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Ejaculation Disorders in Male Patients With Cancer: A Systematic Review and Meta-Analysis of Prevalence

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Abstract

Purpose: Ejaculatory dysfunction (EjD) and erectile dysfunction after cancer treatment are clinically important complications, but their exact prevalence by various kinds of cancer site and type of treatment is unknown. The aim of this systematic review and meta-analysis was to examine the available evidence and provide pooled estimates for prevalence of EjD and erectile dysfunction in relation to all cancer sites and identify characteristics associated with EjD in cancer patients.

Materials and Methods: We performed a systematic review and meta-analysis of cross-sectional and case-control studies. We searched 4 electronic databases (Medline!, CINAHL, PsychInfo and Embase!) until July 22, 2020. All retrospective or prospective studies reporting the prevalence of EjD in male patients with cancer were included in this review. A random effects meta-analysis was conducted calculating prevalence proportions with 95% confidence intervals. Prevalence proportions were calculated for the incidences of EjD by cancer site and type of treatment.

Results: A total of 64 studies (a total of 10,057 participants) were included for analysis. The most common cancer sites were bladder, colon, testis and rectum. The prevalence rates of EjD after surgical intervention ranged from 14.5% (95% CI 2.2e56.3) in colon cancer to 53.0% (95% CI 23.3e80.7) in bladder cancer. The prevalence rates of erectile dysfunction ranged from 6.8% (95% CI 0.8e39.1) in bladder cancer to 68.7% (95% CI 55.2e79.6) in cancer of the rectum.

Conclusions: In a large study-level meta-analysis, we looked at a high prevalence of EjD and erectile dysfunction at various cancer sites and across different treatment types. Prospective studies of EjD and erectile dysfunction after various kinds of cancer treatments are warranted.
**Introduction**

Cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or 1 in 6 deaths in 2018.\(^1\) The cancer burden continues to grow globally, but the survival rates of many types of cancers are improving thanks to accessible early detection, quality treatment and survivorship care.\(^1\) Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men with a wide range of physical and psychological adverse health impacts, including those associated with sexual function caused by the disease as well as the treatment. In turn, the worsening of sexual function is associated with anxiety, low mood and reductions in personal and couple’s quality of life.\(^2\)

Recently, a prevalence of 40.72% of erectile dysfunction was reported in cancer survivors, with a multimodal etiology including a variety of psychological and physical factors,\(^3\) which is vastly higher than a recent study of a representative sample of U.S. adults that have estimated erectile dysfunction at 11.3%.\(^4\) Other sexual problems associated with cancer and related treatments are ejaculatory disorders. The 3 main types of ejaculatory complications include premature, delayed and retrograde or dry orgasm.\(^5\) Especially for urological cancer, patients who undergo surgical therapy most frequently experience dry/ retrograde ejaculation (RE)da rare disorder leading to the lack of ejaculate during orgasms (dry orgasm or anejaculation) or to semen transport backwards into the bladder instead of through the urethra.\(^5\) Although this condition does not represent a danger to health, it is a discomfort for men and reduces fertility.\(^5\)

The mechanism by which RE occurs is a result of injury to the nerves or muscles that surround the bladder neck causing semen to move into the bladder rather than through the urethra.\(^5\) Recent evidence reported that ejaculatory dysfunctions (EjDs) occur at a high rate after retroperitoneal lymph node dissection, frequently performed in testicular and other pelvic cancers.\(^6\) Moreover, EjDs are commonly associated with transurethral resection associated with an enlarged prostate and also represent significant side effects following the treatment lower urinary tract symptoms caused by prostate cancer.\(^7\)

To date, the main reviews and meta-analyses consider the association between specific cancer and EjDs and erectile dysfunction, but no comprehensive reviews exist on their prevalence. Therefore, the aim of this systematic review and meta-analysis was to examine the available studies and provide pooled estimates for EjD prevalence in relation to all cancer
sites and identify characteristics associated with EjD in cancer survivors. In addition, we evaluated the prevalence of erectile dysfunction in the same patients. This topic is of importance because EjD is associated with a significant decrease in the quality of life.\(^2\)

**MATERIALS AND METHODS**

**Search Strategy**

We searched 4 electronic databases (Medline, CINAHL, PsychInfo and Embase) targeting reports published from inception to July 22, 2020. The following search strategy was used: ("Ejaculation" OR "ejaculatory disorders" OR "ejaculatory complications" OR "premature ejaculation" OR "early ejaculation" OR "rapid ejaculation" OR "retrograde ejaculation") AND ("cancer" OR "solid cancer" OR "neoplasia" OR "tumour" OR "solid tumour" OR "Sarcoma" OR "Carcinoma" OR "Lymphoma" OR "Colon carcinoma" OR "Prostate cancer" OR "Lung cancer" OR "Skin cancer" OR "Liver cancer" OR "Bone cancer" OR "Pancreas cancer" OR "Brain cancer" OR "Head cancer" OR "Neck cancer" OR "Kidney cancer" OR "Renal Cancer" OR "Thyroid cancer" OR "Neuroblastoma" OR "Wilms’ Tumor" OR "Retinoblastoma" OR "Posterior uveal melanoma" OR "Hodgkin" OR "Non-Hodgkin" OR "Rhabdomyosarcoma" OR "Osteogenic Sarcoma" OR "Ewing’s Sarcoma" OR "Angiosarcoma" OR "Chondrosarcoma").

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 in the analysis 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 2 investigators (MT, DP). The results were then compared and, in case of discrepancies, a consensus was reached with the involvement of a third senior investigator (LS). There was no language restriction.

**Type of Studies, Inclusion and Exclusion Criteria**

Following the PICOS (Participants, Intervention, Comparisons, Outcomes, Study Design) criteria, we included studies assessing Pdmales with any type of cancer, I'd cancer treatment (in longitudinal studies), C'd men who undertook the same procedure with the absence of the respective outcome (eg EjD vs no EjD), O'd number of participates with versus without the respective outcome, and S'd observational (case-control, cross-sectional) studies.
The prevalence of ejaculation disorders was reported based on patient referral; for some studies on RE, it was proven by the searching and finding of sperm in urine after ejaculation. The prevalence of erectile dysfunction was reported only when a validated instrument for the diagnosis of erectile dysfunction was used such as the International Index of Erectile Function or the Sexual Health Inventory for Men.

Quality Assessment
This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.\textsuperscript{8} We assessed the quality of the studies using the Newcastle-Ottawa Scale (NOS).\textsuperscript{9} Two researchers (MT, DP) performed the scoring independently. The Newcastle-Ottawa Scale ranges from 0 to 9 stars and the study was assumed to have a high quality when the total score was more than 6 stars.

Data Extraction and Statistical Analyses
For each eligible study, 2 independent investigators (NV, DP) extracted name of the first author and year of publication, setting, sample size, mean age of the population, cancer type and site, percent and type of EjD, percent of erectile dysfunction, body mass index, testosterone level, percent smoking, percent diabetes, percent hypertension and percent depression.

A random effects meta-analysis was conducted using the DerSimonian and Laird method, weighting studies based on the inverse variance, and calculating prevalence proportions with 95% confidence intervals using comprehensive meta-analysis.\textsuperscript{10,11} The meta-analysis was conducted using the following steps: 1) prevalence proportions and 95% CIs were calculated for the prevalence of EjD by cancer site and type of treatment, and were included in the analysis if there were more than 2 outcomes per cancer site and treatment type; 2) heterogeneity was assessed with the I\textsuperscript{2} statistic;\textsuperscript{12} and 3) publication bias was assessed with a visual inspection of funnel plots and with the BeggMazumdar-Kendall's tau\textsuperscript{13} and Egger bias test.\textsuperscript{14} As per recommendations from Fu et al\textsuperscript{15} and Sterne et al,\textsuperscript{16} these tests were only conducted if the number of studies in each analysis exceeded 10. Meta regressions were calculated to determine if mean age and year of study were independently correlated with prevalence across all cancer sites individually.
RESULTS

Studies Evaluated

The electronic search yielded 1,213 studies that were assessed for inclusion in the review. Of those, 102 were potentially eligible and subsequently scrutinized in full text to check for eligibility (fig. 1), yielding 64 studies (see supplementary Appendix, https://www.jurology.com, for full references of included studies). The final studies included a total of 10,057 participants. The most affected sites were testis (43 studies), rectum (15), prostate (7), bladder (3) and colon (3). Full descriptive characteristics can be found in table 1.

The median quality of the studies was 6.2 (range: 4e9), indicating an overall good quality of the studies, according to the NOS (supplementary table, https://www.jurology.com).

Advanced Bladder Cancer

Dry Orgasm. The pooled prevalence of dry orgasm in patients who had surgery was 53.0% (95% CI 23.3-80.7). Pooled effect sizes for each treatment type can be found in table 2 and figure 2.

Erectile Dysfunction. The pooled prevalence of erectile dysfunction in patients who had surgery was 6.8% (95% CI 0.8-39.1). Pooled effect sizes for each treatment type can be found in table 2 and figure 2.

Colon Cancer

Dry Orgasm. The pooled prevalence of dry/RE in patients who had surgery was 14.5% (95% CI 2.2-56.3). Pooled effect sizes for each treatment type can be found in table 2 and figure 3.

Erectile Dysfunction. The pooled prevalence of erectile dysfunction in patients who had surgery was 14.9% (95% CI 3.9-43.2). Pooled effect sizes for each treatment type can be found in table 2 and figure 3.

Cancer of the Rectum

Dry Orgasm. The pooled prevalence of dry orgasm across all treatment types was 21.8% (95% CI 18.3-25.7), with the largest prevalence being in participants who had surgery and radiotherapy (52.9%, 95% CI 25.9-78.3), followed by traditional proctectomy (32.7%, 95% CI 18.6-50.7), and the lowest prevalence in participants who had laparoscopic surgery and chemotherapy (20.0%,
95% CI 16.5-23.9). Pooled effect sizes for each treatment type can be found in table 2 and figure 4.

Erectile Dysfunction. The pooled prevalence of erectile dysfunction across all treatment types was 51.2% (95% CI 41.6-60.7), with the highest prevalence in participants who had surgery and radiotherapy (68.7%, 95% CI 55.2-79.6) followed by participants who had laparoscopic surgery (38.0%, 95% CI 25.1-52.8), and participants who had chemotherapy yielding the lowest prevalence (32.1%, 95% CI 14.4-57.1). Pooled effect sizes for each treatment type can be found in table 2 and figure 4.

Testicular Cancer
Dry Orgasm. The pooled prevalence of dry orgasm in participants who had surgery (retroperitoneal lymph node dissection) was 18.8% (95% CI 5.6-47.3). Pooled effect sizes for each treatment type can be found in table 2 and figure 5.

Demonstrated RE. The pooled prevalence of erectile dysfunction in participants who have had retroperitoneal lymph node dissection was 43.5% (95% CI 27.0-61.5). Pooled effect sizes for each treatment type can be found in table 2 and figure 5.

Premature Ejaculation. The pooled prevalence of premature ejaculation in participants who had surgery (radical orchidectomy) and radiotherapy was 4.8% (95% CI 0.1-72.0) (14%). Pooled effect sizes for each treatment type can be found in table 2, and figure 5.

Erectile Dysfunction. The pooled prevalence of erectile dysfunction in participants who had surgery and chemotherapy was 9.7% (95% CI 6.0-15.3). Pooled effect sizes for each treatment type can be found in table 2 and figure 5.

Meta Regression
The meta regressions did not show significant associations between mean age, study year, or quality of study and prevalence in any type of EjD across any cancer sites.

DISCUSSION
In this systematic review, the search yielded 1,213 studies, of which 64 were included with a total of 10,057 participants for analysis. Our study firstly provided pooled estimates for EjD
in different treatment types in the most affected cancer sites. The most common cancer sites reported in the literature were bladder, colon, testis and rectum. The sexual dysfunction that yielded the highest prevalence rate was erectile dysfunction in patients with cancer of the rectum who were treated with surgery and radiotherapy (68.7%), with premature ejaculation in testicular cancer (treated with radical orchidectomy and radiotherapy) yielding the lowest prevalence rate (4.8%).

This meta-analysis firstly provided a detailed analysis of the prevalence of EjD, demonstrated RE, premature ejaculation and delayed ejaculation stratified by primary cancer site and treatment approach using a structured method and transformation calculations. Other strengths include the reduction of publication bias via inspection and bias test and funnel plots, as well as controlling for mean age and publication year using multivariate regression analysis. The stratification of data by treatment type for each cancer site improves applicability of the results to clinical practice. Categorizing treatment types and their associated unwanted side effects prevalence should facilitate a more informed consultation with the patients. Categorizing prevalence for each symptom experienced by these different treatment approaches should facilitate the presentation of risks, as well as the side-effects associated with the treatment for patients, although it should be noted that there is no control of whether the symptoms were recorded pre or post-intervention.

Limitations of this analysis include an overrepresentation of cancer sites in the pelvic region, which is expected considering the pathophysiology of EjD and erectile dysfunction. The small number of primary studies conducted looking at the clinical and biochemical features of the participants results in the inability of running regression analysis for confounders, such as established risk factors for erectile dysfunction (including hyperlipidemia, tobacco use, hypertension, diabetes mellitus). Furthermore, regarding surgical procedures, rarely is the type specified and it was not possible to group patients by specific type of intervention. A further limitation is the paucity of studies that include pre and post intervention data, making causal conclusions challenging. Moreover, there are differences in the terminology in various studies: some use “dry orgasm” whereas others use “anejaculation” or “demonstrated retrograde ejaculation,” with some using both as clearly differentiated outcomes. The disparity in terminology may influence the overarching standardization of definition across the various studies and therefore limit the power of our analysis. We have reported the outcomes using the original terminology from the studies to avoid introducing
any bias into the analysis. Finally, other nonsurgical variables such as stress, depression and related therapies are not reported as only depression in 3 papers; while it should be investigated due to their influence on ejaculation. Sexual dysfunction including both EjD and erectile dysfunction has multiple causes beyond the surgical procedure per se. It is not possible, based on the existing literature, to differentiate between the side effects caused by surgery, side effects of other treatments including antidepressants, or coexisting psychiatric disorders (eg depressive spectrum, stress-related, anxiety disorders). This meta regression did not show significant associations between mean age or study year and prevalence in any type of erectile disorder across any cancer site.

Meta-analyses of studies reporting on the prevalence of EjD demonstrated that RE and dry orgasm in men across multiple treatment types are rare in certain cancers and common in other sites. This analysis showed that the individual studies reported EjD prevalence between 4.8% and 53%, whilst dry orgasm prevalence was between 14.5% and 53%. The highest prevalence of dry orgasm was observed in bladder cancer at 53% (95% CI 23.3e80.7) caused by removal of the bladder en bloc with seminal vesicles and prostate. It is worth noting, however, that the authors consider this value to be biased by the fact that a greater proportion of patients included in the analysis were well selected and had undergone prostate sparing cystectomies. This is biased compared with the general population that undergoes the standard procedure of radical cystectomy.17-20

All studies included in this meta-analysis focused on cancers located within the pelvic region (bladder, colon, prostate, rectum and testicular), whereby one will expect a strong correlation with neurovascular damage associated with its treatment.

It is common knowledge that after radical prostatectomy no semen is produced, making the patient infertile. On the other hand, among the studies included in the present paper bladder cancer patients had the highest prevalence of dry orgasm. This is the fifth most common cancer in the United States, which typically presents as a superficial transitional cell carcinoma which is resected endoscopically; however, local recurrence rates are extremely high (66% at 5 years), and between 10%-30% progress to invasive cancer. For such cases which have progressed further, the standard treatment is neoadjuvant therapy (surgery and chemotherapy), whereby various chemotherapeutic agents could induce vascular insufficiency in the corpus cavernosum of the penis and neurotoxicity leading to sexual health
Indeed, the high prevalence of sexual dysfunction after treatment for bladder cancer has led to increased efforts to prevent damage from treatment. Montorsi et al, as an example, have assessed postoperative intracavernous injection of alprostadil for the recovery of erectile function after nerve-sparing retropubic prostatectomy, with the conclusion that the earlier injection increases recovery rate of spontaneous erections. Some believe prophylaxis for deconditioning the vasculature of the penis is critical. Mancini et al studied Doppler duplex sonographic changes to compare alprostadil, sildenafil citrate and placebo using chronic dosing of arterial conditioning. The outcome demonstrated an improvement of peak systolic velocity by 30% with alprostadil and 39% with sildenafil.

Cancer of the rectum closely follows with the prevalence of sexual dysfunction. The main cause appears to be the injury to the autonomic nerves in the pelvis, along with the distal aorta and on the anterior surface of the rectum. It also appears that the direct effect of radiotherapy may irradiate autonomic nerves, and even with autonomic nerve preservation sparing men also report impotence. Finally, for testicular cancer, around a third of nonseminoma patients undergo retroperitoneal lymph node dissection that can greatly affect ejaculatory function. There has also been modification in techniques of surgery to include nerve sparing procedures to maintain antegrade ejaculation. Polychemotherapy induces loss of libido, decreases erectile function and arousal, and can also affect the hormonal, vascular, and nervous systems’ contributions to normal sexual function.

CONCLUSIONS
This analysis has demonstrated a high prevalence for EjD among cancer survivors of various sites and across different treatment types. This study is an exemplar and information summary of the prevalence associated with each cancer site and the most common treatment types. The output from this study is to help guide clinicians and patients in the consultation room and ultimately to inform and determine the most optimal treatment. This study also hopes to bring more awareness to these potentially taboo subjects and to help patients deal with sexual health. Open conversations before cancer treatment and managing any ideas, concerns and expectations are paramount for a better patient experience. Given the high rate of EjD, fertility preservation for those men interested should be offered prior to therapy. As has been recommended in previous studies, clinicians should be encouraged to routinely ask and encourage a discussion on sexual health problems that may arise. Normalizing this is important to not only help patients early on but to also help
reviews such as this to make it even more accurate. Some men may go through this hardship during the most sexually active period of their life, and thus the impact on quality of life with fertility and body image in particular is very important. A good relationship with good rapport goes a long way and may be all a patient needs to help them recover on a difficult journey.

REFERENCES
