Damiano Pizzol, Tao Xiao, Lee Smith, Guillermo F López Sánchez, Andrea Garolla, Christopher Parris, Yvonne Barnett, Petre Cristian Ilie, Pinar Soysal, Jae Il Shin, Mark A Tully, Lin Yang, Nicola Veronese and Igor Grabovac

Prevalence of erectile dysfunction in male survivors of cancer:

a systematic review and meta-analysis of cross-sectional studies

Abstract

Background
Prevalence of erectile dysfunction (ED) in male survivors of cancer across cancer types has not been systematically analysed.

Aim
To estimate the prevalence of ED in all types of cancer and identify characteristics associated with ED in survivors of cancer.

Design and setting
Systematic review and meta-analysis (MA) of cross-sectional studies.

Method
MEDLINE, CINAHL, PsycINFO, and EMBASE were searched, targeting reports published from inception to 1 February 2020. All retrospective or prospective studies reporting prevalence of ED in male patients with cancer and using a validated tool for detection of ED were included. A random-effects MA model was used to pool prevalence of ED as absolute estimates at three different stages, that is, 'healthy', 'at diagnosis', and 'after treatment'. A univariate MA regression including the three-level group variable as the only independent variable was used to assess the difference in ED prevalence across the three groups. Further MAs were conducted for studies involving patients at diagnosis and after treatment, and statistical inferences were made with setting for multiple testing controlling for a false discovery rate (FDR) <0.05.

Results
In total, 1301 studies were assessed for inclusion. Of these, 141 were potentially eligible and subsequently scrutinised in full text. Finally, 43 studies were included with a total of 13 148 participants. Overall, pooled data of the included studies showed an ED prevalence of 40.72% (95% confidence interval [CI] = 31.80 to 50.29) in patients with cancer, with prevalences of 28.60% (95% CI = 12.10 to 53.83) at time of diagnosis and 42.70% (95% CI = 32.97 to 53.03) after treatment, with significant difference between these two stages and across cancer locations, controlling for an FDR <0.05.

Conclusion
Erectile dysfunction was particularly high in male survivors of cancer and was associated with cancer treatment, cancer site, and age.

Keywords
erectile dysfunction; male cancer; meta-analysis; systematic review; prevalence.

INTRODUCTION

Cancers located in the pelvic region represent >25% of all newly diagnosed cancers worldwide in males.[1] This localisation of cancer has also been associated with long-term severe sexual dysfunction in at least half of all patients.[2] Erectile dysfunction (ED), the inability to obtain or maintain an erection that allows for sexual intercourse, is one of the most distressing consequences of cancer diagnosis and treatment in males.[3]

Erectile dysfunction has a complex aetiology influenced by cancer in both direct and indirect ways. Males diagnosed with prostate cancer, the second most common type of cancer (except for non-melanoma skin cancer) in males,[1] are expected to have the same risk factors (cardiovascular disease and metabolic disorders) for ED when compared with cancer-free age-matched males. However, risks for ED are increased given a higher incidence of lower urinary tract symptoms and psychological distress in males with prostate cancer.[4,5] Indirect pathways, mostly associated with cancer treatment modalities (surgery, chemo- and radiotherapy, and hormone treatment) seem to be the most common causes.[6,7]

Moreover, few males are able to achieve a normal erection following pelvic surgery, with studies noting that, even in males with excellent baseline erections, <25% retained or recovered the erection quality as before treatment. Pelvic surgeries most associated with ED are radical prostatectomy, radical cystectomy, and low anterior or abdominoperineal resections.[8] Furthermore, the results from a 12-year follow-up study showed that 84% and 80%, respectively, of males with prostate cancer who had radical prostatectomy or were under active surveillance reported ED, compared with 43% in the matched control group.[9] Similar results have been reported for males who had treatment for other types of pelvic cancer, such as anal, rectal, or

D Pizzol, MD, public health researcher, Italian Agency for Development Cooperation, Khartoum, Sudan. **T Xiao**, PhD, public health researcher, College of Mathematics and Statistics, Shenzhen University, Shenzhen, China. **L Smith**, PhD, public health researcher, Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK. **C Parris**, PhD, public health researcher; **Y Barnett**, PhD, public health researcher, Biomedical Research Group, Faculty of Science and Engineering, Anglia Ruskin University, Cambridge, UK. **GF López Sánchez** (ORCID: 0000-0002-9897-5273), PhD, public health researcher, Faculty of Sport Sciences, University of Murcia, Spain. **A Garolla**, MD, public health researcher, Unit of Andrology and Reproductive Medicine, Department of Medicine, University of Padova, Padua, Italy. **PC Ilie**, MD, public health researcher, Queen Elizabeth Hospital King's Lynn NHS Foundation Trust, King's Lynn, UK. **P Soysal**, MD, public health researcher, Department of Geriatric Medicine, Bezmialem Vakif University, Istanbul, Turkey. **JI Shin**, MD, public health researcher, Department of Paediatrics, Yonsei University College of Medicine, Seoul, Korea. **MA Tully**, PhD, public health researcher, School of Health Sciences, Institute of Mental Health Sciences, Ulster University, Newtownabbey, Northern Ireland. **L Yang**, PhD, public health researcher, Department of Cancer Epidemiology and Prevention Research, Alberta Health Services, Holy Cross Centre, Canada. **N Veronese**, MD, public health researcher, Neuroscience Institute, Aging Branch, National Research Council, Padua, Italy. **I Grabovac**, MD, public health researcher, Department of Social and Preventive Medicine, Centre for Public Health, Medical University of Vienna, Vienna, Austria.

Address for correspondence
Lee Smith, Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge CB1 1PT, UK.

Email: lee.smith@anglia.ac.uk

How this fits in

In male survivors of cancer, normal sexual function may be disturbed owing to the occurrence of erectile dysfunction (ED). The present systematic review and meta-analysis reports 40.72% prevalence of ED in survivors of cancer, with the prevalence being somewhat higher (42.70%) in studies that focused on reporting prevalence after cancer treatment. The reasons for high occurrence of ED in male survivors of cancer is multimodal and includes a variety of factors, such as psychological and physical ones. Clinicians should be aware that ED has a large effect on the quality of life and mental health of male survivors of cancer.

bladder cancer.[10–15] However, it is noteworthy that ED is not only prevalent in males with pelvic cancers but may also be the result of intensive chemo- or radiotherapy, causing hypogonadism or pelvic nerve damage. Studies have shown ED also after lung cancer, haematological malignancies, and head and neck tumours.[16–18]

Sexuality and intimacy are important aspects of quality of life and may also reduce some of the psychosocial distress associated with the cancer diagnosis. In this light it has been reported that maintaining normal sexual function in males with cancer can be important to help relieve suffering.[19,20] Given the growing incidence of cancer globally and new therapeutic modalities that are prolonging life expectancy in survivors of cancer, questions of quality of life post-diagnosis and treatment are increasingly relevant. However, studies on ED in survivors of cancer are rare, and mostly focused on cancer localisations in the pelvic region, making prevalence estimates of ED in survivors of cancer rare. Providing pooled estimates of ED prevalence as well as its associations should provide important information not only on the scale of the issue but also help clinicians working with survivors of cancer to easily identify patients who are at risk of ED, and provide comprehensive cancer care associated with long-term quality of life.

Therefore, the aim of this systematic review and meta-analysis (MA) was to examine the available studies and provide pooled estimates for ED prevalence in relation to all cancer sites and identify characteristics associated with ED in survivors of cancer. To the authors' knowledge, this is the first study of its kind.

METHOD

Search strategy

Four electronic databases, MEDLINE, CINAHL, PsycINFO, and EMBASE, were searched, targeting reports published from database inception to 1 February 2020. Terms included in the search strategy are reported in Supplementary Table S1.

The references of retrieved articles, together with the proceedings of relevant conferences, were hand-searched in order to identify other potentially eligible studies for inclusion that were missed by the initial search, or any unpublished data.

The literature search, assessment of inclusion and exclusion criteria, quality of studies, and extraction of data were independently undertaken and verified by the first and second authors. The results were then compared and, in case of discrepancies, a consensus was reached with the involvement of the third author. There was no language restriction.

Type of studies, inclusion and exclusion criteria

All retrospective or prospective studies reporting the prevalence of ED in male patients with cancer and using a validated tool for ED detection, for example, the International Index of Erectile Function (IIEF-5), were included in this review. Studies that did not meet the inclusion criteria were excluded.

Types of outcome measures

All outcomes were defined before conducting the literature search. The primary outcome was the prevalence of ED across relevant cancer treatment stages, that is, 'healthy', 'at diagnosis', and 'after treatment'.

Data extraction and statistical analyses

Descriptive tables for population and study characteristics were generated for all included studies. The first author, publication year, country of investigators, sample size, age, method of assessment of ED, and cancer type and site were recorded. Furthermore, number of patients with ED among case and control groups, body mass index, hormonal levels, smoking status, and presence of hypertension, diabetes, dyslipidaemia, and cardiovascular diseases were recorded. All statistical analyses based on these data were performed using R (version 3.6.1).

For the included studies at the three different stages, that is, 'healthy', 'at diagnosis', and 'after treatment', a random-effects MA model with the between-

Table 1. Study counts and pooled prevalence of ED across three stages

Counts/prevalence	Stage			
	Healthy control	**At diagnosis**	**After treatment**	**Total**
Study count, *n*	3	5	35	43
Pooled number of patients with ED, *n*	250	782	2794	3826
Pooled sample size, *n*	1240	2403	9505	13 148
Pooled prevalence (95% CI)	0.1370 (0.0394 to 0.3808)	0.2861 (0.1229 to 0.5340)	0.4269[a] (0.3311 to 0.5286)	—

[a]The ED prevalence among patients with cancer 'after treatment' was statistically significantly different from that of 'healthy control' at level 0.05 (P = 0.0322; this can also be seen by the fact that the point estimate of ED prevalence for 'healthy control', 0.1370, is not included in the 95% CI of ED prevalence for patients with cancer after treatment). CI = confidence interval. ED = erectile dysfunction.

Figure 1. Comparisons of prevalence of ED among patients with cancer and healthy control. Pooled prevalence of ED represented by red square and the corresponding CIs shown in red extending line (blue circles are centred at the prevalence of ED reported in each of the included primary studies with circle size proportional to sample size of each primary study). ED = erectile dysfunction.
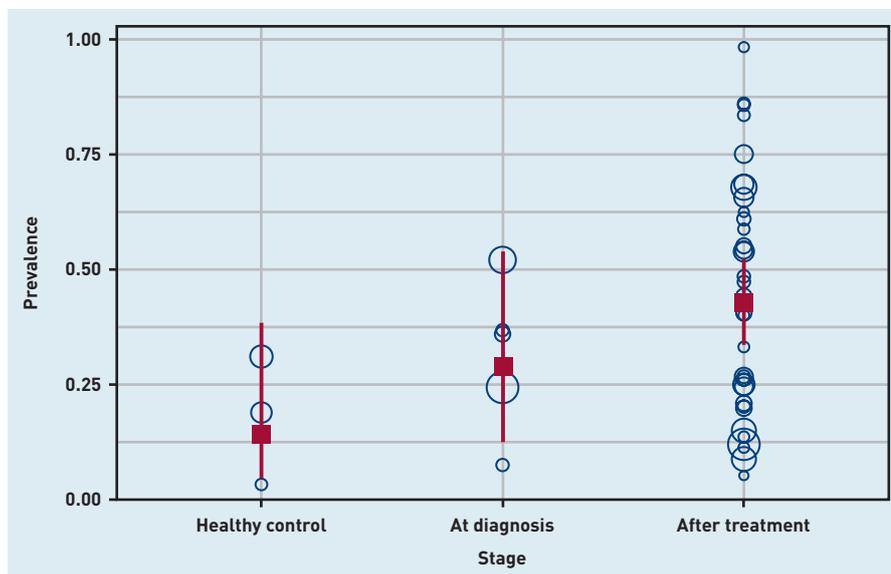
study heterogeneity parameter estimated by DerSimonian–Laird (DL) method[21] was used to pool the prevalence of ED as absolute estimates (%) with their 95% confidence intervals (CIs) for each stage. A univariate MA regression including the three-level group variable for healthy/at diagnosis/after treatment stages as the only independent variable was used to assess the difference in ED prevalence across the three stages. A scatter plot with point and CI estimates of prevalence of ED across three different groups of patients is illustrated. Publication bias was assessed by a visual inspection of funnel plots and calculating the Egger bias test.[22] The authors planned to apply the trim and fill analysis[23] for overcoming possible publication bias (*P*<0.10).

Further MA were conducted for the 40 studies only involving patients at diagnosis and after treatment, that is, excluding healthy control. Graphical comparisons of the prevalence of ED across these two stages of cancer treatment were given by a classic forest plot. Heterogeneity across these 40 studies involving the two cancer treatment stages was assessed by the I^2 metric and taking, as measure of high heterogeneity, an I^2 >50% or *P*<0.05 for testing the χ^2-distributed Q statistic for between-studies heterogeneity (a high value of Q would result in a high value of I^2 since $I^2 = [Q-K+1]/Q$ where K is the number of studies).[24] In case of high ED-prevalence heterogeneity and having at least 10 studies for the outcome, the authors used stage, continent, mean age, age range, age standard deviation, method of ED assessment, cancer site, proportion of patients that underwent radiotherapy, proportion of patients with diabetes, and proportion of patients that underwent chemotherapy as possible predictors for MA regression analyses. The plots of study count distribution for each of the above moderators across their observed values are given. A univariate MA regression model for each moderator was fitted. The stage predictor as well as the significant moderators screened out by these univariate MA regression analyses were used as potential predictors to fit a multiple MA regression with manual variable selection procedure applied. The conclusions by the final multiple MA regression model were drawn with multiple testing concern by controlling for a false discovery rate (FDR).[25] Back-transformed estimated prevalence values of ED with 95% CI for studies with different levels of predictor variables in the final multiple MA regression model are given.

For all MA regression, the authors applied the logit transformation to the observed prevalence across primary studies to make the transformed prevalence follow a normal distribution, and the MA regression analysis was based on the transformed scale.

Assessment of study quality
Study quality was assessed by two investigators (first and third authors) using the Newcastle–Ottawa Scale (NOS).[26,27] This scale has been adapted from the Newcastle–Ottawa Quality Assessment Scale for cohort studies to perform a quality assessment of cross-sectional studies for the systematic review. A third reviewer was available for mediation (thirteenth author). The NOS assigns a maximum of 9
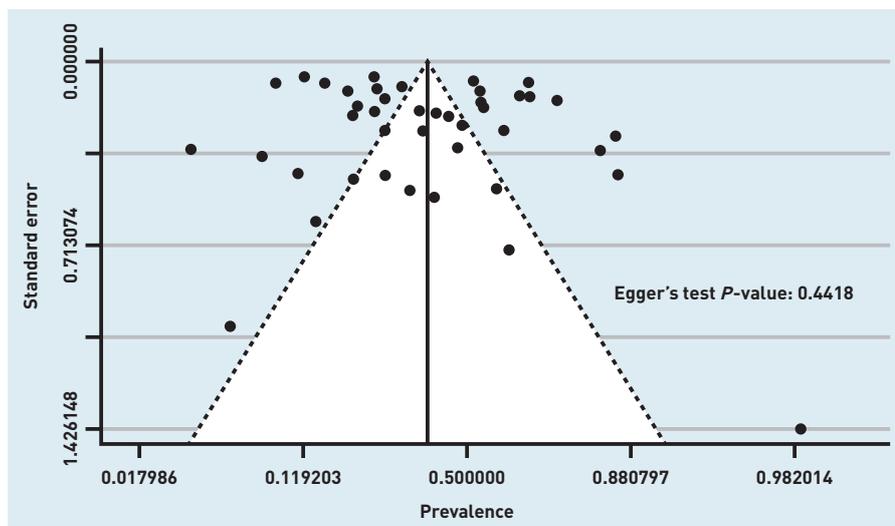
Figure 2. Funnel plot.

points based on three quality parameters: selection, comparability, and outcome.

RESULTS

The electronic search yielded 1301 studies, after de-duplication, that were assessed for inclusion in the review. Of these, 141 were potentially eligible and subsequently scrutinised in full text (see Supplementary Figure S1).

Excluded studies

Among the relevant studies, 98 failed to meet the inclusion criteria and were excluded from this review. Of these, 37 used

no validated tools for ED assessment, 36 had no useful data on ED prevalence, 18 were longitudinal studies, four had no data on the association between ED and cancer, and three were double publications.

Included studies

The 43 studies that were included, 36 prospective and 7 retrospective, contained a total of 13 148 participants.[28–59] The majority of the studies ($n = 25$) were conducted in Europe, with those remaining in North America ($n = 6$), Asia ($n = 6$), the Middle East ($n = 5$), and Oceania ($n = 1$). The most affected cancer sites were prostate and rectum ($n = 12$ studies, respectively), testis ($n = 6$), haematological ($n = 5$), multiple ($n = 3$), colorectal ($n = 2$), and penis, colon, and anus ($n = 1$ each).

According to NOS, the median quality of the studies was 4.97 (range 3–7), indicating an overall good quality of studies (Supplementary Table S2). In particular, the majority of the studies ($n = 18$) scored 5, followed by 11 studies with 4. Only three studies scored 3 while six and five studies scored 6 and 7, respectively.

Meta-analysis on prevalence of ED across three stages: healthy, at diagnosis, and after treatment

Distribution of study counts and the corresponding pooled prevalence of ED at the three different stages are shown in Table 1. The pooled prevalence of ED at the 'after treatment' stage was statistically significantly different from that of 'healthy control' by the univariate MA regression analysis with dummy variables for stage ($P = 0.0322$).

The pooled prevalence of these three groups is illustrated in Figure 1 to compare prevalence of ED among patients in the two cancer treatment stages with that of 'healthy control' individuals.

Small study effect (including publication bias) was not found among the included studies and the trim and fill analysis did not modify the results. Figure 2 shows the funnel plot, with non-significant Egger's test result for funnel plot asymmetry ($P = 0.4418$).

Meta-analysis on prevalence of ED across the two cancer treatment stages: at diagnosis and after treatment

Pooling data of the 40 studies of patients with cancer only, that is, excluding three studies of healthy controls, an overall prevalence of 40.72% (95% CI = 31.80% to 50.29%) was found, with a prevalence of 28.60% (95% CI = 12.10% to 53.83%) at time

Table 2. Study counts of the 10 possible predictors for ED prevalence and *P*-value for the uni-predictor (or smallest *P*-value for the uni-predictor dummy variables) in the univariate MA regression analysis

Predictor	Study count, *n*	Coefficient estimate	95% CI	*P*-value
Stage	40	0.6210	−0.5253 to 1.7673	0.2883
Continent	40	1.2655	−0.3051 to 2.8362	0.1143
Mean age	40	0.0503	0.0243 to 0.0762	0.0002[a]
Age range	40	0.0057	−0.0210 to 0.0325	0.6739
ED assessment method	40	1.5236	−0.1845 to 3.2316	0.0804
Cancer site	40	−1.8135	−2.5841 to −1.0429	<0.0001[b]
Age standard deviation	17	−0.0078	−0.0733 to 0.0576	0.8144
Proportion of patients who underwent radiotherapy	15	1.0584	−1.0225 to 3.1393	0.3188
Proportion of patients with diabetes	12	−3.6361	−19.1360 to 11.8639	0.6457
Proportion of patients who underwent chemotherapy	12	0.1348	−1.9925 to 2.2621	0.9012

[a]*Significance code controlling for type I error rate <0.05 and >0.01.* [b]*Significance code controlling for type I error rate <0.0001. CI = confidence interval. ED = erectile dysfunction. MA = meta-analysis.*
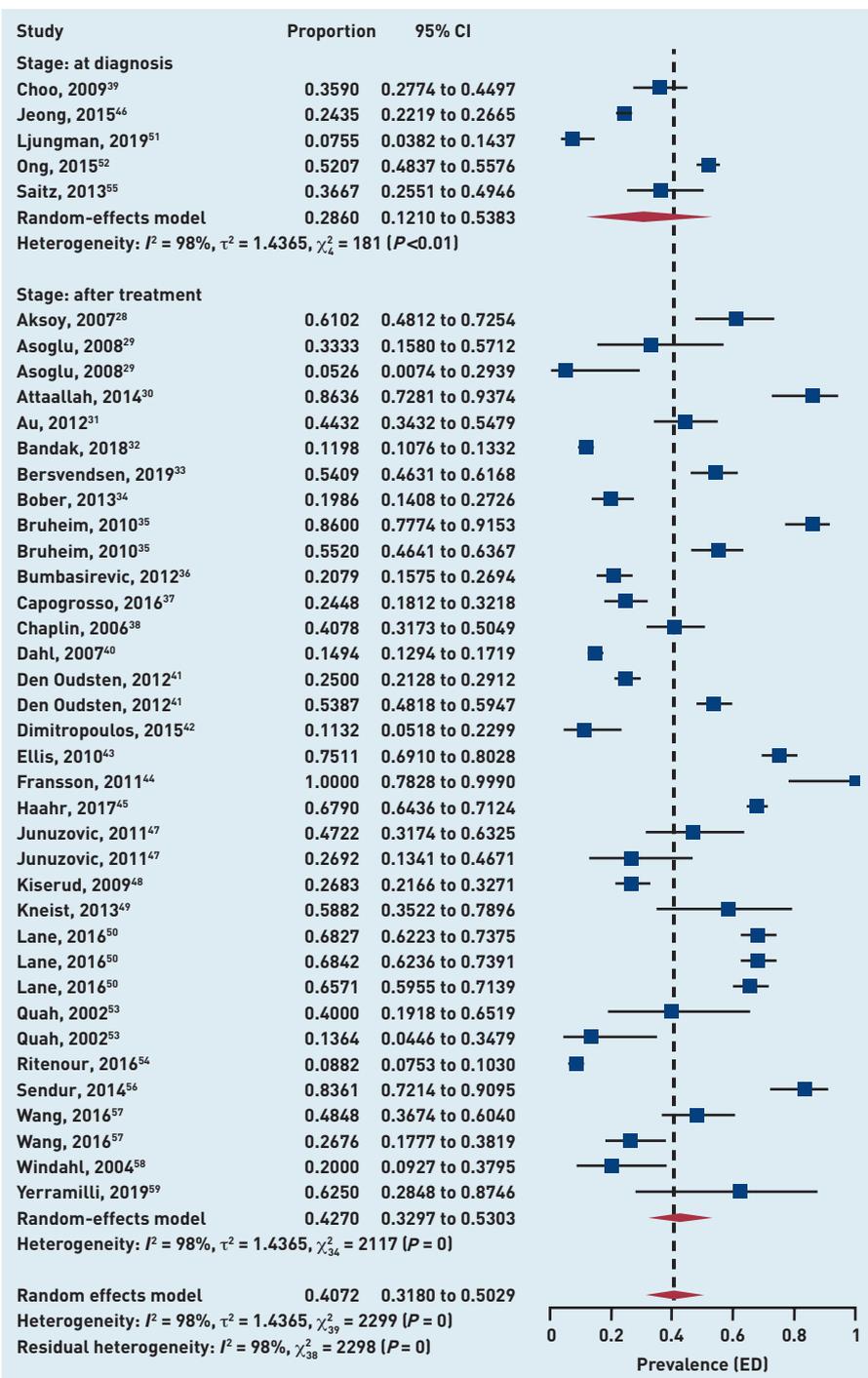
Study	Proportion	95% CI
Stage: at diagnosis		
Choo, 2009[39]	0.3590	0.2774 to 0.4497
Jeong, 2015[46]	0.2435	0.2219 to 0.2665
Ljungman, 2019[51]	0.0755	0.0382 to 0.1437
Ong, 2015[52]	0.5207	0.4837 to 0.5576
Saitz, 2013[55]	0.3667	0.2551 to 0.4946
Random-effects model	**0.2860**	**0.1210 to 0.5383**
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1.4365$, $\chi^2_4 = 181$ ($P<0.01$)		
Stage: after treatment		
Aksoy, 2007[28]	0.6102	0.4812 to 0.7254
Asoglu, 2008[29]	0.3333	0.1580 to 0.5712
Asoglu, 2008[29]	0.0526	0.0074 to 0.2939
Attaallah, 2014[30]	0.8636	0.7281 to 0.9374
Au, 2012[31]	0.4432	0.3432 to 0.5479
Bandak, 2018[32]	0.1198	0.1076 to 0.1332
Bersvendsen, 2019[33]	0.5409	0.4631 to 0.6168
Bober, 2013[34]	0.1986	0.1408 to 0.2726
Bruheim, 2010[35]	0.8600	0.7774 to 0.9153
Bruheim, 2010[35]	0.5520	0.4641 to 0.6367
Bumbasirevic, 2012[36]	0.2079	0.1575 to 0.2694
Capogrosso, 2016[37]	0.2448	0.1812 to 0.3218
Chaplin, 2006[38]	0.4078	0.3173 to 0.5049
Dahl, 2007[40]	0.1494	0.1294 to 0.1719
Den Oudsten, 2012[41]	0.2500	0.2128 to 0.2912
Den Oudsten, 2012[41]	0.5387	0.4818 to 0.5947
Dimitropoulos, 2015[42]	0.1132	0.0518 to 0.2299
Ellis, 2010[43]	0.7511	0.6910 to 0.8028
Fransson, 2011[44]	1.0000	0.7828 to 0.9990
Haahr, 2017[45]	0.6790	0.6436 to 0.7124
Junuzovic, 2011[47]	0.4722	0.3174 to 0.6325
Junuzovic, 2011[47]	0.2692	0.1341 to 0.4671
Kiserud, 2009[48]	0.2683	0.2166 to 0.3271
Kneist, 2013[49]	0.5882	0.3522 to 0.7896
Lane, 2016[50]	0.6827	0.6223 to 0.7375
Lane, 2016[50]	0.6842	0.6236 to 0.7391
Lane, 2016[50]	0.6571	0.5955 to 0.7139
Quah, 2002[53]	0.4000	0.1918 to 0.6519
Quah, 2002[53]	0.1364	0.0446 to 0.3479
Ritenour, 2016[54]	0.0882	0.0753 to 0.1030
Sendur, 2014[56]	0.8361	0.7214 to 0.9095
Wang, 2016[57]	0.4848	0.3674 to 0.6040
Wang, 2016[57]	0.2676	0.1777 to 0.3819
Windahl, 2004[58]	0.2000	0.0927 to 0.3795
Yerramilli, 2019[59]	0.6250	0.2848 to 0.8746
Random-effects model	**0.4270**	**0.3297 to 0.5303**
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1.4365$, $\chi^2_{34} = 2117$ ($P = 0$)		
Random effects model	**0.4072**	**0.3180 to 0.5029**
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1.4365$, $\chi^2_{39} = 2299$ ($P = 0$)		
Residual heterogeneity: $I^2 = 98\%$, $\chi^2_{38} = 2298$ ($P = 0$)		

Prevalence (ED): 0 — 0.2 — 0.4 — 0.6 — 0.8 — 1

Figure 3. Prevalence of ED among patients with cancer. ED = erectile dysfunction.

were conducted, with 10 predictors used. Distribution plots of study counts for each of the 10 possible predictors are shown in Supplementary Figure S2. Study counts of these 10 possible predictors for the ED prevalence among patients with cancer and P-values for continuous predictor (or smallest P-value for the dummy variables of categorical predictor) in the univariate MA regression analysis are shown in Table 2. The results by the univariate MA regression showed that 'mean age' and 'cancer site' variables were significantly associated with the ED prevalence.

After a manual variable selection accounting for the multicollinearities of the predictors, a parsimonious MA regression model was built to predict the highly heterogeneous ED prevalence. Regression coefficient estimates of this prediction model are shown in Table 3. This model only included two predictors: stage and cancer site. Since both of these predictors are categorical variables, dummy variables were created to represent them. The reference level for stage was selected as 'at diagnosis', and the reference level for cancer site was selected as 'prostate', since prostate cancer has the highest count ($n = 12$) in the collected primary study data (this count is the same as for rectum cancer) and prostate cancer is a common cancer in urology. Both predictors are significantly controlling for an FDR <0.05 in this MA regression model, indicating that the ED prevalence estimates reported by primary studies were significantly associated with factors of stage and cancer site. The interpretations of those significant regression coefficients are given as follows: study-reported odds of ED at after-treatment stage are estimated to be 2.4823 (exponential of 0.9092) times that of at-diagnosis stage controlling for other covariates (95% CI = 1.3054 to 4.7204; adjusted P-value controlling for FDR = 0.0204); study-reported odds of ED for patients with colon cancer are estimated to be 0.2300 (exponential of −1.4697) times that of patients with prostate cancer controlling for other covariates (95% CI = 0.0697 to 0.7587; adjusted P-value controlling for FDR = 0.0434); study-reported odds of ED for patients with lymphoma cancer are estimated to be 0.2530 (exponential of −1.3744) times that of patients with prostate cancer controlling for other covariates (95% CI = 0.0756 to 0.8470; adjusted P-value controlling for FDR = 0.0473); study-reported odds of ED for patients with multiple cancers are estimated to be 0.1041 (exponential of −2.2625) times that of patients with prostate cancer controlling for other covariates (95% CI = 0.0419 to 0.2586; adjusted P-value controlling for FDR <0.0001); study-reported

of diagnosis and 42.70% (95% CI = 32.97% to 53.03%) after treatment, across cancer locations. A high degree of overall heterogeneity ($I^2 = 98\%$; $P<0.001$) was found. Figure 3 shows the prevalence of ED among patients with cancer.

To locate the potential predictors that account for the very high heterogeneity of ED prevalence among all the primary studies involving patients with cancer in the two treatment stages, MA regression analyses

Table 3. Prediction model for highly heterogeneous ED prevalence

Regression coefficients	Estimate	Standard error	z	P-value	Adjusted P-value
Intercept	−0.5380	0.2720	−1.9778	0.0479	0.0659
Stage: after treatment	0.9092	0.3279	2.7726	0.0056	0.0204[a]
Cancer site					
Colon	−1.4697	0.6089	−2.4136	0.0158	0.0434[a]
Colorectal	0.9628	0.4856	1.9830	0.0474	0.0744
Haematological	−0.0742	0.4759	−0.1560	0.8761	0.9637
Lymphoma	−1.3744	0.6165	−2.2293	0.0258	0.0473[a]
Multiple	−2.2625	0.4643	−4.8726	<0.0001	<0.0001[b]
Penis	−1.7574	0.7535	−2.3324	0.0197	0.0433[a]
Anus	0.1397	0.9449	0.1478	0.8825	0.8825
Rectum	−0.3761	0.2919	−1.2888	0.1975	0.2414
Testis	−2.0001	0.3148	−6.3533	<0.0001	<0.0001[b]

[a]Significance code controlling for false discovery rate (FDR) <0.05 and >0.01. [b]Significance code controlling for FDR <0.0001. ED = erectile dysfunction.

Table 4. Back-transformed estimated ED prevalence values for studies with patients of different cancers at two stages by the predictive MA regression model

Cancer site	Prevalence at diagnosis, % (95% CI)	Prevalence at treatment, % (95% CI)
Prostate	59.2 (48.7 to 68.9)	78.3 (58.2 to 90.3)
Colon	25.0 (9.8 to 50.4)	45.3 (18.6 to 75.0)
Colorectal	79.1 (61.8 to 89.9)	90.4 (76.4 to 96.5)
Haematological	57.4 (37.0 to 75.5)	77.0 (53.9 to 90.5)
Lymphoma	26.8 (10.6 to 53.2)	47.6 (19.9 to 77.0)
Multiple	13.1 (6.3 to 25.2)	27.2 (11.8 to 51.2)
Penis	20.0 (5.7 to 50.7)	38.3 (11.6 to 74.6)
Anus	62.5 (21.6 to 91.0)	80.5 (37.9 to 96.6)
Rectum	49.9 (40.4 to 59.4)	71.2 (53.9 to 83.9)
Testis	16.4 (10.7 to 24.3)	32.7 (16.8 to 53.9)

CI = confidence interval. MA = meta-analysis.

odds of ED for patients with penis cancer are estimated to be 0.1725 (exponential of −1.7574) times that of patients with prostate cancer controlling for other covariates (95% CI = 0.0394 to 0.7553; adjusted P-value controlling for FDR = 0.0433); study-reported odds of ED for patients with testis cancer are estimated to be 0.1353 (exponential of −2.0001) times that of patients with prostate cancer controlling for other covariates (95% CI = 0.0730 to 0.2508; adjusted P-value controlling for FDR <0.0001).

The R^2 value of this MA regression is as high as 75.70%, indicating that this MA regression model already accounts for 75.70% heterogeneity of ED prevalence reported by the 40 studies involving patients with cancer (data not shown). The back-transformed estimated ED prevalence values for studies with patients of different cancers at the two stages by this MA regression are shown in Table 4.

DISCUSSION
Summary
In the present systematic review the search yielded 1301 individual studies, of which 43 studies with a total of 13 148 participants were included in the analysis. The study provides pooled estimates for ED in survivors of cancer across all cancer sites, providing this kind of synthesised data for the first time. Overall, pooled data of the included studies showed an ED prevalence of 40.72% (95% CI = 31.80% to 50.29%) in patients with cancer, with a prevalence of 28.60% (95% CI = 12.10% to 53.83%) at time of diagnosis and 42.70% (95% CI = 32.97% to 53.03%) after treatment, across cancer locations.

Erectile dysfunction was particularly high in male survivors of cancer and was found to be associated with cancer treatment, cancer site, and age.

Strengths and limitations
This systematic review and MA provide a comprehensive overview of evidence on ED prevalence in survivors of cancer in general, with studies using validated self-reported methods.

Limitations of the present analysis include the inherent limitations from the included studies. Study populations were on average aged >60 years, which may have contributed to the prevalence as ED risks increase with age. This is similar to the over-representation of cancer sites in the pelvic area. Again, because of the small number of primary studies that provided complete clinical and biological (for example, serum testosterone or oestradiol levels) features of the participants, the authors were not able to run some meta-regression analyses using well-known independent risk factors for ED (such as dyslipidaemia, hypertension, diabetes mellitus, and depression) as moderators of the present findings. Lastly, the results pertaining to survivors of cancer with multiple cancer sites need to be taken with caution given that there were only three primary studies that were included in the analysis.

Comparison with existing literature
Meta-analyses of studies reporting ED prevalence levels in healthy males are rare and mostly focus on samples of Asian males. These studies report that ED prevalence in individual studies has been reported

from 2% to 82%, differing among age groups and how ED has been assessed. Generally, lowest reports have been found among younger males aged between 20 and 29 years at 15.1% (99% CI = 12.2% to 18.1%), while the highest have been found in the groups aged ≥60 years at 70.0% (99% CI = 62.3% to 77.7%).[60] Studies have noted that self-reporting leads to lower estimates than measuring by a standardised questionnaire.[61,62] Overall pooled estimate for ED prevalence has been reported at 49.69% (95% CI = 39.29% to 60.10%) for Chinese samples.[63]

Most studies included in the presented MA focused on cancers located in the pelvic region (prostate and rectum) and testis, where the effects would be expected to be strongest given the possible neurovascular damage associated with treatment. Androgen-deprivation therapy (ADT), which is used in prostate cancer management, leads to ED in most males who did not have dysfunction before therapy.[64–66] Various chemotherapeutic agents may induce micro-angiopathy and vascular insufficiency in the *corpus cavernosum* of the penis as well as neurotoxicity that may result in ED.[67] In a study of >260 males on platinum-based chemotherapy, 40% were reported to have ED on standardised questionnaires, which corresponds to pooled data in the present analysis.[68] Erectile dysfunction is also a common finding after radiation therapy for prostate cancer with varying incidence reported in studies depending on dose, technique, associated treatments, and time post-treatment, with brachytherapy showing lower rates of ED compared with external-beam radiation therapy in some studies.[69,70]

Surgical cancer treatment in the pelvic area may also lead to post-operative sexual dysfunction, depending both on the surgical techniques and methods used in assessing ED post-operatively. In one study, >90% of patients who had radical prostatectomy reported lower scores on the IIEF-5 than before surgery,[71] with an Italian-based study reporting that reaching perioperative levels does not equal patient satisfaction, with little over 25% of patients who reported preoperative scores being satisfied. Only males who achieved scores >22, as measured by the IIEF-5, and who returned to the same levels post-operatively were also satisfied with their sexual function.[72] Similarly, 86% of males who had radical cystectomy were not able to achieve vaginal penetration[73] and studies report between 10% and 50% of males having sexual dysfunction following colorectal surgery, where the proposed mechanism may lie in the injury to the hypogastric plexus.[43,74] In survivors of testicular cancer, a study measuring blood flow and erectile haemodynamic using duplex ultrasonography reported that 12 months after treatment there were no differences between males with or without hypogonadism, suggesting hyperadrenergic mediated causes of ED.[75]

Sexual function may be influenced by systemic chemo- or radiotherapy, as well as by psychological factors, such as depression, anxiety, low self-esteem, or issues with body image, which are known conditions in all patients with cancer and survivors, regardless of the primary cancer site.[18,76–81] However, very few studies examine the effects of cancer sites outside of the pelvic area on overall sexual function or ED, specifically, in males. An MA on sexual functioning in male lymphoma survivors reported prevalence of sexual dysfunction between 20% and 54%.[82] Anecdotal evidence also suggests similar prevalence in patients with lung cancer. In fact, though this is the most prevalent cancer in males globally, to the authors' knowledge there is still no research on sexual function in male patients with lung cancer or survivors, as most of the focus is on short-term survival rather than post-treatment quality of life.[83]

Implications for practice

The present analysis has shown high prevalence of ED in survivors of cancer at various points and across cancer types. The aetiology of ED in survivors of cancer is multimodal with a variety of factors, including psychological and physical ones. The results should improve the visibility of this issue and allow healthcare professionals to more easily identify survivors of cancer under higher risk of ED. Moreover, it is important that clinicians be aware of the impact of ED on the quality of life and mental health of survivors of cancer, especially as sexuality and intimacy may reduce some of the psychosocial issues associated with receiving a cancer diagnosis.[19,20] Various therapeutic modalities exist and healthcare providers should facilitate an open exchange with patients before cancer treatment and manage expectations. Primary care physicians are of great importance here given their role in follow-through during cancer care and beyond. As males are generally less prone to discuss sexual health problems in a clinical setting, clinicians should routinely and proactively ask about sexual health, recognising and acknowledging any concerns. This approach may increase patient satisfaction and improve the doctor–patient relationship.[84]

Discuss this article
Contribute and read comments about this article: **bjgp.org/letters**

REFERENCES

1. World Cancer Research Fund, American Institute for Cancer Research. Worldwide cancer data. Global cancer statistics for the most common cancers. https://www.wcrf.org/dietandcancer/cancer-trends/worldwide-cancer-data (accessed 15 Mar 2021).

2. Sadovsky R, Basson R, Krychman M, *et al*. Cancer and sexual problems. *J Sex Med* 2010; **7(1 Pt 2):** 349–373.

3. Virag R, Zwang G, Dermange H, Legman M. Vasculogenic impotence: a review of 92 cases with 54 surgical operations. *Vasc Surg* 1981; **15(1):** 9–17.

4. Kakehi Y. Watchful waiting as a treatment option for localized prostate cancer in the PSA era. *Jpn J Clin Oncol* 2003; **33(1):** 1–5.

5. Gettman MT, Blute ML. Critical comparison of laparoscopic, robotic and open radical prostatectomy: techniques, outcomes, and cost. *Curr Urol Rep* 2006; **7(3):** 193–199.

6. Steineck G, Helgesen F, Adolfsson J, *et al*. Quality of life after radical prostatectomy or watchful waiting. *N Engl J Med* 2002; **347(11):** 790–796.

7. Bacon CG, Giovannucci E, Testa M, Kawachi I. The impact of cancer treatment on quality of life outcomes for patients with localized prostate cancer. *J Urol* 2001; **166(5):** 1804–1810.

8. Zippe C, Nandipati K, Agarwal A, Raina R. Sexual dysfunction after pelvic surgery. *Int J Impot Res* 2006; **18(1):** 1–18.

9. Johansson E, Steineck G, Holmberg L, *et al*. Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian Prostate Cancer Group-4 randomised trial. *Lancet Oncol* 2011; **12(9):** 891–899.

10. Mohamed NE, Chaoprang Herrera P, Hudson S, *et al*. Muscle invasive bladder cancer: examining survivors' burden and unmet needs. *J Urol* 2014; **191(1):** 48–53.

11. Traa MJ, De Vries J, Roukema JA, *et al*. The sexual health care needs after colorectal cancer: the view of patients, partners, and health care professionals. *Support Care Cancer* 2014; **22(3):** 763–772.

12. Yau I, Vuong T, Garant A, *et al*. Risk of hypogonadism from scatter radiation during pelvic radiation in male patients with rectal cancer. *Int J Radiat Oncol Biol Phys* 2009; **74(5):** 1481–1486.

13. Modh RA, Mulhall JP, Gilbert SM. Sexual dysfunction after cystectomy and urinary diversion. *Nat Rev Urol* 2014; **11(8):** 445–453.

14. Tal R, Stember DS, Logmanieh N, *et al*. Erectile dysfunction in men treated for testicular cancer. *BJU Int* 2014; **113(6):** 907–910.

15. American Cancer Society. How cancer can affect erections. 2020. https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/fertility-and-sexual-side-effects/sexuality-for-men-with-cancer/erections-and-treatment.html (accessed 15 Mar 2021).

16. Lindau ST, Surawska H, Paice J, Baron SR. Communication about sexuality and intimacy in couples affected by lung cancer and their clinical-care providers. *Psychooncology* 2011; **20(2):** 179–185.

17. Thygesen KH, Schjødt I, Jarden M. The impact of hematopoietic stem cell transplantation on sexuality: a systematic review of the literature. *Bone Marrow Transplant* 2012; **47(5):** 716–724.

18. Nelson CJ, Mulhall JP, Roth AJ. The association between erectile dysfunction and depressive symptoms in men treated for prostate cancer. *J Sex Med* 2011; **8(2):** 560–566.

19. Hordern AJ, Currow DC. A patient-centered approach to sexuality in the face of life-limiting illness. *Med J Aust* 2003; **179(Suppl 6):** S8–S11.

20. Wimberly SR, Carver CS, Laurenceu JP, *et al*. Perceived partner reactions to diagnosis and treatment of breast cancer: impact on psychosocial and psychosexual adjustment. *J Consult Clin Psychol* 2005; **73(2):** 300–311.

21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7(3):** 177–188.

22. Sterne JAC, Egger M. Regression methods to detect publication and other bias in meta-analysis. In: Rothstein HR, Sutton AJ, Borenstein M, eds. *Publication bias in meta-analysis: prevention, assessment and adjustments*. Chichester: Wiley, 2005: 99–110.

23. Duval S, Tweedie RL. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; **56(2):** 455–463.

24. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327(7414):** 557–560.

25. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc B* 1995; **57(1):** 289–300.

26. Wells GA, Shea B, O'Connell D, *et al*. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 15 Mar 2021).

27. Luchini C, Brendon S, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: advantages and limitations of the Newcastle Ottawa Scale. *World J Meta-Anal* 2017; **5(4):** 80–84.

28. Aksoy S, Harputluoglu H, Kilickap S, *et al*. Erectile dysfunction in successfully treated lymphoma patients. *Support Care Cancer* 2008; **16(3):** 291–297.

29. Asoglu O, Matlim T, Karanlik H, *et al*. Impact of laparoscopic surgery on bladder and sexual function after total mesorectal excision for rectal cancer. *Surg Endosc* 2009; **23(2):** 296–303.

30. Attaallah W, Ertekin C, Tinay I, Yegen C. High rate of sexual dysfunction following surgery for rectal cancer. *Ann Coloproctol* 2014; **30(5):** 210–215. Epub 2014 Oct 28.

31. Au TY, Zauszniewski JA, King TM. Demographics, cancer-related factors, and sexual function in rectal cancer patients in Taiwan: preliminary findings. *Cancer Nurs* 2012; **35(5):** E17–E25.

32. Bandak M, Lauritsen J, Johansen C, *et al*. Sexual function and quality of life in a national cohort of survivors of bilateral testicular cancer. *Eur Urol Focus* 2020; **6(4):** 711–719.

33. Bersvendsen HS, Haugnes HS, Dahl AA, *et al*. Sexual function in long-term male lymphoma survivors after high-dose therapy with autologous stem-cell transplantation. *Bone Marrow Transplant* 2020; **55(5):** 891–905.

34. Bober SL, Zhou ES, Chen B, *et al*. Sexual function in childhood cancer survivors: a report from Project REACH. *J Sex Med* 2013; **10(8):** 2084–2093.

35. Bruheim K, Guren MG, Dahl AA, *et al*. Sexual function in males after radiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2010; **76(4):** 1012–1017.

36. Bumbasirevic U, Bojanic N, Pekmezovic T, *et al*. Health-related quality of life, depression, and sexual function in testicular cancer survivors in a developing country: a Serbian experience. *Support Care Cancer* 2013; **21(3):** 757–763.

37. Capogrosso P, Boeri L, Ferrari M, *et al*. Long-term recovery of normal sexual function in testicular cancer survivors. *Asian J Androl* 2016; **18(1):** 85–89.

38. Chaplin BJ, Crop SR, Bangma CH, *et al*. Sexual function following treatment of localised prostate cancer with HDR-Ir-192 brachytherapy combined with external beam radiotherapy. *Sexologies* 2006; **15(4):** 255–261.

39. Choo R, Long J, Gray R, *et al*. Prospective survey of sexual function among patients with clinically localized prostate cancer referred for definitive radiotherapy and the impact of radiotherapy on sexual function. *Support Care Cancer* 2010; **18(6):** 715–722.

40. Dahl AA, Bremnes R, Dahl O, *et al*. Is the sexual function compromised in long-term testicular cancer survivors? *Eur Urol* 2007; **52(5):** 1438–1447.

41. Den Oudsten BL, Traa MJ, Thong MS, *et al*. Higher prevalence of sexual dysfunction in colon and rectal cancer survivors compared with the normative population: a population-based study. *Eur J Cancer* 2012; **48(17):** 3161–3170.

42. Dimitropoulos K, Karatzas A, Papandreou C, *et al*. Sexual dysfunction in testicular cancer patients subjected to post-chemotherapy retroperitoneal lymph node dissection: a focus beyond ejaculation disorders. *Andrologia* 2016; **48(4):** 425–430.

43. Ellis R, Smith A, Wilson S, *et al*. The prevalence of erectile dysfunction in post-treatment colorectal cancer patients and their interests in seeking treatment: a cross-sectional survey in the West-Midlands. *J Sex Med* 2010; **7(4 Pt 1):** 1488–1496.

44. Fransson P, Widmark A. Does one have a sexual life 15 years after external beam radiotherapy for prostate cancer? Prospective patient-reported outcome of sexual function comparison with age-matched controls. *Urol Oncol* 2011; **29(2):** 137–144.

45. Haahr MK, Azawi NH, Andersen LG, *et al*. A retrospective study of erectile function and use of erectile aids in prostate cancer patients after radical prostatectomy in Denmark. *Sex Med* 2017; **5(3):** e156–e162.

46. Jeong CW, Lee S, Jeong SJ, *et al*. Preoperative erectile function and the pathologic features of prostate cancer. *Int Braz J Urol* 2015; **41(2):** 265–273.

47. Junuzovic D, Hasanbegovic M, Omerbegovic D. Erectile dysfunction as a complication after treatment of prostate cancer. *Mater Sociomed* 2011; **23(4):** 230–231.

48. Kiserud CE, Schover LR, Dahl AA, *et al*. Do male lymphoma survivors have impaired sexual function? *J Clin Oncol* 2009; **27(35):** 6019–6026.

49. Kneist W, Kauff DW, Rubenwolf P, *et al*. Intraoperative monitoring of bladder and internal anal sphincter innervation: a predictor of erectile function following low anterior rectal resection for rectal cancer? Results of a prospective clinical study. *Dig Surg* 2013; **30(4–6):** 459–465.

50. Lane A, Metcalfe C, Young GJ, *et al*; ProtecT Study group. Patient-reported outcomes in the ProtecT randomized trial of clinically localized prostate cancer treatments: study design, and baseline urinary, bowel and sexual function and quality of life. *BJU Int* 2016; **118(6):** 869–879.

51. Ljungman L, Eriksson LE, Flynn KE, *et al*. Sexual dysfunction and reproductive concerns in young men diagnosed with testicular cancer: an observational study. *J Sex Med* 2019; **16(7):** 1049–1059.

52. Ong WL, McLachlan H, Millar JL. Prevalence of baseline erectile dysfunction (ED) in an Australian cohort of men with localized prostate cancer. *J Sex Med* 2015; **12(5):** 1267–1274.

53. Quah HM, Jayne DG, Eu KW, Seow-Choen F. Bladder and sexual dysfunction following laparoscopically assisted and conventional open mesorectal resection for cancer. *Br J Surg* 2002; **89(12):** 1551–1556.

54. Ritenour CW, Seidel KD, Leisenring W, *et al*. Erectile dysfunction in male survivors of childhood cancer — a report from the childhood cancer survivor study. *J Sex Med*. 2016; **13(6):** 945–954.

55. Saitz TR, Serefoglu EC, Trost LW, *et al*. The pre-treatment prevalence and types of sexual dysfunction among patients diagnosed with prostate cancer. *Andrology* 2013; **1(6):** 859–863.

56. Sendur MA, Aksoy S, Ozdemir NY, *et al*. Evaluation of erectile dysfunction risk factors in young male survivors of colorectal cancer. *J BUON* 2014; **19(1):** 115–123.

57. Wang G, Wang Z, Jiang Z, *et al*. Male urinary and sexual function after robotic pelvic autonomic nerve-preserving surgery for rectal cancer. *Int J Med Robot* 2017; **13(1):** DOI: 10.1002/rcs.1725.

58. Windahl T, Skeppner E, Andersson SO, Fugl-Meyer KS. Sexual function and satisfaction in men after laser treatment for penile carcinoma. *J Urol* 2004; **172(2):** 648–651.

59. Yerramilli D, Drapek L, Nipp RD, *et al*. Sexual function, quality of life, and mood after radiation therapy in patients with anal cancer. *J Gastrointest Cancer* 2020; **51(1):** 204–210.

60. Cheng JYW, Ng EML, Chen RYL, Ko JSN. Prevalence of erectile dysfunction in Asian populations: a meta-analysis. *Int J Impot Res* 2007; **19(3):** 229–244.

61. Wu C-J, Hsieh J-T, Lin JS-N, *et al*. Comparison of prevalence between self-reported erectile dysfunction and erectile dysfunction as defined by five-item International Index of Erectile Function in Taiwanese men older than 40 years. *Urology* 2007; **69(4):** 743–747.

62. Cappelleri JC, Siegel RL, Osterloh IH, Rosen RC. Relationship between patient self-assessment of erectile function and the erectile function domain of the International Index of Erectile Function. *Urology* 2000; **56(3):** 477–481.

63. Wang W, Fan J, Huang G, *et al*. Meta-analysis of prevalence of erectile dysfunction in mainland China: evidence based on epidemiological surveys. *Sex Med* 2017; **5(1):** e19–e30.

64. Mazzola CR, Mulhall JP. Impact of androgen deprivation therapy on sexual function. *Asian J Androl* 2012; **14(2):** 198–203.

65. Donovan KA, Gonzalez BD, Nelson AM, *et al*. Effect of androgen deprivation therapy on sexual function and bother in men with prostate cancer: a controlled comparison. *Psychooncology* 2018; **27(1):** 316–324.

66. White ID, Wilson J, Aslet P, *et al*. Development of UK guidance on the management of erectile dysfunction resulting from radical radiotherapy and androgen deprivation therapy for prostate cancer. *Int J Clin Pract* 2015; **69(1):** 106–123.

67. Chatterjee R, Andrews HO, McGarrigle HH, *et al*. Cavernosal arterial insufficiency is a major component of erectile dysfunction in some recipients of high-dose chemotherapy/chemo-radiotherapy for haematological malignancies. *Bone Marrow Transplant* 2000; **25(11):** 1185–1189.

68. Wiechno P, Demkow T, Kubiak K, *et al*. The quality of life and hormonal disturbances in testicular cancer survivors in Cisplatin era. *Eur Urol* 2007; **52(5):** 1448–1455.

69. Demanes DJ, Ghilezan MI. High-dose-rate brachytherapy as monotherapy for prostate cancer. *Brachytherapy* 2014; **13(6):** 529–541.

70. Putora PM, Engeler D, Haile SR, *et al*. Erectile function following brachytherapy, external beam radiotherapy, or radical prostatectomy in prostate cancer patients. *Strahlenther Onkol* 2016; **192(3):** 182–189.

71. Fode M, Frey A, Jakobsen H, Sønksen J. Erectile function after radical prostatectomy: do patients return to baseline? *Scand J Urol* 2016; **50(3):** 160–163.

72. Rossi MS, Moschini M, Bianchi M, *et al*. Erectile function recovery after nerve-sparing radical prostatectomy for prostate cancer: is back to baseline status enough for patient satisfaction? *J Sex Med* 2016; **13(4):** 669–678.

73. Krajewski W, Halska U, Poletajew S, *et al*. Influence of transurethral resection of bladder cancer on sexual function, anxiety, and depression. *Adv Exp Med Biol* 2018; **1116:** 37–50.

74. Sendur MAN, Aksoy S, Ozdemir NY, *et al*. Evaluation of erectile dysfunction risk factors in young male survivors of colorectal cancer. *J BUON* 2014; **19(1):** 115–123.

75. Tal R, Stember DS, Logmanieh N, *et al*. Erectile dysfunction in men treated for testicular cancer. *BJU Int* 2014; **113(6):** 907–910.

76. Schover LR, van der Kaaij M, van Dorst E, *et al*. Sexual dysfunction and infertility as late effects of cancer treatment. *EJC Suppl* 2014; **12(1):** 41–53.

77. Voznesensky M, Annam K, Kreder KJ. Understanding and managing erectile dysfunction in patients treated for cancer. *J Oncol Pract* 2016; **12(4):** 297–304.

78. Roth AJ, Weinberger MI, Nelson CJ. Prostate cancer: psychosocial implications and management. *Future Oncol* 2008; **4(4):** 561–568.

79. Moore TM, Strauss JL, Herman S, Donatucci CF. Erectile dysfunction in early, middle, and late adulthood: symptom patterns and psychosocial correlates. *J Sex Marital Ther* 2003; **29(5):** 381–399.

80. Rossen P, Pedersen AF, Zachariae R, von der Masse H. Sexuality and body image in long–term survivors of testicular cancer. *Eur J Cancer* 2012; **48(4):** 571–578.

81. Fingeret MC, Teo I, Epner DE. Managing body image difficulties of adult cancer patients: lessons from available research. *Cancer* 2014; **120(5):** 633–641.

82. Arden-Close E, Eiser C, Pacey A. Sexual functioning in male survivors of lymphoma: a systematic review (CME). *J Sex Med* 2011; **8(7):** 1833–1840.

83. Furlow B. Sexual dysfunction in patients with lung disease. *Lancet Respir Med* 2014; **2(6):** 439.

84. Sadovsky R. The role of the primary care clinician in the management of erectile dysfunction. *Rev Urol* 2002; **4(Suppl 3):** S54–S63.