Pediatr Blood Cancer 2012;58:85–89

Hereditary Cancer Risk Assessment in a Pediatric Oncology Follow-Up Clinic

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Background. Pediatric cancer survivors are at risk for multiple late effects including second malignancies, some a direct consequence of genetic susceptibility. Appropriate surveillance and management for the survivor and at-risk family members can often be established if the genetic predisposition is recognized and/or diagnosed. Numerous published guidelines outline which adult cancer patients and survivors should be referred for hereditary cancer risk assessment. In the pediatric oncology setting, minimal guidance exists for healthcare providers to determine which patients and families to refer for genetic evaluation. ***Procedure.*** The aim of this project was to determine what percentage of childhood cancer survivors are appropriate for further evaluation in a hereditary cancer program or genetics clinic and characterize indications for referral. Participants included pediatric cancer survivors seen for follow-up in a large cancer survivor center. Medical and family histories were obtained and reviewed by a certified genetic counselor at the survivor's annual visit. Eligibility for genetics referral was determined based on personal/family medical history and published literature. ***Results.*** Of 370 survivors of childhood cancer, 109 (29%) were considered eligible for genetics follow-up or referral. Family history of cancer is the most prevalent reason identified for eligibility for further genetics evaluation (61%) followed by tumor type (18%), medical history (16%), and family history of another condition (6%). ***Conclusions.*** This project provides evidence that inclusion of genetic evaluation is feasible and relevant in the care of childhood cancer survivors. Further study is warranted to determine optimal timing and clinical utility of this multidisciplinary and family-centered approach. Pediatr Blood Cancer 2012;58:85–89.

Key words: cancer; genetic; hereditary; late effects; oncology; pediatric

INTRODUCTION

Although most pediatric cancers are thought to be either sporadic or multifactorial, some studies have revealed that up to 10% of all childhood cancers are due to a genetic syndrome or inherited susceptibility [1,2]. The actual incidence may, in fact, be higher due to under-recognition and under-reporting. Identifying those pediatric cancer patients and survivors who have cancer predisposition syndromes often allows for individualized risk assessment for additional malignancies for the patient as well as existing relatives and future offspring [3]. Accurate risk assessment will often guide the implementation of appropriate clinical surveillance and management. This may allow for earlier detection and treatment of neoplasms resulting in reduced morbidity and mortality and optimizing chances of cure [4,5].

For the common hereditary cancer syndromes with onset in adulthood such as Lynch syndrome and Hereditary Breast and Ovarian Cancer syndrome, numerous guidelines exist for risk assessment and appropriate referral of patients [6–8]. Although there is some limited published guidance for pediatricians when evaluating a family history and physical features in the patient and family [4] there is no such review that is comprehensive and focuses specifically on hereditary cancer syndromes presenting as childhood cancers. A handful of examples of the cancer predisposition syndromes in childhood and implications for affected families were recently reviewed [2]. Authors highlighted the complexity and clinical nuances of each of the highlighted conditions; though no specific guidelines for identifying or evaluating patients for further consideration of such syndromes were proposed. In addition, Rao and Nichols provided guidance on surveillance in specific tumor predisposition syndromes "with the aim of detecting cancers at early and hence more curable stages" [4]. Conclusions from this article include that much work is still needed to determine the optimal interventions and screening for the remaining majority of hereditary cancer syndromes that present in childhood. This resource also does not focus on how or why patients were considered at-risk. Although our study is not intended to be a comprehensive referral guide, it is an important initial evaluation of the relevance of genetic risk assessment in the childhood cancer survivor.

Recognition of cancer syndromes with risk for onset in childhood has been described in the medical literature. A systems-based approach was outlined in the context of congenital anomalies identifiable on physical exam [5]. A handful of individual publications address the incidence of germline mutations in children with specific tumors such as retinoblastoma [9] and hepatoblastoma [10]. In addition, review of the features of specific hereditary cancer syndromes has been provided [11]. The current study characterized the indications for eligibility for referral to a specialized genetics program in childhood cancer survivors.

At Cincinnati Children's Hospital Medical Center (CCHMC), the Cancer Survivor Clinic follows patients who are at least 5 years from their initial cancer diagnosis and 2 years off therapy. A multidisciplinary team of healthcare providers is available to survivors and families including the addition of a certified genetic counselor in 2007. Inclusion of genetic counseling services for long-term survivors of childhood cancer has been previously proposed [3,12], although, until now, there has been no significant study of the practical integration of such services into the survivor's regular follow-up. This study aims to quantify eligibility for genetics' referrals from a long-term survivor clinic

Additional supporting information may be found in the online version of this article.

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Conflict of interest: Nothing to declare.

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Received 13 October 2010; Accepted 22 June 2011

DOI 10.1002/pbc.23283
Published online 17 August 2011 in Wiley Online Library (wileyonlinelibrary.com).

as well as characterize the features of the clinical or family history which warrant eligibility.

METHODS

Approval for this review was obtained from the Institutional Review Board (IRB) at Cincinnati Children's Hospital Medical Center. Participants included pediatric cancer survivors seen in the Cancer Survivor Center at Cincinnati Children's Hospital Medical Center between March 2007 and March 2009.

Medical and family histories were obtained at the patient's annual visit in clinic either in person by a certified genetic counselor or by completion of a screening form (Appendix A) which were subsequently reviewed by a certified genetic counselor. Records for family members other than the index patient were not obtained to confirm diagnoses or reported histories. Therefore, evaluation of the family history was based on reported history. Informants included appointment attendees such as parents and the patients themselves. Additional information was not generally sought from parents or other informants who did not attend the appointment. Eligibility for genetics referral was determined based on personal/family history and published literature. Survivors and families who were to be eligible for genetic risk assessment were either counseled at the time of the oncology appointment or offered a separate visit within the genetics department at CCHMC. Those who were identified as eligible for genetics referral by screening form were either contacted by phone and offered an appointment in genetics clinic or were slated to discuss genetic risk at the next annual oncology visit. All families who filled out the screening form rather than meeting with a genetic counselor in person were offered a follow-up discussion by telephone with the genetic counselor.

Data for the study were collected from the clinical visit/chart and included age at time of oncology appointment, specific diagnosis and age of diagnosis, treatment for cancer, medical and developmental history prior to and since the cancer diagnosis and treatment, documentation of physical features/characteristics, family history of cancer and other major medical conditions/anomalies in at least three generations of the family (if available), method of history collection (in person vs. screening form) and whether or not a genetics referral was indicated (either offered at the visit, by telephone or next visit by clinical staff). Of note, although a physical exam was performed by the pediatric oncologist or advanced practice nurse, a clinical geneticist did not perform a morphological exam.

RESULTS

A total of 370 patients/families provided information about their personal and family histories. The age range of the proband at the time of evaluation was 5 years–59 years. Approximately half of the patients were less than 18 years of age while the remaining were adults. Ninety-five (26%) patients completed screening forms at their visit, 269 (73%) met with a certified genetic counselor in-person and 6 (1.6%) were known to have had family histories previously recorded at a genetics evaluation that was not repeated during the visit (Table I). Fifteen patients (4%) have previous genetic diagnoses including Down syndrome [8], Neurofibromatosis type 1 (NF1) [2], and one patient each with WAGR, Beckwith–Weidemann syndrome, Li–Fraumeni syndrome, Turner syndrome, and Williams syndrome. As noted, six additional patients had been seen for a previous genetics evaluation for indications including two patients with multiple café au lait macules, two patients with optic pathway gliomas (all four were referred to evaluate for NF1), one patient with a medulloblastoma and features suggestive of Gorlin syndrome and one patient with a pheochromocytoma (genetic testing for the latter two patients was not informative). Overall, the types of cancers diagnosed in participants are summarized by malignancy in Table II.

TABLE I. Participant Demographics

Total	370
Gender	
Male	195 (53%)
Female	175 (47%)
Age at evaluation	
5–17 years	176 (48%)
≥18 years	194 (52%)
Median	18 years
Range	5–60 years
Method	
In person	269 (73%)
Screening form	95 (26%)
Previously collected	6 (1.6%)

A total of 109 patients/families (29%) were considered eligible for genetics follow-up or referral. Six of these are patients who had a previous genetic diagnosis or evaluation who warranted further follow-up for genetic counseling or additional testing. Thirty-seven (34%) of the 109 were considered eligible based on review of a completed screening form only while 69 (63%) were evaluated in person by a certified genetic counselor.

McNemar's Chi-squared test with continuity correction was utilized to determine if there was a significant change in the proportion of patients who were considered genetics eligible before and after the addition of genetic counseling to the clinic. This test yielded a P-value of <0.0001 which is statistically significant.

Cancer types for participants overall and those eligible for genetics referral are summarized in Table II. All (100%) of individuals with retinoblastoma, hepatoblastoma, choroid plexus carcinoma, and pheochromocytoma were considered eligible for genetics referral. Other diagnoses with high proportions (>25%) individuals eligible for genetics referral included medulloblastoma (43%), optic glioma (50%), Wilms tumor (34%), Hodgkin and Non-Hodgkin lymphoma (37% each), ALL (28%), and neuroblastoma (27%). In contrast, no patients (0%) with CML or Ewing sarcoma were considered eligible for genetics referral.

After review of data, four categories for referral were established and included indications based primarily on cancer type, family history of cancer, family history of other anomaly or genetic condition and clinical/medical history of patient. Of the 109 patients who were considered eligible for genetics follow-up or referral (Table III), 66 (61%) were based on a family history of early onset or multiple other cancers. Twenty (18%) were eligible due to a cancer diagnosis suggestive or pathognomonic for a hereditary cancer syndrome. Seventeen (16%) were eligible based on the patient's personal clinical history being suggestive of a genetic condition or hereditary cancer syndrome. Lastly, six (6%) were eligible for genetics referral due to a family history of a potentially genetic factor unrelated to cancer.

TABLE II. Summary of Cancer Diagnosis by Type, Genetic Assessment Eligibility and Primary Reason for Eligibility

Diagnosis	Overall	Total genetics eligible at time of visit, N (%)	Cancer type	Family history cancer	Family history other	Clinical history	Prior genetics evaluation or diagnosis	Prior genetics evaluation or diagnosis—no additional follow-up indicated	% of cancer type genetics eligible
Acute leukemia	129	25 (19)	0	18 (72)	3 (12)	4 (16)	13 (10)	11 (9)	28
Burkitt lymphoma	9	2 (22)	0	2 (100)	0	0	0	0	22
Choroid plexus carcinoma	1	1 (100)	1 (100)	0	0	0	1 (100)	0	100
CML	4	0	0	0	0	0	0	0	0
Ewing sarcoma	10	0	0	0	0	0	0	0	0
Hepatoblastoma	9	9 (100)	8 (89)	0	0	1 (11)	0	0	100
Hodgkin disease	30	11 (37)	0	9 (82)	1 (9)	1 (9)	0	0	37
Medulloblastoma	7	3 (43)	0	2 (67)	0	1 (33)	1 (33)	0	43
Neuroblastoma	34	9 (27)	0	8 (89)	0	1 (11)	0	0	27
Non-Hodgkin lymphoma	19	7 (37)	0	7 (100)	0	0	0	0	37
Optic glioma	6	1 (17)	1 (100)	0	0	0	3 (50)	2 (33)	50
Osteosarcoma	6	1 (17)	0	1 (100)	0	0	0	0	17
Pheochromocytoma	1	1 (100)	1 (100)	0	0	0	1 (100)	0	100
Retinoblastoma	8	8 (100)	8 (100)	0	0	0	0	0	100
Rhabdomyosarcoma	15	3 (39)	0	3 (100)	0	0	0	0	20
Wilms	35	12 (34)	1 (8)	4 (33)	0	7 (58)	2 (6)	0	34
Other	47	16 (34)	0	12 (75)	2 (13)	2 (13)	0	0	34
Total	370	109 (29)	20 (18)	66 (61)	6 (6)	17 (16)	21 (6)	13 (4)	33

TABLE III. Summary of Indications for Eligibility for Genetics Evaluation

Indication for referral	Number of patients
Family history of Cancer	66 (61%)
Cancer type	20 (18%)
Patient's clinical/med hx	17 (16%)
Family history of other	6 (6%)
Total	109

DISCUSSION

Pediatric cancer patients and survivors are at risk for multiple late effects including second malignancies, some of which are a direct consequence of an inherited or genetic susceptibility [3]. For example, individuals with heritable retinoblastoma have a significantly increased risk of second malignancies including sarcomas, melanomas, and other epithelial malignancies [13–15] and individuals with Li–Fraumeni syndrome have a significant risk of developing a second or third malignancy, with the high risk of multiple malignancies in those who developed a childhood or young adult cancer [16,17].

Relevant literature includes a recent study that evaluated the incidence of malformation syndromes in children with cancer diagnosed by clinical morphological examination [18]. In this study, 7.2% of pediatric cancer patients were diagnosed with or suspected to have a syndrome. Although clinical examination by a geneticist or a skilled pediatrician may ascertain children with physical features of genetic syndromes, those with predisposition syndromes specific to cancer risk could be missed by this approach. In addition, this publication does not provide an algorithm for when it is appropriate to refer the patient and family for a genetics evaluation.

In this study, prior to the addition of a certified genetic counselor to the Cancer Survivor Clinic, approximately 6% of the patients had previous genetic diagnoses or had been evaluated in genetics clinic. Following the addition of the genetic counselor, 29% of patients were identified as eligible for further genetics evaluation or referral. Therefore, in this study, addition of a genetic counselor to the team of specialists involved in the care of childhood cancer survivors significantly increased the percentage of patients who are considered eligible for genetics evaluation (McNemar's test, $P < 0.0001$).

A number of cancer types had a high proportion that were eligible for genetic assessment such as retinoblastoma, hepatoblastoma, choroid plexus carcinoma, pheochromocytoma, optic glioma and Wilms tumor based on the known association of each of these diagnoses with hereditary cancer syndromes. An argument could be made that all patients with specific tumor types listed here such as optic glioma and Wilms tumor should be eligible for genetic assessment. However, in this study, eligibility for these cancer types was based on the presence of additional features. Interestingly, other cancer types also had a high proportion being eligible such as medulloblastoma, lymphomas, and acute leukemia. Although cancer type alone is considered as the threshold for referral for some types of childhood cancer, other cancer types may emerge as more relevant to consider for genetic assessment. This approach may be especially important in conditions with a high rate of de novo heritable genetic mutations such as presentation with leukemias and brain tumors in Li–Fraumeni syndrome and hepatoblastoma as a feature of familial adenomatous polyposis (FAP) syndrome, for example, where the family history may be negative in at risk patients [4]. Due to the patterns specific to the CCHMC Cancer Survivor Clinic, the

number of patients who were diagnosed with brain tumors is markedly low compared to the incidence of childhood brain tumors. There are several reasons for this discrepancy including the historical follow-up of patients with brain tumors in a specific neuro-oncology clinic as well as the high relapse rate and decreased survival of patients with specific types of brain tumors. Therefore, the data in this study are only reflective of those patients seen in the Cancer Survivor Clinic and not of all childhood cancers diagnosed at our center.

In this study, family history of cancer is the most prevalent reason for genetics evaluation in survivors of childhood cancer. Therefore, it is critical that collection and review of thorough family history be a standard element in the ongoing care of childhood cancer survivors. Also important to consider is that family history of cancer, especially in young children, is dynamic. As the child's parents and other relatives grow older, the family history and subsequent risk assessment can change significantly. Families should be encouraged to provide updates to the providers involved in the long-term care of the childhood cancer survivor and the clinical staff should emphasize the importance of updated information at each annual visit.

An additional benefit to including a genetic evaluation in the care of childhood cancer survivors is that most patients and families are determined to be a low risk of a hereditary cancer predisposing syndrome and can be counseled as such. This relative reassurance may alleviate anxiety for the family. It is important to counsel the family about the remaining relative/familial risks and to separate the genetic risk assessment from other potential risk factors for the patient or family such as second malignant neoplasm risk due to therapy or environmental exposures. In contrast, if a hereditary cancer syndrome is identified through molecular testing in a family, mutation specific testing can determine not only who in the family is at increased risk and is appropriate for high risk screening and management, but also who in the family did not inherit the genetic risk release these individuals from unnecessary screening and anxiety.

One of the challenges associated with the identification of patients with risk of a hereditary cancer syndrome is determining when testing is indicated as standard of care. Considerations for when and if to offer testing may include the likelihood of finding a mutation, the probability of developing a malignancy as well as the availability of evidence-based and effective means of screening and risk reduction [2,4,8]. These considerations are especially relevant and complex when focusing on pediatric patients and their families. For example, conditions such as familial retinoblastoma, multiple endocrine neoplasia (MEN) and FAP are accompanied by stringent management guidelines while recommendations for individuals with Li–Fraumeni syndrome are less established due to the variable expressivity and penetrance of this condition [2,17]. Of note, new surveillance guidelines for Li–Fraumeni syndrome are in discussion and may include regular full body MRI. Although unpublished, initial studies on the utility of such screening have reportedly been promising and, therefore, identifying patients with this condition may be essential in effective implementation of screening. Much attention is being paid to such advances through efforts such as the recent Li–Fraumeni syndrome Workshop and Consortium through the National Cancer Institute (NCI). ASCO [8] has provided input on the complexities of cancer susceptibility testing in children but comments that with appropriate pre- and post-test counseling, testing affected children is permissible. Testing unaffected children requires particularly thorough attention to both medical and ethical implications.

Limitations of this study include that the method of family history collection and review were not consistent between all participants. Therefore, there may be an over representation in the genetics eligible vs. overall participants of those families who completed screening forms (34% vs. 26%, respectively) in contrast to those who met with a genetic counselor in person (63% vs. 73%). It is possible that not all of the selected families who completed screening forms may actually be candidates for genetics referral if incomplete information was provided or if more information than was collected on the form was needed to determine eligibility for referral. Many of the families who were eligible for genetics follow-up based on review of a screening form were determined so due to family history factors which may influence the proportion of patients referred based on family history factors overall. In addition, although referral eligibility was based on published literature, some subjectivity was inherent on the part of the genetic counselor in determining threshold for referral. For instance, although all patients with hepatoblastoma were considered candidates for evaluation for FAP, this was not the case for patients with rhabdomyosarcomas or osteosarcomas of which a similar proportion may be due to Li–Fraumeni syndrome. Of note, none of the patients in this study were diagnosed at very early ages (no rhabdomyosarcoma diagnosed at <3 years of age and no osteosarcoma diagnosed at <10 years of age) which may be a helpful determinate of risk. Evaluation of genetic risk with respect to family size and number of unaffected vs. affected relatives is also a potential area of subjectivity. As noted in this study, genetic risk assessment was performed primarily by a certified genetic counselor with input from the physical exam performed in the oncology clinic. Although inclusion of a clinical geneticist for the purpose of screening for eligibility for genetics follow-up was not feasible in this study, clinical geneticists were available to see the patients and families once they presented at the genetics visit. Future investigation is warranted to determine if there are limitations imposed by having a genetic counselor be the sole genetics provider who determines eligibility for genetics evaluation in this and other settings.

The focus of this project on the population of patients who are at least 5 years from their diagnosis allows for genetic risk assessment when issues such as treatment and cure of the patient are no longer competing priorities. In addition, families may recall and retain information more effectively when not in the shadow of the crisis of a recent diagnosis or treatment. The timing also allows for the dynamic aspect of family histories, permitting additional relatives' more recent diagnoses to be incorporated into the risk assessment. There are some potential risks, however, in waiting until long term survivorship to perform genetic risk assessment. These include development of malignancies in the cancer survivor or other relatives that may have been prevented if a genetic condition had been identified in the family. In addition, for those children who do not survive through their treatment, these families may be missed and therefore at high risk of developing unexpected and potentially advanced stage malignancies if genetic risk evaluation is delayed. Future studies are indicated to determine the most appropriate time in the care of the childhood cancer patient to integrate genetic assessment and counseling. Other opportunities for future research include

assessing how many of the genetics eligible patients/families followed through on the referral and how many were actually diagnosed with a specific genetic risk factor.

This project provides evidence that inclusion of genetic evaluation is feasible and relevant in the long-term multidisciplinary care of childhood cancer survivors. Further study is warranted to determine the optimal timing and clinical utility of this multidisciplinary and family-centered approach.

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