Radiation and Malignancies

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Abstract

After the radiation leak from Japan's quake-stricken Fukushima Daiichi nuclear plant, concern about radiation exposure arose. There are a variety of radiation-related health problems, including acute exposure toxicities, radiotherapy-related malignancy, and malignancies from imaging, environmental, and occupation-related radiation. As medical staff, we should be aware of radiation-related problems. A discussion of radiation-related malignancies is presented. This review is not intended to discuss the mechanisms of radiation, the tissue effects or other acute effects. (J Intern Med Taiwan 2011; 22: 174-182)

Key words: Millisieverts (mSv), Gray (Gy), Acute myeloid leukemia (AML), Radiation exposure, Malignancy

Radiation from Japan's quake-stricken Fukushima Daiichi nuclear plant has reached harmful levels. After the explosions and fire on Tuesday, March 15, 2011, radiation dosages of up to 400 millisieverts (mSv) per hour were recorded at the Fukushima Daiichi site, about 250 km northeast of Tokyo.

The radiation dosages in Fukushima were up to 400 mSv–approximately 200 times the dose from the average brain CT scan, 50 times the dose from an abdominal CT scan, and 1/5 the daily dose of radiation treatment for brain cancer[1]. According to the World Nuclear Association, the typical background radiation experienced by people is 2 mSv/yr, with an average of 1.5 mSv in Australia and 3 mSv in North America. Experimental and epidemiologic evidence has linked exposure to ionizing radiation with the development of solid cancers and leukemia. This event reminds us that medical staff nowadays should place more concern on radiation exposure-related diseases, including that of patients who undergo medical imaging procedures in daily clinical practice.

Persons at risk of repeated radiation exposure, such as workers in health care and the nuclear industry, are typically monitored and restricted to

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effective doses of 100 mSv every 5 years (i.e., 20 mSv per year, with a maximum of 50 mSv allowed in any given year)[2,3]. However, the radiation exposure of patients who undergo medical imaging procedures is not usually monitored, and patient data on longitudinal radiation exposure from these procedures are scant, even though in clinical practice these types of procedures are frequently performed multiple times for the same patient, especially cancer patients. Cancer patient treatment accounts for a lot of the health coverage in our health system.

Follow-up repeat imaging exams are usually required. Take colon cancer for example, the National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2011 suggest that this type of patient, when at a high risk, should receive chest/abdomen/pelvic CT scans annually for 3 years, and in the Guidelines Version 2.2011, breast cancer patients usually require abdominal ± pelvic CT or ultrasound or magnetic resonance imaging. For breast cancer in which the nature of the tumor is unknown, annual imaging exams for up to 10 years are probably needed. The accumulated dosages range from 20 mSv to 120 mSv, depending on how many images are performed each time and in the following years; this dosage is beyond the safety range for special workers. This is not to mention that some physicians overuse imaging procedures, up to 3 or 4 times per year, due to the increasing number of lawsuits for medical problems or patient requirements. Besides, some cancer types need to be followed up by imaging to evaluate the treatment effects.

There was a recent report of radiation exposure from medical imaging in patients with hydrocephalus, pulmonary thromboembolic disease, renal colic, and cardiac disease for 5 years; they were identified as receiving a high dose of radiation exposure (total effective dose > 50 mSv; dose to the ocular lens >150mSv)[4].

Second Neoplasms in Survivors of Cancer after Radiation Therapy

It is well known that some chemotherapy agents are related to secondary malignancy. After chemotherapy treatments, it is clear that patients with malignant lymphoma, pediatric cancers, ovarian cancer, and breast cancer get higher 2nd cancers than the age-matched normal populations. Many reviews of this topic are now available in the medical literature[5-8]. The use of radiotherapy has increased, so that today about 40% of cancer patients receive some treatment with radiation[9]. Secondary solid tumors are mainly associated with radiotherapy (OR=4.5, 95% CI: 2.5-8.0)[10]. Radiotherapy has been repeatedly reported to increase the risk of secondary malignant neoplasm[11]. Even a small amount of radiation, up to 0.1 Gy for the treatment of skin hemangioma in childhood, has been associated with an increased risk of thyroid cancer and tumors of the bone and soft tissues[12]. Skin cancer often presents 36 years after radiotherapy[13,14].

Children with acute lymphoblastic leukemia receiving cranial radiation had 27 times greater risk of brain tumors within 20 years than those without cranial radiation treatment[15,16]. The estimated cumulative risk of this appearing within 20 years after diagnosis was 2.9%[15]. Brain irradiation also may cause secondary malignancies 3 to 15 years later[17], and a 4.3 relative risk has been reported[18].

Radiotherapy has long been the main treatment for head and neck tumor. After an average latency period of 10-15 years, the diagnosis of radiation-induced tumor, including sarcomas and skin carcinoma[19,20,21], and thyroid cancer[22-25] has been made. The occurrence of upper aerodigestive tract cancer 5 years after radiotherapy has been reported[26].

Sarcoma has also been reported after a mean of 16.8 years at the site radiation therapy was given[27, 28]. Malignant fibrous histocytoma of the bone has occurred after a median of 14.5 years after radiation therapy (ranging from 4 to 47 years) with a median dosage of 57Gy[39-34].

Lung cancer[35], myeloid leukema[36], and esophageal cancer[37] have also been implicated to develop after radiation therapy for breast cancer, although there is some disagreement[38]. Breast cancer risk increased up to 1.9[39] or the incidence increased 15 years[40,41] after radiotherapy for Hodgkin disease; radiation exposure to the chest also led to the development of sarcomas[42], esophagus cancer[43,44], acute leukemia[45], and breast cancer[46].

Malignancies in the urinary bladder, endometrium, ovaries, and colon, and anorectal cancer have been reported in excess of 10 years after irradiation for carcinoma of the uterine cervix[47-51]. Some report that the risk of leukemia only increases within the 10 years after pelvic irradiation[52]. After pelvic radiotherapy, the risk of secondary leukemia peaked at 5 to 10 years after primary treatment, and remained elevated even 10 to 15 years after initial treatment[53,54]. Lung cancer has also been reported as the main secondary cancer after curative brachytherapy for cervical cancer. Most patients with an excess risk of cancer never returned to normal, even after 30 years[55]. Other cancer types, including uterine sarcoma and endometrial adenocarcinoma, have also been recorded[56,57].

Within five years of radiation for testicular tumors, the occurrence of secondary testicular tumors was higher, and 15-19 years after radiation, the incidence of tumors in the urinary and gastrointestinal tract was higher[58,59]. Radiation-induced carcinoma of the penis has also been reported[60]. The incidence of secondary cancers of the bladder and rectum has increased 10 years after radiotherapy for prostate cancer. The distant sites of lung cancer have also increased[61] after radiotherapy.

The thyroid gland is highly susceptible to the carcinogenic effects of ionizing radiation. The Childhood Cancer Survivor Study (CCSS), a nested case-control study, showed an increased risk of thyroid cancer with radiation doses as high as 29 Gy, but a decrease in the risk of secondary thyroid cancer at doses greater than 30 Gy. Chemotherapy exposure was not associated with the risk of subsequent thyroid cancer in this study, but exposure was associated with an increased risk of subsequent glioma (OR=6.8) and meningioma (OR=9.9)[62].

Other rare cancers in case reports, including glioglastoma[63],

Occupational exposure to extremely low frequency magnetic fields

1. Parental occupational exposure and the children

Extremely low frequency magnetic fields have been linked to possible carcinogenesis in humans. A Swedish study showed that paternal exposure, but not maternal occupational magnetic field exposure, was associated with an increased risk of childhood leukemia, with a relative risk of 2.0 (95% CI 1.1-3.5), but not brain tumor[64]. Four cancer types occurred more often among children of fathers in specific radiation-related occupations: rhabdomyosarcoma among children whose fathers were petroleum industry foremen, retinoblastoma among children whose fathers were radio and television repairmen, and central nervous system cancers and other lymphatic cancers among children whose fathers were in the air force[65] in a small study number. Bone cancer and Wilms' tumor also have been suggested to occur more frequently among children of fathers in all industries with moderate potential ionizing radiation exposure[66].

However, a German case-control study[55] showed that there was no increased cancer risk in children whose fathers were occupationally exposed to magnetic fields above 0.2 micr0T, as well as mothers. Maternal occupational exposure to electromagnetic fields before, during, and after pregnancy was not a risk factor for childhood leukemias, childhood brain cancer, or any other known childhood cancers[67].

2. Environmental exposure

A significant association between all major types of childhood cancer and residing near high-voltage facilities has been found in Denmark since the 1940s[68]. Of a number of cancers other than leukemia studied in the Sutton-Coldfield area, only skin melanoma and bladder cancer showed a decline in the ratio of observed to expected cases with distance from the transmitter. The following study from Great Britain[69] failed to replicate the results. They found there was no association between adult leukemias, skin melanoma, bladder cancer and radio transmitters

The risk of cancer in Finnish children living close to power lines did not constitute a major public health problem in relation to childhood cancer[70]. There was also no relationship between childhood cancer and magnetic fields from high-voltage power lines in England and Wales[71-73]. The Sutton-Coldfield study[74], covering the period 1974-1986, found a decline in the ratio of observed to expected cases of adult leukemia with distance from the transmitter over a 10 km radius, with a risk within 2 km of the transmitter of 1.83 (95% Cl 1.22-2.74) relative to the West Midlands regional average.

A high background average annual effective dose of 6.4 mSv in China was not associated with cancers of the stomach, colon, liver, lung, bone, female breast and thyroid, nasopharynx, esophagus, rectum, pancreas, skin, cervix uteri, brain and central nervous system, or malignant lymphoma[75].

3. Occupational exposure

A study of Norwegian workers[76] showed a possible association between electrical work and the risk of leukemia of 1.41 (95% Cl 1.10-1.76). The risk of four cancers, leukemia, lymphopoietic cancers, lung cancer and mesothelioma, has been studied in workers from shipyards involved in nuclear-powered ship overhauls. The risk increased at exposures above 10.0 mSv. An internal comparison of workers with 50.0 mSv exposure with workers with exposures of 5.0-9.9 mSv indicated relative risks for leukemia of 2.31 (95% CI: 0.5, 23.9), for lymphopoietic cancers, 2.94 (95% CI: 1.0,12.0), for lung cancer, 1.26 (95% CI: 0.9, 1.0), and for mesothelioma, 1.61 (95% CI:0.4, 9.7) for the higher exposure group[77]. A cohort of 9,285 nuclear workers employed at a French company showed significant positive trends with cumulative doses for colon and liver cancer, and for respiratory disease[78]. Men with continuous exposure to electromagnetic fields in Denmark, mainly electricians doing installation work and iron foundry workers, had an excess risk of leukemia (1.64, 95% CI1.20-2.24), but not brain tumors or melanoma[79]. A risk for breast cancer was suggested in men but not in women. The Australian nuclear industry workers study showed an observed increase in the risk of cancer of the pleura and small intestine, but not leukemia. The authors concluded that these might all be due to unmeasured exposure or due to chance[80]. A cohort of Italian plastic-ware workers exposed to radiofrequency-electromagnetic fields had been found to have an increase risk of leukemia; however, the study power was small and the confounding effects of exposure to solvents and vinyl chloride monomer could not be ruled out[81]. The largest study population ever known was the 15-country collaborative study of cancer risk among radiation workers in the nuclear industry, including 407,391 workers; a significant association was seen between radiation dose and all-cause mortality[82].

A 43-year follow-up study of 22 cases of cumulative doses of about 100mSv in a French electrical company found no significant cancer risk, but an increased risk of cerebrovascular diseases[83]. Another electrical welders study also showed no association with leukemia[84].

Chromosomes, cancer and radiosensitivity

Genetic diseases involving increased chromosome breakage or defective chromosome repair are associated with a greatly increased cancer incidence. Three such diseases have been recognized: 1) Fanconi's anemia, associated with leukemias and lymphomas, 2) Bloom's syndrome, associated with acute leukemias and lymphosarcoma, and 3) ataxia telangiectasia, associated with Hodgkin's disease, leukemia, and lymphosarcomas. Radiation therapy for cancers has been fatal in patients who received as little as 30Gy[85].

Germline mutations in *BRCA1*, *BRCA2*, ataxia telangiectasia mutated (ATM) or *CHEK* may double the risk of radiation-induced contralateral breast cancer following radiotherapy for a first breast cancer[86].

Others

Chemotherapy-associated acute myeloid leukemia and myelodysplasia have long been known. AML generally occurs from 2-11 years after the therapy[87]. There are still many sequelae that are related to radiotherapy, including new cavernous malformation[88], laryngeal stenoses, fibrous strictures of the upper esophagus[89], strictures of the recto-sigmoid[90], benign pleural schwannoma[91], meningioma[92,93], alopecia[94], and alteration of pubertal timing[95]. Abdominal-pelvic radiation also may cause an increased infertility risk of 23%, compared to those with surgery alone[96].

Although suggestive associations between electrical/magnetic fields and cancer or leukemia have been made, no one has established a causal relationship between these fields and cancer or leukemia. All the reports on human exposure have numerous deficiencies, which include: lack of or imprecise measurements of electrical or magnetic field intensities, questionable subject identification, lack of statistical significance, confounding with uncontrolled variables such as socioeconomic differences, smoking, X rays, drugs, population mobility, and the unreliability of occupational classification.

To make things more complicated, there are some reports regarding the protective effects of low-dose ionizing radiation[97], focusing on medical radiation staff. There is also some documentation suggesting that regular sun exposure is associated with substantial decreases in death rates from certain cancers and a decrease in overall cancer death rates, which is attributed to the body's vitamin D metabolic pathway[98].

Conclusion

The existence of radiation-related secondary malignancies is well-established. Environmental or occupational exposure as the cause of malignancy is favored by some, but disputed by others. As medical staff nowadays, we need to learn more about this. The more we know, the better we can protect ourselves, as well as our patients.

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輻射與癌症相關性

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摘 要

日本福島四座核能電廠在地震和海嘯後，成爲目前危機問題。和輻射相關的疾病包含急性曝射，放射性治療後引發的相關癌症，影像學檢查，環境和職業相關輻射，身爲醫療人員應所有了解。本文章主要是探討輻射引起的癌症問題。