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Prevalence and impact of bladder and bowel disorders in women with breast cancer: a systematic review with meta-analysis

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All authors contributed to the systematic review. Study selection was conducted by Udari Colombage and Kuan-Yin Lin. Data extraction and analysis were performed by Udari Colombage. All authors were involved in data interpretation. The first draft of the manuscript was written by Udari Colombage and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Miss Colombage has nothing to disclose. Dr Lin has nothing to disclose. Dr Soh has nothing to disclose. Associate Professor Frawley has nothing to disclose.

Abstract

Background: One of the consequences of breast cancer treatments may be the onset of new, or aggravation of pre-existing bladder and bowel disorders. However, the presence and impact of these disorders in women with breast cancer are poorly documented. The aim of this systematic review was to assess the prevalence, incidence and impact of bladder and bowel disorders in women undergoing breast cancer treatment. **Methods**: A systematic search of six databases was conducted. Pooled prevalence rates and impact of bladder and bowel disorders were calculated using random-effects models. **Results**: 32 studies met the inclusion criteria, and 17 studies were included in the meta-analyses. The pooled estimate of women who experienced bladder disorders following sensitivity analysis, which removed one study reporting a result that deviated from the pooled estimate, was 38% [95%CI 32-44%; I^2=98%; n=4,584]. The impact of bladder and bowel disorders on women's daily lives was relatively low [bladder (scale 0-4): mean 0.8; 95%CI 0.4-1.1; I^2=99%;

n=4,908; bowel (scale 0-100): mean 14.2; 95%CI 9.4-19; I^2=95%; n=1,024]. **Conclusion**: This is the first study to comprehensively document the magnitude of bladder and bowel disorders in the breast cancer population. This meta-analysis found that women with breast cancer had a higher prevalence of urinary incontinence (38%) compared to women without breast cancer (21%). Given the extent and impact of our findings, screening and management of bladder and bowel disorders may be indicated in women with breast cancer in order to improve their health-related quality of life.

Keywords: Bladder disorders, Bowel disorders, Breast cancer, Pelvic floor dysfunction.

Introduction

Breast cancer is the most common cancer affecting women[1]. The consequences of breast cancer treatments may impact on many aspects of physical and mental health[2], including for some women, pelvic floor health[3]. This is presumed to be a result of ovarian suppression and failure secondary to chemotherapy in premenopausal women, and the use of endocrine therapy (including aromatase inhibitors and tamoxifen) in both pre- and postmenopausal women[4]. Prolonged effects of hypoestrogenism may be an etiological factor in the development of pelvic floor disorders, including bladder and bowel disorders[5]. In women who have undergone breast cancer treatments, the abrupt onset of symptoms attributed to menopause – vasomotor symptoms and sexual dysfunction – are well documented[3]. However, much less is known about bladder and bowel disorders and how these disorders impact on health-related quality of life (HRQoL) of women during and after their breast cancer treatment. While there is evidence of chemotherapy and endocrine therapy causing ovarian suppression[4], whether the type of breast cancer or the type breast cancer treatment received is

associated with the prevalence and impact of bladder and bowel disorders remains unknown.

A systematic review by Donovan et al[4] investigated the prevalence of urinary disorders in women with breast cancer. Authors did not conduct a meta-analysis and an overall prevalence and impact of bladder disorders was not reported[4]. Pooled prevalence and impact data of bladder and bowel disorders will allow for the comparison of these disorders to women without breast cancer. This will improve our understanding of whether having breast cancer has an effect on the presence and impact of bladder and bowel disorders in women.

As further studies, representing double the number of women with breast cancer, have been published since 2012, an update to Donovan et al[4] is warranted. Additionally, no systematic review to date has investigated bowel disorders in this population, representing a significant knowledge gap. Such data provide insight into the extent of this often over-looked problem in women with breast cancer. Therefore, the aim of this systematic review was to assess the prevalence, incidence and impact (severity or bother) of bladder and bowel disorders in women undergoing treatment for breast cancer.

Methods

Search and study selection

Relevant studies were identified through a search of six electronic databases (Ovid Medline, Ovid Embase, Ovid EmCare, Cumulative Index to Nursing and Allied Health Literature plus (CINAHL plus), PsychINFO and Scopus) from inception to December 2018. The Medical Subject Heading [6] search terms used included “breast neoplasms”, “urogenital system” and “pelvic floor disorders” (See Appendix 1). The

search strategy was limited to studies published in English. Reference lists of identified articles were also hand-searched. Two reviewers (UC, KYL) independently applied the eligibility criteria to identified studies based on titles and abstracts, then full texts[7]. Any disagreements were resolved by a third reviewer[7] (HF).

Selection criteria

Studies were included if it: (1) included women over 18 years old with breast cancer (stages 0-IV); (2) reported data on the prevalence and/or incidence, and/or impact of bladder and bowel disorders; and (3) full papers published in English. Studies had to report data on an identifiable and separately analysed group of women with breast cancer. If not, authors had to report that at least 75% of the full cohort represented women with breast cancer to be eligible for inclusion. Systematic reviews and qualitative studies were excluded.

Data extraction

One reviewer (UC) independently completed the data extraction using a customised and piloted data extraction table, following which a second reviewer (RA) cross-checked for accuracy. Extracted data included study characteristics, participant demographics, prevalence, incidence and impact of bladder and bowel disorders. Percentages or the number of women with bladder or bowel disorders were extracted to assess prevalence and incidence. Any type of questionnaire assessing the impact (severity or bother) of bladder and bowel disorders was accepted and the means and standard deviations of questionnaire scores were extracted. Impact was measured only in participants who reported the presence of bladder or bowel symptoms. Attempts were made to contact authors of studies for missing data.

Risk of bias assessment

The risk of bias of all included studies was assessed using a customised risk of bias assessment tool (Appendix 2) which comprised items from the Joanna Briggs Institute's critical appraisal tool for prevalence studies[8] and the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement[9]. Two reviewers (UC, KYL) completed the risk of bias assessment independently by assessing all items of the checklist, scoring yes, no, or unclear. Any disagreements were resolved by a third reviewer[7] (HF).

Synthesis of results

The pooled proportion of women experiencing bladder or bowel symptoms was calculated using random effects meta-analysis. Variances of the raw proportions were transformed using a Freeman-Tukey arcsine square root transformation so that confidence intervals of proportions became asymmetrical and did not exceed the range of 0 to 1[10]. A DerSimonian-Laird random effects model was used to pool the transformed proportions, which incorporated a measure of the extent of between-study heterogeneity[10]. A random effects model was used to pool impact scores of bladder and bowel disorders in women with breast cancer when I^2 was greater than 50%, indicating statistical heterogeneity[10]. Data were pooled in a meta-analysis when at least four studies reported on either the number of women experiencing bladder or bowel disorders, or the impact of these disorders[11]. Where data were unable to be pooled in a meta-analysis, a descriptive analysis was performed[23]. Sensitivity analyses were conducted to determine the robustness of prevalence and impact outcomes where outliers were detected[12]. Additional subgroup analyses for the prevalence and impact of specific bladder and bowel disorders as well as breast cancer treatments, stage and time since diagnosis were conducted where possible in order to identify

sub-groups of women with breast cancer who were most at risk and impacted by bladder and bowel disorders. All meta-analyses were performed using Stata v16.0 (StataCorp, LLC).

Results

Search yield

A total of 3,405 articles were identified, 32 studies were included in the qualitative synthesis, and 17 studies were included in the meta-analysis (see Figure 1). Our review included seven randomised controlled trials[13,14,15,16,17,18,19], eight cohort studies[20,21,22,2,23,24,25,26] and 17 cross-sectional studies[27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43]. A total of 12,611 women with breast cancer were represented in this systematic review; 10,441 of these women were in the meta-analysis.

< Insert Figure 1 here >

Figure 1: PRISMA flowchart of study selection process

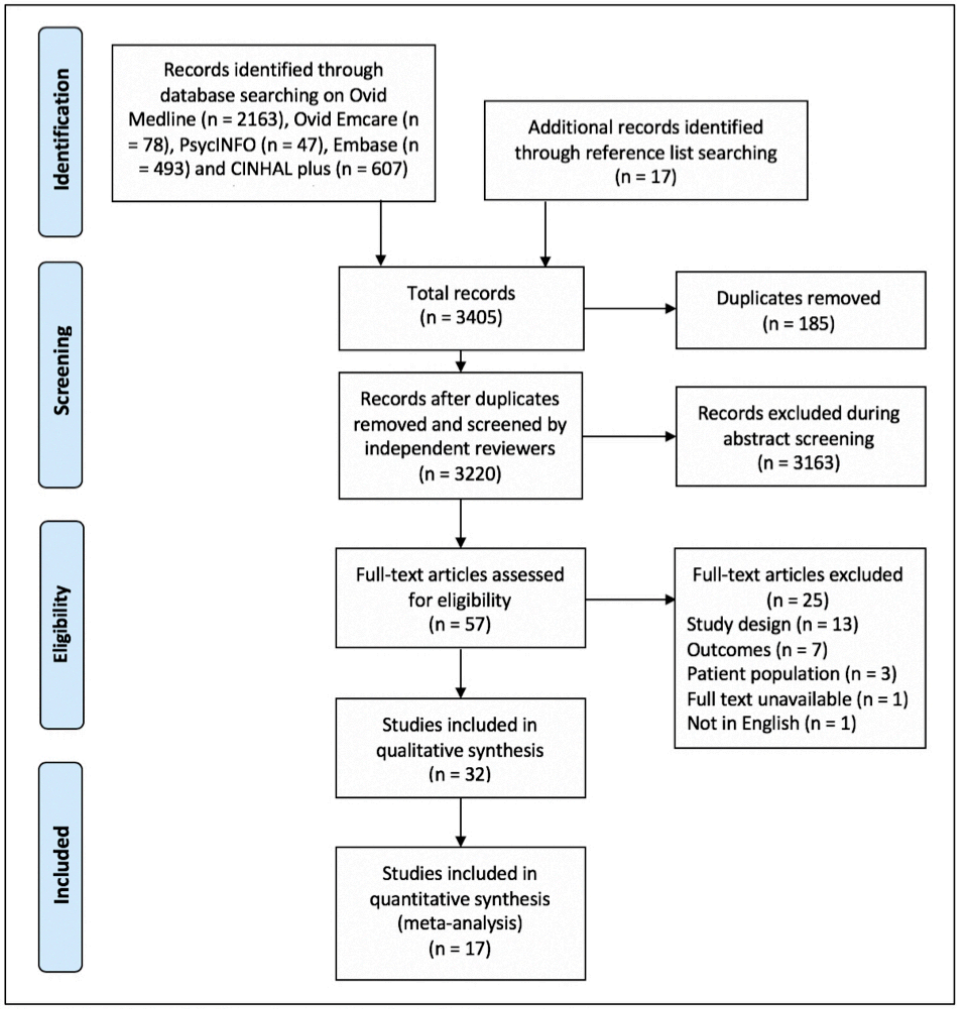


Figure 1: PRISMA flowchart of study selection process

Risk of bias assessment

A summary of the risk of bias assessment is presented in Table 1. The risk of bias for RCTs were considered low, and moderate for cohort and cross-sectional studies. Only three studies[10, 24,25] used outcome measures validated for the purpose of assessing the prevalence and impact of bladder and bowel disorders. A number of studies[13,19,20,22,24] were unclear regarding the sampling frame included in the study, especially around breast cancer stage, treatment type or the number of years since breast cancer diagnosis. Furthermore, most studies[10,11,12,13,14, 17,18, 20,22,28,31,32,33,34,36,40] did not

explicitly state the statistical analysis method for assessing the prevalence and impact of bladder and bowel disorders.

Table 1: Risk of bias assessment

< Insert Table 1 here >

Y, yes; N, no; U, unclear; NA, not applicable.

Demographic and clinical characteristics of included studies

The characteristics of the included studies is shown in Table 2. The mean age across all studies was 54.3 years, and sample sizes ranged from 35 to 2,208 participants. Most studies collected data during or shortly after primary cancer treatment. In studies that reported follow-up time points, the median time post-diagnosis when participants were assessed was two years (range 1 month-5 years)[2,20,13,18,24,25,29,36,38,40,42]. Of the studies that provided a range of follow-up time-points, all were within five years post diagnosis[14,32,37,39,43], except two studies[27,35] which followed-up for 10 years. Fourteen studies did not indicate the number of years post diagnosis[15,19,21,26,28,30,31,33,17,22,16,23,34,41]. A detailed description of the outcome measures used in included studies have been summarised in Appendix 3.

Table 2: Characteristics of included studies

α: Authors provided proportions of women in age range.

ß: Authors provided mean age for each sample. Sample 1: 56, Sample 2: 50, Sample 3: 57.

γ: Authors provided staging for each group. Sample 1: 0-II; Sample 2: 0-II; Sample 3: I-II.

NR, not reported; DCIS, ductal carcinoma in situ; Chemo, chemotherapy; Radio, radiation therapy; Endo, endocrine therapy; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; MRS, Menopause Rating Scale; BCPT, Breast Cancer Prevention Trial; CARES, Cancer Rehabilitation Evaluation System; UDI-6, urinary distress inventory; FACT, Functional Assessment of Cancer Therapy; BFLUTS, Bristol Female Lower Urinary Tract Symptoms questionnaire; GCS, Greene Climacteric Scale; QUID, Questionnaire for Urinary Incontinence Diagnosis; VAS, Visual Analog Scale.

Prevalence of bladder disorders

The pooled estimate of the proportion of women with breast cancer experiencing any type of bladder disorder was 0.33 [95%CI 0.24-0.42; I^2=99%; n=5,384] (see Figure 2). As two studies[20,39] reported different data values for stress UI, the value most closely aligned with accepted definitions of stress UI[44] was extracted. Subgroup analyses according to breast cancer treatment type, stage, and time since diagnosis were not conducted as these details were not reported by the included studies.

< Insert Figure 2 here >

Figure 2: Meta-analysis of the proportion of women reporting any bladder disorders

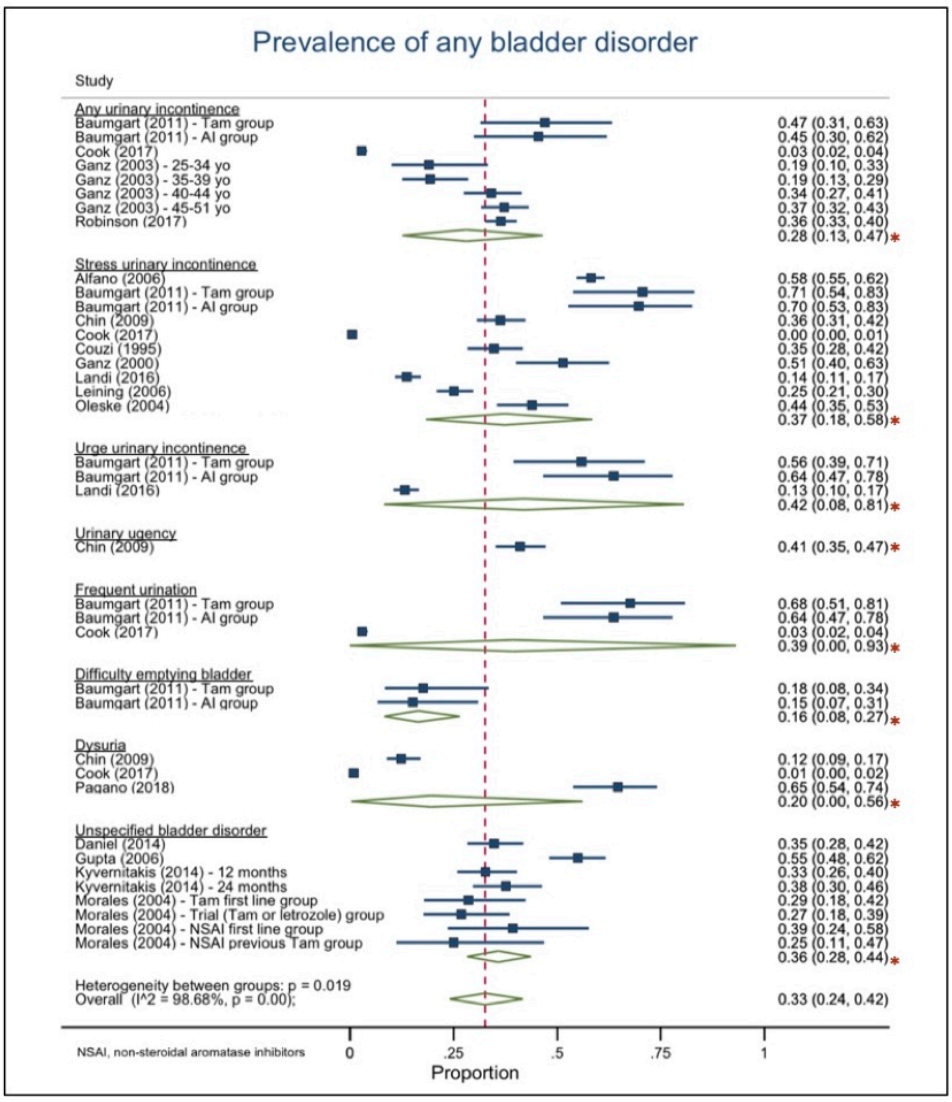


Figure 2: Meta-analysis of the proportion of women reporting any bladder disorders
***** Asterisks indicate the pooled prevalence estimates for each bladder or bowel disorder type.

* Asterisks indicate the pooled prevalence estimates for each type of bladder disorder. The prevalence rate reported in Cook et al[32] appeared to deviate from the pooled estimate, most likely as the authors performed a retrospective search of medical records for the presence of bladder disorders. When this study was excluded from the analysis (not shown), the pooled estimate of the proportion of women with breast

cancer experiencing bladder disorders increased from 0.33 to 0.38 [95%CI 0.32-0.44; I^2=98%; n=4,584].

Subgroup analysis showed the pooled estimate of the proportion of women with breast cancer experiencing UI was 0.36 [95%CI 0.24-0.48; I^2=99%; n=4,562]. Following sensitivity analysis, the estimate increased slightly to 0.38 [95%CI 0.30-0.48; I^2=99%; n=3,762].

Prevalence of bowel disorders

Despite a number of studies commenting on the impact of bowel disorders on women with breast cancer[17,19,24,30], only one study presented prevalence rates of bowel disorders[27]. This study reported that 18% of women with breast cancer experienced faecal incontinence (FI)[27].

Impact of bladder and bowel disorders

The impacts of bladder and bowel disorders were documented in two different ways. Studies reporting the impact of bladder disorders commented on the severity of bother of bladder disorders, while studies reporting the impact of bowel disorders reported on the severity of bowel disorders.

Severity of bother of bladder disorders

Studies measuring the severity of bother of bladder disorders using the Breast Cancer Prevention Trial (BCPT) symptom checklist were pooled. The pooled mean estimate was 0.8 [95%CI 0.5-1.1; I^2=100%; n=4,908], corresponding to slight bother (see Figure 3A). The pooled severity of bother of stress UI was 0.7 [95%CI 0.3-1; I^2=99%; n=4,173] corresponding to slight bother (see Figure 3A). A sensitivity analysis did not result in a change to the overall pooled estimate, nor the corresponding bother rating.

No meta-analyses were undertaken for studies reporting the severity of bother of other bladder disorders as there were either too few studies, or variance in the outcome measures used (summarised in Appendix 4).

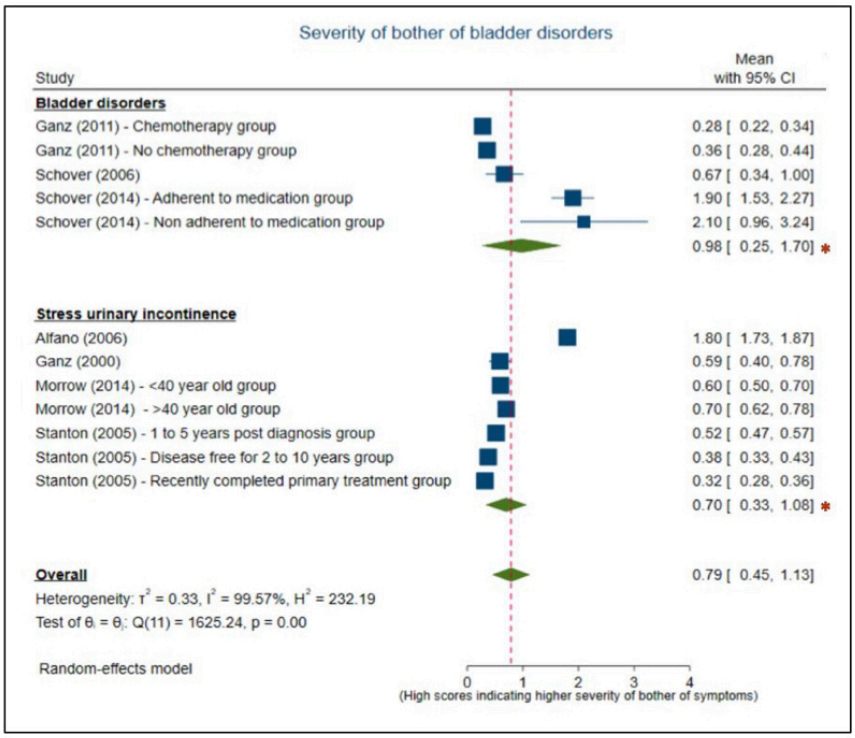
Severity of bowel disorders

Four studies[17,19,24,30] measured the severity of constipation and diarrhoea using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (see Figure 3B). The pooled mean estimate of the severity of bowel disorders was 14.2 [95%CI 9.4-18.9; I^2=95%; n=1,024] which corresponds to low severity. Sub-group analysis showed that the pooled mean estimate of the severity of constipation was 17.8 [95%CI 12.1-23.5; I^2=95%; n=1,024], and diarrhoea was 10.5 [95%CI 4.9-16.1; I^2=95%; n=1,024]. Both correspond to low severity. Sensitivity analysis did not result in a difference to the overall pooled estimate, nor to the severity of the bowel symptoms.

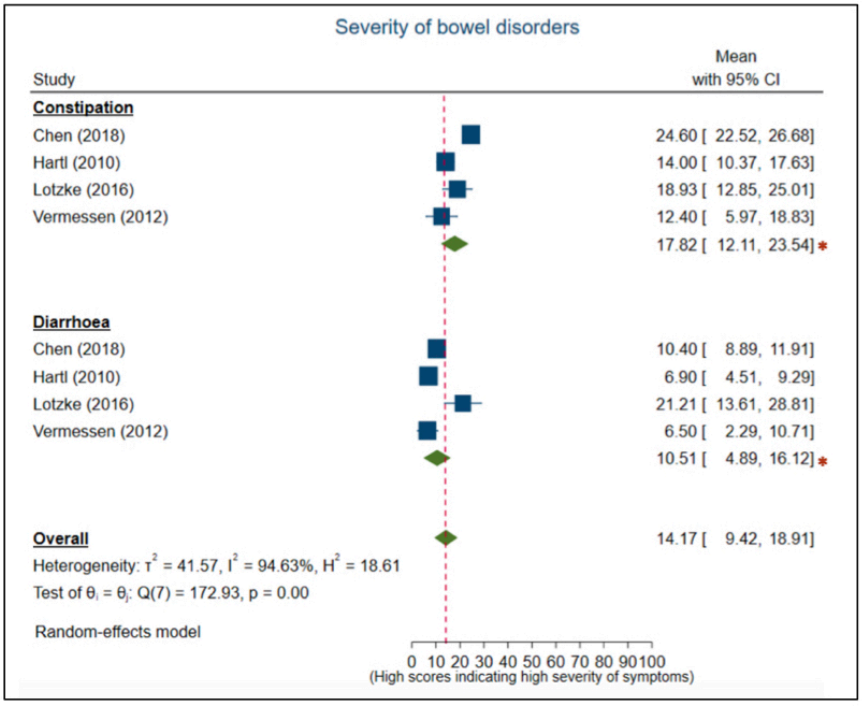
< Insert Figure 3 here >

Figure 3: A) Meta-analysis of the impact of bladder disorders as measured by the BCPT symptom checklist, B) Meta-analysis of the impact of bowel disorders as measured by the EORTC QLQ-C30

A)



B)



* Asterisks indicate the pooled impact estimates for each bladder or bowel disorder type.

Discussion

This review identified an overall prevalence of bladder disorders in women with breast cancer of 38%. One study reported a prevalence of faecal incontinence of 18%[27]. Despite these data suggesting substantial prevalence, bladder and bowel disorders were rated as having low impact on the lives of women at short and medium-term follow-up of breast cancer treatment.

Following sensitivity analysis, our meta-analysis showed a pooled estimate of 38% of women with breast cancer experiencing UI. Given that 25-45% of women without breast cancer experience UI[45], our findings suggests that the prevalence of UI in this population is similar to women without cancer. However, prevalence data of UI in women without cancer have been established from studies that drew from a range of prevalence frequencies from 'currently' to have 'ever' leaked[45]. Comparatively, women with breast cancer were asked to report presence of UI if they experienced leakage in the past four weeks, a stricter definition. When we compare the prevalence of UI using the same definition and age group, we find that women with breast cancer may have a higher prevalence (38%) compared to women without breast cancer (21%[46]). Similarly, the single study reporting the prevalence of FI in women with breast cancer (18%[27]) is higher than in women without breast cancer (8-10%[47]). This is the first study to document this comparative finding and indicates that that the extent of these disorders in the breast cancer population is higher than previously acknowledged. This result has implications for screening and management of these symptoms in women with breast cancer who are bothered by their symptoms.

We found the level of bother or severity of bladder and bowel symptoms to be slight in women with breast cancer, which is consistent with women without breast cancer[48].

However, it is quite feasible that in the context of cancer diagnosis, treatment and treatment recovery, the impact of a non-fatal condition such as a bladder or bowel disorder may be rated comparatively lower[49]. In this review, most studies collected data during or shortly after primary cancer treatment, using cancer-specific questionnaires. The five-year survivorship point post-diagnosis is a milestone many women with breast cancer anticipate and health conditions unrelated to their cancer may be of lower priority during this time. Breast cancer survivors tend to seek information and treatment on their 'unmet needs', including menopausal symptoms caused by breast cancer treatments, once they have met their survivorship milestone[50]. As most studies in this review assessed the impact of bladder and bowel disorders before this five-year milestone, it is possible that women prioritised cancer-related symptoms, and under-reported the impact of other symptoms. The two studies which followed women for 10 years did not report the impact of bladder and bowel disorders[27,35]. Therefore, the longer-term impact of bladder and bowel disorders in women with breast cancer, and whether this impact changes over time, remains unknown.

None of our included studies reported the incidence of bladder and bowel disorders. This is important to acknowledge as women included in these studies may have had pre-existing bladder and bowel disorders, before their breast cancer diagnosis. Therefore, we are unable to determine whether receiving treatment for breast cancer has any effect on the presence or impact of bladder and bowel disorders. It is also possible that women may not be interested to seek treatment for bladder and bowel disorders if these conditions pre-dated the cancer diagnosis.

Since the previous published systematic review[4], we have included 17 additional articles representing double the number of women with breast cancer (6,397 women in Donovan et al[4]; 12,611 women in this study). We were also able to conduct meta-analyses which provided us with pooled prevalence rates and impact scores to understand the magnitude and burden of bladder and bowel symptoms in women with breast cancer compared to women without breast cancer. This is also the first systematic review to document bowel disorders in women with breast cancer.

Limitations of research

Our search strategy was limited to studies in English and studies in other languages may have been missed. The majority of studies included were cross-sectional in nature. Whilst causal inferences cannot be drawn from our findings, this is the first study to pool prevalence rates in women with breast cancer. Finally, studies included women at various time-points along their treatment trajectory, however the prevalence or impact of bladder and bowel disorders according to breast cancer stage, treatment type, or duration of time on each treatment were not specified. We were therefore unable to complete any sub-group analyses according to these characteristics which would have provided information on identifying sub-groups of women with breast cancer who were perhaps most at risk of bladder and bowel disorders. As such, our findings may not be generalised to specific sub-groups of women with breast cancer (e.g. women on specific endocrine therapies such as tamoxifen or aromatase inhibitors). Future studies should attempt to stratify analyses according to breast cancer stage, treatment type and time since breast cancer diagnosis.

Conclusion

This is the first study to comprehensively document the magnitude of bladder and bowel disorders in the breast cancer population. This meta-analysis found that women with breast cancer had a higher prevalence of urinary incontinence (38%) compared to women without breast cancer (21%[46]). Given the extent and impact of our findings, screening and management of bladder and bowel disorders may be indicated in women with breast cancer in order to improve their health-related quality of life.

Appendix 1: Search strategy

Database(s): **Ovid MEDLINE(R)** 1946 to December 06, 2018

Search Strategy:

#	Searches	Results
1	breast neoplasms/ or breast carcinoma in situ/ or breast neoplasms, male/ or carcinoma, ductal, breast/ or carcinoma, lobular/ or "hereditary breast and ovarian cancer syndrome"/ or inflammatory breast neoplasms/ or unilateral breast neoplasms/ or triple negative breast neoplasms/	269564
2	chemoprevention/ or chemoradiotherapy/ or chemotherapy, adjuvant/ or consolidation chemotherapy/ or electrochemotherapy/ or hormone replacement therapy/ or estrogen replacement therapy/ or induction chemotherapy/ or maintenance chemotherapy/	78402
3	radiotherapy/ or chemoradiotherapy/ or heavy ion radiotherapy/ or lymphatic irradiation/ or proton therapy/ or radioimmunotherapy/ or radiosurgery/ or radiotherapy setup errors/ or radiotherapy, adjuvant/ or radiotherapy, computer-assisted/ or radiotherapy, high-energy/ or radiotherapy, image-guided/ or re-irradiation/ or whole-body irradiation/ or x-ray therapy/	111442
4	Adjuvant therap*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	21743
5	Aromatase Inhibitors/ or Tamoxifen/	22689
6	Endocrine therap*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	6170
7	pelvic floor disorders/ or urination disorders/ or urinary incontinence/ or urinary incontinence, stress/ or urinary incontinence, urge/ or urinary retention/	44356
8	Urinary Bladder, Neurogenic/ or Urinary Bladder, Overactive/	10680
9	MENOPAUSE, PREMATURE/ or MENOPAUSE/ or Menopause.mp.	39301
10	UROGENITAL SYSTEM/	6476
11	Fecal Incontinence/	9316
12	bowel dysfunction.mp.	1083
13	2 or 3 or 4 or 5 or 6	210293
14	7 or 8 or 9 or 10 or 11 or 12	104824
15	1 and 13 and 14	2163

Appendix 2: Customised risk of bias assessment tool

Sample characteristics

1. Were study participants sampled in an appropriate way?
2. Was the sample frame appropriate to address the target population?
3. Were the inclusion criteria defined?
4. Were the study subjects and the setting described in detail?
5. Was the sample size adequate?

Confounding

6. Were confounding factors identified?
7. Were strategies for dealing with confounding factors stated?

Outcomes and analysis

8. Was the outcome (prevalence or impact of bladder/bowel conditions) measured in a valid and reliable way for all participants?
9. Was there appropriate statistical analysis for analysis of prevalence or impact of bladder/bowel conditions?
10. Were the reasons for incomplete follow up or missing data described?
11. Was the response rate adequate, and if not, was the low response rate managed appropriately?
12. Were key findings stated?
13. Were limitations of the study described, taking into account sources of potential bias?

Assessing risk of bias

Number of Yes's:

- 0-4 = High risk of bias
- 5-9 = Moderate risk of bias
- 10-13 = Low risk of bias

Appendix 3: Outcome measures used in included studies to assess the presence or impact of bladder and bowel disorders.

Author (year)	**Measurement tool used**	**Question wording**	**Validated questionnaire**	**Validated for the purpose of assessing the presence or impact of bladder/bowel disorders**
Duijts (2012)[10]	BFLUTS	Does urine leak before you can get to the toilet?	Yes	Yes
Ganz (2000)[11]	Menopause symptom scale from BCPT symptom checklist	How bothered have you been by difficulty with bladder control in the past 4 weeks. • SUI: difficulty with bladder	Yes	No

		control at other times (coughing, sneezing)		
Ganz (2016)[12]	BCPT symptom checklist	How bothered have you been by difficulty with bladder control in the past 4 weeks. • SUI: difficulty with bladder control at other times (coughing, sneezing)	Yes	No
Land (2004)[13]	Selected questions from BCPT symptom checklist	How bothered have you been by difficulty with bladder control in the past 4 weeks. • SUI: difficulty with bladder control at other times (coughing, sneezing)	Yes	No

Appendix 3: Outcome measures used in included studies to assess the presence or impact of bladder and bowel disorders (continued)

Author (year)	**Measurement tool used**	**Question wording**	**Validated questionnaire**	**Validated for the purpose of assessing the presence or impact of bladder/bowel disorders**
Lötzke (2016)[14]	EORTC QLQ-C30	Have you been constipated? Have you had diarrhea?	Yes	No

Schover (2006)[15]	Menopausal Symptom Scale	Please indicate the extent to which you are bothered by any of these symptoms: • SUI: difficulty with bladder control while laughing or crying and difficulty with bladder control at other times.	Yes	No
Versmessen (2012)[16]	EORTC QLQ-C30	Have you been constipated? Have you had diarrhea?	Yes	No
Alfano (2006)[17]	BCPT symptom checklist	How bothered have you been by difficulty with bladder control in the past 4 weeks. • SUI: difficulty with bladder control at other times (coughing, sneezing)	Yes	No
Biglia (2010)[18]	GCS	Indicate the extent to which you are bothered at the moment by urogenital symptoms.	Yes	No
Hartl (2010)[21]	EORTC QLQ-C30	Have you been constipated? Have you had diarrhea?	Yes	No

Appendix 3: Outcome measures used in included studies to assess the presence or impact of bladder and bowel disorders (continued)

Author (year)	Measurement tool used	Question wording	Validated questionnaire	Validated for the purpose of assessing the presence or impact of bladder/bowel disorders
Kyvernitakis (2014)[19]	Menopausal Rating Scale	Which of the following symptoms apply to you at this time? Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	Yes	No
Ganz (2011)[2]	BCPT symptom checklist	How bothered have you been by difficulty with bladder control in the past 4 weeks. • SUI: difficulty with bladder control at other times (coughing, sneezing)	Yes	No
Morales (2004)[23]	Author-designed questionnaire	Did you have urinary problems?	Yes	No
Oleske (2004)[22]	Symptom Rating Scale from BCPT symptom	How bothered have you been by difficulty with bladder control in	Yes	No

	checklist	the past 4 weeks. • SUI: difficulty with bladder control at other times (coughing, sneezing)		

Appendix 3: Outcome measures used in included studies to assess the presence or impact of bladder and bowel disorders (continued)

Author (year)	**Measurement tool used**	**Question wording**	**Validated questionnaire**	**Validated for the purpose of assessing the presence or impact of bladder/bowel disorders**
Pagano (2018)[20]	Visual analogue scale	Participants were assessed for dysuria (pain on urination) by rating on visual analogue scale	Yes	No
Avis (2004)[26]	CARES	To what extent are you bothered by any of these symptoms - difficulty with bladder control while laughing or crying and difficulty with bladder control at other times.	Yes	No
Baumgart (2011)[25]	UDI-6	Do you experience and, if so, how much are you bothered by: Frequent Urination? Urine leakage related	Yes	Yes

		to urgency? Urine leakage related to physical activity (walking, running, laughing, sneezing, coughing)? Difficulty completely emptying bladder?		
Chen (2018)[27]	EORTC QLQ-C30	Have you been constipated? Have you had diarrhea?	Yes	No
Chin (2009)[28]	Author-designed questions	Author-designed questions relating to urinary incontinence, dysuria and urgency.	No	No

Appendix 3: Outcome measures used in included studies to assess the presence or impact of bladder and bowel disorders (continued)

Author (year)	**Measurement tool used**	**Question wording**	**Validated questionnaire**	**Validated for the purpose of assessing the presence or impact of bladder/bowel disorders**
Cook (2017)[29]	NA	Authors retrospectively searched medical records.	NA	NA
Couzi (1995)[30]	Author-designed	Author-designed questionnaire assessing the presence and bother of difficulty with bladder control.	No	No
Daniel	Menopause	Which of the following apply to	Yes	No

(2014)[31]	Rating Scale	you at this time? Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)		
Ganz (2003)[32]	BCPT symptom checklist	How bothered have you been by difficulty with bladder control in the past 4 weeks.	Yes	No
Greendale (2001)[33]	BCPT symptom checklist	How bothered have you been by difficulty with bladder control in the past 4 weeks.	Yes	No
Gupta (2006)[34]	Menopause Rating Scale	Which of the following apply to you at this time? Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	Yes	No

Appendix 3: Outcome measures used in included studies to assess the presence or impact of bladder and bowel disorders (continued)

Author (year)	**Measurement tool used**	**Question wording**	**Validated questionnaire**	**Validated for the purpose of assessing the presence or impact of bladder/bowel disorders**

Landi (2016)[35]	Interview	How often do you leak urine?	NA	NA
Leining (2006)[36]	BCPT symptom checklist	How bothered have you been by difficulty with bladder control in the past 4 weeks. • SUI: difficulty with bladder control at other times (coughing, sneezing)	Yes	No
Morrow (2014)[37]	Menopause symptom scale from BCPT symptom checklist	How bothered have you been by difficulty with bladder control in the past 4 weeks.	Yes	No
Park (2013)[38]	Menopause Rating Scale	Which of the following apply to you at this time? Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	Yes	No

Appendix 3: Outcome measures used in included studies to assess the presence or impact of bladder and bowel disorders (continued)

Author (year)	**Measurement tool used**	**Question wording**	**Validated questionnaire**	**Validated for the purpose of assessing the presence or impact of bladder/bowel disorders**
Robinson	QUID	Do you leak urine (even small drops),	Yes	Yes

(2017)[24]		wet yourself, or wet your pads or undergarments when you cough or sneeze?		
Schover (2014)[39]	BESS	How bothered have you been by difficulty with bladder control in the past 4 weeks.	Yes	No
Stanton (2005)[40]	BCPT symptom checklist	How bothered have you been by difficulty with bladder control in the past 4 weeks. • SUI: difficulty with bladder control at other times (coughing, sneezing)	Yes	No

SUI, stress urinary incontinence; UUI, urge urinary incontinence; BFLUTS, Bristol Female Lower Urinary Tract Symptoms; BCPT, Breast Cancer Prevention Trial; Breast Cancer Prevention Trial Eight Symptom Scale, BESS; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire; QUID, Questionnaire for Urinary Incontinence Diagnosis; UDI-6, Urinary Distress Inventory-6 questionnaire. CARES, Cancer Rehabilitation Evaluation System; GCS, Greene Climacteric Scale.

Appendix 4: Type of bladder disorder and associated severity of bother

Study	**Type of bladder disorder**	**Proportion of women reporting severity of bother n, (%)**				**Severity of bother score, mean (SD)**
		None	**Mild**	**Moderate**	**Severe**	
Avis (2004)[26]	Stress UI	150 (74)	30 (14)	24 (12)		-

Baumgart (2011)[25]	Stress UI	-	-	Tam: 24 (73)		-
				AI: 23 (70)		
	Urge UI	-	-	Tam: 19 (56)		-
				AI: 21 (64)		
	Frequent urination	-	-	Tam: 23 (68)		-
				AI: 21 (63)		
	Small amounts of leakage	-	-	Tam: 24 (47)		-
				AI: 23 (46)		
	Difficulty emptying bladder	-	-	Tam: 6 (18)		-
				AI: 5 (16)		
Biglia (2010)[18]	Urogenital symptoms*	-	-	-	-	3.4 (3.7)
Chin (2009)[28]	Any UI	158 (63)	76 (30)	15 (6)		-
	Urinary urgency	144 (57)	68 (27)	35 (14)		-
	Dysuria	217 (87)	26 (10)	5 (2)		-
Couzi (1995)[30]	Difficulty with bladder control	-	101 (55)	40 (22)	42 (23)	-
Daniel (2014)[31]	Bladder	122 (65)	28 (15)	26 (14)	11 (6)	-

	problems					
Ganz (2016) [12]	Bladder problems	-	-	-	-	Tam: 1
						AI: 0.8
Gupta (2006)[34]	Bladder problems	-	-	78 (39)	-	-

Appendix 4: Type of bladder disorder and associated severity of bother (continued)

-						
Kyvernitakis (2014)[19]	Bladder problems	107 (67)	23 (15)	16 (10)	13 (8)	-
Morales (2004)[23]	Urinary problems	Tam: 120 (73)	-	Tam: 45 (27)		-
		Trial: 121 (74)		Trial: 43 (26)		
		NSAI: 100 (61)		NSAI: 64 (39)		
		(N)SAI: 41 (75)		(N)SAI: 41 (25)		
Oleske (2004)[22]	Difficulty with bladder control	-	31 (25)	20 (16)	5 (4)	-
Park (2013)[38]	Bladder problems	-	-	-	-	3.1 (2.4)

*Includes both vaginal and urinary symptoms.

UI, urinary incontinence; Tam, tamoxifen; AI, aromatase inhibitor; Trial, receiving tamoxifen or letrozole; NSAI, non-steroidal aromatase inhibitors; (N)SAI, non-steroidal and steroidal aromatase inhibitors.

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Table 1: Risk of bias assessment

Author (year)	Sample characteristics					Confounders		Outcomes and analysis					
	Participants sampled	Appropriate sample	Inclusion criteria	Participants and setting	Appropriate sample	Confounding factors	Strategies dealing with	Outcome measured in a	Appropriate statistical	Reasons for incomplete	Response rate adequate	Key findings stated	Limitations stated
Randomised controlled studies													
Duijts (2012)[10]	Y	Y	Y	Y	Y	Y	Y	Y	U	N	Y	Y	Y
Ganz (2000)[11]	Y	Y	Y	Y	Y	Y	Y	N	U	Y	Y	Y	Y
Ganz (2016)[12]	Y	Y	Y	Y	Y	Y	Y	N	U	N	Y	Y	Y
Land (2004)[13]	Y	U	Y	Y	Y	Y	Y	N	U	N	Y	Y	Y
Lötzke (2016)[14]	Y	Y	Y	Y	Y	N	N	N	U	N	N	Y	Y

Schover (2006)[15]	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	Y	Y
Versmessen (2012)[16]	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	Y	Y
Cohort studies													
Alfano (2006)[17]	Y	Y	Y	Y	Y	Y	Y	N	U	Y	Y	Y	Y
Biglia (2010)[18]	N	Y	Y	Y	N	Y	Y	N	U	N	NA	Y	Y
Hartl (2010)[21]	Y	Y	Y	Y	N	N	N	N	Y	N	Y	Y	Y
Kyvernitakis (2014)[19]	U	U	N	N	N	N	N	N	Y	N	Y	Y	Y
Ganz (2011)[2]	U	Y	N	N	Y	Y	Y	N	Y	N	Y	Y	Y
Morales (2004)[23]	Y	Y	N	Y	N	N	N	N	Y	Y	Y	Y	Y

Oleske (2004)[22]	Y	U	Y	N	N	Y	Y	N	U	Y	Y	Y	Y
Pagano (2018)[20]	Y	U	U	Y	N	Y	Y	N	N	Y	Y	Y	Y

Y, yes; N, no; U, unclear; NA, not applicable.

Table 1: Risk of bias assessment (continued)

Author (year)	Sample characteristics					Confounders		Outcomes and analysis					
	Participants sampled	Appropriate sample	Inclusion criteria	Participants and setting	Appropriate sample	Confounding factors	Strategies dealing with	Outcome measured in a	Appropriate statistical	Reasons for incomplete	Response rate adequate	Key findings stated	Limitations stated
Cross-sectional studies													
Avis (2004)[26]	Y	Y	Y	Y	N	NA	NA	N	Y	N	Y	Y	Y
Baumgart (2011)[25]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	Y
Chen (2018)[27]	Y	Y	Y	Y	Y	NA	NA	N	Y	N	U	Y	Y

Chin (2009)[28]	Y	Y	Y	Y	Y	NA	NA	N	U	N	N	Y	Y
Cook (2017)[29]	NA	Y	Y	Y	Y	NA	NA	N	Y	NA	NA	Y	Y
Couzi (1995)[30]	Y	Y	Y	U	Y	NA	NA	N	Y	Y	Y	Y	N
Daniel (2014)[31]	Y	Y	Y	Y	N	NA	NA	N	U	N	Y	Y	N
Ganz (2003)[32]	Y	Y	Y	N	Y	NA	NA	N	U	Y	Y	Y	Y
Greendale (2001)[33]	Y	Y	Y	Y	N	NA	NA	N	U	N	N	Y	Y
Gupta (2006)[34]	U	Y	U	Y	N	NA	NA	N	U	N	Y	Y	N
Landi (2016)[35]	Y	Y	Y	Y	Y	NA	NA	N	Y	Y	Y	Y	Y

Leining (2006)[36]	N	Y	Y	U	Y	NA	NA	N	U	Y	N	Y	Y
Morrow (2014)[37]	Y	Y	Y	Y	Y	NA	NA	N	Y	Y	N	Y	Y
Park (2013)[38]	N	Y	Y	Y	N	NA	NA	N	Y	N	U	Y	N
Robinson (2017)[24]	Y	U	U	U	Y	NA	NA	Y	Y	Y	Y	Y	Y
Schover (2014)[39]	Y	Y	Y	N	N	NA	NA	N	Y	Y	N	Y	Y
Stanton (2005)[40]	N	Y	Y	N	Y	NA	NA	N	U	N	U	U	U

Y, yes; N, no; U, unclear; NA, not applicable.

Table 2: Characteristics of included studies

Study		**Population**			**Exposure**		**Outcomes**				
Author (year)	**Country**	**Sample**	**Mean age**	**Menopausal status (% of**	**Stag**	**Treatment type**	**Tool**	**Assessm**	**Prevalence**	**Incidence**	**Impact**

		size	e (years)	women)			e of breast cancer						entime-point			
				Pre	Peri	Post		Surgery	Chemo	Radio	Endo					
Randomised controlled trials																
Duijts (2012)[10]	Netherlands	422	48.2	100	-	-	I-IV	Yes	Yes	No	Yes	BFLUTS	Post	×	×	✓
Ganz (2000)[11]	USA	72	54.5	No	Yes	Yes	I or II	Yes	Yes	Yes	Yes	MSS	Post	✓	×	✓
Ganz (2016)[12]	USA	1,193	NR[α]	-	-	100	DCIS	Yes	No	Yes	No	BCPT	Post	×	×	✓
Land (2004)[13]	USA	160	NR[ß]	NR	NR	NR	NR	Yes	No	No	No	BCPT	NR	✓	×	×
Lötzke (2016)[14]	Germany	92	51.0	NR	NR	NR	I-III	No	Yes	Yes	Yes	EORTC QLQ-C3	Peri	×	×	✓

												0				
Schover (2006)[15]	USA	48	49.3	19	NR	NR	0-III	Yes	Yes	No	Yes	MSS	Peri	×	×	✓
Versmessen (2012)[16]	Belgium	121	55.0	NR	NR	NR	I–II	Yes	No	Yes	Yes	EORTCQLQ-C30	Post	×	×	✓
Cohort studies																
Alfano (2006)[17]	USA	803	56.0	18	NR	75	NR	Yes	Yes	Yes	No	BCPT	Post	✓	×	✓

Table 2: Characteristics of included studies (continued)

Biglia (2010)[18]	Italy	35	45.7	91	-	9	NR	Yes	Yes	Yes	Yes	GCS	Post	×	×	✓
Hartl (2010)[21]	Germany	203	58.4	22	-	78	I-IV, DCIS	Yes	Yes	Yes	Yes	EORTCQLQ-C30	Post	×	×	✓
Kyvernitakis (2014)[19]	Germany	180	63.2	-	-	100	I-IV	Yes	Yes	Yes	No	MRS	Peri	✓	×	✓
Ganz (2011)[2]	USA	558	56.9	35	-	65	I-II	Yes	Yes	Yes	Yes	BCPT	Post	×	×	✓

Morales (2004)[23]	Belgium	164	62.0	-	-	100	NR	No	No	No	Yes	Author-made	Peri	✓	×	✓
Oleske (2004)[22]	USA	123	58.3	NR	NR	NR	I-VI, DCIS	No	No	No	Yes	BCPT	Post	✓	×	✓
Pagano (2018)[20]	Italy	82	44.0	NR	NR	12	NR	No	Yes	No	Yes	VAS	NR	✓	×	×
Cross-sectional studies																
Avis (2004)[26]	USA	204	43.5	NR	NR	NR	I-III	Yes	Yes	Yes	No	CARES	Post	×	×	✓
Baumgart (2011)[25]	Sweden	202	62.7	-	-	100	NR	No	No	No	Yes	UDI-6	Post	✓	×	✓
Chen (2018)[27]	China	608	48.0	45	-	55	0-IV	No	Yes	No	No	EORTC QLQ-C30	Post	×	×	✓
Chin (2009)[28]	Canada	251	60.5	-	-	100	NR	No	No	No	Yes	Author-made	Peri	✓	×	✓
Cook (2017)[29]	USA	800	56.1	19	-	78	NR	No	No	No	Yes	NA	Post	✓	×	×
Couzi (1995)[30]	USA	190	54.9	-	-	100	NR	Yes	Yes	Yes	Yes	Author-mad	Post	✓	×	✓

												e				

Table 2: Characteristics of included studies (continued)

Daniel (2014)[31]	England	196	56.0	55	NR	NR	NR	No	Yes	No	Yes	MRS	NR	✓	×	✓
Ganz (2003)[32]	USA	577	49.5	16	13	60	0-II	Yes	Yes	No	Yes	BCPT	Post	✓	×	×
Greendale (2001)[33]	USA	61	54.5	-	-	100	I-II	Yes	Yes	No	Yes	BCPT	Post	×	×	✓
Gupta (2006)[34]	UK	200	53.9	6	9	66	NR	Yes	Yes	Yes	Yes	MRS	Post	✓	×	×
Landi (2016)[35]	USA	548	58.1	-	-	100	0-III	No	Yes	No	Yes	Interview	Post	✓	×	×
Leining (2006)[36]	USA	371	36.2	100	-	-	0-III	Yes	Yes	Yes	Yes	BCPT	Post	✓	×	×
Morrow (2014)[37]	USA	1,090	47.6	82	1	13	I-IV	Yes	Yes	No	Yes	BCPT	Post	×	×	✓
Park (2013)[38]	Korea	200	45.6	64	16	20	I-IV	Yes	Yes	No	No	MRS	NR	×	×	✓

Robinson (2017)[24]	Australia	625	65.1	NR	NR	NR	I	Yes	Yes	Yes	Yes	QUID	Post	✓	×	×
Schover (2014)[39]	USA	129	64.0	NR	NR	NR	I-II	Yes	Yes	No	No	BESS	Post	×	×	✓
Stanton (2005)[40]	USA	2,208	47.0-57.0[γ]	NR	NR	NR	0-III[δ]	Yes	Yes	No	Yes	BCPT	Post	×	×	✓

α: Authors provided proportions of women in age range.

ß: Authors provided proportions of women in age range.

γ: Authors provided mean age for each sample. Sample 1: 56, Sample 2: 50, Sample 3: 57.

δ: Authors provided staging for each group. Sample 1: 0-II; Sample 2: 0-II; Sample 3: I-II.

NR, not reported; DCIS, ductal carcinoma in situ; Chemo, chemotherapy; Radio, radiation therapy; Endo, endocrine therapy; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; MRS, Menopause Rating Scale; MSS, Menopausal Symptom Scale; BCPT, Breast Cancer Prevention Trial; CARES, Cancer Rehabilitation Evaluation System; FACT, Functional Assessment of Cancer Therapy; BFLUTS, Bristol Female

Lower Urinary Tract Symptoms questionnaire; GCS, Greene Climacteric Scale; QUID, Questionnaire for Urinary Incontinence Diagnosis; VAS, Visual Analog Scale.