New Cancers Among Long-Term Survivors of Retinoblastoma

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Abstract

Patients who survive retinoblastoma (RB), particularly those affected by the hereditable bilateral form, are at risk for developing additional malignant neoplasms, including bone and soft-tissue sarcomas, melanoma, brain tumors and a variety of epithelial malignancies. According to current literature, the development of second malignancies in survivors of RB is due to a combination of genetic factors, treatment received, particularly radiotherapy, and environmental factors. The raised risk for second malignancies in RB patients emphasizes the need for lifelong surveillance for early detection and for the control of environmental and behavioral risk factors, such as UV exposure and cigarette smoking.

Introduction

Retinoblastoma (RB) represents the most frequent primary eye cancer in the pediatric age, accounting for approximately 4% of all childhood malignancies. It is estimated that 5,000–8,000 new cases occur yearly worldwide (Balmer et al. 2005). RB represents the prototypic model for inherited cancers and the RB1 gene was the first tumor suppressor gene to be identified. Based on his observations on the differences in tumor development in patients with unilateral versus bilateral retinoblastoma, Knudson (1971) proposed his two-hit hypothesis for tumorigenesis.

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The RB1 tumor suppressor gene was subsequently cloned, and it is now recognized that the loss of normal functioning RB1 is involved in the development of many adult nonocular malignancies. The tumor suppressor activity of the encoded protein is mainly due to its ability to inhibit cell division by blocking S-phase entry (Goodrich et al. 1991), but it also contributes to cell differentiation and survival (Goodrich 2006).

The development of RB requires the inactivation of both alleles of the RB gene on chromosome 13, band 13q14. In the familial and bilateral form of RB, patients carry a germline mutation of one allele, which is present in most or all cells in the body, and the tumor develops after a somatic mutation occurs in the second allele in a retinal cell. Since only one mutational event is necessary, this explains the bilateral occurrence and the multifocality of familial RB. The development of sporadic retinoblastoma requires that the mutation of both alleles occurs in the same retinoblast, and since this chance is very small, this explains the low incidence and unifocality.

Several treatment options are currently available for RB at any clinical stage, which result in a 5-year relative survival rate higher than 95%. However, survivors of RB, particularly of the familial form, are at risk for developing multiple secondary malignancies both as a result of genetic predisposition and of the treatment with radiotherapy, which further enhances the risk of tumors arising in the radiation field. A review of the current knowledge on the epidemiology of second malignancies in RB patients and a discussion of the possible causes is presented herein.

Epidemiology

Several studies have examined the epidemiology of second malignancies arising in RB patients, including analyses of large cohorts of patients. In a study that included 1927 cases of retinoblastoma diagnosed in Great Britain between 1951 and 2004, MacCarthy et al. (2009) observed a cumulative risk of developing a non-ocular tumor of 48.3% (95% confidence interval: 38.1–59.7%) in the heritable and 4.9% (1.9–12.4%) in the

non-heritable cases. The main categories of non-ocular tumours observed in the heritable cases were bone and soft-tissue sarcomas, carcinomas, central nervous system tumors and melanoma.

According to the study of Kleinerman et al. (2005), the cumulative incidence for developing a new cancer at 50 years after hereditary RB, adjusting for competing risk of death, was 33%, while it was 11% for nonhereditary RB. Overall, this risk observed in this study appears to be reduced in comparison with early reports, probably because of the lower doses of scatter radiation received by patients after 1960. However, the persistently elevated cancer risk in hereditary RB in comparison with nonhereditary RB points to the role of germline RB1 mutations in a variety of secondary tumors, and emphasizes the need for life-long surveillance for subsequent cancers in hereditary RB patients, especially those treated with radiation.

Studies considering mortality have observed no evidence of excess mortality from non-neoplastic causes compared with the general population, while there is general agreement of an excess mortality for malignant neoplasms among hereditary retinoblastoma survivors. Yu et al. (2009) examined cause-specific mortality among 1854 RB survivors who were diagnosed between 1914 and 1996 at two US institutions. Cumulative mortality from subsequent malignant neoplasms at 50 years was 25.5% (95% CI = 20.8–30.2%) for hereditary RB survivors and 1.0% (95% CI = 0.2–1.8%) for nonhereditary RB survivors. In addition, the relative rates of mortality from subsequent malignant neoplasm were higher in patients who had been treated with radiotherapy than in those who had not, both among hereditary and nonhereditary RB survivors. Among hereditary RB survivors, the high mortality risks persisted for neoplasms of the bone, connective tissue, and brain and other parts of the nervous system, and for melanoma. In addition, the Authors observed an increased risk of death due to cancer of the corpus uteri (primarily sarcomas) and lung cancer.

In a study of 998 Dutch RB survivors diagnosed from 1862 to 2005 (median follow-up 30.8 years), cause-specific mortality for second

malignancies among hereditary retinoblastoma survivors was statistically significantly increased with 12.8-fold (Marees et al. 2009). Higher mortality was observed from cancers of the bone and soft tissues, lung and bladder. In addition, a higher mortality was observed for melanoma and breast cancer. Non-hereditary retinoblastoma patients had similar overall cancer mortality as the general population and no significantly increased mortality for any site-specific cancer was found. However, in a recent update on the Dutch cohort, the majority of the observed second primary malignancies were of epithelial origin, possibly due to longer follow up and to a larger use of surgery alone to initially treat RB (Marees et al. 2010).

The observation of an excess mortality from subsequent malignant neoplasms among nonhereditary RB survivors has been more controversial. A significantly elevated risk of mortality from second malignancies among non-hereditary RB survivors has been observed in some studies (Acquaviva et al. 2006; Yu et al. 2009), but it was not confirmed in others (Fletcher et al. 2004; Marees et al. 2009). These differences may reflect both different protocol treatments with or without radiotherapy, or alternatively, the excess mortality may also be due to some potential misclassification in hereditary status. Indeed, most epidemiological studies lacked genetic confirmation and classified all unilateral retinoblastoma patients without a family history as nonhereditary RB, but still a fraction of unilateral retinoblastoma survivors without a family history of retinoblastoma may have had a germline mutation in RB1, thus resulting in some misclassification of nonhereditary RB.

Finally, RB patients who suffered a second malignancy, are at risk for developing a third malignant tumor. In a recent analysis, the risk of a subsequent malignancy after a second primary malignancy was increased more than sevenfold (Marees et al. 2010). This risk further increased threefold when patients were treated with radiotherapy for their retinoblastoma. Furthermore, overall survival was significantly worse among retinoblastoma patients diagnosed with a third primary malignancy compared with patients

diagnosed with a second primary malignancy only (Marees et al. 2010).

Pathogenesis

The development of second cancers is under the influence of several factors, including late sequelae of treatment (radiotherapy and chemotherapy), lifestyle factors (tobacco and alcohol consumption, diet), environmental exposures, and host factors (genetics, immune system, hormonal), as well as of combinations of influences, including gene – environment and gene – gene interactions (Travis et al. 2006).

Among RB patients, those affected by the familial form are more prone to develop second tumors, due to the presence of a germline mutation of RB gene that affect all somatic cells, and therefore just the "second hit" is required to start tumor development. Unfortunately, it is still unclear which mechanisms underlie development of a subsequent primary malignancy, and why some hereditary retinoblastoma patients develop subsequent primary malignancies, whereas others do not.

Role of Radiotherapy

There is general agreement in indicating a role of radiotherapy in the pathogenesis of second malignancies arising in RB patients, particularly of brain tumors, bone and soft tissue tumors, tumors of the sinonasal tract, and eye and orbit. Several studies (Wong et al. 1997; Yu et al. 2009) have demonstrated that many of the bone and some of the soft tissue sarcomas developed in irradiated sites in a manner that suggested an interactive effect between genetic susceptibility and radiation exposure. Radiation-related second malignancies occur at earlier ages than other cancer types. (Draper et al. 1986; Eng et al. 1993; Moll et al. 1996; Roarty et al. 1988; Kleinerman et al. 2007; Marees et al. 2009). Overall, radiation induced second malignancies are mainly bone and soft tissue sarcomas and brain tumors, whereas second tumors not related to radiotherapy are mainly carcinomas and melanoma. Meningiomas are among

the most commonly reported radiation-induced brain tumors and are also frequently observed as second brain tumors in RB patients.

Among soft tissue tumors, leiomyosarcoma is the most frequently observed subtype, both in irradiated and non irradiated patients (Kleinerman et al. 2007), followed by liposarcoma and fibrosarcoma, while osteosarcoma and Ewing's sarcoma are the most frequently observed bone tumors. Radiation related sarcomas occur preferentially in the head and neck region, but soft tissue sarcomas, particularly leiomyosarcoma, occur at other sites, including the uterus, probably in relation with a predisposition conferred by the mutation of RB1 gene present in these patients (Kleinerman et al. 2007).

The age of irradiation appears to be an important factor in determining the risk for radiation induced malignancies. Among irradiated hereditary retinoblastoma survivors, the risk of death for second malignancies was higher for those who were irradiated at 12 months of age or younger than for those irradiated at older ages (Abramson and Frank 1998). An increased susceptibility to subsequent malignant neoplasms among survivors diagnosed at very young ages has been reported (Abramson and Frank 1998; Yu et al. 2009), and this could be due to age-related sensitivity to radiation, or this increased risk may be a marker of other risk factors for subsequent malignant neoplasms (Moll et al. 2001). An excess risk of breast cancer has been observed in irradiated patients with hereditary and nonhereditary RB (Kleinerman et al. 2005; Marees et al. 2009). The risk of radiation-related breast cancer is known to be heightened when the exposure occurs at very young ages. Other cancers related to irradiation have been observed in the salivary glands, tongue, and nasopharynx (Kleinerman et al. 2005).

Patients with heritable RB are prone to develop a lethal condition known as trilateral retinoblastoma (TRB), which can be defined as a midline intracranial malignancy associated with bilateral retinoblastoma. The histopathological features of these tumors have been variable. In their review of 80 cases, Marcus et al. (1998) identified one third of tumors for which histopathological detail was provided. Overall, 61.5% were undifferentiated round cell tumors which could be considered primitive neuroectodermal tumors (PNETs), whereas the remaining demonstrated various degrees of neuronal or photoreceptor differentiation. Although in no case evidence of pineal origin was demonstrated histologically, the concept of the pineal organ as the "third eye" and the embriologic relationship of the pineal gland to the retina have been emphasized leading to the tendency to diagnose these intracranial tumors as pinealoblastomas. Therefore, according to Marcus et al. (1998), trilateral retinoblastoma should be considered within the spectrum of PNETs, and the analysis of the histopathologic similarities among human PNETs, pinealoblastoma, retinoblastoma, and transgenic murine PNETs suggests that subependymal primitive cells are the likely origin of TRB (Marcus et al. 1991). However, the occurrence of TRB is decreasing, possibly due to changes in the use of radiotherapy (Kleinerman et al. 2005; Moll et al. 2002) or because of the introduction of chemoreduction with a three-drug protocol (Meadows and Shields 2004).

Second Tumors Not Related to Radiotherapy

Environmental or behavioral risk factors may also be considered for the onset of second malignancies in RB patients. An excess of lung cancer deaths, which is unrelated to radiotherapy and possibly due to increased susceptibility to cigarette smoking has been reported in analysis of large cohort of RB survivors (Kleinerman et al. 2005; MacCarthy et al. 2009; Yu et al. 2009; Marees et al. 2009). Somatic mutations in the RB-1 gene are implicated in the development of lung cancer (Harbour et al. 1988; Xu et al. 1991). Another tumor frequently reported in long-term hereditary RB survivors not treated with radiation is bladder cancer which can be also presumably attributed to tobacco smoking (Kleinerman et al. 2005). The increased risk for melanoma is probably due to genetic factors independent of radiation, because risks were elevated in both irradiated and nonirradiated patients (Kleinerman et al. 2005). Excess risks of malignancies of the

colon and corpus uteri have also been noted in the hereditary patients (Kleinerman et al. 2005). Interestingly, uterine and colonic tumors are often leiomyosarcomas. Finally, a very high incidence of second cancers in patients with bilateral disease who received no irradiation have been reported in the head and neck region (Abramson et al. 1979).

Genetics of Second Tumors

Although epidemiological studies have outlined the frequency and the risk for the development of different types of malignancies in RB patients, there are currently no data regarding the influence that specific genetic alterations of the RB gene could have on the risk of developing second malignancies. In addition, only few second tumors have been analyzed for the status of RB gene and/or for other genetic alterations.

Elias et al. (2001) reported the case of a child with bilateral retinoblastoma and subsequent cerebellar medulloblastoma. An insertion of the q12.3q21.3 segment of chromosome 13 into chromosome 18 at band q23 was identified in members of the patient's family.

Considering sinonasal tumors occurring as second malignancies in RB patients, analysis of the RB gene has led to conflicting results. While Greger et al. (1990) found a deletion at the RB locus in a metastasis from the nasal tumor that was not present in normal tissues, in the case studied by Saw et al. (1992) there was no cytogenetic alteration at the band 13q14. We have recently reported two pediatric patients previously treated for RB with surgery and irradiation, who developed a second tumor in the sinonasal tract with features of a poorly differentiated carcinoma with neuroendocrine differentiation (Franchi et al. 2009), with a review of similar cases involving the sinonasal tract. Both tumors showed diffuse nuclear immunoreactivity for RB protein, indicating that inactivation of the RB gene is not likely to have occurred (Franchi et al. 2009). We also examined the status of TP53 tumor suppressor gene, which is the most common target of mutation in head and neck cancer. We found that one patient presented the R72P

polymorphism in exon 4, resulting in a substitution of Pro for Arg in the transactivation domain. This polymorphism has been extensively studied with regard to its possible involvement in increased risk for cancer development, but results have been controversial. While some authors have reported a correlation between the presence of Arg allele (Soulitzis et al. 2002), as well as between homozygous proline (Boltze et al. 2002) and development of carcinoma at different anatomic sites, this has not been confirmed in studies conducted on head and neck cancer (Hamel et al. 2000; McWilliams et al. 2000). However, the possible role of this polymorphism in the susceptibility to the development of second malignancies in patients treated for retinoblastoma deserves further investigation. The remaining p53 mutation was a single-nucleotide substitution without aminoacid change in exon 4 (CCG to CCA). It is possible that these polymorphisms could be responsible for an enhanced cancer risk or, alternatively, that the p53 allele carrying the nucleotide substitution could be in linkage with other loci involved in controlling genomic stability (Yarbrough et al. 1996).

Conclusions

The development of second malignancies in survivors of RB if a well known complication, due to a combination of genetic factors, treatment received, and environmental factors (Abramson 2005). The current knowledge on the genetic basis of susceptibility to develop second tumors is limited, as it is the genetic and morphologic characterization of second tumors. Epidemiological studies indicate a reduction in the incidence of second tumors, possibly because of changing therapy protocols. Further reduction could be achieved by minimizing the role of environmental and behavioral risk factors, such as UV exposure and cigarette smoking (Abramson 2005). Lifelong follow-up is needed to evaluate the full spectrum of subsequent mortality risk in hereditary retinoblastoma survivors and to design screening programs for the early detection and treatment of second malignant neoplasms.

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