

Radiotherapy-induced late effects among female pelvic cancer survivors

- sexual health, wellbeing and impact of nurse-led interventions

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Cover illustration: The feather and the knife by Kajsa Åkeflo

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To my family, always in my heart

Den mätta dagen, den är aldrig störst
Den bästa dagen är en dag av törst.
Nog finns det mål och mening i vår färd
men det är vägen, som är mödan värd.

Karin Boye

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ABSTRACT

Background: Pelvic radiotherapy is commonly a life-saving treatment for gynecological, rectal, and anal cancer, but frequently entails lifelong unwanted late effects due to the treatment affecting healthy tissue. This thesis addresses the unmet needs concerning sexual health issues and low wellbeing in an increasing number of female pelvic cancer survivors.

Aim: The aim of this thesis was to improve knowledge about sexual health, wellbeing and vaginal changes in female cancer survivors with a history of pelvic radiotherapy. More specific aims were to study whether sexual health and wellbeing can improve after nurse-led biopsychosocial interventions targeting physical radiotherapy-induced late effects, to study the impact on health of female pelvic cancer survivors having a history of sexual abuse, and to explore women's experiences and difficulties of performing vaginal dilator therapy following pelvic radiotherapy.

Methods: A combination of quantitative and qualitative methods were used. Studies I-III (n=605, n=260, n=570) are prospective, population-based cohort studies using study-specific questionnaires covering psychosocial-, intestinal-, urinary tract-, and sexual health, and lymphedema. Study IV (n=12) is a qualitative individual interview study using a semi-structured interview guide, analyzed using qualitative content analysis.

Results: We found improvements in satisfaction with overall sexual health and quality of life, and reduced genital pain, depression, and anxiety following individualized nurse-led interventions (n=260). No improvements

were shown in sexual function. Reduced urgency to defecate was associated with improved satisfaction with overall sexual health. Reduced fecal leakage was associated with lower levels of anxiety. Depression, anxiety, and genital pain were statistically significantly more common among women with a history of sexual abuse than those without (n=570). One overarching theme, *Being unprepared* for receiving information and performing vaginal dilator therapy, emerged in the qualitative content analysis of the interview study (n=12). Along with physical and emotional reactions while performing the therapy, the women described complex psychological and practical barriers. Some women developed useful strategies to increase their motivation for vaginal dilator therapy.

Conclusions: Nurse-led individualized interventions can lead to marked improvements in depression, anxiety, quality of life and sexual health, even with interventions primarily focusing on physical late effects. The increased risk for low sexual health and wellbeing in women having a history of sexual abuse needs to be taken into account. A study to assess the needs and impact of nurse-led interventions in the longer term and among women with a history of both pelvic radiotherapy and sexual abuse is warranted. The situation for women having difficulty maintaining vaginal dilator therapy can be improved through clinical application of the data from this and other studies. The results from this thesis can be applied to achieve clinical implications through meeting women's need for preparedness for self-care interventions and thereby strengthening sexual health and quality of life after pelvic cancer.

Keywords: Female pelvic cancer survivors, Nurse-led interventions, Pelvic radiotherapy, Rehabilitation, Sexual health, Survivorship

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Majoriteten av kvinnor som drabbas av cancer i bäckenområdet (gynekologisk, anal-, och rektal-cancer) behandlas med strålbehandling, vilket för många är en livräddande behandling. Det finns dock en stor risk att behandlingen påverkar frisk vävnad vilket kan ge livslånga och ibland svåra konsekvenser på kroppens funktioner såsom tarm, urinvägar, lymfsystem och sexuell hälsa med påverkan på livskvaliteten. Några av de vanligaste, mest besvärande och samtidigt minst utforskade seneffekter är nedsatt sexuell hälsa, vaginala förändringar och nedsatt sexuell funktion. Som en del i omhändertagandet behövs evidensbaserade interventioner. Sjuksköterskeledda interventioner genom stöd, behandling och uppföljning kan tänkas vara användbara i det arbetet.

Syfte: Syftet med avhandlingen var att bidra till kunskap om sexuell hälsa hos kvinnor som genomgått strålbehandling mot cancer i bäckenområdet. Mer specifikt; att undersöka om sexuell hälsa och välbefinnande förbättras efter sjuksköterskeledda interventioner riktade mot fysiska strålinducerade seneffekter, att studera påverkan på hälsa hos bäckencanceröverlevare med tidigare erfarenheter av sexuella övergrepp och att undersöka kvinnors upplevelser av användande, information och rådgivning av vaginalstavsterapi (prevention genom egenvård för att motverka vaginala förändringar).

Metod: Avhandlingens tre första delstudier utgörs av självrapporterad studiespecifik enkät-data insamlad före och efter intervention i en populationsbaserad kohort mellan år 2011-2017. Studie I (n=605) beskriver datainsamling med studiespecifika frågeformulär, interventioner och studiedeltagarnas karaktäristika. I studie II (n=260), studeras förändring i sexuell hälsa och välbefinnande före och tre månader efter avslutad intervention. Studie III (n=570) undersöker sexuell hälsa och välbefinnande hos kvinnor efter bäckenstrålbehandling utifrån rapportering om tidigare utsatthet för sexuella övergrepp. I delstudie IV (n=12) genomfördes intervjuer med ett urval av kvinnliga bäckencanceröverlevare som uppgett svårigheter med egenvård av att förebygga strålinducerade vaginala förändringar, om deras upplevelser av att få information och att genomföra vaginalstavsterapi.

Resultat: Efter interventionerna rapporterade fler kvinnor statistiskt signifikanta förbättringar än försämringar vad gällde nöjdhet med generell sexuell hälsa (26.0% vs. 15.3%, $p=0.035$), minskad ytlig genital smärta (25.8% vs. 13.1% $p=0.025$) och minskad djup genital smärta (23.1% vs. 8.0%, <0.001) vid vaginalsex, ökad livskvalitet (42.7% vs. 22.4%, $p<0.001$) och lägre nivåer av depression (43.1% vs. 28%, $p=0.003$) och ångest (45.9% vs. 24.4%, $p<0.001$). Minskning av akuta avföringsträngningar var statistiskt signifikant associerat till ökning av tillfredställelse med sexuell hälsa ($p=0.004$, RR 3.12, 95% CI 1.27-7.68) medan minskat fekalt läckage var statistiskt signifikant associerat med minskad ångestnivå ($p=0.021$, RR 1.56 95% CI 1.02-2.33). Statistisk signifikant högre andel kvinnor med tidigare erfarenhet av sexuella övergrepp rapporterade depression (19.4% vs 9%, $p=0.007$) och ångest (22.6% vs 11.8 %, $p=0.007$). De hade också en tvåfaldigt ökad risk för djup genital smärta (52 % vs 25.1 %, $p=0.011$, RR 2.07, CI 1.24-3.16) vid sexuell aktivitet jämfört med kvinnor utan sådan erfarenhet. Ytlig genital smärta vid sexuell aktivitet var mer vanligt förekommande efter rektalcancerbehandling jämfört med efter behandling av andra cancerdiagnoser i bäckenområdet, medan djup genital smärta var mer vanligt efter behandling mot cervixcancer. Genital smärta bekräftades också vara associerat med vaginal förkortning och oelasticitet. I intervjustudien med kvinnor som hade svårigheter att fördra vaginalstavsterapin framkom att de upplevde sig vara oförberedda på att få information och på att genomföra terapin. Både fysiska och emotionella svårigheter beskrevs i samband med vaginalstavsanvändningen. Att motivera sig till terapin var förknippat med psykologiska och praktiska hinder och skapade ångest men vissa kvinnor fann strategier för att överkomma detta.

Slutsats: Denna avhandling har identifierat faktorer som är viktiga att beakta i cancerbehandling när vi utvecklar och förbättrar omhändertagandet av kvinnor med risk för framtida eller med manifesta seneffekter och påverkad sexuell hälsa, såsom att behandla tarmbiverkningar och att identifiera och erbjuda stöd till kvinnor som tidigare varit utsatta för sexuella övergrepp. Resultaten visar på vikten av biopsykosocialt stöd och att se cancerrehabiliteringen som förlängning av behandlingen. Resultatet i avhandlingen kan användas för att utveckla sjuksköterske-ledda rehabiliteringsinterventioner, vilka har potential att vara en del av lösningen mot förbättrad sexuell hälsa efter bäckencancer. Tidig och tydlig kommunikation, psyko-edukativa insatser och stödjande vård vid vaginala

förändringar föreslås vara integrerade i cancerbehandling, uppföljning, såväl som i rehabilitering. Framtida studier behövs för att ytterligare evidens-basera omhändertagande, information och rådgivning före, under och efter cancerbehandling hos kvinnor både med och utan tidigare historia av sexuella övergrepp. Resultaten från studien kan användas för klinisk implikation för att möta kvinnors behov av att vara förberedd för egenvård och därigenom stärka sexuell hälsa och livskvalitet efter cancer.

LIST OF PAPERS

This thesis is based on the following papers referred to in the text by their Roman numerals.

- I. **Åkeflo L**, Dunberger G, Elmerstig E, Skokic V, Steineck G, Bergmark K. Cohort profile: an observational longitudinal data collection of health aspects in a cohort of female cancer survivors with a history of pelvic radiotherapy – a population-based cohort in the western region of Sweden, *BMJ Open*. 2021 Jul 21;11(7) e049479.
- II. **Åkeflo L**, Dunberger G, Elmerstig E, Skokic V, Steineck G, Bergmark K. Sexual health and wellbeing among female pelvic cancer survivors following individualized interventions in a nurse-led clinic. *Support Care Cancer*. 2022 Aug 5. doi: 10.1007/s00520-022-07294-x.
- III. **Åkeflo L**, Elmerstig E, Dunberger G, Skokic V, Arnell A, Bergmark K. Sexual health and wellbeing after pelvic radiotherapy among women with and without a reported history of sexual abuse: important issues in cancer survivorship care. *Support Care Cancer*. 2021 Nov;29 (11):6851-6861.
- IV. **Åkeflo L**, Elmerstig E, Bergmark K, Dunberger G. Barriers and strategies dealing with vaginal dilator therapy – female pelvic cancer survivors’ experiences, a qualitative study. Submitted.

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ABBREVIATIONS

3D-CRT	Three-Dimensional Conformal Radiation Therapy
BT	Brachytherapy
CT	Computed Tomography
EBRT	External Beam Radiotherapy
Gy	Gray, the International System of units (SI) used to measure the total absorbed radiation (energy per mass unit)
HPV	Human Papilloma Virus
IMRT	Intensity-modulated radiation therapy
LARS	Low Anterior Resection Syndrome
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
PLISSIT	Permission, Limited Information, Specific Suggestions, Intensive Therapy
RCT	Randomized Controlled Trial
SRHR	Sexual and Reproductive Health and Rights
SSRI	Selective serotonin reuptake inhibitors, a widely used type of antidepressant
STI	Sexual Transmitted Infections
WHO	World Health Organization

DEFINITIONS IN SHORT

Gynecological cancer	Cancer types affecting the gynecological organs (endometrial, cervical, vulvar, vaginal cancers). Ovarian cancer is not included in the background or in the focus of this thesis since it is not usually treated with radiotherapy.
Invasive lymph node staging	Lymphadenectomy to obtain prognostic information (surgical staging) from lymph node status. This is associated with a risk of lymphedema, lymphocysts, cellulitis, and damage to nearby nerves.
Sentinel lymph node (SLN) mapping	Alternative to lymphadenectomy to obtain prognostic information (surgical staging) from lymph node status, a more targeted lymphadenectomy that is proposed to minimize collateral damage.
Women and females	Used in this thesis to describe individuals with gynecological organs even though there are transmen and non-binary individuals who have gynecological organs. All participants in the thesis identified themselves as cisgender women, which means that their legal gender was the same as their self-reported gender.

1 PREFACE

In the painting on the cover of this thesis, the feather symbolizes for me sexual health and wellbeing when life is easy and is going well. The knife symbolizes something sudden, unexpected, and life-threatening that happens in life, such as cancer. Although everything may change, it is fascinating to see how human beings can get through hard times. My interpretation of the colorful background is the hope for a bright future.

My interest in the subject of this thesis was awakened when I worked in the radiotherapy department. I recognized that there was a lack of adequate and consistent information provided concerning treatment-induced vaginal changes affecting female pelvic cancer patients. Subsequently, with the support of a gynecological oncologist, I established a follow-up routine, which aimed to provide information about vaginal changes and how these can be prevented through self-care and vaginal dilator therapy. Over time, I met several women who expressed difficulties in adopting the therapy and who said “The therapy feels almost like sexual abuse”. This bothered me and sparked my interest in research. I started trying to look into how we could develop and improve the methods used for therapy and the counseling for treatment-induced effects of vulvovaginal changes, which inevitably also affect sexual health. Cancer impacts questions of existence, intimate relationships, sexuality, body image, fertility, and much more, both when receiving the diagnosis, during treatment and most often in the long term. My intention was to shed light on women’s perspectives.

Previous pioneering research in pelvic cancer survivorship that has challenged the stigma and taboos surrounding cancer, intestinal problems, and sexuality, and paved the way for breaking these, has served as a starting point for this project. However, under-recognition of vaginal changes and the effects on sexuality in female pelvic cancer survivors in oncology care and research remains, which triggered the search for a deeper understanding and the best evidence for the support of women surviving pelvic cancer. Hence, with this background, this research seemed much needed.

2 BACKGROUND

About 4700 women receive a pelvic cancer diagnosis every year in Sweden (1). Increased survival rates due to improvement in cancer treatment have led to a continuously growing population of cancer survivors. As a consequence, an increased number of cancer survivors live with treatment-induced late effects and conditions. This includes unwanted late effects in the organs and organ systems that are important for sexuality (2-4). Since a cancer diagnosis and cancer treatment affect both the physical body and psychosocial health, there is a need for combined interventions, counseling, and support for persons with treatment-induced late effects. Sexual dysfunction is one of the most troublesome late effects and is often overlooked in healthcare, although the impact on quality of life and psychosocial health is well recognized (5-7). This thesis investigates sexual health, wellbeing and vaginal changes in female cancer survivors with a history of pelvic radiotherapy, and the outcomes from interventions provided in a nurse-led rehabilitation clinic.

2.1 FEMALE PELVIC CANCER

In this thesis, female pelvic cancer refers to gynecological cancer (endometrial, cervical, vulvar, and vaginal cancer), rectal cancer, and anal cancer (1). These cancer types differ regarding incidence and treatment modalities.

2.1.1 Endometrial cancer

With 417000 cases diagnosed annually worldwide, endometrial cancer is globally the 6th most common cancer type among women, and is the most common gynecological cancer in developed countries. In Sweden, the annual incidence is 1322 cases (2020) (1). The incidence increases with age and is highest among postmenopausal women. Endometrial cancer is usually diagnosed and treated at an early stage due to early signs of post-menopausal irregular vaginal bleeding. Besides increasing age, other risk factors for endometrial cancer include conditions involving high estrogen levels with no balancing effect of progesterone (e.g. infertility and obesity), diabetes, hypertension, and hormone therapy for breast cancer. Endometrial cancers type I and type II have different etiologies, genetics, and prognoses. Type I

involves obesity as a risk factor, while type II is a non-hormone dependent tumor with a poorer prognosis (8). According to analyses of the global patterns and trends of incidence, the risk of endometrial cancer increases in countries undergoing rapid socioeconomic transitions (9).

The treatment of endometrial cancer is decided based on the type of tumor and the stage of the disease. Surgery that includes hysterectomy, bilateral salpingo-oophorectomy and the removal of lymph nodes, if affected, is the standard procedure. Based on the risk for recurrence, adjuvant treatment, radiotherapy, chemotherapy, or a combination of these may be indicated (10).

2.1.2 Cervical cancer

Cervical cancer is the 4th most common cancer globally and has a lower mean age than many other types of cancer. The majority of cervical cancer cases are found in low-income countries, which reflects differences in exposure to risk factors, lack of screening, and a shortage of effective treatment for the early stages of the disease (11). In Sweden, the incidence of cervical cancer in 2020 was 565 cases (1). Almost all cervical cancers are caused by a persistent infection with Human Papilloma Virus (HPV), one of the most common sexually transmitted diseases and likely to affect almost all women in the world. In most cases the infection clears, but in some rare cases a persistent HPV infection can develop into dysplasia and cancer. Additional risk factors are smoking, young age at first intercourse, sexually transmitted diseases, multiple sexual partners, a long-term use of oral contraceptives, and weakened immune systems (12). The incidence of cervical cancer has decreased in high-income countries due to screening programs, early treatment (13), and prevention through HPV vaccination. In recent years, HPV vaccination programs have been introduced, which in Sweden include all children (both boys and girls from grade 5 – age 10-12 years), and these have effectively reduced the risk for cervical cancer (14). Although promising steps have been taken, further improvements are needed to be able to achieve the goal set by the World Health Organization (WHO) to eliminate cervical cancer globally (15).

Depending on the stage and spread of the cancer, the standard treatment for patients with early stage cervical cancer is surgery by cervical conization, total simple hysterectomy, or radical hysterectomy. More advanced stages are treated with definitive chemoradiotherapy (16, 17).

2.1.3 Vaginal cancer

In Sweden, approximately 40 women are diagnosed annually with vaginal cancer, and it is more common in postmenopausal women. The cause is similar to cervical cancer – a persistent HPV infection, although chronic inflammation is also considered a risk factor. Treatment depends on the stage, which in some early cases means surgery, but more commonly involves radiotherapy or radio- and chemotherapy in combination (16, 18).

2.1.4 Vulvar cancer

Vulvar cancer accounts for 5% of all malignancies of the female genital tract (after endometrial, ovarian, and cervical cancers) (19, 20). In Sweden, around 160 new cases of vulvar cancer are diagnosed each year (1). There are two types of vulvar cancer, where the most common is primarily a disease of the elderly, with lichen sclerosus being a predisposing risk factor. Correlating factors found in the incidence of this type of vulvar cancer are diabetes mellitus, hypertension, and obesity (20). The other type of vulvar cancer occurs more often in younger patients (35-65 years of age), involves an HPV infection (20), and currently has an increasing incidence rate (19). The incidence rate is, however, expected to decrease in high-income countries due to HPV vaccination programs. The primary therapy is surgery, with chemoradiotherapy being considered in advanced stages (21).

2.1.5 Rectal cancer

Rectal cancer belongs to the group of colorectal cancers, globally the 3rd most common form of cancer in women. A higher incidence is reported in high-income countries due to hereditary and lifestyle (e.g. dietary patterns) factors (22). In Sweden, approximately 800 women receive a colorectal cancer diagnosis annually (1). In addition to dietary patterns and a family history of colorectal cancer, other factors that increase the risk for colorectal cancer are smoking, alcohol consumption, obesity, inflammatory bowel disease, and diabetes. In recent years, screening for colorectal cancer has been shown to be effective in lowering the incidence (23) and screening programs have been established in several high-income countries (24).

The treatment depends on the stage of the disease. Surgical removal of the main tumor or tumors and affected tissues is the primary treatment. The most common treatments are surgery that includes either total removal of the

rectum (proctectomy) or removal of both the rectum and part of the colon (proctocolectomy). Preoperative radiotherapy, with or without chemotherapy, in locally advanced rectal cancer is a common additional treatment. Some patients receive a temporary ostomy, and in some cases chemotherapy after surgery is considered in order to reduce the risk of relapse (25, 26).

2.1.6 Anal cancer

The incidence of anal cancer globally is relatively low, accounting for 2% of all cancers; however, it is increasing and is higher in women (27). Annually, approximately 160 women in Sweden are diagnosed with anal cancer (1). HPV infection is recognized as the major cause of anal cancers and has similar risk factors to the development of cervical cancer (28).

The standard treatment for anal cancer is chemoradiotherapy. In some cases, surgery may be necessary to reduce the risk of locoregional relapse (28).

2.2 RADIOTHERAPY-INDUCED LATE EFFECTS

2.2.1 Radiotherapy

Radiotherapy has been utilized for over 100 years and is a life-saving cancer treatment. It is used in more than half of all cancer treatments and, in some diagnoses, is the most effective treatment. Ionizing radiation generates reactive oxygen species and free radicals, which cause DNA damage and cell death. The irradiation activates cellular signaling pathways that lead to the expression and activation of pro-inflammatory and pro-fibrotic cytokines. Coagulation cascades and vascular injury also occur. All these changes contribute to inflammatory responses, edema, and erythema in the skin and tissue. The DNA damage and cell death affect cancer cells more severely than normal cells. However, since radiotherapy must always be planned with the addition of margins to ensure that the treatment field does not miss the cancer, radiation side effects occur. These are classified as acute or late. Acute side effects involve epithelial surfaces of the skin or tissues. Late side effects are a result of a complex interplay between the pathophysiological processes that occur in tissues in the walls of the intestine, urogenital tissues, the lymphatic system, and muscles.

Technical advancement has resulted in limited doses being given to nearby tissue and organs through reducing the irradiated volume as much as possible and using small dose fractions, which are all strategies to avoid side effects (29, 30). There are two major types of radiation therapy: external-beam radiation therapy (EBRT) and internal radiation therapy. EBRT delivers radiation from a machine outside the body. Three-Dimensional Conformal Radiation Therapy (3D-CRT) is a conventional therapy that uses 3D pictures of the cancer tumour generated by CT or MRI scans and enables delivery of radiation with the same intensity throughout the therapy, precisely and at high doses. Intensity Modulated Radiation Therapy (IMRT) is a more complex form of EBRT which, unlike 3D-CRT, can vary the intensity of the radiation within each field (31).

Brachytherapy is internal radiation therapy, which gives the possibility of directing a large dose of radiation to the tumor while minimizing exposure to surrounding normal structures (32). The treatment entails the placement of a radiation emitting source in immediate proximity to a macroscopic tumor. The radiation source (usually Iridium-192) slowly emits radiation over a short distance. This therapy is commonly utilized for gynecological cancers. Brachytherapy with high-dose-rate (HDR) combined with external beam radiotherapy is the most commonly used technique in the treatment of gynecological cancer. Intracavitary treatment (cervical cancer treatment) is usually performed using spinal or general anesthesia, while vaginal brachytherapy (endometrial cancer treatment) can be performed without anesthesia.

External radiotherapy places specific demands on pelvic cancer survivors due to its impact on essential organs and functions situated in the pelvic area. Along with the effects on genital and sexual health in women after treatment, varying degrees of dysfunction in the intestinal tract, urinary tract, genitals, pelvic bone, pelvic muscles or the lymphatic system can coexist (4, 33, 34). While physical long-term side effects of brachytherapy are mild due to the minimum radiation exposure to surrounding organs and tissues, psychological consequences have been reported in terms of post-traumatic stress disorder (PTSD) (35).

This thesis focuses on sexual health issues and wellbeing aspects. However, there are other common and bothersome symptoms associated with cancer and cancer treatment that can persist for years after treatment, which in some cases can be lifelong. These include menopause symptoms, vulvovaginal symptoms, pain, intestinal- and urinary tract symptoms, fatigue and lymphedema and more, which can all lower quality of life. A brief outline of some of these late effects follows.

2.2.2 Premature or exacerbation of the menopause

Since the ovaries are highly radiosensitive, the high doses required for treating gynecological, anal, and rectal cancers result in an abrupt premature ovarian insufficiency or an exacerbation of the menopause, which can in turn lead to definitive menopause and loss of fertility (36). Surgical oophorectomy also induces premature menopause or exacerbation of the menopause. Unlike this abrupt, premature, therapy-induced entry into menopause, the natural menopause transition can last for several years due to a successive reduction of the ovarian hormones (estrogen, progesterone, and androgens), with the final menstrual period being at an average age of 51 years (37, 38).

Regardless of the cause of menopause, the consequences of estrogen depletion result in vulvovaginal atrophy, which may lead to urogenital symptoms, such as vaginal dryness, itching and discomfort, vulvar pain, and loss of tissue elasticity. For some women, this results in impaired sexual function, such as reduced arousal, lubrication, orgasm, and pain during vaginal sex (37, 38). Cognitive changes, anxiety, depression, and mood changes are also symptoms directly or indirectly related to menopausal transition that negatively affect quality of life. Vasomotor symptoms, such as hot flushes and night sweats, are reported to various degrees in up to 80% of women in menopausal transition. Most symptoms resolve within a few months but, for some women, can persist for several years. Factors suggested to affect vasomotor symptoms include body mass index, exercise, smoking, depression, and age at onset of menopause (39). The long-term effects of estrogen reduction due to premature menopause (before age 40 years) have been reported to increase the risk for cardiovascular diseases (40) and decreased bone density (37).

Treatment-induced menopause can result in more severe symptoms. Management of radiotherapy-induced menopause includes information about induced menopause, possible symptoms and available treatments. Systemic menopausal hormone therapy is recommended to female pelvic cancer survivors in premenopausal age until the age of expected natural menopause unless there are contraindications, such as having an estrogen-dependent gynecological cancer or hormone receptor-positive breast cancer (37). Menopausal hormone therapy can be administered systemically as oral or transdermal therapy. Current evidence suggests topical estrogen can be administered to women for the management of vulvovaginal symptoms, irrespective of age and diagnosis (41, 42).

2.2.3 Vulvovaginal late effects

The above mentioned reduced or absent ovarian function (43) results in vulvovaginal atrophy, reduced lubrication and elasticity, and thinner vaginal mucosa. In addition, the mucosa is affected by radiotherapy due to pathophysiological processes, which can lead to a high risk for the development of vaginal changes, such as narrowing and inelasticity, as well as partial or total vaginal stenosis (2, 44). Varying degrees of vaginal changes have been reported in up to 88% of women with a gynecological cancer (4, 38) and, though less well studied, in about two thirds of women with rectal or anal cancer (45). The incidence depends on site of disease, radiation dose, and concurrent chemotherapy. The highest incidence is reported in women undergoing definitive treatment for locally advanced cervical cancer (46), with an increased risk reported in women over the age of 50 years (44). Increased radiation dose and vaginal volume are associated with vaginal stenosis (47). The consequences of vaginal stenosis impede adequate physical gynecological examination in the follow-up after treatment to detect recurrence of cancer (48), and in sexually active women lead to difficulties having vaginal sex, including experiences of pain and bleeding during vaginal sex (45). In addition, worrying about bodily changes and sexual dysfunction are commonly reported, and have been associated with survivors experiencing shame, damaged body image, and fear of embarrassment in sexual situations (49).

The underlying pathophysiological processes of radiotherapy-induced vaginal changes have been studied. In one study in women treated with curative

radiochemotherapy (EBRT 45-50 Gy with concomitant Cisplatin 40 mg/m²) for cervical cancer, the occurrence of the following morphological parameters were identified: mucosal pallor (a marker for mucosal atrophy), telangiectasia, fragility of the vaginal wall, ulceration, and adhesions (50). In a study by Hofsjö et al. (51) on a sample of vaginal biopsies collected in cervical cancer survivors treated with pelvic radiotherapy (EBRT 44.3-52.4 Gy), mucosal atrophy was observed in 91% and fibrosis in 97%. Dense collagen and entangled elastin fibers were found in the vaginal wall tissue. Since elastic fibers, such as collagen and elastin, give elasticity and resistance to the body structures, dense collagen and entangled elastin fibers may explain the impact of radiotherapy on the vaginal tissue in women treated with pelvic radiotherapy. Surgery and chemotherapy can also affect vaginal length and elasticity (52).

2.2.4 Pain

Pain is a vital signal of bodily threat. In an acute pain situation, such as in treatment-associated tissue injury, a cascade of inter-related events begins and further activates multiple pain systems. Through a complex physiological process, which interacts with genetics and psychosocial factors, the pain sometimes shifts from acute to chronic (53). The development of persistent pain after an acute pain episode has been recognized as affecting about 30% of all cancer patients (54), especially after radiotherapy and surgery. Chronic pain contributes to insomnia, depression, and decreased quality of life for many survivors (55). One study reported that one in ten long-term gynecological cancer survivors experienced pain from the pubic bone (33). Intestinal late effects, cystitis, fistulas, and pelvic fractures can also cause pain in the pelvic area. Genital pain experienced during vaginal sex, as well as pain in the genitals, termed vulvodynia and vulvovaginal pain, is described in the chapter on sexual dysfunction.

2.2.5 Intestinal late effects

In pelvic cancer survivorship research five bothersome intestinal syndromes, consisting of 28 different symptoms, have been identified (56), including urgency to defecate, fecal leakage, loose stools, excessive mucus, excessive gas production, and blood discharge. Urgency to defecate in combination with fecal leakage was frequently reported in a study of gynecological cancer

survivors, and almost half of those treated with both surgery and radiotherapy reported that defecation urgency with fecal leakage occurred occasionally. It is estimated that around ten percent of cancer survivors are at risk of having the symptom, which involves all stools emptying from the bowel into clothing without forewarning. The highest reported relative risks of intestinal late effects found in a comparison between gynecological cancer survivors and a control population of healthy women was leakage of loose stools, defecation urgency, and the emptying of all stools into clothing without forewarning (57). Studies of anal cancer survivors after chemoradiotherapy report urgency in 64% of the patients and any degree of stool incontinence in 43% (58).

In rectal cancer research and clinical work, the term LARS is commonly used to describe the prevalent condition that can develop after low anterior resection of the rectum (59), a surgical method used to avoid the need for a permanent colostomy. Along with incomplete evacuation, the syndrome includes symptoms similar to those described in the literature as affecting gynecological and anal cancer survivors (incontinence, urgency) in varying degrees of severity. There are studies reporting intestinal late effects in up to 80% of rectal cancer survivors, with preoperative radiotherapy increasing the risk for fecal incontinence (60). Around 45% of patients who have undergone surgical low anterior resection (LAR) (sphincter-preserving surgery) report major LARS scores, which includes a collection of symptoms, such as extremely increased frequency of bowel movements, urgency, and fecal incontinence (61).

Irrespective of the origin of the pathological process, the symptoms and management of the late effects can be similar (62). Intestinal treatment-induced late effects have been reported to affect women's quality of life and social function to a high extent (4, 63).

2.2.6 Urinary tract late effects

Both surgery and radiotherapy can result in bladder dysfunction and urinary tract symptoms. Combined surgery and radiotherapy contributes to bothersome symptoms and decline in quality of life, and can be disabling in relation to social activities, work, and sexual life (4, 64). Common symptoms from the urinary tract, such as urethritis with frequency, urgency and dysuria,

leakage, voiding symptoms and urgency to empty the bladder, affect up to 15% of cancer survivors treated with pelvic radiotherapy (4). Hematuria occurs in up to 9% of patients after radiotherapy (64).

2.2.7 Lymphedema

The lymphatic system consists of a network of vessels with absorbing and transportation functions that are found in almost every tissue in the body. The lymph serves as a reservoir for fluids generated by filtering plasma through the microvascular walls and interstitial space, and is also important for the immune system (65). Lymphedema is reported in up to 69% of cervical cancer survivors treated with surgery. This is a result of insufficiency in the lymphatic system, characterized by swelling in one or both lower limbs, heaviness, itching, pain, skin changes, infection, discomfort, and decreased mobility (66). Along with surgery, radiotherapy is associated with a risk of lower limb lymphedema (34) and lymphedema in the genitals (67, 68), which have been shown to highly impact quality of life and daily life activities (69). The condition increases with age, invasive lymph node staging, cellulitis, lymphocyst formation, insufficient physical activity, and higher body mass index (66). In recent years, the sentinel lymph node procedure that has been introduced into gynecological cancer surgery has been shown to reduce the risk of lymphedema compared to the lymphadenectomy technique. The aim of both of these techniques is to inform about the prognostic factors of the cancer and guide decisions concerning further cancer treatment (70). The treatment for lymphedema is wearing a graduated pressure elastic garment during the day. Untreated, lymphedema is likely to progress.

2.3 SEXUAL HEALTH

The terms *Health*, *Sexual health* and *Sexuality* all have broad, multidimensional meanings that often interact in a complex manner. The definitions of these terms have shifted over time and are briefly outlined in the following paragraphs.

The term *health* is stated by WHO (71) as “complete physical, mental and social wellbeing and not merely the absence of disease and infirmity”, and

also applies to sexual health. *Sexual health* is fundamental to overall health and wellbeing. It relates to sexual orientation, gender identity, gender expression, body image, sexual self-esteem, reproduction, experiences of unwanted violence and coercion, relationships and intimacy, pleasure, and sexual activities (72). Sexual health is influenced by personal and social factors, such as culture, values and beliefs, religion, personal experiences, societal expectations, and legal and sexual rights. The concept sexual and reproductive health and rights (SRHR) is a field of healthcare which, along with human rights, includes gender equality and the right for all individuals to decide over their own bodies across the life course. It also includes the negative consequences of conditions such as sexual dysfunction and sexual violence (73).

In contrast to sexual health, *sexuality* includes how someone thinks about and expresses themselves as a sexual human being and can also involve sexual activity. WHO (72) defines sexuality as "...a central aspect of being human throughout life that encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction. Sexuality is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviors, practices, roles and relationships. While sexuality can include all these dimensions, not all of them are always experienced or expressed. Sexuality is influenced by the interaction of biological, psychological, social, economic, political, cultural, legal, historical, religious and spiritual factors." Hence, sexuality is an important part of life for most individuals and has been described as a part of every person's identity, which can change throughout life, comprising a combination of emotion and behaviors, and being both sensual and sexual.

In research, sexual health and sexuality is studied in several disciplines, for example psychology, sociology, gender studies, public health, nursing and medicine. One key aspect in nursing and medical research is sexual health and sexuality related to quality of life. In this thesis, sexuality is approached as a multidimensional concept, including both physiological, psychological and social dimensions. Although permanent infertility is a well-known side effect following pelvic radiotherapy, which can cause considerable distress (74) and is an important part of sexual health especially among younger

female pelvic cancer survivors (7), infertility issues are not included in this thesis.

The sexual side effects of treatment are of multifactorial etiology. Along with the direct physical treatment-induced effects on sexual function, negative effects from cancer and its treatment can vary depending on prediagnosis function, treatment modality, and the psychological impacts of cancer diagnosis. The complexity of treatment modality, prediagnosis function, medication, psychological impacts and partner relationship can all have negative impacts on sexual desire and sexual function (5).

2.3.1 Sexual function and dysfunctions

The most frequently reported female sexual health concern in the general population is low sexual desire. In a population-based study in the UK, differences in the level of interest in sex between partners were reported (with lower interest among women) as was low sexual desire in about one third of the women (75). Sexual response problems lasting at least three months in the preceding years were reported in half of all the women while distress concerning their sexual life was reported in about one in ten women. There is a lack of studies, both in cancer and non-cancer women, on whether there are differences in how homosexual women experience sexual dysfunctions compared to heterosexual women.

The understanding of female sexuality and sexual response is continuously expanding. Over the past few decades diverse ways of explaining sexual response have been suggested. Basson et al. (76, 77) have developed a commonly used model. In contrast to previous explanations of female sexual function, the model incorporates the importance of emotional intimacy, sexual stimuli and satisfaction with a relationship. Moreover, the focus is on subjective sexual arousal and the responses of mind and body, which can overlap in different phases in a circular cycle rather than beginning with sexual desire, sexual thoughts and fantasies. The model of the sexual response cycle combines interpersonal, contextual, personal, psychological, and biological factors. The reasons for agreeing to or initiating sex with partners vary and are more complex than the presence or absence of sexual desire. Sexual arousal is modulated by thoughts, and emotions triggered by sexual excitement.

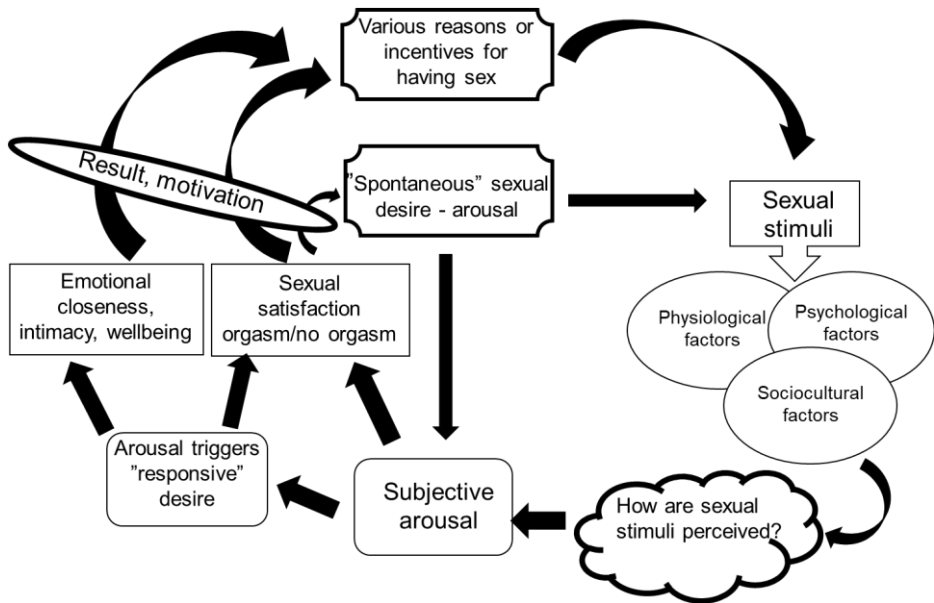
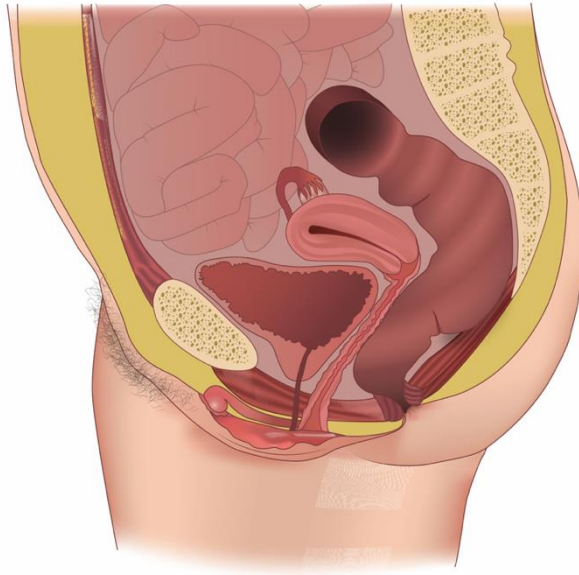


Figure 1. Sexual response model R.Basson (76, 77). Modified by Elmerstig (78)

From a physiological perspective, sexual arousal begins in the brain and is explained by neurophysiological mechanisms. Regions of the brain important for sexual motivation, and parietal areas modulating emotional and motor responses, can be activated by erotic stimulation. The autonomic nerves connect the central nervous system to the genitalia (79). The physiological response in the genitalia is a neuro-vascular process that is highly dependent on the structural and functional genital tissue, in which estrogen levels have an impact (80). The genital sexual arousal response in women includes clitoral engorgement, swelling of the genital tissues, lubricating and fluid transudate from the cervix, periurethral glands, and vagina, and increased compliance of the vaginal wall. The late effects in female pelvic cancer survivors that affect sexual function can be a result of damage to nerves and vessels that supply the pelvic area.



Drawing of the female pelvis (midsagittal view) shows the anatomy of the urinary bladder, uterus, vagina, anus, rectum, clitoris, urethra, and pelvic floor muscles

In gynecological cancer survivors treated with radiotherapy, pain during vaginal sex (dyspareunia) has been reported by 67% of women, with an association with vaginal inelasticity being shown (81). Pain during vaginal sex results from a complex interaction of anatomical, physiological, psychological and relationship factors related to the cancer and cancer treatment. Pain during vaginal sex (dyspareunia) is defined as “recurrent or persistent genital pain associated with sexual intercourse” (82) which, together with vaginismus (a recurrent and persistent involuntary spasm of the musculature of the distal part of the vagina that interferes with sexual intercourse), is included in a subcategory of the sexual dysfunction diagnostic category. According to the International Society for the Study of Vulvovaginal Disease (ISSVD), two categories of persistent vulvar pain are proposed: vulvar pain, defined as being caused by infection or dermatitis, and vulvodynia that refers to a condition of chronic vulvar pain, either provoked by touch or occurring spontaneously (83). Vulvovaginal pain is a sexual dysfunction and is termed in the literature in various ways. Vulvodynia is characterized by pain upon touch and/or pain during sexual or non-sexual situations. In the general population, vulvodynia is reported to affect about 10-15% of women, occurring more frequently in younger women (83).

Societal norms connected to sexuality are common, especially norms connected to sexual practice in heterosexual relationships. The norms and expectations connected to sexuality often make it complicated when sexual dysfunctions are involved (84, 85). Furthermore, body image is related to sexual function in women. In a previous study, body image problems were reported to be poor among almost half of the anal and rectal cancer survivors, and were particularly associated with younger age, comorbidity, and gastrointestinal symptoms (86).

2.3.2 Sexual abuse

Up to one third of women in the general population are affected by sexual abuse and intimate partner violence (87). Such issues can cause lifelong physiological consequences, such as chronic pain, psychological distress and sexual dysfunctions (88, 89), including vulvar pain (90). As mentioned earlier, the vast majority of women in the general population are infected with HPV during their sexual life. Most commonly, an HPV infection clears. However, there are some rare cases when a persistent HPV infection can develop into potential premalignant dysplasia or cancer (12). Evidence suggests that, in some cases, HPV-induced cancer relates to sexual abuse (91). In one study of cervical cancer survivors, women with a reported history of sexual abuse were shown to have an up to 30 times higher risk for low sexual health and wellbeing compared to healthy controls (92).

The literature suggests that women with a history of sexual abuse have a higher risk for somatic disorders, such as fibromyalgia, chronic pain, and gastrointestinal disorders (93). For women with such a history, one study states that cancer treatment situations can trigger thoughts and emotions associated with previous abuse (94).

2.4 WELLBEING

There is no consensus concerning the definition of wellbeing. According to the Centers for Disease Control and Prevention US (95), wellbeing can be defined subjectively as an individual's own experience of their life. Objective

wellbeing measured through self-report may include aspects such as adequate food, physical health, education and safety, or can be measured through, for example, mortality rates. Subjective wellbeing includes aspects such as life satisfaction, emotions and meaningfulness and, in its broadest sense, wellbeing encompasses physical, mental and social domains.

Women with cancer in the gynecological organs may have to deal with the loss of female body-parts that are symbolically charged and associated with being a woman and with sexuality. Besides, they have to deal with a potential existential threat (96). One study reported a prevalence of anxiety in 18% of long-term cancer survivors, compared to 14% in healthy controls, while depression was also reported to be slightly higher among cancer survivors (12% vs. 10%) (97). Physical late effects affecting female pelvic cancer survivors' quality of life have been mainly studied in gynecological cancer populations (6), while they have been much less well studied in populations with other pelvic cancers, such as rectal or anal cancer survivors. In one study of women with breast cancer, the factors identified as affecting women's wellbeing during treatment was having children under ten years of age in relation to undergoing stressful and time-consuming treatments, and worrying about their partner relationship (98). In another study of patients having undergone prostatectomy, low psychological wellbeing in long-term cancer treatment was reported to be associated with being shocked by their cancer diagnosis, having low self-esteem, anxiety, and having no one to confide in (99).

In this thesis, wellbeing refers to subjective psychological wellbeing, assessed by the self-report of how patients estimate their level of quality of life, depression, anxiety, and self-efficacy.

2.5 NURSE-LED INTERVENTIONS

Nurse-led follow-up care for cancer patients is reported to provide safe, efficient, high quality care (100). As a result of healthcare services moving towards more outpatient-based care and self-management of symptoms, and with the increasing number of cancer survivors, research calls for studies concerning nurse-led interventions in cancer care and rehabilitation. Nurse-

led interventions commonly involve teaching and providing information, and assessing, monitoring and giving advice about symptoms (101). In recent years, cancer nurses have developed new roles and responsibilities, including the support of people living beyond cancer. The development of autonomous functions for cancer nurses has been driven by the optimization of healthcare worker's roles and the shift from hospitalized cancer care to outpatient-based care. In addition, more advanced cancer treatment has led to a need for individualized follow-up during treatment. The most commonly provided nurse-led interventions are supportive care, psychosocial and psychosexual care, and the management of signs and symptoms during the treatment phase. These interventions commonly include direct care, psychological support, teaching, care management and coordination.

When this project was initiated, large well-designed studies of female pelvic cancer survivors who had undergone radiotherapy were lacking. In 2012, Dunberger & Bergmark illustrated the benefits of the nurse-led clinic that is studied in this thesis, which focused on providing structured information and tailored interventions in order to increase knowledge and empower patients to perform self-care interventions (102). In Sweden, this was the first rehabilitation clinic to focus on long-term physical symptoms and sexual dysfunction, albeit with a psychosocial approach.

2.5.1 Psychoeducation

The strategies used in the nurse-led clinic to support self-management of physically radiation-induced issues have been described in an ethnographic study (103). It was found that nurses support patients in self-management by intertwining their medical knowledge and specific clinical practice with elements of the patient's experience. This refers to anatomical, physiological, and psychoeducational interventions, such as showing pictures and models of their anatomy to describe the treatment-induced changes, which are considered to increase knowledge about late effect management and reduce fear of recurrence. Psychoeducational interventions are also used in sexual health counseling and in the management of women's sexual pain disorders (104), generally recognized as being clinically effective for cancer patients and their partners to reach improvements in self-care, depressed mood, and anxiety, although studies (mostly pilot studies) have not always reported

statistically significant results (105). A study of breast cancer patients showed that psychoeducational interventions can be beneficial when provided during the diagnostic phase, as well as during treatment and in the recovery phase (106). The self-management interventions recommended to pelvic cancer survivors regarding vaginal and sexual health include vaginal moisturizers, lubricants, pelvic floor exercises, local estrogen and vaginal dilator therapy (107, 108).

2.5.2 Vaginal dilator therapy

The best available recommendation to prevent and restore radiotherapy-induced vaginal changes is vaginal dilator use. This therapy aims to mechanically separate the vaginal walls, which is important for various reasons. These reasons can be to enable completion of gynecological examinations, preservation of the female anatomy, and to enable vaginal sex. The therapy consists of inserting a vaginal dilator (a cylindrically-shaped device) into the vagina and stretching the tissue for about 10 minutes, 2-3 times per week (109). Regular therapy is recommended for use by women for 2-3 years post completed radiotherapy (110), a recommendation supported by the American Cancer Society (111) and international guidelines (48). However, low adherence has been recognized and previous studies report a variety of barriers for dilator use, including pain, lack of time, and uncertainty about how to use dilators (109). Nowadays, there are dilators in multiple forms (plastic, silicone, latex, and medical-grade material) and some have vibration as a special feature, which is considered to facilitate the therapy, increase blood flow, and make it less uncomfortable, although this has not been scientifically evaluated.



Photos of vaginal dilators with different shapes and materials recommended to women post pelvic radiotherapy

2.6 THEORETICAL PERSPECTIVES

2.6.1 Rehabilitation and prehabilitation

The term and concept of rehabilitation has evolved over time. In 2001, the WHO (71) stated that rehabilitation could be defined as a goal-oriented process involving an individual, relatives, and professionals over a specific time period. There was no broad consensus as to what constituted a cancer survivorship model when the current nurse-led clinic was initiated, especially outside of the psychosocial domain. Rehabilitation and caring for pelvic cancer survivors should address patients' needs regarding the promotion of quality of life using a comprehensive approach, which includes physical, mental, psychosocial, and sexual health.

There are various definitions of cancer survivorship in the literature. A person can be called a cancer survivor from the moment they are diagnosed or when medically defined as disease free. Survivors remain patients and can experience a number of health challenges that need to be improved (112).

One of the aims of cancer rehabilitation is to reduce the consequences of cancer and its treatments. There is evidence showing the efficacy of interventions that are provided before and during the treatment of patients with cancer, which is termed prehabilitation. Such interventions can be designed to increase function and help reduce the impact of predicted upcoming treatment-induced acute or late effects (113).

2.6.2 Biopsychosocial model

A biopsychosocial approach is considered highly relevant and of great importance when assessing and managing problems in female pelvic cancer survivors (114, 115). Such a model can facilitate the understanding of the follow-up and support provided to women in the nurse-led clinic. The biopsychosocial model was conceptualized by George Engel in 1977 (116) as a reaction to the prevailing traditional biomedical model. The model was suggested to describe a person's health status, not limited to the traditional boundaries based on affected organ systems, but based on an integrated approach, including biological, psychological, and social factors, and contributing to a broader perspective on health and illness (117). The model

identifies different levels of an illness. For example, the biomedical approach to chronic pain limits the understanding of patients' experiences and focuses on presumed biomedical or structural abnormalities. A biopsychosocial perspective takes biomedical variables, behavior, emotions and beliefs, as well as social variables, into consideration (117). In this thesis, female pelvic cancer survivor's sexual health, needs, and outcomes are viewed from a biopsychosocial perspective.

2.6.3 PLISSIT model

Sexual counseling models can be used for the purpose of initiating patient discussions on sexuality, and to identify and address sexuality and sexual health in a respectful and sensitive way. The PLISSIT model is a widely used model developed by Annon (118) that consists of four levels of intervention: Permission, Limited Information, Specific Suggestion and Intensive Therapy. Permission is about giving patients permission to raise sexual issues, Limited information is giving limited information about common sexual side effects of treatment, while making Specific Suggestions is based on a full evaluation of the presenting problems, and Intensive Therapy includes psychological interventions, sex therapy, and/or biomedical interventions. This model, which has been shown to be effective, simple, and useful in healthcare (119), is used in the interventions in this thesis.

2.6.4 The Fear-Avoidance model of pain

The fear-avoidance model has a biopsychosocial perspective that relates to pain being not necessarily a sign of harm and injury. Untreated acute pain may lead to the individual experiencing pain that may become trapped in a vicious cycle of more pain (120). Research in gynecological cancer survivors shows that pain during vaginal sex interplays with biopsychosocial aspects, such as anxiety (i.e. fear of pain) and pain catastrophizing (82), thereby intensifying the pain. Individuals experiencing pain may initiate a pattern of interference with daily activities; furthermore, pain-related fear might be associated with avoidance behavior (121). This avoidance behavior affects opportunities for intimacy, sexual desire and sexual pleasure, and is closely connected to the sexual response model described earlier.

3 AIM

3.1 GENERAL AIM

The aim of this thesis was to improve knowledge of sexual health, wellbeing and vaginal changes in female cancer survivors with a history of pelvic radiotherapy.

3.2 SPECIFIC AIMS

- PAPER I To describe the study base and outline the data collection procedures, treatments and interventions directed at female pelvic cancer survivors in a nurse-led clinic.
- PAPER II To study whether sexual health and wellbeing can improve after nurse-led biopsychosocial interventions targeting physical radiotherapy-induced late effects.
- PAPER III To explore sexual health and wellbeing after pelvic radiotherapy in women with and without a history of sexual abuse.
- PAPER IV To explore women's experiences and difficulties of performing vaginal dilator therapy following pelvic radiotherapy.

4 PATIENTS AND METHODS

The studies in this thesis are based on data collected in a population-based cohort of female pelvic cancer survivors and data from an interview study of female pelvic cancer survivors. All participants in the thesis reported being cisgender women, which means that their legal gender was the same as their self-reported gender. The initial study described the cohort, data collection procedure, and the interventions provided in a nurse-led clinic. This was followed by a longitudinal study (Paper II), an observational descriptive study (Paper III), and an interview study (Paper IV). The studies all relate to sexual health and wellbeing in women treated with pelvic radiotherapy explored from biopsychosocial perspectives with the use of different scientific methods. Study IV has a qualitative design with data collected through face-to face interviews. A summary of the papers is presented in Table 1.

Table 1. Summary of the papers.

Study	Type of study	Data collection	Study population	Number of patients	Main outcomes	Data analysis
I	A description of the data collection procedure, the study cohort and the interventions provided in Studies II and III	A 175-item validated study-specific questionnaire during 2011-2017	Women treated with pelvic radiotherapy	605	Characteristics of study participants	Descriptive statistics, t-test
II	An observational longitudinal cohort study pre- and post-interventions	Self-reported questionnaire pre- and post-interventions in a nurse-led clinic	Women treated with pelvic radiotherapy who completed the baseline and the 3-month follow-up questionnaires	260	Patient-reported aspects of wellbeing and sexual health	Descriptive statistics, multivariable analysis, RR
III	An observational cohort study	Self-reported questionnaire during 2011-2017	Women treated with pelvic radiotherapy with and without a history of sexual abuse	570	Patient-reported aspects of wellbeing and sexual health	Sub-group analysis, descriptive statistics t-test, RR
IV	Qualitative interview study	Semi-structured interviews	Women treated with pelvic radiotherapy having difficulties adopting vaginal dilator therapy	12	Experiences of counseling and of maintaining vaginal dilator therapy	Qualitative content analysis

4.1 STUDY PARTICIPANTS

4.1.1 Studies I-III

The patient population in Papers I-III consisted of women with a history of gynecological (endometrial, cervical, vulvar, vaginal), anal, or rectal cancer who received pelvic radiotherapy as part of their cancer treatment at Sahlgrenska University Hospital, Sweden. The radiotherapy dose, target, and supplementary treatment modalities for pelvic cancer differ, primarily due to diagnosis and stage of disease. The severity of treatment-induced late effects differs in relation to radiotherapy dose, target, age, lifestyle, co-morbidity, and age. The population in Paper I comprised 605 women, Paper II 260 women, and Paper III 570 women. The study participants were recruited from a population-based study cohort inventoried from 2007 onwards and from female pelvic cancer survivors referred to the rehabilitation clinic. The time since completed radiotherapy varied from 6 months to more than 4 years. Exclusion criteria were having a recurrence of cancer and age under 18 years.

4.1.2 Study IV

In study IV, the recruited participants were a selected sample of women who had various difficulties adopting the recommendation of vaginal dilator therapy after completed curative pelvic radiotherapy. They were identified by the interviewing researcher and two clinical nurses. All study participants had an ongoing or previous contact with an outpatient clinic. The exclusion criterion was having ongoing nurse counseling with the interviewing researcher.

4.2 DATA COLLECTION

Data in studies I-III were collected between January 2011-2017. An introductory letter was sent to eligible women describing the study and included an invitation to participate. It also informed the women about a phone call they would receive. One week later a study secretary phoned the women to ask if they were willing to participate in the study. A questionnaire was sent to those who agreed together with a written informed consent form

and a pre-stamped return envelope. A reminder was sent to those who did not return the questionnaire at time points determined in advance. The procedure is outlined in Figure 2.

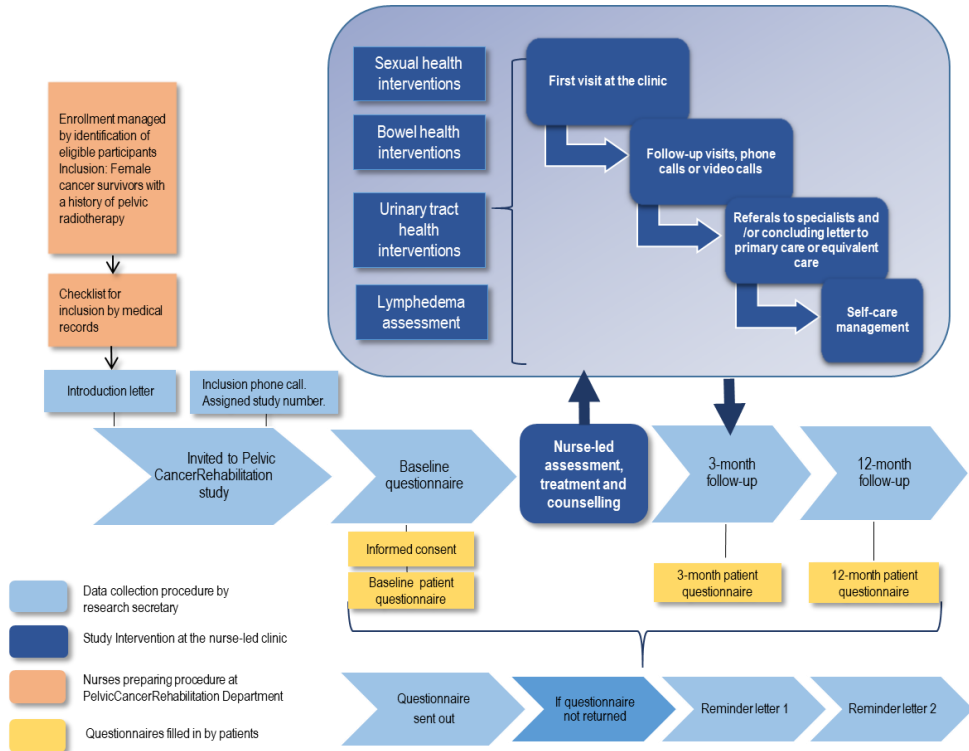


Figure 2. Schematic figure of the data collection in studies I-III

In study IV, a semi-structured interview study was considered appropriate to capture female pelvic cancer survivors' experiences of received information and of performing vaginal dilator therapy. Women who were identified as being eligible received written information about the study. When the consent form had been returned, the author phoned the study participant and a time and place for the interview was decided. The semi-structured interviews, which included open-ended questions, were performed between 2016-2021.

4.2.1 Questionnaire, Studies I-III

A study-specific questionnaire was used in Papers I-III. The questionnaire had been previously constructed, used and tested in face-validity interviews in previous studies carried out by our research group at the Division of Clinical Cancer Epidemiology in Stockholm and Gothenburg. The scales used in studies I-III for the measurement of wellbeing aspects: sexual-, intestinal-, and urinary tract health, and symptoms of lymphedema, have been previously validated and used in cancer survivorship research (2, 4, 57, 122, 123).

The questionnaire was refined for this data collection to fit the specific study cohort and consisted of 175 questions. The areas covered in the questionnaire were education, work, psychosocial health, childbirth, intestinal-, urinary tract-, and sexual health, sexual abuse and lymphedema. The questionnaire addressed frequency and duration of symptoms during the past six months (baseline) or last month (follow-up) and allowed respondents to comment freely. Three outcome measures indicating psychological health, indicators of impaired quality of life previously regarded as valid and sensitive (122) and psychosocial health (123, 124) were included in the questionnaire. One question assessed quality of life: “How would you describe your quality of life during the past month?” with responses given on a seven-point visual digital scale anchored by 1-7, with number 1 meaning “No quality of life at all” and number 7 “Best possible quality of life”. The prevalence of feeling depressed or anxious was assessed by the question “Have you been feeling depressed/anxious during the past six months?” with possible response alternatives ranging from 1-7, where 1 was classified as “never” and 7 as “all the time”. At the end of the questionnaire they were asked to rank their most bothersome symptom and were invited to visit the nurse-led clinic for counseling, treatment, and support of treatment-induced late effects. The women who underwent the interventions were asked to respond to a three-month follow-up questionnaire. In the three-month follow-up questionnaire, women were asked to recall their symptoms during the last month. The women had the option to answer “Not relevant” to each question.

On the baseline-questionnaire, some questions served to rank the patient’s most distressing symptoms. On the three-month follow-up questionnaire, a

self-reported evaluation was included to measure how helpful the interventions had been perceived.

4.2.2 Setting, Studies I-III

Women participating in studies I-III were offered visits and follow-up interventions at a nurse-led clinic situated in the oncology clinic at Sahlgrenska University Hospital, Gothenburg, Sweden. Since late 2010, the clinic has been supported by the Regional Cancer Centre of Västra Götaland, which was developed as a result of the regulation proposed by the Swedish government in 2009: “A National Cancer Strategy” (SOU 2009:1) (125). The clinic focuses primarily on providing interventions and treatment for long-term physical symptoms and sexual dysfunction after pelvic radiotherapy. A psychosocial approach is used by the team, which currently consists of three clinical oncology nurses, trained and specialized in pelvic cancer survivorship late effects. The nurses work independently dealing with patient education, medication management, life-style interventions and sexual counseling. The senior medical consultant sees patients with specific needs, holds regular meetings with the team, and has the primary formal and medical responsibility for the clinic.

4.2.3 Interventions

The goal was to provide interventions that minimize the impact of treatment-induced late effects on quality of life. This includes the assessment and management of late effects 6 months after completed treatment. The baseline questionnaire served as a basis for counseling. Both physical and psychosocial health challenges were described and referrals were sent to experts when appropriate. Intestinal-, urinary tract-, and sexual health problems were addressed, as were symptoms of lymphedema. Psychoeducational interventions were provided with combined components of information provision and psychological support with the aim of enhancing acceptance of the disease, as well as recovery from the illness and treatment. Discussions about self-care strategies and interventions were followed by shared decision-making (126). Recommendations concerning medication, nutrition, and psychological and social challenges were discussed. Interventions followed evidence-based recommendations and

programs developed by previous studies on survivorship and are detailed in Papers I-III (102, 127, 128).

With regard to sexual counseling, the first three levels in the PLISSIT model for sex therapy (118) provided by the nurses were helpful for most patients. For patients and partners who had particularly complex issues, the final stage in the PLISSIT model was sometimes provided by a nurse/sexual consultant and sometimes by a sexologist or psychotherapist; women received intensive therapy in the clinical setting and a referral was sent to a sexologist or psychotherapist if appropriate.



Examples of local estrogen products that are prescribed to the women. .

4.2.4 Interviews and setting, Study IV

In the development phase, the semi-structured interview guide was tested in a pilot interview that resulted in an interview guide comprising 10 main questions. After initial small-talk, the interviews started and were recorded. If the interview elicited an emotional reaction that required counseling, a careful and supportive discussion followed the completed interview. The semi-structured approach allowed open and broader questions, followed by more probing questions in areas of relevance. Follow-up questions were used to ask for more details, for example “Could you tell me more about this?”. The domains included were: thoughts and feelings emerging at the time of receiving information about vaginal changes and vaginal dilator therapy; thoughts and feelings emerging when carrying out vaginal dilator therapy;

thoughts and feelings about the ways in which vaginal dilator therapy might affect sexuality at present and in the future; previous experiences with regard to feminine hygiene products, sexual abuse, vaginal pain, or discomfort; and when and how women would prefer to receive information. Finally, the advice given regarding vaginal dilator therapy was explored. The first interview was the pilot interview to test the interview guide. Since the interview-guide was then used unchanged, the first interview was included in the analysis.

The interviews took place at a time and place chosen by the study participant. Ten of the women were interviewed in a secluded room in an outpatient clinic, while two interviews took place in the participant's home. The interviews were conducted by the author between 2016 and 2021 and were audio recorded. They lasted 27-62 minutes and the women were encouraged to expand their answers freely. The interviews were then transcribed verbatim by a professional transcriber.

4.3 ANALYSIS

4.3.1 Quantitative data

In studies I-III the responses to the questionnaires were entered into the software EpiDataSoftware V.3.1 (EpiData Association) then exported to Microsoft Excel to enable safe data processing. The procedure included data management, for example if two answers were provided where only one was allowed, the procedure was to alternate entering the first provided answer and then the second provided answer and so on. In study II, patients who reported having a stoma were excluded to minimize bias in the analysis of intestinal health problems, thereby obtaining comparable groups which facilitated the analysis of intestinal health symptoms (e.g. fecal incontinence and defecation urgency) in relation to sexual health.

Qualitative content analysis methodology, developed by Graneheim and colleagues (129, 130), was applied throughout the process in study IV. The computed assisted qualitative data analysis software NVivo (Version 12) SR International Pty Ltd. (2018) was used to aid the analysis process.

In study I, statistical analysis was performed and descriptive data were reported as means, percentages, and proportions. In study II, Wilcoxon signed-rank tests were performed to analyze individual differences between pre- and post-intervention in the outcome measures for sexual health and wellbeing aspects. One example of the distribution of changes along the scale is shown in Table 2.

Table 2. An example of the distribution of changes along the scale (time feeling depressed) by Wilcoxon signed-rank test.

Distribution of changes along the scale baseline vs. 3-month follow-up										
Scale	-4	-3	-2	-1	0	1	2	3	4	6
N	11	19	24	52	71	39	16	6	6	2
Distribution of changes along the scale baseline vs. 3-month follow-up trichotomized										
Scale				-1	0	1				
N				106	73	69				

Reduced (-) levels indicate an improvement regarding self-reported level of how often feeling depressed, where 0 indicates no change and increased levels indicate feeling depressed more often. In the Wilcoxon signed-rank test for feeling depressed, the p-value was 0.004.

Before the analysis, the scale was trichotomized into the categories: increase, no change, and decrease. To assess if improvement in overall satisfaction with sexual life and wellbeing was associated with improvement in bowel symptoms, changes in the categories *improvement* and *no improvement* were dichotomized, i.e. the category *no change* was discriminated. Each pair of the dichotomized changes in overall sexual health or wellbeing and the dichotomized changes in bowel symptom intensities were assessed using a log-binomial regression. Likelihood Ratio Test p-values were calculated to assess the level of statistical significance for the estimated outcome measures (RR).

For study III, a subgroup of study participants was identified. Socio-demographic and descriptive characteristics were compared between the groups using the chi-2 test for categorical variables when feasible, otherwise

Fisher's exact test was applied. Outcome measures were presented as relative risks. In the case of continuous variables, analysis of variance (ANOVA) was used to assess the statistical significance of the differences in demographical characteristics as regards a reported history of sexual abuse. All statistical analyses were carried out using the statistical program R, version 3.5.2 and 4.0.0. A p-value of 0.05 was set for the level of significance in the studies.

4.3.2 Qualitative data

In qualitative research, trustworthiness is a concept of high relevance and used to support the argument that the inquiry's results are "worth paying attention to" (129). To reach trustworthiness, the data collection and the data processing need to be described in a systematic and honest way. The concept trustworthiness, as described by Graneheim et al. (129), comprises *credibility*, *dependability*, and *transferability*. These concepts are further described in the methodological discussion in this thesis.

The analysis phase started during the interview process. When the interviews were transcribed, two of the authors (LÅ, GD) read the transcripts several times and independently performed an open coding. They subsequently and independently identified meaning units that captured the essence of the experiences of the women concerning vaginal dilator therapy. The two authors then compared and summarized the meaning units that emerged from the material. Meaning units were then condensed, without loss of meaning, and assigned descriptive codes, which functioned as content labels. This step was followed by an abstraction phase, creating categories and subcategories. Finally, an overarching theme emerged. There was movement back and forth between the parts of the data and the whole throughout the process. The two first authors discussed the development of subcategories, categories and the theme, which were then discussed with all authors. The qualitative analysis process is displayed in Figure 3.

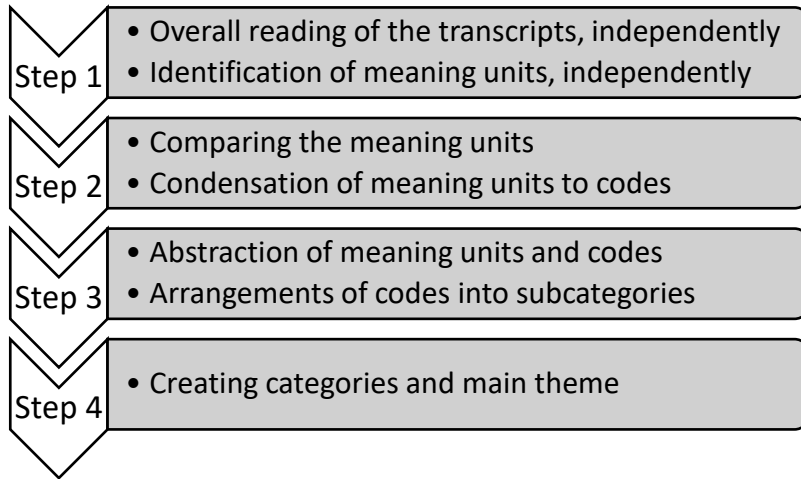


Figure 3. The qualitative analysis process

5 ETHICAL CONSIDERATIONS

When planning a study involving people, there are ethical issues and dilemmas to consider, including protecting confidentiality and respecting the integrity of the participants. Moreover, participants need to be approached carefully and protected from all kinds of inconvenience and harm. These aspects, along with autonomy and informed consent, have been addressed in these studies.

The concerns regarding the preservation of integrity, dignity and participants' control is particularly important in research involving vulnerable groups, such as in our study which included women with a previous history of cancer and sexual abuse. This study addresses very personal and emotionally-charged issues, such as sexuality, sexual abuse, anxiety and depression. However, some studies have shown that study participation may reduce the psychological burden due to the confirmation of a bothersome situation and have therefore been described as therapeutic (131).

In these studies, participants were approached in a sensitive way, being contacted first by a letter giving information about the study and notice about an upcoming phone call. The possibility to decline participation and the need for reminders was enabled through the possibility of returning an empty questionnaire without the need for any explanation. Since emotional reactions could arise during the interview study due to the private and sensitive nature of the subject for many women, steps were taken in advance to ensure that women were offered counseling and support after the interview.

The Ethical Review Board in Gothenburg in Sweden approved Studies I-III with reference number 686-10, and Study IV with reference number 605-18.

6 RESULTS

6.1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

6.1.1 Papers I-III

The first part of this project formed the basis for studies II and III. From January 2011 to June 2017, 605 women were recruited. Of these, 464 were from the population-based cohort (invited), while 141 were recruited from the referred cohort. In Figure 1, the responses and completeness of the questionnaires are presented.

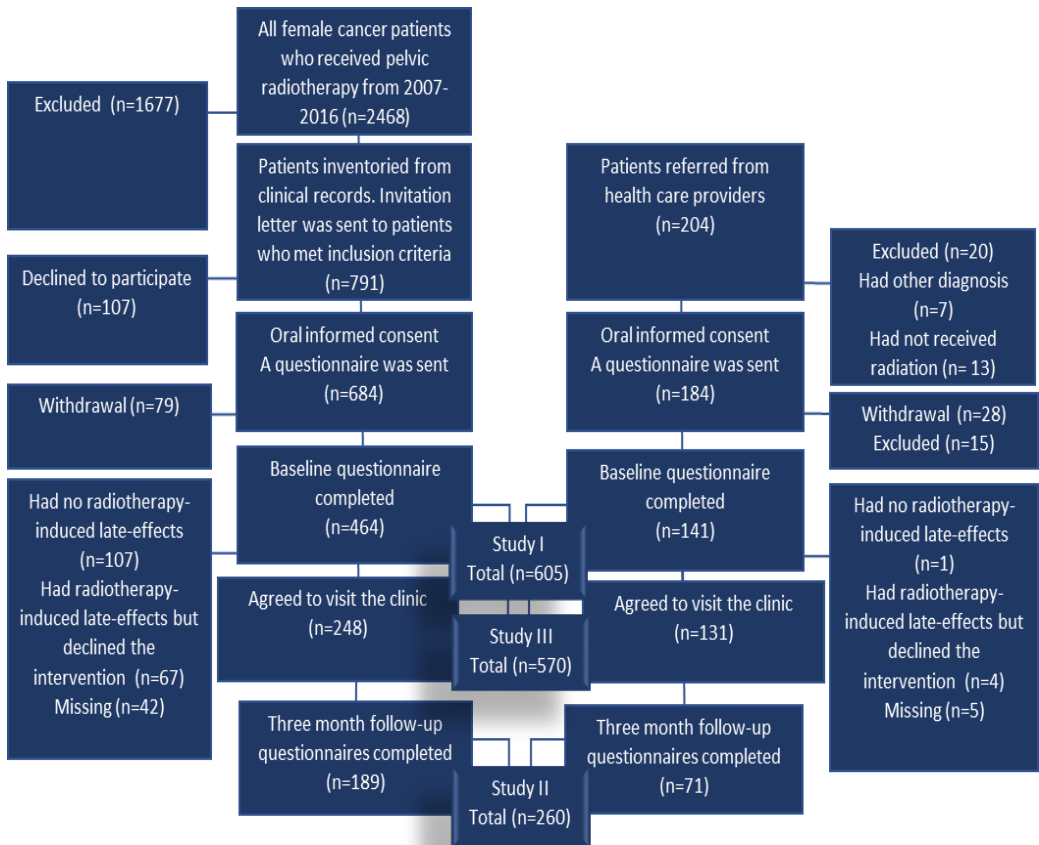


Figure 4. Enrolment and dropouts

The study cohort consists of women with a history of gynecological cancer, rectal cancer or anal cancer treated with pelvic radiotherapy (Table 4). The majority (63%) of the women received surgery as part of their cancer treatment in addition to external radiotherapy and brachytherapy. The mean age of participants was 64.5 years with a range of 26-94 years. Women referred to the clinic and those with a reported history of sexual abuse were slightly younger (57.6 and 57.2 years, respectively) and more commonly had a cervical cancer diagnosis. Women with a history of sexual abuse also more commonly had a partner but were living alone.

Among women in the total cohort (n=605), 9% were on sick leave, which was shown to be more common among referred women compared to those invited (26.2% vs. 3.7%), and among women with a reported history of sexual abuse compared to those without (36.7% vs. 8.5%). Post interventions, 7.7% women were on sick leave.

Table 3. Socio-demographics and clinical characteristics of the study participants in studies I-III

Variable	Total	Invited	Referred	History of sexual abuse		P-value	3-months post interventions
				No	Yes		
				N=570			
Participants, n (%)	605	464 (76.7)	141 (23.3)	508 (89.1)	62 (10.9)		260
Invited, n (%)				394 (77.6)	41 (66.1)	0.066	189 (72.7)
Referred, n (%)				41.1 (66.1)	21 (33.9)		71 (27.3)
Cancer type, n (%)							
Endometrial cancer	216 (35.7)	181 (39.0)	35 (24.8)	187 (36.8)	16 (25.8)	0.063	85 (32.7)
Cervical cancer	132 (21.8)	80 (17.2)	52 (36.9)	109 (21.5)	20 (32.3)		54 (32.7)
Ovarian cancer	2 (0.3)	1 (0.2)	1 (0.7)				
Vaginal cancer	5 (0.8)	3 (0.6)	2 (1.4)				
Vulvar cancer	21 (3.5)	19 (4.1)	2 (1.4)	19 (3.7)	1 (1.6)		6 (2.3)
Anal cancer	80 (13.2)	58 (12.5)	22 (15.6)	63 (12.4)	11 (17.7)		44 (16.9)
Rectal cancer	145 (24.0)	122 (26.3)	23 (16.3)	126 (24.8)	12 (19.4)		67 (25.8)
Other	4 (0.7)		4 (2.8)	4 (0.8)	2 (3.2)		4 (1.5)
Age in years at baseline							
Mean	64.5	66.5	57.6	64.9	57.2	<0.001	62.5
SD	12.6	11.5	13.6	12.4	12.3		11.7
Min-max				27-94	26-76		
Missing, (%)	11	7 (1.5)	4 (2.8)	0 (0)	0 (0)		
Years since radiotherapy at baseline, grouped							
0	35 (5.8)	6 (1.3)	29 (20.6)				16 (6.2)
1	219 (36.1)	166 (35.8)	53 (37.6)				90 (34.6)
2	98 (16.1)	86 (18.5)	12 (8.5)				39 (15.0)
3	139 (23.0)	131 (28.2)	8 (5.7)				68 (26.2)
≥4	105 (17.3)	69 (14.9)	36 (25.5)				46 (17.6)
Missing	9 (1.5)	6 (1.3)	3 (2.1)				0 (0)
Mean	2.6	2.2	3.9				2.9
SD	3.4	1.2	6.7				4.2
Cancer treatment, n (%)							
EBRT, only	145 (24.0)	101 (21.8)	44 (31.2)				
EBRT and BT	20 (3.3)	16 (3.4)	4 (2.8)				
EBRT, BT and surgery	180 (29.7)	157 (33.8)	23 (16.3)				
EBRT and surgery	260 (43.0)	190 (40.9)	70 (49.6)				
EBRT with and without BT				133 (88)	17 (11.3)	0.955	70 (26.9)
Surgery and EBRT with and without BT				375 (89.3)	45 (10.7)		190 (73.1)
Marital status, n (%)							
Married or living with a partner	402 (66.4)	309 (66.6)	93 (66.0)	346 (68.1)	39 (62.9)	<0.001	186 (71.5)
Widow	70 (11.6)	59 (12.7)	11 (7.8)	62 (12.2)	0 (0)		22 (8.5)
Has a partner but lives alone	30 (5.0)	15 (3.2)	15 (10.6)	19 (3.7)	10 (16.1)		13 (5.0)
Single	102 (17.0)	80 (17.2)	22 (15.6)	81 (15.9)	13 (21)		39 (15.0)
Missing	1 (0.2)	1 (0.2)		0 (0)	0 (0)		
Education level, n (%)							
Elementary school	173 (29.1)	150 (32.3)	23 (16.3)				55 (21.2)
Secondary school	227 (38.2)	169 (36.4)	58 (41.1)				111 (42.7)
College/University	194 (32.0)	135 (32.3)	59 (41.8)				93 (35.8)

Missing	11 (1.8)	10 (2.2)	1 (0.7)			1 (0.004)
Employment status, n (%)					0.024	
Student	4 (0.7)	3 (0.6)	1 (0.7)	3 (0.6)	1 (1.7)	2 (0.8)
Unemployed job seeker	12 (2.0)	10 (2.2)	2 (1.4)	10 (2)	1 (1.7)	5 (1.9)
Employed	162 (27.0)	116 (25.0)	46 (32.6)	137 (27.1)	21 (35)	96 (36.9)
Housewife	4 (0.7)	2 (0.2)	2 (1.4)	4 (0.8)	0 (0)	1 (0.4)
On sick leave	54 (9.0)	17 (3.7)	37 (26.2)	43 (8.5)	10 (36.7)	20 (7.7)
Disability pension	35 (5.7)	26 (5.6)	9 (6.4)	26 (5.1)	6 (10)	17 (6.5)
Retired	328 (54.7)	284 (61.2)	44 (31.2)	282 (55.8)	21 (35)	118 (45.4)
Missing	6 (1.0)	6 (1.3)		0 (0)	0 (0)	1 (0.004)
Resident, n (%)						
In a big city	182 (30.6)	131 (28.2)	51 (36.2)			52 (20.0)
In a small or medium-sized city	309 (50.2)	244 (52.6)	61 (43.3)			123 (47.3)
In the countryside	116 (18.9)	87 (18.8)	29 (20.6)			85 (13.7)
Missing	2 (0.3)	2 (0.4)				0 (0)
Smoker, n (%)					0.063	
No	448 (74.0)	339 (73.1)	109 (7.3)	380 (87.4)	51 (85)	204 (86.8)
Yes	67 (11.0)	52 (11.2)	17 (12.1)	55 (12.6)	9 (15)	31 (13.2)
Missing	88 (14.5)	73 (15.7)	15 (10.6)	0 (0)	0 (0)	25
Repeated sexual abuse, n (%)						
Yes					17 (27.4)	
No					44 (71.0)	
Not relevant					1 (1.6)	
Incest, n (%)						
Yes					6 (9.7)	
No					56 (90.3)	
Age at first sexual abuse, years					13.6	
Mean					6.6	
SD					8.2-17.0	
IQR					4-35	
Min-Max					4 (6.5)	
Missing						
Exposure to sexual abuse has affected sexual life, N, (%)						
Moderately or a lot					20 (32.3)	
Not at all or a little					34 (54.8)	
Not relevant					5 (8.1)	

N (number) and proportion (%) of women are presented. SD=Standard Deviation, IQR= Interquartile range, P-values in bold font indicate statistical significance

Approximately 11% of the participants reported experience of sexual abuse on the baseline questionnaire, while such experience was reported by 13% of the women on the follow-up questionnaire.

6.1.2 Paper IV

Participants included in the interview study consisted of a convenience sample of women with previous cervical, rectal, anal, or vaginal cancer who had difficulties adopting vaginal dilator therapy following pelvic radiotherapy (Table 4). The age of the participants ranged from 31 to 69 years.

Table 4. Characteristics of study participants in study IV

Participants	Age	Type of cancer	Marital status
1	40	Anal cancer	Cohabitant
2	44	Vaginal cancer	Single
3	55	Cervical cancer	Married
4	31	Cervical cancer	Married
5	46	Cervical cancer	Married
6	65	Anal cancer	Married
7	69	Rectal cancer	Has a partner, living apart
8	65	Rectal cancer	Has a partner, living apart
9	65	Rectal cancer	Married
10	32	Cervical cancer	Married
11	64	Cervical cancer	Single
12	50	Cervical cancer	Single

6.2 MAIN FINDINGS

6.2.1 Studies I-III

More than half of the women invited to participate in the study agreed to visit the clinic to take part in the nurse-led interventions (study I). More than 14% of the women in the invited group declined a visit despite reporting bothersome treatment-induced late effects.

Superficial genital pain during vaginal sex was reported in a statistically significantly higher proportion of women treated for rectal cancer (27.0%), while deep genital pain during vaginal sex was reported in a higher proportion of women treated for cervical cancer (41.8%). A statistically significant association was found between vaginal pain and vaginal inelasticity ($p < 0.001$) (study III).

In study II, analysis of changes in sexual health and wellbeing three months after completed interventions showed that more women attending the nurse-led clinic had increased rather than decreased satisfaction with their overall sexuality and sexual life post interventions (26.0% vs. 15.3%, $p = 0.035$). They also reported reduced amount of time feeling depressed (43.1% vs. 28%, $p = 0.003$) or anxious (45.9% vs. 24.4%, $p < 0.001$) post intervention. More women reported an increased rather than a decreased level of QoL (42.7% vs. 22.4%, $p < 0.001$) post interventions. Our analysis did not show improvements in sexual function, such as lubrication, genital swelling, orgasm frequency, or vaginal shortness or inelasticity.

In a log-binomial regression analysis, statistically significant associations were found between improvement in intestinal symptoms of urgency to defecate and improved satisfaction with overall sexual health ($p = 0.004$, RR 3.12, 95% CI 1.27-7.68), and between urgency to defecate with fecal leakage and reduced anxiety ($p = 0.021$, RR 1.56 95% CI 1.02-2.33). Improvement in almost all intestinal symptoms was slightly associated with improved quality of life, although this was not statistically significant (study II).

Table 5. Improved intestinal health aspects as explanatory factors for improved sexual health and reduced anxiety

Satisfaction with overall sexuality and sexual health			
	N, (%)	RR (95% CI)	P-value
Urgency to defecate	No improvement 5/46 (10.9)	Ref 1.0	0.004
	Improvement 20/59 (33.9)	3.12 (1.27-7.68)	
How often feeling worried or anxious			
	N, (%)	RR (95% CI)	P-value
Urgency to defecate with fecal leakage	No improvement 20/57 (35.1)	Ref 1.0	0.021
	Improvement 47/86 (54.7)	1.56 (1.04-2.33)	

N (number) and proportion (%) of women are presented. SD = Standard Deviation

Reduced superficial genital pain (25.8% vs. 13.1% $p=0.025$) and reduced deep genital pain (23.1% vs. 8.0 %, $p<0.001$) were found post interventions. Furthermore, severe intestinal symptoms were reported less frequently post intervention (study II).

Although no statistical analysis was conducted comparing intestinal symptoms at baseline versus follow-up, there were clear differences in many of the symptoms, see Figure 5.

Women evaluated the interventions on the three-month follow-up questionnaire. As seen in Figure 6, the majority of the women reported that they were moderately or very satisfied with the help and advice received in the nurse-led clinic.

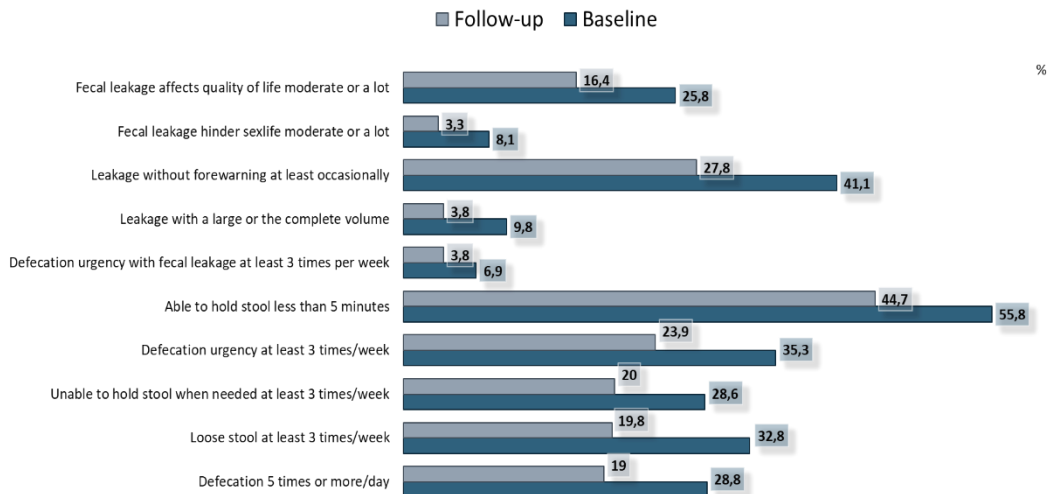


Figure 5. Proportion of self-reported intestinal symptoms pre- and post-interventions

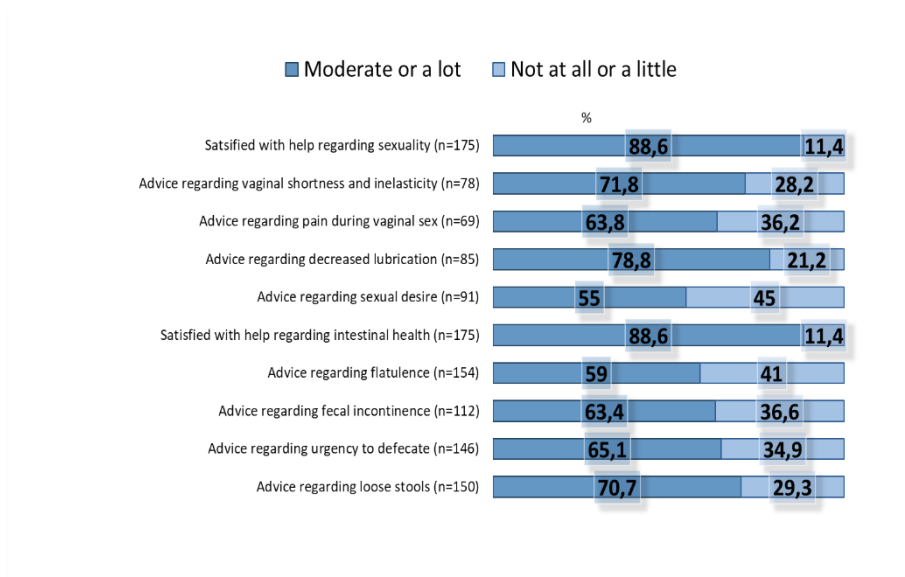


Figure 6. Number (n) and proportions (%) of patient-reported evaluation, three months post interventions

In study III (see Figure 7) it was shown that a statistically significantly higher proportion of women with experience of sexual abuse reported feeling depressed and anxious compared to women without such a history ($p=0.007$). A statistically significantly higher proportion of women without experience of sexual abuse reported a high level of QoL. Among those who had engaged in vaginal sex during the previous 6 months, a higher proportion of women with a history of sexual abuse reported experiencing deep genital pain during vaginal sex compared to women without such a history ($p=0.011$, RR 2.07, 95% CI 1.24-3.16).

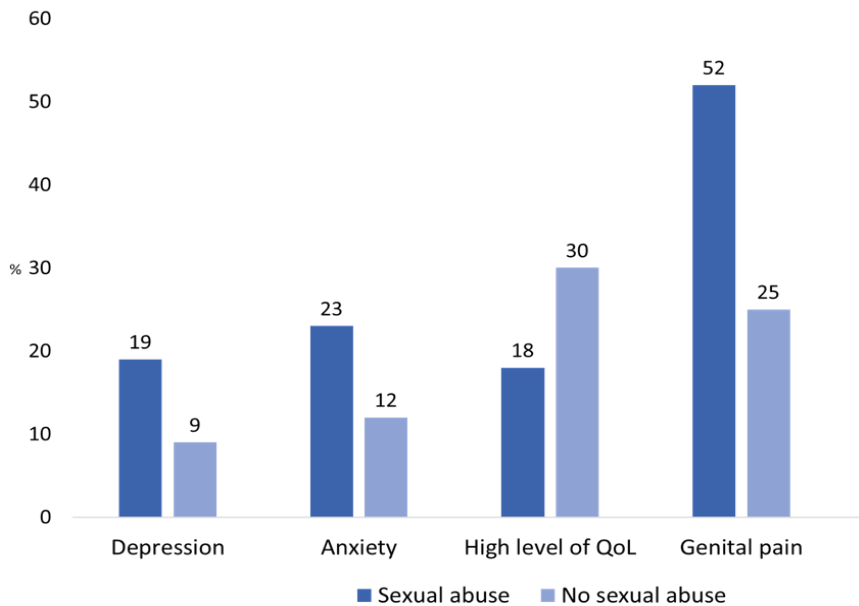


Figure 7. Wellbeing aspects reported in female pelvic cancer survivors with and without a history of sexual abuse

Increased self-esteem after cancer and cancer treatment was reported by more women with a history of sexual abuse compared to those without ($p=0.009$), and a lower satisfaction with a partner as a friend/fellow human being was reported in women with experience of sexual abuse compared to those without ($p=0.0100$). There were no statistically significant differences

regarding overall satisfaction with sexual life, level of distress if overall problems with sexual life persist, or frequency of vaginal sex. Although not statistically significant, topical estrogen use was slightly more common among women with a history of sexual abuse than those without.

6.2.2 Study IV

The analyses of the interviews with women who had expressed difficulties adopting vaginal dilator therapy resulted in one overarching theme: “Being unprepared”. This theme emerged from three main categories and six sub-categories, as presented in Figure 8.

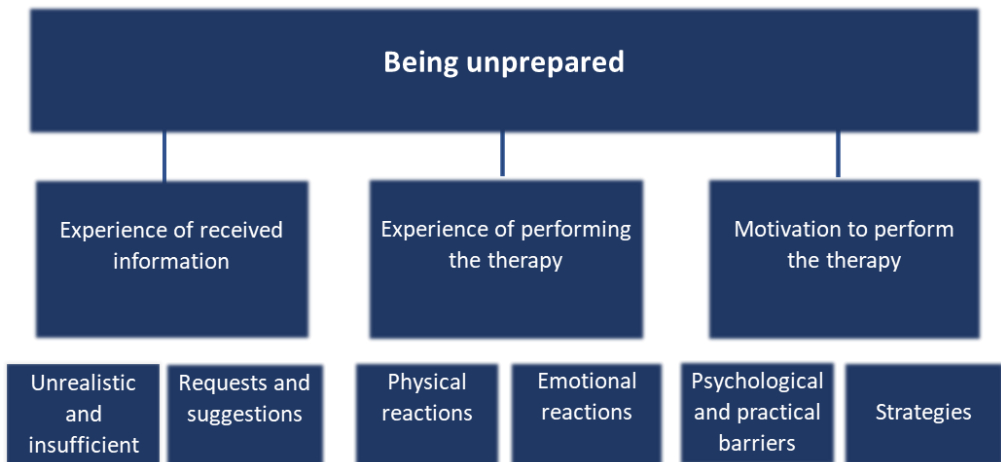


Figure 8. Experiences of vaginal dilator therapy, and barriers to and strategies for motivation to perform the therapy.

Being unprepared relates both to receiving information about vaginal dilator therapy, experiences of performing the therapy, and motivation to perform the therapy. The information received was perceived as *unrealistic and insufficient*. Some women described their experience of receiving the information as “really shocking” and “unreal”. Although not explored in this study, the type of information provided to the women seemed to vary in structure, approach, and extent. However, all the women had received some

information from a nurse or a physician a few weeks after completing radiotherapy. The women expressed that they would have preferred to receive information at an early stage in the cancer treatment. Even though the women had insights into the complexity of the interventions and described being in crisis during the treatment, they expressed a need for the subject of vaginal changes and actions for preventing vaginal stenosis not to be ignored. Women described their situation after completed cancer treatment as being left alone and in need of extended support regarding vaginal dilator therapy. *Requests and suggestions* provided by the women for improved information included clearer communication, as well as supportive care in specific situations, such as with previous experience of childhood abuse or sexual abuse. Furthermore, the shape of the received dilator was described as straight, stiff, clinical, cold, “not-nice!”, and unpleasant. The women expressed a wish for a softer design.

Being unprepared was related to the *experience of performing the therapy*. The women experienced both *physical reactions* of bleeding and pain, which generated mixed and contradictory feelings due to these signals from the body being related to injury and harm. When these reactions occurred, thoughts of a possible recurrence of cancer and feelings that reminded them of their previous cancer and cancer treatment emerged. The *emotional reactions* refer to unexpected distress and feeling anxious when inserting the dilator into the vagina. A cut off between body and mind was described.

Barriers to *motivation for approaching the therapy* consisted of *psychological and practical barriers*. Once again, these included feelings of mental cut-off from the body and perceiving that performing the dilator therapy seemed to be in conflict with being attentive to bodily signals and the way the body had reacted during previous unpleasant experience of dilator use. In addition, women experienced practical hinders and barriers to the therapy, such as daily life, co-existing bothersome intestinal symptoms and fatigue, and feeling that the therapy was a kind of self-abuse or self-harm. Complicated feelings therefore arose when approaching the therapy. However, some women had developed *strategies* to enhance their motivation to perform the therapy. Such strategies could be creating routines, prioritizing the therapy, pre-warming the dilator, relaxation exercises or breathing exercises. Furthermore, distractions (e.g. watching TV), searching for

something positive, as well as managing the therapy together with their partner were some of the useful strategies described by the women. For some women, having an established contact with a nurse and a sexual counsellor resulted in improved motivation to perform the therapy.

7 DISCUSSION

7.1 METHODOLOGICAL CONSIDERATIONS

One major strength of this thesis is the use of data collected from a population-based cohort in an observational prospective longitudinal study. The data are considered adequate to be able to answer our research questions related to sexual health and interventions. In the last study, a qualitative method was deemed suitable for being able to understand women's experiences. Together, the four studies considered some of the radiotherapy-induced consequences affecting sexual health and wellbeing, as well as the outcomes following interventions in a novel nurse-led clinic and experiences of vaginal dilator therapy. The various research methods used were chosen to ensure that the aspects that are most meaningful for the female pelvic cancer survivor were elucidated in according with the aims of the studies.

7.1.1 Studies I-III

This section outlines the use of a model to minimize possible sources of error and describes how potential threats to the validity of our studies were dealt with. With regard to the identification of sources of bias, we consider how the real-life study differs from "the perfect study". The validity of a study refers to the extent to which systematic error is minimized during all stages of data collection and the extent to which the results provide a basis for generalization to other situations. Thus, the quality of the studies in this thesis equates to assessing whether the inferences drawn from them are justified when taking into account the methods, the study sample, the nature of the population from which it is drawn, and the representativeness of the study sample.

In research, the ideal is to design "the perfect study", with no errors, in order to provide valid data. In real-life studies, this is a utopia because we have to deal with certain factors that may influence our results. By recognizing the possible sources of errors, the probable impact on a study's results can be assessed. Consequently, bias in a study does not necessarily mean that the study is unacceptable. In the epidemiological cancer survivorship field, a

hierarchical step-model for causation of bias has been developed (132). This step model is used for the purpose of clarifying, identifying and trying to minimize possible sources of errors. Systematic errors can derive from all aspects of research. They may be caused by unintended mistakes by respondents and can occur due to a systematic reaction by the respondents. For example, in a patient-reported questionnaire study, one source of systematic error can occur when using a scale that can be easily misunderstood and thereby consistently measures symptoms as being more severe than they actually are. A questionnaire with leading questions that prompt participants to answer or act in unauthentic ways can also lead to systematic errors. Such systematic errors can be reduced by using validated questionnaires.

Random errors relate to factors caused by unknown or unpredictable changes, for example due to natural variations in the real world or individual differences (e.g. experience of pain). Such errors cannot or will not be controlled. Collecting data from a large sample can reduce random error. Random errors are normally distributed and to test whether or not a result is likely to have occurred by random changes, statistical significance is used in Papers II and III, as well as a prevalence ratio with 95 percent confidence intervals for statistical evaluation of the effect. We also use p-values to test the statistical significance of the unknown probability distribution of variables.

As shown in Figure 9, the step model demonstrates that each step of the research process introduces a special source of error. The model proceeds step-wise towards the calculated effect, where each step intends to identify possible threats that may risk the study's validity. A study begins with a research question or a *hypothesis*. Person-time refers to the time during which a person has been studied. The *perfect person-time* is a philosophical term used to describe a theoretical situation of possible worlds. For example, if we could create an exact duplicate of our world, then introduce an exposure in our world (such as in study II), we could conduct a study for the purpose of comparing interventions provided to women after radiotherapy for pelvic cancer in our world, but not in the duplicate world. All differences between the two worlds could then be interpreted as a direct causal link to the interventions provided. Since the *perfect person-time* is an unattainable

situation, we strive towards finding an appropriate *targeted person-time* that would support valid conclusions.

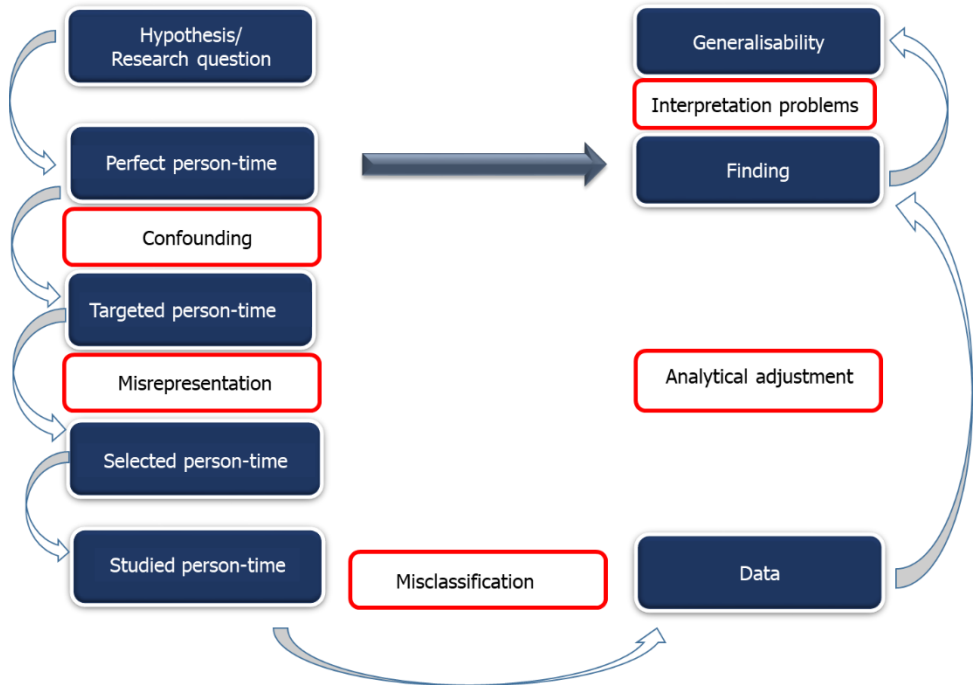


Figure 9. Hierarchical step-model – different steps in a clinical study for identifying causation of bias

Hence, all studies in the real world deal with factors or threats that may influence the results. Actual threats in a study include *confounding*, *misrepresentation*, and *misclassification*, concepts that are denoted as systematic errors, which cause measurement problems that can be predicted. *Confounding factors* are always present in a real-life study of human beings. They are associated with both the exposure to treatment and the outcome being studied, and can be identified between the perfect person-time and the targeted person-time. *Misrepresentation* refers to the imbalance in the distribution between groups in the analysis and occurs when there is a loss of individuals between the targeted person-time and the studied person-time resulting in incomplete collection of data from the targeted person-time.

Misclassification refers to measurement problems and occurs when the information collected, such as data collection using a self-reported questionnaire, is incorrect. By identifying such potential threats or systematic errors, we can try to avoid introducing analytical errors and interpretation problems. When systematic errors are identified, they can be handled through adjustment and the statistical methods used.

7.1.1.1 Confounding

Confounding refers to a type of bias that can be caused by an extraneous factor that is associated with both the exposure and the outcome. Such factors can lead to over- or underestimation of an effect. A confounding factor affects the true association between exposure and outcome, and can suggest that there is a correlation between variables or exposure and outcomes when, in actual fact, there is not. In the preparatory phase of the studies in this thesis, detailed preventive procedures were carried out by collecting as much information as possible. This information was received through the study questionnaire and patients' medical records and included age, time since completed radiotherapy, education, marital status, smoking habits, diagnosis, surgery as additional cancer treatment, and whether the patients were invited or referred to the clinic. Suspected or known factors considered in the analyses were the relationship between having severe intestinal symptoms (frequency of defecation, defecation urgency with and without fecal leakage, leakage volume, leakage without forewarning), and wellbeing aspects (quality of life, anxiety, depression). For example, we found that women with a reduced urgency to defecate were more likely to have improved satisfaction with their overall sexual health. Thus, caution needs to be taken in the interpretation of the finding of improved satisfaction with sexual health following interventions, where reduced urgency to defecate is considered a mediating factor in intervention outcomes. One strength is that the variables concerning sexual function cover the outcomes among women who reported they were sexually active, which ensures a more precise measurement without a diluting effect. While a randomized clinical trial would have minimal bias and confounding factors, and provide a more straightforward cause-effect relationship, a single-arm prospective study, such as the current one, was considered to provide reasonably useful results. This method was chosen mainly for ethical reasons, since it was considered important to offer all patients the best available intervention, irrespective of approval to study

participation, due to the limited practice of rehabilitation when this project started.

One limitation is that we include data in our analysis (studies II and III) from women referred to the clinic. More women in the referred group were currently employed, while the invited women were to a higher extent retired. We consider that this is probably explained by more of the referred women being younger. The cohort studied is population-based but was not controlled for cancer stages in the different diagnosis groups, nor the planned treatment target size, which is also related to technological advancement in recent decades. This may have introduced confounding factors. Furthermore, possible confounders of associations about which we have no information are pre-treatment data regarding anxiety and depression, genital pain, and satisfaction with overall sexual health. There is also no information regarding anti-depressant medication, such as selective serotonin reuptake inhibitor (SSRI), which has been shown to induce difficulty with sexual function (desire, arousal, and orgasm) (133), analgesics, or other medication. The analysis in study II follows the individual's self-reported changes pre- and post-interventions, which is considered advantageous for minimizing the impact of these factors. We are aware that there is no information about ethnicity or cultural differences, which could affect the way a person views their sexuality and thereby their responses; however, this is considered to be equally balanced in distribution across the groups (study III).

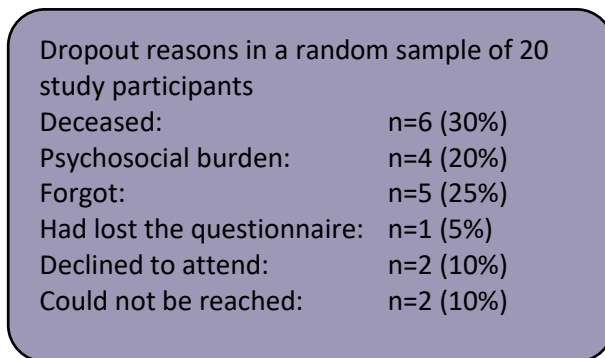
In study III, the only differences in demographics between the sub-groups of women with and without a history of sexual abuse were notable differences regarding age (younger) and diagnosis (a higher proportion with cervical cancer). These differences can be explained by either early exposure to HPV, early sex debut, sexual abuse, sexual risk-taking, or a combination of these factors, since they can increase the risk for the development of cancer. Hence, these can be considered mediating factors, and constitute part of the causal chain.

7.1.1.2 Misrepresentation

The second step in the hierarchical step-model represents non-participation and loss of follow-up, e.g. misrepresentation, which can occur when shifting from the *targeted person-time* (study-population) to the *selected person-time*

(participants). The total participation rate for agreeing to the interventions was 63%. In the invited cohort, 53.4% agreed to visit the clinic while 93% of the referred cohort agreed to a visit, suggesting that those who were referred had already reached an agreement to visit (study I). Despite having troublesome symptoms, reasons for non-participation could be that women experienced their symptoms to be too severe to enable travel to the clinic, age-related problems, having multiple health conditions or needing long-distance transportation. Efforts were made to avoid the loss of follow-up subjects through repeated phone calls and reminder letters.

The baseline questionnaire included participants with symptoms who agreed to visit the clinic and participants with symptoms who declined a visit (studies I and III). The follow-up questionnaires in study II were sent to participants who visited the clinic and underwent interventions. However, we had no information regarding the reasons for 119 dropouts; these were women who were undergoing interventions but who did not respond to the follow-up questionnaire. A dropout analysis was, therefore, conducted in study II in a small randomly selected number (20 individuals out of 119 dropouts) of non-respondents (Figure 10). Of these, ten women (age range 50-82 years) agreed to participate in a short telephone interview about their reasons for dropout. However, one who had agreed to participate in the dropout analysis could not be reached by phone. Thus, nine individuals were reached by phone and responded.



Dropout reasons in a random sample of 20 study participants	
Deceased:	n=6 (30%)
Psychosocial burden:	n=4 (20%)
Forgot:	n=5 (25%)
Had lost the questionnaire:	n=1 (5%)
Declined to attend:	n=2 (10%)
Could not be reached:	n=2 (10%)

Figure 10. Dropout reasons in a random sample of 20 out of 119 dropouts (Study II)

Table 6. Symptoms reported after completed interventions among non-respondents (Study II)

	No, not at all	Yes, a little	Yes, moderate	Yes, a lot
Intestinal health	1	1	4	3
Urinary tract health	3	2	1	3
Sexual health	4	3		2
Lymphedema	5	1	1	2
	Never	Sometimes	All the time	
Feeling depressed	3	6		
Feeling anxious	7	1	1	

As shown in Table 6, intestinal health symptoms directly after completed interventions were reported as “moderate to a lot” by 7 of 9 women who participated in the dropout analysis, while urinary tract problems were reported as “moderate or a lot” by 4 of 9 dropout analysis participants. The majority, 7 of 9 of the dropout analysis participants, reported low levels of sexual health problems. Three of 9 reported that they were affected by lymphedema “moderate to a lot”. Most dropout analysis participants reported feeling depressed sometimes, and the majority of the participants reported never feeling anxious. Although not statistically analyzed in the dropout analysis, the non-respondents’ symptom burden did not seem to differ from that of the respondents. However, due to the small sample, we cannot exclude that the effect measures could be different among the non-respondents, which in turn might wrongly represent the *targeted person-time*.

A slightly higher proportion of women who reported a history of sexual abuse completed the three-month follow-up questionnaire (13% compared to 11% in the baseline), which might indicate a higher need for support in this group; however, this was not statistically analyzed.

7.1.1.3 Misclassification

When the information collected in a study is incorrect, the data have the potential to induce systematic errors caused by measurement errors. This can occur in the case of questions that are misunderstood. The sensitivity and specificity are then reduced in relation to the truth. No study has a 100 percent sensitivity and specificity, despite the efforts made. In this study, the questionnaire had previously undergone a validation process assessing face-to-face validity (122), as has been used in previous studies, with the cooperation of the target population. This decreases the risk of misclassification and increases the likelihood that the women had answered the questions as intended.

An anonymous questionnaire, completed in private, is considered to reduce the risk of misclassification. This dimension might be affected in the studies since the questionnaire was not only included in the research, but was also used as a clinical assessment tool by the nurses. Although previously validated for pelvic cancer survivors, the questionnaire was not validated for survivors invited to undergo interventions at a clinic. However, according to a previous study on cancer survivors, study participation has been reported to be valuable (95%) and answering a questionnaire as having a positive impact (54%) (131). Nevertheless, despite the attempt to avoid therapist-induced bias, there is a risk for misclassification due to the questionnaires not being as anonymous as when they were used in previous studies (4, 63). A feasibility study could have preceded the studies to determine this risk.

Since there is no guarantee that any of the patients did not have a partner who was controlling their responses, there is a risk that the results could underestimate, for example, the level of women affected by sexual abuse (study III). There is also no reason to believe that this was over-reported since the proportion of women reporting a history of sexual abuse is slightly lower than previous reports in general female populations (134). There is a risk for both over- or underestimation when trying to recall symptom occurrences during the past six or three months, and recall bias could also be a problem in the current study (135).

7.1.1.4 Analytical adjustments

The analytical process can start when the data have been collected. The analytical steps were preceded by a process of reducing some of the errors previously mentioned: confounding factors, misrepresentation, and misclassification. A statistician co-author was involved in this process. Discussions, stratification and regression modeling have been used throughout to reduce potential errors. A strict selection criterion for significant association was applied to avoid random selection of true predictors (study II). Likelihood Ratio Test p-values were calculated to test the statistical significance for the estimated effect measures (RR), Wilcoxon signed-rank test (a non-parametric statistical hypothesis test) was used to compare baseline and follow-up data in study II. A log-binomial regression model was performed to assess the association between dichotomized changes in the variables of overall sexual health and wellbeing. Although corrected for biases, variability in the data may exist.

7.1.1.5 Interpretation problems

The possibility of generalizing the findings to other populations than those studied might be limited due to the continuous and ongoing development of cancer treatments, treatment techniques, supportive care, and changes in healthcare settings and organizations. Our results reflect female pelvic cancer survivors' sexual health and wellbeing in a Swedish context and can be generalized to this population in Sweden, and probably also to other high-income countries.

7.1.2 Study IV

Qualitative content analysis is a method used to analyze qualitative data, for example, transcripts from an interview. Although there are other qualitative research methods, such as phenomenology, hermeneutics, and grounded theory that could be considered, content analysis was deemed most suitable, involving both descriptions and, also during the analytical process, interpretations of abstraction (130). The content of the interviews was rich, reflecting the women's experiences with respect to the aim of the study. In qualitative research, important concepts throughout the research procedure refer to achieving trustworthiness, an overarching concept including credibility, dependability, and transferability (129).

Credibility, which refers to how confident the researcher is in the truth of the findings in the study, is considered to be facilitated by long engagement in the field. The preunderstanding among the research team is considered to have had a positive impact on the results. The team consisted of two oncology nurses and one gynecological oncologist with several years' experience of counseling about vaginal changes and vaginal dilator therapy following pelvic radiotherapy in a clinical context, and one midwife/sexologist with long experience of clinical work and research in sexology. Two of the researchers (LÅ, GD) read the transcribed interviews separately and also met afterwards for a discussion about the analysis and categorization. Subsequently, an evaluation was made by all authors regarding how well the categories covered the data, and the similarities and differences between the categories. In the interview situation, trust was built by giving information and providing a supportive space, both before and after the interview. The credibility of content analysis also refers to selecting the most appropriate sample and sample size; in our study this was reached by answering the aim of the study, which was to increase knowledge about women's experiences of vaginal dilator use among those who had reported having difficulties. The data was considered saturated by the content within the sample size in our study, since the interviews no longer gathered any new data.

Through the systematic coding and the use of the software NVivo, which facilitated the organization of the transcripts in our study, and by following a sequence of steps during the analysis, we consider that consensus building among the research team contributed to the consistency of our study. Training is a necessity in order to reduce bias and trustworthiness in qualitative methods. Despite long clinical experience, the first author had received limited training in the performance of an interview study, which could affect trustworthiness. However, experience of conducting interview studies existed within the research group.

To ensure stability of the data, we followed the principles and criteria when detailing the participants' characteristics with regard to the aspect of *dependability*. Dependability refers to the degree to which the data change over time and decisions made during the analysis process, which we have

tried to outline to enable others to follow the decision trail used. Although questions in the same areas were used in all interviews and followed a semi-structured interview guide, interviewing is an evolving process, and the follow-up questions used might have been influenced by previously performed interviews. However, this could also have given more comprehensive results since the interviews might have continuously generated richer data.

To facilitate *transferability*, which refers to the potential for the findings to be generalized, we outlined the characteristics of the participants in our study. The participants had different pelvic cancer diagnoses, were of a wide range of ages, and had a variety of marital statuses. In addition, the vaginal dilator information procedures and follow-up, and the scope of the information previously received, varied but were not detailed in the current study. The study participants are not considered to represent all female cancer survivors treated with pelvic radiotherapy, but are considered to reasonably describe the experiences of women struggling with vaginal dilator therapy. The aim of this was to try to understand the underlying causes and strategies to maintain and motivate the therapy. The outlined quotations and the information provided about the analysis process aimed to improve transferability.

7.2 SUMMARY AND DISCUSSION OF MAIN FINDINGS

The knowledge that has emerged from the studies in this thesis contributes to both biological, psychological, social, and sexual perspectives. The originality primarily comprises the improvement in aspects of sexual health and wellbeing among female pelvic cancer survivors treated with pelvic radiotherapy following directed interventions. The factors studied that were found to be associated with these improvements showed that improved intestinal late effects explain increased satisfaction with overall sexual health, and reduced anxiety and depression. Other key findings are the crucial effect that a history of sexual abuse has on sexual health and wellbeing after completing radiotherapy. Moreover, women experienced being unprepared for the information given and for the performance of dilator therapy to prevent or reduce vaginal changes after completing radiotherapy. Taken

together, the results emerging from this thesis can contribute to the development of survivorship care of female pelvic cancer survivors.

7.2.1 Wellbeing

One main finding of the thesis is that women reported high levels of depression and anxiety at baseline, which were shown to be markedly reduced following the interventions in the nurse-led clinic, even though the focus of the interventions was mainly on physical health outcomes. The low levels of wellbeing stated at baseline are most likely explained by the high impact on daily life of severe late effects, such as the intestinal dysfunctions reported in our study. It is most likely that not only intestinal and sexual dysfunctions, but also urinary tract symptoms, lymphedema, fatigue, and pain contribute to lower wellbeing. This is where the importance of having a rehabilitation frame of reference with a biopsychosocial perspective becomes apparent. According to the WHO's definition of rehabilitation (136), there is a focus on optimizing function in an individual's everyday life activities. Our result shows the need for rehabilitation of severe late effects in order to optimize function in cancer survivors' daily lives. Combining rehabilitation with a biopsychosocial perspective, which according to Engel (116) consists of an approach connecting biological, psychological and social domains, seems necessary in cancer care.

Encouraging results from this study are that, through biopsychosocial and sexual interventions and the provision of sufficient support in a well-established nurse-led clinic, female pelvic cancer survivors can achieve an improved quality of life. These results confirm the advantages of nurse-led self-management support, as delivered in the current clinic and as described by Cerna et al. (103), using a biopsychosocial model to understand the illness. Social variables, behavior, and emotions are all taken into account – the patient's personality, experiences, attitudes, and expectations – and are critically centered on the person and thereby individualized. The model underpins goal-setting processes, which are widely used in rehabilitation. While the current health systems were founded on the biomedical model, the biopsychosocial approach can be developed through healthcare professionals working across existing boundaries. The biopsychosocial perspective underpins goal-setting processes, which are widely used in rehabilitation. While the current health systems were founded on the biomedical model, the

biopsychosocial approach can be developed through healthcare professionals collaborating across existing boundaries (117).

Low levels of quality of life have previously been reported among gynecological cancer survivors with fecal incontinence (137). These are very likely related to the constant uncertainty and the shame and degradation in social situations due to fecal leakage, as has been previously described (138). In our study, reduced urgency to defecate with fecal leakage was statistically significantly associated with reduced anxiety, indicating that physical illness should be prioritized with the purpose of lowering levels of anxiety. As has earlier been shown, fecal incontinence prevents women from being physically active (139). This is also an important and reasonable motivation for the treatment of late effects and states following radiotherapy. Furthermore, in light of gastrointestinal syndromes having been shown to affect work-life-related parameters in terms of a higher risk of disability pension (140), the health cost-effectiveness could be considered valuable. The use of a biopsychosocial approach in cancer rehabilitation seems, therefore, to be advantageous on a number of levels.

Another concept in cancer care that has been emphasized in the past decade is prehabilitation. According to Silver et al. (113) this serves multiple goals, including obtaining a baseline of function and reducing treatment-induced impairments (141). Prehabilitation may start during or at the beginning of treatment, or as preventative exercises prior to the start of cancer treatment. It involves a process of assessment and provision of physical and psychological interventions that promote future health. In study IV, women provided reasonable and sound suggestions, such as giving early information and counseling that relates to prehabilitation for the purpose of maintaining preventative vaginal dilator therapy. If the vagina is viewed as an anatomical structure that can be stretched and exercised, it is likely that early information and counseling regarding vaginal therapy is the most optimal regimen for preventing vaginal stenosis, as well as for enabling women to view the therapy as part of the cancer treatment. This has some similarities with the prevention of radiotherapy-induced fibrosis in patients with head and neck cancer where the best practice considered for preventing dysphagia is prophylactic swallowing exercises (142). In women treated for pelvic cancer, this could be seen in a wider perspective and include a comprehensive

prehabilitation program including both physical, psychosocial and sexual interventions. Previous reports show improvements among lung cancer patients participating in preoperative physical therapy programs (e.g. pulmonary prehabilitation breathing exercises, nutrition optimization, aerobic exercises, and strength training) (113). There is also a study on women with breast cancer showing that a training program during chemotherapy effectively improved vital aspects of health-related quality of life, fatigue, and muscle strength, even in the long term (143). A prehabilitation approach could likely be applied to women undergoing pelvic cancer treatment, although this is outside the scope of this thesis.

When addressing needs during treatment, preparedness for physical late effects is shown to lower the risk of future anxiety and depression (144). In prostate cancer survivors, being prepared for late sexual effects has been proven to reduce uncertainty and positively influence both physical-, psychosocial- and sexual health outcomes (145), and this is also likely to be the case for female pelvic cancer survivors. This is an area for future research.

7.2.2 Sexual health aspects

The low satisfaction with overall sexual health found in the baseline data improved following visits to the nurse-led clinic (study II). This finding is valuable for healthcare professionals in the follow-up care of women treated with pelvic radiotherapy. The association between improved satisfaction with overall sexual health and reduced fecal leakage was a finding in line with clinical experience and therefore somewhat expected; however, to our knowledge this has not been previously studied. Previous qualitative data (138) show that the daily struggle with fecal incontinence leads to insecurity and lack of control, which is important when it comes to engaging in sexual activities. For obvious reasons, it seems that sexual health problems become important for some women only when intestinal health symptoms, such as fecal leakage, are reduced. These findings can be explained through the sexual response model, where sexual stimuli can be hindered by both physiological and psychological factors, and also socio-cultural factors (77). When an individual is stressed, it is difficult to be aware of sexual stimuli, and this process leads to decreased sexual desire and decreased sexual satisfaction. A biopsychosocial perspective is therefore important in

rehabilitation. For healthcare providers, the PLISSIT model (118) with four levels for addressing sexual health issues fits well and could ideally be integrated into the cancer continuum and contribute to improved quality of life for pelvic cancer survivors.

Genital pain during vaginal sex was a frequently reported problem among sexually active women in our study, but was statistically significantly more common in women with a history of sexual abuse. In study III, we show that women with a cervical or anal cancer diagnosis were more likely to have a history of sexual abuse. A reported history of sexual abuse was also associated with younger age. Moreover, more women with a history of sexual abuse or having a cervical cancer diagnosis reported deep genital pain. According to previous research, sexual abuse is probably linked to HPV-exposure (146). It has also been shown that women with a history of sexual abuse are more likely not to attend cervical cancer screening, and thereby have an increased risk of having a higher stage of disease at diagnosis. This often leads to treatment with a higher radiation dose and a higher risk for vaginal stenosis and inelasticity, which in turn increases the risk for genital pain. This link has been previously described (92, 146) and, along with the higher risk for sexual pain caused by sexual abuse, this probably explains why a higher proportion of cervical cancer survivors report genital pain. One possible explanatory factor for superficial pain during vaginal sex being more common in rectal cancer survivors than in other pelvic cancer survivors could be due to rectal cancer survivors being less likely to use topical estrogen, as shown in our study, which is a recommended intervention for reducing vaginal pain and discomfort. According to the results of study II, and in summary, about one in four cancer survivors reported some degree of genital pain during vaginal sex, irrespective of their original cancer diagnosis. Both the current and previous studies show that women with anal cancer more frequently reported superficial genital pain (147), while cervical cancer survivors more frequently reported deep genital pain. The high impact of the irradiation is likely to explain the frequently reported genital pain. This knowledge should be used to support women with high risk for genital pain, either superficial or deep pain. Existing or previous sexual dysfunction or vulvar complaints, such as STI, candida vulvovaginitis, lichen sclerosus, vulvodynia, and a history of sexual abuse increase the risk for genital pain and other sexual dysfunctions (148). These issues could be identified at an

early stage of cancer treatment with the intention of offering these women extended support. Considering that cancer treatment has been described as triggering thoughts and emotions associated with a previously experienced abuse, this is also important information in the prevention of re-traumatization (94).

An association with a lifetime diagnosis of somatic disorders (e.g. chronic pain, gastrointestinal disorders, fibromyalgia) has been reported among women with a history of sexual abuse when seeking general medical care. One would therefore expect higher participation rates by this group in the nurse-led interventions (study II) (93). Nevertheless, only a slightly higher proportion (13% compared to 11% at baseline) had a history of sexual abuse among the women who completed the three-month follow-up questionnaire. In a previous study of women diagnosed with provoked chronic vulvar pain, although a history of sexual abuse was associated with other comorbid chronic pain conditions such history was shown not to affect the efficacy of the treatment of pain (149). In the current study, the outcomes of the interventions among women with a history of sexual abuse were not explored. However, the total cohort of female pelvic cancer survivors reported reduced pain during vaginal sex following the interventions.

The many psychological and biological factors that have been previously considered to negatively influence sexual function in women treated for pelvic cancer, for example anxiety, depression, desire, and vaginal stenosis (7), were confirmed (study II and III). The improvements found (study II) are probably explained by the psychoeducational interventions provided in relation to the complex biopsychosocial and sexual interactions around the occurrence of pain during vaginal sex. Furthermore, psychoeducational interventions consisting of basic advice on topical estrogen and lubricants were provided along with advice that the women should not engage in vaginal sex if painful. By using the PLISSIT model (118) when approaching women's information and their need for support and therapy, the level of care could be adapted to each individual. When the patient and their partner were interested, attempts were made to widen the perspectives of what sex can involve. Finding different sexual practices or different ways to be intimate, was suggested. The treatment-induced premature or exacerbated menopause symptoms can affect multiple aspects of sexual function, such as vaginal

dryness and loss of tissue elasticity, as has been previously described (3, 51, 150).

In study III, vaginal pain during vaginal sex was found prevalent among the female pelvic cancer survivors, and statistically significantly more common among women with a history of sexual abuse. This has been described in previous research in the normal population, which reports that one in ten women are affected by pain during vaginal sex and, among them, one in ten reports a history of sexual abuse (149). One study of gynecological cancer survivors reports that approximately half of all women had pain during vaginal sex (81), which is in line with our result. Whether pain during vaginal sex should be classified as a pain disorder rather than a sexual disorder has been discussed (82, 151). In our study, we found that reports of pain during vaginal sex were significantly associated with vaginal shortness and inelasticity. This has also been described in previous studies (2, 152). Improvements in pain during vaginal sex (study II) are probably explained by the nurse-led interventions provided. Manifestation of genital pain is a complex condition that can be explained using the Basson model as being due to a disruption at any point of the response cycle that can contribute to genital pain (77). Sexual pain disorders remain a complex problem even in women without a cancer history (121). Many women probably suffer in silence. A study by Rees et al. (79) emphasizes the importance of having a biopsychosocial approach in the treatment of sexual pain and that the treatment should involve both partners' perspectives. One way to support women could be through the perspective of long-term pain problems in terms of the psychosocial correlations, which has been earlier described by Tomthén et al. (121). The theoretical fear-avoidance model (82, 153) that focuses on general pain management can also be applied to genital pain. Experience among cancer survivors of painful/discomfort treatment and late effects that affect elasticity and dryness in the vagina can easily generate fear of experiencing pain/discomfort again. The fear of pain causes a vicious circle that inhibits sexual response, sexual satisfaction, and sexual interactions. There is, therefore, a need for a biopsychosocial approach integrating the PLISSIT model, psychoeducation, and the fear-avoidance model in the management of genital pain among female pelvic cancer survivors.

From a radiobiological viewpoint, the potent ionizing radiation that starts pathophysiological processes in the tissues and organs near the tumor might lead to irreversible effects. This might, to some extent, explain why there was no improvement in arousal, lubrication, genital swelling, orgasm, vaginal length, or elasticity. However, the promising advancements in surgical and radiotherapy techniques that spare functional anatomy may change the prevalence of sexual dysfunctions in the future. Studies of cervical cancer survivors show that women who underwent nerve-sparing surgery had greater vaginal blood flow during sexual arousal compared to women who underwent conventional surgery (52, 154). Furthermore, studies of vessel-sparing radiotherapy to preserve sexual function in patients with prostate cancer have shown promising results; this could also be considered in the treatment of a female pelvic cancer diagnosis, which is more than has been done to date. Along with desire and other psychosocial components involved in the sexual response, the prerequisite of the erectile tissues (bulbocavernosus) is sufficient blood flow. Our results indicate that further research is required to establish methods for measuring female sexual function outcomes due to radiation-related damage (155), as well as to establish methods for nerve- and vessel-sparing radiotherapy to preserve sexual function. In the current study, the findings of decreased ability to have an orgasm can relate to either psychosocial reasons, such as lack of sexual interest, fatigue or marital relationship factors, or physiological reasons. Although not investigated in the current study, sexual desire and intimacy in couples are important factors for women with sexual dysfunction (76).

7.2.3 Nurse-led interventions

In oncology health care, the high workload and a lack of time available for sexual counseling may, along with the topic being regarded as uncomfortable or one where there is a lack of knowledge, may explain why patients report that sexual health needs are neglected. In the current nurse-led clinic, the nurses are trained in sexual health counseling and women are offered a generous amount of time for each counseling session.

The finding that satisfaction with overall sexual health improved although sexual function did not (study II) may be explained by women progressing to a new orientation in their sexuality as a result of communication around sexual health issues. Through repeated assessment of patients' needs using

the PLISSIT model, some women went from receiving limited information to being given specific suggestions. Women were offered generous amounts of time for individual counseling, and, when appropriate, the woman's partner was also involved. There is a possibility that the couples' difficulties in engaging in sexual recovery were alleviated. In a previous study of prostate cancer patients, psychosocial aspects of sexual recovery after treatment were discussed and found that grief and mourning were found to be a gateway to new and satisfying sexuality after cancer treatment (156). This is outside the scope of this thesis but needs more study since this is also considered to be important in female pelvic cancer survivors' sexual rehabilitation.

Considering that the data in study II were collected only three months post interventions, a more long-term follow-up data collection one year after completed intervention could have facilitated an understanding of the more long-term outcomes. Assessment by a questionnaire prior to the cancer treatment would have facilitated the detection of predictors influencing sexual health and sexual functioning.

Although there was a lack of improvement in sexual functioning in our study, high levels of satisfaction with the interventions received were observed. This might reflect the advantages of survivorship struggles being confirmed through careful discussions of the impact of cancer and cancer treatments as regards sexual health and quality of life. Along with the interventions provided, the questionnaire used in our study might have had a therapeutic effect. This has been previously described in a study using a similar questionnaire which reported that cancer survivors perceived participation as valuable due to their feelings of confirmation and being valued. Participation and completion of a questionnaire allowed them to reflect on their disease and treatment, and gave them increased knowledge about illness and survivorship. Furthermore, they felt that their contribution could lead to improvements in health care (131).

The positive outcomes of the interventions given in the nurse-led rehabilitation clinic primarily include improved wellbeing. Our results demonstrate the advantages of providing sexual counseling in combination with individualized interventions for additional physical late effects, thus using a biopsychosocial approach in rehabilitation. Does it matter if the interventions are nurse-led or led by other healthcare professionals? Based on

previous research, which shows that sexual health issues are high-incidence areas of holistic nursing care, nurses are in an excellent position to address sexual health issues (157). The development of the advanced and autonomous nursing roles suggested in previous studies implies that nurse-led interventions can be delivered at all stages of the cancer continuum (101).

Our study shows that a nurse-led follow-up with an individualized and holistic approach provides a wide range of interventions, such the above mentioned that facilitate patients' rehabilitation. This has not been previously studied in a Swedish context. Health care delivered by nurses with advanced roles has been proven to impact important care quality factors, such as safety, symptom burden, patient experiences, and cancer care coordination, and could also prevent readmissions (158). Female pelvic cancer survivors were provided with multi-dimensional (e.g. medication for intestinal symptoms and sexual counseling) and wide-ranging interventions based on their own ranking of how bothersome each symptom was and, in this way, the interventions were individualized. The complexity of nursing interventions challenges both the nurses and the healthcare organizations. According to a study describing strategies in the current pelvic cancer rehabilitation setting (103), this process includes three nursing strategies: encouraging self-reflection, tailoring solutions together with the patient, and keeping patients motivated. In the long run, all cancer survivors, who are experts regarding their own body, mind, and general health, are responsible for their acts and behaviors. The nurses' role is to enhance self-care, something which is much needed in a female pelvic cancer survivor's life. Nurses and allied healthcare professionals are responsible for supporting patients during and after treatment; however, patients' participation in the decision-making concerning their care is expected and an objective to strive for.

The observed lack of preparedness for the preventative use of vaginal dilators among women (study IV) might be a result of them stating that they mainly received the information after the completed radiotherapy. This does not necessarily mean that they did not receive any information in advance but that they might not have been receptive to it when delivered. These findings shed light on prehabilitation, an area that is in need of development. As previously described, the taboo and stigma surrounding sexual health issues and vaginal changes are considered to hinder a fruitful discussion, and such issues are therefore at risk of being left unspoken (159). The potential benefit

of prehabilitation during cancer treatment, as described in the literature (113), suggests using screening to identify problems early in the cancer continuum in order to provide interventions aimed at reducing the incidence and/or severity of future impairments. In order to create good opportunities for increasing patients' preparedness for survivorship, guidance by both nurses and physicians during cancer treatment could be provided. Optimal sexual healthcare is impeded by the lack of professional confidence in dealing with these issues, and might also be impeded by the complex healthcare system, as described earlier (157). The benefits of psychoeducational interventions delivered in the rehabilitation phase in our study are similar to those shown in a previous study (110).

Prehabilitation is a concept that has been emphasized in the past decade (141). It may start during or at the beginning of cancer treatment, or as preventative exercises before the start of treatment, and involves a process of assessment and provision of physical and psychological interventions that promote future health. According to Silver et al. (113), prehabilitation serves multiple goals in cancer care, including obtaining a baseline of function and reducing treatment-induced impairments. Promising results are described in a recent study of the preparation of patients through nurse and peer-led psychoeducational interventions in the prehabilitation phase, which were shown to lower sexuality needs, and improve adherence to vaginal self-care (160). In our study (study IV), the women provided reasonable suggestions that relate to prehabilitation, such as giving early information and counselling with the purpose of maintaining preventative vaginal dilator therapy. This could also be seen in a wider perspective, with such interventions being part of a comprehensive rehabilitation program that includes physical, psychosocial, and sexual interventions. In previous studies, improvements have been reported among lung cancer patients participating in preoperative physical therapy programs (e.g. pulmonary prehabilitation breathing exercises, nutrition optimization, aerobic exercises, and strength training) (113). A study of women with breast cancer showed that a training program during chemotherapy effectively improved vital aspects of health-related quality of life, fatigue, and muscle strength, also in the long term (143). Similar prehabilitation programs could also be applied to women undergoing pelvic cancer treatment and, based on our findings (study IV), this could also be effective in the long term.

Due to the way the clinical setting described in this thesis is currently organized, the medical consultants are essential members of the team because they hold discussions and meetings with patients with specific needs and prescribe medications. Since the clinical setting was established back in early 2011, and is still ongoing, interventions have developed as a result of new evidence and more autonomous nursing roles. As part of a wider team, nurses have established routines for multi-professional meetings with physiotherapists, dietitians, and psychologists to facilitate the follow-up of women living with late effects after cancer. Our study adds to previous research giving evidence concerning nurse-led care in cancer rehabilitation. The majority of female pelvic cancer survivors are most likely to be in need of the basic care that is provided by contact nurses. In their central role in health care, cancer nurses act as the patient's key worker and function as a consistent point of reference throughout the care pathway. However, they also have the additional role of providing a wide range of interventions, including counseling, teaching, and guidance. When it comes to female pelvic cancer survivors with more complex symptoms, our study shows that there is a need for counseling with cancer nurses who are specialized in survivorship care. This nursing role could be expanded to enable the further development of survivorship care. As previously described, nursing development should be underpinned by a robust evidence base (101).

7.2.3.1 Vaginal dilator therapy

The women in study IV described their experiences in their own words. The sample of study participants was specifically selected for the purpose of giving explicit focus to the difficulties experienced since low adherence to dilator therapy remains a problem. The findings concerning their being unprepared for vaginal dilator therapy related to them being unprepared for the overall survivorship challenge. It seemed as if the dilator therapy was viewed as an additional factor to deal with in their coming to terms with survivorship, both disturbing and intruding on the rehabilitation process. At the same time, the women stated that their difficulties were not associated with previous negative experiences, such as sexual abuse or vaginal difficulties, and expressed insecurity and concern that the intervention would negatively affect their future sexual health. Performing the therapy could involve bleeding, pain, and discomfort, as well as feelings of guilt and fear.

This can be somewhat explained by the by the fear-avoidance model, described as leading to avoidance behavior (121). Women also described that a mind-body disconnection occurred when performing the dilator therapy (study IV). These results concur with a previous study showing that women undergoing breast cancer treatment experienced a mind-body disconnection, describing the treatment as objectifying and traumatic (161). There is also a study describing a mind-body disconnection among women with experience of childhood abuse or sexual abuse (162). Although in our study sexual abuse was not found to cause difficulties with vaginal dilator use, and that the magnitude of the suffering from sexual violence cannot be compared with undergoing cancer treatment, there are some similarities in the processes and reactions in the aftermath of cancer treatment that can be reflected on. Whereas in a previous study women described using the dilator in terms of relieving the trauma of cancer treatment, which inevitably involves exposure of intimate parts of the body (163), it is likely that the mind-body disconnection is an unconscious reaction, or a strategy, to enable the therapy to be tolerated. In our study (study IV), the process of reclaiming the body following a challenging cancer treatment seemed to be related to the complexity regarding experiences of strong emotional reactions, pain and discomfort, something which is highly important to discuss. In both prehabilitation and rehabilitation, these issues should be viewed from biopsychosocial and sexual perspectives. Our findings (study IV) indicate that the most optimal treatment to prevent vaginal stenosis is probably to regard dilator therapy as part of the cancer treatment.

Our findings (study IV) add to previous research concerning helpful strategies for patients (distraction, preheating the dilator, breathing exercises during the therapy) and the clear suggestions that the women would give to healthcare professionals, including early and individualized support and follow-up. Comparable findings and suggestions have been reported by Cullen et al. (164), and there is a link to the evidence concerning nurse-led prehabilitation interventions that can optimize the conditions for both the physical and the psychosocial survivorship experience (160). The suggestions from the women in our study also included identifying previous experiences of abuse, which have not been described in vaginal dilator therapy studies, but nevertheless reported to be important for the prevention of re-traumatization of women during cancer treatment (94). Based on the results

in study III in this thesis, it is important to identify and support women with experience of sexual abuse since they may experience great challenges concerning treatments, interventions, and late effects.

In recent years, some strategies aiming to reduce the potential for late effects and vaginal stenosis have been explored. For example, preventative planning of organ-sparing radiotherapy will likely reduce vaginal toxicity. Advanced radiation technologies that allow more precise dose delivery, such as MRI and PET imaging, and proton therapy, are being investigated as an option for pelvic cancer patients (165); however, more evidence is needed. There is also an ongoing RCT concerning vaginal dilator use during treatment (166). Despite the efforts and advances, late effects from pelvic radiotherapy continue to be a clinical problem. There is, therefore, a need for further research and the development of counseling for patients about treatment-induced late effects in clinical oncology settings.

8 CONCLUSIONS

As a result of increased survival rates after a cancer diagnosis, there is a continuously growing population of cancer survivors living with treatment-induced late effects. We found poor quality of life, high levels of depression and anxiety, and low levels of satisfaction with sexual health among female pelvic cancer survivors after completing radiotherapy. The findings in this thesis add to previous research that nurse-led interventions can lead to marked improvements in depression, anxiety, quality of life and sexual health, although with interventions primarily focusing on physical late effects. The biopsychosocial approach to psychoeducational interventions in the novel nurse-led clinic described, specifically targeting female pelvic cancer survivors, including patients with gynecological, rectal, or anal cancer, was found to lead to improved wellbeing, and reduced sexual and intestinal dysfunctions. A relationship between reduced fecal leakage and improved satisfaction with overall sexual health was described, as well as a relationship between reduced urgency with fecal leakage and reduced anxiety. Through the findings from this thesis, we can better understand the factors that are important for the sexual health and wellbeing of female pelvic cancer survivors, such as the impact of co-existing intestinal dysfunctions and having a history of sexual abuse.

Our findings can be used to improve the situation of women with pelvic cancer by identifying those in need of extended support before, during, and after treatment.

Lack of preparedness for vaginal dilator use was found among women with difficulties performing the therapy. Healthcare professionals could utilize the information emerging in this thesis to improve the situation for women with pelvic cancer by repeatedly providing prehabilitation interventions through giving consistent, early, and clear information, as well as individualized support and counseling.

9 FUTURE PERSPECTIVES

In this thesis, evidence was obtained concerning the levels of sexual dysfunction and wellbeing among female pelvic cancer survivors following radiotherapy pre and post nurse-led interventions; knowledge was also gained about women's difficulties and experiences with vaginal dilator therapy. In light of the findings, there is a need for more advanced follow-up and support to be given to female pelvic cancer survivors. It would also be interesting to further investigate how to optimize sexual health interventions in this complex area, for example:

- Studies focusing on longitudinal follow-up of sexual health and wellbeing over a longer period of time in the current population, following nurse-led interventions, are needed.
- Future studies should assess the impact of nurse-led interventions on women with a history of sexual abuse compared to women without such a history, to enable the development of supportive care targeting this patient group.
- Future studies should identify potential risk factors for late effects, including sexual dysfunctions and vaginal changes, in order to develop prevention strategies.
- It would be interesting to study the outcomes of early introduction of vaginal dilator therapy to optimize the conditions for preventing vaginal stenosis and inelasticity. This could be performed by conducting a randomized clinical trial on vaginal dilation therapy to test the hypothesis of its early intervention.
- Studies of the impact of preparedness and prehabilitation interventions are needed.
- Interventional studies of alternative devices for prevention of vaginal stenosis would be of interest
- Studying the late effects, quality of life, and sexual health following proton therapy would be of interest
- Investigation into how the marital relationships of female pelvic cancer survivors and their spouses are affected by treatment-induced sexual late effects would be of interest

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