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Mutation Risk Associated with Paternal and Maternal Age in a Cohort of Retinoblastoma Survivors

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Abstract

Autosomal dominant conditions are known to be associated with advanced paternal age, and it has been suggested that retinoblastoma (Rb) also exhibits a paternal age effect due to the paternal origin of most new germline *RBI* mutations. To further our understanding of the association of parental age and risk of *de novo* germline Rb mutations, we evaluated the effect of parental age in a cohort of Rb survivors in the United States. A cohort of 262 retinoblastoma patients was retrospectively identified at one institution, and telephone interviews were conducted with parents of 160 survivors (65.3%). We built two sets of hierarchical stepwise logistic regression models to detect an increased odds of a *de novo* germline mutation related to older parental age compared to sporadic and familial Rb. The modeling strategy evaluated effects of continuous increasing maternal and paternal age and five-year age increases adjusted for the age of the other parent. Mean maternal ages for patients with *de novo* germline mutations and sporadic Rb were similar (28.3 and 28.5 respectively) as were mean paternal ages (31.9 and 31.2 respectively), and all were significantly higher than the weighted general U.S. population means. In contrast, maternal and paternal ages for familial Rb did not differ significantly from the weighted U.S. general population means. Although we noted no significant differences between mean maternal and paternal ages between each of the three Rb classification groups, we found increased odds of having a *de novo* germline mutation for each five-year increase in paternal age, but these findings were not statistically significant (*de novo* versus sporadic ORs: 30-34 = 1.65 [0.69-4], 35 = 1.34 [0.54-3.3]; *de novo* versus familial ORs: 30-34 = 2.82 [0.95 – 8.4], 35 = 1.61 [0.57-4.6]). Our study suggests a weak paternal age effect for Rb resulting from *de novo* germline mutations consistent with the paternal origin of most of these mutations.

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Introduction

Retinoblastoma (Rb) is a malignant tumor of the retina that occurs in children typically under the age of five. It is estimated that Rb affects 1:15,000 births in the United States (U.S.) (Abramson and Scheffer 2004; Lin and O'Brien 2009). *RB1* is a tumor suppressor gene involved in regulating the cell cycle, and malignant tumors occur in retinal cells with mutations in both copies of the *RB1* gene. Approximately 65-75% of Rb cases are unilateral, occurring in only one eye, and occur sporadically when “two hits” occur in the same retinal cell (Knudson 1971). Approximately 25-35% of Rb cases are bilateral, affecting both eyes. Individuals who inherit an *RB1* mutation, either in an autosomal dominant manner from a parent or from a *de novo* germline mutation, typically develop bilateral Rb. Approximately 10% of all retinoblastoma cases can be attributed to family history with autosomal dominant inheritance. In addition, family history information and genetic testing has revealed that some unilateral cases (10-15%) involve a germline mutation in the *RB1* gene (Lohmann et al. 1997; Lohmann and Gallie 2004; Newsham et al. 2009; Richter et al. 2003).

Several autosomal dominant genetic conditions are now known to be associated with advanced paternal age (generally considered to be 40 to 45 years of age or older) (Thacker 2004; Sartorius and Nieschlag 2010). These include Marfan syndrome, achondroplasia, and Apert syndrome, among others. It has also been suggested that there is a paternal age effect with Rb, albeit a weaker effect than the conditions mentioned above (Kühnert and Nieschlag 2004; Risch et al. 1987; Sivakumaran et al., 2000). Further, it has been estimated that 85% of new *RB1* germline mutations are paternal in origin, therefore, it would be expected that older paternal age might be related to the appearance of *de novo* Rb (Dryja et al., 1989).

Studies in Sweden, the Netherlands, Japan, France and more recently the U.S., have examined the association between Rb and advanced paternal and maternal ages (Bunin et al., 1989; DerKinderen et al. 1990; Johnson et al. 2009; Matsunaga et al. 1990; Moll et al. 1996; Pellié et al., 1973, Yip et al. 2006). Some but not all of these studies reported older paternal and maternal age related to occurrence of retinoblastoma. At present, there is no consensus regarding the impact of advanced paternal or maternal age on the incidence of Rb caused by *de novo* germline mutations. This study aims to further our understanding of the association of parental age and risk of *de novo* germline Rb mutations by evaluating parental age in a cohort of Rb survivors in the United States. Our hypothesis is that Rb survivors with a *de novo* germline mutation are more likely to have a father of advanced paternal when compared to survivors of sporadic or familial Rb, and to the general population.

Subjects

The retrospectively defined cohort used for this study consists of 262 Rb patients diagnosed from January 1, 1985 through December 31, 1996 at a medical center in New York, NY. This cohort is currently part of a larger study of secondary cancer incidence and cause-specific mortality in long-term Rb survivors (Kleinerman et al, 2005; Yu et al., 2009). Hospital records were used to identify study subjects and to collect medical history and treatment data. Demographic data, including parental age at the birth of the Rb patient, was collected via telephone interviews conducted in 1998. Of the original 262 Rb patients, four did not survive one year and thirteen had died by the time of the interview in 1998. Therefore, parents of 245 survivors were eligible to be interviewed for the study and parents of 160 (65.3%) survivors agreed to participate. We did not identify statistically significant differences between the respondents and non-respondents for hereditary status, year of birth or sex of their child; however, respondents were more likely to be white and report a family history of retinoblastoma. Family history was defined as a first or second degree relative with Rb.

We excluded one individual from the analysis who was born in 1950 because all other members of the cohort were born between 1975 and 1996. Maternal age data was not available for two survivors and paternal age for five survivors, but all other available data for these survivors were included. Therefore, we analyzed 159 of the 160 survivors for this study.

Methods

The cohort survivors were grouped into one of three Rb classifications:

- Survivors with unilateral Rb were classified as sporadic if they had no or unknown family history of Rb;
- Survivors with bilateral Rb were classified as having a *de novo* germline mutation if they had no or unknown family history of Rb; and
- Survivors with unilateral or bilateral Rb, who had a family history of Rb, were classified as family history.

The sporadic and *de novo* germline mutation classifications based on laterality of Rb tumors are an approximation, because mutation testing data were not available for the cohort. Published mean maternal age data for the U.S. is available for the years 1970 to 2000 (Mathews and Hamilton 2002), however mean paternal age data is not, so we calculated mean paternal age from public use files available from the U.S. Centers for Disease Control and Prevention, National Center for Health Statistics Reproductive Statistics Branch, Division of Vital Statistics (U.S. CDC data) for births for the years 1975 to 1996. We also calculated mean maternal age for each year from 1975 to 1996 and then compared these data to the data published by Mathews and Hamilton (2002) and found our calculations to be accurate to within 0.1 years (Appendix A). Paternal age data for the U.S. was missing for 11.1% of fathers in 1975 up to a high of 16.9% of fathers in 1991. Thus, the mean paternal age data used for this study is an approximation and may overestimate mean paternal age in the U.S. from 1975 to 1996. For comparison to the mean parental ages in our cohort, we calculated a weighted mean for mean maternal and paternal age in the U.S. general population based on the years of birth of our cohort of survivors.

Statistical Analysis

Associations between categorical predictors and the three Rb classification groups were assessed with either Chi-square tests or the Freeman-Halton extension of the Fisher's exact test when small expected cell frequencies were noted. Two sets of hierarchical stepwise logistic regression models were built to look for increased odds of a *de novo* germline mutation versus sporadic and familial Rb associated with increased maternal and paternal age. The first modeling strategy looked for effects of continuous increasing maternal and paternal age while controlling for differences in race (White, African-American, Hispanic, other/unknown) and age of the other parent. To assess nonlinear age effects, a second set of models using parental age groupings of <30, 30–34, and ≥35 years were subsequently analyzed while controlling for differences in race and age of the other parent. We used parental age <30 years as our reference group because we had a limited number of fathers and mothers less than age 25 years. Parental age groupings of <25, 25–29, 30–34, and ≥35 years were also analyzed and are included in Appendix B. All differences between means were compared using either one sample t-tests or one-way ANOVAs. For all tests, statistical significance was declared for two tailed p-values $p < .05$. All calculations were performed using SAS Enterprise Guide version 4.22, SAS version 9.21 (Cary, NC).

Results

We classified 75 (47.2%) survivors as sporadic, 46 (28.9%) as *de novo* germline mutation and 38 (23.9%) as familial (Table 1). We found no noteworthy differences between sex, race, year of birth, age of mother at birth, and age of father at birth for each of the three groups. Laterality and family history differed for each of the Rb classification groups by definition. As expected, *de novo* germline mutation and the familial cases of Rb were more likely to be diagnosed less than 1 year of age as compared to sporadic cases ($p < 0.001$).

Mean maternal and paternal ages for the *de novo* germline mutation classification were significantly higher than the weighted mean maternal (28.3 vs. 26.2 years, $p = 0.003$) and paternal (31.9 vs. 29.3 years $p = 0.007$,) ages of the general U.S. population, (Table 2). Similarly, maternal and paternal ages for the sporadic Rb classification group were significantly higher than the mean maternal and paternal ages of the general U.S. population ($p < 0.001$ and $p = 0.01$, respectively). Conversely, the parental ages for the familial classification group did not differ significantly from the general U.S. population. Although the three Rb classification groups did not differ significantly from each other (Table 3), the mean maternal and paternal ages for both *de novo* and sporadic Rb were similar (28.3 and 28.5, and 31.9 and 31.2 respectively) whereas the mean ages for the familial parents were approximately 1.7 years younger for mothers of sporadic and *de novo* survivors and approximately 1.8 years younger than the average age for fathers of sporadic and *de novo* survivors.

In our analysis of continuous parental age, there was no statistically significant effect of maternal or paternal age when the odds of having a *de novo* germline mutation were compared to the odds of having sporadic Rb or familial Rb. The odds ratios for almost all scenarios were close to 1.0 (Table 4). In addition, there continued to be no statistically significant effect when the analysis was adjusted for race and the age of the other parent (Table 4).

When we examined the odds of having a *de novo* germline mutation versus the odds of having familial Rb by five-year age groups for paternal age, we found increased odds of having a *de novo* germline mutation versus the odds of having either sporadic Rb or familial Rb (Table 5). The effect was highest for the 30-34 paternal age group but no effects were significant, even when adjusted for race and age of the other parent (Table 5). We found a non-significant increase in the odds for maternal ages 30-34 (OR=2.80 [0.9-8.8]). However, the odds of having a *de novo* germline mutation versus the odds of having familial Rb, for maternal age greater than 35, was reduced (0.80, 95% CI = 0.19-3.3).

Discussion

In this study, we have assessed the influence of older parental age on Rb caused by *de novo* autosomal dominant mutations using a cohort of Rb survivors diagnosed and treated at one institution. To our knowledge, this is the first study to evaluate parental age effects for three different categories of Rb (hereditary Rb resulting from a *de novo* germline mutation, sporadic Rb, and familial Rb inherited from an affected parent), and to investigate parental age differences between these three groups.

Although we found no significant differences between maternal and paternal ages when comparing between the three Rb groups, there was some evidence of a signal for older paternal age and the odds of a *de novo* germline mutation based on the modeling. We also noted that mean parental ages related to *de novo* germline mutations and sporadic Rb, but not familial Rb, were higher than the general population. This finding supports the notion that, in general, those with familial Rb reproduce at ages similar to the general population,

but have a 50/50 chance of passing on the mutated *RB1* allele with each pregnancy. It was not surprising to find younger parental ages for familial Rb cases when compared with sporadic Rb because this was reported in a previous study (Yip et al. 2006). However, the similarity of mean maternal and paternal ages for *de novo* germline mutations and sporadic Rb was unexpected, because it has not been previously reported.

When comparing our study to previous studies regarding parental age data for Rb (see Table 6), it is important to note that we compared our hospital-based cohort to the general population in our analysis of mean maternal and paternal age. We did not use matched general population controls for our logistic regression analysis nor did we use incidence data for Rb in the United States. Unlike previous studies, we compared the odds of being in the *de novo* germline mutation classification group versus the sporadic and familial Rb groups given increasing parental age in our cohort of individuals. Our comparisons of parental age to general population means were similar to findings reported by DerKinderen et al. (1990) and Moll et al. (1996) for *de novo* mutations, but in contrast to these studies, we also saw significant differences for sporadic non-hereditary Rb.

In our cohort we had relatively few parents over age 35 years making it difficult to estimate the odds of having a child with a Rb *de novo* mutation for fathers of advanced paternal age (greater than 40-45 years of age) (Table 1). The theory behind *de novo* mutations and advanced paternal age is that errors occur in mitotic divisions during male spermatogenesis (Thacker 2004; Sartorius and Nieschlag 2010). Although our results suggested a pattern of increased odds of a *de novo* mutation with paternal age, we believe this is a preliminary finding that should be followed up with additional analysis with a greater number of Rb survivors with increased enrichment for advanced parental age. Only 65% of the cohort agreed to participate, and having more subjects would allow for statistical power to determine if the patterns we observed in this analysis are valid. In addition, more complete information on subject characteristics, such as race, would allow for a more detailed analysis of this potential confounder. Future research could consider the influence of other covariates such as environmental exposures of one or both parents that could increase the risk of *de novo* retinoblastoma mutations (Bunin, et al. 2011).

Future work regarding Rb and parental age should include mutation status gathered from genetic testing rather than by proxy with laterality and family history since some unilateral survivors in our cohort may have a *de novo* mutation that predisposed them to Rb. A dataset including mutation status and mutation type (missense versus nonsense, etc.) would allow for a more precise analysis of the differences in parental ages of the three Rb classification groups, given an adequate number of patients to achieve statistical power. Although prior studies have benefited from larger sample sizes, we believe this is the first study to include familial inherited Rb in an analysis of parental age.

Overall, our findings show that, as previously reported for other countries, the mean parental age of Rb survivors with a *de novo* mutation is statistically significantly higher than the mean age of the general U.S. population. The similarity of mean maternal and paternal ages for *de novo* germline mutations and sporadic Rb was unexpected and deserves further attention. Our study suggests a greater paternal rather than maternal contribution to *RB1* mutations, perhaps during gametogenesis, for the *de novo* germline mutations, however we have insufficient data for investigating paternal age over age 40 years to test this hypothesis further. Our findings do not indicate statistically significant effects for advanced paternal age and thus would not be appropriate for use in genetic counseling at this time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Abramson D, Scheffler A. Update on retinoblastoma. *Retina*. 2004; 24(6):828–848. [PubMed: 15579980]
- Bunin GR, Felice MA, Davidson W, Friedman DL, Shields CL, Maidment A, O'Shea M, Nichols KE, Leahey A, Dunkel IJ, Jubran R, Rodriguez-Galindo C, Schmidt ML, Weinstein JL, Goldman S, Abramson DH, Wilson MW, Gallie BL, Chan HS, Shapiro M, Cnaan A, Ganguly A, Meadows AT. Medical radiation exposure and risk of retinoblastoma resulting from new germline RB1 mutation. *Int J Cancer*. 2011 May 1. 2011; 128(10):2393–404. doi: 10.1002/ijc.25565.
- Bunin GR, Meadows AT, Emanuel BS, Buckley JD, Woods WG, Hammond GD. Pre- and postconception factors associated with sporadic heritable and nonheritable retinoblastoma. *Cancer Res*. 1989; 49(20):5730–5735. [PubMed: 2790788]
- DerKinderen DJ, Koten JW, Tan KE, Beemer FA, Van Romunde LK, Den Otter W. Parental age in sporadic hereditary retinoblastoma. *Am J Ophthalmol*. 1990; 110(6):605–609. [PubMed: 2248323]
- Dryja TP, Mukai S, Petersen R, Rapaport JM, Walton D, Yandell DW. Parental origin of mutations of the retinoblastoma gene. *Nature*. 1989; 339(6225):556–558. doi:10.1038/339556a0. [PubMed: 2733786]
- Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, Mueller BA, Puumala SE, Reynolds P, Von Behren J, Spector LG. Parental age and risk of childhood cancer: A pooled analysis. *Epidemiology*. 2009; 20(4):475–483. doi:10.1097/EDE.0b013e3181a5a332. [PubMed: 19373093]
- Kato MV, Ishizaki K, Shimizu T, Ejima Y, Tanooka H, Takayama J, Kaneko A, Toguchida J, Sasaki MS. Parental origin of germ-line and somatic mutations in the retinoblastoma gene. *Hum Genet*. 1994; 94(1):31–38. [PubMed: 8034292]
- Kleinerman RA, Tucker MA, Tarone RE, Abramson DH, Seddon JM, Stovall M, Li FP, Fraumeni JF Jr. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: An extended follow-up. *J Clin Oncol*. 2005; 23(10):2272–2279. doi:23/10/2272 [pii] 10.1200/JCO.2005.05.054. [PubMed: 15800318]
- Knudson AG Jr. Mutation and cancer: Statistical study of retinoblastoma. *Proc Natl Acad Sci U S A*. 1971; 68(4):820–823. [PubMed: 5279523]
- Kuhnert B, Nieschlag E. Reproductive functions of the ageing male. *Hum Reprod Update*. 2004; 10(4):327–339. doi:10.1093/humupd/dmh030 dmh030 [pii]. [PubMed: 15192059]
- Lin P, O'Brien JM. Frontiers in the management of retinoblastoma. *Am J Ophthalmol*. 2009; 148(2): 192–198. doi:S0002-9394(09)00268-2 [pii]10.1016/j.ajo.2009.04.004. [PubMed: 19477707]
- Lohmann DR, Gallie BL. Retinoblastoma: Revisiting the model prototype of inherited cancer. *Am J Med Genet C Semin Med Genet*. 2004; 129C(1):23–28. doi:10.1002/ajmg.c.30024. [PubMed: 15264269]
- Lohmann DR, Gerick M, Brandt B, Oelschlager U, Lorenz B, Passarge E, Horsthemke B. Constitutional rb1-gene mutations in patients with isolated unilateral retinoblastoma. *Am J Hum Genet*. 1997; 61(2):282–294. doi:S0002-9297(07)64053-1 [pii]10.1086/514845. [PubMed: 9311732]
- Mathews TJ, Hamilton BE. Mean age of mother, 1970–2000. *Natl Vital Stat Rep*. 2002; 51(1):1–13. [PubMed: 12564162]

- Matsunaga E, Minoda K, Sasaki MS. Parental age and seasonal variation in the births of children with sporadic retinoblastoma: A mutation-epidemiologic study. *Hum Genet.* 1990; 84(2):155–158. [PubMed: 2298450]
- Moll AC, Imhof SM, Kuik DJ, Bouter LM, Den Otter W, Bezemer PD, Koten JW, Tan KE. High parental age is associated with sporadic hereditary retinoblastoma: The dutch retinoblastoma register 1862-1994. *Hum Genet.* 1996; 98(1):109–112. [PubMed: 8682494]
- Newsham IF, Hadjililianou T, Cavenee WK, Amberger J, Bocchini CA, Scott AF, Hamosh A. Retinoblastoma. Mckusick's online mendelian inheritance in man (omim). *Nucleic Acids Res.* 2009; 37(Database issue):D793–796. doi:gkn665 [pii] 10.1093/nar/gkn665.
- Pellié C, Briard ML, Feingold J, Frézal J. Parental age in retinoblastoma. *Humangenetik.* 1973; 20:59–62. [PubMed: 4776529]
- Richter S, Vandezande K, Chen N, Zhang K, Sutherland J, Anderson J, Han L, Panton R, Branco P, Gallie B. Sensitive and efficient detection of *rb1* gene mutations enhances care for families with retinoblastoma. *Am J Hum Genet.* 2003; 72(2):253–269. doi:S0002-9297(07)60537-0 [pii] 10.1086/345651. [PubMed: 12541220]
- Risch N, Reich EW, Wishnick MM, McCarthy JG. Spontaneous mutation and parental age in humans. *Am J Hum Genet.* 1987; 41(2):218–248. [PubMed: 3618593]
- Sanders BM, Draper GJ, Kingston JE. Retinoblastoma in Great Britain 1969-80: Incidence, treatment, and survival. *Br J Ophthalmol.* 1988; 72(8):576–583. [PubMed: 3415951]
- Sartorius GA, Nieschlag E. Paternal age and reproduction. *Hum Reprod Update.* 2010; 16(1):65–79. doi:dmp027 [pii] 10.1093/humupd/dmp027. [PubMed: 19696093]
- Sivakumaran TA, Ghose S, Kumar H, A S, Kucheria K. Parental age in indian patients with sporadic hereditary retinoblastoma. *Ophthalmic Epidemiol.* 2000; 7(4):285–291. [PubMed: 11262675]
- Thacker PD. Biological clock ticks for men, too: Genetic defects linked to sperm of older fathers. *JAMA.* 2004; 291(14):1683–1685. doi:10.1001/jama.291.14.1683 291/14/1683 [pii]. [PubMed: 15082678]
- Yip BH, Pawitan Y, Czene K. Parental age and risk of childhood cancers: A population-based cohort study from sweden. *Int J Epidemiol.* 2006; 35(6):1495–1503. doi:dyl177 [pii] 10.1093/ije/dyl177. [PubMed: 17008361]
- Young, JL., et al. Retinoblastoma.. In: Ries, LA., et al., editors. *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program, 1975-1995*. National Cancer Institute; Bethesda, MD.: 1999.
- Yu CL, Tucker MA, Abramson DH, Furukawa K, Seddon JM, Stovall M, Fraumeni JF Jr. Kleinerman RA. Cause-specific mortality in long-term survivors of retinoblastoma. *J Natl Cancer Inst.* 2009; 101(8):581–591. doi:djp046 [pii] 10.1093/jnci/djp046. [PubMed: 19351917]
- Zhu XP, Dunn JM, Phillips RA, Goddard AD, Paton KE, Becker A, Gallie BL. Preferential germline mutation of the paternal allele in retinoblastoma. *Nature.* 1989; 340(6231):312–313. doi: 10.1038/340312a0. [PubMed: 2568588]

Table 1

Selected characteristics of retinoblastoma survivors.

	Type of Retinoblastoma ^I							Total	
	de novo		Sporadic		Familial				
	No. Survivors	%	No. Survivors	%	No. Survivors	%		p-value [*]	No. Survivors
Total Number of Survivors	46	100	75	100	38	100		159	100.0
Laterality							na		
Bilateral	46	100	na	na	30	79		76	47.8
Unilateral	na	na	75	100	8	21.1		83	52.2
Age at Rb Diagnosis, yrs							<0.001		
<1	23	50.0	13	17.3	30	79.0		66	41.5
1	17	37.0	12	16.0	4	10.5		33	20.8
2	5	10.9	34	45.3	3	7.9		42	26.4
3-10	1	2.2	16	21.3	1	2.6		18	11.3
Sex							1.00		
Female	24	52.2	39	52	20	52.6		83	52.2
Male	22	47.8	36	48	18	47.4		76	47.8
Race							0.16		
Unknown	24	52.2	32	42.7	14	36.8		70	44.0
African American	5	10.9	7	9.3	7	18.4		19	12.0
Asian/Pacific Islander	0	0.0	2	2.7	0	0.0		2	1.3
Hispanic	1	2.2	6	8.0	7	18.4		14	8.8
Caucasian	16	34.8	28	37.3	10	26.3		54	34.0
Year of Birth							0.42		
1975-1979	na	na	4	5.3	1	2.6		5	3.1
1980-1984	8	17.4	13	17.3	5	13.2		26	16.4
1985-1989	18	39.1	29	38.7	19	50.0		66	41.5
1990-1994	18	39.1	27	36.0	9	23.7		54	34.0
1995-1996	2	4.4	2	2.7	4	10.5		8	5.0
Family History of Rb							na		
No	46	100	75	100	na	na		121	76.1
Yes	na	na	na	na	38	100		38	23.9
Age of Mother at Birth							0.48		
<25	10	21.7	15	20.0	12	31.6		37	23.3
25-29	18	39.1	27	36.0	16	42.1		61	38.4
30-34	14	30.4	24	32.0	5	13.2		43	27.0
>35	4	8.7	7	9.3	5	13.2		16	10.1
No Data	0	0.0	2	2.7	0	0.0		2	1.3

	Type of Retinoblastoma ^I						p-value *	Total	
	de novo		Sporadic		Familial				
	No. Survivors	%	No. Survivors	%	No. Survivors	%		No. Survivors	%
Age of Father at Birth							0.68		
<25	3	6.5	11	14.7	7	18.4		21	13.2
25-29	13	28.3	21	28.0	13	34.2		47	29.6
30-34	16	34.8	20	26.7	7	18.4		43	27.0
>35	13	28.3	20	26.7	10	26.3		43	27.1
No Data	1	2.2	3	4.0	1	2.6		5	3.1

na = not applicable

^{*} Chi-square or Freeman-Halton Exact Test. Significant p-values indicated in bold.

^I Survivors were classified as sporadic if they had no family history of Rb and were diagnosed with unilateral Rb. Survivors were classified as having a de novo mutation if they had no family history of Rb and were diagnosed with bilateral Rb. Survivors who had a family history of Rb were classified as family history regardless of their laterality.

Table 2

Mean maternal and paternal ages at birth of retinoblastoma survivors by type of retinoblastoma compared to the United States general population.

	Mean Maternal Age			Mean Paternal Age		
	Number of Mothers ²	Mean (yrs)	p-value*	Number of Fathers ²	Mean (yrs)	p-value
Retinoblastoma Type						
<i>de novo</i> Mutation	46	28.3	0.003	45	31.9	0.007
Sporadic	73	28.5	<0.001	72	31.2	0.01
Familial	38	26.7	0.56	37	29.8	0.61
U.S. General Population¹	--	26.2		--	29.3	

* Two sided one sample T-Test comparing the three Rb mutation classifications (*de novo* Mutation, Sporadic, Familial) to a weighted average for the U.S. general population. Significant p-values indicated in bold.

¹ Mean maternal and paternal age data for the U.S. general population for the years 1975 to 1996 were obtained from public use files available from the U.S. Centers for Disease Control and Prevention, National Center for Health Statistics Reproductive Statistics Branch, Division of Vital Statistics (see Appendix A).

² Maternal age data was not available for two survivors and paternal age was not available for five survivors.

Table 3

Comparison of mean maternal and mean paternal age for the three Rb classification types (*de novo* Mutation, Sporadic, Familial) using an ANOVA procedure for multiple comparisons.

	Mean Maternal Age				Mean Paternal Age			
	Number of Mothers	Mean (yrs)	SD (yrs)	p-value	Number of Fathers	Mean (yrs)	SD (yrs)	p-value
Retinoblastoma Type								
<i>de novo</i> Mutation	46	28.3	4.6	0.2	45	31.9	6.2	0.3
Sporadic	73	28.5	5.2		72	31.2	6.1	
Familial	38	26.7	5.6		37	29.8	5.9	
Total	157	28.0	5.2		154	31.1	6.1	

SD = Standard Deviation

Table 4

Odds ratios (ORs) for risk of having a *de novo* mutation versus sporadic retinoblastoma and familial retinoblastoma by maternal and paternal ages.

	Maternal Age			Maternal Age Adjusted for Race and Paternal Age ¹			Paternal Age			Paternal Age Adjusted for Race and Maternal Age ¹		
	No. of Survivors	Odds Ratio	95% CI	No. of Survivors	Odds Ratio	95% CI	No. of Survivors	Odds Ratio	95% CI	No. of Survivors	Odds Ratio	95% CI
Retinoblastoma Type												
<i>de novo</i> vs. Sporadic	46/73	1.0	0.92-1.1	45/71	0.9	0.83-1.1	45/72	1.0	0.96-1.1	45/71	1.1	0.97-1.2
<i>de novo</i> vs. Familial	46/38	1.1	0.98-1.2	45/37	1.0	0.83-1.1	45/37	1.1	0.98-1.1	45/37	1.1	0.95-1.2

¹ Logistic regression model adjusted for race (White, African-American, Hispanic, other/unknown) and age of the other parent.

Table 5

Odds ratios (ORs) for risk of having a *de novo* mutation versus the sporadic and familial retinoblastoma classification groups by five-year age category.

Retinoblastoma Type	Odds Ratio Estimates		
	Mean Maternal Age (yr)		
	<30	30–34	35
<i>de novo</i> vs. Sporadic	1.00	0.92	0.90
95% Confidence Interval		0.41-2.1	0.24-3.4
No. Mothers (<i>de novo</i> / Sporadic)	28/42	15/24	4/7
<i>de novo</i> vs. Familial	1.00	2.80	0.80
95% Confidence Interval		0.9-8.8	0.19-3.3
No. Mothers (<i>de novo</i> / Familial)	28/28	15/5	4/5

Retinoblastoma Type	Odds Ratio Estimates		
	Mean Paternal Age (yr)		
	<30	30–34	35
<i>de novo</i> vs. Sporadic	1.00	1.65	1.34
95% Confidence Interval		0.69-4	0.54-3.3
No. Fathers (<i>de novo</i> / Sporadic)	16/32	17/20	13/20
<i>de novo</i> vs. Familial	1.00	2.82	1.61
95% Confidence Interval		0.95-8.4	0.57-4.6
No. Fathers (<i>de novo</i> / Familial)	16/20	17/7	13/10

Table 6

Comparison to previous studies of Retinoblastoma and parental age.

Reference	Source of retinoblastoma patients	Sample Size	Source of controls/comparison group	Comment
Pell�� et al., 1973	Retinoblastoma patients at H��pital des Enfants Malades, France	289 sporadic unilateral 155 sporadic bilateral	French Vital Statistics	Increased paternal age effect with sporadic bilateral Rb (p=0.05).
Bunin et al., 1989	Childrens Cancer Study Group member hospitals (U.S.)	201 cases and 201 controls	Random digit dialing and individually matched to cases	Non-significant positive association of older maternal and paternal age with sporadic heritable retinoblastoma compared to controls.
Matsumaga et al., 1990	Nationwide retinoblastoma registry in Japan	408 sporadic unilateral 225 sporadic bilateral	Japanese general population data	No evidence of a paternal or maternal age effect.
Moll et al., 1996	Dutch Retinoblastoma Registry	437 sporadic unilateral 178 sporadic bilateral	General population data for the Netherlands.	Mean maternal and paternal age of sporadic hereditary parents was significantly higher compared to the general population (Maternal p = .015, one sided; Paternal p=0.03, one-sided). Mean maternal and paternal age was significantly higher in the sporadic hereditary compared to the sporadic non-hereditary Rb patients (Maternal p = 0.005, one sided; Paternal p=0.025, one-sided).
Yip et al., 2006	Swedish Cancer Registry	226 retinoblastoma cases	General population data for Sweden.	Maternal age 40 years associated with elevated risk of retinoblastoma (IRR = 2.39, 95%CI =1.17-4.85).
Johnson et al., 2009	Population-based state cancer registries in U.S. (California, Minnesota, NY State, Texas, Washington)	412 sporadic unilateral 162 sporadic bilateral	Random controls from birth registries.	No significant older maternal or paternal age effects.
Mills et al., 2011	National Cancer Institute Cohort of Retinoblastoma Survivors (U.S.)	75 sporadic unilateral 46 sporadic bilateral 38 familial	U.S. general population data and sporadic unilateral and familial survivors.	A weak paternal age effect for Rb resulting from <i>de novo</i> germline mutations.