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Paediatric Update

Second tumours

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1. Introduction

Predictions concerning an increase in survival rates for childhood cancer were made as long ago as 1974, and have indeed been borne out. Approximately 75% of children with cancer can now be expected to live long enough to reach young adulthood and most will have a normal life span. Much has been written during the past two decades about the need to focus on problems of long-term morbidity for this population of surviving children, and more and more attention is being paid to the quality of their survival. Studies are now focusing on the specific factors that could contribute to an increased risk for the development of adverse sequelae, to developing ways by which survivors at greatest risk might be recognised, and to the means of preventing or ameliorating morbidity.

A general concern with second cancers (SMN) as one of the most serious of these sequelae is apparent in the so-called 'late-effects' literature during the past two decades. However, it is only recently that large enough populations of survivors, who have lived for long enough periods of time following treatment, have been studied so that the magnitude of specific risk factors for SMN can be appreciated. It is still too early to determine what the life-time risk for excess cancers will be in childhood cancer survivors. However, for survivors of some neoplasms, we are now able to estimate relative and absolute risks for SMN up to 25 years from diagnosis.

In this review, we will consider aetiological factors commonly associated with SMN, including specific prior therapy, and predisposing conditions. Both therapy and genetic factors play a prominent role in their aetiology [1–5]. With regard to genetic factors, although tumour suppressor genes, such as *RB-1* and *NF-1* now assume the most prominent role, in the future, genetic polymorphisms are likely to emerge in importance. These genetic variations may determine the spectrum of many long-term sequelae associated with radiation and specific chemotherapy, including carcinogenic risks. In addition, life-style practices that promote carcinogenesis may be more likely to affect patients who have already been exposed to other potential risk factors.

In order to understand the influence that these factors have on the total life-time incidence of second cancers, and in order to provide the most rational follow-up care, children cured of cancer should be followed throughout their lives and the information collated and published.

2. Prevalence and patterns of second malignant neoplasms

Specific associations between first and second cancers have been noted, some of which can be explained by genetic susceptibilities or by the specific treatment modalities used (Table 1). The most well-known condition associated with a genetic predisposition is the genetic form of retinoblastoma [6,7]. In that condition, bone and soft-tissue sarcomas occur at an ever-increasing rate with time, especially in irradiated fields. Other non-treatment associated combinations have been recognised in the past two decades, since larger numbers of children have survived. These include Wilms' tumour with neoplasms of the central nervous system [3,8], bone sarcoma with breast cancer [9–12], and hepatoblastoma with colon cancer [13].

In the treatment category, Hodgkin's disease has long been recognised for therapy-related neoplasms, including sarcomas of bone and soft tissue, breast and lung cancer following radiation, and leukaemia following alkylating agents [14–17]. Soft-tissue and bone sarcomas are also important first neoplasms in survivors, with SMN associated with high doses of radiation [18–23]. However, survivors of childhood leukaemia who have not had cranial radiation have relatively low risks of

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Table 1
First and second tumours associated with specific risk factors

First tumour	Second tumours	Risk factors
Retinoblastoma	Bone and soft tissue sarcoma, pineal, melanoma, Langerhans cell histiocytosis	Genetic disease; radiation
Wilms' tumour	Bone and soft tissue sarcoma, leukaemia, brain, liver (?)	Radiation
Neuroblastoma	Thyroid, bone and soft tissue sarcoma	Radiation
Sarcomas	Other sarcomas of bone and soft tissue	Radiation; neurofibromatosis
Lymphoma	Leukaemia, other lymphoma, sarcoma	Alkylating agents; epipodophyllotoxins; radiation

SMN [24–28], unless their treatment included alkylating agents and epipodophyllotoxins, especially in high doses such as those associated with the need for stem cell rescue [29–37]. It has been suggested that therapy with antimetabolites contributes to the risk of radiation-associated brain tumours [38].

Studies of SMN in large cohorts of survivors have been reported for unselected cohorts such as the Late Effects Study Group [3,39], the Childhood Cancer Survivor Study [40], the UK [41], a European consortium [42], and the Nordic countries [4]. The largest of these, the Childhood Cancer Survivor Study is a consortium of 25 institutions in North America [40]. Information concerning treatment and follow-up is available for approximately 14 000 survivors and a median follow-up time of 15 years. Eligible patients were diagnosed between 1970 and 1986 and had survived at least 5 years at the time of the survey. There were 314 second cancers in 298 individuals for an estimated cumulative incidence 20 years after diagnosis of 3.2% and an excess absolute risk of 1.9 per 1000 years of follow-up. Bone tumours and breast cancer comprised the most common SMN. Controlling for the effect of radiation, highest risks were associated with young age at diagnosis, Hodgkin's disease, soft tissue sarcomas, anthracycline and epipodophyllotoxin exposure.

A cohort of approximately 4000 French and British subjects who had survived for more than 3 years after a cancer diagnosis, that included 56 bilateral retinoblastoma patients as well, found a cumulative incidence of 4.9% (excluding secondary leukaemia) after 25 years and 7.7% after 30 years, with a relative risk of 9.2 [41]. As in other reports, radiation played a significant role in the aetiology of bone, soft-tissue sarcomas, breast, brain and thyroid SMN. As survivors age, there is a decrease in the risk of cancer for survivors *relative* to others in the same age population, since the background cancer risk increases with age. However, the actuarial risk SMN, especially solid tumours that occur in radiation therapy fields, increases with longer follow-up.

3. Genetic susceptibility

Overall, constitutional genetic changes play a role in increasing susceptibility to childhood cancer in fewer than 3% of cases [41]. However, second cancer susceptibility is greatly increased in two conditions common to paediatrics, neurofibromatosis type I and the genetic form of retinoblastoma [1,5–7,42,43] (Table 2). These conditions have much in common: both involve loss of tumour suppressor gene activity and impart a dominant predisposition while behaving recessively at the level of the cell, and both increase the probability that radiation therapy imposes an additional risk for second cancer [44–47].

The genetic form of retinoblastoma, involving a constitutional alteration of chromosome 13q14 and comprising approximately 1% of childhood cancer cases, was the first neoplasm in 16% of all second cancers reported by the Late Effects Study Group [3]. Draper and colleagues reported second cancers in survivors of retinoblastoma at a 6-fold risk greater than expected in an age-matched population [6], and a more recent analysis of more than 1500 retinoblastoma survivors reported a 50% probability of developing a second cancer by 50 years of age [7]. The most common second neoplasms, with or without radiation therapy, are bone and soft-tissue sarcoma and melanoma. The pineal tumours that occur in 3–10% of familial cases are probably not true 'second' tumours, but reflect the fact that the pineal gland develops from stem cells similar to the retina and has been considered the 'third eye' [49]. There is some suggestion that breast cancer, lymphomas and Langerhans cell histiocytosis are also increased in mutation carriers.

Neurofibromatosis type 1 (NF-1) caused by either an inherited or a spontaneous new mutation in the gene on chromosome 17, is the most common genetic condition seen in paediatric cancer, accounting for approximately 0.5% of children with cancer [43]. This gene increases the risk for gliomas, neurofibromas and neurofibrosarcomas, as well as leukaemia (especially chronic myelomonocytic leukaemia) [42,45] and perhaps rhabdomyosarcoma and neuroblastoma. These tumours may also occur as second neoplasms in affected individuals.

Other examples of conditions in which the tumour suppressor gene mechanism operates include the Li–Fraumeni syndrome [9–11], neurofibromatosis type 2 and other phacomatoses, such as tuberous sclerosis, the nevoid basal cell carcinoma syndrome (Gorlin's), von

Hippel–Lindau, juvenile polyposis, Peutz–Jeghers, and familial adenomatous polyposis [48]. In the Li–Fraumeni syndrome, more than one cancer developed in 30 of 200 patients with this syndrome, for a cumulative probability of 57% at 30 years for a second cancer, and 38% 10 years after the second cancer for a third cancer [9]. This condition probably also increases the likelihood that children treated with radiation will develop second radiation-associated neoplasms.

Familial adenomatous polyposis associated with a mutation in the *APC* gene also increases the risk of hepatoblastoma [13]. Some patients with hepatoblastoma may have an undetected *APC* mutation and would be at risk for colon cancer; appropriate surveillance for such survivors is therefore indicated.

While Down syndrome and recessively inherited disorders leading to a defect in DNA repair, such as ataxia-telangiectasia (AT), Bloom's syndrome and xeroderma pigmentosum are also associated with an increased risk of specific cancers, second neoplasms have not been reported in excess in these conditions. Reduced survival following the first cancer may limit the number of years-at-risk for developing SMN. Although radiation has been shown to have a profound effect on the ability of AT cells to repair DNA damage by failure to delay progression through the cell cycle, this may result in lethal damage rather than mutation and carcinogenesis.

Recent evidence has revealed another class of genes involved in DNA repair, the genes predispose to syndromes associated with hereditary non-polyposis colon cancer [50]. The major mechanism of action of these genes involves an increase in the number of target cells in a particular tissue and an increase in mutation rate, a mechanism that would be important when multiple events are necessary to make cancer. Although these genes have not been observed to affect the risk of childhood cancers, since embryonal tumours probably require only two events, individuals harbouring such mutations may be at risk for SMN following treatment in childhood. Studies of these genes in survivors who develop SMN are underway.

4. Radiation effects

It has been known for some time that children treated with radiation for a first cancer have an increased risk of developing additional neoplasms in the irradiated sites. Variables determining the risk of neoplasia include age at irradiation, type of normal tissue in the field, and dose. Doses of radiation in the therapeutic range from 1200 to 6000 cGy affect subsequent cancer risk, with the higher doses increasing the risk for sarcomas of the bone and soft tissue. Relatively low doses (less than 3000 cGy) are associated with thyroid and CNS tumours, while bone and soft-tissue sarcomas occur following doses greater than 3000 cGy [51,52]. Beginning 5 years after the treatment of sarcomas, such as rhabdomyosarcoma and Ewing's tumour, cumulative risks of SMN from 5 to 25% have been reported [18–23]. Dose–response relationships have been observed with excesses ranging from 3 to 40 times expected [22]. Adjacent tissues are often exposed to lower doses because of internal scatter, and second neoplasms may also arise in this relatively low-dose sites.

Tissues such as the brain, thyroid, bone and breast appear to be more susceptible if exposed during normal

Table 2
Inherited cancer syndromes and associated neoplasms[a]

Syndrome	Primary tumour	Secondary/associated tumours	Gene
Genetic retinoblastoma	Retinoblastoma	Sarcomas, pineoblastoma, melanoma	*RB1*
Neurofibromatosis type 1	Neurofibromas	Neurofibrosarcoma, AML, JMML, glioma	*NF1*
Neurofibromatosis type 2	Vestibular schwannomas	Meningiomas, astrocytomas, ependymomas	*NF2*
Li–Fraumeni	Sarcomas, breast cancer	Adrenocortical, brain tumours, leukaemia	*p53*
Familial adenomatous polyposis	Colorectal cancer	GI cancer, hepatoblastoma, thyroid, desmoid	*APC*
Gardner's	Colorectal cancer	Hepatoblastoma	*APC*
Turcot's	Colorectal cancer	Medulloblastoma	*APC*
Hereditary nonpolyposis colorectal cancer	Colorectal cancer	Endometrial, ovarian, gastric, pancreatic Cancer	*MSH2*/*MLH1*
Familial breast cancer 1	Breast cancer	Ovarian cancer	*BRCA1*
Familial breast cancer 2	Breast cancer	Pancreatic, ovarian cancer	*BRCA2*
Multiple endocrine neoplasia type 1	Pancreatic islet cancer	Parathyroid, thyroid, pituitary cancer	*MEN1*
Multiple endocrine neoplasia type 2A	Medullary thyroid	Parathyroid, pancreas, pheochromocytoma	*RET*
Multiple endocrine neoplasia type 2B	Medullary thyroid	Adrenocortical, ganglion, pheochromocytoma	*RET*
Nevoid basal cell carcinoma (Gorlin's)	Basal cell carcinoma	Medulloblastoma	*PTCH*
Beckwith–Wiedmann	Wilms' tumour	Hepatoblastoma, adrenocortical carcinoma	*?*
Von Hippel–Lindau	Renal clear cell	Brain tumours, pheochromocytoma	*VHL*
Tuberous sclerosis	Renal cancer	Brain tumours	*TSC2*

GI, gastrointestinal; JMML, acute myelogenous leukaemia; AML, acute myelogenous leukaemia.
[a] Adapted from Ref. [5].

Table 3
Therapy-related acute myelogenous leukaemia[a]

	Alkylating agent-related	Epipodophyllotoxin-related
Type of leukaemia	Myelodysplasia	M4/M5 AML, some M1,M2
Latent period	4–7 years	1–3 years
Cytogenetics	del (5q), del (7q), -5, -7	Translocations, especially involving 11q23
Prevalence	1 to >20%	2 to 12%
Survival	Poor	Poor
Preleukaemic phase	Common	Rare

[a] Adapted from Ref. [24].

periods of rapid growth (i.e. early childhood or puberty). The actuarial risk of breast cancer 30 years following radiation to the mediastinum for Hodgkin's disease ranges from 10 to 33% [14–17] with adolescent girls in the highest risk categories. Age at exposure has also been shown to be a significant variable for CNS and thyroid neoplasms, with young children affected primarily [25–27,52]. However, embryonal neoplasms have not been reported when very young children are treated with doses in the therapeutic range. Alkylating agents and anthracyclines have also been implicated in affecting the radiation therapy-associated risk for bone tumours [6,23,37,51]. In childhood acute lymphocytic leukaemia (ALL), treatment with cranial radiation led to a SMN risk of 3.5% at 15 years, but without radiation, the same intensive BFM therapy resulted in a significantly lower risk of 1.2%, with no change in efficacy [26]. Combined modality therapy may increase the risk of leukaemia as well as second solid tumours, but studies have failed to demonstrate an increase in leukaemia following therapeutic radiation alone [37]. Doses in the therapeutic range may be lethal to haematopoietic stem cells.

Second cancers associated with radiation are considerably more frequent in children who are genetically predisposed. This was first seen in children with the genetic form of retinoblastoma. A report of the largest series of long-term retinoblastoma survivors confirms the high risk of new cancers in those with the genetic form (bilateral and familial cases)—25% at 50 years—and the elevated risk following radiation—50% at 50 years [7]. That there is an added effect of radiation comes from the study of patients with Gorlin's syndrome or the nevoid basal cell carcinoma syndrome in which tumours occur at earlier than expected ages and after a shorter latent period [3]. This syndrome is characterised by posterior fossa tumours and basal cell carcinomas, the latter appearing within months following radiation in multiple sites.

5. Chemotherapy

Chemotherapeutic agents such as alkylating agents and epipodophyllotoxins are well-known as being associated with secondary leukaemias [24–33]. Different and characteristic chromosomal alterations accompany the leukaemias that occur in association with alkylators or epipodophyllotoxins, with deletions of chromosomes 5 and 7 in the former, and translocations involving 11q23, the locus of the *MLL* gene, in the latter (Table 3). It has been suggested that the high rate of therapy-related myelodysplasia and AML after high-dose chemotherapy and autologous stem cell transplantation is primarily a result of preconditioning therapy, rather than the conditioning or the preparation of stem cells, since the latent period for these neoplasms is typically quite short [32]. Alkylating agent-associated secondary leukaemias are dependent upon dose and specific agent. For instance, nitrogen mustard, chlorambucil, and the nitrosoureas are more potent leukaemogens than is cyclophosphamide. These secondary leukaemias usually occur within 7–8 years of exposure, but therapy with epipodophyllotoxins may increase the risk and reduce the latent period [35]. Schedule may be important in the development of the secondary leukaemias associated with the topoisomerase II inhibitors, but there does not appear to be a clear dose–response relationship [33,36]. The usual latent period is between 6 months and 3 years.

In a recent report, an association between antimetabolite therapy and second malignant neoplasms was suggested [38]. The authors proposed that second cancers develop because of an enzyme deficiency, and recommend that drug doses be adjusted to patients' enzyme levels in order to avoid acute, and perhaps, delayed toxicity.

Cyclophosphamide has been associated with secondary bladder cancer, probably as a result of the inflammation caused by retention in the bladder of the metabolites of that agent. The current practice of using mesna as a uroprotectant with both cyclophosphamide and ifosfamide may prevent damage to the transitional epithelium of the bladder and render this risk obsolete.

6. Other risk factors and opportunities for intervention

Associations between cancer risk and an increase in cell proliferation secondary to infection or inflammation

have long been noted. These include hepatoma following chronic hepatitis and gastrointestinal neoplasms in individuals with inflammatory bowel disease. Survivors who may be carriers of hepatitis B or C virus, the latter referable especially to patients treated prior to the routine testing of blood products for that virus, are at increased risk for chronic liver disease and for hepatocellular carcinoma. Children treated for cancer often develop serious infections (renal, pulmonary) and acute inflammatory reactions. Whether or not such states increase the risks for neoplasms in affected organs is not yet known, but many of the broad spectrum antibiotics used to treat these infections can cause specific organ damage that may lead to proliferation and tumours. Expectant surveillance and follow-up of large numbers of childhood cancer survivors might provide the answer in the future.

Physicians who follow childhood cancer survivors have numerous opportunities for intervention. Childhood cancer survivors should be counselled to avoid exposure to agents known to be associated with cancer risk in the general population, such as smoking and sun. They may be at greater risk for cancers that involve organs affected by previous disease and treatment, and such exposures are likely to impose additional risks. For example, cigarette smokers who have received bleomycin or busulfan, or who have had pulmonary radiation, may be at greater risk of developing carcinomas of the lung and smokers who have received cyclophosphamide, ifosfamide, or any of the platinum compounds may have an increased risk of bladder cancer.

Since cancer is generally a disease of the aged, and since many childhood cancer survivors have not yet reached the ages at which most cancers occur in the general population, we still have no idea what the total life-time excess risk of cancer will be in our patients. For this reason, standardised follow-up protocols need to be developed and data concerning survivors' outcome analysed and reported. This will also assure the same degree of excellence in follow-up care that our patients have become accustomed to during active treatment and will enable paediatric oncologists to develop and test treatment plans in the future that are less likely to lead to adverse late effects.

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Commentary

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Over 20 years ago, it became apparent that survivors of childhood cancer experience an increased risk of developing new primary cancers ("second malignant neoplasms" (SMNs)), compared with the general population. In her article, Professor Meadows has provided a characteristically trenchant and comprehensive review of current knowledge and future opportunities concerning SMNs after childhood cancer. Professor Meadows acknowledges that full and accurate information about the

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