Comment on ‘Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors’

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Willemse et al (2013) recently reported their results regarding prevalence of metabolic syndrome and risk of cardiovascular disease (CVD) in survivors of testicular cancer who were treated with chemotherapy. This topic has particular relevance as cure rates are increasing across all cancer types due to increase in uptake of screening, better imaging modalities and effective treatments. However, we have certain reservations regarding the data presented and the conclusions drawn by the authors.

The authors do not report on the number of survivors who were on antihypertensive, lipid modifying and antidiabetic medication and whether those who were on these medications were excluded from the analysis in calculating the 10-year risk for CVD using the Framingham Risk Score (FRS) and Systemic Coronary Risk Examination (SCORE) predictive models. We assume that none of the controls were on cardiac-modifying drugs as the authors’ state that controls were healthy men who were screened for CVD. If survivors on cardiac-modifying drugs were included in calculating the 10-year CVD risk, then there is a distinct possibility of diluting the calculated risk.

Furthermore, it appears rather contradictory that despite robust evidence that metabolic syndrome predisposes individuals to a nearly twofold risk of CVD (Gami et al, 2007), the results in the study do not support this. This may be explained by the small number of patients in the study (the authors do not describe any calculations as to how the study was powered) and also by the fact that actuarial analysis suggest that the risk of CVD in testicular cancer survivors only becomes apparent after 10 years or so (Huddart et al, 2003).

Additionally, the accuracy of risk prediction models such as FRS and SCORE in the younger population is debatable (Berry et al, 2007; Cavanaugh-Hussey et al, 2008; Cooney et al, 2010). Both FRS and SCORE models place emphasis on age to predict risk. Thus, notwithstanding their risk profile all young individuals will have a low absolute risk of CVD.

Perhaps a more pertinent analysis would be to derive lifetime risk rather than a 10-year risk for this cohort of survivors, as majority of these survivors are <40 years of age at the completion of their treatment and the risk of CVD is most manifest beyond 50 years of age. Another option, which could be recommended for counselling survivors regarding the risk of CVD in survivorship clinics, would be the use of relative risk charts to predict risk (Graham et al, 2007).

In the discussion section, the authors state that ‘most of the GCT survivors have long-term partial or complete hypogonadism’. There is conclusive evidence that demonstrates that approximately only 12–16% of survivors have complete hypogonadism (Huddart et al, 2005), the severity of which is expectedly associated with increased treatment burden, particularly chemotherapy. Three studies in GCT survivors (Nuver et al, 2005; Haugnes et al, 2007; de Haas et al, 2013) have previously demonstrated the association of hypogonadism and metabolic syndrome. Though we agree with the authors that follow-up guidelines should include assessment of lipid profile, blood pressure and gonadal function (van As et al, 2008), there is currently no evidence to support testosterone supplementation in those with testosterone levels in the lower range of normal. In the United Kingdom, we are currently recruiting patients into a double blind multi-centre placebo controlled trial (TRYMS) to assess the feasibility and effectiveness of testosterone replacement in those survivors who have a low-normal testosterone (7–12 nmol l⁻¹).

In conclusion, we acknowledge that the study by Willemse et al (2013) is topical and corroborates previous studies; however, we feel the authors’ conclusion regarding cardiovascular risk is misleading. Large-scale longitudinal cohort studies of survivors, who are at high risk, are needed to accurately ascertain cardiovascular risk.

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We read with interest the Letter to the Editor by Singhera and Huddart (2013) and are pleased to respond to their comments. Regarding their comments on missing data, the median follow-up time after completing treatment seems to have escaped their attention, as it was provided for all survivors and for separate treatment groups in Table 2 of our published article (Willemsen et al, 2013).

We indeed had omitted to report on the actual number of survivors on antihypertensive, lipid modifying and/or antidiabetic medication had a Framingham Risk Score (FRS) and Systemic representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil 14(suppl 2): S1–S113. Haugnes HS, Aas N, Fossa SD, Dahl O, Klepp O, Wist EA, Svarthberg J, Wilsgraadt T, Brennes RM (2007) Components of metabolic syndrome in long-term survivors of testicular cancer. Ann Oncol 18: 241–248. Huddart RA, Norman A, Moynihan C, Horwich A, Parker C, Nicholls E, Dearnaley DP (2005) Fertility, gonadal and sexual function in survivors of testicular cancer. Br J Cancer 93: 200–207. Huddart RA, Norman A, Shahidi M, Horwich A, Coward D, Nicholls I, Dearnaley DP (2003) Cardiovascular disease as a long-term complication of treatment of testicular cancer. J Clin Oncol 21: 1513–1523. Nuvé, Smit AJ, Wolffenbuttel BHR, Sluiter J, Hoekstra HJ, Sleijfer DT, Gietema JA (2005) The metabolic syndrome and disturbances in hormone levels in long-term survivors of disseminated testicular cancer. J Clin Oncol 23: 3718–3725. van As NJ, Gilbert DC, Money-Kyrle J, Bloomfield D, Breeley S, Dearnaley DP, Horwich A, Huddart RA (2008) Evidence-based pragmatic guidelines for follow-up of testicular cancer: optimising the detection of relapse. Br J Cancer 98: 1894–1902. Willemsen PM, Burggraaf J, Hamdy NAT, Weijl NL, Vossen CY, van Wulfen L, van Steijn-van Tol AQMJ, Rosendaal FR, Osanto S (2013) Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors. Br J Cancer 109: 60–67.