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Original Research

Single-nucleotide polymorphism in the 5-α-reductase gene (*SRD5A2*) is associated with increased prevalence of metabolic syndrome in chemotherapy-treated testicular cancer survivors☆

Hink Boer [a], Nico-Derk L. Westerink [a], Renske Altena [a], Janine Nuver [a], D.A. Janneke Dijck-Brouwer [b], Martijn van Faassen [b], Frank Klont [b], Ido P. Kema [b], Joop D. Lefrandt [c], Nynke Zwart [a], H.Marike Boezen [d], Andries J. Smit [c], Coby Meijer [a], Jourik A. Gietema [a,*]

[a] *Medical Oncology, University Medical Center Groningen, University of Groningen, The Netherlands*
[b] *Laboratory Medicine, University Medical Center Groningen, University of Groningen, The Netherlands*
[c] *Vascular Medicine, University Medical Center Groningen, University of Groningen, The Netherlands*
[d] *Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands*

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Abstract ***Purpose:*** Chemotherapy-treated testicular cancer survivors are at risk for development of the metabolic syndrome, especially in case of decreased androgen levels. Polymorphisms in the gene encoding steroid 5-α-reductase type II (*SRD5A2*) are involved in altered androgen metabolism. We investigated whether single-nucleotide polymorphisms (SNPs) rs523349 (V89L) and rs9282858 (A49T) in *SRD5A2* are associated with cardiometabolic status in testicular cancer survivors.

Methods: In 173 chemotherapy-treated testicular cancer survivors, hormone levels and cardiometabolic status were evaluated cross-sectionally (median 5 years [range 3–20] after chemotherapy) and correlated with SNPs in *SRD5A2*.

Results: The metabolic syndrome was more prevalent in survivors who were homozygous or heterozygous variant for *SRD5A2* rs523349 compared to wild type (33% versus 19%, $P = 0.032$). In particular, patients with lower testosterone levels (<15 nmol/l) and a variant genotype showed a high prevalence of the metabolic syndrome (66.7%). Mean intima-media thickness of the carotid artery and urinary albumin excretion, both markers of vascular

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* *Corresponding author:* Department of Medical Oncology, University of Groningen, University Medical Center Groningen, P.O. Box 30 001, 9700 RB Groningen, The Netherlands. Tel.: +31 50 361 28 21; fax: +31 59 3614862.
E-mail address: j.a.gietema@umcg.nl (J.A. Gietema).

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damage, were higher in the group of survivors homozygous or heterozygous variant for rs523349 (0.62 versus 0.57 mm, $P = 0.026$; 5.6 versus 3.1 mg/24 h, $P = 0.017$, respectively). No association was found between cardiometabolic status and SNP rs9282858 in *SRD5A2*.
Conclusion: Metabolic syndrome develops more frequently in testicular cancer survivors homozygous or heterozygous variant for SNP rs523349 in *SRD5A2*. Altered androgen sensitivity appears to be involved in the development of adverse metabolic and vascular changes in testicular cancer survivors and is a target for intervention.

1. Introduction

Since the introduction of platinum-based chemotherapy, metastatic testicular cancer has become a curable disease and most testicular cancer patients have an excellent prognosis. However, long-term toxicity can undermine life after treatment of testicular cancer [1,2]. Cardiovascular disease, e.g. myocardial infarction, is more prevalent in testicular cancer survivors in comparison with age-matched controls [3,4]. Several studies have shown that testicular cancer survivors are prone to develop cardiovascular risk factors, often clustered in the metabolic syndrome, following orchidectomy and platinum-based chemotherapy [5–8].

The metabolic syndrome comprises central obesity, dyslipidemia, hypertension and insulin resistance. Due to its pre-diabetic and pro-atherogenic characteristics, the metabolic syndrome forms a seedbed for cardiovascular disease. Studies in the general population have shown that low levels of testosterone are associated with metabolic syndrome [9,10]. The relationship is probably bi-directional. On one hand, an increase in adipose tissue enhances aromatization of testosterone, thereby contributing to hypogonadism. On the other hand, testosterone and its more potent metabolite dihydrotestosterone have several regulatory functions in adipose tissue and lower levels of androgens may lead to adverse metabolic changes, such as central obesity and insulin resistance [11,12]. Testosterone is also a vasoactive hormone, as well as a regulating factor in glucose and lipid metabolism [13–15].

Subclinical hypogonadism appears to be a prominent risk factor for the metabolic syndrome in testicular cancer survivors [16]. A substantial proportion of testicular cancer survivors have a deteriorated gonadal function after chemotherapy that may persist for >10 years [17,18]. It is difficult to predict which cancer survivors would benefit from testosterone supplementation. In a recent study by Finkelstein *et al.* in which 198 healthy men received different amounts of testosterone, the authors concluded that the amount of testosterone required for maintaining lean mass, fat mass, strength, and sexual function varied widely in men and argued that more personalized approaches for treating hypogonadism are needed [19].

Genetic variations that result in functional changes in androgenic enzymes may explain why some patients are more at risk for hormonal or metabolic changes and may help identify patients that are more likely to benefit from interventions, like testosterone supplementation therapy. In a recent study by Aschim *et al.*, it was shown that polymorphisms in genes involved in androgen metabolism may partially explain inter-individual differences in gonadal toxicity in testicular cancer survivors [20].

Functional single-nucleotide polymorphisms (SNPs) in steroid 5-α-reductase type II (*SRD5A2*) result in variations in enzymatic activity of 5-α-reductase type II, affecting the conversion of testosterone into dihydrotestosterone [21]. We investigated whether SNPs rs523349 (V89L) and rs9282858 (A49T) in *SRD5A2* are associated with cardiometabolic status in testicular cancer survivors.

2. Patients and methods

2.1. Study population

Patients belonged to a cohort of long-term survivors of metastatic non-seminomatous testicular cancer treated between 1977 and 2004 with platinum-based chemotherapy at University Medical Center Groningen [7]. The study population consisted of 173 patients (Fig. 1). Inclusion criteria were attained age <60 years and a follow-up duration of minimum 3 years and maximum 20 years. Because our aim was to investigate newly developed cardiovascular risk factors after therapy, exclusion criteria were history of cardiac disease (defined as myocardial infarction or coronary artery disease before or after chemotherapy) and radiotherapy to the mediastinum. Participants of a previous study on cardiovascular risk profiles in testicular cancer survivors were also excluded to prevent overlap among cohorts [22]. The local medical ethics committee approved the study and all participants gave written informed consent.