
CHAPTER

REPRODUCTIVE BEHAVIOR OF INDIVIDUALS WITH AN INCREASED RISK OF HAVING A CHILD WITH RETINOBLASTOMA

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ABSTRACT

To investigate reproductive behavior of individuals at increased risk of having a child with retinoblastoma (Rb), we conducted a cross-sectional questionnaire survey among 118 counselees visiting the clinical genetics department of the National Rb Center in the Netherlands. The recurrence risk for counselees ranged from < 1% to 50%.

The response rate was 69%. Of 43 respondents considering having children after becoming aware of their increased risk, Rb influenced reproductive behavior for 25 (58%), of whom 14 had a recurrence risk < 3%. Twenty of these 25 decided against having more children and 5 used prenatal diagnosis. Eighteen of the 43 respondents did not use any of the alternative reproductive options and had children (or more children), although half indicated having had doubts about their decisions. Multiple logistic regression showed that only perceived risk ($p = 0.003$) was significantly associated with Rb influencing reproductive behavior. Of 17 respondents planning children (or more children), 11 (65%) considered using one of the alternative reproductive options.

We conclude that reproductive behavior is greatly influenced by Rb and that perceived risk, not objective risk, is the most important factor of influence. It is important to offer individuals at increased risk continued access to genetic counseling, even when this risk is relatively small.

INTRODUCTION

Retinoblastoma (Rb) is a childhood cancer of the eye, affecting around 1:17,000 live births.[1] About 40% of Rb cases are hereditary in an autosomal dominant way based on a positive family history, bilateral disease and/or a germline mutation in the retinoblastoma tumor suppressor gene *RB1*. Of all non-familial unilateral cases, around 15% are caused by a de novo germline *RB1* mutation.[2] Therapy for retinoblastoma may include: enucleation of an affected eye, local therapy (laser photocoagulation and cryotherapy), chemotherapy and radiation therapy. Rb can have substantial late effects, such as visual impairment[3], facial abnormalities and an increased risk for germline *RB1* mutation carriers of developing second primary malignancies.[4] Rb survivors also run an increased risk of having a child with Rb, as do healthy parents of a child with Rb. Recurrence risks for offspring may vary between less than 1% and 50%.

To accommodate the needs of couples at increased risk of having a child with Rb, during genetic counseling, it is important to obtain more insight into their reproductive behavior and into difficulties they may experience. Couples have several reproductive options: remain childless, or, if they already have an affected child, have no more children; adopt a child or choose gamete donation. If a germline *RB1* mutation is detected, couples can choose prenatal diagnosis (PND), with the option to terminate the pregnancy or pursue preimplantation genetic diagnosis (PGD), if one of the parents is RB1 mutation carrier. Alternatively, couples can decide to accept the risk and have biological children without using these options.

Little is known about reproductive behavior of couples at increased risk of having a child with Rb. Based on research primarily aimed at investigating other aspects of living with Rb[5-7], it appears that for many individuals the risk of Rb influences childbearing. One study assessed long-term consequences of Rb by interviewing Rb survivors around 30 years of age[5], showing that fewer Rb survivors than controls reported a pregnancy. However, participants were interviewed in the pre-molecular era, making it difficult to use this data in current-day practice. Another study reported that 12% of 92 adult Rb survivors intended to refrain from having children, due to the risk of hereditary Rb[6]. Investigation of long-term consequences of *RB1* mutation testing showed that healthy parents of *RB1* mutation carriers were more likely to decide against having more children.[7] None of these studies provided details on use of reproductive options such as PND or PGD, nor on factors of influence on reproductive behavior.

We recently published a qualitative study that showed that the diagnosis of Rb in the family influences subsequent family planning in different ways.[8] Some used prenatal diagnosis, while others refrained from having more children. An important factor that seemed to influence couples' reproductive decisions was their perceived risk of having a child with Rb. Other factors included the perceived

impact of ophthalmological screening under anesthesia until the age of 4 years that is offered to all children at increased risk for Rb.[9]
To quantify our qualitative findings, we conducted a cross-sectional questionnaire survey among counselees with different recurrence risks of having a child with Rb, who previously had received genetic counseling. The aim of the study was to: 1) investigate the reproductive decision-making process of these counselees; 2) examine past reproductive behavior and future reproductive intentions; 3) determine factors of influence on past reproductive behavior.

MATERIALS AND METHODS

Participants

The VU University Medical Center (VUMC) in Amsterdam is the National Rb Center in the Netherlands. All Rb survivors and parents of new Rb patients are offered genetic counseling, which includes oral and written information on recurrence risk for offspring. Between January 1998 and January 2009, 169 families visited our Clinical Genetics Department (VUMC) for genetic counseling regarding Rb. Counselees eligible for the study were Rb patients between 18 and 50 years of age and parents of children affected by Rb. Females above childbearing age at the time of counseling (here taken to be over 43 years old) were excluded (n = 22). We also excluded all participants of our qualitative study8 (n = 15), counselees with insufficient understanding of the Dutch language (n = 5), Rb patients with mental retardation (n = 3), critically ill patients (n = 1) and couples whose child or partner with Rb had recently died of a second primary malignancy (n = 4). Based on information obtained from the medical records, counselees fell into four groups, depending on who in the family was affected by Rb and results of *RB1* germline mutation testing with a sensitivity of 90%.10 *RB1* testing of tumor tissue was not available at the time.
Group A: The counselee has had familial or bilateral Rb and/or is carrier of a germline *RB1* mutation; risk of children being mutation carrier is 50%.
Group B: Healthy parents of a child with a de novo *RB1* mutation; recurrence risk for subsequent children is 2-3%, based on possible (germline) mosaicism of one of the parents.
Group C: The counselee has had unilateral non-familial Rb, without a detectable germline *RB1* mutation; recurrence risk for children is 0.5-1%.
Group D: Healthy parents of a child affected by unilateral non-familial Rb without a detectable germline *RB1* mutation; recurrence risk for subsequent children is <1%.

Questionnaire

The questionnaire was composed by the research team (two ophthalmologists, a psychologist, a clinical geneticist and two health scientists) and developed based

on available literature, clinical experience, and results of our qualitative study.[8] The questionnaire included questions concerning demographics: age, sex, offspring, marital status, religious beliefs, ancestral origin and educational level. Participants were also asked who in the family was affected by Rb and what Rb treatment they had received (i.e. enucleation, local therapy, chemotherapy, radiotherapy). Besides marital status, respondents were asked to give their opinion on the following statement: "I am not engaged in an intimate relationship due to Rb" on a 5-point scale: 1 (does not apply to me at all) to 5 (applies to me very much). The questionnaire further addressed the topics listed in **Table 1**.

Procedure

In March 2009, self-administered questionnaires were sent to the eligible families' home addresses. After three weeks a reminder was sent. Informed consent was obtained from all participants. If one of the counselees was affected by Rb, it was suggested that they should fill out the questionnaire. The study was approved by the Medical Ethical Committee of the VUMC.

Data analyses

All statistical analyses were done in SPSS 15.0. Non-response and demographic variables were analyzed using chi-square tests for categorical variables and *t*-tests for continuous variables. The 7-point answering scales for the questions: whether Rb has or has had influence on reproductive decisions, whether respondents had been doubtful, and whether respondents had changed their minds about having children were reduced to two categories. This was based on the median outcome of two: > 2 was coded as "Yes"; ≤ 2 was coded as "No".
If respondents indicated refraining from having children, having been sterilized or to having used one of the other alternative reproductive options (PND, PGD, adoption or gamete donation) due to Rb, they were coded: "Rb influenced reproductive behavior: Yes". If respondents had had a child after becoming aware of their increased risk without using one of the alternative options, they were coded "Rb influenced reproductive behavior: No". Differences in possible factors of influence on reproductive behavior between respondents from the "Yes" and "No" groups were analyzed using chi-square tests for categorical variables, and with *t*-tests for continuous variables (i.e. "objective recurrence risk", "having a child with Rb", "type of therapy", "perceived risk", "perceived severity", "perceived consequences of Rb", "perceived family burden of Rb" and "perceived impact of ophthalmological screening"). Variables that showed statistical significance (with $p < 0.1$) were entered in a stepwise multiple logistic regression model. Factors were accepted as significant when $p < 0.05$.
The 5-point scale of reproductive intentions was dichotomized to avoid empty cells. If a respondent had chosen an answer of 3 or more, it was taken to be an option the respondent would consider using.

Table 1. Questionnaire topics, questions and answer scales

Topic	Question	Answer scales
Reproductive decision-making process	Does Rb influence/has Rb had influence on reproductive decisions? Are you in doubt or have you ever been doubtful about your reproductive decisions, due to Rb? Have you ever changed your mind about having children, due to Rb?	1 (not at all) - 7 (very much) 1 (not at all) - 7 (very much) 1 (never) - 7 (all the time)
Past reproductive behavior	Did you refrain from having any (or more) children due to Rb? Did you, due to Rb, make use of: Sterilization PND PGD Adoption Gamete donation	Yes/No Yes/No
Factors associated with past reproductive behavior:		
Perceived risk	How big do you feel your risk of having a child with Rb is?	1 (very small) – 7 (very big)
Perceived severity of Rb *Sumscore, α = .82*	5 items of the Consequences Subscale using IPQ-R[a]	1 (totally disagree) – 5 (fully agree)
Perceived consequences of Rb[b] *Sumscore, α = .91*	In what way did the following issues affect your decisions towards childbearing: Seriousness of Rb Risk of getting a child with Rb Risk of passing Rb on to offspring Risk that my child may have impaired vision or become blind due to Rb Impact of treatment of Rb Fear or worries about developing second primary tumors later in life	1 (not at all) - 4 (very much)
Perceived family burden of Rb[b] *Sumscore, α = .90*	Caring for a child with Rb Presence of a child with Rb in the family The absence of a healthy child in the family Work-related problems for parents of children with Rb Problems with school/work for Rb patients Impact of Rb on the family Impact of Rb on relationship with partner	1 (not at all) - 4 (very much)

Table 1. Continued

Topic	Question	Answer scales
Perceived impact of ophthalmological screening[b] *Sumscore, Spearman's rho = .64*	Ophthalmological screening for healthy children at risk Ophthalmological screening for children with Rb	1 (not at all) - 4 (very much)
Reproductive intentions	If you are planning any (or more) children, do you intend to use: PND PGD Adoption Gamete donation	1 (definitely not) – 5 (certainly)

[a] Dutch version for at-risk individuals of the Revised Illness Perception Questionnaire 30.
[b] Principal axis factor analysis with varimax rotation was performed to investigate the possibility of combining different factors in order to make scales. Subsequently, a reliability analysis was performed on each scale to determine its internal consistency. Combining items resulted in a single measure for three subscales (perceived consequences of Rb, perceived family burden of Rb and perceived impact of ophthalmological screening).
Rb = retinoblastoma, PND = prenatal diagnosis, PGD = preimplantation genetic diagnosis

RESULTS

Of 118 eligible families who were sent questionnaires, 81 participated (response rate 69%). Twenty-seven did not respond (23%) and ten declined to participate (8%). Age, sex, and years since genetic counseling were similar for non-responders and responders. Significantly more eligible counselees with affected children responded than did eligible counselees without affected children (p = 0.04). Characteristics of the respondents are presented in **Table 2**.

Table 2. Characteristics of the respondents (*n* = 81) from the different groups

	Group[a]				
	A n = 21	**B n = 28**	**C n = 11**	**D n = 21**	**Total n = 81**
Mean age (SD)	35 (9.2)	39.5 (6.3)	35.2 (7.6)	39.8 (5.1)	37.8 (7.4)
Range	19-49	32-52	25-47	32-51	19-52
Gender *n* (%)					
Female	14 (77)	24 (86)	8 (73)	17 (81)	63 (78)
Children *n* (%)					
Yes	10 (48)	28 (100)	7 (64)	21 (100)	66 (82)
Marital status *n* (%)					
Married/living together	15 (71)	27 (96)	10 (90)	21 (100)	73 (89)
Actively religious *n* (%)	6 (29)	13 (46)	2 (18)	5 (24)	26 (32)
Ancestral origin[b] *n* (%)					
Indigenous (Dutch)	20 (95)	22 (79)	10 (91)	16 (76)	68 (84)
Level of education[c] *n* (%)					
Low	4 (19)	3 (11)	2 (18)	4 (19)	13 (16)
Intermediate	8 (38)	12 (43)	2 (18)	10 (48)	32 (40)
High	9 (43)	13 (46)	7 (64)	7 (33)	36 (44)
Person with Rb in the family[d] *n* (%)					
Respondent	17 (81)	--	11 (100)	--	28 (35)
Child or children	7 (33)	28 (100)	--	21 (100)	56 (69)
Type of therapy *n* (%)					
Enucleation UL/ local therapy	5 (24)	6 (21)	10 (91)	14 (67)	35 (43)
Enucleation BIL/ chemotherapy/ radiotherapy	16 (76)	22 (79)	1 (9)	7 (33)	46 (57)
Objective recurrence risk for a child with Rb	50%	2-3%	0.5-1%	<1%	

[a] A = respondent *RB1* mutation carrier, B = healthy parents, child *RB1* mutation carrier, C = respondent UL Rb, no *RB1* mutation detected, D = healthy parents, child UL Rb, no *RB1* mutation detected.

[b] Indigenous (Dutch): a person whose parents were both born in the Netherlands.

[c] Low: primary school, lower level of secondary school. Intermediate: higher level of secondary school, intermediate vocational training. High: higher vocational training, university.

[d] Four respondents from group A were carriers of a low-penetrant germline *RB1* mutation and did not develop Rb themselves. For three respondents from group A, both the counselee and a child had had Rb.

Rb = retinoblastoma, UL = unilateral, BIL = bilateral

Reproductive decision-making process

Of the 21 carriers of an *RB1* mutation (group A), two stated they had not engaged in a relationship due to Rb, as did one of the 11 unilaterally affected respondents, without an *RB1* mutation (group C). Forty-four percent (35 out of 79) of respondents from all four groups had had doubts about their reproductive decisions as a result of Rb, while 38% (28 out of 74) had changed their minds about their decision whether or not to have any (or more) children. Seven respondents changed their opinion and decided not to have another child, after having a child with Rb. Six respondents changed their mind the other way, deciding to have children (or more children), for different reasons (e.g. some time having passed since treatment of their child, after testing negative for a germline *RB1* mutation, after talking to other parents of affected children).

Past reproductive behavior

Thirty-eight (47%) of the 81 respondents indicated that Rb had not (yet) been a factor in their reproductive decisions, either because they had completed their family irrespective of Rb (n = 19), they did not have a desire to have any (or more) children (n = 11); or they reported other reasons for not having a (subsequent) child (n = 8) (e.g. gynecological problems, no partner, considering themselves past childbearing age).

Of 43 respondents considering having children after becoming aware of their increased risk, Rb changed reproductive behavior for 25 (58%) (**Table 3**). Twenty (80%) of these 25 respondents decided against having any (or more) children, including 11 respondents from groups B, C and D, with recurrence risks < 3%. Three respondents (12%) were sterilized to avoid having children affected by Rb. Two of them were from group A (*RB1* mutation carrier), who both stated they had only become aware of their increased risk after having had an affected child. The third respondent was from group B, who was sterilized after their child with sporadic bilateral Rb was born. Five couples (20%) had used PND (chorionic villi sampling) to determine whether the fetus was affected, including three couples from group B. One fetus was affected and the parents (at 50% risk) decided to terminate the pregnancy. This couple is now opting for PGD.

Eighteen (42%) of the 43 respondents considering children after becoming aware of their increased risk decided to have a (subsequent) child and did not choose any of the alternative reproductive options (**Table 3**). However, nine respondents indicated that Rb had influenced their reproductive decision-making process and that they were doubtful about their decisions.

Table 3. Past reproductive behavior among respondents from the different groups considering having children after becoming aware of their increased risk (n = 43)[a]

Rb influenced reproductive behavior	Group[b] A n = 15	B n = 11	C n = 6	D n = 11	Total n = 43
Yes *n* (%)	11 (73)	6 (55)	2 (33)	6 (55)	25 (58)
Refrained from having any (or more) children	7	2	2	6	17
Sterilization	2	1	0	0	3
PND	2[c]	3	NA	NA	5
No[d], *n* (%)	4 (27)	5 (45)	4 (67)	5 (45)	18 (42)

[a] Respondents who had not (or not yet) had a child or another child, irrespective of Rb, are not shown in this table (n = 38).

[b] A = respondent RB1 mutation carrier, B = healthy parents, child RB1 mutation carrier, C = respondent UL Rb, no RB1 mutation detected, D = healthy parents, child UL Rb, no RB1 mutation detected.

[c] One fetus turned out to be a carrier of the familial RB1 mutation and the pregnancy was terminated.

[d] Had a child after increased risk was known and did not use any of the alternative reproductive options.

Rb = retinoblastoma, UL= unilateral, PND = prenatal diagnosis, NA = not applicable

Factors of influence on reproductive behavior

We examined possible differences between respondents for whom Rb had influenced reproductive behavior (n = 25) and respondents for whom Rb had not influenced reproductive behavior (n = 18) (**Table 4**). Significant differences ($p < 0.1$) were found in type of Rb therapy, participants' perceived risk of having a child with Rb, and perceived consequences of Rb. The only factor significantly associated with influence of Rb on reproductive behavior in multiple logistic regression was perceived risk (Odds Ratio 1.9; 95% Confidence Interval 1.2 - 2.8; $p = 0.003$).

Reproductive intentions

Seventeen respondents were planning to have children (or more children). Eleven (65%) of these respondents considered using an alternative reproductive option to avoid a child with Rb: PND, PGD, adoption or gamete donation (**Table 5**). All but two respondents from groups A and B were considering the use of alternative reproductive options. For groups C and D, the only available options for having any (or more) children are adoption and gamete donation. Only six of these 32 (19%) respondents were planning any (or more) children, of whom two were considering adoption.

Table 4. Differences between respondents for whom Rb did or did not influence reproductive behavior

	Rb influenced reproductive behavior		p-value
	Yes n = 25	No n = 18	
Objective recurrence risk (%)			.31
50%	44	22	
2-3%	24	28	
≤1%[a]	32	50	
Having a child with Rb (%)			.86
Yes	64	67	
Type of therapy (%)			.06*
Enucleation UL / local therapy	32	61	
Enucleation BIL / chemotherapy/ radiotherapy	68	39	
Perceived risk, 1-7, mean (SD)	4.50 (2.2)	2.59 (1.5)	< .01*
Perceived severity, 1-5, mean (SD)	3.41 (.83)	3.18 (.89)	.39
Perceived consequences of Rb, 1-4, mean (SD)	2.82 (.81)	2.17 (.75)	.02*
Perceived family burden of Rb, 1-4, mean (SD)	1.88 (.87)	1.54 (.47)	.12
Perceived impact of ophthalmological screening, 1-4, mean (SD)	2.00 (.98)	1.56 (.66)	.10

[a] Groups C and D with recurrence risks of 0.5-1% and <1% are taken together because of small groups.*

Significant at $p < 0.1$.

Rb = retinoblastoma, UL = unilateral, BIL = bilateral

Table 5. Reproductive intentions*a* among respondents from the different groups planning to have (more) children (*n* = 17)

	Group[b]			
	A n = 5	B n = 6	C n = 5	D n = 1
PND	3	4	NA	NA
PGD	2	NA	NA	NA
Adoption	2	2	2	0
Gamete donation	1	0	0	0
Would (probably) not use any of the above	1	1	3	1

[a] More than one option possible.

[b] A = respondent *RB1* mutation carrier, B = healthy parents, child *RB1* mutation carrier, C = respondent UL Rb, no *RB1* mutation detected, D = healthy parents, child UL Rb, no *RB1* mutation detected.

Values are expressed as *n*.

Rb = retinoblastoma, UL = unilateral, PND = prenatal diagnosis, PGD = preimplantation genetic diagnosis, NA = not applicable

DISCUSSION

This study demonstrates that reproductive behavior is strongly influenced by Rb, both for Rb survivors and for unaffected parents of a child with Rb. This applies therefore not only to *RB1* mutation carriers with a 50% recurrence risk, but also for individuals with a recurrence risk of less than 3%. Perceived risk of having a child with Rb – not objective risk – was the most important factor influencing past reproductive behavior.

Of 43 respondents considering having children (or more children) after becoming aware of their increased risk, Rb influenced reproductive behavior for 58%. The majority decided not to have a (subsequent) child and one-fifth made use of PND. Our study supports the limited previous findings that Rb may have a substantial effect on reproductive behavior.[5-7] Nine out of 49 unaffected parents with a child with Rb from our study decided to refrain from having another child, which is very similar to findings by Cohen et al. (10 out of 49).[7] Several studies about reproductive decisions of individuals at increased risk for children with other genetic diseases found that many had decided against having more children to avoid having an affected child. For example, two studies on reproductive decisions of hemophilia carriers showed that carriers not choosing PND often decided not to have any (or more) children.[11,12] Forty-one percent of 230 parents of children with metabolic diseases[13] and 32% of 181 parents of children with cystic fibrosis had no further children.[14] This is similar to our results: 20 out of 43 (47%) respondents desiring (more) children decided to refrain from having any (or more) offspring. However, the recurrence risk for couples in the studies mentioned above was 25%, whereas for the majority of our respondents the recurrence risk was much lower. So even individuals with a relatively small recurrence risk of a child with Rb may decide not to have any (or more) children, or choose PND.

Multiple logistic regression showed that perceived risk was the most important factor associated with influence of Rb on reproductive behavior. Risk perception is a complex process and is influenced by many factors.[15] Risk magnitude is just one aspect of interpreting risk. Understanding of risk information, personal beliefs about risk prior to counseling, psychological impact of the family history and emotional aspects also influence risk perception.[15,16] In reproductive decision-making, counselees tend to see their risk in binary terms rather than in terms of probability: either a child will be affected or it will not be affected.[8,15-19]

Two other factors differed between the group with and the group without influence of Rb on reproductive behavior: more extensive therapy for Rb and perceived consequences of Rb. Studies on quality of life of Rb survivors show poorer health-related quality of life reported by parents than by Rb survivors themselves.[20-22] This may also be reflected in the effect of treatment and perceived consequences of Rb on reproductive decisions: if parents experience treatment and consequences of Rb as leading to a worse quality of life for their children, they may be more inclined to change their reproductive behavior.

PND and/or PGD is an option for 11 respondents planning children in the future, seven (64%) of whom were indeed contemplating the use of PND or PGD, including four unaffected respondents from group B. In studies assessing attitudes towards PND and/or PGD for other hereditary cancers[23-26], between 33% and 71% considered the use of these methods to avoid the birth of an affected child. Again, in our study some respondents considering PND have a much lower risk (2-3%). None of the participants in our study had used PGD, although one couple had been referred for PGD. Since 1999, four couples have opted for PGD for Rb in the Netherlands (personal communication C. de Die-Smulders, PGD working group the Netherlands).[27]

All respondents had previously received genetic counseling. Many respondents had doubts about their reproductive decisions or changed their mind due to Rb, regardless of the magnitude of the recurrence risk. Offering easy access to follow-up genetic counseling sessions to discuss the reproductive options in the light of new views of counselees is therefore important, as was also pointed out by others.[28,29] For some counselees, exchanging information with other counselees can be helpful and others may benefit from extra support from a psychologist.

The strength of the study is that it is drawn from a nationwide cohort of Rb patients and that all counselees received genetic counseling, including a summary letter of the information provided. Some limitations should be considered, however. First, because of the sensitive nature of the subject, individuals may have been less likely to participate if Rb has had a high impact on their lives. Secondly, some respondents made their reproductive decisions several years before filling out the questionnaire and there may have been selective retention of information. This study was done among counselees who visited our department. Their reproductive decisions may differ from individuals who declined genetic counseling or who visited a genetic counselor elsewhere. Lastly, the study would have benefited from a larger study group, because small subgroups impeded quantitative analyses for some variables.

In conclusion, this study shows that Rb has a high impact on reproductive decision-making; both for individuals affected by Rb themselves and for parents of affected children. Perceived risk – not objective risk – was the most significant factor influencing reproductive behavior. Many individuals had doubts about their reproductive decisions and continued to change their minds over time. It is therefore important to offer individuals at increased risk of a child with Rb continued access to genetic counseling, even when the recurrence risk is relatively small. In genetic counseling, specific attention should be given to the interpretation of the objective risk and the perceived consequences of Rb, including the impact of extensive treatment of Rb patients.

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