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### Childhood cancer survivors: Evidence and care

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**Publication date**  
2013

[Link to publication](#)

#### **Citation for published version (APA):**

Sieswerda, E. (2013). *Childhood cancer survivors: Evidence and care*. [Thesis, fully internal, Universiteit van Amsterdam].

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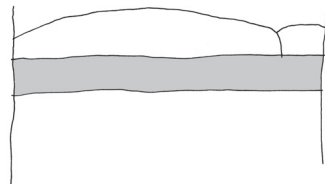
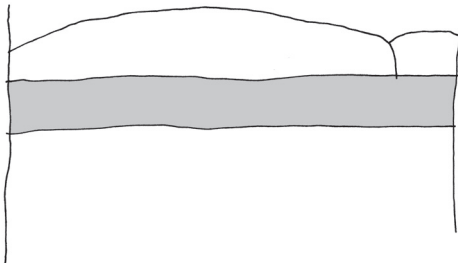
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# Chapter 1

Introduction and outline of the thesis





## Introduction

Late adverse effects of treatment for childhood cancer are a serious problem for survivors, their families and their health care providers. Four decades after the primary cancer diagnosis, more than 15% of childhood cancer survivors have died due to *other causes* than the primary cancer.<sup>1</sup> The majority of these non-primary cancer deaths are related to the initial cancer treatment, such as radiotherapy and chemotherapy. For every ten childhood cancer survivors, more than three suffer from at least one severe, disabling or life-threatening health problem, especially when treated with radiotherapy.<sup>2,3</sup> Also, during the first 25 years after primary cancer diagnosis, the total number of second cancers in childhood cancer survivors is four times more than in the general population.<sup>4</sup> After secondary malignancies, cardiovascular disease accounts for a more than six-fold increased mortality in survivors compared to the general population.<sup>5,6</sup>

The impact of late adverse effects of childhood cancer treatment is also increasing on a population level, because of the expanding group of childhood cancer survivors. Although survival rates differ per cancer type, overall five year childhood cancer survival in Western countries is between 75% and 80% on average nowadays, due to effective treatments and high quality supportive care.<sup>7,8</sup> It has been estimated that in 2010 in the Netherlands 1 in 250 young adults survived a primary cancer diagnosis during childhood.<sup>9</sup> The high survival rates and the general long-life-expectancy at young age account for a growing and aging population at risk for health problems that likely effects population health and health care systems.

### Gaps in evidence of late adverse treatment effects

After initial successes from the late 1960s onwards in the cure rates of childhood cancer, the awareness developed among those involved that several survivors suffered from health problems, including organ dysfunction and second malignancies. With increasing numbers of survivors, scientists were able to study these health problems and relate them to previous cancer treatment. Since the 1980s, a considerable and growing number of scientific studies have been published studying a wide range of late effects of (childhood) cancer treatment and their impact.<sup>10</sup> However, even though the knowledge of late adverse effects in childhood cancer survivors is expanding, much is still unknown. Gaps in the current evidence range from the exact risk of late effects after specific cancer treatments to the clinical and socio-economic consequences of late effects. There are similar gaps in evidence about diagnostic strategies and effective interventions during follow-up of childhood cancer survivors to decrease the burden of late effects.<sup>11</sup> Therefore, ongoing epidemiological studies are needed to increase understanding of late effects of childhood cancer treatment and of optimal care for childhood cancer survivors.

## **Increasing evidence of late adverse treatment effects**

Epidemiological studies that increase evidence on the occurrence of late adverse treatment effects and their clinical consequences are indispensable within childhood cancer survivorship research.<sup>11</sup> They define the focus for further studies on strategies to improve the health of and care for childhood cancer survivors. Ideally, well-conducted randomized controlled trials (RCTs) with unbiased estimates would contribute to our understanding about late treatment effects and their consequences.<sup>12, 13</sup> In an RCT childhood cancer patients or survivors at random receive study treatment or study control treatment and are prospectively followed during long-term clinical follow-up to compare beneficial and adverse effects of both treatments.<sup>14</sup> However, there are many reasons why large RCTs within childhood cancer survivorship research are difficult, or sometimes almost impossible to perform. Childhood cancer is relatively rare, making it hard to include a large enough sample of patients that enable strong conclusions about differences between study treatments. This could be overcome by performing national and international multicenter trials, as is frequently done for the assessment of treatment efficacy and acute toxicity in childhood cancer. However, RCTs are also costly, especially when a long follow-up duration is needed. The potential long duration between cancer treatment and treatment-induced late adverse effects makes the RCT a very expensive study design for many research questions in the field of childhood cancer survivorship.

Therefore, historically, most evidence of late effects of cancer treatment in children came from observational studies such as retrospective or cross-sectional cohort studies.<sup>11</sup> The main limitation of these study designs compared to the RCT is that a comparison group, if available, is never as optimal as in a well-designed RCT. However, observational research can certainly produce valid evidence.<sup>15, 16</sup> This is especially the case when studying adverse effects of treatment, as there is lower risk of the so-called confounding-by-indication bias, such as in studies of beneficial effects of treatment.<sup>17</sup> Also, the risk of confounding by indication may be lower in children when there is generally no co-morbidity that could change initial treatment strategies.<sup>11</sup> The obvious prerequisite of high quality observational research is that other types of bias are prevented as much as possible.

## **Synthesizing evidence of late adverse treatment effects**

In order to appraise evidence in medicine, findings of primary studies should be synthesized taking into account the quality of the studies. The systematic review plays an important role in this process. The Cochrane collaboration defines the systematic review as “a high-level overview of primary research on a particular research question that tries to identify, select, synthesize and appraise all high quality research evidence relevant to that question in order to answer it” (available at: <http://www.cochrane.org/about-us/evidence-based-health-care>).<sup>18</sup> A well-executed systematic review produces the highest level of evidence available in medicine and is therefore a useful study design to increase the evidence of

late adverse effects of childhood cancer treatment. Although it is most straightforward to perform a systematic review if the included studies are RCTs or clinically controlled trials, systematic reviews can summarize all types of study designs, including observational studies about adverse effects.<sup>17, 19, 20</sup> Another principal feature of a systematic review is that it clearly shows if there are any gaps in evidence on a certain topic and thus what the priorities for new studies should be.<sup>21</sup>

### **Optimal care for childhood cancer survivors**

After synthesizing evidence about the late effects of childhood cancer treatment, the step to clinical care for childhood cancer survivors has to be made. Historically, when health care professionals recognized the problem of late adverse effects of treatment, the call for structured follow-up care for this population emerged.<sup>22</sup> Survivors had specific health problems that could potentially benefit from additional follow-up care: diseases that are rare in the general population at young age (such as meningioma, heart failure, endocrine disorders); early development of treatable or preventable risk factors for common diseases (such as hypertension, dyslipidemia, obesity); diseases that theoretically could benefit from early discovery and treatment (such as heart failure, breast cancer); specific psychosocial issues (such as fatigue, chronic pain); and multi-morbidity (such as growth hormone deficiency, meningioma and psychosocial problems after cranial irradiation).<sup>22-27</sup> Several coordinated groups initiated recommendations about specialized follow-up care for childhood cancer survivors, including screening for late adverse effects of cancer treatment.<sup>28-30</sup>

However, it is now recognized that care based on assumed benefits is not always truly a benefit for patients, even though the care is set-up with the best intentions. For example, screening for certain types of cancer in the general population does not always only benefit the screened population, as there is the risk of false-positive findings and even an increased risk for being treated for cancer in the screened population compared to the unscreened population.<sup>31-33</sup> For those involved in the care for childhood cancer survivors this implies that in addition to the need for high quality evidence about the *risk* of late effects, also high quality evidence about *optimal care* for survivors is needed, including its benefits and risks.

### **Increasing evidence of optimal care for childhood cancer survivors**

When it comes to evidence about the best care for a certain patient population, several study designs can be used. Again a randomized controlled setting would be an ideal study design, in which the intervention that is randomly allocated can range from a diagnostic intervention (such as echocardiography versus cardiac MRI), to a medical treatment (such as an ace-inhibitor versus placebo intervention) and to complete follow-up care or preventive interventions (such as screening for breast cancer versus no screening).<sup>34-36</sup> Unfortunately, the same limitations of RCTs as in childhood cancer survivorship research on the occurrence

of late effects of childhood cancer treatment apply, i.e. relatively low patient numbers and long-term follow-up that is generally needed.<sup>37</sup> Moreover, with many follow-up strategies for childhood cancer survivors already implemented, it may sometimes be difficult to set up a classical RCT of such a strategy, in which one part of the study group should not receive the already implemented strategy anymore. Thus, clever alternative study designs should be thought of, aiming for the lowest risks of the several forms of bias these (often non-randomized) studies are at risk of. Appropriate study designs range from well set-up observational studies with statistical adjustments for confounding, to alternative clinical trial designs and decision analytic studies.<sup>34-36, 38-40</sup> Again, systematic reviews and meta-analyses should synthesize the findings of primary studies on such interventions to appraise all available evidence.<sup>21, 41</sup>

### **Translating available evidence into recommendations for care**

Synthesizing evidence on disease occurrence and follow-up care in a systematic review is not always sufficient to change daily practice. There may be lack of awareness among clinicians about the latest clinical evidence, or there is awareness, but changing the existing structure of care may be challenging.<sup>42</sup> The clinical practice guideline is a potential tool to improve the quality of evidence-based care by translating evidence into daily clinical practice.<sup>43</sup> Clinical practice guidelines (or just guidelines) try to integrate the best available evidence, clinical expertise and patient values into recommendations for health care professional and patient decisions in clinical care. Well-executed guidelines can contribute to decreasing variation between health care professionals in their decisions. They can stimulate effective care, communication, and collaboration between health care professionals and between health care professionals and patients. Guidelines can also ensure a decrease in health care costs.<sup>44</sup> The development of clinical practice guidelines for childhood cancer survivors can thereby contribute to high-quality and uniform follow-up care.

### **Objective and outline of this thesis**

The objective of this thesis was to increase evidence of (1) late adverse effects of childhood cancer treatment and (2) optimal care for childhood cancer survivors, with the ultimate goal to improve quality of care and quality of life of childhood cancer survivors. Within the first three studies in this thesis, our topics of interest were study design and general clinical consequences of childhood cancer treatment. Within the further studies in this thesis, we focused on survivors at risk for cardiac late effects of treatment, which are generally associated with anthracycline chemotherapy and/or cardiac radiotherapy.

## **Part I. Late adverse effects of childhood cancer treatment**

In part I of this thesis we increased evidence of late adverse effects of childhood cancer treatment using two study designs: a cohort study and a systematic review. **Chapter 2** introduces in detail the design and characteristics of the longitudinal cohort study of childhood cancer survivors that was initiated in 1996 in the Emma Children's Hospital/Academic Medical Center (EKZ/AMC). In **Chapter 3**, we introduce and evaluate a medical record linkage study design in which we linked the EKZ/AMC cohort of childhood cancer survivors with national administrative register in order to study clinical consequences of late adverse effects of childhood cancer treatment (by way of hospitalizations) in comparison to the general population. We assessed if it is feasible and valid to perform such studies in the Netherlands. Using the study designs presented in chapter 2 and 3, we aimed to increase evidence on the clinical consequences of late adverse effects of cancer treatment as measured by hospitalization rate and by hospitalization characteristics in childhood cancer survivors compared to the general population (**Chapter 4**). Finally, in **Chapter 5** we aimed to synthesize the evidence of benefits and risks within children of a specific cancer treatment that has been developed to decrease the risk of heart failure: liposomal anthracyclines.

## **Part II. Optimal care for childhood cancer survivors**

In part two, the step to optimal care for childhood cancer survivors is made by increasing the evidence on this topic using three study designs: a cohort study, a systematic review and a clinical practice guideline. **Chapter 6** assesses the value of monitoring childhood cancer survivors at risk of cardiac disease after anthracyclines with exercise echocardiography. **Chapter 7** synthesizes the evidence of treatment options for childhood cancer survivors with anthracycline-induced cardiotoxicity. The second part of this thesis finalizes with a clinical practice guideline with the aim to ensure optimal and uniform follow-up care in childhood cancer survivors. **Chapter 8** describes the development of an evidence-based guideline for follow-up care of childhood cancer survivors at risk for cardiac dysfunction. This guideline integrates both objectives of this thesis by summarizing evidence about late adverse effects of childhood cancer treatment and about optimal care for survivors at risk of late effects.

## **Part III. General discussion**

**Chapter 9** summarizes the main findings, conclusions, strengths and limitations of the studies in this thesis and provides recommendations for future studies within the field of childhood cancer survivorship research and for clinical practice in childhood cancer survivor care.

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