

Does diabetes mellitus as a comorbid condition affect the health-related quality of life in prostate cancer survivors? Results of a population-based observational study

Floortje Mols^{*†}, Annelies E. Aquarius^{*}, Marie-Louise Essink-Bot[‡], Neil K. Aaronson[§], Paul J.M. Kil[¶] and Lonneke V. van de Poll-Franse^{*†}

^{*}CoRPS – Center of Research on Psychology in Somatic diseases, Tilburg University, Tilburg, [†]Comprehensive Cancer Centre South (CCCS), Eindhoven Cancer Registry, Eindhoven, [‡]Department of Public Health, Erasmus MC-University Medical Center, Rotterdam, [§]Department of Psychosocial Research and Epidemiology, the Netherlands Cancer Institute, Amsterdam, and [¶]Department of Urology, Sint Elisabeth Hospital, Tilburg, the Netherlands

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OBJECTIVE

To assess the health-related quality of life (HRQoL) of long-term, disease-free prostate cancer survivors and compare it with that of prostate cancer survivors with diabetes mellitus (DM), and a Dutch normative population, as comorbidity can have a major impact on HRQoL in cancer survivors.

PATIENTS AND METHODS

The Eindhoven Cancer Registry was used to select all men diagnosed with prostate cancer from 1994 to 1998. Questionnaires on HRQoL (Short Form 36) and prostate

specific problems (University of California, Los Angeles Expanded Prostate Cancer Index) were sent to 964 patients, and 780 (81%) responded. Excluding patients with disease progression, the sample comprised 525 with prostate cancer and 65 with both prostate cancer and DM. Survivors with DM were more likely to have other comorbid conditions at the time of survey besides DM than were those without DM (74% vs 60%, $P = 0.05$). At 5–10 years after diagnosis, patients with DM reported worse General Health Perceptions than patients without DM or the normative population (means 52, 61 and 63; $P < 0.001$). Patients with DM also reported worse Vitality scores (59 vs 63; $P < 0.001$) than the normative population. Regression analysis indicated that DM was negatively associated with General Health Perceptions ($\beta = -0.13$; $P < 0.01$) and Vitality ($\beta = -0.12$; $P < 0.01$). Survivors with DM did

not report worse urinary and bowel function or bother, nor more sexual problems than those without DM.

CONCLUSIONS

Except for general health perceptions and vitality, the HRQoL of prostate cancer survivors with or without DM was comparable to a normative population. Survivorship selection can possibly explain, in part, why patients with DM did not report worse generic or disease-specific HRQoL than those without DM, as had been expected.

KEYWORDS

prostate cancer, diabetes mellitus, long-term survivors, health-related quality of life

INTRODUCTION

It was estimated that, in 2000, $\approx 5\%$ of the total Dutch population had two or more chronic diseases [1]. In patients diagnosed with cancer and aged ≥ 65 years, 60% have at least one other serious comorbid condition, e.g. diabetes mellitus (DM) [2]. In a recent population-based study, 9% of all patients with cancer had DM at diagnosis [3]. The risk of prostate cancer is somewhat lower in patients with DM than for other cancers [4].

DM concurrent with prostate cancer can have many consequences for patients; those with

DM have a significantly higher overall mortality than patients without DM [3]. Furthermore, prostate cancer and DM both affect specific domains of health-related quality of life (HRQoL) (e.g. urinary, sexual and bowel functioning and bother) as well as general HRQoL (e.g. physical, psychological, social and spiritual functioning) [5–17].

Many studies have investigated the HRQoL of patients with prostate cancer or with DM separately, but only a few have focused on the combined effect of having both conditions [13,14]. The results of these latter studies indicate that the presence of DM in such

patients compromises urinary functioning [13] and genitourinary complications [14] after treatment. However, these studies focused on the disease-specific HRQoL of selected patients treated with either prostatectomy [13] or radiotherapy [14]. The effects of concurrent DM on generic and disease-specific HRQoL in diabetic patients with prostate cancer treated with other therapies remain unclear. The aim of the present population-based study was to determine the role of DM (at the time of survey) in long-term prostate cancer survivors (treated with radical prostatectomy, radiotherapy, hormonal therapy or watchful

waiting), for HRQoL and prostate-specific problems (urinary, bowel and sexual function). In addition, the HRQoL of patients with prostate cancer with and without DM was compared to that of an age- and sex-matched normative sample of the general population. We hypothesized that patients with prostate cancer and DM would have a significantly lower HRQoL and report more prostate-specific problems than those without DM.

PATIENTS AND METHODS

A population-based, cross-sectional survey was conducted at the Eindhoven Cancer Registry (ECR). The ECR records data on all patients newly diagnosed with cancer in the southern region of the Netherlands, an area with 2.3 million inhabitants, 10 hospitals, with 17 hospital locations and two large radiotherapy institutes [18]. The ECR was used to select all patients diagnosed with prostate cancer between 1994 and 1998. Participants aged >75 years at diagnosis were excluded, as it was expected that they would have difficulty in completing a self-reported questionnaire without assistance. To exclude all persons who had died before 1 November 2004, our database was linked with the database of the Central Bureau for Genealogy, which collects data on all deceased Dutch citizens via the civil municipal registries. Data collection was started in November 2004. Approval for this study was obtained from a local certified Medical Ethics Committee. Additional details of the study methods were described previously [17].

Urologists sent their (former) patients a letter to inform them about the study, together with the questionnaire. If the questionnaire was not returned within 2 months, a reminder-letter with an additional copy of the questionnaire was sent.

The ECR routinely collects data on tumour characteristics, including date of diagnosis, grade, clinical stage (TNM clinical classification [19]), treatment, and patient background characteristics, including date of birth and comorbidity at the time of diagnosis (a slightly adapted version of the Charlson comorbidity index [20]). The questionnaire also included questions on disease progression (new primary tumour, metastasis or recurrence), and sociodemographic data, including marital status, current occupation and educational level.

The questionnaire contained a checklist on comorbidity 'at this moment or in the past year'. The list included asthma, chronic bronchitis, chronic obstructive pulmonary disease, heart disease, high blood pressure, stroke, serious kidney disease, DM, malignant disorders, arthrosis or rheumatoid arthritis, skin disease, liver disease and thyroid disease. If patients indicated that they had DM they were included in the DM group.

Primary treatment was classified as radical prostatectomy (usually retropubic), radiotherapy, primary hormonal therapy only and watchful waiting (including TURP). The radiotherapy group only included patients who received external beam radiotherapy; brachytherapy was not available as a treatment option in the region of the Comprehensive Cancer Centre South between 1994 and 1998.

The Dutch version of the Short Form-36 questionnaire was used to assess generic HRQoL [21]; this incorporates two composite scales, the physical component scale (PCS) and the mental component scale (MCS) [22], derived from eight domains; Physical Functioning (PF), Role Limitations due to Physical Health Problems (RP), Bodily Pain (BP), General Health Perceptions (GH), Vitality (VT), Social Functioning (SF), Role Limitations due to Emotional Problems (RE) and General Mental Health (MH) [23]. According to standard scoring procedures, all scales were linearly converted to a 0–100 scale, with higher scores indicating better functioning. Differences of ≥ 5 points (the general health dimension) [24], 6.5 points (the physical dimensions) and 7.9 points (the mental health dimensions) were considered clinically meaningful [25]. For the other subscales, we used Norman's 'rule of thumb' that the threshold of discrimination for changes in HRQoL scores for a chronic disease appears to be ≈ 0.5 SD [26].

The Short Form-36 scores of the patient sample were compared with those of an age-matched male normative sample drawn from a large, random, nationwide normative sample of adults (1742) taken from the general Dutch population [23].

Urinary and bowel function were measured with the Dutch version of the urinary and bowel modules of the University of California, Los Angeles (UCLA) Expanded Prostate Cancer Index (EPIC) [27]. Four of six EPIC scales were

used, the four scales assessing the level of urinary functioning (five items) and bowel functioning (seven items) (e.g. frequency of urinary leakage, number of pads worn to control urinary leakage, frequency of diarrhoea or abdominal cramps) and the degree of urinary and bowel bother (seven items each). All scores were transformed linearly and ranged from 0 to 100; a score of 100 indicates the best level of functioning or no bother. Norman's 'rule of thumb' was also applied to these results [26].

Sexual function and bother were assessed using a Dutch sexual-activities module that consists of 12 single items that do not form an additive scale [16,28]; this questionnaire contains, among others, questions on sexual activity, reasons for not being active (if applicable), the ability to have and maintain an erection, and the use of treatments for erectile dysfunction (ED). Each item has three to five answer categories.

Routinely collected data from the ECR on patient and tumour characteristics allowed a comparison of the group of respondents, non-respondents and patients who were lost to follow-up, using *t*-tests for continuous variables and chi-square analyses for categorical variables. The sociodemographic and clinical characteristics of the patients were analysed using chi-square tests for categorical variables. Patients with (self-reported) disease progression were excluded from the primary analyses, resulting in 590 patients to be analysed. The prevalence of DM at the time of the survey did not differ between patients with or without disease progression.

Linear regression analyses were used to investigate the association of sociodemographic variables (age, marital status, education and employment status) and clinical variables (stage, grade, treatment, time since diagnosis, comorbidity at time of survey other than DM, and DM) with the composite and subscale scores of the Short Form-36 and the UCLA-EPIC scale scores. On the basis of the univariate results, multivariate models were constructed to determine which patient and tumour characteristics were associated independently with HRQoL outcomes. We considered $P < 0.01$ to indicate statistical significance, to compensate, at least in part, for multiple testing. We controlled for these variables in the analysis of covariance, which was used to

FIG. 1.
Flow-chart of the data-collection process.

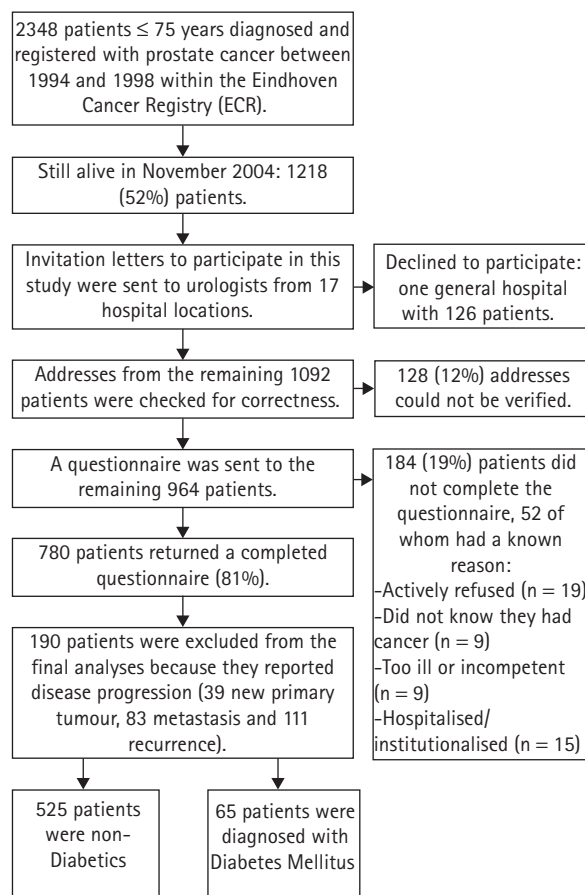
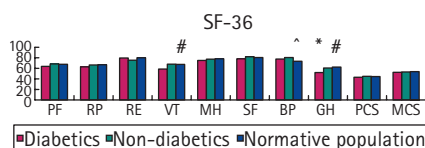


FIG. 2. Short Form-36 scores among Dutch prostate cancer survivors with (65) or without (525) DM, and an age-matched normative population (666).



compare the means of Short Form-36 and UCLA-EPIC scores between different subgroups. The independent variables were categorized as follows: Age and time since diagnosis were entered as continuous variables; tumour stage was entered as stage I, II, III, IV, unknown, and this was similarly done for grade; therapies were entered as therapies vs no therapies; DM was entered as DM vs no DM; marital status was entered as married vs not married or divorced; education was entered as high vs low; and employment status was entered as work vs no work/retired. Sexual activity and ED in prostate cancer

survivors with or without DM were presented in percentages.

RESULTS

Of the 964 prostate cancer survivors, 780 (81%) returned a completed questionnaire (Fig. 1); a comparison of respondents, non-respondents and patients with unverifiable addresses indicated that non-respondents were significantly older ($P < 0.01$), were more often diagnosed with stage I disease ($P < 0.01$) and were less likely to have been treated with radical prostatectomy ($P < 0.001$) than respondents or patients with unverifiable addresses. Non-respondents were more often not treated ('watchful waiting') than respondents and patients with unverifiable addresses ($P < 0.001$). These data were reported previously in greater detail [17].

There were no statistically significant differences between prostate cancer survivors with or without DM at the time of the survey in age, marital status, educational level, current occupation, years since diagnosis,

treatment, stage or tumour grade (Table 1). Although not meeting the more stringent (< 0.01) criterion for statistical significance, survivors with DM were more likely to have had other comorbid conditions (at the time of survey) besides DM than were patients without DM (74% vs 60%; $P = 0.05$). According to the Charlson comorbidity index registered by the cancer registry, 3% of prostate cancer survivors (24) had DM at time of cancer diagnosis. According to our questionnaire, 11% of the total group of survivors (65) reported DM at the time of the survey.

Patients with DM reported significantly worse mean Short Form-36 GH and VT scores than the age- and sex-matched normative sample from the general Dutch population (51.9 vs 62.5; $P < 0.001$), respectively (58.7 vs 67.4; $P < 0.001$; Fig. 2). BP scale scores were, on average, better among prostate cancer survivors without DM than in the normative sample (80.5 vs 73.5; $P < 0.001$). The mean GH scores were worse in patients with DM than in those without DM (51.9 vs 60.7; $P < 0.01$). All of these differences were clinically relevant [24,26].

DM was negatively associated with GH ($P < 0.01$) and VT ($P < 0.01$). Also, the age at time of the survey was negatively associated with PF ($P < 0.001$), RP ($P < 0.01$) and the PCS ($P < 0.001$). Tumour grade was negatively associated with RP ($P < 0.01$). Finally, marital status was positively associated with MH ($P < 0.01$) and occupation was positively associated with GH ($P < 0.001$) (Table 2).

Patients with DM did not differ from those without DM in urinary functioning (mean 83.2 vs 83.6; $P = 0.854$), urinary bother (78.3 vs 77.5; $P = 0.731$) and the urinary summary score (79.9 vs 79.9; $P = 0.854$). In addition, patients with DM did not differ from those without DM on the subscales of bowel functioning (90.9 vs 89.7; $P = 0.685$), bowel bother (88.9 vs 86.1; $P = 0.328$) and the bowel summary score (89.8 vs 87.7; $P = 0.366$).

Most patients with (45, 78%) and without DM (363, 75%) stated that they were not sexually active. For 47–49% of these patients this was due to erectile problems (Fig. 2). Sexually active patients with and without DM also indicated that they had problems with getting an erection (77% and 75%, respectively). Two patients with and one without DM had problems with maintaining an erection. In all,

244 (50%) prostate cancer survivors with DM and 30 (52%) without DM had erectile problems.

DISCUSSION

In this sample of 5–10-year survivors of prostate cancer, patients with DM (at time of survey) reported having significantly poorer perceptions of their general health, and significantly lower levels of vitality than those without DM. There were no other significant differences in self-reported generic HRQoL, as measured by the Short Form-36, between these groups. Also, patients with DM reported lower GH than men of similar age from the general Dutch population. Prostate cancer survivors with DM did not differ significantly from those without DM in urinary and bowel function and bother, or sexual functioning. About half of both those with and without DM reported having erectile function problems.

There were no significant differences between the prostate cancer survivors with and without DM on any of the sociodemographic or clinical background variables assessed. Based on previous reports we expected patients with DM to be older [3,29], and to have lower educational levels [30] than those without DM. One possible explanation for this could be that the large majority (75%) of the study sample developed DM after being diagnosed and treated for prostate cancer. Thus it is likely that our sample was composed of relatively healthy, younger patients with DM, whose prostate cancer had been treated as aggressively as those without DM.

Although the importance of comorbidity is increasingly recognized, few studies have investigated the HRQoL of long-term patients with prostate cancer and DM. A Dutch study among 368 diabetic patients showed that the PCS of the Short Form-36 was significantly lower among diabetics with comorbid diseases than among those without. However, no differences were found for DM patients with cancer on this scale [12]. In addition, patients with prostate cancer and no comorbid diseases were more likely to return to baseline physical health (odds ratio 2.5, $P=0.01$) 1 year after radical prostatectomy than were those comorbid diseases [31]. This last finding could possibly explain why patients with DM in the present study reported lower GH than those without DM, although these are long-term survivors.

	<i>n</i> (%) or value			<i>P</i>
	No DM	DM		
No. of patients	525	65		
Mean age, years				
At survey	74.9	74.1	0.258	
Age group			0.362	
60–69	104 (20)	19 (29)		
70–74	140 (27)	16 (25)		
75–79	184 (35)	19 (29)		
80–85	97 (18)	11 (17)		
Years since diagnosis			0.571	
5–7	312 (59)	41 (63)		
8–10	213 (41)	24 (37)		
Primary treatment			0.362	
Prostatectomy	174 (33)	16 (25)		
Radiotherapy	229 (44)	33 (51)		
Hormonal therapy	59 (11)	10 (15)		
Watchful waiting	63 (12)	6 (9)		
Stage at diagnosis			0.196	
I	120 (23)	12 (18)		
II	300 (57)	33 (51)		
III	54 (10)	12 (18)		
IV	16 (3)	4 (6)		
Unknown	35 (7)	4 (6)		
Grade*			0.113	
I	210 (40)	24 (37)		
II	217 (41)	23 (35)		
III	71 (14)	16 (25)		
Unknown	27 (5)	2 (3)		
Comorbidity at time of survey (other than DM)			0.050	
None	212 (40)	7 (26)		
1	192 (37)	26 (40)		
≥2	121 (23)	22 (34)		
Most frequent comorbid conditions			0.010	
Hypertension	146 (27)	28 (43)		
Arthrosis	116 (22)	19 (29)		
Asthma	75 (14)	9 (14)		
Marital status			0.193	
Married	402 (77)	50 (77)		
Not married/divorced	30 (6)	6 (9)		
Widowed	73 (14)	9 (9)		
Unknown	19 (4)	3 (5)		
Education level			0.939	
Low	229 (44)	29 (45)		
Medium	165 (37)	21 (32)		
High	107 (20)	12 (18)		
Unknown	23 (4)	3 (5)		
Current occupation			0.268	
Employed	34 (7)	1 (2)		
Unemployed	12 (2)	1 (2)		
Retired	457 (90)	59 (97)		

TABLE 1

Sociodemographic and clinical characteristics of prostate cancer survivors with or without DM, and with no recurrent disease or new primary malignancies

*Grade was based on the TNM clinical classification [19]; Grade I is comparable to a Gleason score of 2–4, grade II to Gleason score of 5–7 and grade III to a Gleason score of 8–10.

Patients with DM reported poorer GH than the normative sample; these results are similar, in part, to those of a Dutch study of primary-care patients. Patients with DM or cancer

reported lower scores on the Short Form-36 GH scale than patients without those conditions [32]. A Canadian study among rural residents found that DM (without

TABLE 2 Multivariate linear regression model evaluating independent variables for the Short Form-36 subscale scores

Independent variable	Subscales [§]									
	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
Age (time of survey)	-0.24 [‡]	-0.14 [‡]	NS	NS	NS	NS	NS	NS	-0.19 [‡]	0.11 [*]
Time since diagnosis	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Tumour stage	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Tumour grade	NS	-0.13 [‡]	NS	NS	NS	NS	-0.11 [*]	NS	NS	NS
Prostatectomy	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Radiotherapy	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Hormonal therapy	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Watchful waiting	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
DM	NS	NS	NS	-0.13 [‡]	-0.12 [‡]	NS	NS	NS	NS	NS
Marital status	NS	NS	NS	NS	NS	NS	NS	0.11 [‡]	NS	NS
Education	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Employment status	NS	NS	-0.10 [*]	0.15 [‡]	0.11 [*]	NS	NS	NS	0.10 [*]	NS

^{*}P < 0.05; [‡]P < 0.01; [‡]P < 0.001; [§]Standardized β coefficients.

prostate cancer) is associated with significantly lower scores on the Short Form-36 GH scale (but not the VT scale) [33].

The present results indicate that survivors with DM did not differ significantly from those without DM in urinary and bowel function or bother. The results differed from those of a study among 944 patients with prostate cancer, where patients with DM had significantly more late grade 2 gastrointestinal toxicity and late grade 2 genitourinary toxicity than those without DM [14]. However, that study was not population-based and only included patients treated with radiotherapy. It is known that radiotherapy results in a high incidence of gastrointestinal complications, and therefore differences between men with and without DM might have been more easily found in a study that only includes radiotherapy patients (that study) than one that includes all treatment options (the present study). Furthermore, that study had a mean follow-up of 36 months while the present study measured gastrointestinal and genitourinary complications 5–10 years after diagnosis. It is possible that differences in such treatment-related complications are relatively transient, and thus differences observed between patients with and without DM diminish over time. Such a time-related phenomenon might be amplified because, in studies such as the present, with a longer follow-up, patients who had more treatment-related side-effects might have been in poorer health in general, and thus might have died earlier. In that case,

the patients with DM who survived for a longer period might have also had better HRQoL and fewer treatment-related side-effects immediately after primary treatment. Another explanation could be that we investigated patients who were mostly diagnosed with DM *after* cancer treatment. It is possible that the additional detrimental effect of DM on urinary and bowel functioning and bother is not experienced strongly after having had cancer therapies, therefore explaining why we did find no significant differences between those with and without DM. Longitudinal studies are necessary to evaluate the effect of DM on symptoms and HRQoL in the different phases of cancer survival.

About half of the present prostate cancer survivors had problems with erectile function, regardless of whether DM was present. Sexual dysfunction is a common complication of DM; it can cause significant bother and can affect HRQoL. The estimated prevalence of ED in DM is 20–71% [34]; furthermore, ED is a common complication of primary treatment for prostate cancer. According to a recent review, ED was a problem in 60–70% of patients after radiotherapy [35]. In addition, ED was reported by 88% of patients treated with radical prostatectomy and by 64% treated with external beam radiotherapy in a 5-year follow-up study among patients treated for localized prostate cancer [16]. This was also found in a study among 1187 long-term prostate cancer survivors, in which ED was more prevalent in the radical

prostatectomy group (79%) than in the radiotherapy group (64%) [36]. At 1 year after hormonal therapy, 80% of patients with localized prostate cancer reported ED, vs 30% of those on watchful waiting [37]. In the present study, a third of the patients with DM treated with prostatectomy, and 57% of those treated with radiotherapy, reported ED.

The present study has several limitations: First, we do not know what the current health status was of the 12% of patients who could not be sent a questionnaire because of unverifiable addresses, and the 19% who did not respond. Although the latter were more often diagnosed with stage I disease, they were also older (80–85 years) and more often received no therapy. It is therefore possible that our results cannot be generalized to the oldest group of prostate cancer survivors. In addition, we only included disease-free survivors in our analyses, and therefore cannot generalize the results to those who had disease progression. Second, although there were no significant differences between the prostate cancer survivors with and without DM on any of the sociodemographic or clinical background variables assessed at diagnosis, there was a difference in comorbid conditions at the time of survey. Third, the cross-sectional nature of the study did not allow a determination of causal associations or documentation of HRQoL changes over time. It is more difficult to draw conclusions from a cross-sectional study than a longitudinal study, because differences between groups can already exist at baseline.

However, there were no significant differences between the prostate cancer survivors with and without DM on any of the sociodemographic or clinical background variables assessed. Fourth, the group of patients with DM was rather small. Finally, classification of DM at the time of survey was based on self-reported data, unconfirmed by medical-record data. Unfortunately, we only had medical-record data related to the presence of DM at the time of diagnosis of prostate cancer. Despite the relatively large sample size, there were too few patients with DM at the time of prostate cancer diagnosis (3%) to allow for a meaningful analysis. The increase in prevalence of DM between the time of cancer diagnosis and time of the questionnaire, 5–10 years later, can be explained by ageing. We were unable to control for the severity of diabetes in the patients and our results are therefore preliminary and should be confirmed by longitudinal studies.

Despite these limitations, the results of this study represent an important contribution to the limited information available on HRQoL in the growing group of long-term prostate cancer survivors with DM. This study included an unselected group of men, treated in a range of community hospitals and not only specialized tertiary treatment centres, as is typically the case in randomized clinical trials. Results of a population-based study are more easily generalized to the larger population of survivors than are the results from randomized controlled trials. Also, the relatively large sample size and response rate allow us to extrapolate the findings to the larger population of long-term prostate cancer survivors with DM.

In conclusion, the present results indicate that long-term prostate cancer survivors with DM view their general health as poorer than do those without DM, and report lower levels of vitality than male peers from the general population. In the future, prospectively designed studies are needed to more fully document the role of DM in generic and condition-specific HRQoL and symptom experience of patients with prostate cancer over time.

CONFLICT OF INTEREST

None declared.

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Correspondence: Floortje Mols, CORPS, Department of Medical Psychology, Tilburg University, Tilburg, the Netherlands. e-mail: F.Mols@uvt.nl

Abbreviations: DM, diabetes mellitus; HRQoL, health-related quality of life; ECR, Eindhoven Cancer Registry; UCLA-EPIC, University of California, Los Angeles Expanded Prostate Cancer Index; (P)(M)CS, (physical) (mental) component scale; PF, Physical Functioning; RP, Role Limitations due to Physical Health Problems; BP, Bodily Pain; GH, General Health Perceptions; VT, Vitality; SF, Social Functioning; RE, Role Limitations due to Emotional Problems; MH, General Mental Health; ED, erectile dysfunction.