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RESEARCH

Lymphedema and self-reported swelling among Danish survivors of prostate cancer – prevalence, clinical associations and functional implications

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Abstract

Purpose To study lymphedema prevalence, risk factors, and the effect on physical and emotional functioning among survivors of prostate cancer.

Methods Using the Danish SEQUEL cohort, we identified 44,101 survivors diagnosed with prostate cancer (2010–2021). Lymphedema was assessed using hospital-based treatment records of lymphedema from the National Patient Registry and for a sub-cohort of 9619 men as self-reported swelling in the leg(s) and other areas using EORTC items. Physical and emotional functioning were assessed using the EORTC QLQ-C30. Cox models and logistic regression analyses examined the associations between clinical, lifestyle factors and lymphedema treatment/swelling, and the relationship between swelling and physical/emotional functioning.

Results Among survivors, 2% received lymphedema treatment and 8% reported swelling. The risk of receiving lymphedema treatment was higher for survivors with metastatic vs. low-risk disease (hazard ratio (HR) 5.38, 95% confidence interval (CI) 4.50–6.44), radical prostatectomy vs. active surveillance (HR 4.80, 95% CI 3.37–6.82), and radiation or endocrine therapy vs. watchful waiting (HR 3.44, 95% CI 1.92–6.15; HR 9.01, 95% CI 5.43–14.96, respectively). Survivors with obesity vs. healthy weight had a higher risk of self-reported swelling (odds ratio (OR) 3.52, 95% CI 2.87–4.34). Swelling was associated with impaired physical (OR 3.75, 95% CI 3.20–4.41) and emotional function (OR 4.41, 95% CI 3.44–5.62).

Conclusion Radical prostatectomy, radiation, endocrine therapy, metastatic disease, and obesity increase the risk of lymphedema treatment. Self-reported swelling was associated with impaired physical and emotional functioning, underscoring the need for targeted monitoring and lifestyle interventions.

Keywords Endocrine therapy · Lymphedema · Obesity · Prostate cancer · Quality of life · Radical prostatectomy · Radiotherapy · Survivorship

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Introduction

Prostate cancer is the most common cancer among men in Denmark and worldwide [1, 2]. Most cases are detected at a localized stage, with radical prostatectomy being a common primary treatment. Depending on cancer stage, pelvic lymph node dissection is performed alongside prostatectomy and was previously done for high-risk patients undergoing radiotherapy [3]. However, lymph node dissection increases the risk of postoperative complications, including lower limb, pelvic, and scrotal lymphedema [4, 5]. Lymphedema, characterized by swelling due to insufficient lymphatic drainage, leads to pain, functional impairments, and diminished quality of life [5, 6]. If detected early, there is a higher chance of containing the swelling using exercise, compression therapy, and lymphatic drainage [5, 7]. However, in most cases lymphedema becomes a chronic and potentially disabling condition requiring lifelong attention and treatment [5]. Detailed knowledge about risk factors to inform patients and allow early diagnosis and management is critical.

Although lymphedema is a recognized complication after prostate cancer treatment [5], most research has focused on upper limb lymphedema after breast cancer or lower limb lymphedema in gynecological cancers [8–10]. In prostate cancer, a substantial gap remains in understanding its incidence, detection, and consequences. The existing research shows a wide variation in incidence rates due to differences in disease and treatment factors, as well as a lack of standardized measurements. A systematic review by Clinckaert et al. reported leg lymphedema rates of 0–14% after radical prostatectomy with lymph node dissection [5], while the prevalence was 18–29% among patients who received pelvic radiotherapy post-dissection. Another study found a 29% prevalence of self-reported leg swelling 12 months post-radiotherapy [11].

The impact of lower limb lymphedema on quality of life in men is understudied [12]. However, research has shown a negative association with physical and mental function [7, 13, 14]. In most countries, there is no systematic approach for detection or follow-up of lymphedema, which often rely on self-referrals and patients' resources, leading to potential underreporting. Population-based data on the prevalence and risk factors of lymphedema remain limited.

This study aims to address this gap in a large cohort of 44,101 prostate cancer survivors in Denmark, including a sub-cohort of 9619 survivors with patient-reported outcomes. Specifically, the study aims to investigate 1) the prevalence of hospital-treated lymphedema and self-reported swelling, 2) associations between clinical and lifestyle factors with lymphedema risk, and 3) the association of swelling with physical and emotional functioning.

Materials and methods

Study design and study population

We used data from the national SEQUEL cohort study [15], which includes 44,101 survivors of prostate cancer diagnosed between 2010 and 2021 identified in the Danish Prostate Cancer Database (DaProCa) [16]. Eligible survivors were aged ≥ 40 years at diagnosis, residents in Denmark, and had no prior cancer diagnosis (except non-melanoma skin cancer). A sub-cohort of 23,781 survivors diagnosed between 2010 and 2019 was invited to a cross-sectional questionnaire study (the SEQUEL study) via e-Boks, the Danish national digital mail system, with data collected between January and March 2022. In total, 9619 survivors participated (Supplementary Fig. 1). All participants provided informed consent, and the study was approved by the National Board of Health Data (Region Zealand (REG-059–2021)).

In Denmark, all residents have a personal identification number that was used to track vital status and migration during follow-up by linkage to the Central Population Registry (CPR) [17]. Survivors were followed from diagnosis until emigration, new primary cancer (except non-melanoma skin cancer), death, or December 31 st, 2022. Cohort data were linked to national administrative and health registers to obtain information on sociodemographic and health factors, including education, cohabitation, comorbidities, and lymphedema treatment.

Sociodemographic, clinical, and lifestyle factors

Date of birth, cohabitation status, and educational attainment were retrieved from the CPR and Statistics Denmark [17]. Cohabitation was classified as living with a partner or alone, assessed at cancer diagnosis. Education was recorded two years prior to diagnosis and categorized as short (≤ 9 years), medium (10–12 years), and long (> 12 years).

Clinical data (stage, nodal involvement, prostate-specific antigen (PSA), Gleason score, treatment) were abstracted from DaProCa [16]. Stage was classified per TNM (8th edition) as low-risk (≤ T2b and N0/Nx and M0/Mx), high-risk (> T2b and N0/Nx and M0/Mx or N1 and M0/Mx), or metastatic (any T and any N and M1). Nodal involvement was categorized into yes (N1) vs. no (N0/Nx). Treatment comprised active surveillance, watchful waiting, prostatectomy, radiotherapy, and endocrine therapy. Comorbidity included diagnoses from 3 years up to 3 months prior cancer diagnosis, scored using a modified Charlson Comorbidity index and categorized into a score of 0, 1, or ≥ 2 [18].

Self-reported lifestyle data from the sub-cohort included alcohol consumption (none; consumption within the limits

by Danish health authorities (≤ 14 units per week); and consumption exceeding these recommendations (> 14 units)), smoking status (never, former, current), and body measurements (height and weight) to ascertain Body Mass Index (BMI) (kg/m^2) (healthy weight (≤ 24.9), overweight (25–29.9), and obese (≥ 30)).

Lymphedema treatment

Lymphedema treatment included physical therapy, compression treatment, and manual lymphatic drainage and was identified via the Danish National Patient Registry [17] (Supplementary Table 1). Survivors with at least one treatment code for lymphedema were classified as having received lymphedema treatment.

Self-reported swelling, physical, and emotional function

Self-reported swelling was assessed using two validated items from the European Organization for Research and Treatment of Cancer (EORTC) Item Library, one item measuring *swelling in the leg* and one item measuring *swelling in other areas of the body* (e.g. ankles, legs) available in the EORTC item library. Physical and emotional function were measured using the EORTC Quality of Life Core Questionnaire (QLQ-C30) [19]. Both items for swelling and the items for physical and emotional function were measured using a 4-point Likert scale (i.e., 1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much), and scored from 0–100 following the EORTC guidelines, with higher scores indicating more swelling or a better level of functioning [20]. Binary variables were created to classify 'moderate to severe swelling' by selecting a cut-off at ≥ 33.334, as this corresponds to a response of 'quite a bit' or 'very much'. To define impaired physical and emotional functioning, we applied clinically validated thresholds of a score below 83 and 58, respectively [21].

Statistical analysis

Descriptive statistics summarized sociodemographic, clinical, and lifestyle characteristics, as well as the prevalence of registry-based lymphedema treatment and self-reported swelling. Due to overlapping in the prevalence of reporting both *swelling in the leg* and *swelling in other areas of the body*, we combined the items into a single variable for self-reported swelling. Registry-based treatment for lymphedema was also combined into a single variable. The combined variables were used in the statistical analyses.

In the total cohort, cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between clinical factors (stage, nodal involvement, treatment, PSA, Gleason score, comorbidity) and lymphedema treatment, using time since diagnosis as the underlying time scale and adjusting for age and potential confounders (education, cohabitation status, comorbidity, stage) depending on the exposure variable. In the sub-cohort, logistic regression models estimated odds ratios (ORs) and 95% CIs for associations between clinical and lifestyle factors (smoking, alcohol, BMI) and swelling, adjusting for age, time since diagnosis, and potential confounders (education, cohabitation status, lifestyle factors, comorbidity, stage). A sensitivity analysis, including a less stringent definition of swelling by including responses of "a little swelling" was performed to test the robustness of our findings. Additional logistic models examined the relationships between swelling and physical/emotional functioning, with adjustment for age, time since diagnosis, education, cohabitation, comorbidity, stage, treatment, and BMI. All statistical analyses were conducted using R (version 4.1.2).

Results

Among the 44,101 survivors, the median age at diagnosis was 70 years (IQR 65; 76) and median follow-up was 5 years (IQR 2; 8). Most had medium-level education (53%), were cohabiting (76%), had low-risk disease (41%), and were treated with radical prostatectomy (23%), radiation (33%), or endocrine therapy (45%) (Table 1). The sub-cohort who provided self-reported data (n = 9619) was younger (median age of 67 years (IQR 62; 71)), with 51% having medium education, 85% were cohabiting, and 53% had low-risk disease. Treatment included prostatectomy (41%), radiation (32%), and endocrine therapy (32%) (Table 1). Most were former smokers (51%), had an alcohol intake within national guidelines (61%), and had overweight or obesity (67%) (Table 1).

In the total cohort, 1117 men (2%) received physical therapy for lymphedema, of which 155 were specified as compression treatment and 98 as manual lymphatic drainage (Supplementary Table 2). The median time to any treatment of lymphedema was 549 days, with longer delays for compression and drainage (median of 694 and 833 days, respectively) (Supplementary Table 3). In the sub-cohort, 806 (8%) reported swelling (Supplementary Table 4), with most having overweight or obesity (80%) and being former smokers (58%) (Fig. 1). The highest prevalence of lymphedema treatment was in survivors with nodal involvement (7%), metastasis (5%), those treated with radical prostatectomy and endocrine therapy (6%), or radiation and endocrine therapy with palliative intent (6%) (Supplementary Table 4). The highest prevalence of swelling was among survivors with high-risk disease (12%), nodal involvement (13%), radio- and endocrine therapy (12%), or endocrine therapy with palliative intent (12%) (Supplementary Table 4). When

Table 1 Sociodemographic, clinical, and lifestyle characteristics for 44,101 survivors after prostate cancer, and 9619 prostate cancer survivors in the sub-cohort of participants providing questionnaire data in the SEQUEL study, n (%)

	Total cohort ($n=44,101$)	Sub-cohort ($n=9619$)
Age at diagnosis, years, median (IQR)	70 (65; 76)	67 (62; 71)
Time since diagnosis, years, median (IQR)	5 (2; 8)	6 (4; 9)
Education		
Short	8803 (20)	1090 (11)
Medium	22930 (53)	4921 (51)
Long	11556 (27)	3592 (37)
Cohabitation		
Alone	10664 (24)	1417 (15)
With partner	33437 (76)	8161 (85)
Stage		
Low risk	18301 (41)	5056 (53)
High risk	9090 (21)	1753 (18)
Metastasis	4845 (11)	394 (4)
Missing	11865 (27)	2416 (25)
Nodal involvement		
Yes	2911 (7)	356 (4)
No	28874 (65)	7278 (76)
Missing	12316 (28)	1985 (20)
PSA		
<4	1341 (3)	293 (3)
4.0–10.0	12808 (29)	3872 (40)
≥10	19631 (45)	3437 (36)
Missing	10321 (23)	2017 (21)
Gleason score		
≤6	10770 (24)	2914 (30)
7	16474 (37)	4043 (42)
≥8	12271 (28)	1681 (17)
Missing	4586 (10)	981 (10)
Primary treatment with curative intent		
Active surveillance	6410 (14)	1720 (18)
Radiotherapy and endocrine therapy	9290 (21)	1744 (18)
Radical prostatectomy	7860 (18)	3077 (32)
Adjuvant treatment after radical prostatectomy		
Radical prostatectomy and radiation	522 (1)	240 (2)
Radical prostatectomy and endocrine therapy	261 (1)	84 (1)
Radical prostatectomy, radiation, and endocrine therapy	1319 (3)	535 (6)
Primary palliative treatment		
Watchful waiting	3504 (8)	463 (5)
Radiotherapy	1884 (4)	490 (5)
Endocrine therapy	6955 (16)	626 (6)
Radiotherapy and endocrine therapy with palliative intent	1742 (4)	114 (1)
None	4354 (10)	526 (5)
Comorbidity		
0	37470 (85)	8758 (91)
1	4507 (10)	655 (7)
≥2	2124 (5)	206 (2)
Smoking		
Never		3795 (39)
Former		4923 (51)
Current		749 (8)

Table 1 (continued)

	Total cohort ($n=44,101$)	Sub-cohort ($n=9619$)
Missing		152 (2)
Alcohol		
0 units per week		1325 (14)
Within the recommended weekly intake		5902 (61)
Above the recommended weekly intake		1737 (18)
Missing		655 (7)
BMI		
Healthy weight (< 25)		3039 (31)
Overweight (25–29.9)		4615 (48)
Obesity (≥ 30)		1793 (19)
Missing		172 (2)

IQR inter quartile range, *PSA* prostate specific antigen, *BMI* body mass index

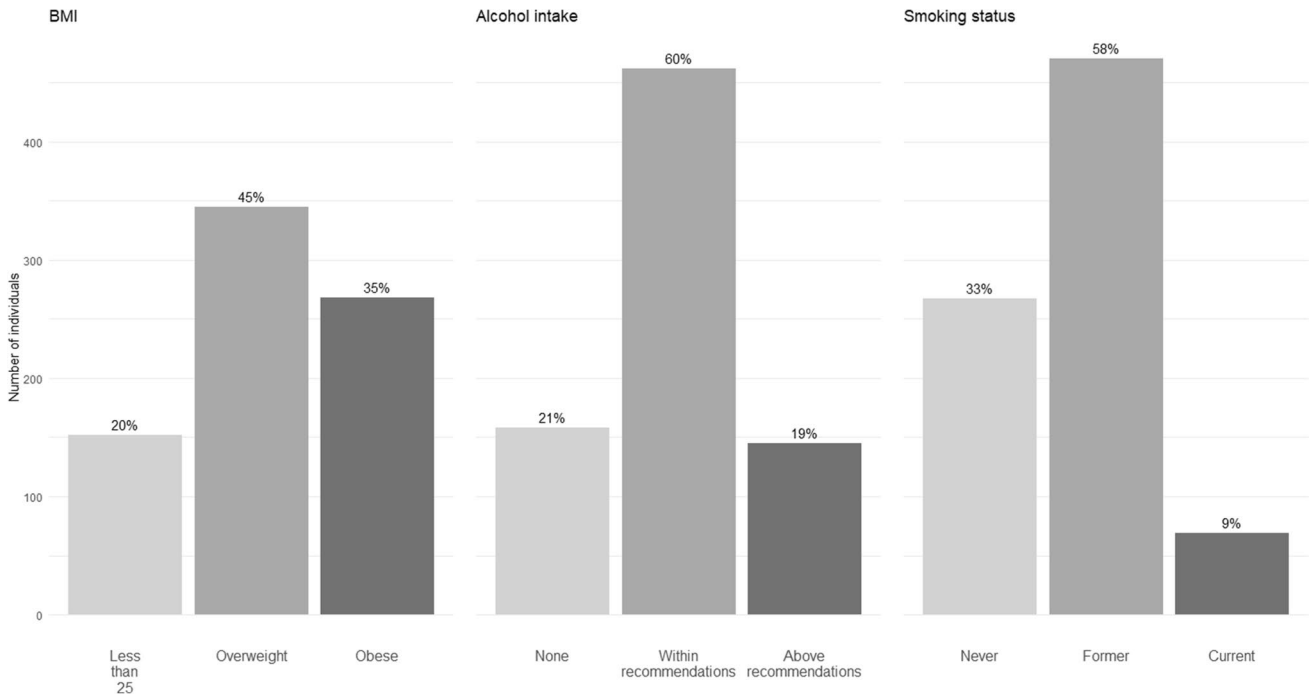

Fig. 1 Prevalence of self-reported swelling stratified by levels of self-reported BMI, alcohol intake, and smoking status in 806 survivors after prostate cancer, n (%). BMI, Body Mass Index

comparing survivors who received lymphedema treatment and those who reported swelling, similar proportions had high-risk stage disease at diagnosis, while three times more survivors who received lymphedema treatment had nodal involvement and four times more had metastasis compared to those who self-reported swelling (Supplementary Table 4).

Adjusted Cox proportional hazard models showed that survivors with high-risk disease or metastatic disease had a 3.0 (95% CI 2.56–3.51) and 5.38 (95% CI 4.50–6.44) times higher HR for lymphedema treatment, respectively, compared to low-risk disease (Table 2). Survivors who received radical prostatectomy or radiation and endocrine therapy had higher risks of treatment for lymphedema (HR 4.80, 95% CI 3.37–6.82, and HR 3.88, 95% CI 2.08–7.21, respectively) (Table 2). Radiation and/or endocrine therapy adjuvant to prostatectomy further increased the risk of lymphedema treatment (Table 2). Likewise, among men receiving treatment with palliative intent, those who received radiotherapy and/or endocrine therapy had a higher risk of lymphedema treatment compared to survivors in watchful waiting (Table 2). Similar associations were observed when further adjusting analyses for sociodemographic and clinical factors (Supplementary

Table 2 Cox proportional hazards and logistic regression analyses of the association between clinical, lifestyle factors and lymphedema treatment for 44,101 survivors of prostate cancer and swelling among 9619 survivors in the sub-cohort

	Lymphedema treatment[a]			Self-reported swelling[b]	
	Events/total	Person-time (years)	HR (95% CI)	n/N	OR (95% CI)
Total	1117/44,101	227,550		806/9619	
Stage					
Low-risk disease	284/18,301	104,982	Ref	372/5056	Ref
High-risk disease	340/9090	45,580	**3.00 (2.56; 3.51)**	209/1753	**1.62 (1.35; 1.93)**
Metastasis	225/4845	14,623	**5.38 (4.50; 6.44)**	39/394	1.19 (0.83; 1.68)
Nodal involvement					
No	646/28,874	151,245	Ref	561/7278	Ref
Yes	198/2911	9610	**4.15 (3.54; 4.88)**	45/356	**1.47 (1.04; 2.02)**
Primary treatment with curative intent					
Active surveillance	35/6410	35,137	Ref	91/1720	Ref
Radiotherapy and endocrine therapy	317/9290	48,413	**3.88 (2.08; 7.21)**	213/1744	**2.28 (1.76; 2.96)**
Radical prostatectomy	229/7860	48,718	**4.80 (3.37; 6.82)**	216/3077	**1.35 (1.05; 1.75)**
Adjuvant treatment after radical prostatectomy					
Radical prostatectomy	229/7860	48,718	Ref	216/3077	Ref
Radical prostatectomy and radiation	14/522	3967	**2.35 (1.42; 3.91)**	21/240	1.34 (0.81; 2.10)
Radical prostatectomy and endocrine therapy	16/261	1476	1.32 (0.97; 1.78)	8/84	1.37 (0.60; 2.72)
Radical prostatectomy, radiation, and endocrine therapy	51/1319	8450	**1.66 (1.39; 1.98)**	51/535	1.37 (0.98; 1.87)
Primary palliative treatment					
Watchful waiting	16/3504	18,621	Ref	39/463	Ref
Radiotherapy	40/1884	11,906	**3.44 (1.92; 6.15)**	47/490	1.28 (0.81; 2.02)
Endocrine therapy	236/6955	27,156	**9.01 (5.43; 14.96)**	77/626	**1.51 (1.01; 2.29)**
Radiotherapy and endocrine therapy with palliative intent	106/1742	5521	**14.99 (8.84; 25.43)**	13/114	1.42 (0.70; 2.72)
PSA					
< 4	17/1341	7031	Ref	18/293	Ref
4.0–10.0	205/12,808	75,139	1.33 (0.81; 2.18)	284/3872	1.14 (0.71; 1.93)
≥ 10	663/19,631	91,547	**3.83 (2.36; 6.22)**	352/3437	1.53 (0.96; 2.60)
Gleason score					
≤ 6	68/10,770	66,603	Ref	172/2914	Ref
7	328/16,474	83,687	**4.04 (3.11; 5.24)**	339/4043	**1.34 (1.11; 1.63)**
≥ 8	559/12,271	48,693	**12.42 (9.62; 16.02)**	205/1681	**1.92 (1.54; 2.39)**
Comorbidity					
0	998/37,470	198,888	Ref	696/8758	Ref
1	77/4507	20,400	**0.75 (0.59; 0.95)**	82/655	**1.62 (1.25; 2.06)**
≥ 2	42/2124	8262	0.98 (0.72; 1.34)	28/206	**1.82 (1.19; 2.71)**
Smoking					
Never				267/3795	Ref
Former				470/4923	**1.40 (1.19; 1.63)**
Current				69/749	**1.40 (1.06; 1.84)**
Alcohol					
0 units per week				159/1325	**1.68 (1.38; 2.03)**
Within the recommended weekly intake				466/5902	Ref
Above the recommended weekly intake				145/1737	1.07 (0.88; 1.30)

Table 2 (continued)

	Lymphedema treatment[a]			Self-reported swelling[b]	
	Events/total	Person-time (years)	HR (95% CI)	n/N	OR (95% CI)
BMI					
Healthy weight (18.5–24.9)				159/3039	Ref
Overweight (25–29.9)				363/4615	**1.57 (1.30; 1.91)**
Obesity (≥ 30)				279/1793	**3.52 (2.87; 4.34)**

RP radical prostatectomy, *PSA* prostate specific antigen, *BMI* Body Mass Index

All analyses are adjusted for age and time since diagnosis

Bold marks statistically significant estimates

[a]Analyses performed in the total cohort of 44,101 men with prostate cancer

[b]Analyses performed in the sub-cohort of 9619 men with prostate cancer

Table 5). Among the sub-cohort, survivors who received radical prostatectomy or radiation and endocrine therapy had higher risks of swelling (OR 1.35, 95% CI 1.05–1.75, OR 2.28, 95% CI 1.76–2.96, respectively) compared to men in active surveillance (Table 2). Former/current vs never smokers, and survivors with overweight or obesity vs. men with a healthy weight had a higher risk of swelling (Table 2). We observed similar estimates after further adjusting for sociodemographic, clinical, and lifestyle factors (Supplementary Table 5). In sensitivity analyses where self-reported swelling included respondents reporting "a little swelling", the associations remained consistent, although the effect estimates were attenuated (results not shown). Survivors reporting swelling had a statistically significant 3.75 (95% CI 3.20–4.41) and 4.41 (95% CI 3.44–5.62) higher adjusted odds of impaired physical or emotional function, respectively (Table 3).

Discussion

This study represents the largest investigation into the prevalence of lymphedema treatment and swelling among short- and long-term survivors of prostate cancer, exploring clinical characteristics and risk factors. We found that 2% received hospital-based lymphedema treatment, while 8% in the sub-cohort reported moderate to severe swelling. High-risk disease, metastasis, radical prostatectomy, radiotherapy, and endocrine therapy were associated with higher risks of treatment for lymphedema and self-reported swelling. Lifestyle factors such as overweight, obesity, and smoking, were linked to self-reported swelling, which was significantly associated with physical and emotional functioning, suggesting a substantial effect on quality of life.

Our findings align with a systematic review showing lymphedema prevalence rates of 0% to 14% among survivors after prostate cancer, and 18% to 29% in survivors who underwent pelvic lymph node dissection and radiotherapy [5]. While we lacked direct data on lymph node dissection, we assumed that men with nodal involvement underwent this procedure. We found a 7% prevalence of registry-based lymphedema treatment and 13% self-reported swelling in men with nodal involvement. A study by Fokdal et al. found a 29% prevalence of self-reported lower limb lymphedema at 12 months post-radiotherapy in men with prostate cancer [11], exceeding our finding of 10% self-reported swelling in a similar population. Thresholds for self-reported swelling included responses indicating "a little" swelling and not only "quite a bit" in the study by Fokdal et al., and survivors 2 to 12 years post-diagnosis were included in the present study, extending beyond the first 12 months after treatment. These differences in applied thresholds and in length of survivorship may explain this discrepancy between study findings.

Table 3 Logistic regression analyses of the association between lymphedema treatment, swelling and physical function for 9619 survivors providing questionnaire data in the SEQUEL sub-cohort

	Impaired physical function		Impaired emotional function	
	Model 1	Model 2	Model 1	Model 2
Self-reported swelling	**4.51 (3.88; 5.25)**	**3.75 (3.20; 4.41)**	**5.18 (4.08; 6.54)**	**4.41 (3.44; 5.62)**
Any lymphedema treatment	1.16 (0.85; 1.56)	1.21 (0.87; 1.66)	0.93 (0.44; 1.72)	0.94 (0.44; 1.76)

Model 1: adjusted for age, time since diagnosis

Model 2: further adjusted for education, cohabitation, comorbidity, stage, treatment, BMI

Bold marks statistically significant estimates

BMI has consistently been associated to lymphedema in various cancer populations, including women with breast or cervical cancer [9, 10]. Studies have found that breast cancer patients with obesity are 2–3 times more likely to develop lymphedema after surgery compared to those with a healthy weight [22]. Our study showed that a BMI above 25 may be associated with a higher likelihood of swelling, with obesity increasing the odds by 3.5-fold compared to survivors with healthy weight.

Our findings regarding impaired physical and emotional function in survivors with swelling corresponds to those of Neuberger et al., who found similar impairments in men with prostate cancer and active lymphedema [7]. Previous studies also highlight the compounded impact of obesity on lymphedema, showing that men with prostate cancer, obesity and lymphedema had almost eightfold higher infection risks, more frequent hospitalizations, more physical limitations, higher psychological distress, and poorer management of symptoms [23]. Weight management may be essential for minimizing lymphedema and improving the quality of life in these survivors.

The clinical significance of the observed associations, including an HR of 4.80 for lymphedema treatment after radical prostatectomy, and HRs of 2.35 and 1.32 for survivors who additionally received radiation or endocrine therapy, respectively, compared to only being treated with radical prostatectomy, is noteworthy. To our knowledge, this is one of the first studies to identify endocrine therapy as a potential risk factor for lymphedema. While endocrine therapy was associated with both lymphedema treatment and self-reported swelling, interpretation should be cautious as endocrine therapy use may partially reflect a higher burden of advanced disease and other treatments that may influence lymphedema risk. Although the direct link between endocrine therapy and lymphedema remains unclear, metabolic alterations associated with therapies like androgen deprivation therapy could increase the risk of lymphedema due to their effect on inflammation, insulin resistance, and obesity risk [22, 24–29]. Consequently, survivors receiving endocrine therapy, particularly those who develop metabolic syndrome and obesity, might face an elevated lymphedema risk. In exploratory analysis restricted to the sub-cohort with information on BMI (results not shown), the estimates for the association between endocrine therapy and self-reported swelling did not change meaningfully after adjusting for BMI, suggesting that differences in weight alone is unlikely to account for the observed association. The interplay between endocrine therapy, metabolic syndrome, and obesity suggests a multi-faceted risk profile where lymphedema could emerge as a late effect, warranting careful monitoring and management in this population.

Strengths and limitations

A major strength of this study is the inclusion of a nationwide cohort, providing a comprehensive and large-scale study suitable for investigations of lymphedema. Another strength lies in the use of reliable national registry data. However, the lack of systematically collected data on lymphedema is a major limitation, as hospital-based treatment records may likely underrepresent the true prevalence of lymphedema, excluding care from general practitioners and private practicing physiotherapists, or individuals that receive compression garments provided by the municipalities. Consequently, our findings are likely to not fully represent the extent of lymphedema in the survivor population as we expect only the most severe cases are managed in hospital settings. Additionally, we could not confirm whether self-reported swelling was due to cancer-related lymphedema or to a different medical condition, such as left ventricular failure or venous return deficiency, which i.e. may cause lower limb edema [30]. The results might also be affected by selection bias, as the sub-cohort were younger, had less comorbidities, and a greater proportion had low-risk stage disease than in the full cohort. Survivors with more advanced stage disease or poorer functioning may have been less likely to participate in the questionnaire study, which could lead to an underestimation of the prevalence of swelling and potentially distort the association between swelling and functioning outcomes. Another limitation is our use of lymph node involvement (N1) as a proxy for pelvic lymph node dissection, as patients with N0 likely also have had lymph nodes removed. Furthermore, information on clinical factors such as stage at diagnosis was predominantly missing among survivors in active surveillance, watchful waiting, with no information on nodal involvement, and survivors who received no treatment. Because this subgroup of survivors likely has a different, and probably lower, risk of lymphedema, this group of "missing stage" survivors was included as a separate category rather than excluded from analyses. Consequently, the estimates for the association between stage, lymphedema treatment, and swelling might be underestimated. Despite these limitations, this study offers valuable insight into the potential dark numbers of lymphedema in prostate cancer survivors and the need for increased awareness.

Conclusions

Advanced cancer stages, radical prostatectomy, radiation, and endocrine therapy are associated with a higher risk of treatment for lymphedema and self-reported swelling in survivors after prostate cancer. Overweight and obesity

emerged as strong and potentially modifiable risk factors for swelling. Swelling was also associated with notable impairments in physical and emotional functioning, contributing to reduced quality of life. These findings highlight the importance of early screening and monitoring for lymphedema in survivors, especially those who are obese or receive endocrine therapy. Proactive management of lymphedema risk may improve long-term outcomes and quality of life.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-026-10675-1.

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Author contributions Contributors: AKGL, GA, TKK, and SOD conceived and designed the study. AKGL analyzed the data, and AKGL, GA, TKK, SB, and SOD interpreted the results. AKGL and GA drafted the manuscript, and TKK, SOD, SB, and MB completed critical revisions, reviewed, revised the manuscript, and approved the final manuscript for submission.

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Data availability The supporting data are not publicly available due to research participant privacy restrictions. The data that support the findings of this study are available for collaborative research project upon reasonable request.

Declarations

Ethical approval The SEQUEL study is approved by the National Board of Health Data (Region Zealand (REG-059–2021)). Ethical review and approval were waived for this study, as no human biological material was included in the project. The study was registered in the Danish Cancer Society Research Database (2019-DCRC-0066). We obtained informed consent from all participants in the study. Data were stored and protected following the guidelines of the Danish legislation regarding GDPR.

Data access and responsibility AKGL had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interest The authors declare no competing interests.

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