Reply to “Phase II prospective randomized trial of weight loss prior to radical prostatectomy”

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We commend Henning et al. [1] and their randomized controlled trial of a weight loss intervention (WLI) among prostate cancer patients in the presurgical setting. Abbreviated study periods and complicated logistics make these trials challenging. We speak from experience, since we completed a trial of similar design [2–4]. While Henning et al. discussed our trial [1–3], our findings were not presented, possibly due to publication overlap [4]. Both trials were undertaken with the same scientific premise: weight loss would slow tumor proliferation and reduce biomarkers of insulin signaling, inflammation, and androgenic control. Thus, we submit this letter to compare and contrast these two pioneering efforts.

Both trials employed open label, 2-arm randomized controlled designs in which participants were assigned to a WLI or wait-list control. Henning et al. [1] prescribed a structured diet plan of 1200 or 1500 kcal/day that utilized meal replacements and 1 h/day of aerobic, resistance training, and stretching exercises. In our trial [2, 4], men were counseled to achieve dietary deficits of 1000 kcal/day and 250 kcal/day of aerobic exercise.

Henning et al. [1] stopped accrual early; 44 participants were enrolled and 34 (18 controls/16 WLI) completed. Our accrual target of 40 was achieved, and we had 34 trial completers (16 controls/18 WLI) [4]. Samples were similar, with men of mean age 60–63, body mass indexes of 30–33, and ~30% African-Americans. Inclusion/exclusion criteria were comparable, though Henning et al. [1] excluded men with diabetes (diabetics comprised 25% of our sample) [2]; mean days on intervention was 51 vs. 47 days, respectively.

While our study period was shorter [4], our WLI group lost 4.7 vs. 3.7 kg [1]. Both trials experienced “drop-in”; our controls lost 2.2 kg and the Henning et al. controls lost 1.6 kg [1, 4]. Both trials found significant, yet dissimilar, between-arm differences in biomarkers. Henning et al. [1] reported significantly reduced triglycerides, LDL-cholesterol, and insulin with the WLI (but, no differences in leptin, total testosterone, sex hormone binding globulin [SHBG], and cytokines), whereas we found significant reductions in leptin and increases in total testosterone and SHBG, and also no differences in cytokines or insulin [4]. Neither trial reported between-arm differences in prostate-specific antigen [1, 4].

Importantly, neither trial observed lower proliferation rates with the WLI that were hypothesized [1]. Figure 3 of Henning et al. [1] shows Ki67 as ~7% in the WLI vs. ~6% among controls, though no significant differences were found using independent t-tests. We found significantly higher Ki67 in the WLI vs. controls using similar statistical tests (unpublished), and non-parametric tests on pre-/post-paired data (since we also had biopsy data). Therefore, unlike Henning et al. we hesitate to support the statement, “future more intensive weight loss interventions trials are warranted”, since this preliminary evidence suggests that rapid weight loss may incite greater, rather than reduced proliferation, and our tumor gene expression data suggest upregulation of several genes associated with increased transcription, proliferation, and migration. More investigation is needed, but instead we advocate for studies that will
provide a better understanding of the optimal rate of weight loss, and the role of physical activity in influencing tumor biology.

Compliance with ethical standards

Conflict of interest While none of the following relationships affect the content of this letter, in the spirit of full disclosure, we acknowledge the following: SR-B (Philips/InVivo Corp.: Advisor); ESY (Bayer, Inc.: Advisor/Nanostring Technologies: Honoraria/Lilly, Inc. and Abbvie, Inc. Research Funding); WEG (TEVA and Amgen; Stock Ownership/Bristol-Myers Squibb: Advisor, Honoraria and Travel).

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