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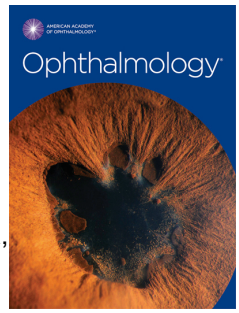

Recommendations for long-term follow-up of adults with heritable retinoblastoma

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Recommendations for long-term follow-up of adults with heritable retinoblastoma

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ABSTRACT

Objective: Generate recommendations for long-term follow-up for adult survivors of heritable retinoblastoma.

Design: We convened a meeting of providers from retinoblastoma centers around the world to review the state of the science and to evaluate the published evidence.

Subjects: Retinoblastoma is a rare childhood cancer of the retina. Approximately forty percent of retinoblastoma cases are heritable, due to a germline mutation in *RB1*. Dramatic improvements in treatment and supportive care have resulted in a growing adult survivor population. Survivors of heritable retinoblastoma, however, have significantly increased risk of subsequent malignant neoplasms, particularly bone and soft tissue sarcomas, uterine leiomyosarcoma, melanomas, and radiotherapy-related central nervous system tumors, which are associated with excess morbidity and mortality. In spite of these risks, no surveillance recommendations for this population are currently in place and surveillance practices vary widely by center.

Methods: Following the Institute of Medicine procedure for clinical practice guideline development, a PubMed, EMBASE, and Web of Science search was performed, resulting in 139 papers; after abstract and full text review, 37 papers underwent detailed data abstraction to quantify risk and evidence regarding surveillance, if available. During an in-person meeting, evidence was presented and discussed, resulting in consensus recommendations.

Main outcome measures: Diagnosis and mortality from subsequent neoplasm.

Results: While evidence for risk of subsequent neoplasm, especially sarcoma and melanoma, was significant, evidence supporting routine testing of asymptomatic survivors was not identified. Skin examination for melanoma and prompt evaluation of signs and symptoms of head and neck disease were determined to be prudent.

Conclusions: This review of the literature confirmed some of the common second cancers in retinoblastoma survivors, but found little evidence for a benefit to currently available surveillance

for these malignancies. Future research should incorporate international partners, patients, and family members.

INTRODUCTION

Retinoblastoma (RB) is a rare childhood cancer of the retina. Survival from RB has increased dramatically over the past decades and currently exceeds 95% in resource-rich settings.[1-4] Approximately forty percent of RB cases are heritable, carrying a germline mutation in *RB1*, and frequently develop bilateral RB. Survivors of heritable RB, especially those who received external beam radiotherapy, have significantly increased risk of developing subsequent malignant neoplasms (SMN).[5, 6] Commonly described SMN include bone and soft tissue sarcomas, malignant melanomas, and radiotherapy-related central nervous system tumors; SMN are associated with excess morbidity and mortality. Among other childhood cancer survivors, SMN risk and appropriate surveillance (testing asymptomatic survivors) have been identified.[6, 7, 8] Despite these risks, SMN surveillance for adults with a history of heritable RB varies widely based on local practices, and no guidelines are currently available.

In recognition of these discrepancies, we convened a meeting of specialists from RB centers around the world to review the state of the science and evaluate the published evidence in the Spring of 2017. This international interdisciplinary panel included ocular oncologists, epidemiologists, survivorship specialists, pediatric oncologists, radiologists, and a geneticist. The objective of the meeting was to develop evidence- and consensus-based international SMN surveillance guidelines for survivors of heritable RB, using standardized guideline-writing practices.[6, 9-12] In preparation for the meeting, we created a Delphi process for generating the meeting agenda, as in other guideline development settings.[13-16] Potential SMN sites to be reviewed were circulated to the attendees, who anonymously indicated their priorities for discussion. After review of these submissions, the list of SMNs to be reviewed was generated

and a literature search for relevant studies was conducted. Notably, as the guidelines are intended to adults (those over the age of 18) with a history of heritable RB, pinealoblastoma or trilateral blastoma, and surveillance for recurrent disease, were excluded from discussion.

An English language PubMed, EMBASE, and Web of Science search was performed to identify all relevant literature. Keywords and medical subject heading terms were used to identify potentially relevant titles and abstracts. Search terms included “retinoblastoma,” “neoplasms, second primary,” “mass screening,” “population surveillance,” and “follow up.” Details of the search and the selection of papers for data abstraction are reported in the **Appendix**. Initially, 139 papers were identified. After evaluation by two authors (ET and DB), 37 manuscripts were selected for data abstraction. Attendees were assigned SMN sites for abstraction and received the relevant manuscripts for review prior to the meeting.

On the meeting day, participants presented the abstracted data. Evidence for the magnitude of risk and of the benefits and harms associated with SMN surveillance was reviewed and graded using National Comprehensive Cancer Network (NCCN) Categories of Evidence and Consensus, which is the standard method for grading the evidence in developing NCCN guidelines across cancer types.[17,18,19] Recommendations were drafted and circulated to the attendees, with continued revision and clarification, as well as supplemental literature searches, where helpful.The Memorial Sloan Kettering Institutional Review Board approval was not required for this work.

Recommendations for long-term follow-up of adults with heritable RB, developed as a result of this process are presented here, with quality of evidence and strength of recommendation gradings. Surveillance recommendations for SMN (in alphabetical order) are summarized in **Table 1** and presented in detail below.

EVIDENCE REVIEW

Bone and soft tissue sarcoma

Evidence of risk: Yes

Grade of evidence for risk: A

Recommendation for surveillance: Recommendation not to do

Among all SMN subtypes, survivors of heritable RB are at highest risk for subsequent bone and soft tissue sarcoma.[20-34] We reviewed 32 publications, including 28 that reported the results of cohort studies and 4 case reviews or clinical series, describing subsequent sarcoma in heritable RB survivors.[3, 20, 22-25, 34-481, 14, 26, 27, 29, 33, 49-53] In an analysis of subsequent malignancy risk in 963 one-year RB survivors with heritable disease diagnosed between 1914 and 1984, survivors were found to be at highest risk for subsequent cancers of the bone (standardized incidence ratio [SIR] 360, 95% confidence interval [CI] 283–451), predominantly osteosarcoma, and connective and soft tissue (SIR 122, 95% CI: 84–170).[32] Very high risks have been identified for a variety of soft tissue subtypes, including fibrosarcomas, rhabdomyosarcomas, and malignant fibrous histiocytomas, as well as late-onset leiomyosarcomas.[23] Risk is particularly pronounced among those with prior radiotherapy and systemic chemotherapy exposure; [26, 27, 29, 32, 44, 46] several reports have demonstrated even higher risk among those irradiated in the first year of life.[54-56]

In addition to radiotherapy -related risk, heritable RB survivors are also at risk for sarcomas of bone and soft tissue outside the field of radiotherapy[22, 23, 32] and in the absence of any history of radiotherapy,[23, 33] thus underscoring a genetic predisposition to sarcomas independent of radiation exposure. Note that further information about uterine tumors (predominantly leiomyosarcomas) is provided below in a separate section. Recent reports have suggested that

risk may be attenuated in the presence of specific genetic alterations[39] and/or after treatment with proton radiotherapy[52, 57] but further research is required to confirm these findings.

In some institutions, it is common practice to periodically image the head and neck region of RB survivors. We found no studies that quantified the potential benefits of such surveillance practices. In addition, there has been much enthusiasm about the use of surveillance whole-body magnetic resonance imaging (whole-body MRI) for patients with genetic predisposition syndromes.[58-61] One study demonstrated the feasibility of performing these studies in heritable RB survivors,[41] but the analysis was limited by small sample size and retrospective design. Given these limited data, our panel does not recommend annual whole-body or regional MRI surveillance in hertiable RB survivors. This recommendation is based on a preliminary lack of evidence for benefit coupled with concern for possible harms, including: the need for additional testing after false positives; potential for gadolinium deposition, although whole-body MRI is often performed without contrast;[62, 63] and increased testing-related anxiety and/or psychosocial distress.[64] Based on the experience with other predisposition syndromes, however, it could be worthwhile to formally open an international prospective surveillance trial to delineate the utility of this test.

Therefore, in accord with the recent consensus guidelines from the American Association for Cancer Research (AACR) Childhood Cancer Predisposition Workshop,[65] our multidisciplinary panel recommends an annual comprehensive history and physical exam, with an emphasis on educating adult patients and families about concerning signs and symptoms (**Table 1**). Heritable RB survivors should receive prompt medical evaluation for any new concerns. However, routine surveillance for bone and soft tissue sarcoma with whole-body MRI, MRI of the head and neck, or other imaging modalities in asymptomatic heritable RB survivors is not recommended.

Brain and central nervous system

Evidence of risk: Yes

Grade of evidence for risk: A

Recommendation for surveillance: Recommendation not to do

We reviewed 21 papers including 20 cohort studies and 1 case series that reported the risk of CNS tumors (excluding pineoblastoma or trilateral RB) among heritable RB survivors.[1, 14, 22, 26, 28, 29, 32-37, 45, 46, 48, 50-53, 66, 67] Radiotherapy-related CNS tumors are well-known sequelae following radiotherapy for childhood tumors,[68, 69] as reflected in these studies. In a cohort of 963 survivors of heritable RB treated in the United States, 10 cases of CNS tumors were described, resulting in a SIR of 3.96 (95% CI: 1.9-7.3);[32] no CNS tumors were observed among heritable RB survivors who did not receive radiotherapy (SIR = 0.0; 95%CI: 0-33). Notably, in a recent paper describing SMN risk in 55 RB survivors treated with proton radiotherapy and followed for a median of 6.9 years (range 1-24), no subsequent CNS tumors were observed.[52] However, given the small size of this sample and the relatively short reported follow-up, there is insufficient evidence to draw definite conclusions about subsequent malignancy risk after proton beam therapy. Furthermore, no study has demonstrated a benefit of routine CNS surveillance in RB survivors with or without a history of radiotherapy. Therefore**,** routine CNS surveillance is not recommended among asymptomatic heritable RB survivors, regardless of prior radiation exposure.

Breast cancer

Evidence of risk: Yes

Grade of evidence for risk: A

Recommendation for surveillance: as per local guidelines

Sixteen studies, including 15 cohort analyses and one case-control study, examined risk of breast cancer among heritable and non-heritable RB survivors.[22, 26-29, 32, 34, 39, 45-48, 53, 66, 70, 71] Modest evidence suggests that there may be an increased breast cancer risk among heritable RB survivors, with a standardized incidence ratio (SIR) of approximately 3.0-4.5. In most cases, breast cancer was diagnosed among women over the age of 40 years, as in the general population.[72] No evidence to support early initiation of surveillance or expansion of existing screening programs for heritable RB survivors was identified. Therefore, the panel recommends that heritable RB survivors undergo surveillance for breast cancer as per local guidelines.

Based upon the association between therapeutic radiotherapy and SMN risk in RB survivors, there is an inferred or theoretical risk of ionizing radiation from diagnostic testing such as mammography. To date, no studies have quantified an incremental risk with diagnostic imaging that uses ionizing radiation among heritable RB survivors. Nevertheless, the panel was unanimous in recommending prioritization of non-radiation exposing imaging modalities, when possible.

Colon cancer

Evidence of risk: No

Grade of evidence for risk: A

Recommendation for surveillance: as per local guidelines

We reviewed results of 14 cohort studies that included cases of colorectal cancer among heritable RB survivors.[22, 26-29, 32, 34, 35, 39, 45, 47, 53, 66, 73] While several cohorts include heritable RB survivors with colorectal cancer, adenocarcinoma cases were small in number (1-4 cases per publication) and at older age of onset (range 30-71.2 years).[22, 28, 38, 39, 47, 53] In one cohort, two

cases of gastrointestinal leiomyosarcoma were described.[32] These tumors would not be expected to be amenable to surveillance practices and survival would not be impacted by surveillance for these tumors.[74, 75] Therefore, while no increased risk of colorectal adenocarcinoma has been categorically identified in heritable RB survivors, ongoing observation is needed, possibly through the oversight of an international combined cohort study.

Hematologic malignancies

Evidence of risk: No

Grade of evidence for risk: A

Recommendation for surveillance: Recommendation not to do

With regards to risk of subsequent hematologic malignancies, primarily leukemia and lymphoma, we evaluated results from 19 cohort studies and one systematic review/meta-analysis.[1, 14, 22, 26, 28, 29, 32-35, 37, 38, 45-47, 49, 50, 53, 66, 67] We found cases of Hodgkin lymphoma,[26] non-Hodgkin lymphoma,[47] acute lymphoblastic leukemia,[1, 14] and acute myeloblastic leukemia.[45] Studies which included chemotherapy exposures described a known link between chemotherapy and therapy-related leukemia, usually related to delivery of an alkylating agent or an epipodophyllotoxin.[53] Existing protocols and guidelines call for surveillance for leukemia after treatment that includes these drugs;[76] no evidence for a long-term risk among heritable RB survivors that is *independent* of these known associations could be found. Therefore, additional surveillance for those without prior exposure to alkylating agents and/or epipodophyllotoxin is not recommended.

Lung cancer

Evidence of risk: Yes

Grade of evidence for risk: B

Recommendation: as per local guidelines

We reviewed 11 cohort studies and 1 systematic review/meta-analysis that included cases or deaths due to lung cancer among heritable RB survivors.[22, 27, 32, 39, 45-47, 53, 66, 67, 77] Estimates of standardized mortality ratios ranged from 6.85 (95%CI: 2.75-14.1)[47] to 15.2 (95% CI: 4.9-35).[77] Unfortunately, many cohort studies lack data on smoking status, which may differ by heritable status.[22, 47, 66, 78] In addition, some studies censored patients after the first subsequent malignant neoplasm, thereby reducing the chance of observing lung cancer cases, which are more likely to occur at an older age.[22, 66] With evidence of uncertain or potentially biased results, lung cancer surveillance is not recommended for heritable RB survivors. RB survivors who have a history of smoking should be considered for surveillance as per local recommendations.[79,80] Future studies that include relevant tobacco exposures and allow for multiple subsequent malignant neoplasms in risk estimates are needed.

Melanoma

Evidence of risk: Yes

Grade of evidence for risk: A

Recommendation for surveillance: Strong recommendation to do (**Table 1**)

Modality: Single skin exam before age 8[81] to identify those who are developing dysplastic nevi; annual skin exam with dermoscopy, where available, after adolescence; skin protection measures for survivors of all ages.

We reviewed 19 publications, including cohort studies from Germany, Italy, the Netherlands, the United Kingdom, and the United States. We found an increased risk of incident melanoma (SIR 18.6, 95% CI: 9.6-32.4)[66] as well as increased melanoma-related deaths (SMR 23.3- 89.0).[22, 29] Evidence for a benefit of annual skin exams to prevent melanoma-related mortality is

extrapolated from the literature from other high-risk populations as well as case-control and ecologic studies of population-based screening.[82, 83] When melanoma cases within the US cohort were examined, many tumors were large and detected at a late stage, possibly related to decreased visual acuity in the RB survivor population. Therefore, patient education on skin protection measures and identification of nevi is suggested. Dysplastic nevi, when identified, should be carefully monitored and removed if changing in a manner suspicious for melanoma.[84]

Thyroid cancer

Evidence of risk: No

Grade of evidence for risk: C

Recommendation for surveillance: Recommendation not to do

We found information about thyroid cancer occurrence among heritable RB survivors in 10 publications, including 9 cohort studies and 1 systematic review/meta-analysis.[26-29, 44, 45, 48, 53, 66, 67] Among 953 heritable RB survivors representing 25,409 person-years of risk, two cases of thyroid cancer were observed, resulting in an SIR of 3.34 (95% CI: 0.4-12), which was not statistically significant.[32] In a study of mortality risk among heritable RB survivors, no deaths from thyroid cancer were observed, although thyroid cancer is rarely fatal.[29] The existing evidence does not support an increased risk of thyroid cancer among RB survivors. Therefore, routine surveillance for thyroid cancer is not recommended in this population.

Uterine cancer

Evidence of risk: Yes

Grade of evidence for risk: A

Recommendation for surveillance: Recommendation not to do

Among the publications on SMN among heritable RB survivors, we found 12 that described uterine cancer, primarily uterine leiomyosarcoma.[23, 24, 26-29, 32, 35, 47, 48, 66, 85] One paper, which specifically focused on uterine leiomyosarcoma,[85] described 7 cases of uterine leiomyosarcoma in a cohort of 525 heritable RB survivors, associated with 4 deaths and resulting in an SIR of 277 (95%CI: 90-646) and an absolute excess risk of 3.8/10000 person-years. An SMR of 154 (95%CI: 50-359) was reported for uterine cancer including leiomyosarcomas.[29] The ages of diagnosis of uterine leiomyosarcoma ranged from 32 to 51 years. Nonetheless, evidence for a benefit of current surveillance is not available and surveillance for uterine leiomyosarcoma is not recommended. While an increased risk is evident, especially of leiomyosarcoma of the uterus, no uterine imaging modality has been shown to be beneficial in this setting.[86]

DISCUSSION

Adult survivors of heritable RB are at risk for developing SMN decades following diagnosis, especially sarcomas of bone and soft tissue, melanoma, and radiotherapy-related tumors. After a rigorous process of priority development and evidence review, we present the results regarding SMN surveillance of adult heritable RB survivors (**Table 1**). We recommend against surveillance in cases where risk is increased but current surveillance is not demonstrated to be beneficial, such as uterine leiomyosarcoma. We strongly support routine dermatologic surveillance in this population given the increased risk of melanoma, its relative ease of detection, and the potential lethality of melanoma when detected at later stages. We recommend prompt evaluation of concerning signs and symptoms, such as persistent sinusitis, pain, or skeletal tenderness. Although not reviewed specifically for this population, smoking prevention or cessation should be encouraged and supported in any healthcare setting.

While adult survivors of heritable RB are at increased risk for sarcomas of bone and soft tissue, the use of radiologic surveillance modalities such as whole body, head, or orbit MRI is not supported by the evidence. A recent meta-analysis suggests an emerging role for the use of whole-body MRI for SMN surveillance in other cancer predisposition syndromes.[59] We reviewed one case series describing 25 heritable RB survivors who underwent surveillance whole-body MRI. In that retrospective review, eight initial scans were abnormal and 2 osteosarcomas were detected. Both patients diagnosed with osteosarcoma died during the study period. An additional sarcoma was diagnosed three months after a normal whole-body MRI. Even in retrospect, the lesion was not visible on the scan.[87] Therefore, surveillance whole-body MRI provided no clear benefit. Given these findings as well as potential harms in this surveillance strategy, including cost, evaluation of incidential finidings, and patient anxiety, our present recommendations do not support the use of MRI for sarcoma surveillance in heritable RB survivors. The need for prospective evaluation of a surveillance protocol, which may include whole body MRI, circulating cell-free (cf) DNA testing, skin exam with dermatascope, or other modalities, is clear. Methods for early detection of uterine leiomyosarcoma, in which the case fatality rate is high and current methods of detection are inadequate, should be prioritized.

Ionizing radiation exposure is an established risk factor for numerous malignancies, with some evidence suggesting that risks are particularly high for individuals exposed at younger ages. Numerous studies have reported radiotherapy as a risk factor for subsequent neoplasms among heritable RB survivors, but there is limited evidence regarding whether this represents a sensitivity to the carcinogenic effects of ionizing radiation. Unfortunately, this question has not been addressed directly due to a paucity of studies of RB survivors with detailed data on radiation dose-response relations or genomic data.[88] Although some individuals may be radiosensitive,[89] such sensitivity has not been clearly demonstrated in the cancer predisposition syndromes such as Li-Fraumeni syndrome with germline *TP53* mutations.[90] Nevertheless, given

the importance of retinoblastoma protein in cell cycle control and the high risk of radiotherapy - induced tumors in this population, minimizing exposure to ionizing radiation, as is currently recommended for individuals with Li-Fraumeni syndrome, is reasonable.[59, 60]

The evidence review for this work involved multiple rigorous steps intended to strengthen the basis for the recommendations. Several country or region-specific heritable RB or cancer survivors cohorts were critical to this effort. Nonetheless, large-scale collaborative efforts with systematic, long-term follow-up of heritable RB survivors, which could include periodic protocol-guided imaging, are clearly needed. Inclusion of genetic data, as well as self-reported or objectively measured psychosocial, cognitive, and quality of life outcomes in these studies would be valuable; use of validated measures would be critical. Furthermore, our process did not include a patient representative or community stakeholder. We suggest that future efforts in understanding risk among the heritable RB populations incorporate international partners, patients, and family members to maximize overall impact as well as number of cases and heterogeneity of therapy. Finally, further characterization of potential differences in SMN risk by *RB1* mutation type and other genetic factors may enable more precise risk stratification and would impact calculations regarding potential benefit of surveillance or other risk-reducing strategies.

CONCLUSION

In conclusion, adult heritable RB survivors are a growing population at risk for SMNs, most notably uterine leiomyosarcoma, bone and soft tissue sarcoma, and melanoma. With the acknowledgement that no surveillance modality has been shown to extend life in this population,

prompt evaluation of signs or symptoms and dermatologic evaluation in long-term follow-up is recommended.

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Table 1. Summary of recommendations for SMN surveillance of heritable RB survivors.

What subsequent malignant neoplasms are heritable RB survivors at risk for?
Strong evidence of risk: • Bone and soft tissue sarcoma • Melanoma • Uterine leiomyosarcoma Strong evidence of risk which may be limited to those with a history of radiotherapy: • Brain and central nervous system tumors Moderate evidence of risk: • Breast cancer after the age of 40 years • Lung cancer No or low evidence of risk: • Gastrointestinal malignancies, including colon cancer • Hematologic malignancies, apart from those attributable to systemic chemotherapy • Thyroid cancer
What surveillance is recommended for heritable RB survivors?
Strong recommendation to do: • Annual skin examination, especially among those with dysplastic nevi. Moderate recommendation to do: • Annual history and physical exam with attention to bony structures. • Prompt evaluation of signs and symptoms such as persistent sinusitis, pain, or skeletal tenderness. Weak recommendation to do: • Consideration should be given in favor of surveillance modalities that do not include ionizing radiation, although evidence for or against this recommendation in heritable RB survivors is lacking. Recommendation not to do: • We do not recommend surveillance for uterine leiomyosarcoma, as surveillance is not likely to be beneficial and may result in harm. • We do not recommend annual thyroid ultrasound for thyroid cancer surveillance, as there is no clear increased risk in this population. Furthermore, surveillance is not likely to benefit thyroid cancer-related mortality and may result in harm. • We do not recommend additional surveillance (beyond what is recommended based on local guidelines) for bone, brain, breast, colorectal, hematologic, or lung cancers, where risk is uncertain or benefit cannot be anticipated.

Long-term follow-up of adults with heritable retinoblastoma: Evidence-informed recommendations

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Precis

We convened an international meeting to review evidence for long-term follow-up of retinoblastoma survivors. Risk for subsequent neoplasm, notably sarcoma and melanoma, is significant. Yet, no studies demonstrate benefit of radiologic testing in asymptomatic survivors.