B Non-cancer diseases and abnormalities

(1) Thyroid diseases

(a) Benign tumors

Summary

A representative form of non-cancer thyroid nodules, also known as benign nodules, is benign thyroid tumors (follicular adenoma or thyroid adenoma). Also falling under the classification benign thyroid nodules in terms of non-neoplastic lesions are adenomatous nodules, which are hyperplastic lesions, and nodular lesions accompanying chronic thyroiditis. For certain diagnoses of benign thyroid tumor, histological testing based on surgical biopsy is essential, imposing a limitation on research into benign tumors. For that reason, investigations in the field of radiation epidemiology frequently target benign and malignant solid thyroid nodules together or benign nodules alone. In cross-sectional prevalence research of A-bomb survivors and persons exposed to radiation other than from the atomic bombings, risks of thyroid nodules, benign nodules, and benign tumors increased with increasing thyroid radiation dose. However, continued longitudinal study of this topic is necessary.

(b) Functional disorders

Summary

Thyroid dysfunctions include hypothyroidism and hyperthyroidism. In research on A-bomb survivors thus far, no significant association has been observed between thyroid radiation dose and hypothyroidism or its main cause chronic thyroiditis (thyroid autoantibody positivity). In a study of Nagasaki A-bomb survivors in the 1980s, however, association with thyroid radiation dose was suggestive only in the case of thyroid autoantibody positive hypothyroidism, a result that could not be reproduced in a study of the Hiroshima and Nagasaki survivors that took place in the first decade of the 2000s. No observational results have suggested an association between hypothyroidism at the clinically detectable level and radiation exposure from accidents at nuclear power plants or other nuclear facilities, or from nuclear weapons testing. Nevertheless, among studies after the Chernobyl nuclear accident, results in one report suggested an association with increased levels of thyroid stimulating hormone (TSH), although most of the report's cases comprised subclinical hypothyroidism. Moreover, reports of several studies noted a significant association between thyroid autoantibody positivity and thyroid radiation dose, whereas others indicated the contrary, making a continuous large-scale study based on precise thyroid radiation dose data and uniform diagnostic standards desirable in the future. With respect to hyperthyroidism, no results have as yet suggested clear effects of radiation exposure, although few studies have taken up that theme, leaving the topic an important research consideration for future investigation.

(2) Parathyroid diseases (dysfunctions)

Summary

Regarding primary parathyroid diseases among A-bomb survivors, prevalence of parathyroid tumor and hyperparathyroidism has been reported to increase with increasing

radiation dose. The prevalence of hyperparathyroidism increased 4.1 times per Gy of radiation exposure, with greater risk the younger the age at exposure. Numerous reports have indicated that, following radiation treatment for benign tumors in childhood, the risks of developing parathyroid tumor and hyperparathyroidism increase after a relatively lengthy latency period. As of this writing, however, no reports have shown a rise in hyperparathyroidism following iodine-131 (I-131) treatment for thyroid diseases.

(3) Ocular diseases

Summary

Among the various types of ocular tissue, the lens is the most susceptible to radiation's effects. Radiation injures the epithelial cells of the eye lens and denatures lens fibers, giving rise to posterior subcapsular cataract. It is difficult to distinguish this type of cataract from senile cataract caused by aging based only on properties of the cataract. For 'radiation cataract,' which appeared fairly early after the atomic bombings, the existence of definite radiation effects with a threshold dose is considered possible. Over the long term, however, the threshold level at which effects take place has been shown to be lower than previously believed, allowing the possibility that there might in fact be no threshold. In research conducted by Minamoto et al. on Hiroshima and Nagasaki A-bomb survivors 55 years after the atomic bombings, significant radiation effects were observed in posterior subcapsular cataract and cortical cataract. Nakashima et al. reexamined the issue using the same cohort based on DS02, and found the same significant radiation effects in posterior subcapsular cataract and cortical cataract, with threshold doses of 0.7 Sv and 0.6 Sv, respectively. However, because the study's 90% confidence interval (CI) lower limit was less than 0 Sv, the conclusion was drawn that no threshold exists. Neriishi et al. conducted a study of A-bomb survivors who had undergone cataract surgery, resulting in the finding that the estimated threshold dose for cataract surgery is 0.1 Gy, with a CI upper limit of 0.8 Gy. This dose is significantly lower than the threshold dose conventionally used for radiation cataract that obstructs vision. Studies of victims of the Chernobyl nuclear power plant accident have suggested a threshold dose of around 0.35 Gy for posterior subcapsular cataract developing shortly after the accident, pointing to the possibility of cataract development even at low doses. Some reports have indicated numerous cases of posterior subcapsular cataract among medical practitioners, and many others have shown large numbers of cases of posterior subcapsular cataract and cortical cataract among astronauts and airplane pilots. The possible lack of a threshold dose in radiation cataract is a topic that requires further investigation given the increasing numbers of elderly among A-bomb cataract patients and the increasing aspects of senile cataract among such cataract cases. Moreover, the issue of radiation exposure among astronauts and pilots, together with occupational exposure among medical practitioners, is expected to grow ever more important in the future.

(4) Circulatory diseases

Summary

Follow-up studies on the cardiovascular system after high-dose irradiation of at least 40 Gy for treatment of malignant tumors have revealed an association with circulatory disease incidence and mortality many years after treatment. With respect to

cerebrovascular disease, it is now understood that high-dose irradiation of the cervical region can cause stroke through stenosis of the carotid artery. Radiation damage in circulatory disease mainly comprises vascular endothelium injury and tissue fibrosis. Low-dose radiation effects have been investigated in follow-up studies of patients undergoing radiotherapy for benign disease, radiation workers, and other radiation-exposed populations, but no definite conclusion has yet been reached with respect to an association between radiation exposure and circulatory disease. Arteriosclerotic cardiovascular disease, the most prevalent of the circulatory diseases, involves many modifying factors, such as age, blood pressure, and smoking. Differences in study details and analysis methods among the epidemiological research efforts conducted into radiation's effects on this disease are suspected of being at the root of the disparate results. In a follow-up study of clean-up workers in the Chernobyl nuclear accident, an association between cardiovascular disease and daily radiation exposure levels, not only cumulative doses, has been observed.

With respect to cardiovascular disease in the Hiroshima and Nagasaki A-bomb survivors, a significant association has been observed between radiation dose and mortality from stroke and circulatory disease other than stroke in the LSS cohort. On the other hand, with regard to incidence of circulatory disease, research involving the AHS has not to this point indicated a significant association with radiation dose. Nevertheless, in A-bomb survivors exposed at ages less than 40, an indirect dose-response relationship has been observed between incidence of myocardial infarction and radiation. In testing for arteriosclerosis, even after eliminating effects of age and the most important related factor ischemic heart disease, pulse wave velocity (PWV) was found to be high in men proximally exposed to the atomic bombings.

The possibility exists that low-dose radiation exposure may lead to increased cardiovascular disease occurrence years later, but no definitive conclusion has yet been reached regarding that issue. For this reason, continued follow-up of the A-bomb survivors is of vital importance.

(5) Liver diseases

Summary

Among A-bomb survivors, an association has been shown between radiation dose and an increase in hepatitis B virus carriers. However, no findings have indicated such an association among hepatitis C virus antibody-positive individuals to date. Prevalence of liver cirrhosis based on autopsy diagnoses has been found to be significantly associated with radiation dose only in Hiroshima females, but in studies with greater case numbers, association with radiation dose was merely suggestive. Moreover, reports on radiation dose and mortality from liver cirrhosis have been inconsistent, with some showing a significant association, some a suggestive association, and others no association.

As for individuals exposed to other forms of radiation, whole-liver radiotherapy exceeding 30 Gy over three weeks is thought to give rise to parenchymal liver disease. Internal exposure to thorotrast is associated with significantly increased mortality from liver cirrhosis, but no findings have been obtained pointing to an association with such mortality in persons occupationally exposed to low-dose radiation.

(6) Gynecologic disorders

Summary

Research into A-bomb radiation exposure effects on reproductive function was initiated in September 1945, shortly after the bombings. Many reports have shown no association between radiation exposure and age at menarche. The proportion of females experiencing amenorrhea—absence of menstruation—immediately after the bombings was higher among proximal survivors and among those who experienced acute radiation symptoms. Average age of menopause onset was lower in the exposed group and markedly lower among those who experienced acute radiation symptoms. Research into A-bomb survivors has not demonstrated a significant association between radiation exposure and fertility. The AHS conducted by RERF has found a significant association between uterine radiation dose and prevalence of uterine nodules. In females who received radiotherapy for childhood cancer and benign uterine hemorrhage, which employ doses that are higher than those received by the A-bomb survivors, associations have been observed between radiation dose, menstrual irregularities, early menopause, delayed pubertal development, decreased fertility rates, and low birth weight. Some reports have linked developmental disorders in puberty and low rates of fertility to irradiation of sites other than the abdominal region, such as the hypothalamus and pituitary gland

(7) Skin diseases

Summary

Radiation-induced skin disorders depend on type of radiation, source, dose, dose rate, exposure period, dose distribution, irradiated site, and extent of exposed site. A-bomb survivors experienced burns and injury due to the thermal rays and blast from the atomic bombs, and the poor hygienic conditions in that period caused delayed treatment. In severe cases, contraction of scars produced deformities and functional disorders. Epilation, which is an acute radiation symptom, was observed in association with exposure distance and shielding conditions. Hyperproliferation of scar tissue, such as hyperplastic scarring and keloids, was observed at scar sites. Although there were many recurrences of such cases following surgical procedures performed for the purpose of treatment, the number of cases declined after peaking around 1946-47. In a clinical dermatological study conducted within the AHS during 1964-66, increases in atrophic scarring, pigmentation, depigmentation, fine dilation of capillaries of the upper extremities, gray hair, and senile elastosis of the face were observed.

Other skin disorders during the early years due to exposure to radiation other than A-bomb radiation were acute/chronic radiation dermatitis resulting from technical problems. There is still a need to address this issue due to reported cases of aftereffects of radiotherapy and skin injuries attributable to accidents with widely used radiation and isotopes.

(8) Bone, musculoskeletal diseases

Summary

Many reports have pointed out an occurrence of decreased bone mass following radiotherapy in childhood and adolescent cancer patients. The mechanisms behind such effects are thought to be cranial radiotherapy-induced decrease in growth hormones, as well

as central hypogonadism and gonadal functional decline due to irradiation of the abdominal and pelvic regions. Local irradiation of 40 Gy or more has been reported to lead to bone fracture resulting from osteosclerosis and osteonecrosis.

Among A-bomb survivors, there is as yet no evidence of increasing risk of osteoporosis, bone fracture, or rheumatoid arthritis with increasing radiation dose.

(9) Psychological effects

Summary

In an instant, the atomic bombings caused not only injury and disability but also loss and destruction of human relationships as well as social and physical environments. Based on research conducted by the departments of psychiatry at the medical schools of Hiroshima and Nagasaki Universities, various complaints, neurosis-like symptoms, and autonomic disorders among persons exhibiting symptoms of acute radiation disorder increased markedly, with their frequency decreasing gradually over time. Some of the symptoms observed in A-bomb survivors during a few years to more than a decade after the atomic bombings reported in a study conducted by U.S. and Japanese psychologists are consistent with typical post-traumatic stress disorder (PTSD) symptoms. Acute radiation symptoms as well as physical, material, and economic destruction experienced immediately after the bombings, anxiety due to subsequently reported radiation-induced physical disorders such as increased incidence of leukemia and other cancers, and resultant discrimination and difficulties in everyday life are all thought to have exacerbated the psychological stress felt by survivors. Studies related to psychological effects of the atomic bombings are far fewer in number than those involving physical effects, but a survey around 50 years later based on the General Health Questionnaire-12 items (GHQ-12), which was carried out among the survivors who were directly exposed to the Nagasaki atomic bombing, revealed that the physical and psychological well-being of the subjects worsened inversely to exposure distance. The degree of decline in well-being was most pronounced in persons who had lost one or more family members to the bombing and in those who had experienced acute radiation symptoms.

By the latter half of the 20th century, use of radiation had become widespread, with radiation accidents due to events such as improper management of radiation source as well as accidents at nuclear test sites and nuclear facilities leading to anxiety not only among the workers involved but also among the general public, and reports showed dramatic psychological effects of such accidents. When radiation risks are not accurately understood, psychological stress could give rise to grave consequences. It is, therefore, necessary to assuage anxiety by educating clinicians engaged in primary care, local researchers, and high-risk populations and by providing psychological intervention for victims of radiation accidents.

(10) Growth and developmental diseases

Summary

Research conducted at ABCC-RERF on growth indices among A-bomb survivors exposed as children include a study around 1950 that compared height, weight and skeletal indices between exposed children and their controls or by distance from the hypocenter and a study on longitudinal changes in height and weight by radiation dose since 1990. These

studies have shown that exposure to A-bomb radiation in early childhood causes growth retardation. However, growth also can be impaired by nutritional status and stressors arising from disturbance in everyday life, requiring caution when interpreting such results. Various biological mechanisms are plausible for radiation-induced growth disturbance, and studies of infants who experienced high radiation doses from medical exposure have considered possible factors, such as radiation effects on hormone secretion. Yet, no concrete evidence has been obtained. The assessment of growth indices was also conducted for children exposed to radiation from the Chernobyl accident, but the effects on growth have not been determined fully.

(11) Effects on aging and lifespan

Summary

This section covers research results involving the hypothesis that ionizing radiation accelerates the aging process. Much research has been conducted on A-bomb survivors from the varied perspectives of many fields of study. In the area of pathology, studies have investigated tissues such as skin, testes, and blood vessels, and research in the field of physiology has examined blood pressure, atherosclerosis, and physiological aging markers, based in part on longitudinal analyses, but no involvement of radiation was found in any of these studies. Clinical research has not yielded consistent results, but acceleration of aging of the immune system has been shown with respect to immunological markers. In clinical epidemiological research, an association between cataract and radiation has been observed, but no association has been found between radiation and dementia, femoral neck fracture, or other health issues. With this in mind, clear evidence of an association between A-bomb radiation and acceleration of aging remains elusive.

Studies suggest that lifespan in the A-bomb survivors is shortened by approximately 1-2% per Gy of exposure. Research into persons exposed to other forms of radiation besides that from the atomic bombings has not generated clear results but does indicate a shortening of lifespan due to mortality from cancers.