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The Impact of Diabetes and Other Metabolic Disorders on Prostate Cancer Prognosis

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ABSTRACT

Aims: To investigate the impact of diabetes mellitus (DM) and other metabolic disorders on the survival of men with prostate cancer (PCa).
Methods: We conducted a retrospective cohort-study based on 715 men with PCa, originally enrolled in an Italian case-control study between 1995 and 2002. Anthropometric measures, self-reported medical conditions, and Gleason score were assessed at enrollment. Adjusted hazard ratios (HRs) of death, with 95% confidence intervals (95% CIs), were estimated using Fine and Gray's regression model.
Results: After a median follow-up of 11.6 years, 244 (34.1%) deaths occurred, 77 (31.6%) due to PCa. Excess mortality from all causes was reported in PCa patients with DM (HR = 1.56, 95% CI: 1.03–2.36), which increased to 1.76 (95% CI: 0.99–3.13) when at least two out of three metabolic disorders (i.e., waist circumference ≥102 cm, drug-treated hypertension, and hypercholesterolemia) were additionally present. The impact of metabolic disorders was stronger on non-PCa-specific mortality with HRs equal to 2.21 (95% CI: 1.38–3.54) for DM, 1.45 (95% CI: 0.97–2.19) for waist circumference ≥102 cm, and 1.63 (95% CI: 1.19–2.22) for drug-treated hypertension.
Conclusions: DM and other metabolic disorders unfavorably affected the survival of PCa patients, mainly impacting on the risk of death from causes other than PCa.

1. Introduction

Since the introduction of prostate-specific antigen (PSA) testing in the 1990s, prostate cancer (PCa) incidence rates steadily increased to become the most frequent male cancer in high-income countries (Ferlay et al., 2013). The prognosis of PCa is generally favorable because of the predominance of positive factors at diagnosis (*e.g.*, low Gleason score, reduced tumor size, non-metastatic disease), leading to a growing number of men living with PCa (Bray, Ren, Masuyer, & Ferlay, 2013). Therefore, the identification of modifiable lifestyle factors that could impact the prognosis of PCa in the long-term is of great importance.

Several studies have investigated the role of diabetes mellitus (DM) and other specific metabolic disorders, suggesting independent effects of these conditions on the risk of death of men with PCa (Cai, Xu, Xu, Yu, & Zou, 2014; Hammarsten & Högstedt, 2005; Ma et al., 2008). However, the existing evidence is mainly focused on PCa-specific death risk, i.e., when PCa is considered the underlying cause of death. Information on mortality from all causes and, in particular, on deaths not due to PCa (non-PCa-specific deaths) is also of importance in view of a comprehensive management of PCa patients. Indeed, PCa patients with long follow-up time, and thus increasing age, are expected to increasingly die from causes other than PCa (Chowdhury et al., 2013).

Although metabolic conditions often occur together, few studies — mainly derived from small series of PCa patients — have evaluated the survival of PCa patients in relation with metabolic syndrome (MetS), *i.e.*, a cluster of conditions such as abdominal obesity, DM, elevated blood pressure, and hypercholesterolemia (Flanagan et al., 2011; Hammarsten & Högstedt, 2005).

This study aimed to investigate the impact of both specific metabolic disorders and MetS on long-term survival after PCa diagnosis, focusing on the risk of PCa-specific and non-PCa-specific death.

2. Materials and Methods

A retrospective cohort-study was conducted on men with PCa originally enrolled as cases in a multicentre hospital-based case–control

Conflict of interest: None to declare.

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study, carried out in Italy to explore the associations between lifestyle factors and PCa onset (Dal Maso et al., 2004; Polesel et al., 2015). Briefly, 780 patients with histologically confirmed PCa diagnosed at the age of 46–74 years had been enrolled between 1995 and 2002 in the Pordenone area, Northeastern Italy. PCa cases were consecutive patients newly identified in major local hospitals (where most of the patients with PCa are referred to for diagnosis and treatment), without previous cancer diagnosis at any site, and who did not undergo cancer treatments before enrollment. Sixty-five patients without information on waist circumference were excluded, thus leaving 715 PCa patients eligible for the present analysis. All cases signed an informed consent, according to the recommendations of the Board of Ethics, which approved the original study protocol and the prospective extension.

Cases were interviewed during their hospital stay by trained nurses, using a structured questionnaire to assess information on socio-demographic characteristics and lifestyle factors (e.g., education, physical activity, tobacco smoking and alcohol drinking habits, family history of cancer, and a food-frequency section on usual diet in the two years prior to diagnosis). Data on self-reported height and weight one year prior to diagnosis were also collected to compute the body mass index (BMI, i.e., weight divided by squared height kg/m^2). The interviewers measured the circumference of the waist (2 cm above the umbilicus). Information on clinical diagnosis of medical conditions including DM, drug-treated hypertension, and hypercholesterolemia was self-reported and included age at diagnosis. Other diseases that occurred less than one year before PCa diagnosis were not considered in the present analysis. No PCa patients were diagnosed with DM in the year preceding cancer onset.

Since metabolic disorders (e.g., DM and obesity) are often inter-correlated, we have further evaluated the cumulative impact on survival through the MetS indicator. MetS was determined, according to the criteria established in the 2009 joint interim statement by various scientific associations (Alberti et al., 2009), as the presence of at least three of the following conditions: DM, waist circumference ≥102 cm, drug-treated hypertension (as a proxy of elevated blood pressure), and hypercholesterolemia. Satisfactory reproducibility and validity of the questionnaire were previously reported (Bosetti et al., 2001). A pathologist centrally reviewed PCa characteristics at diagnosis and Gleason score from the original medical records.

Information on vital status and, in case of death, the date and the underlying cause of death were obtained through a record-linkage procedure with regional health system databases, given the availability of population-based Cancer Registries in the study areas (*i.e.*, Friuli Venezia Giulia and Veneto) (Dal Maso et al., 2008). For each patient person–time at risk was calculated from the date of PCa diagnosis up to the date of death, the date of last follow-up, or to December 31st, 2013, whichever came first. Follow-up was truncated at 15 years.

Survival analysis of death from all causes was conducted according to Kaplan–Meier method (Kalbfleish & Prentice, 2002). To account for competing causes of death, the cumulative incidence method (Kalbfleish & Prentice, 2002) was applied for PCa-specific and non-PCa-specific mortality. Cumulative mortality rates between groups were compared by means of the Gray's test (Gray, 1988). To estimate the hazard ratios (HRs) of death and the corresponding 95% confidence intervals (CIs), the Cox proportional hazard regression model (Cox, 1972) was used for death from all causes, and the Fine and Gray's regression model (Fine & Gray, 1999) was used for PCa-specific and non-PCa-specific mortality. HRs were adjusted for area of residence at diagnosis (Friuli Venezia Giulia or Veneto region), calendar period (1995–97, 1998–00, 2001–02), age at diagnosis (46–59, 60–64, 65–69, 70–74 years), years of education (<7, 7–11, ≥12), Gleason score (2–6, 7–10, unknown), and smoking habits (never, former, current ≤15 cigarettes/day, current >15 cigarettes/day).

3. Results

A total of 8260 person–years were observed (median length of follow-up: 11.6 years; interquartile range: 9.0–14.7 years) among 715 PCa patients, (Table 1). The majority of PCa patients were aged 65 years or older at the time of diagnosis (59.4%; median age: 66 years) and were living in Friuli Venezia Giulia Region (64.2%). The majority of PCa patients (51.0%) were diagnosed with Gleason scores 2–6. Overall, 244 (34.1%) deaths were recorded (median follow-up 7.5 years): 77 (31.6%, median follow-up 5.7 years) were due to PCa and 167 (68.4%, median follow-up 7.9 years) were due to other causes. The Kaplan–Meier estimates of men alive after 10 and 15 years from PCa diagnosis were 73% (95% CI: 70%–76%) and 64% (95% CI: 60%–67%), respectively.

PCa patients with MetS were similar to those without MetS with respect to age, year of diagnosis, area of residence, education, and Gleason score (Table 1), regardless of DM. Conversely, PCa patients with MetS and DM reported shorter follow-up than those without DM ($p = 0.05$), mainly because of the elevated proportion of deaths ($n = 14$; 60.9%) in this group. PCa patients with MetS and DM were also more likely to be current smokers than those without DM or MetS ($p = 0.05$).

The risk of death from all causes was directly associated to age at PCa diagnosis (p for trend <0.01), Gleason score (p for trend <0.01), and tobacco smoking (p for trend <0.01) (Table 2). However, Gleason score was significantly associated only to PCa-specific mortality; whereas, age at diagnosis was relevant only for non-PCa-specific mortality (Table 2).

DM was significantly associated to the risk of death from all causes (HR = 1.56, 95% CI: 1.03–2.36), whereas the effects of waist circumference (HR for ≥102 vs. <94 cm = 1.27, 95% CI: 0.91–1.77) and drug-treated hypertension (HR = 1.14, 95% CI: 0.88–1.50) were not statistically significant (Table 3). However, the impact of these metabolic conditions was stronger on non-PCa-specific mortality, with HRs equal to 2.21 (95% CI: 1.38–3.54) for DM, 1.45 (95% CI: 0.97–2.19) for waist circumference ≥102 cm, and 1.63 (95% CI: 1.19–2.22) for drug-treated hypertension. Interestingly, men with DM diagnosed more than 10 years prior to PCa diagnosis had a higher risk of non-PCa-specific death (HR = 3.97; 95% CI: 2.04–7.74) than those with a DM diagnosed 10 years or less before PCa diagnosis (HR = 1.45; 95% CI: 0.79–2.65).

Although of borderline statistical significance, the risk of death from all causes increased with increasing number of metabolic disorders (HR for any additional metabolic disorders was: 1.11; 95% CI: 0.97–1.27) (Table 4). This effect was magnified for non-PCa-specific mortality, where PCa patients with 3 or 4 metabolic disorders had a 2-fold higher risk of death (95% CI: 1.10–3.66) than those with none. Compared to PCa patients without MetS, those with MetS showed a higher risk of non-PCa-specific death (HR = 1.88; 95% CI: 1.09–3.25), which rose up to 2.96 (95% CI: 1.53–5.74) in men with MetS including DM. However, caution is claimed in the interpretation of these results, as they are based on few PCa cases.

No differences in cumulative 15-year PCa-specific mortality emerged according to the number of metabolic disorders (Fig. 1A), with a cumulative PCa-specific mortality below 13%, irrespective of the number of metabolic disorders. Conversely, the risk of 15-year non-PCa-specific mortality greatly increased with the number of metabolic disorders (Fig. 1B), rising from 20% in PCa patients without metabolic disorders to 41% in those patients with 3 or 4 metabolic disorders ($p < 0.01$).

4. Discussion

The study results confirmed that DM and other metabolic disorders unfavorably affect the prognosis of PCa in men, mainly impacting on the risk of death from causes other than PCa. In addition, our findings showed that PCa patients with MetS had worse prognosis than those without. We acknowledge that DM may account for the majority of these effects, nonetheless, an excess of mortality was still appreciable — although not significant — in PCa patients with MetS in absence of DM.

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