include alcohol abuse, aflatoxins, chemicals, immunologic status, nutrients (e.g., iron) and chronic HBV infection.

Cancer epidemiology in Southeast Asia One workshop was held on cancer epidemiology in Southeast Asia. Special attention was being paid to the influence of lifestyle, diet and habits on the occurrence of cancer and precancerous lesions. Two reports on other subjects were exceptional. A. Hakura (Osaka) described the occurrence of skin cancer in 36 of 66 patients with epidermodysplasia verruciformis, all but two of whom had human papilloma virus type 17 or 20. The other unusual finding, reported by Hiraku Takebe (Kyoto), was the absence of neurological abnormalities in Korean patients with xeroderma pigmentosum, unlike Japanese and other patients with complementation group A or D. One conclusion of the workshop was that it seems better to move from clinical observations to epidemiologic and laboratory research rather than to formulate hypotheses based solely on epidemiologic observations.

November 1987: Dr. Sugano and Dr. Miller, who may well be discussing subjects for next year's seminars.

Cancer clusters A seminar on cancer clusters, held in 1994, concerned aggregations of cancer, in time and space or family. Makoto Goto (Tokyo Metropolitan Otsuka Hospital) spoke on the remarkable number of case-reports of cancer in Japanese with Werner's (premature aging) syndrome. His collection of cases was unknown to oncologists until Sugano noted a brief description in a weekly newsletter, and, after discussions, invited him to speak at the seminar. Patients with this rare recessive disorder had marked excesses of soft-tissue sarcoma, osteosarcoma, melanoma, meningioma, thyroid carcinoma and myeloid disorders. A complete bibliography had not yet been assembled. Over the next 15 months Goto, Miller, Ishikawa and Sugano searched the literature for reports on Japanese (127 cases) and non-Japanese (35 cases), and prepared a paper for publication.[20] The non-Japanese had a marked excess of sarcomas and meningioma but not of thyroid carcinoma or melanoma — which in the Japanese was of the feet (13 cases) or intranasal (5 cases, including two sisters). Unusual features of Werner's syndrome include short survival of its fibroblasts in culture — 20 instead of the usual 60 doublings, chromosomal instability *in vitro,* diminished level of telomerase, and disequilibrium of genetic markers near the gene locus (chromosome 8) in Japanese cases, but not in occidental cases of the syndrome.

Genetic syndromes with high risk of cancer At the next seminar, which concerned genetic syndromes with high risk of cancer, it was shown that a different array of cancers occurs in other hereditary chromosomal disorders with congenital anomalies (Bloom's syndrome, Fanconi's syndrome, and ataxia-telangiectasia), and that

Li-Fraumeni family cancer syndrome bears some resemblance to Werner's syndrome in its excess of osteosarcoma and soft-tissue carcinoma, but not in the other four cancers most often seen in LFS. Also, unlike Werner's syndrome, LFS has no systemic disorders. These peculiarities of occurrence should be explained when the gene for Werner's syndrome is cloned, and its mechanism of action determined. Cancer in Werner's syndrome will be the subject of a seminar in 1996.

In perspective The exchange of information was interdisciplinary across an array of topics and within each topic, often ranging from population studies to DNA findings. As reflected above, each side brought information to the other, which provided basis for research of benefit not only to the participants but also to the wider world of cancer etiologists.

(Received September 4, 1995/Accepted December 6, 1995)

REFERENCES

1) Purtilo, D. T. and Sullivan, J. L. Immunological bases for superior survival of females. *Am. J. Dis. Child.*, **133**, 1252–1253 (1979).
2) Miller, R. W., Gilman, P. A. and Sugano, H. Differences in lymphocytic diseases in the United States and Japan. *J. Natl. Cancer Inst.*, **67**, 739–740 (1981).
3) Kadin, M. E., Berard, C. W., Nanba, K. and Wakasa, H. Lymphoproliferative diseases in Japan and Western countries. *Hum. Pathol.*, **14**, 745–772 (1983).
4) Sondel, P. M. Tumor immunology and pediatric cancer. *In* "Principles and Practice of Pediatric Oncology," 2nd ed., ed. P.A. Pizzo and D.G. Poplack, pp. 92–93 (1993). J.B. Lippincott, Philadelphia.
5) Ikehara, S. Intractable diseases and bone marrow transplantation. *Pathol. Int.*, **44**, 817–826 (1994).
6) Miller, R. W. and Sugano, H. U.S.-Japan Cooperative Cancer Research Program report of a seminar on adult-type cancer under age 30. *Gann Monogr. Cancer Res.*, **33**, 193–204 (1987).
7) Miller, R. W., Li, F. P. and Sugano, H. The family syndrome of sarcoma, breast cancer and other neoplasms: meeting report. *Jpn. J. Cancer Res.*, **79**, 1155–1158 (1988).
8) Tsunematsu, Y., Watanabe, S., Oka, T., Kawa-Ha, K., Hirata, Y., Yamanaka, H., Ohira, M. and Ono, M. Familial aggregation of cancer from proband cases with childhood adrenal cortical carcinoma. *Jpn. J. Cancer Res.*, **82**, 893–900 (1991).
9) Greene, M. H. Rashomon and the Procrustean bed: A tale of dysplastic nevi. *J. Natl. Cancer Inst.*, **83**, 1720–1724 (1991).
10) Elwood, J. M. Epidemiology and control of melanoma in white populations and in Japan. *J. Invest. Dermatol.*, **92**, 214S–221S (1989).
11) Jimbow, K., Wick, M. M., Kukita, A., Fitzpatrick, T. B. and Hori, Y. (eds.) Proceedings of the United States-Japan Melanoma and Skin Cancer Seminar on the Biology and Comparative Features. *J. Invest. Dermatol.*, **92**, 199S–331S (1989).
12) Kudo, A., Blot, W. and Yanagawa, T. Japan-U.S. conference on biostatistics in the study of human cancer. *Environ. Health Perspect.*, **32**, 1–307 (1979).
13) Aoki, K., Hoel, D. G. and Yanagawa, T. The third Japan-U.S. conference on biostatistics in the study of human cancer. *Environ. Health Perspect.*, **87**, 1–182 (1990).
14) Blot, W. J., Hirayama, T. and Hoel, D. G. (eds.) "Statistical Methods in Cancer Epidemiology" (1985). Radiation Effects Research Foundation, Hiroshima.
15) Gardner, M. J., Snee, M. P., Hall, A. J., Powell, C. A., Downes, S. and Terrill, J. D. Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear power plant in West Cumbria. *Br. Med. J.*, **300**, 423–429 (1990).
16) Doll, R., Evans, H. J. and Darby, S. C. Paternal exposure not to blame. *Nature*, **367**, 678–680 (1994).
17) Neutra, R. R., Swan, S. and Freedman, D. Clusters galore. *Arch. Environ. Health* (abstr.), **45**, 314 (1990).
18) Tomatis, L. Transgenerational carcinogenesis: a review of the experimental and epidemiological evidence. *Jpn. J. cancer Res.*, **85**, 443–454 (1994).
19) London, W. T. and Kitagawa, T. Summary of the U.S.-Japan seminar on hepatitis B virus and hepatocellular carcinoma, January 29–30, 1987. *Jpn. J. Cancer Res.*, **78**, 869–874 (1987).
20) Goto, M., Miller, R. W., Ishikawa, Y. and Sugano, H. Excess of rare cancers in Werner syndrome. *Cancer Epidemiol. Biomarkers Prev.* (in press).