

## Comment on: 'Subgroup effects in a randomized trial of different types and doses of exercise during breast cancer chemotherapy'

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Sir,

Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting adverse event of frequently used chemotherapeutic agents and it can negatively influence cancer survivors' quality of life (Mols *et al*, 2013). Despite multiple studies, there is still no consensus on the prevention or treatment of CIPN with a pharmaceutical approach (Hershman *et al*, 2014). Non-pharmacologic interventions are not considered in the recent guideline (Hershman *et al*, 2014). However, in our opinion non-pharmacological interventions, like rehabilitation, are promising in preventing and treating CIPN, especially since they can easily be incorporated in daily clinical care. For that reason, we read your recent publication from Courneya *et al* (2014) concerning the different types and doses of exercise during breast cancer chemotherapy with a great interest.

Nowadays in the Netherlands, patients can participate in cancer rehabilitation programs, which have demonstrated physiological and psychological benefits in the majority of studies (Galvao and Newton, 2005; Courneya *et al*, 2013). To our knowledge, these studies have not investigated the effect of rehabilitation on typical CIPN problems like balance, coordination and muscle strength in subgroups of cancer patients with CIPN. However, rehabilitation programs have already shown to be effective in patients with diabetic peripheral neuropathy (Balducci *et al*, 2006). The study of Courneya *et al* (2014) therefore is important as it showed that healthy-weight younger premenopausal women who underwent high-dose exercise interventions during breast cancer treatment reported less taxane/neuropathy symptoms. Nevertheless, as specific symptoms of CIPN and muscle strength were not main outcomes, the severity and the differences in exercise efficacy between patients with and without CIPN and the influence of received chemotherapy on these symptoms were not reported.

However, we carried out a retrospective analysis on differences in muscle strength among the 231 women participating in rehabilitation programs and investigated differences between patients who received neurotoxic ( $n = 173$ ) or non-neurotoxic ( $n = 58$ ) chemotherapy. This study showed a trend of lower muscle strength in those receiving neurotoxic chemotherapy (Table 1). The earlier analysis of Courneya *et al* (2008) also showed that taxane treated patients had less muscle strength after exercise treatment. Therefore, this emphasizes that it is important to take chemotherapy

protocols into account when investigating rehabilitation, as patients who received neurotoxic chemotherapy are a specific subgroup of patients and need to be identified. In addition to this, we are planning a prospective study to investigate the efficacy of different-intensity rehabilitation programs in the specific subgroup of patients with CIPN and the impact of sport and exercise on the development of symptoms of CIPN.

In addition, it should be mentioned that the development of a valid tool that assesses the extent and severity of CIPN is necessary in order to compare intervention studies and draw firm conclusions on their results. However, there is currently no consensus on which factors (e.g., subjective or objective measurements) are the most important in determining clinical severity of neuropathy, as clinicians tend to underreport CIPN and objective measurements do not always correspond with patient-reported outcomes (Cavaletti *et al*, 2010). Therefore, it is also necessary to take into account the differences in objective, clinician- and patient-reported outcomes when developing such a tool.

CIPN is becoming a major survivorship issue, especially because prevention and treatment of CIPN remains difficult and pharmacological interventions did not prove to be beneficial (Hershman *et al*, 2014). In our opinion, non-pharmacological interventions, like rehabilitation, which can easily be incorporated into daily clinical care, are promising in preventing and treating CIPN. Therefore, we believe that studies investigating the rehabilitation modalities in patients with CIPN are warranted and should be encouraged. In addition, future research should be aimed at reaching consensus in the assessment of CIPN.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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**Table 1. Comparison of muscle strength<sup>a</sup> between women who received non-neurotoxic chemotherapy vs neurotoxic chemotherapy ( $n = 231$ )**

|                                       | Chemotherapeutic agent      |                        | P-value |
|---------------------------------------|-----------------------------|------------------------|---------|
|                                       | Not neurotoxic<br>$n = 173$ | Neurotoxic<br>$n = 58$ |         |
|                                       | Mean rank                   | Mean rank              |         |
| Vertical row (1-RM kg <sup>-1</sup> ) | 112.4                       | 105.2                  | 0.463   |
| Leg press (1-RM kg <sup>-1</sup> )    | 115.2                       | 110.4                  | 0.629   |
| Chest press (1-RM kg <sup>-1</sup> )  | 75.5                        | 58.9                   | 0.087   |
| Pull over (1-RM kg <sup>-1</sup> )    | 33.2                        | 33.8                   | 0.913   |
| Fly (1-RM kg <sup>-1</sup> )          | 74.3                        | 53.3                   | 0.026   |
| Lunge (1-RM kg <sup>-1</sup> )        | 98.0                        | 91.4                   | 0.491   |

<sup>a</sup>Muscle strength was measured with the 'one-repetition maximum' (1-RM), which means the maximal weight that a person can replace at one-repetition.

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