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Systematic Review

Sexual health outcomes among adolescent and young adult cancer patients: a systematic review and meta-analysis

Niki Oveisi, MPH[1,2], Vicki Cheng, PharmD[1,2], Lori A. Brotto, PhD[3], Stuart Peacock, DPhil[4,5], Helen McTaggart-Cowan, PhD[4,5], Gillian Hanley, PhD[3], Sharlene Gill, MD[3], Meera Rayar, MD[3], Amirrtha Srikanthan, MD[6,7,8], Ursula Ellis, MLIS[9], Mary A. De Vera, PhD[1,2,10,*]

[1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada
[2]Collaboration for Outcomes Research and Evaluation, Vancouver, BC, Canada
[3]Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
[4]BC Cancer, Vancouver, BC, Canada
[5]Faculty of Health Sciences, Simon Fraser University, Burnaby, BC, Canada
[6]Faculty of Medicine University of Ottawa, Ottawa, ON, Canada
[7]Division of Medical Oncology, Department of Medicine, The Ottawa Hospital, Ottawa, ON, Canada
[8]The Ottawa Hospital Research Institute, Ottawa, ON, Canada
[9]University of British Columbia Library, Vancouver, BC, Canada
[10]Centre for Health Evaluation and Outcome Sciences, Vancouver, BC, Canada

*__Correspondence to:__ Mary A. De Vera, PhD, Faculty of Pharmaceutical Sciences, University of British Columbia, 2405 Wesbrook Mall, Vancouver, BC V6T 1Z3, Canada (e-mail: mdevera@mail.ubc.ca).

Abstract

Background: Sexual health outcomes (SHO), which entail the physical, emotional, mental, and social impacts, are an important consideration for adolescent and young adults (AYA, ages 15-39) affected by cancer. The objective of this systematic review and meta-analysis is to summarize the current literature and evaluate AYA cancer impact on SHO.

Methods: EMBASE and MEDLINE were searched from January 1, 2000 to September 28, 2022 to identify epidemiologic studies that used an analytic observational design, included individuals with AYA cancer and non-cancer control participants, and evaluated SHO. Odds ratios and prevalence ratios were calculated; random effects models were used to obtain pooled measures where possible.

Results: Of 2621 articles, 8 were included that investigated 23 SHO in 9038 AYA cancer patients. Based on the sexual response cycle, outcomes were categorized as those occurring among males (desire = 1, arousal = 1, orgasm = 4, other = 3) and females (desire = 2, arousal = 1, orgasm = 2, pain = 6, other = 3). It was feasible to conduct meta-analysis for 3 female SHO and 5 male SHO. There were associations between AYA cancer and 3 SHO: vaginal dryness (pooled odds ratio = 3.94; 95% confidence interval (CI) = 2.02 to 7.70), ejaculatory dysfunction (pooled odds ratio = 3.66; 95% CI = 2.20 to 6.08), and testosterone level (pooled mean difference = -2.56 nmol/liter; 95% CI = -3.46 to -1.66; $P = .00001$).

Conclusion: This study found increased ejaculatory dysfunction and reduced testosterone levels in male AYA cancer patients and increased vaginal dryness in female AYA cancer patients, highlighting the need for sexual health resources in this population.

Studies have reported increasing cancer incidence by nearly 30% over the last 50 years in adolescents and young adults (AYAs), those aged 15 to 39 years old (1). Although treatments have been improving, the impacts of cancer as well as its treatment are lifelong (2,3). AYA cancer diagnosis and treatment can have a substantial physiologic impact on the individual (4), leading to long-term challenges that span psychosocial (5-8), reproductive, and sexual health domains (9,10).

The World Health Organization defines sexual health as "a state of physical, emotional, mental and social wellbeing in all matters relating to: the reproductive system and to its functions and processes [reproductive health]/sexuality [sexual health]" (11). Sexual health is an all-encompassing term that is of particular interest as AYA cancer patients may experience bleeding during intercourse, early menopause, vaginal dryness, reduced libido, reduced sperm count, body image issues, and overall decreased mental health (12).

Indeed, sexual health is an essential component of quality of life for AYA cancer patients. A 2020 retrospective cohort study using administrative health data in the United States by Chao et al (10) quantified the risk of chronic comorbidities among AYA cancer patients. Their study showed that female AYA cancer patients had a higher risk of being diagnosed with early menopause compared to AYA control participants (incident rate ratio [IRR] = 2.87, 95% confidence interval [CI] = 1.56 to 5.28), likely due to impacts of cancer treatment. As early menopause impacts

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vaginal dryness and libido, this outcome has a direct impact on female AYA cancer patients' sexual health. A 2017 study by Moules et al conducted interviews with female and male AYA cancer patients (aged 19 to 26) to explore sexuality after cancer. They observed that AYA cancer patients "felt behind" compared to AYAs without cancer in romantic relationships due to their reduced self-esteem and sex drive (13).

There is growing literature on AYA cancer and sexual health. In 2021, Cherven et al conducted a scoping review, identifying 22 quantitative, 7 qualitative, and 3 mixed-methods research studies on AYA cancer on sexual function, which they defined as "physical, psychosocial, and developmental factors that contribute to sexual health, all of which may be negatively impacted by cancer and treatment" (14). Of particular interest are key findings from quantitative research of a range of 12% to 100% of sexual dysfunction, with female patients experiencing more pain than male patients. Additionally, they found salient negative impacts on sexual and romantic relationships and on body image. However, as these were based largely on narrative synthesis, the impacts of AYA cancer and, potentially, cancer treatment remain unclear as included studies lacked comparator groups, and there was no empirical synthesis across specific sexual health outcomes. To expand on, comprehensively assess, and quantify the impacts of AYA cancer on sexual health, we conducted a systematic review and meta-analysis across studies with comparator groups to synthesize sexual health outcomes evaluated in both male and female AYA cancer patients.

Methods

Search methods and databases

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols 2020 guidelines (15). The search strategy was developed in collaboration with a research librarian to identify peer-reviewed, published articles that evaluated the impact of AYA cancers on sexual health outcomes (Supplementary Tables 1 and 2, available online). The search was run in 1) EMBASE Ovid; and 2) Ovid MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review, and Other Non-Indexed Citations, Daily and Versions. Subject headings and keywords were used to encompass the following concepts: 1) the AYA age span (eg, "young adult" OR "adolescent"); 2) cancer (eg, "neoplasms" OR "early detection of cancer") and cancer treatment (eg, "chemotherapy" OR "radiation"); and 3) sexual health outcomes (eg, "dyspareunia" OR "libido"), which were extracted from the disorders related to sexuality in the International Classification of Diseases (ICD)-11 (16). Furthermore, we added limits to restrict results to human studies that were published from January 1, 2000, to September 28, 2022. Once included, the bibliographies of studies were hand-searched for further studies that could meet the inclusion criteria.

Study screening and inclusion criteria

Search results were uploaded, duplicates removed, and screening was completed by two reviewers (NO and MDV). We screened records to identify studies that: 1) used an analytic observational epidemiologic design (eg, cross-sectional, cohort, case-control study); 2) largely included AYA cancer patients diagnosed between 15 to 39 years and a comparator group of individuals without cancer; and 3) evaluated at least one sexual health outcome (eg, ejaculatory dysfunction, vulvodynia, vaginal dryness) (16). No restrictions were placed on geography or language. Covidence, a review management software, was used to support study screening (17).

Data extraction

Data were extracted on study characteristics such as study design (eg, cross-sectional, cohort), sample size, country, length of follow-up, and data source (eg, questionnaire, administrative health database, biosample). Of particular interest were participants' demographic and cancer characteristics. Information regarding reported age at study, sex assigned at birth (eg, female, male, or intersex), and gender (eg, woman, man, nonbinary, transgender) were extracted from studies as well (18). We extracted information on whether studies reported on sex and/or gender, their reported definitions, and whether there was conflation of these constructs. With respect to cancer characteristics of participants, we extracted information on the type of cancer and treatment, and age at diagnosis. Reported means and standard deviations of age at diagnosis and age at study were pooled through StataSE 17 (19).

Importantly, we extracted information on sexual health outcomes (ie, the outcome, who it impacts, when is it measured) that were reported on in included studies. We assigned sexual health outcomes into 1 of 5 categories: 1) desire (libido, sex drive, and overall desire to engage in sexual acts) (20); 2) arousal (sense of sexual pleasure and the accompanied changes to heart rate, breathing, etc) (20); 3) orgasm (peak of sexual activity and pleasure) (20); 4) pain (as it relates to the sexual organs, regardless of sexual activity status) (20); and 5) other (outcomes that did not clearly fit into the other categories). These categories are based on how it impacts an individual's sexual response cycle (21), as per ICD-11 guidelines on classification of sexual dysfunction (16). Wherever possible, measures such as counts, proportions, and measures of associations (eg, odds ratios [OR] and prevalence ratios [PR]) with accompanying 95% confidence intervals were also extracted or calculated.

Quality assessment

Quality assessment was also completed on included studies. This was done using the Newcastle-Ottawa Scale (22) separately by both NO and VC, and then compared; if needed, conflicts were discussed. We used McPheeters et al's previously described categories for study quality according to design: cohort studies (Good, 6–8; Fair, 3–5, Poor, 0–2) (23); and for cross-sectional studies, the following breakdown was used: (Good, 7–9; Fair, 4–6; Poor 0–3) (23,24).

Meta-analysis and heterogeneity

Random effects models were used to pool measures for sexual health outcomes that were reported by two or more studies. For each outcome, we used RevMan5 to obtain pooled proportions, ORs and PRs, corresponding 95% CIs (25), and generate corresponding forest plots and funnel plots. Studies that used different tools to measure the same outcome were pooled without modification, with recognition that this will increase heterogeneity of the meta-analysis. We also assessed heterogeneity using the chi-squared test with a P less than .10 indicating statistically significant heterogeneity as opposed to the traditional P less than 0.05 (26) to increase power. The I^2 test for inconsistency was also used and interpreted according to Cochrane's Handbook: 1) 0–40% little to no heterogeneity; 2) 30–60% moderate heterogeneity; 3) 50–90% substantial heterogeneity; and 4) greater than or equal to 75% considerable heterogeneity (26).

Results

Search results

The search had an output of 921 records from MEDLINE, and 1956 records from Embase between January 1, 2000 and September 28, 2022 (Figure 1). Title and abstract screening of 2621 articles resulted in the exclusion of 2521 articles. At the full-text screening stage, 95 articles were excluded mainly due to: 1) lack of comparator group in the study (n = 31); 2) patient population not AYA cancer patients (n = 25); 3) wrong study design (n = 14); and 4) comparator not AYA control participants (n = 12). The reference lists of the 5 included studies were then hand searched, further identifying 3 studies, bringing the total included to 8 studies in this systematic review.

Study characteristics

The characteristics of the 8 included studies are summarized in Table 1. Sample sizes ranged from 18 to 6778 participants, with 4 of the included studies using a cross-sectional design (27-30) and another 4 a cohort design (10,31-33). Cohort studies had a follow-up range of 3 to 96 months. All included studies were conducted in high-resource countries, such as the United States (10,31), Norway (27), Denmark (29,32), United Kingdom (28), Sweden (30), and Italy (33). Six studies used questionnaires to collect data (27,29-33), 2 collected biosamples (eg, blood, semen) (28,33), and 2 used administrative health databases (10,31).

Our quality assessment of included studies resulted in a "good" ranking on all cohort studies and 3 cross-sectional studies, and a "fair" ranking (score = 6) on 1 cross-sectional study (28).

Participant characteristics

Sociodemographic characteristics

A total of 9038 AYA cancer patients were included in the 8 studies. With respect to demographic characteristics, 5 studies conflated gender and sex by using the terms "women" and "female" or "men" and "male" interchangeably (28,30-33). Across all studies, 2 studies included females/women (terms used interchangeably) (31,32), 1 study included only females (29), 2 studies included males/men (terms used interchangeably) (28,33), 1 study included only males (27), 1 study included both females and males (10), and 1 study included females/women and males/men (terms used interchangeably) (30). Age was reported using various measures, including mean age either with standard deviation or range, or count(s) and proportion(s) of patients according to age groups (eg, 15–18, 19–24, 25–30 years). All studies included information regarding the age of participants at the time of study. The pooled mean age at the time of study was 35.3 years (95% CI = 27.8 to 42.9).

Cancer characteristics

Six studies included information on the age at diagnosis of AYA cancer patients. The pooled mean and standard deviation of age of AYA cancer diagnosis was 29.9 years (95% CI = 27.5 to 32.3). With respect to cancer characteristics, the types of cancers studied were testicular cancer (n = 2) (27,33), cervical cancer (n = 1) (32), breast cancer (n = 1) (29), and any non-hormone-dependent cancer (n = 1) (28). Three studies considered any type of cancer, which included thyroid, breast, lymphoma, melanoma, genital and/or urinary, germ cell, gastrointestinal, ovary, brain, leukemia, myeloma, renal, oropharynx, sarcoma, bone, lung, or other (10,30,31). Also, 6 studies included participants who received any treatment type (chemotherapy, radiation, surgery) (10,27-31) and 2 studies restricted recruitment based on treatment type (eg, only recruited patients receiving chemotherapy, or focused on cancer-specific surgical treatments) (32,33). Two studies provided information on type, dosage, and location of treatment (10,31), 2 studies provided information on type and location of treatment (28,32), and 4 studies provided information only on type of treatment (27,29,30,33). With respect to the studies that reported on location of treatment, this was generally reported as area targeted with radiation therapy (abdomen, chest, pelvis, neck and above). Overall, only 3 studies reported sexual health outcomes stratified by treatment information (10,27,32).

Sexual health outcomes

Across the 8 included studies, 23 sexual health outcomes were reported (Table 2). As all studies reported sex as male and female, or gender as men and women, we categorized outcomes according to who is impacted and how these outcomes impact their sexual response cycle with categories representing desire, arousal, orgasm, pain, and other (16,21). Figure 2 illustrates our developed sex-based framework including the progression of these categories through the sexual response cycle. Altogether, there were 14 sexual health outcomes among female patients and 9 among male patients. Sexual health outcomes that did not clearly fall under one of the first 4 categories were placed in the "other" category for each sex (eg, sexual inactivity, importance of sex). Female patients had outcomes across desire (n = 2), arousal (n = 1), orgasm (n = 2), pain (n = 6), and other (n = 3). Male patients had outcomes across desire (n = 1), arousal (n = 1), orgasm (n = 4), and other (n = 3). Below, we provide a narrative description of the reporting of these sexual health outcomes in included studies and our meta-analysis, where applicable. Details regarding PRs can be found in Table 2 and Supplementary Figures 1-4 (available online). Funnel plots for all AYA cancer sexual health outcomes indicate various levels of publication bias (Figures 4 and 6).

Female sexual health outcomes (n = 14)

Desire outcomes (n = 2)

Desire outcomes are related to libido, sex drive, and overall desire to engage in sexual acts (20), and we identified 2 female desire outcomes: decreased libido and sexual aversion in 2 included studies. Decreased libido was explored by Cameron et al (31) through structured interviews. Cameron et al found that AYA cancer patients were 4.97 times more likely to experience decreased libido (n = 124) compared to female AYA control participants (95% CI = 2.46 to 10.04). Olsson et al (30) used a validated study-specific questionnaire developed in a 24-month qualitative phase to explore decreased libido. However, when Olsson et al compared female AYA cancer patients (n = 74) to female AYA control participants, they did not see a statistically significant difference in the odds of decreased libido (OR = 1.42; 95% CI = 0.63 to 3.19). Meta-analysis of data for female AYA cancer patients (n = 221) and female AYA control participants (n = 248) resulted in a pooled OR (pOR) of 2.70 (95% CI = 0.79 to 9.25) (Figure 3, A). This suggests that AYA cancer patients are not more likely to have decreased libido compared to AYA control participants. Regarding heterogeneity for this outcome, there is evidence of substantial to considerable heterogeneity across studies (chi-squared statistic: 5.25, $P = .02$; $I^2 = 81\%$). Another outcome related to desire, sexual aversion, was explored by Kedde et al (29) in a sample of 332 female AYA breast cancer patients (both actively in treatment and completed) compared to AYA control participants using the Questionnaire for Screening

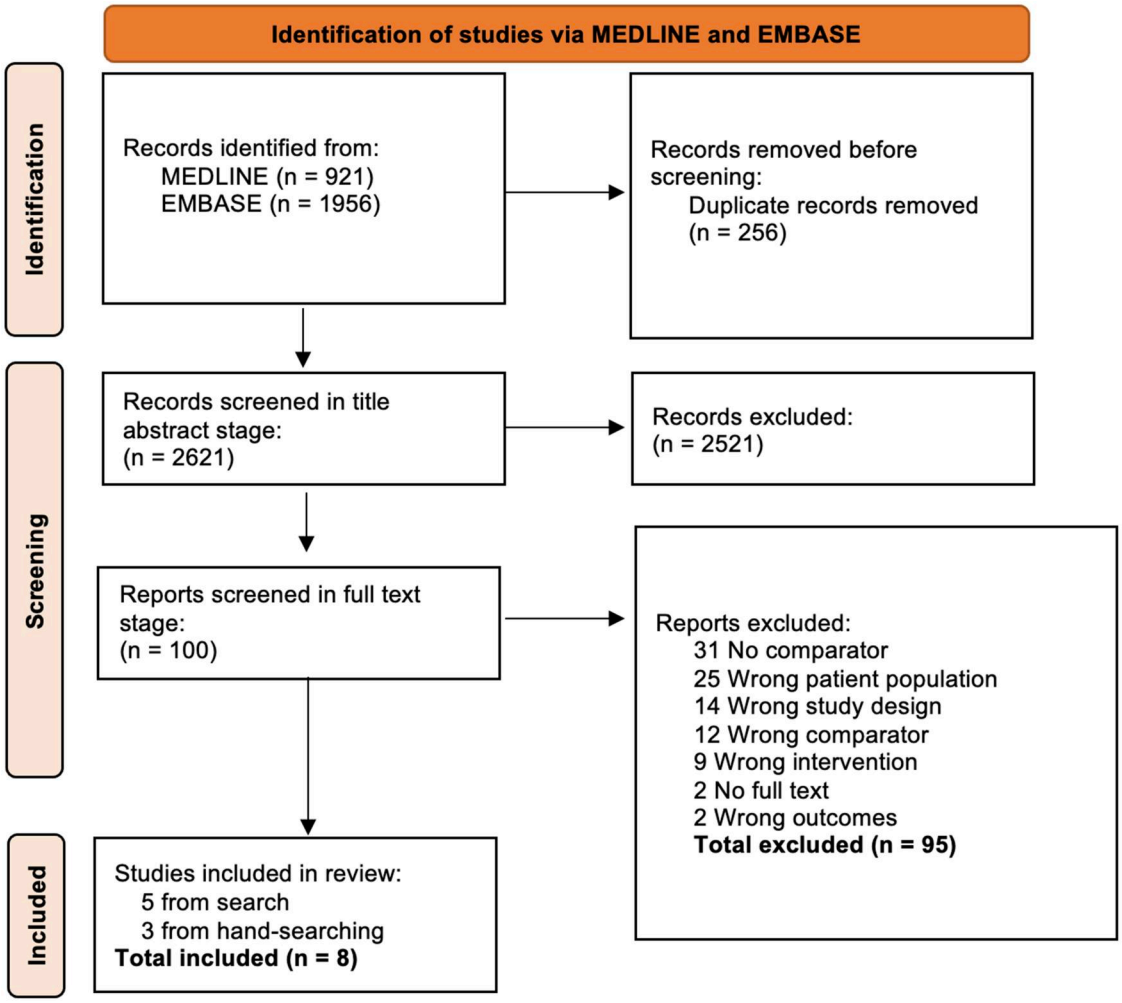


Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow chart of search results.

Sexual Dysfunctions, and they found that AYA patients with breast cancer have statistically significantly higher sexual aversion compared to female AYA control participants (OR = 4.14; 95% CI = 2.82 to 6.07).

Arousal outcomes (n = 1)

Arousal refers to the sense of sexual pleasure, which is usually accompanied by increased rate of breathing, heart rate, blood pressure, and blood flow to genitals (20). One outcome related to arousal, that is, subjective sexual arousal problems, was explored by Kedde et al (29) in their study comparing 332 female AYA breast cancer patients to AYA control participants using the Questionnaire for Screening Sexual Dysfunctions. They found that female AYA cancer patients with breast cancer currently under treatment had stastically significantly higher odds of subjective sexual arousal problems compared to AYA female control participants (OR = 4.25; 95% CI = 2.71 to 6.66).

Orgasm outcomes (n = 2)

Orgasm refers to the peak of sexual activity and pleasure and is usually accompanied by contractions of muscles in genitalia and/or reproductive organs (20). The reviewed studies looked at 2 outcomes related to orgasms in females, satisfaction and orgasm problems. Satisfaction was explored by Olsson et al (30) through their validated study specific questionnaire, and they saw that the odds of issues with satisfaction in female AYA cancer patients (n = 147) was 3.17 times the odds in AYA female control participants (95% CI = 1.61 to 6.24). Furthermore, Olsson et al also investigated orgasm problems and saw that this outcome was not statistically significantly higher in female AYA cancer patients compared to control participants (OR = 1.27; 95% CI = 0.65 to 2.48). Orgasm problems were also investigated by Kedde et al (29) using the Questionnaire for Screening Sexual Dysfunctions, and they saw that AYA breast cancer patients (n = 332) do have statistically significantly higher issues with orgasm compared to AYA control participants (OR 3.22; 95% CI: 2.39 to 4.35). Pooling of these 2 studies that include 475 female AYA cancer patients and 1578 female AYA control participants suggest that there is not a statistically significant difference in the odds of orgasm problems (pOR = 2.13; 95% CI = 0.86 to 5.29) (Figure 3, B). Heterogeneity was substantial to considerable across studies (chi-squared statistic: 6.23, $P = .01$; $I^2 = 84\%$).

Pain outcomes (n = 6)

Pain outcomes refer to pain in the sexual organs with or without sexual activity (20). Six female pain outcomes were extracted from the included studies for this review: premature menopause, vaginal dryness, dyspareunia, superficial dyspareunia, deep dyspareunia, and genital chaffing. Chao et al looked at premature menopause using administrative health data in 6778 female AYA cancer patients and found that there are statistically significantly higher odds of premature menopause in female AYA

Table 1. Characteristics of included studies on sexual health outcomes among adolescent and young adult cancer (AYAC) patients (N = 8)

Study	Country	Study design	Data source	Follow-up timeline (mo)	Sex (% female)	Type of cancer	N (AYAC)[l]	Age at diagnosis AYAC (yr)	AYA age at study AYAC (yr)	Quality assessment[b]
Dahl 2007 (27)	Norway	Cross-sectional	Questionnaire[e]	–	0	Testicular	429	31.3 ± 7.5	42.5 ± 7.8	Good (7)
Greenfield 2007 (28)	United Kingdom	Cross-sectional	Biosample collection	–	0	Any non-hormone dependent cancer[d]	176	28.6 ± 8.3	37.3 ± 5.8	Fair (6)
Froeding 2013 (32)	Denmark	Cohort	Questionnaire[f]	12	100	Cervical	18	–	29 (23–42)[c]	Good (7)
Kedde 2013 (29)	Denmark	Cross-sectional	Questionnaire[g]	–	100	Breast	332	–	38.7 (22–49)[c]	Good (7)
Cameron 2018 (31)	United States	Cohort	Questionnaire and administrative health data[h]	3	100	Any[a]	124	26.9 ± 1.25	26.9 ± 1.25	Good (8)
Olsson 2018 (30)	Sweden	Cross-sectional	Questionnaire[i]	–	51.6	Any[a]	285	15–18 yr: 39 19–24 yr: 119 25–30 yr: 116	28 (19–35)[c]	Good (7)
Pallotti 2019 (33)	Italy	Cohort	Questionnaire[j] and biosample collection	96 (median)	0	Testicular	241	31.3 ± 6.9	31.3 ± 6.9	Good (6)
Chao 2020 (10)	United States	Cohort	Administrative health data[k]	73 (mean)	65	Any[a]	6778	31.3 ± 6.5	15–19 yr: 521 (7.7%) 20–29 yr: 1706 (25.2%) 30–39 yr: 4551 (67.1%)	Good (8)

[a] "Any" cancer includes but is not limited to thyroid, breast, lymphoma, melanoma, genital and/or urinary, germ cell, gastrointestinal, ovary, brain, leukemia, myeloma, renal, oropharynx, sarcoma, bone, lung, or other.
[b] The Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies.
[c] Range.
[d] Hormone-dependent cancers are dependent on hormones for growth and survival.
[e] Brief Male Sexual Function Inventory.
[f] Female Sexual Function Index, Female Sexual Distress Scale, the Sexual Function-Vaginal Changes Questionnaire, and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module.
[g] Questionnaire for Screening Sexual Dysfunctions (short).
[h] Questionnaire delivered through a structured interview; medical records from University of Pennsylvania in collaboration with the Children's Hospital of Philadelphia, Ann & Robert H. Lurie Children's Hospital of Chicago, the University of North Carolina at Chapel Hill, and the University of California San Diego.
[i] Validated, study-specific questionnaire.
[j] International Index of Erectile Function Questionnaire.
[k] Kaiser Permanente Southern California Surveillance, Epidemiology, and End Results (SEER) affiliated cancer registry.
[l] AYAC = Adolescent and Young Adult Cancer Patient

Table 2. Summary of sexual health outcomes reported from included studies (N = 23)

Outcome	Study	Crude event rates reported? (Y/N)	Crude estimate (95% confidence interval)[a]	Prevalence ratio (95% confidence interval)
Sexual health outcomes among females (n = 14 outcomes)				
Desire disorders (n = 2 outcomes)				
Decreased libido				
	1 Cameron 2018 (31)[b]	Y	OR 4.97 (2.46 to 10.04)	PR 3.04 (1.83 to 5.05)
	2 Olsson 2018 (30)	Y	OR 1.42 (0.63 to 3.19)	PR 1.37 (0.65 to 2.89)
Sexual aversion				
	1 Kedde 2013 (29)	Y	OR 4.14 (2.82 to 6.07)	PR 3.62 (2.58 to 5.09)
Arousal disorders (n = 1 outcome)				
Subjective sexual arousal problems				
	1 Kedde 2013 (29)	Y	OR 4.25 (2.71 to 6.66)	PR 3.86 (2.55 to 5.85)
Orgasm disorders (n = 2 outcomes)				
Orgasm problems				
	1 Kedde 2013 (29)	Y	OR 3.22 (2.39 to 4.35)	PR 2.63 (2.08 to 3.34)
	2 Olsson 2018 (30)	Y	OR 1.27 (0.65 to 2.48)	PR 1.23 (0.69 to 2.20)
Satisfaction				
	1 Olsson 2018 (30)	Y	OR 3.17 (1.61 to 6.24)	PR 2.56 (1.45 to 4.52)
Pain disorders (n = 6 outcomes)				
Vaginal dryness				
	1 Cameron 2018 (31)[b]	Y	OR 4.09 (1.82 to 9.18)	PR 3.38 (1.65 to 6.94)
	2 Kedde 2013 (29)	Y	OR 5.76 (4.30 to 7.72)	PR 4.08 (3.26 to 5.10)
	3 Olsson 2018 (30)	Y	OR 1.49 (0.46 to 4.81)	PR 1.46 (0.48 to 4.50)
Premature menopause				
	1 Chao 2020 (10)	Y	OR 3.12 (1.70 to 5.72)	
Dyspareunia				
	1 Kedde 2013 (29)	Y	OR 5.22 (3.72 to 7.31)	PR 4.20 (3.16 to 5.58)
Superficial dyspareunia				
	1 Olsson 2018 (30)	Y	OR 1.37 (0.83 to 2.24)	PR 1.19 (0.90 to 1.57)
Deep dyspareunia				
	1 Olsson 2018 (30)	Y	OR 1.42 (0.82 to 2.46)	PR 1.29 (0.86 to 1.93)
Genital chaffing				
	1 Olsson 2018 (30)	Y	OR 0.54 (0.32 to 0.92)	PR 0.54 (0.36 to 0.80)
Other (n = 3 outcomes)				
Sexually active				
	1 Cameron 2018 (31)[b]	Y	OR 1.83 (1.09 to 3.07)	PR 1.49 (1.05 to 2.12)
Importance of sex				
	1 Olsson 2018 (30)	Y	OR 1.51 (0.86 to 2.64)	PR 1.38 (0.88 to 2.14)
Overall female sexual health				
	1 Froeding 2013 (32)			
	Female Sexual Function Index	N	Mean difference for radical vaginal trachelectomy (RVT): 9.1 ($P = .002$) Mean difference for radical abdominal hysterectomy (RAH): 3.57 ($P = .011$)	–
	Female Sexual Distress Scale	N	Mean difference for RVT: 6.3 ($P = .232$) Mean difference for RAH: 2.3 ($P = .274$)	–
	Sexual Function-Vaginal Changes Questionnaire	N	<u>Sexual desire/interest</u> Mean difference for RVT: 20.18 ($P = .041$) Mean difference for RAH: 17.28 ($P = .038$) <u>Sexual satisfaction</u> Mean difference for RVT: 22.32 ($P = .004$) Mean difference for RAH: 4.75 ($P = .016$) <u>Lubrication</u> Mean difference for RVT: -24.69 ($P = .035$) Mean difference for RAH: -10.4 ($P = .096$) <u>Dyspareunia</u> Mean difference for RVT: -20.99 ($P = .004$) Mean difference for RAH: -9.41 ($P = .017$) <u>Reduced vaginal size</u> Mean difference for RVT: -34.69 ($P < .001$) Mean difference for RAH: -12.66 ($P = .001$) <u>Orgasm</u> Mean difference for RVT: 14.81 ($P = .336$) Mean difference for RAH: 6.48 ($P = .531$) <u>Worried about sex</u> Mean difference for RVT: -22.64 ($P = .056$)	–

(continued)

Table 2. (continued)

Outcome	Study	Crude event rates reported? (Y/N)	Crude estimate (95% confidence interval)[a]	Prevalence ratio (95% confidence interval)
	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module	N	Mean difference for RAH: -3.12 ($P = .139$) Worry sex painful Mean difference for RVT: -33 ($P < .001$) Mean difference for RAH: -13.2 ($P < .001$) Sexual activity Mean difference for RVT: 2.7 ($P = .921$) Mean difference for RAH: 8.3 ($P = .550$) Vagina dryness Mean difference for RVT: -21 ($P = .057$) Mean difference for RAH: -14.1 ($P = .085$) Vagina shortness Mean difference for RVT: -28.4 ($P < .001$) Mean difference for RAH: -24.1 ($P < .001$) Vagina narrowness Mean difference for RVT: -9.9 ($P = .068$) Mean difference for RAH: -4.4 ($P = .186$) Dyspareunia Mean difference for RVT: -24.7 ($P < .001$) Mean difference for RAH: -13.8 ($P = .003$) Sexual enjoyment Mean difference for RVT: 8.6 ($P = .328$) Mean difference for RAH: 14.1 ($P = .090$)	–
Sexual health outcomes among males (n = 9 outcomes)				
Desire disorders (n = 1 outcome)				
Decreased libido				
	1 Dahl 2007 (27)	Y	OR 0.81 (0.52 to 1.27)	PR 0.83 (0.55 to 1.24)
	2 Olsson 2018 (30)	Y	OR 2.87 (0.92 to 9.00)	PR 2.68 (0.91 to 7.91)
Arousal disorders (n = 1 outcome)				
Erectile dysfunction				
	1 Dahl 2007 (27)	Y	OR 1.02 (0.61 to 1.69)	PR 1.02 (0.64 to 1.62)
	2 Olsson 2018 (30)	Y	OR 0.98 (0.67 to 1.42)	PR 0.98 (0.95 to 1.01)
	3 Pallotti 2019 (33)[c]	Y	OR 4.02 (1.75 to 9.26)	PR 3.10 (1.65 to 5.83)
Orgasm disorders (n = 4 outcomes)				
Ejaculatory dysfunction				
	1 Dahl 2007 (27)	Y	OR 3.64 (2.18 to 6.10)	PR 3.18 (1.98 to 5.11)
	2 Olsson 2018 (30)	Y	OR 4.25 (0.20 to 89.49)	PR 4.18 (0.20 to 86.09)
Satisfaction				
	1 Dahl 2007 (27)	Y	OR 0.52 (0.34 to 0.80)	PR 0.57 (0.39 to 0.83)
	2 Olsson 2018 (30)	Y	OR 1.66 (0.71 to 3.90)	PR 1.55 (0.73 to 3.29)
Premature ejaculation				
	1 Olsson 2018 (30)	Y	OR 0.72 (0.40 to 1.27)	PR 0.83 (0.61 to 1.14)
Orgasm problems				
	1 Olsson 2018 (30)	Y	OR 0.76 (0.21 to 2.69)	PR 0.77 (0.23 to 2.58)
Other (n = 3 outcomes)				
Testosterone level				
	1 Greenfield 2007 (28)	N	Mean difference: -2.67 nmol/liter (-3.76 to -1.58; $P = .003$)	–
	2 Pallotti 2019 (33)[c]	N	Mean difference: -2.3 nmol/liter (-3.92 to -0.68; $P = .002$)	–
Importance of sex				–
	1 Olsson 2018 (30)	Y	OR 1.59 (0.80 to 3.16)	PR 1.47 (0.83 to 2.59)
Overall male sexual health				
	1 Greenfield 2007 (28)	N	Derogatis Interview for Sexual Functioning-SR II (male version): Mean difference = -11.26 ($P < .005$)	–

[a] If not provided, odds ratio calculated from crude numbers. N = No; OR = odds ratio; PR = prevalence ratio; Y = yes.
[b] Measured at post-treatment.
[c] Measured at the sixth time point.
[d] Measured 12 months after treatment.

cancer patients compared to control participants (OR = 3.12; 95% CI = 1.70 to 5.72) (10).

Vaginal dryness was explored by three studies. Cameron et al (31) did so by using structured interviews with 128 female AYA cancer patients and found 4.09 times the odds of vaginal dryness in female AYA cancer patients compared to AYA control participants (95% CI = 1.82 to 9.18). This outcome was also explored by Kedde et al (29) using the Questionnaire for Screening Sexual Dysfunction, who found that AYA breast cancer patients (n = 332) are statistically significantly more likely to experience vaginal dryness than control participants (OR = 5.76; 95% CI = 4.30 to 7.72). Lastly, vaginal dryness was explored by Olsson et al (30), who saw that female AYA cancer patients (n = 147) were not statistically significantly more likely than control participants to experience vaginal dryness (OR = 1.49; 95% CI = 0.46 to 4.81). Comparison of 571 female AYA cancer patients to 1703 female AYA control participants resulted in a pOR of 3.94 (95% CI = 2.02 to 7.70), which suggests that female AYA cancer patients are statistically significantly more likely to experience vaginal dryness compared to AYA female control participants (Figure 3, C).

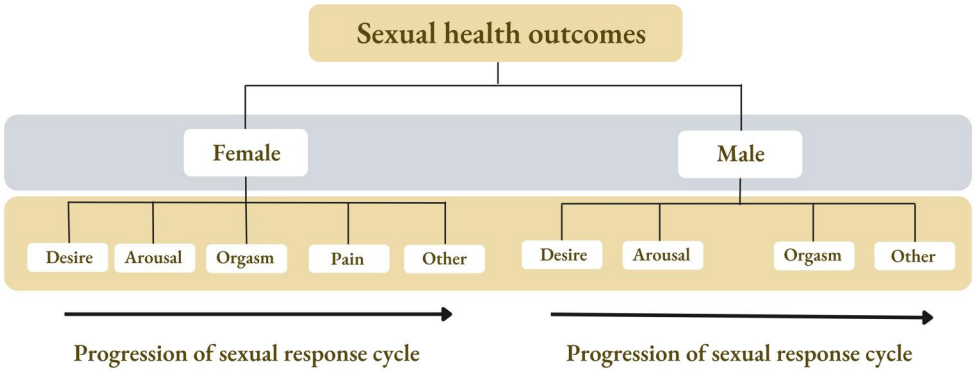
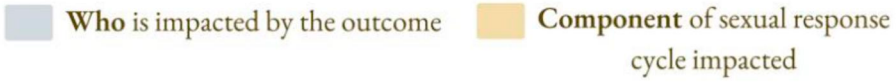


Figure 2. Sex-based framework of current literature on adolescent and young adults cancer patients and their sexual health outcomes.



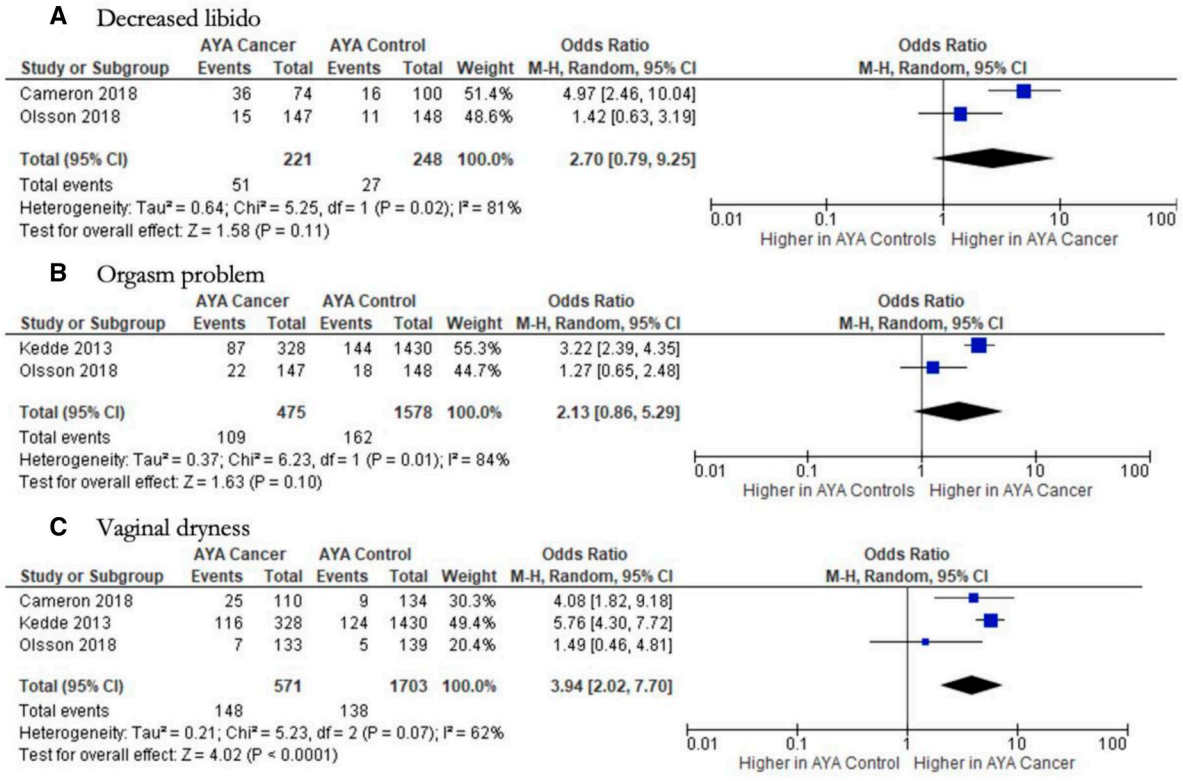


Figure 3. Forest plots of pooled odds ratios of female sexual health outcomes. A) (30,31), B) (29,30), C) (29-31); (n = 3).

Heterogeneity was moderate to substantial in this outcome (chi-squared statistic = 5.23, $P = .07$; $I^2 = 62\%$).

Dyspareunia, which is defined by recurrent or persistent female genital pain, was measured by Kedde et al (29) using the Questionnaire for Screening Sexual Dysfunction. They found that AYA breast cancer patients (n = 332) are statistically significantly more likely to experience dyspareunia compared to AYA female control participants (OR = 5.22; 95% CI = 3.72 to 7.31). Superficial (OR = 1.37; 95% CI = 0.83 to 2.24) and deep (OR = 1.42; 95% CI = 0.82 to 2.46) dyspareunia were evaluated by Olsson et al (30) using their validated study-specific questionnaire, and they did not find a statistically significant difference of odds of either outcome in female AYA cancer patients (n = 147) compared to AYA control participants.

Other (n = 3)

Three outcomes could not be assigned into the four aforementioned categories and thus were placed in a fifth category of other outcomes. These were sexual inactivity, importance of sex, and overall female sexual health. Using structured interviews, Cameron et al (31) saw that there were statistically significantly higher odds of sexual inactivity in their female AYA cancer participants (n = 124) (OR = 1.83; 95% CI = 1.09 to 3.07) compared to female AYA control participants. Using their validated study-

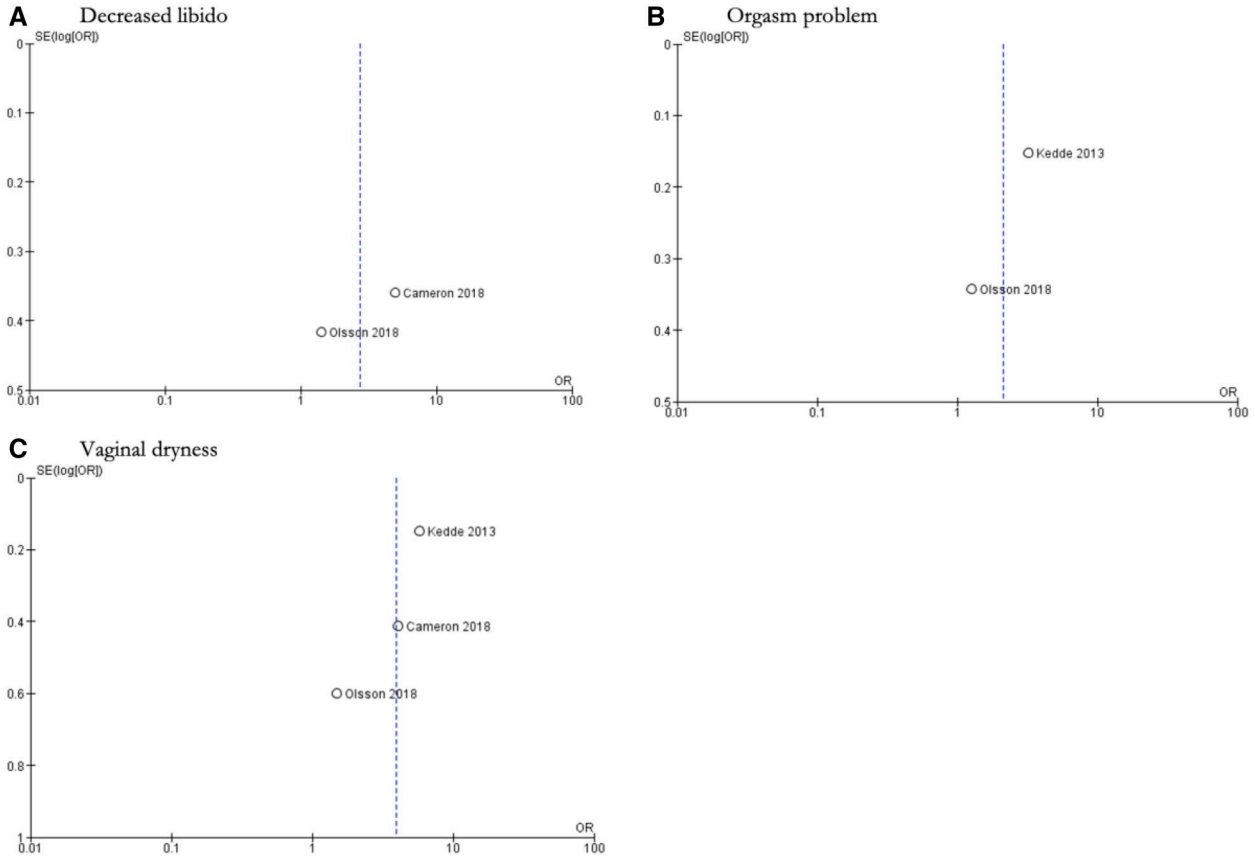


Figure 4. Funnel plots of pooled odds ratios of female sexual health outcomes. A) (30,31), B) (29,30), C) (29-31); (n = 3). SE = standard error; OR = odds ratio.

specific questionnaire, Olsson et al (30) saw that there was no statistically significant difference between AYA female cancer patients (n = 147) and AYA control participants regarding how important sex is to them (OR = 1.51; 95% CI = 0.86 to 2.64).

Also included in this category is a composite outcome "overall female sexual health" assessed in one study (32) that did not provide score cutoffs for case definitions—hence, the participants could not be categorized based on disorder status. Specifically, Froeding et al (32) used 4 questionnaires to assess overall female sexual health differences between AYA cervical cancer patients stratified by treatment type, and AYA control participants, 12 months after treatment. The authors used the Female Sexual Function Index (FSFI) and found that mean scores statistically significantly differed between female AYA cervical cancer patients who received radical vaginal trachelectomy (RVT) and control participants (mean difference [MD] = 9.1; $P = .002$). This trend persisted for those who received radical abdominal hysterectomies (RAH) (MD = 3.57; $P = .011$). However, they measured distress through the Female Sexual Distress Scale (FSDS) and did not find statistically significantly higher distress in either the female AYA cancer patients who received RVT (MD = 6.3; $P = .232$), or those who received RAH (MD = 2.3; $P = .274$) compared to control participants. Furthermore, they used the Sexual Function-Vaginal Changes Questionnaire (SVQ) and found statistically significantly less "sexual desire/interest" (MD = 20.18; $P = .041$), "sexual satisfaction" (MD = 22.32; $P = .004$), "lubrication" (MD = 24.69; $P = .035$), and statistically significantly more "dyspareunia" (MD = 20.99; $P = .004$) and "reduced vaginal size" (MD = 34.69; $P < .001$) in females with AYA cervical cancer treated with RVT compared to control participants, and 2 domains (orgasm and worried) were unchanged. The same trends persisted for female AYA cervical cancer patients treated with RAH across the majority of domains, with "lubrication" not showing a statistically significant difference compared to AYA control participants in this treatment group (MD = 10.4; $P = .096$).

Lastly, Froeding et al (32) also used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module (EORTC QLQ—CX24) and found that the "worry sex painful" (RVT MD = 33; $P < .001$ and RAH MD = 13.2; $P < .001$), "vaginal shortness" (RVT MD = 28.4; $P < .001$ and RAH MD = 24.1; $P < .001$), and "dyspareunia" (RVT MD = 24.7; $P < .001$ and RAH MD = 13.8; $P = .09$) were statistically significantly higher in both AYA cervical cancer patients treatment groups compared to AYA control participants. The remaining 4 domains ("sexual activity," "vaginal dryness," "vaginal narrowness," and "sexual enjoyment") did not statistically significantly differ between female AYA cervical cancer patients and female AYA control participants across both treatment groups.

Male sexual health outcomes (n = 9)

Desire outcomes (n = 1)

One desire outcome was evaluated in male AYA cancer patients in the included studies. Specifically, decreased libido was explored by Dahl et al (27) through the Brief Male Sexual Function Inventory, where they found that male AYA testicular cancer patients (n = 429) did not have a statistically significantly lower libido compared to male AYA control participants (n = 364) (OR = 0.81; 95% CI = 0.52 to 1.27). Using their validated study-specific questionnaire, Olsson et al (30) had similar results (OR = 2.87; 95% CI = 0.92 to 9.00) when comparing male AYA cancer

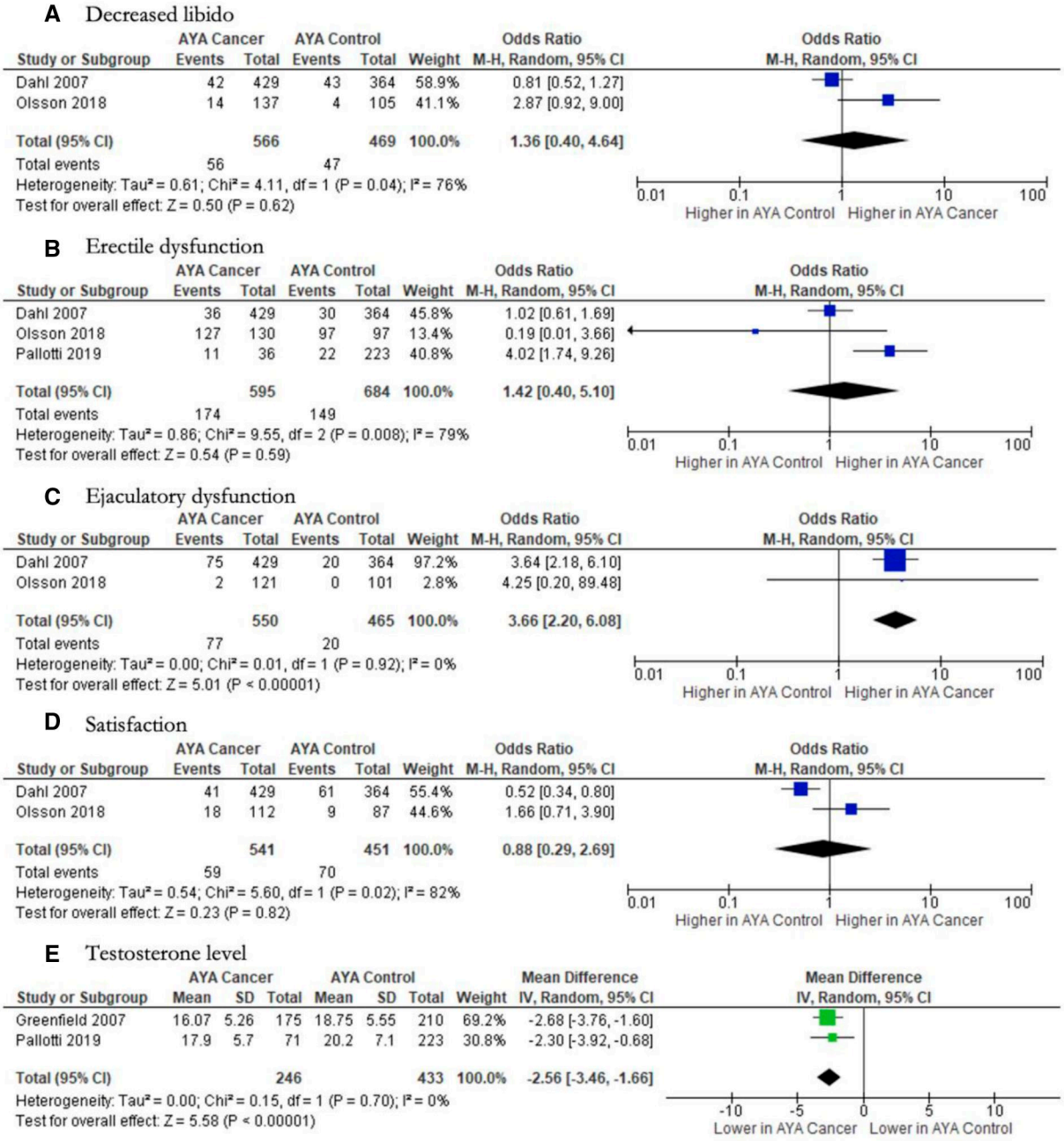


Figure 5. Forest plots of pooled odds ratios (A–D) and mean difference (E) of male sexual health outcomes. A) (27,30), B) (27,30,33), C) (27,30), D) (27,30), E) (28,33); (n = 5).

patients (n = 137) with male AYA control participants (n = 105). Pooling of 566 male AYA cancer patients from 2 studies also suggested that there was no statistically significant difference in the odds of decreased libido in male AYA cancer patients (n = 566) compared to control participants (n = 469) (pOR = 1.36; 95% CI = 0.40 to 4.64) (Figure 5, A). This meta-analysis had substantial to considerable heterogeneity (chi-squared statistic = 4.11, $P = .04$; $I^2 = 76\%$).

Arousal disorders (n = 1)

Erectile dysfunction was explored by 3 studies in this review. Dahl et al (27) evaluated this outcome using the Brief Male Sexual Function Inventory and found that there was not a statistically significantly higher odds of erectile dysfunction in male AYA testicular cancer patients (n = 429) (OR = 1.02; 95% CI = 0.61 to 1.69). Olsson et al (30) also did not find a statistically significant difference between the male AYA cancer patients (n = 130) and their control participants (n = 97) using their validated study-specific questionnaire (OR = 0.98; 95% CI = 0.67 to 1.42). However, Pallotti et al (33) found that male AYA testicular cancer patients (n = 36) in their cohort study were statistically significantly more likely to have erectile dysfunction than their control participants counterparts at the final follow-up, a median of 96 months after diagnosis (OR = 4.02; 95% CI = 1.75 to 9.26).

Although Dahl et al (27) and Olsson et al (30) did not limit their study to those who are sexually active, Palloti et al (33) did. Meta-analysis of this outcome based on data for 595 male AYA cancer patients showed no statistically significant difference of the odds of erectile dysfunction when comparing to 684 male AYA control participants (pOR = 1.42; 95% CI = 0.40 to 5.10) (Figure 5, B). Heterogeneity was substantial to considerable in this outcome (chi-squared statistic = 9.55, $P = .008$; $I^2 = 79\%$).

Orgasm disorders (n = 4)

Four orgasm disorders were explored in male AYA cancer patients: ejaculatory dysfunction, satisfaction, premature ejaculation, and orgasm problems. Ejaculatory dysfunction was explored by Dahl et al (27) using the Brief Male Sexual Function Inventory, and they found statistically significantly higher odds of ejaculatory dysfunction in male AYA testicular cancer patients (n = 429) compared to male AYA control participants (n = 364) (OR = 3.64; 95% CI = 2.18 to 6.10). Olsson et al (30) also explored this outcome using their validated study-specific questionnaire, and they did not find a statistically significant difference in the odds of ejaculatory dysfunction between male AYA cancer patients (n = 121) and control participants (n = 101) (OR = 4.25; 95% CI = 0.20 to 89.49). Pooling data from 550 male AYA cancer patients and 465 male AYA control participants resulted in a statistically significantly higher odds of ejaculatory dysfunction in male AYA cancer patients (pOR = 3.66; 95% CI = 2.20 to 6.08) (Figure 5, C). There was little to no heterogeneity in this outcome (chi-squared statistic = 0.01, $P = .92$; $I^2 = 0\%$).

Satisfaction was explored by Dahl et al (27) through the Brief Male Sexual Function Inventory. They found that male AYA cancer patients (n = 429) had statistically significantly lower odds of satisfaction problems compared to male AYA control participants (n = 364) (OR = 0.52; 95% CI = 0.34 to 0.80). Olsson et al (30) also explored satisfaction using their validated study-specific questionnaire, and they did not find a statistically significant difference in satisfaction in male AYA cancer patients (n = 112) compared to male AYA control participants (n = 87) (OR = 1.66; 95% CI = 0.71 to 3.90). Pooling across studies resulted in a comparison of 541 male AYA cancer patients and 451 male AYA control participants. The meta-analysis did not show a statistically significantly higher odds of satisfaction problems in male AYA patients (pOR = 0.88; 95% CI = 0.29 to 2.69) (Figure 5, D). Heterogeneity was substantial to considerable for this outcome (chi-squared statistic = 5.60, $P = .02$; $I^2 = 82\%$).

Premature ejaculation was also explored in this review. Using their validated study-specific questionnaire, Olsson et al (30) found that there was no statistically significant difference in the likelihood of premature ejaculation in male AYA cancer patients (n = 138) compared to male AYA control participants (OR = 0.72; 95% CI = 0.40 to 1.27). Lastly, Olsson et al also explored orgasm problems and did not find any difference in the likelihood of this outcome (OR = 0.76; 95% CI = 0.21 to 2.69).

Other outcomes (n = 3)

Testosterone level has established impacts on sexual function in males and was captured in this review. Greenfield et al (28) found statistically significantly lower testosterone levels in male AYA cancer patients (n = 175) compared to male AYA control participants (n = 210) (MD = -2.67 nmol/L; 95% CI = -3.76 to -1.60; $P = .003$). Pallotti et al (33) also found statistically significantly lower testosterone levels in their male AYA testicular cancer patients (n = 71) compared to male AYA control participants (n = 223) at the sixth time point (MD = -2.30 nmol/L; 95% CI = -3.92 to -0.68; $P = .002$). Pooling across these 2 studies resulted in 246 male AYA cancer patients, which had statistically significantly lower testosterone levels than 433 male AYA control participants (pooled mean difference = -2.56 nmol/liter; 95% CI: -3.46 to -1.66; $P = .00001$) (Figure 5, E). There was little to no heterogeneity in this meta-analysis (chi-squared statistic = 0.15, $P = .70$; $I^2 = 0\%$).

Importance of sex was also explored by Olsson et al using their validated study-specific questionnaire, and they did not find a statistically significant difference between male AYA cancer patients (n = 138) and control participants (OR = 1.59; 95% CI = 0.80 to 3.16). Funnel plots for all male AYA cancer sexual health outcomes indicate various levels of publication bias (Figure 6).

One study used questionnaires to evaluate overall male sexual health that did not provide score cutoffs for case definitions. Greenfield et al (28) used the Derogatis Interview for Sexual Functioning-SR II (male version), and they found that male AYA cancer patients (n = 176) have statistically significantly less sexual function compared to male AYA control participants (mean difference = -11.26; $P < .005$).

Discussion

Through this systematic review and meta-analysis, we synthesized the current evidence on the impact of AYA cancer on sexual health outcomes among females and males. The search resulted in the inclusion of 8 studies that explored 23 sexual health outcomes in 9038 AYA cancer patients. A key contribution of our review is the establishment of a sex-based framework to conceptualize sexual health outcomes evaluated among females (desire = 2, arousal = 1, orgasm = 2, pain = 6, and other = 3) and males (desire = 1, arousal = 1, orgasm = 4, and other = 3) across the sexual response cycle. Furthermore, the meta-analysis that we were able to conduct for 8 sexual health outcomes showed associations between AYA cancer patient status and outcomes of vaginal dryness among females (pOR = 3.94; 95% CI = 2.02 to 7.70), ejaculatory dysfunction among males (pOR = 3.66; 95% CI = 2.20 to 6.08), and testosterone level among males (pooled mean difference = -2.56 nmol/L; 95% CI = -3.46 to -1.66; $P = .00001$). Pooled PRs followed similar trends. Although the impacts of AYA cancer on sexual health outcomes have been observed in clinical settings, our findings provide quantitative evidence regarding the strength of the impact of AYA cancer on sexual health outcomes, as well as the gaps in evidence based on the sexual response cycle.

Our sex-based framework for organizing AYA cancer patient sexual health outcomes explored in the literature indicate several gaps. First, there are 14 outcomes that are only explored by single studies. In our meta-analysis, we were only able to pool across 8 outcomes, and those that were feasible were further limited by number of studies, with only 2 outcomes pooled across 3 studies, and the remainder pooled across 2 studies. It is also important to note that there are a number of sexual health outcomes that we explored in our literature search that did not appear in the included studies (Supplementary Tables 1 and 2, available online). These outcomes include but are not limited to female sexual arousal disorder, vulvodynia, vaginismus, and retrograde ejaculation, which remain to be evaluated among patients with AYA cancer in studies with comparator groups. Among reported sexual health outcomes, we also noted a higher number of pain-related sexual health outcomes for female patients and a higher number of orgasm-related sexual health outcomes for male patients. Another component of this is the lack of exploration of pain outcomes in male AYA cancer patients. Whereas 6 pain sexual health outcomes were captured

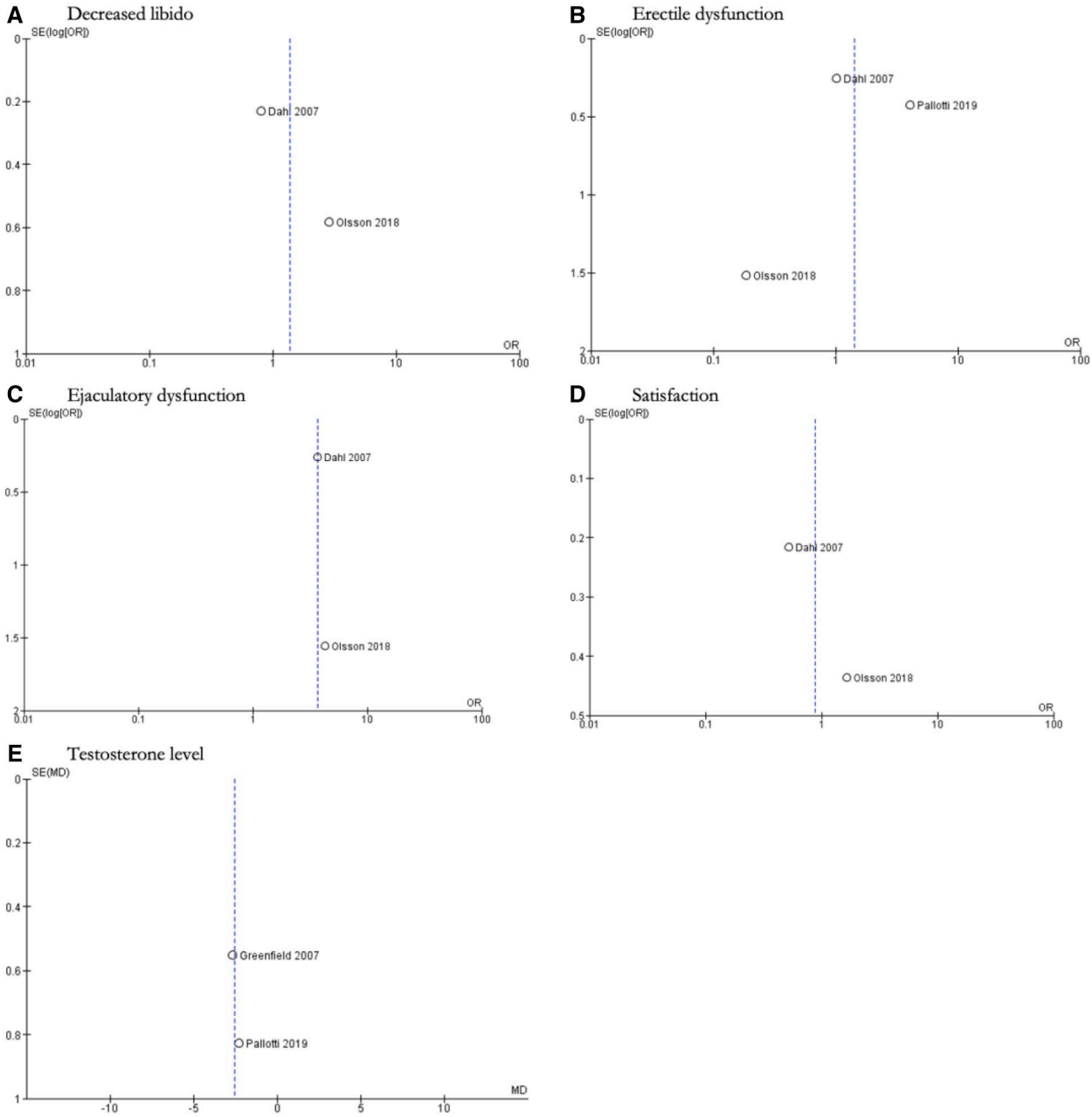


Figure 6. Funnel plots of pooled odds ratios (A–D) and mean difference (E) of male sexual health outcomes. A) (27,30), B) (27,30,33), C) (27,30), D) (27,30), E) (28,33); (n = 5). SE = standard error; OR = odds ratio; MD = mean difference.

in this review for females, there was none for males. However, evidence suggests that chronic pain in male cancer patients is statistically significantly correlated with sexual health and function overall (34). As sexual function is impacted across the domains of the sexual response cycle in this patient population, exploration of the understudied domains such as desire, arousal, and pain for male patients and desire, arousal, and orgasm for female patients are warranted.

This review also integrated components of sex and gender-based analyses (18) to consider how sex (biological attributes that are traditionally coupled with one's sex chromosomal status) and gender (the social and cultural roles attributed to sex status) were considered in the included studies. Although all studies in this review reported sex and/or gender in the binary, 5 studies conflated gender and sex terminology (ie, using the term "women" when discussing "females"). The resultant sex-based framework (Figure 2) reflects limitations with considerations of sex and gender in the literature to date on sexual health outcomes in AYA cancer as the framework itself is binary in nature and does not include information regarding gender diversity. Indeed, none of the studies included information regarding sex and gender-diverse folks, which is problematic as it has been established that trans and nonbinary folks experience hardships when accessing appropriate sexual health care at both individual and institutional levels, which is indicative of the overall lack of health equity faced by this population (35).

Our review provides empiric evidence on the impact of AYA cancer on sexual health outcomes on vaginal dryness (females), ejaculatory dysfunction (males), and testosterone levels (males). In 2021, Cherven et al (14) completed a scoping review that found

32 studies that explored the impact of AYA cancer on sexual function. Although their findings mirror ours in terms of negative impacts on sexual health outcomes, they were not able to complete a meta-analysis as they included studies without comparator groups. Stanton et al (36) also completed a systematic review in 2018 to explore the impact of AYA cancer on sexual function. However, they also included studies that did not contain comparator groups and only included studies that used validated measures. This would exclude studies that use administrative health databases, which contribute robust data to the investigation. Nonetheless, some of our meta-analyses also showed unconfirmed associations between AYA cancer and 2 female sexual health outcomes (decreased libido and orgasm problems) and 3 male sexual health outcomes (decreased libido, erectile dysfunction, and satisfaction). As previously described, the large number of outcomes reported by single studies limited our meta-analyses, as well as a small number of studies in meta-analyses themselves. Furthermore, as our review included cross-sectional studies with smaller samples than administrative cohort studies, we expected small sample sizes that can drive a lack of statistical significance (37).

Although different treatment types can have varying impacts on sexual health, the majority of studies captured in our review did not report the impact on sexual health outcomes stratified by different types of treatment, types of cancer, dosage, or location of treatment. Prior research has investigated the impact of cancer treatment on sexual health. For example, radiation to the cranial regions can reduce the production of sex hormones from the hypothalamic-pituitary axis, which can alter sex drive as well as arousal (38). Radiation to the pelvic regions can also result in vaginal stenosis and permanent scarring, which can cause major pain during intercourse (39). Additionally, the impact of psychosexual changes is prominent in those with severe weight changes and permanent scarring due to cancer treatment (40). Without details on sexual health outcomes across treatment types, location, and dosage, it is difficult to provide empiric evidence on how different treatment regimens impact sexual health outcomes.

There are strengths and limitations to this systematic review and meta-analysis. The search strategy used in this review was co-developed with a research librarian, and we only included studies with comparators that allowed for a meta-analysis. Also, we employed an sex and gender-based analyses approach that allowed us to see the impact of AYA cancer while considering sex and gender nuances. Heterogeneity was also prevalent in our meta-analysis, with a range of 0% to 95%. This can be due to the mix of cohort and cross-sectional studies included in the review, as well as variability in sample sizes (26). Nonetheless, heterogeneity in meta-analysis of observational studies is expected, as the participants are not randomized to reduce potential selection and confounding biases (26). As we did not have sufficient information regarding demographics of the participants, we could not conduct subgroup analyses to determine where the heterogeneity lies. Furthermore, sensitivity analyses were also not feasible due to the small number of included studies, which can reduce the specificity of our results. An important limitation of our methods is pooling sexual health outcomes from studies that focus on one cancer type (eg, breast) (29) with studies that include any cancer type (30), as this can result in dilution of associations. Furthermore, as studies used different tools to evaluate sexual health outcomes, it is possible that definitions varied across outcomes that were pooled, which can reduce specificity.

Conclusions

Overall, this systematic review and meta-analysis thoroughly investigated and summarized the existing literature on AYA cancer and sexual health outcomes. Specifically, we found increased ejaculatory dysfunction and reduced testosterone levels in male AYA cancer patients and increased vaginal dryness in female AYA cancer patients. This study provides evidence for the need for sexual health resources before, during, and after AYA cancer treatment in order to support long-term livelihood. This study also highlights the importance of sexual health research that is specific to cancer type, as sexual health outcomes are expected to differ according to treatment type, location, and dosage.

Data availability

The data underlying this article are available on request to the corresponding author.

Author contributions

Niki Oveisi, BSc, MPH (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing—original draft; Writing—review & editing) Vicki Cheng, PharmD (Data curation; Formal analysis; Writing—original draft; Writing—review & editing) Lori Anne Brotto, BSc, MA, PhD (Conceptualization; Supervision; Writing—review & editing) Stuart Peacock, BA, MSc, DPhil (Conceptualization; Supervision; Writing—review & editing) Helen McTaggart-Cowan, BSc, MSc, PhD (Conceptualization; Supervision; Writing—review & editing) Gillian Hanley, BSc, MBBCH, MA, PhD (Conceptualization; Supervision; Writing—review & editing) Sharlene Gill, BScPharm, MD, MPH, MBA (Conceptualization; Supervision; Writing—review & editing) Meera Rayar, MD, MSc (Conceptualization; Supervision; Writing—review & editing) Amirrtha Srikanthan, MD, MHSc (Conceptualization; Supervision; Writing—review & editing) Ursula Ellis, MLIS (Conceptualization; Methodology; Writing—review & editing) Mary De Vera, BSc, MSc, PhD. (Conceptualization; Supervision; Writing—review & editing).

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Conflicts of interest

None declared.

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