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Radiation Sensitive Genetically Susceptible Pediatric Sub-populations

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Abstract

Major advances in pediatric cancer treatment have resulted in substantial improvements in survival. However, concern has emerged about the late effects of cancer therapy, especially radiation-related second cancers. Studies of childhood cancer patients with inherited cancer syndromes can provide insights into the interaction between radiation and genetic susceptibility to multiple cancers. Children with retinoblastoma (Rb), neurofibromatosis type 1 (NF1), Li-Fraumeni syndrome (LFS), and nevoid basal cell carcinoma syndrome (NBCCS) are at substantial risk of developing radiation-related second and third cancers. A radiation dose-response for bone and soft tissue sarcomas has been observed for hereditary Rb patients, with many of these cancers occurring in the radiation field. Studies of NF1 patients irradiated for optic pathway gliomas have reported increased risks for developing another cancer associated with radiotherapy. High relative risks for second and third cancers were observed for a cohort of 200 LFS family members, especially children, possibly related to radiotherapy. Children with NBCCS are very sensitive to radiation and develop multiple basal cell cancers in irradiated areas. Clinicians following these patients should be aware of their increased genetic susceptibility to multiple primary malignancies enhanced by sensitivity to ionizing radiation.

Keywords

second cancers; radiotherapy; retinoblastoma; neurofibromatosis type 1; Li-Fraumeni syndrome; Nevoid Basal Cell Carcinoma Syndrome

Introduction

Epidemiologic studies have demonstrated that children are considerably more sensitive to the carcinogenic effects of ionizing radiation than adults. Further, children live longer and thus have a larger window of opportunity for expressing radiation damage [1]. Based on epidemiologic studies of the Japanese atomic bomb survivors [2] and children and infants irradiated for benign diseases, such as Tinea Capitis [3] and hemangiomas [4], a distinct pattern of risk for radiation-related tumors has emerged. This risk is greatest for those exposed to radiation early in life and persists for decades following exposure [5]. Dose-related increased risks for cancers of the thyroid gland, breasts, brain, non-melanoma skin cancer and leukemia have been observed for adults who were irradiated for benign diseases in childhood [6,7].

The past several decades have brought new advances in cancer treatments resulting in substantial improvements in long-term survival of pediatric patients. The 5-year relative survival rate among children diagnosed with cancer has increased from 58% in 1975–1977 to

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80% in 1996–2003 [8]. Despite this success, concern has emerged about the potential late effects of cancer therapy, especially radiation-related second cancers. Childhood cancer survivors are at a 6-fold increased risk of developing another cancer compared to the general population, and risk for subsequent cancers among 5-year survivors of a first cancer reached 8-fold among those who received initial radiotherapy for their cancer [9].

Selected Inherited Cancer Predisposition Syndromes

Several factors likely contribute to the appearance of second cancers in children in addition to treatment for the first cancer. These can include inactivation of tumor suppressor genes, alterations in DNA repair genes or immunodeficient conditions [10]. One of the factors affecting the risk of a radiation-related second cancer, in addition to young age at initial therapy, is genetic susceptibility to cancer caused by a mutation in a tumor suppressor gene. Although inherited cancer predisposition syndromes are rare and account for only between 1 and 10% of childhood tumors, studies of these patients can provide insights into the interaction between radiation and genetic susceptibility to cancer. Epidemiologic studies of children with inherited cancer predisposition syndromes, such as retinoblastoma (Rb) caused by mutations in the *RB1* tumor suppressor gene, Li-Fraumeni (LFS) caused by mutations in the *p53* gene, neurofibromatosis type 1 associated with mutations in the *NF1* gene, and nevoid basal cell carcinoma syndrome characterized by mutations in the PTCH gene provide examples of pediatric cancer patients who are at substantial risk of developing second cancers due to their genetic susceptibility to cancer and apparent sensitivity to radiation [11–14]. Table 1 describes the main features of each of these tumor suppressor gene syndromes. This paper will review the risk of second and third tumours related to radiotherapy for a first malignancy among these four rare, but informative pediatric patient populations.

Retinoblastoma

Very extensive data from several countries exist on the association of second cancers with radiotherapy among childhood cancer patients with retinoblastoma (Rb) patients [15–19]. Retinoblastoma is rare, occurs in 1/20,000 births and accounts for 3% of all pediatric cancers. Survival is excellent; approximately 90% at 10 years in the U.S. [20]. Retinoblastoma occurs in two forms: heritable and sporadic, which was described by Knudson in his classical two-hit theory [21]. In the heritable form, a child is born with a germline mutation in the *RB1* gene and has disease usually in both eyes, whereas, in the sporadic form, the child acquires mutations in the *RB1* gene and has disease in only one eye. Patients with the heritable Rb are typically diagnosed at less than one year of age, whereas, patients with the sporadic form are more likely to be diagnosed at two years of age and later. During the past century, external beam radiotherapy and occasionally brachytherapy has been used to treat heritable Rb, whereas, patients with sporadic Rb are typically treated surgically. Survivors of heritable Rb are at increased risk of dying from a bone or soft tissue sarcoma, melanoma or brain tumor in childhood and early adulthood.

Hereditary Rb predisposes to a variety of new cancers over time, with radiotherapy further enhancing the risk of tumors arising in the radiation field. Long-term follow up of a large cohort of 1,601 Rb one-year survivors diagnosed between 1914 and 1984 at two U.S. centers, revealed very high risks for bone and soft tissue sarcomas, primarily in the radiation field among those with heritable Rb compared to the general U.S. population [17]. Scatter radiation doses from treatment for Rb were estimated to different parts of the head for individual patients in the cohort, and a radiation dose-response for bone and soft tissue sarcomas reached 11-fold at 60 Gy [17].

Very high risks were noted for soft tissue sarcomas following radiotherapy for Rb (SIR=212, 95% CI 164–270), and 70% of these sarcomas occurred in the head region in the radiation field

[19]. The cumulative risk for a soft tissue sarcoma 50 years after radiotherapy was 13.1% (95% CI 9.7%-17%). Risks for individual subtypes of soft tissue sarcoma were estimated, and the most frequently diagnosed histologic subtype was leiomyosarcomas. Interestingly, the leiomyosarcomas started appearing between 20 and 35 years after radiotherapy for Rb. Although most of the soft tissue sarcomas occurred in the radiation field, some sarcomas were diagnosed outside the radiation field, indicating a genetic predisposition to the development of these tumors.

The cumulative risk of a second cancer among hereditary patients was 36% (95% CI 31%–41%) at 50 years compared to 5.7% (95% CI 2.4-11%) in the sporadic patients. The cumulative risk of a second cancer among irradiated hereditary patients was 38% (95% CI 33%–44%) at 50 years compared to 21% (95% CI 9%–36%) among non-irradiated hereditary patients [18]. Use of protons to treat Rb patients at some centers may reduce the risks of sarcomas in head by optimizing the beam and sparing exposure to the contralateral eye, brain tissue and pituitary gland [22], although there is non-negligible scatter from secondary neutrons, and the lifetime cancer risk is significantly greater for very young children compared to adults [23].

Neurofibromatosis Type 1

Neurofibromatosis Type 1 (NF1) is a dominantly inherited, tumor-predisposing disorder that is caused by a mutation in the *NF1* gene, and occurs in 1/3500 births [24]. Children with NF1 typically develop neurofibromas and are at risk for developing malignant peripheral-nerve sheath tumors (MPNST), leukemia, and gliomas [25]. Optic pathway gliomas (OPG) are low-grade gliomas that appear in early childhood, and about half of these tumors occur in NF1 patients. The long-term risk of a developing a second glioma or MPNST was evaluated in a cohort of 58 NF1 patients in the UK who had an OPG [26]. Despite the high baseline risk of MPNST in NF1 patients of 1.6 per 1000 [27], radiation used to treat OPGs (25–50 Gy) was associated with a higher risk of developing another nervous system tumor. Half of the patients who were treated with radiotherapy for OPG developed another cancer compared with only 20% of those not treated with radiation, resulting in a relative risk of 3.0 (95%CI 1.3–7.2). An even higher risk was noted for children who were under 15 years of age at time of treatment for OPG (RR=5.53, 95%CI 2.0–15). These second tumors developed 7 to 27 years after radiotherapy (median = 14 years). All 5 MPNSTs following radiotherapy arose in the radiation field, whereas the only MPNST that was diagnosed in a non-irradiated patient arose distant to the cranium. There have been several other evaluations of the incidence of radiation-related MPST, which have reported increased risks for these tumors in the NF1 patients who had been previously irradiated for OPG [28,29].

Because there is a high incidence of second nervous system tumors in NF1-OPG patients, and the risk is heightened by radiation, investigators have recommended that radiotherapy should be avoided in NF1 patients with OPG, because the radiation-related risks clearly outweigh any benefit of the usually benign course of OPG in NF1 patients especially in young children [24,25,28,29].

Li-Fraumeni Syndrome (LFS)

The Li-Fraumeni syndrome (LFS) is a rare, dominantly inherited disorder, associated with germline mutations in the *p53* tumor suppressor gene [10]. Approximately 70% of classical LFS patients carry these mutations [10,30]. LFS is characterized by early onset breast cancer, sarcomas, brain tumors, adrenal cortical tumors and acute leukemia in families [31]. The risk of developing a cancer is approximately 50% by age 30 and 90% by age 60 [32].

The incidence of second and third cancers was evaluated in 200 individuals with a first cancer from 24 Li-Fraumeni families, compared to general population rates of cancer [33]. Overall,

there was a 5-fold relative risk of developing a second cancer among 30 individuals resulting in a cumulative probability of a second cancer of 57% (±10%) at 30 years. There was a strikingly high risk of second cancer among individuals less than age 20 at first cancer (RR=83, 95% 37–187) which decreased to 9.7 (95%CI 4.9–20) for ages 20–44, and to RR=1.5, 95% CI 0.5–4.2 for age 45 years and older at first cancer diagnosis. Although inherited susceptibility to cancer was the major predisposing factor, Hisada et al. suggested that radiation sensitivity may have played a role in the appearance of some second cancers in their study, because eight solid cancers were diagnosed in 6 patients who had received radiotherapy. The appearance of these cancers 3 to 22 years later also indicated a possible radiation association.

The diversity of these tumors occurring in LFS families prompted other investigators to evaluate the use of F18-Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT scan) to screen for new primary cancers in 15 asymptomatic members of LFS families [34]. Three tumors were detected (two thyroid and one esophageal cancer) using this surveillance method. Masciari et al estimated the effective dose of the total FDG-PET/CT scan to be 2.4 rem, and concluded that these preliminary data provide evidence for a potential cancer screening method for patients at high risk of multiple tumors.

Nevoid Basal Cell Carcinoma Syndrome (NBCCS)

Nevoid Basal Cell Carcinoma Syndrome (NBCCS), or Gorlin Syndrome, is a rare autosomal dominant disease, characterized by multiple basal cell carcinomas, jaw cysts, and sketetal abnormalities [35]. Children with NBCCS are at very high risk of developing multiple basal cell carcinomas in irradiated areas, usually from six months to three years following radiotherapy [36]. Additionally, NBCCS predisposes to medulloblastoma, which accounts for 20% of all brain tumors. The age at diagnosis of medulloblastoma in children with NBCCS tends to be younger than in the general population (2 versus 6 years) [37]. A series of 173 medulloblastoma patients from the UK, diagnosed over a 35-year period, reported a 1–2% incidence overall of NBCCS, and a population-based study of 73 NBCCS patients from 29 families, also in the UK, reported a 3–5% incidence of medulloblastoma [37]. A study of second malignancies in 88 children irradiated for medulloblastoma reported a 39-fold increased risk of second cancers (95%CI 10–99), based on cancer in four children [38]. Two of the four children who developed another malignancy had NBCCS, both of whom developed multiple basal cell carcinomas in the radiation field 3 and 6 years after radiation for medulloblastoma at age 2 [38]. With increased survival associated with medulloblastoma, careful follow-up with physician examination for the identification of second malignancies, magnetic resonance imaging scans, and patient education about early signs of skin cancer have been recommended [38,39].

Summary

Studies of childhood cancer patients with inherited cancer syndromes can provide insights into the interaction between radiation and genetic susceptibility to multiple cancers. The risks of second and third cancers many years later, primarily in the radiation treatment field, are consistent with a radiation effect. Clinicians following these patients with inherited cancer syndromes should be aware of their increased susceptibility to second and third cancers that is enhanced by sensitivity to radiation.

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References

1. National Research Council of the National Academies. Health risks from exposure to low levels of ionizing radiation, BEIR VII Phase 2. Washington, DC: National Academies Press; 2006.
2. Preston D, Cullings H, Suyama A, et al. Solid cancer incidence in atomic bomb survivors exposed in utero or as young children. JNCI 2008;100:428–436. [PubMed: 18334707]
3. Ron E, Modan B, Boice JD Jr, et al. Tumors of the brain and nervous system after radiotherapy in childhood. N Engl J Med 1988;319:1033–1039. [PubMed: 3173432]
4. Lundell M, Holm LE. Mortality from leukemia after irradiation in infancy for skin hemangioma. Radiat Res 1996;145:595–601. [PubMed: 8619025]
5. Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 1995;141:259–277. [PubMed: 7871153]
6. Ron E. Cancer risks from medical radiation. Health Phys 2003;85:47–59. [PubMed: 12852471]
7. Kleinerman RA. Cancer risks following diagnostic and therapeutic radiation exposure in children. Pediatric Radiol 2006;36:121–125.
8. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer Clin J 2008;58:71–96.
9. Inskip PD, Curtis RE. New malignancies following childhood cancer in the United States, 1973–2002. Int J Cancer 2007;121:2233–2240. [PubMed: 17557301]
10. Malkin D, Jolly KW, Barbier N, et al. Germline mutations of the p53 tumor-suppressor gene in children and young adults with second malignant neoplasms. N Engl J Med 1992;326:1309–1315. [PubMed: 1565144]
11. Bhatia S, Sklar C. Second cancers in survivors of childhood cancer. Nature Rev Cancer 2002;2:124–132. [PubMed: 12635175]
12. Meadows AT. A mouse model for studying therapy-induced cancers (editorial). Cancer Cell 2005;8:271–273. [PubMed: 16226702]
13. Strahm B, Malkin D. Hereditary cancer predisposition in children: Genetic basis and clinical implications. Int J Cancer 2006;119:2001–2006. [PubMed: 16642469]
14. Evans DGR, Birch JM, Ramsden RT, et al. Malignant transformation and new primary tumours after therapeutic radiation for benign disease: substantial risks in certain tumour prone syndromes. J Med Genet 2006;43:289–294. [PubMed: 16155191]
15. Moll AC, Imhof SM, Bouter LM, et al. Second primary tumors in hereditary retinoblastoma: A register-based follow-up study, 1945–1994. Int J Cancer 1996;67:515–519. [PubMed: 8759610]
16. Draper GJ, Sanders BM, Kingston JE. Second primary neoplasms in patients with retinoblastoma. Br J Cancer 1986;53:661–671. [PubMed: 3718823]
17. Wong FL, Boice JD Jr, Abramson DH, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 1997;278:1262–1267. [PubMed: 9333268]
18. Kleinerman RA, Tucker MA, Tarone RE, et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: An extended follow-up. J Clin Oncol 2005;23:2272–2279. [PubMed: 15800318]
19. Kleinerman RA, Tucker MA, Abramson DH, et al. Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. J Natl Cancer Inst 2007;99:24–31. [PubMed: 17202110]
20. Ries, LAG.; Melbert, D.; Krapcho, M., et al. SEER Cancer Statistics Review, 1975–2004. Bethesda, MD: National Cancer Institute; 2006 [accessed in month 2004]. Available from URL: http://seer.cancer.gov/csr/
21. Knudson AG Jr. Mutation and cancer: Statistical study of retinoblastoma. Proc Natl Acad Sci USA 1971;68:820–823. [PubMed: 5279523]
22. Krengli M, Hug EB, Adams JA, et al. Proton radiation therapy for retinoblastoma: Comparison of various intraocular tumor locations and beam arrangments. Int J Rad Oncol Biol Phys 2005;61:583–593.
23. Jarlskog CZ, Paganetti H. Risk of developing second cancer from neutron dose in proton therapy as function of filed characteristics, organ, and patient age. Int J Rad Oncol Biol Phys 2008;72:228–235.
24. Listernick R, Ferner RE, Liu GT, et al. Optic pathway gliomas in neurofibromatosis-1: Controversies and recommendations. Ann Neurol 2007;61:189–198. [PubMed: 17387725]

25. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet 2007;44:81–88. [PubMed: 17105749]
26. Sharif S, Ferner R, Birch JM, et al. Second primary tumors in neurofibromatosis 1 patients treated for optic glioma: Substantial risks after radiotherapy. J Clin Oncol 2006;24:2570–2575. [PubMed: 16735710]
27. Evans DGR, Baser ME, McGaughran J, et al. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet 2002;39:311–314. [PubMed: 12011145]
28. Ducatman B, Scheithauer B, Piepgras D, et al. Malignant peripheral nerve sheath tumors: A clinicopathological study of 120 patients. Cancer 1986;57:2006–2021. [PubMed: 3082508]
29. Loree TR, North JH, Werness BA, et al. Malignant peripheral nerve sheath tumors of the head and neck: Analysis of prognostic factors. Otolaryngol Head Neck Surg 2000;122:667–672. [PubMed: 10793343]
30. Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas and other neoplasms. Science 1990;250:1233–1238. [PubMed: 1978757]
31. Li FP, Fraumeni JF Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med 1969;71:747–752. [PubMed: 5360287]
32. Li FP, Fraumeni JF Jr, Mulvihill JJ, et al. A cancer family syndrome in 24 kindreds. Cancer Res 1988;48:5358–5362. [PubMed: 3409256]
33. Hisada M, Garber JE, Fung CY, et al. Multiple primary cancers in families with Li-Fraumeni syndrome. J Natl Cancer Inst 1998;90:606–611. [PubMed: 9554443]
34. Masciari S, Van den Abbeele AN, Diller LR, et al. F18-Fluorodeoxyglucose-positron emission tomography/computed tomography screening in Li-Fraumeni syndrome. JAMA 2008;299:1315–1319. [PubMed: 18349092]
35. Gorlin RJ. Nevoid basal-cell syndrome. Medicine 1987;66:98–113. [PubMed: 3547011]Strong L (1977) Genetic and environmental interactions. Cancer 40(Suppl 4):S1861-1866.
36. Evans DGR, Farndon PA, Burrell LD, et al. The incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma. Br J Cancer 1991;64:959–961. [PubMed: 1931625]
37. Stravrou T, Bromley CM, Nicholson HS, et al. Prognositc factors and secondary malignancies in childhood medulloblastoma. J Ped Hematol Oncol 2001;23:431–436.
38. Goldstein AM, Yuen J, Tucker MA. Second cancers after medulloblastoma: population-based results from the United States and Sweden. Cancer Causes Control 1997;8:865–871. [PubMed: 9427429]

Table 1

Selected inherited cancer predisposition syndromes

Syndrome	Gene	Frequency	Primary tumor	Subsequent or related tumors	Gene-radiation interaction
Hereditary Retinoblastoma	*RB1*	1/20,000 births	Retinoblastoma	Bone sarcoma, STS[a], melanoma, brain	Definite for bone and soft tissue sarcomas in the head
Li-Fraumeni	*p53*	Rare	soft tissue sarcoma, breast cancer	Brain, leukemia, adrenocortical	Possible
Neurofibromatosis Type 1	*NF1*	1/3500 births	Neurofibroma, optic pathway glioma	Gliomas, MNPST[b], STS, leukemia	Probable
Nevoid Basal Cell Carcinoma (Gorlin syndrome)	*PTCH*	Rare	Basal cell cancer	Medulloblastoma	Definite

[a] STS, soft tissue sarcoma

[b] MPNST, malignant peripheral-nerve sheath tumors

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