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## **THE LOSS OF A CHILD TO CANCER – FOCUSING ON SIBLINGS**

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The loss of a child to cancer – focusing on siblings

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## ABSTRACT

**Aims** The overall aim of this thesis was to investigate the long-term psychological health consequences in bereaved families of children who have died from cancer, with a focus on the siblings. Further, we investigated if health-care and family related stressors might affect the long-term psychological health in bereaved siblings. Part of the aim was also to examine bereaved siblings' experience of participation in a research study about their loss.

**Subjects and Methods** In the initial study, parents who lost a child to cancer four to nine years earlier in Sweden were asked to participate in a nationwide follow-up study, 80% (449/561) participated together with a group of non-bereaved parents from the general population, 69% (457/659). A study-specific, anonymous questionnaire assessing anxiety, depression, quality-of-life and marital status together with a number of other outcomes were distributed to participating parents. In another nationwide follow-up study, we contacted 240 siblings, in Sweden, who had lost a brother or sister to cancer between the years 2000 and 2007; among those, 73% (174) participated in our study. A control group of non-bereaved siblings, matched for age, gender and place of residence, were also invited, 75% (219/293) participated. A study-specific and anonymous questionnaire assessed the siblings' experience of participating in the study, their psychological health (anxiety, depression), and their communication with family and others prior to and after the death of their brother or sister, together with other factors.

**Results** Bereaved parents were more likely to be living with the child's other parent, 74% (329/442) compared to non-bereaved parents, 69% (312/452), RR=1.1 (1.0-1.1). None, (0/168), of the bereaved siblings thought that their participation in the study would effect them negatively long-term. Ninety-nine percent of the siblings (171/173) found it valuable to conduct such a study and a vast majority, 84% (142/169) found it to be a positive experience. At follow-up self-assessed low self-esteem ( $p=0.002$ ), difficulties falling asleep ( $p=0.005$ ) and low personal maturity ( $p=0.007$ ) were more prevalent among bereaved siblings. However, anxiety ( $p=0.298$ ) and depression ( $p=0.946$ ) according to the Hospital Anxiety and Depression Scale (HADS) were similarly distributed between bereaved and non-bereaved siblings. Siblings who avoided the health-care professionals, for fear of being in their way during their brother or sisters last month in life, reported an increased risk of anxiety, RR=2.2 (1.1-4.6) as

compared with those who did not avoid the health-care professionals. Siblings who talked less about their feelings regarding their brother or sister's illness reported an increased risk of anxiety, RR=2.8 (1.3-6.2) as compared with those who talked more frequently. An increased risk of anxiety was also prevalent among siblings who avoided talking to their parents about their deceased brother or sister, out of respect for their parent's feelings, RR=2.4 (1.1-5.4) as compared with those siblings who reported talking to their parents about the deceased child.

**Conclusions** Parents bereaved due to cancer are not more likely to be separated or divorced from the child's other parent compared with non-bereaved parents. Bereaved siblings are at increased risk of low self-esteem, low personal maturity and sleeping difficulties as compared with non-bereaved peers. Avoiding health-care professionals prior to the brother or sisters death and avoiding talking to their parents following the loss increased the bereaved siblings' risk of long-term (two to nine years following the loss) anxiety. Most siblings reported finding it valuable to participate in this type of research.

## LIST OF PUBLICATIONS

This thesis is based on the following papers, referred to by the Roman numerals:

- I. Eilegård A, Kreicbergs U. Risk of Parental Dissolution of Partnership Following the Loss of a Child to Cancer: A Population-Based Long-term Follow-up. *Arch Pediatr Adolesc Med.* 2010 Jan; 164 (1): 100-1.
- II. Eilegård A, Steineck G, Nyberg T, Kreicbergs U. Bereaved siblings' perception of participating in research – a nationwide study. *Psycho oncology.* 2011 Dec 14. doi: 10.1002/pon.2105. [Epub ahead of print].
- III. Eilegård A, Steineck G, Nyberg T, Kreicbergs U. Psychological health in siblings who lost a brother or sister to cancer 2 to 9 years earlier. *Psycho oncology.* 2012 Feb 20. doi: 10.1002/pon.3053. [Epub ahead of print].
- IV. Eilegård A, Steineck G, Nyberg T, Kreicbergs U. The impact of communication prior to and following the loss of a brother or sister to cancer – A nationwide long-term follow-up. Submitted.

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## **INTRODUCTION**

My journey to achieve a Ph.D. started one summer during my nursing education when I got a scholarship for a research summer school at Karolinska Institutet in Stockholm. One task during these research weeks was to join a research group and write a short report on some of their data. I had the opportunity to join the group of Clinical Cancer Epidemiology at Karolinska Institutet and to work with Ulrika Kreicbergs and Gunnar Steineck. I wrote on some of the data from Ulrika's research project on parents who had lost a child to cancer four to nine years earlier in Sweden. I found this kind of research very interesting and was pleased to be offered to work on a sibling project at the department of Clinical Cancer Epidemiology, once I had completed my nursing education. In spring 2007 I was accepted as a Ph.D. student.

### **Childhood cancer**

Worldwide, approximately 250 000 children (0-19 years of age) will be diagnosed with cancer each year, and in Sweden there are almost 300 new cases yearly. Due to improvements in treatment over the last decades, the survival rate from childhood cancer is almost 80% in the Western World<sup>1</sup>. Despite the medical improvements not all children will survive their cancer, with around 60 children in Sweden dying from cancer each year<sup>1</sup>.

### **Having a brother or sister with cancer**

Childhood cancer impacts the whole family. For obvious reasons, the ill child becomes the main focus of their parents. All family members are affected psychologically and it is hard for them to live a normal life. Previous studies on siblings living with a brother or sister who has cancer show that the siblings are vulnerable and invisible and that some parents tend not to inform their well children about the illness, treatment and its side-effects in an attempt to spare them from worry and pain. This may lead to anxiety and depression and make the siblings feel left alone with their thoughts and worries<sup>2-4</sup>.

### **Avoidable and or modifiable stressors**

Potential stressors that might be found within family or the health-care setting such as lack of or sparse communication, among family members and between family members and health-care professionals, may also influence long-term health in the bereaved family members. Involvement or non-involvement in the care of the ill child may be another potential stressor. Insufficient symptom control and suffering as well as a

difficult moment of death are examples of care related factors that have been found to trouble bereaved family members after the loss<sup>5</sup>. It is of importance for health-care professionals to listen to and to support the whole family and they may be a valuable source for family members. Open and honest communication within the family may be valuable both when a child is first diagnosed with cancer, throughout the illness trajectory, and after the child dies. In families where it is not encouraged or a common practice to talk and share feelings, siblings may be ignored and left alone in their grief. It seems like most bereaved siblings benefit from communicating about their deceased brother or sister and that parental support is necessary for them to adjust to the loss<sup>6, 7</sup>. Gender, age and the time since loss may also impact the bereaved siblings' psychological health. Even though these are impossible factors to avoid or manage, they may have an impact on the siblings' psychological well-being. Girls have previously been found to be more vulnerable than boys when living with a brother or sister, who has cancer<sup>8,9</sup>. Similar vulnerability has been reported in bereaved mothers<sup>10-12</sup>. Since a child's age and developmental stage impacts the individual's cognitive thinking, a child's awareness of death will be affected by their understanding of illness and death<sup>13</sup>. In a study by Houtzager and co-workers<sup>9</sup> it was found that siblings were negatively affected by their brother or sister's cancer as much as two years following the diagnosis. Low qualities of life, emotional and psychological problems were also reported. Havermans and co-workers<sup>14</sup> found siblings to be afraid of bothering their parents with questions and concerns regarding their cancer ill brother or sister. All siblings (16/16) reported that their parents were the ones who informed them about the illness, but only one third of these wanted more information. Koch- Hattem<sup>15</sup> found that siblings with a brother or sister treated for cancer who had someone to talk to, preferably the parents, had lower risk of anxiety compared with those who did not have this opportunity. Little is known about whether there are any avoidable and or modifiable health-care and family related stressors affecting cancer bereaved siblings. In order to improve the care of the siblings of children with cancer there is a need to identify potential stressors in the health care and family setting.

### **Loss of a child to cancer and other causes**

Childhood cancer may be manifested as a prolonged struggle between cure and death. Anticipatory grief may begin at diagnosis, when the outcome is uncertain. Witnessing the child's anxiety and pain may also impact the loved ones grief process. Previous knowledge on parental grief is limited and data are sometimes contradictory. In an

effort to sum up the research field on the risk of morbidity among parents bereaved due to childhood cancer Rosenberg and co-workers<sup>16</sup> conducted a review of the existing research studies. Out of 121 identified studies, only 13 met the inclusion criteria for quality and reliability of findings. The included studies were conducted between 1983 and 2011. The review findings confirm that bereaved parents are at increased risk for poor psychosocial outcomes such as prolonged grief, anxiety, depression and poor psychological well being, compared to non-bereaved parents. Another literature review focusing parental morbidity, mortality and grief after the loss of a child due to various causes was conducted by Hendrickson<sup>17</sup> and it also showed conflicting findings. In four of the studies reviewed, an increased risk of mortality was found in bereaved parents, yet in another four no significant difference was found when compared with non-bereaved parents. An increased risk of psychological distress (e.g. anxiety, depression, suicide attempts and drug or alcohol abuse) in bereaved parents, compared to non-bereaved parents was found in nine studies. Since this review showed conflicting findings, Hendrickson<sup>17</sup> concluded that more methodologically comprehensive research is necessary to clarify the relationship between parental grief after the loss of a child and the risk of morbidity and mortality. In a follow-up study in Sweden, Rostila and co-workers<sup>11</sup> found an increased risk of mortality in parents having lost a child to various causes, particularly in mothers following the unnatural death of a young child (age 10-17 years of age). Similar results were found in a Danish follow-up study conducted by Li and co-workers<sup>10</sup>. Yet, they found that the death of a child increases the mother's risk of mortality, both in natural and unnatural deaths. For fathers the risk was increased the first 3 years following the loss and only in unnatural deaths. Parental reactions to the death of a child and how they cope with grief may have a significant impact on the siblings as well. Siblings tend to become unnoticed during this time when they need their parents the most. Some of the previous studies mention sibling loss as a double loss since they are not only losing a brother or sister but also their support and attention from their parents<sup>6, 18</sup>.

### **Loss of a brother or sister to various causes**

Little research has been conducted on bereaved siblings, regardless of the cause of death. More research is very much needed because the loss of a brother or sister causes deep sorrow and possibly long-term psychological distress in siblings. Dyregrov and co-workers<sup>19</sup> studied 83 families in Norway who were bereaved due to suicide during

1997 and 1998. The study was conducted between 12 and 24-month post loss. Seventy siblings participated. Even though for some siblings, there had been warning signs and previous suicidal attempts, they nonetheless described the death of their brother or sisters as unexpected. They initially felt shock, disbelief and confusion and later experienced reactions such as anxiety and depression. Eight out of 11 of the younger siblings, age 15 to 20, and 23/59 of the older siblings, age 21 to 43, suffered from severe posttraumatic stress symptoms at time of follow-up. Another problem faced by the siblings was the sense of lack of support from their parents. The siblings understood their parents suffering and thus avoided talking to them about their deceased brother or sister even though they were in need of their parents' attention. Greeff and co-workers<sup>20</sup> studied indicators of resilience in 89 bereaved parents and 67 bereaved siblings from 89 Belgian families who had lost a child from different causes (e.g. accidents, diseases, suicides and stillbirths). Keeping the family together and getting strength from each other seemed to be the best source of adaption after the loss as well as support from friends and the community.

### **Loss of a brother or sister to cancer**

Treatment for childhood cancer, at least in developed countries, has improved dramatically over the past decades; and subsequently, the number of children dying of the disease, or from its treatment, has decreased. Accordingly, the focus of sibling research has transitioned from bereaved to non-bereaved. The trauma of losing a brother or sister to cancer is difficult for the siblings. They are exposed to their brother or sister's physical and emotional suffering during treatment and their parents' grief both before and after the loss. For both bereaved and non-bereaved siblings, negative outcomes such as loss of childhood, control and security have been described previously. It has been found that siblings seem to be invisible during this difficult time and that some may already suffer from anxiety or depression during treatment, and perhaps more so following the loss of a brother or sister to cancer<sup>2, 3, 21-26</sup>. Notably, positive outcomes such as maturity, personal growth and empathy have also been reported<sup>2, 4</sup>. A majority of the previous studies in this field suffer from design problems, such as insufficient sample size and lack of a control group<sup>2</sup>. This is particularly true for the few studies on bereaved siblings.

## **Grief**

Grief is a normal reaction to loss and is often described by different stages. A stage theory for adjustment to grief was first proposed by Bowlby<sup>27</sup> in the beginning of the 1960<sup>th</sup>. Four phases of grief was described, shock-numbness, yearning-searching, disorganization-despair and reorganization<sup>27</sup>. The stage theory has been further developed by other researchers and has been used by clinicians for many years<sup>28</sup>. Even though grief takes time and is individual the normal course of grief is around one year. This is probably not true when a child dies since this loss is unique in many ways, a child is not supposed to die before his or her parents. The loss of a child is referred to as deeper than any other loss and it seems like the grief continues over many years<sup>29</sup>. Every human is unique and therefore the death of a loved one will be experienced and expressed in different ways. Still, most individuals will experience common or normal grief reactions and cope well. Personality, age, developmental stage, the relationship to the deceased, and earlier experiences of loss will affect how the bereaved individual copes<sup>13</sup>. There are different instruments to measure grief, (e.g. as described above, the Hogan Grief Reaction Checklist<sup>30</sup> and prolonged grief reaction as described by Prigerson and co-workers<sup>31</sup>).

## **Children's grief**

Children grieve in a different way than adults<sup>32,33</sup>. They tend to walk in and out of their grief, using timeout periods as a coping mechanism<sup>26</sup>. Until approximately four decades ago, it was a common practice to protect children from psychological pain by not informing and or involving them in a loved ones illness and death. Although, knowledge about children's capacity to understand death has increased during recent years, their need to be informed and included is still often overlooked. To this day, many children remain uninformed and invisible during their loved one's treatment and after death<sup>13</sup>. Grief in children after the loss of a loved one has yet to be well described. Further research is needed to find out what helps and what hinders grief in children and what they believe can help them to cope with the loss.

## **Ethical considerations**

The reason for the sparse research on bereaved siblings may have its explanation in ethical considerations and in fear of inflicting harm by reopening old wounds. The possible trauma of participating in research that elicits memories and feelings about the death of a loved one must be weighted against the potential benefit, not just to science,

but to the participants themselves who may find that being asked questions about the death may actually decrease their anxiety and facilitate resolution of their grief. Kreicbergs and co-workers<sup>34</sup> surveyed bereaved parents who lost a child to cancer 4 to 9 years earlier, how their participation in research was perceived. It was found that close to all parents 423/427 (99%) felt the study valuable and that a majority 285/421 (68%) were positively affected by their participation. Dyregrov and co-workers<sup>35</sup>, asked 64 bereaved parents about their research participation. A majority (73%) reported the interview to be painful, although none regretted their participation. Also Scott and co-workers<sup>36</sup> examined family members of children with Ewing Sarcoma and their experience of research participation, nearly half of the family members (38/81) expected the interview to be painful and six even more so than anticipated. Notably, not all of the family members were bereaved. Yet, it was found that bereaved family members were more likely to participate than non-bereaved. This seems to reflect a positive attitude towards research on the bereavement experience and may have influence on such research in the future. Still, it is not yet known how siblings bereaved due to the loss of a brother or sister to cancer may react to the experience of participation in research about their loss.

## **AIMS**

The overall aim of this thesis was to investigate the long-term psychological health consequences in cancer-bereaved families, especially in siblings, and to identify avoidable and modifiable stressors in the health-care and family setting that may impact psychological health in bereaved siblings. Another part of the aim for this thesis was to gain an understanding of siblings' perception of participating in research that examined the impact of the loss of their brother or sister to cancer two to nine years earlier.

## **SUBJECTS AND METHODS**

### **Developing the questionnaires**

At the department of Clinical Cancer Epidemiology in Stockholm, Sweden, a step-wise approach has been used for several decades when constructing questionnaires for studies on cancer survivors and bereaved<sup>37-39</sup>. Charlton<sup>40</sup> has described a similar method. We believe this approach has a positive impact on the willingness to participate and the high response rates in our studies. The first step includes search for relevant literature and discussions with experts. The second step involves interviews with those affected. From the interviews, we construct hypotheses and questions to include in the study-specific questionnaires. To test the questions, to see if they are understood as intended, we perform face-to-face validations. Following the face-to-face validation, we conduct a pilot study, or several pilot studies if needed. If we reach appropriate participation and response rates, we continue with the nationwide studies. This method was used for the bereaved parents study and the sibling study that will be described in more detail below.

### **The questionnaire for the bereaved and the non-bereaved siblings**

For our sibling study, we conducted interviews with eight cancer-bereaved siblings who had been identified through the pediatric oncology ward at Astrid Lindgren's Children's Hospital, in Stockholm, Sweden. Questions were formulated from those interviews and were included in the first draft of the study-specific questionnaire. The questions and the response alternatives were then tested face-to-face with another eight bereaved siblings, identified as above, to assess clarity and to determine if the questions were understood as intended by the researchers. The final draft of the questionnaire was tested in two pilot studies during the year 2008. Bereaved siblings were identified in the manner described earlier while the non-bereaved siblings were matched with a deceased child for age, gender and place of residence and traced through the Swedish Population Registry. Twenty-nine bereaved siblings who lost a brother or sister to cancer during the years 1991 and 2004 (4 to 17 years earlier) in Sweden were contacted for the first pilot study as well as 50 matched non-bereaved siblings from the general population. The low response rate, 55% for the bereaved and 50% for the non-bereaved siblings, required a second pilot study. In order to improve the response rate, we changed the years since loss for the second pilot study to include the years 2001 until 2006 (2 to 7 years earlier) based on previous findings by Kreicbergs and co-workers<sup>12</sup> that indicated that parents are at increased risk of anxiety and depression 4 to 6 years



following the loss of a child to cancer while no such risk was found 7 to 9 years post-loss. In the second pilot study we also changed the methodology for the non-bereaved siblings to include a personal phone call prior to sending out the questionnaire, which is routine for the bereaved. Seventeen bereaved and 25-matched non-bereaved siblings from the general population were contacted for this second pilot study. Eighty-two percent of the bereaved and 83% of the non-bereaved siblings responded.

### **The Nationwide study**

#### **The deceased children**

In 2008, 545 children deceased due to cancer were traced through the Swedish Childhood Cancer Registry. Those children were diagnosed with cancer before the age of 17 and died in Sweden before the age of 25 years during the years 2000 and 2007. From this cohort of deceased children, 187 fulfilled our inclusion criteria.

#### **The bereaved and non-bereaved siblings**

Two hundred and seventy-one bereaved siblings of the 187 deceased children, described above, were identified through the Swedish Population Registry. Bereaved siblings were eligible if they were born in one of the Nordic countries, could speak, read and understand Swedish and had a non-confidential and reachable phone number. The bereaved siblings had to be between 12 and 25 years of age at the time of loss and at least 18 years at time of follow-up. The latter inclusion criteria were decided in order for the siblings to be able to respond independently, without their parent's consent, since youth in Sweden reach lawful age at 18 years of age. Out of 271 bereaved siblings, 240 fulfilled the inclusion criteria.

From the Swedish Population Registry, we also received information on a matched control group of non-bereaved siblings from the general population. To be eligible for the study the non-bereaved siblings from the general population should not have lost a brother or sister to cancer. Still, they could have lost a loved one and this was asked for in the questionnaire. The non-bereaved siblings were matched to a deceased child for age, gender and place of residence. Out of 374 non-bereaved siblings 293 met the eligibility criteria.

## **Data collection**

In 2009 we sent an introductory letter to eligible siblings explaining the objectives of the study, together with an invitation to participate. A few days later, a research assistant phoned the siblings and asked about their willingness to participate. All siblings were informed, orally and in writing, that study participation was voluntary and could be terminated at any time. No questionnaire was mailed without consent. The study-specific and anonymous questionnaire was sent together with a separate response letter to those who agreed to participate. This letter was supposed to be returned separate from the questionnaire to guarantee the anonymity. After two to three weeks, a combined thank-you-and-reminder-card was mailed. If the questionnaire still had not been returned by then the same research assistant phoned to check if the siblings needed any assistance in filling out the questionnaire. Contact information for the investigator and the research assistant were given in the questionnaire for the siblings to use at any time and an answering machine was available for use during non-office hours.

## **The questionnaires**

For obvious reasons, the questionnaires differed for bereaved and non-bereaved siblings. The questionnaire for bereaved siblings included 200 questions covering demographics, current psychological health, family and health-care related factors relating to the brother or sister's illness and death. Anxiety and depression was measured using The Hospital Anxiety and Depression Scale (HADS)<sup>41</sup>, a validated scale that is often used in the clinical setting to assess psychological health. For non-bereaved siblings, the questions were the same except for those specific to the illness and death experience. The control-group questionnaire consisted of 91 questions.

## **The Hospital Anxiety and Depression scale (HADS)**

The scale measures anxiety or depression simultaneously and only takes a few minutes to complete. There are 14 questions: 7 that measure anxiety and 7 measuring depression. The possible scores range from 0 to 21 for anxiety and depression, respectively. The answering alternatives are ranked from 0 to 3 for each question. A maximum score of 7 for each group indicates an acceptable level. Eight to 10 indicates high levels of distress and increased anxiety. Eleven points or more indicates anxiety or depression severe enough for the individual to need medical care.

### **Statistical analysis**

All raw data from the questionnaires were inputted manually by means of the data entry program EpiData. The reliability of the data entry was tested by re-inputting 10% of randomly chosen questionnaires. Analyses were conducted by using the Statistical Package for the Social Sciences (SPSS) 17 and the Statistical Analysis System (SAS) 9.2. The results for paper one are reported as relative risks (RR), with 95% confidence interval (CI) calculated as the proportion of bereaved parents reporting living together with or being married to the deceased child's other parents divided with the proportion of non-bereaved parents reporting living together with or being married to the child's other parent. In paper two, Fisher's exact test was used to test for differences in experience of research participation between groups among the bereaved siblings. For paper three, the Wilcoxon-Mann-Whitney rank-sum test was used to test for differences for ordinal outcomes between bereaved and non-bereaved siblings. In paper four, relative risks (RR) were calculated as in paper one, for the proportion reporting anxiety within dichotomized groups of bereaved siblings. The tests performed were two-sided with a 5% significance level. Individuals with missing data were excluded in the calculations.

### **Validity**

As a researcher, one always hopes for a perfect study, yet such a study only exists in theory. In order to come as close as possible to a perfect study different methods are often used. To ensure validity (measurement of what we intended to measure), we included the siblings representing our target population from the beginning of the study and throughout the whole research process. We interviewed siblings who had lost a brother or sister to cancer and asked them to tell us about their experiences. From the interview findings, we conducted hypotheses and questions for the study-specific questionnaire. In order to validate the questions, we met with siblings face-to-face while they read through the questionnaire. If any questions or thoughts occurred to them when filling out the questionnaire, they were told to tell us about them. This process was done to make sure the respondents understood the questions and the response alternatives as intended by the researchers.

## **Biasing factors (errors)**

Errors will always occur in a study. At the department of Clinical Cancer Epidemiology, we use the Hierarchical step-model<sup>42</sup> to identify possible sources of biasing factors (errors) when conducting our studies. Errors that spuriously can influence the effect measure can be caused by confounding factors or be categorized as misrepresentation or misclassification.

## **The Hierarchical step-model with its different steps and corresponding biasing factors (errors)**

### **Perfect person-time**

*Confounding*

### **Targeted person-time**

*Misrepresentation*

### **Observed person-time**

*Misclassification*

### **Collected data**

*Analytical adjustment*

### **Adjusted effect measure**

## **Confounding**

The first step of the Hierarchical step-model<sup>42</sup> is the **Perfect person-time**. Since a perfect study only exists in theory, this step could include e.g. one million siblings living in two exact worlds (the same siblings in both worlds), except that in one world siblings have lost a brother or sister to cancer. If the outcome were anxiety or depression measured by The Hospital Anxiety and Depression Scale (HADS)<sup>41</sup>, which measure these outcomes the previous week, it would give us one million person weeks to study and this would give us the true effect of the loss. The following step is the **Targeted person-time**. Since the perfect study is not possible to conduct, we traced children in Sweden deceased due to cancer between the years 2000 and 2007 (n=545) throughout the Swedish Child Cancer Registry and their siblings (n=271) in the Swedish Population Registry as well as non-bereaved siblings (n=374) from the general population functioning as a control group. To be eligible siblings had to be 18 years of age at time of follow-up, in year 2009. The bereaved siblings should have lost a brother or sister to cancer when they were between 12 and 25 years of age and the deceased

child should have been diagnosed before the age of 17 and died before the age of 25 years to be eligible for the study. The siblings should also have been born in one of the Nordic countries and speak and read Swedish. The non-bereaved siblings were matched for age, gender and place of residence, in an attempt to minimize the influence of confounding factors when comparing the two groups. Some siblings (25 bereaved and 79 non-bereaved) did not fulfill the inclusion criteria's and were therefore excluded from the study. Six bereaved siblings had lost a brother or sister to other causes than cancer and two non-bereaved siblings had lost a brother or sister. This gave us 240 identified and eligible bereaved and 293 eligible non-bereaved siblings.

A perfect study should not include any difference in outcome between the groups compared, except the effect of the studied factor of interest (the exposure). A confounding factor is always associated with both the exposure and the outcome. It can be a problem when there is a discrepancy between the distributions of factors affecting the outcomes between the groups studied. To control for potential confounding, matching may be used. Age, gender and place of residence may be confounding factors. In the present study we matched each non-bereaved sibling with a deceased child's age, gender and place of residence.

### **Misrepresentation**

Another biasing factor (error) called misrepresentation may occur between the targeted person-time and the observed person-time. The **Observed person-time** includes those siblings that we actually observed, 174 bereaved and 219 non-bereaved siblings, who returned the questionnaire and answered all questions for the specific outcome e.g. all 14 questions for HADS<sup>41</sup>. Total numbers of non-participants are 66 bereaved and 74 non-bereaved siblings. Misrepresentation means the loss of individuals (non-participants) from the targeted person-time to the observed person-time (those actually participating in the study). Or in other words, misrepresentation is any discrepancy between the originally defined study base (targeted person-time) and the observed population (observed person-time).

Misrepresentation in the present study is the individuals that fulfill the inclusion criteria's (240 bereaved and 293 non-bereaved siblings) but declined participation (20 bereaved, 23 non-bereaved siblings) together with those not returning the questionnaire (46 bereaved and 51 non-bereaved siblings). Misrepresentation may introduce bias. In

order to reduce misrepresentation we worked with bereaved siblings representing the target population from the very beginning of the study. In the present study, the participation rate was 73% (174/240) for the bereaved and 75% (219/293) for the non-bereaved siblings. For ethical reasons, we did not ask the non-respondent bereaved or non-bereaved siblings why they declined participation.

### **Misclassification**

Between the Observed person-time and the next step **Collected data**, there is another error that can occur, called misclassification. Misclassification means that there are errors in the measurement instrument (the questionnaire) that influence the answers from the participating siblings. During the preparatory phase, we tried to minimize these errors by using questions constructed from the findings from the interviews with the bereaved siblings. We tried to create questions formulated as simply as possible by using the language and wording from the siblings themselves. The use of a self-administered anonymous postal questionnaire may reduce the risk of interview bias.

### **Analytical adjustment**

Analytical adjustment occurs between the collected data and the **adjusted effect measure**. This is a random error where the variability in the data cannot easily be explained. In the present study the relative risk (RR) and P-values are presented with 95% confidence intervals as the measurement of precision.

### **Generalizability**

Our study was conducted in Sweden in 2009 on cancer-bereaved siblings who lost a brother or sister between the years 2000 and 2007 and a comparison group of non-bereaved siblings from the general population. Our results may not be generalizable to other groups of bereaved or in other settings. Still, we believe that our results can be trusted and make a valuable contribution to the existing knowledge in this important and under researched field of study.

## **RESULTS AND COMMENTS**

### **Participation rates and general characteristics for bereaved and non-bereaved parents**

Information was provided among 449/561 (80%) of the bereaved parents, 23 (4%) could not be reached, 30 (5%) declined participation and 59 (11%) failed to return the questionnaire.

#### **Bereaved parents**

665 bereaved parents

104 not eligible

561 eligible

23 not reachable    30 refused participation    59 failed to return the questionnaire

449 participated

In the group of non-bereaved parents 457/659 (69%) provided information, 39 (6%) could not be reached, 50 (8%) declined participation and 113 (17%) failed to return the questionnaire.

#### **Non-bereaved parents**

659 non-bereaved parents

39 not reachable    50 refused participation    113 failed to return the questionnaire

457 participated

### **Risk of parental dissolution of partnership following the loss of a child to cancer**

The commonly believed myth that bereaved parents separate more frequently than non-bereaved parents encouraged the study on parental dissolution of partnership in cancer bereaved parents. Out of 561 cancer-bereaved parents, 449 (80%) responded. Among the 659 non-bereaved parents 457 (69%) responded. A majority of the parents 442 of 449 (98%) of the bereaved and 452 of 457 (99%) of the non-bereaved responded to the questions on marital status. At the time of follow-up, 329 (74%) of the bereaved and 312 (68%) of the non-bereaved parents were married to or living with the child's other parent. Bereaved parents were found to be more likely than the non-bereaved to be married to or living with the child's other parent, unadjusted RR= 1.062 (1.001-1.126), age-adjusted RR=1.068 (1.007-1.133).

## **Comments**

It seems that parents who lost a child to cancer are *not* more likely to separate than others. Since this myth is widely held and may put more strain on already burdened parents, our finding may be beneficial for parents living with a cancer ill child and also for those bereaved.

Previous research is limited on marital status among bereaved parents and researchers have been unable to resolve this issue<sup>43-45</sup>. Rogers and co-workers<sup>44</sup> studied long-term effects in parents bereaved due to different causes and found marital disruption to be more commonly reported in bereaved parents, occurring 30% of the time compared with 24% in non-bereaved parents. During the illness period, parents living with a seriously cancer-ill child are already at increased risk of psychological distress and also possibly marital strain<sup>46, 47</sup>. Sirki and co-workers<sup>47</sup> studied parents who lost a child during active cancer treatment or terminal care and found that divorce was significantly more common among couples with a child in terminal care compared to parents with a child in active cancer therapy.

To our knowledge, there are no conclusive long-term findings on marital status in bereaved parents. Still the belief persists that bereaved parents are more likely to separate. Yet our findings did not support this belief.

## **Participation rates and general characteristics for bereaved and non-bereaved siblings**

Among 240 eligible bereaved siblings, information was supplied by 174 (73%), 20 (8%) declined participation and 46 (19%) failed to return the questionnaire. The most frequent diagnosis among the deceased children was leukemia 51/174 (29%) and brain tumors 40/174 (23%). The mean time from diagnosis to patient's death was 3 years (range 0-17 years). The mean age of the participating siblings were 15 years (range 3-25 years) of age at the time of their brother or sisters diagnosis, 18 years (range 12-25 years) of age at the time of the ill brother or sister's death and 24 years (range 19-33 years) of age at the time of follow-up.



### **Bereaved siblings**

271 bereaved siblings

31 not eligible

240 eligible

20 declined participation 46 failed to return the questionnaire

173 participated

Among 293 eligible non-bereaved siblings, 219 (75%) provided information, 23 (8%) declined participation and 51 (17%) failed to return the questionnaire.

### **Non-bereaved siblings**

374 non-bereaved siblings

81 not eligible

293 eligible

23 declined participation 51 failed to return the questionnaire

219 participated

### **Bereaved siblings' perception of research participation**

Cancer-bereaved siblings are not likely to be part of research nor do we have previous knowledge about their experiences of participating in research. This may have to do with ethical considerations and fear of inflicting harm or reopening old wounds by asking siblings to participate in bereavement studies or by assessing their experiences of participation. To our knowledge, this is the first nationwide study on siblings' experiences of research participation concerning their brother or sister's illness, care and death to cancer.

Findings reported in our second paper, showed that none of the bereaved siblings (0/168) anticipated any long-term negative effect from their research participation. A majority of siblings, 79% (127/160) reported their participation as positive, providing them with an opportunity to revisit their experiences throughout their brother or sisters' illness and death two to nine years following the loss. In a short-term perspective, 84% (142/169) of the siblings reported filling out the questionnaire as a positive experience, whereas 13% (21/168) reported it as negative. Close to all siblings, 99% (171/193) stated that the study was valuable.

## **Comments**

For obvious reasons, negative emotions may arise when revisiting a trauma like the loss of a loved one. Nevertheless, our results show that none of the bereaved siblings anticipated any long-term negative effect from participating in a study-specific questionnaire study on their brother or sister's illness and death 2 to 9 years earlier. Despite our results, we are unable to conclude that no long-term negative effects will arise in the future.

Our findings that a majority of the participating siblings valued the study are supported by previous research on bereaved individual's experience of research participation<sup>34-36</sup>. We believe that large-scale studies with bereaved individuals based on questionnaires may help to improve the care of the seriously ill and also to tailor best possible support for those bereaved. Since the fear of inflicting harm in bereaved individuals by conducting studies using questionnaires, many previous studies have instead used interviews to gather data from bereaved participants. Our results show that population-based studies on cancer-bereaved siblings are feasible and that the participating siblings value their research participation.

Our step-wise approach of including the siblings from the very beginning of the study may have helped to increase their willingness to participate since by doing so they become visible and are given the opportunity to tell their own story.

### **Psychological health in siblings who lost a brother or sister to cancer**

Our third manuscript investigated psychological health in bereaved siblings two to nine years following the loss of a brother or sister to cancer as compared with a group of non-bereaved siblings from the general population. Anxiety, depression and other psychological health related factors e.g. sleep difficulties, level of maturity and self-esteem was assessed in the study-specific and self-assessed questionnaire.

Seventy-three percent (174/240) of the bereaved siblings and 75% (219/293) of the non-bereaved siblings participated in the study. Even though we did not find a statistically significant difference for anxiety ( $p=0.298$ ) or depression ( $p=0.946$ ) according to The Hospital Anxiety and Depression Scale (HADS)<sup>41</sup> between the bereaved and the non-bereaved siblings, there was a tendency towards higher levels of anxiety in the bereaved siblings group. Low self-esteem ( $p=0.002$ ), difficulties falling

asleep ( $p=0.005$ ) and low level of personal maturity ( $p=0.007$ ) at follow-up, 2 to 9 years following the loss, was found to be more prevalent among bereaved siblings as compared with the non-bereaved.

### **Comments**

This study showed that bereaved siblings are at increased risk of reporting difficulties falling asleep, low self-esteem and low personal maturity as much as two to nine years following the loss of a brother or sister to cancer, as compared with non-bereaved siblings from the general population. Notably, anxiety and depression was not more commonly reported among the bereaved siblings.

Research on bereaved siblings is sparse since focus during the last decades has been on siblings during the time when they are living with a cancer ill brother or sister rather than after their loss. Negative outcomes as well as positive (see below) have been shown to affect siblings during their brother or sisters illness as early as from the time of the diagnosis. These effects may also impact siblings when bereaved.

Previous research shows contradictory findings regarding siblings' psychological distress during their brother or sister's cancer trajectory. Anxiety, depression and post-traumatic stress symptoms (PTSD) have been reported in siblings of children with cancer and so have personal growth, enhanced self-esteem and increased maturation<sup>2, 3, 24</sup>. It is not only the illness itself that is distressing for the family-members, but also the treatment and its side effects, which may also be difficult to witness<sup>48, 49</sup>. For siblings living with a cancer ill brother or sister, it seems valuable to have their parent's attention during this difficult period since siblings have reported feeling invisible in some of the previous research<sup>22, 23, 33, 48</sup>.

Our results on sleeping difficulties are supported by Davies<sup>50</sup> who found that almost one third of the cancer-bereaved siblings stated that they suffered from insomnia. Walking and talking in their sleep and having nightmares have also been reported as problems for the bereaved siblings. The lack of personal growth in the bereaved siblings in our study may be explained by the common observation that siblings living with a cancer ill brother or sister become invisible<sup>22, 23</sup>. This lack of attention may begin as soon as the brother or sister are diagnosed, when parents become preoccupied with the ill child and this preoccupation may even be intensified after the loss<sup>26, 33</sup>.

Although it may take some time, most siblings resolve their psychological distress and are able to continue their life after the loss of a brother or sister to cancer<sup>47</sup>. Still, some siblings may need additional support from both family and health-care providers. There may be a number of avoidable and or modifiable health-care and family-related factors associated with the care of the seriously ill child that have an impact on siblings' long-term psychological health.

### **The impact of communication**

Our fourth manuscript focused on communication with health-care professionals, family and others prior to and following the loss, in relation to siblings' long-term psychological health.

Siblings who avoided health-care professionals, due to a fear of being in their way during their brother or sisters last month of life, reported an increased risk of anxiety (HADS  $\geq 11$ ), RR=2.2 (1.1-4.6) as compared with those who did not avoid them. Siblings who talked less often with others about their feelings regarding their brother or sisters illness had an increased risk of anxiety RR=2.8 (1.3-6.2) as compared with those who talked more frequently. And so did siblings who avoided talking to their parents about their deceased brother or sister, out of respect for their parents feelings RR=2.4 (1.1-5.4), as compared with those who did not avoid talking to their parents. Siblings who reported not being satisfied with how often they had talked about their feelings with their family the previous year showed an increased risk of anxiety RR=2.5 (1.3-4.8), as compared with siblings who were satisfied with how often they had talked with their family.

### **Comments**

Communication is valuable in all health-care situations, yet when a child is seriously ill communication might be more of a challenge<sup>51</sup>. To whom, when and to what extent should information be given? Even though it might be difficult to talk about the prognosis and the outcome, it is important to be open to and support such communication throughout the whole illness period. This is highlighted in guidelines by The International Society of Paediatric Haematology and Oncology, SIOP<sup>52</sup>. In the present study, the results showed that siblings' avoidance of health-care professionals for fear of being in their way during the brother or sisters last month of life and

avoidance to talk to others prior to and following the loss increased their risk of anxiety long-term.

Health-care professionals may play a role in encouraging parents to communicate openly and honest with the siblings about the illness and treatment, in order to help the siblings feel informed and involved in the ill brother or sisters cancer journey. Friends and others outside the family are also valuable to the siblings, and it is important to try to keep life as normal as possible for the siblings. Having someone to talk to, and just be with, when life is turned upside down is valuable to all of us. Barrera and co-workers<sup>53</sup> found that siblings of children with cancer who reported having sufficient social support during the illness period had fewer symptoms of psychological distress e.g. anxiety and depression as compared with siblings with insufficient support.

Our findings that siblings who talked to their parents are less likely to report anxiety as compared with siblings who did not are supported by Koch-Hatten<sup>15</sup> who found that having someone to talk to, preferably the parents seemed to reduce the risk of anxiety in siblings living with a cancer ill brother or sister.

To our knowledge our study is the first nationwide study focusing on the long-term effects in bereaved siblings of health-care and family-related stressors associated with the care of the seriously ill child with cancer. A number of stressors occurring during the care of the seriously ill child may not be possible to eliminate. Still, some stressors can be dealt with and modified in the future care of seriously ill children with cancer such as providing support for parents to talk to their children about the illness and possible death. We believe that information about the illness, the treatment and its side effects, as well as pain control and managing the moment of death, are valuable for the siblings' adaption and psychological health in a long-term perspective. There might be other potential stressors not yet studied. We found that communication is crucial in the care of the seriously ill child and that talking may be beneficial for all family members. Health-care professionals may have a significant role to play in talking to siblings, and in promoting families to talk to each other, during the illness period and following the loss. Our results may encourage health-care professionals to further promote communication both with the health-care providers and the families.

## **CONCLUSIONS**

The commonly held myth that bereaved parents are more likely to separate than others is not supported by our results.

Our results show that almost all siblings bereaved to cancer value their participation in research of this kind.

Difficulties falling asleep, feelings of low maturity and low self-esteem were more commonly reported in bereaved siblings than in their peers.

Communication with health-care professionals and others prior to and after the loss seemed important for the sibling's psychological health in a long-term perspective.

Using our methodology, it seems possible to conduct research on cancer-bereaved parents and siblings without inflicting significant harm, especially if using a step-wise approach and a postal study-specific questionnaire constructed in close collaboration with the bereaved.

## **THE FUTURE**

The care of children with cancer and their families has improved over the years, yet there is still room for improvements, and the knowledge gained from our study may help even further. Continued work to identify avoidable and or modifiable health-care and family related stressors in the care of the seriously cancer ill child may help to prevent, or at least reduce, psychological distress long-term in affected parents and siblings.

An increased awareness of the impact of siblings' communication with health-care professionals is needed in order for providers to encourage parents to communicate openly and honest with the siblings about the child's illness and treatment. Such communication may help the siblings to feel more informed and involved in their ill brother or sister's cancer journey.

The network around siblings of children with cancer, e.g. schools, friends and others outside the family, must be made aware of their importance in supporting the siblings of children with cancer, and especially those bereaved. This may be a task for "sibling supporters" in the future.

Other aspects of the siblings' bereavement experience, such as specific types of support should be further investigated, using the same approach taken to conduct this study. In a future study, it might be of interest to investigate Swedish cancer bereaved siblings who were born outside the Nordic countries, to see if there are differences in how they cope with their loss. Further, grandparents' experience of the illness and assessment of their psychological health after the loss of a grandchild to cancer would also be of value to study in the future.

Pediatric oncology units have "sibling supporters". They are there for the siblings of children with cancer. As the siblings vary in age and interests, the "sibling supporters" way of working vary accordingly. Yet, one might from our findings suggest that the "sibling supporters" spend some time with the ill child and enable the parents to leave the hospital to spend quality time with the sibling. This would truly be sibling support.

## SUMMARY IN SWEDISH / SVENSK SAMMANFATTNING

Vi har arbetat efter en modell som använts på enheten för Klinisk Cancerepidemiologi i många år. Först läser vi in oss på ämnet, diskuterar med experter och intervjuar individer ur studiegruppen för att få insikt om deras erfarenheter. Därefter utformas hypoteser och frågor till de studiespecifika frågeformulären. År 2001 tillfrågades 561 föräldrar som mist ett barn i cancer fyra till nio år tidigare, att svara på ett sådant studiespecifikt frågeformulär. Fyrahundrafyrtionio föräldrar som mist ett barn besvarade frågeformuläret liksom 457 föräldrar som inte mist. Nedan följer en mer specifik beskrivning av syskonstudien.

I denna nationella studie, den första i sitt slag, har vi fokuserat på påverkbara och undvikbara vård och familjerelaterade faktorer i omvårdnaden av det svårt cancersjuka barnet som kan inverka på syskonens hälsa på lång sikt. Etthundrasjuttiofyra syskon av 240 (73%) som mist en bror eller syster i cancer mellan åren 2000 och 2007 i Sverige deltog i studien liksom en kontrollgrupp från normalbefolkningen bestående av 219 syskon av 293 (75%) matchade mot de avlidna barnen för ålder, kön och hemkommun, detta för att få så likartade grupper som möjligt. Syskonen besvarade ett anonymt, studiespecifikt frågeformulär utarbetat i nära samarbete med syskon som mist en bror eller syster i cancer.

För att kontrollera logistik och svarsfrekvens genomfördes två förstudier med syskon som mist en bror eller syster i cancer samt en kontrollgrupp från normalbefolkningen som inte mist en bror eller syster i cancer. I den första förstudien ingick 29 syskon som mist mellan åren 1991 och 2004 och 50 syskon som inte mist. Studien gav låg svarsfrekvens, 50% för de som mist och 55% för kontrollgruppen därför genomfördes en andra förstudie. För att förbättra svarsfrekvensen ändrade vi åren sedan förlust för de syskon som mist och för de syskon som ingick i kontrollgruppen ändrade vi så att de fick ett telefonsamtal innan vi skickade ut frågeformuläret. Sjutton syskon som mist mellan åren 2000 och 2006 samt 25 matchade kontroller ingick i den andra förstudien. Svarsfrekvensen blev högre, 82% för de som mist och 83% för kontrollgruppen. Orsaken till att vi ändrade antal år sedan förlust baserades på tidigare studier från enheten Klinisk Cancerepidemiologi om förlustdrabbade föräldrar samt det låga gensvaret i den första förstudien.



Våra resultat stödjer inte den myt som finns att föräldrar som mist ett barn skiljer sig i högre utsträckning än andra. Föräldrar som mist ett barn i cancer, fyra till nio år tidigare, var vid uppföljningen i högre utsträckning gifta eller sammanboende med barnets andra förälder jämfört med föräldrar i kontrollgruppen. De finns få studier med syskon som mist en bror eller syster i cancer vilket kan bero på etiska svårigheter att bedriva forskning på förlustdrabbade individer då rädsla finns att göra mer skada än nytta. Våra resultat visar att en majoritet av syskonen som mist en bror eller syster i cancer två till nio år tidigare i Sverige värdesätter forskning av det här slaget och igen tror sig bli negativt påverkad på lång sikt. Resultaten visar också att syskon som mist har svårigheter att somna, lägre självförtroende och upplever sig själva vara mindre mogna jämfört med syskon som inte mist en bror eller syster i cancer. Undvikande av vårdpersonal av rädsla för att vara i vägen för dem under brodern eller systemens sista månad i livet mer än fördubblar risken för ångest hos syskon som mist, att undvika att tala med sina föräldrar och andra om den avlidna brodern eller systemen fördubblar också syskonens risk för ångest. Vårdpersonal som arbetar nära dessa unga vuxna torde ha en betydande roll i ett fortsatt arbete för att minimera den ohälsa vi sett hos syskonen som mist. Inte minst genom att reflektera över sitt arbete nära dessa unga vuxna i vården av den sjuka brodern eller systemen och speciellt i livets slut. Likaså är betydelsen av kommunikation central och vårdpersonal bör uppmuntra en öppen och ärlig dialog mellan familj och profession samt inom familjen.

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