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ARTICLE

Fertility studies in female childhood cancer survivors: selecting appropriate comparison groups

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Abstract Little information is available on the use of appropriate comparison groups for studies investigating late effects of childhood cancer. Two comparison groups in a nationwide study on reproductive function and ovarian reserve in female childhood cancer survivors were recruited (The Dutch Childhood Oncology Group Long-Term Effects After Childhood Cancer Cohort Study).

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Experiences of this process are reported. Two types of comparison groups were used: sisters of participating survivors and controls from the general population. A total of 352 out of 580 (61%) of the participating survivors who had a sister gave permission to invite them for the study. The participation rate of sisters was much higher than control participants from the general population (74% versus 21%, respectively), whereas considerably more effort was involved in recruiting controls from the general population. Participants in this group were significantly older and more highly educated than sister controls ($P < 0.001$ for both groups). No significant differences were observed between both types of comparison groups in several fertility-related characteristics, suggesting minimal bias owing to selective participation. Researchers setting up a study to investigate late effects among survivors of childhood cancer should carefully consider the advantages and disadvantages of using various types of comparison groups.

KEYWORDS: childhood cancer survivors, comparison groups controls, female fertility, late effects

Introduction

Over the past 40 years, advances in diagnosis and treatment have substantially improved survival of most childhood and adolescent cancers, resulting in overall 5-year survival rates of over 80% in Europe (Gatta et al., 2009) as well as in the USA (Howlader et al., 2013). As a result, the population of young adult survivors of childhood cancer is rapidly growing. Cancer treatment during childhood, however, can induce complications, which may not become apparent until many years later. These treatment-related late effects include secondary neoplasms, cardiac dysfunction, reduced growth, sub- or infertility, impaired cognitive function, psychosocial problems, and a reduced quality of life (Bhatia and Landier, 2005; Geenen et al., 2007; Oeffinger et al., 2006).

In the past decades, many studies have been conducted to assess the long-term adverse effects of treatment in childhood cancer survivors or evaluate screening and surveillance programmes for this group of patients. Study designs typically included retrospective cohort studies (nested), case-control studies or cross-sectional studies (Oeffinger et al., 2011; Robison, 1996). Moreover, the occurrence of adverse events among childhood cancer survivors has been contrasted to different comparison groups. Typical comparison groups that have been used in late-effect studies include individuals who were not treated for cancer during childhood (e.g. siblings or individuals recruited from the general population) or childhood cancer survivors who were not exposed to a certain type of treatment. In addition, data from childhood cancer survivors (CCSs) have been compared with readily available international and or national population norms.

Several reports of late-effect studies have extensively described the study design, as well as the procedures for participant recruitment and data collection (Hawkins et al., 2008; Hudson et al., 2011; McBride et al., 2010; Robison et al., 2002, 2009; Shaw et al., 2004). Also, methodological issues or pitfalls regarding these studies have been summarized (Hawkins and Robison, 2006; Leisenring et al., 2009; Lund et al., 2011; Murphy, 2003; Ness et al., 2009; Oeffinger et al., 2011; Robison, 1996). A frequently reported limitation of late-effect studies is the lack of appropriate comparison groups (Leisenring et al., 2009; Murphy, 2003). To date, however, no published reports have comprehensively summarized the advantages, disadvantages and experiences regarding recruiting different types of comparison groups. Deciding on the type, size, and number of comparison groups, as well as on the procedure for recruiting the control subjects is an important and difficult task when setting up a study.

In the Netherlands The Dutch Childhood Oncology Group Long-Term Effects After Childhood Cancer Cohort Study (DCOG LATER-VEVO) study is being conducted, which is a nationwide study on reproductive function, ovarian reserve, and premature menopause in female childhood cancer survivors (Overbeek et al., 2012). Several types of comparison groups were used in this study, and it provides an ideal opportunity to reflect on which comparison group seems most appropriate when conducting such a study. In this report, the advantages and disadvantages of using different types of comparison groups are reported through the experience of recruiting of participants for comparison groups for the DCOG LATER-VEVO study.

Materials and methods

Design of the DCOG LATER-VEVO study

The DCOG LATER-VEVO study began in the Netherlands in 2006 as a nationwide retrospective cohort study evaluating the effects of cancer treatment on reproductive function, ovarian reserve and risk of premature menopause in female childhood cancer survivors. The study design and cohort characteristics have been described previously (Overbeek et al., 2012). The study consists of three parts: a questionnaire; blood sampling for serum hormone levels; and a transvaginal ultrasound measurement of the reproductive organs. All eligible participants from a cohort of 5-year survivors treated for childhood cancer between 1963 and 2002 were invited to attend at one of the seven Dutch paediatric oncology and stem cell transplant centres, collectively known as DCOG LATER cohort. For the DCOG LATER-VEVO study, the eligible cohort consists of 1860 female childhood cancer survivors. Data collection is still ongoing. The study was approved by the Medical Ethical Committee of VU University Medical Center Amsterdam (reference number 2006/249; approved 4 January, 2007), and informed consent was obtained from all participants.

Comparison groups in the study

Initially, only sisters of participating childhood cancer survivors were invited to participate in the comparison group of the DCOG LATER-VEVO study. For the main outcomes of this study, sisters were primarily considered the most appropriate comparison group as they broadly share the same genetic and socio-demographic background, variables that might