

(2) Cancer risk by site

(a) Esophageal cancer

Summary

The esophagus is not a highly sensitive organ to the effects of radiation, and UNSCEAR, in its reports published in 2000 and 2006, adopted the stance that there is insufficient evidence of an association between radiation exposure and esophageal cancer. UNSCEAR arrived at its position because research into the topic comprises only a follow-up study that investigated esophageal cancer risk in ankylosing spondylitis patients who had been medically irradiated, and because of a lack of any significant link detected in the LSS, among other studies. Research involving medical practitioners and radiation workers has also failed to find an esophageal cancer risk from radiation exposure. Nevertheless, a significant risk was observed when the follow-up time was extended for mortality and cancer-incidence studies among the A-bomb survivors. Other research also has pointed to a risk of esophageal cancer among medically exposed persons due to radiotherapy. Prevalence of esophageal cancer is low, resulting in weak statistical power for detecting radiation risk in cases with low-dose exposures. The keys to thinking about esophageal cancer risk, therefore, may be research on cases with high levels of radiation exposure, such as in the A-bomb survivors and persons exposed to medical irradiation, and longitudinal follow-up studies that allow for observation of larger numbers of cases.

(b) Gastric cancer

Summary

Gastric cancer is the most prevalent cancer among the Japanese people. In research into incidence using the LSS conducted by RERF, a significant ERR with increasing radiation dose (0.34/Gy) was observed. The ERR tended to be higher with lower age at exposure, but this trend was not significant. In the case of gastric cancer, unlike cancers at other sites, no increase in excess incidence with younger age at exposure was observed. Research into histologic type of gastric cancer in low-dose survivor populations has yielded results pointing to a higher number of well-differentiated adenocarcinoma cases compared with poorly differentiated adenocarcinoma. However, in high-dose groups, poorly differentiated cases outnumber well-differentiated cases. Few studies in western European countries have shown a significant association between radiation exposure and gastric cancer, but in follow-up research involving patients with cervical cancer, gastric ulcer, or Hodgkin's disease who had undergone radiotherapy, a significant increase in gastric cancer risk was reported compared to those who had not received radiotherapy. Nevertheless, none of the studies that have looked into the low radiation exposures experienced by nuclear power workers, radiation technicians, and mine workers exposed to radon has found a significant increase in gastric cancer risk.

(c) Colon cancer

Summary

Colon and rectal cancers are frequently treated as one and the same, but they differ slightly with regard to epidemiological characteristics and risk factors, although whether or not these differences reflect variation in carcinogenic mechanisms is unclear. The risks of colon and rectal cancers in terms of mortality and incidence over the long term in the A-bomb survivors of Hiroshima and Nagasaki have been studied in the LSS.

The risk of colon cancer increased with radiation dose in terms of both mortality and incidence, with the ERR at a weighted colon dose of 1 Gy for males and females combined being 0.51 for mortality (90% confidence interval: 0.17, 0.94) and 0.64 for incidence (90% confidence interval: 0.42, 0.90). ERRs for mortality in males and females were nearly equal, whereas the ERR for incidence in males was nearly twice that in females. Moreover, ERRs for mortality and incidence were greater the younger the age at exposure, but declined with increasing attained age. In contrast, the EARs of mortality and incidence were greater with younger age at exposure and higher attained age.

On the other hand, risks of rectal cancer for both mortality and incidence were not significant, with ERR at a weighted colon dose of 1 Gy for males and females combined being 0.36 for mortality (90% confidence interval: <0, 0.88) and 0.18 for incidence (90% confidence interval: <0, 0.46).

In research involving people exposed to radiation other than the A-bomb survivors, follow-up studies of participants exposed to high-dose medical irradiation have reported increased risks of colon and rectal cancers.

With this background in mind, the “UNSCEAR 2006 Report” concluded that there is a risk of developing colon cancer in accordance with a linear dose response to radiation, and that a risk in the case of rectal cancer is plausible in high-dose ranges.

(d) Liver cancer

Summary

In the A-bomb survivors, a significant association between primary liver cancer incidence and radiation dose has been observed based on information from tumor and tissue registries and pathological reviews. On the other hand, study results regarding an association between primary liver cancer mortality and radiation dose are inconsistent. One case-control study using preserved tissue samples showed a super-multiplicative interaction between radiation and hepatitis C virus (HCV) infection in the etiology of hepatocellular carcinoma among study participants without liver cirrhosis. In a nested case-control study using stored sera, radiation exposure was shown to independently contribute to increased risk of hepatocellular carcinoma, even after adjustment was made for hepatitis B virus infection and HCV infection, and shown to be a risk factor for non-B, non-C hepatocellular carcinoma without confounding from alcohol consumption, BMI, or smoking history.

For other victims of radiation exposure, internal exposure due to thorotrast or plutonium was found to be associated with a significant increase in liver cancer incidence and mortality. Moreover, in cohorts comprised of workers at nuclear facilities and power plants, no increase in liver cancer mortality associated with radiation dose was observed, but in cohorts of X-ray technicians, a significant increase in liver cancer associated with dose was found.

(e) Lung cancer

Summary

After smoking, radiation exposure is one of the most important risk factors in lung cancer, with the link between radiation and lung cancer reported mainly in epidemiological studies. Among such studies, research into the A-bomb survivors, represented by the LSS cohort, has played a crucial role in assessing the radiation dose-response relationship in lung cancer, as it has with many other cancer types. Through the LSS cohort research, the

radiation effects on lung cancer mortality and incidence, and their dependence on other factors such as sex, attained age, and age at exposure, have been quantitatively assessed. In recent years, joint effects of smoking and radiation exposure on lung cancer risk and characterization of the risk specific to lung cancer histological type have been of interest. In the latest analysis pooling all lung cancer incident cases in the LSS, the estimated dose response showed no strong departure from the linear model. After adjustment with detailed smoking information, the gender-averaged ERR per Gy of radiation exposure among never-smokers (at age 70 years after exposure at age 30 years) was estimated as 0.6 (95% confidence interval: 0.3, 1.0). The risk was estimated to be about three times larger in females than in males, decreasing with increasing attained age, and increasing with increasing age at exposure. Interaction between smoking and radiation appeared to be super-multiplicative with a rapid increase in radiation-associated excess risk in light to moderate smokers, but there was little or no apparent radiation effect observed for heavy smokers, with the interaction being additive or sub-additive. Both smoking and radiation exposure significantly increased the risk of each of the major lung cancer subtypes (adenocarcinoma, squamous cell carcinoma, small cell carcinoma). While the effects of smoking and radiation differ in magnitude by histological type, the nature of the joint effects of smoking and radiation for different types showed a similar pattern as in the analysis pooling all lung cancer cases. With detailed smoking information, as well as wide-ranging age-at-exposure data and dose estimates, studies with A-bomb survivor cohorts have become an important source of information to estimate the lung cancer risk in other radiation-exposed populations, in particular those who are exposed by radiotherapy of the thoracic region or CT lung scans for diagnostic purposes.

(f) Skin cancer

Summary

It was reported during the early years after the discovery of X-rays that high-dose ionizing radiation increased incidence of skin cancer, particularly non-melanoma skin cancer. In many such cases, skin cancer occurred following chronic cancer dermatitis developing at the irradiated site. Increased incidence of basal cell carcinoma has been observed in A-bomb survivors. A non-linear dose-response relationship with higher risk at higher dose was observed for basal cell carcinoma, with the ERR decreasing significantly with increasing age at exposure. Background rate of basal cell carcinoma is known to be high at sites of exposure to ultraviolet (UV) radiation. However, the ERR of basal cell carcinoma is lower at sites of UV exposure among A-bomb survivors, whereas the EAR is high at such sites. Increased incidence of basal cell carcinoma attributable to ionizing radiation has also been reported among radiotherapy patient populations treated for tinea capitis/cancer as well as occupationally exposed populations of radiological technician/physicians. In the medical care of A-bomb survivors, the significant increase in basal cell carcinoma is a concern, and early diagnosis of skin cancer is crucial. Although no radiation effects have been confirmed with squamous cell carcinoma and malignant melanoma among the survivors, further study is necessary.

(g) Breast cancer

Summary

The rate of breast cancer among Japanese women has risen dramatically over the

past several decades. Mammary glands are one target organ of female hormones, and risk factors in development of breast cancer are known to include early age at menarche, late age at first childbirth, low number of childbirths, late age at menopause, family history of breast cancer, use of oral contraceptives, and hormone replacement therapy, with obesity, alcohol consumption, intake of saturated fats, and other factors also drawing attention.

Ionizing radiation is understood to be one environmental factor in breast cancer development. Research into the Hiroshima and Nagasaki A-bomb survivors has revealed that the excess risk of breast cancer has a linear dose-response relationship with radiation dose to mammary gland tissue, and that women younger than age 20 years when exposed experienced a markedly increased risk of breast cancer onset before the age of 35 years. Moreover, histopathological examination did not show any difference in histological classification between radiation-derived breast cancer and spontaneous breast cancer cases.

Expectations are high for future research in A-bomb survivors to provide an understanding of post-menopausal breast cancer risk in female A-bomb survivors who were younger than 20 years of age at exposure, and to uncover the associations between radiation exposure and intrinsic subtypes of breast cancer through the determination of such subtypes in A-bomb survivor breast cancers.

(h) Ovarian cancer

Summary

An increased risk of ovarian cancer in A-bomb survivors has been confirmed. However, elucidation of the association between A-bomb radiation and ovarian cancer occurred relatively recently, compared with cancers of the thyroid, breast, lung, stomach, and colon. Ovarian cancer has been reported to be a late effect of pelvic irradiation in medical therapy, but in radiation-exposed populations other than the A-bomb survivors, no definitive evidence has been obtained for increasing rates of ovarian cancer due to radiation exposure.

(i) Urinary organ cancers

Summary

In the LSS, risks of bladder cancer mortality and incidence are clearly increased. Because a dose-response relationship has been reported for such risks, sufficient scientific evidence seems to have been gathered with regard to increased risk of bladder cancer in A-bomb survivors. On the other hand, in renal cancer and prostate cancer, statistically significant increases in risk have not been detected in the survivor population. The levels of increase in risk due to radiation exposure for renal and prostate cancers are smaller than that for bladder cancer, with it pointed out that the factors underlying the failure to detect a significant risk of prostate cancer in particular include the common occurrence of the disease in the elderly and the small number of patients with radiation-induced prostate cancer in follow-up studies. Research involving individuals exposed to high radiation doses, such as those common in medical treatment, has resulted in reports of increased risks of bladder, kidney, and prostate cancers, but the results are varied and lack consistency. In research on individuals occupationally exposed to radiation, there are few reports of a significant increase in urinary organ cancers due to the typically low doses received.

(j) Brain and central nervous system tumors

Summary

The classification of brain and central nervous system tumors is defined narrowly as tumors originating from neuro-ectodermal cells. In general, however, the terminology is used to indicate intracranial tumors and vertebral canal tumors, including various other tumors besides those originating from neuro-ectodermal tissue, such as tumors originating in the meninges, the peripheral nerves, and the pituitary gland.

Much is still unknown about the etiology of such brain and central nervous system tumors, but radiation is one of a few definite risk factors, with reports indicating that high-dose medical exposures for the treatment of acute lymphatic leukemia infiltrating the brain and central nervous system constitute a risk factor.

The LSS in Hiroshima and Nagasaki showed the ERR per Sv for brain and central nervous system tumors to be 1.2. By histological type it was 0.64 for meningeal tumors, 4.5 for schwannomas, 0.56 for glial cell tumors, and 0.98 for pituitary gland tumors, with schwannomas showing the strongest dose-response relationship. By gender, males tend to be at higher risk of such tumors than females. Comparing by age at exposure, persons in childhood at the time of bombing tend to be at higher risk than those who were exposed as adults.

(k) Thyroid cancer

Summary

Radiation exposure leading to thyroid cancer is roughly divided into external exposure, as seen in the cases of A-bomb survivors and medical radiation exposure, and selective thyroid internal radiation exposure from radioactive iodine as exemplified by the Chernobyl nuclear power plant accident.

Starting more than a decade after the atomic bombings, increased numbers of thyroid cancer cases were reported in A-bomb survivors. In both longitudinal studies (long-term follow-up incidence studies) based mainly on tumor registry data and cross-sectional studies (prevalence studies) based on thyroid screening, the risk of thyroid cancer increased with increasing radiation dose to the thyroid, and a linear dose-response relationship was observed. Among modifying factors, age at exposure is the most important, with thyroid cancer risk being higher the younger the age at exposure. The excess risk of thyroid cancer among A-bomb survivors continues today, and therefore the potential for disease development persists throughout the entire lifetime. Studies have suggested an association with radiation exposure even in cases of thyroid micro-cancer growths measuring 1 cm or smaller.

Besides A-bomb exposure, medical irradiation is another major source of external radiation exposure to the thyroid. In surveys following radiotherapy for infant cranio-cervical and thoracic diseases and cancer, risk of thyroid cancer increases in a linear fashion with increasing radiation dose. Even with internal exposure following the Chernobyl accident, childhood thyroid cancer risk increased significantly with increasing thyroid dose. With both external and internal exposures, the most important modifying factor for risk of cancer development is age at the time of exposure (or at the time of accident), just as in the case of the A-bomb survivors, with the risk of thyroid cancer higher with younger ages at the time of exposure, the trend being particularly marked for those less than five years of

age at the time of exposure (or accident).

The mechanism underlying radiation carcinogenesis is potentially the important role played by abnormal chromosomal rearrangement following DNA double-strand breaks. A potential for thyroid cancer risk to vary due to differences in individual genetic backgrounds (polymorphisms) also has been suggested.

The increased risk of thyroid cancer due to radiation exposure could persist over several decades (or the entire lifetime) in radiation-exposed populations. For that reason, special attention to the possibility of thyroid cancer development must be paid with persons exposed to radiation in childhood, even in the prime of their lives and into old age.

(l) Multiple myeloma

Summary

1) Nearly 20 years after the atomic bombings many cases of multiple myeloma started to be observed among the A-bomb survivors. Up until 1976, it was reported that incidence of multiple myeloma increased in a manner dependent on bone marrow dose (at 50 rad and greater, according to the T65D dosimetry system), with the number of cases especially large in persons between the ages of 20 and 59 years at the time of radiation exposure.

2) From a pathological perspective, the increase was apparent starting in 1975 in terms of numbers of multiple myeloma cases identified at autopsy. In 1981 and thereafter, the number of multiple myeloma cases in A-bomb survivors increased significantly.

3) In analyses of cause of death in RERF's LSS during the period 1950-90, a slight increase in mortality risk from multiple myeloma was observed dependent on radiation dose (based on dosimetry system DS86).

4) Nevertheless, in analyses of multiple myeloma incidence based on leukemia registries during the period 1950-87 in the LSS, no significant risk increase dependent on radiation dose (DS86) was observed.

5) In both Nagasaki and Hiroshima starting in 1988, monoclonal gammopathy screening was initiated as part of cancer screening in the A-bomb survivors. As a result, cases of monoclonal gammopathy of undetermined significance (MGUS), which is considered a pre-myeloma state, have been discovered in high numbers.

6) At present, for the survivors of Hiroshima's atomic bombing, no significant difference in prevalence of MGUS by distance from the hypocenter has been identified. For the Nagasaki survivors, on the other hand, those who were 20 years old or younger at exposure, 1.5 km or less from the hypocenter, or exposed to at least 0.1 Gy of radiation are reported as having significantly increased prevalence of MGUS. Any association between progression into multiple myeloma and the circumstances surrounding exposure to the bombings in both cities, however, is unclear.

Investigation continues today into the onset of monoclonal gammopathy, a disease considered to be one of the late effects among the A-bomb survivors and a representative form of multiple myeloma that develops when highly radiosensitive plasma cells undergo tumorigenesis. Nevertheless, such research has not led to any definite conclusions concerning an association with radiation exposure.

(m) Leukemia, myelodysplastic syndrome

Summary

There are four major types of leukemia—acute myeloid leukemia, AML; acute

lympho leukemia, ALL; chronic myeloid leukemia, CML; chronic lymphocytic leukemia, CLL—and the A-bomb survivor population is at increased risk of developing all of these types except for CLL. The risks of developing these three types peaked five to 10 years after the atomic bombings, with risks of ALL and CML disappearing over the next 10 years and no resurgence observed as of 2010. On the other hand, risk of AML fluctuated but persisted during the 1960s and 1970s, and reports have been published indicating continued risk in the period between 1990 and 2010. Adult T-cell leukemia/lymphoma (ATLL), first conceptualized as a disease entity in the 1970s, started to appear as early as the 1950s in Nagasaki survivors but had no association with dose.

In addition to risks of the aforementioned leukemia types changing over time, myelodysplastic syndromes (MDS), first conceptualized as a disease category in 1982, were recognized as being AML-related hematopoietic neoplasm in the FAB (French-American-British) classification system proposed in 1976. Results from an epidemiological study of the Nagasaki A-bomb survivors in 2010 verified an association between MDS and distance from the hypocenter as well as radiation dose. Risks of AML and MDS clearly persist even more than 60 years after the bombings, although there are differences in change over time between those exposed to the atomic bombings when young (less than 20 years at the time of bombing) and those exposed in adulthood, with those exposed when young in particular having elevated risks sustained over their lifetimes. Most of the MDS cases among those exposed to high doses comprise high-risk MDS that readily develop into leukemia; chromosomal abnormalities in bone marrow cells in such cases exhibit an extremely complex karyotype abnormality compared with MDS cases among A-bomb survivors exposed to low doses. MDS have already been established as disorders originated in the hematopoietic stem cells. Among A-bomb survivors, it is assumed that radiation-induced genomic instability occurring in the hematopoietic stem cells in 1945 has persisted over the long term, and that this mechanism is the basis for the development of MDS.

(n) Malignant lymphoma

Summary

It is well known that the lymphocyte is a highly radiosensitive cell, but is there an association between radiation and development of malignant lymphoma, the malignancy formed by lymphocytes? Although a proportional relationship between radiation dose and development of acute lymphoblastic leukemia is indicated in Genbaku Hoshasen no Jintai Eikyō (“Effects of A-Bomb Radiation on the Human Body,” 1992), “UNSCEAR 2006 Report,” a compilation of published reports on radiation and carcinogenesis, reports that excess risk from radiation is not high for incidence and mortality in Hodgkin’s and non-Hodgkin’s lymphomas. Few reports of excess risk of radiation have examined lymphoma by histological type, which is assembled of lymphocytes at different stages of maturity, but reports on histological classifications are anticipated. There is also little information about risk modification by age at exposure, time since the bombing, and organ of origin for lymphoma cases among the A-bomb survivors. Some reports detail investigations into onset of malignant lymphoma following therapeutic irradiation, but the focus of all such investigations was limited to acute lymphoblastic leukemia.