

## AUTHOR'S REPLY

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We would like to thank you for your constructive comments on our study and for providing us with an opportunity to further discuss the effect of obesity and Diabetes Mellitus type II (DMII) on aggressive prostate cancer (PCa) at initial diagnosis.

As mentioned in the editorial comment, in our retrospective study we demonstrated that obesity was significantly associated with aggressive PCa and inversely related to non-aggressive PCa. Nevertheless, the relationship between obesity and PCa or DMII and PCa, particularly for tumor aggressiveness, remains still a matter of debate with conflicting epidemiologic data.

Furthermore, given that obesity is a factor for the development of both DM and high-grade PCa, we investigated whether the association between DMII and high-grade disease varied according to obesity. In our Italian cohort study we demonstrated that at initial diagnosis of PCa DMII was significantly linked with high-grade PCa, but only in obese men, with a fourfold higher aggressive PCa risk (OR 4.17). In non-obese men, no association was noted between DMII and PCa, irrespective of grade, suggesting that the effect of DMII on PCa is modified by obesity and dependent of BMI. Moreover, recently Wu et al. showed that DM was related to higher metastasis risk in obese PCa patients but not in non-obese men [1]. Likewise, Hsieh et al. showed that the obese diabetic

patients had higher mortality than did the obese non diabetic patients [2].

The observation of increased aggressive PCa in patients with obesity and DMII could be associated to different biological mechanisms as metabolic imbalance (particularly impaired glucose regulation), hormonal alterations (e.g lower androgens and higher estrogens levels), altered growth factors (e.g increased IGF, reduced IGFBP), chronic inflammation (e.g increased TNF $\alpha$ , IL-6 etc.) and oxidative stress [3, 4, 5]. These changes may contribute significantly to cancer progression via promoting tumor proliferation and survival, reduced tumor apoptosis, increased angiogenesis and invasion, de novo intra-tumoral steroidogenesis with transition to androgen independence.

In light of the high rate of obesity and DMII in western countries it is imperative for physicians to understand these relationships with PCa, to identify modifiable risk factors at initial diagnosis of cancer and to give a multidisciplinary diagnostic and therapeutic approach. The treatment of metabolic dysregulation, hormonal alterations and inflammation as well as diet, exercise, and lifestyle change assistance should be carefully considered in such patients. Lifestyle modification intervention and particularly weight loss, physical activity, a balanced diet may prevent disease progression and improve disease specific quality of life.

## References

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