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The influence of genetic variation on late toxicities in childhood cancer survivors: A review

E. Clemens[a,b,*,1], A.L.F. van der Kooi[a,b,c,1], L. Broer[d], E. van Dulmen-den Broeder[e], H. Visscher[b,f,g], L. Kremer[b,i], W. Tissing[j], J. Loonen[h], C.M. Ronckers[b,i], S.M.F. Pluijm[a,b], S.J.C.M.M. Neggers[a,k], O. Zolk[l], T. Langer[m], A. am Zehnhoff-Dinnesen[n], C.L. Wilson[o], M.M. Hudson[o], B. Carleton[p], J.S.E. Laven[c], A.G. Uitterlinden[d], M.M. van den Heuvel-Eibrink[b]

[a] Department of Pediatric Hematology and Oncology, Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands
[b] Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands
[c] Department of Gynecology, Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands
[d] Department of Internal Medicine, Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands
[e] Department of Pediatric Hematology and Oncology, VU Medical Center, Amsterdam, The Netherlands
[f] Department of Pediatrics, Radboud University Medical Center, Nijmegen, The Netherlands
[g] Department of Pediatrics, Antwerp University Hospital, Antwerp, Belgium
[h] Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands
[i] Department of Pediatrics, Academic Medical Center – Emma Children's Hospital, Amsterdam, The Netherlands
[j] Department of Pediatric Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[k] Department of Medicine, Section endocrinology, Erasmus MC, Rotterdam, The Netherlands
[l] Institute of Pharmacology of Natural Products and Clinical Pharmacology, University Hospital Ulm, Germany
[m] Pediatric Oncology, University Hospital for Children and Adolescents, Lübeck, Germany
[n] Department of Phoniatrics and Pedaudiology, University of Münster, Münster, Germany
[o] Department of Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA
[p] BC Children's Hospital, Vancouver, Canada

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ABSTRACT

Introduction: The variability in late toxicities among childhood cancer survivors (CCS) is only partially explained by treatment and baseline patient characteristics. Inter-individual variability in the association between treatment exposure and risk of late toxicity suggests that genetic variation possibly modifies this association. We reviewed the available literature on genetic susceptibility of late toxicity after childhood cancer treatment related to components of metabolic syndrome, bone mineral density, gonadal impairment and hearing impairment.

Methods: A systematic literature search was performed, using Embase, Cochrane Library, Google Scholar, MEDLINE, and Web of Science databases. Eligible publications included all English language reports of candidate gene studies and genome wide association studies (GWAS) that aimed to identify genetic risk factors associated with the four late toxicities, defined as toxicity present after end of treatment.

Results: Twenty-seven articles were identified, including 26 candidate gene studies: metabolic syndrome (n = 6); BMD (n = 6); gonadal impairment (n = 2); hearing impairment (n = 12) and one GWAS (metabolic syndrome). Eighty percent of the genetic studies on late toxicity after childhood cancer had relatively small sample sizes (n < 200), leading to insufficient power, and lacked adjustment for multiple comparisons. Only four (4/26 = 15%) candidate gene studies had their findings validated in independent replication cohorts as part of their own report.

Conclusion: Genetic susceptibility associations are not consistent or not replicated and therefore, currently no evidence-based recommendations can be made for hearing impairment, gonadal impairment, bone mineral

* Corresponding author at: Erasmus MC – Sophia Children's Hospital, Department of Pediatric Hematology and Oncology, Room NA-1724, Wytemaweg 80, 3015 CN Rotterdam, The Netherlands.
E-mail address: e.clemens@erasmusmc.nl (E. Clemens).
[1] Both authors contributed equally.

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density impairment and metabolic syndrome in CCS. To advance knowledge related to genetic variation influencing late toxicities among CCS, future studies need adequate power, independent cohorts for replication, harmonization of disease outcomes and sample collections, and (international) collaboration.

1. Introduction

Survival rates after childhood cancer now approach 80% in developed countries as a result of enhanced stratification, more effective treatment and optimized supportive care (Gatta et al., 2014). The increasing number of childhood cancer survivors (CCS) has led to the growing awareness of chronic health effects resulting from treatment for childhood cancer (Geenen et al., 2007; Oeffinger et al., 2006). Examples of long-term consequences include hearing impairment, gonadal impairment and cardiotoxicity. The inter-individual variability in the number and magnitude of health problems in similarly treated CCS suggests that genetic variation modifies the association between treatment and risk of late toxicity.

To identify such genetic variants two common approaches have been applied: a candidate gene approach, and more recently, the genome wide association study (GWAS) approach. Candidate gene studies focus on associations between genetic variation within prespecified genes of interest and specific outcomes, while GWASs are hypothesis-free searches that can identify novel single-nucleotide polymorphisms (SNPs) that potentially modify the risk of a late toxicity.

After completion of the Human Genome Project (HGP) (HumanGenomeProject, 2015) in 2003 and the International HapMap project, GWASs have discovered many thousands of genetic variants associated with a variety of diseases (EMBL-EBI, 2017), which catalyzed research on genetic variation underlying late toxicity among cancer survivors (MacArthur et al., 2017). Except for cardiotoxicity (Aminkeng et al., 2016a), the resulting number of genetic variation studies in CCS have not produced unambiguous evidence in this field. The lack of strong evidence has impeded translation into clinical practice, such as patient counseling or dose-reduction trials. In contrast, genotyping of childhood cancer patients in order to risk-adapt treatment based on risk models predicting susceptibility to specific toxicities is expected to become standard of care. A comprehensive review of genetic aspects of acute toxicity was recently published (Mapes et al., 2017). However, a recent overview of genetic susceptibility studies concerning late toxicities in CCS is not yet available.

An international collaboration is currently working on the identification of genetic determinants associated with hearing impairment and female gonadal impairment, in a large cohort of CCS (European Union's Seventh Framework programme project PanCareLIFE). In the current study, we summarize the results of a systematic literature search and evaluate the results and quality of available literature on genetic susceptibility of these two late toxicities (hearing impairment and female gonadal impairment) and three hormone-related late toxicities (male

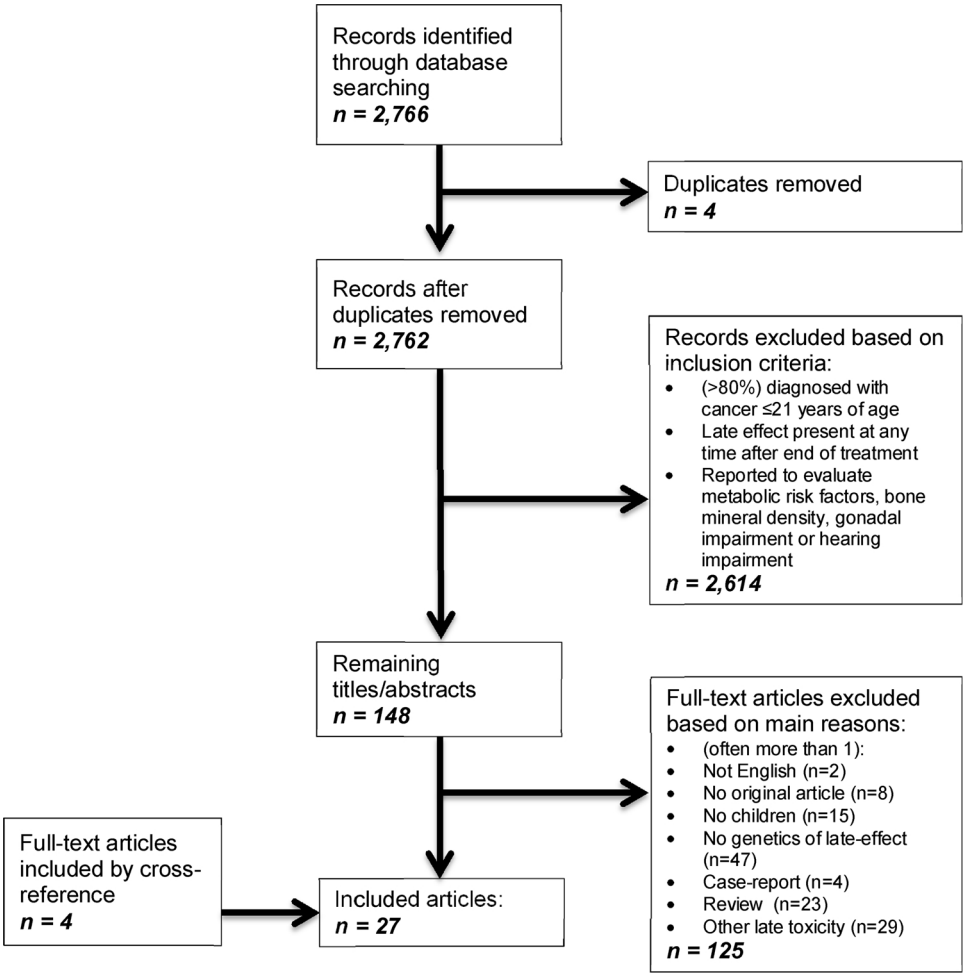

Fig. 1. Flowchart study selection process Review Genetics of Late Effects.