



SAHLGRENSKA ACADEMY

SEXUAL ABUSE, CANCER, AND SEXUAL HEALTH

An exploration of sexual and general health among female cancer survivors with a history of pelvicradiotherapy and experience of sexual abuse

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ABSTRACT – Sexual abuse, cancer, and sexual health

BACKGROUND: Victims of sexual violence – both sexual abuse and intimate partner violence - report a significant decrease in sexual and general health. There exist national screening guidelines for sexual violence in healthcare due to the short and long-term physical and psychological consequences of sexual abuse. However, there is still a gap between the healthcare provided and the needs among women with a history of sexual abuse. Exposure to sexual violence may increase a woman's risk of susceptibility to high-risk human papilloma-associated cancers, particularly cervical cancer.

Globally, one in three women has experienced intimate partner violence, including sexual violence, and the numbers are increasing due to the COVID-19 pandemic. Less than 40 percent of women exposed to intimate partner violence are actively searching for help. There is evidence for a significant correlation between intimate partner violence victims, sexual abuse, and cervical cancer.

In the oncology setting, exposure to previous or current intimate partner violence a history of childhood sexual abuse lowers cancer-related well-being. Screening for sexual abuse on a large scale both overall in healthcare and the oncology setting is of absolute importance to improve or women's cancer-related quality of life. There is limited research into how far sexual health is affected by pelvic radiotherapy-induced site effects among women with a history of sexual abuse. One previous study found a significant synergistic effect for superficial dyspareunia in cervical cancer survivors after pelvic radiation compared to healthy controls.

AIM: The thesis aims to examine sexual and general health among female cancer survivors with a history of pelvic radiotherapy. Further, additional aim was to assess the proportion and the level of severity of women with a history of sexual abuse who have undergone

pelvic radiotherapy with curative intent for gynecological, anal, and rectal cancer suffer from sexual dysfunction compared to women without reported history of sexual abuse.

METHOD: Women were recruited from both a population-based cohort and patients referred to the pelvic rehabilitation clinic by other healthcare providers. All participants were female, over 18 years old, treated with pelvic radiotherapy at Sahlgrenska University hospital between 2007 to 2016. The participants completed a study-specific questionnaire including aspects addressing sexual health, sexual abuse, and well-being. For this thesis, a subgroup of study participants with experience of sexual abuse of any degree (mild, moderate, severe) was identified. Participants grouped as “experience of sexual abuse” or “no experience of sexual abuse.” Chi-Square tests and Fisher’s exact test was used for statistical analysis of categorical variables and, Analysis of Variance (ANOVA) for standard continuous variables were used to compare the two groups’ characteristics. Characteristics of sociodemographic data and sexual health aspects were compared. Also, an assessment of well-being was carried out to estimate women’s self-reported quality of life. Numeric rating scales of 0-7 were used to grade levels of depression and anxiety. Data on cancer diagnosis and treatment modality were collected from medical records. The results are presented in tables and descriptively by means, medians, percentages, and relative risks. The significance level was set at $p < 0.05$.

RESULTS: In total, 570 women participated in the study. 435 self-reported questionnaires were analyzed from the cohort and 135 from a referred patient group. The overall most common diagnosis was endometrial cancer $N=203$ (35.6%), followed by rectal cancer $N=138$ (24.2%). Cervical and anal cancer was the most common diagnosis among women with experience of sexual abuse compared to women without such an experience (32.3% vs. 21.5% $p < 0.063$) (17.7% vs. 12.4%, $p < 0.063$). In total, 62 (11%) of women reported previous experience of sexual abuse. A higher proportion of women reporting experience of

sexual abuse was referred from other health care providers to the pelvic rehabilitation clinic compared to women with no experience of sexual abuse (33.9% vs. 22.4% $p<0.066$). On average, women with experience of sexual abuse were younger compared to women without experience of sexual abuse (57.2 years vs. 64.0 years, $p<0.001$). More women with than without experience of sexual abuse were in a depressed mood (19 % vs. 9 %, $p=0.007$), anxious (23 % vs. 12 %, $p=0.007$), and had vaginal pain during sexual activity (52 % vs. 25 %, $p=0.011$, RR 2.07, CI 1.24-3.16). In the total study cohort, vaginal pain during sexual activity was associated with vaginal shortness (68 % vs. 31 % $p<0.001$) and vaginal inelasticity (67 % vs. 33 %, $p<0.001$). Three-quarters of all women in the study cohort said they would be very distressed if problems with their sexual life persisted.

CONCLUSIONS: Sexual abuse significantly affects the sexual health outcomes and other aspects of well-being for female cancer survivors after pelvic radiotherapy. The results highlight the importance of screening for sexual abuse in oncology settings before, during, and after cancer treatment. These routine changes challenge healthcare to prevent further traumatization and provide appropriate interventions and support. Impaired sexual and general health after pelvic radiotherapy – shown in this thesis – reflects some of the long-term consequences of sexual abuse underlying the importance of developing individually targeted rehabilitation for oncology patients with previous experience of sexual abuse.

Keywords: Sexual abuse, HPV, Cancer, Pelvic radiotherapy, Sexuality, Dyspareunia, Vaginal Stenosis, Vaginal Inelasticity

INTRODUCTION

Today, approximately three times more people survive cancer than 30 years ago, primarily because of the increasingly potent, multi-modal treatment regimens (1). Nevertheless, 20%-25% of cancer patients report a decline in life quality due to treatment's physical consequences (2). Pelvic radiotherapy is an integral part of multi-modal treatment for tumors affecting colorectal, anal, or gynecological areas. Patients treated with pelvic radiotherapy suffer from physical symptoms leading to sexual dysfunction - symptoms such as shortening (3-5), associated with inelasticity of the vagina (6), and dyspareunia (7). Previous studies show that women treated for cervical cancer have persistent vaginal changes, often superficial and deep dyspareunia, leading to considerable distress (8). Vaginal changes compromise sexual activity (9) and result in distress, negatively impacting sexual health and quality of life (10).

Survivors of sexual violence report a significant decrease in sexual (11) and general health (12, 13). The World Health Organization (WHO) has highlighted the need to research the effects of sexual abuse because sexual violence classifies as significant global health, a problem estimated to increase due to the COVID-19 pandemic (14).

Exposure to sexual violence may increase a woman's risk of, and susceptibility to, cancer (15) - particularly cervical cancer (16). There is evidence for a significant, positive correlation between intimate partner violence (IPV) or sexual abuse and cervical cancer (17). Current and past exposure to intimate partner violence is further associated with apparent lower quality of life (QOL) (18), often when violence in combination with low socioeconomic status (19). Intimate partner violence, low quality of life, and childhood sexual abuse (20) show lower

cancer-related well-being indicators. One previous study establishes the importance of screening for intimate partner violence in the oncology setting to improve women's cancer-related life quality (21). There are limited studies of what extent sexual abuse affects the sexual and general health with a history of sexual abuse after pelvic radiotherapy. One previous study reports a significant synergistic effect between sexual abuse and cervical cancer for superficial dyspareunia (22).

Dyspareunia is a common sexual dysfunction that, untreated, can reduce the quality of life (23). The condition is manifested as recurrent or persistent pain before, during, or soon after vaginal penetration. Superficial dyspareunia is pain with initial or attempted penetration of the vaginal introitus, whereas deep dyspareunia occurs with deep vaginal sex (24). Between 8% and 21.1% of sexually active women are affected by dyspareunia, with prevalence variations between countries (24) and age groups (25). The clinical approach for diagnosis and management should address the psychosocial, cultural, sexual, and biological factors which can, independently or in combination, establish and maintain dyspareunia (26, 27).

Mitchell et al. (2017) showed that sexual abuse is associated with dyspareunia for sexually active women aged 16-74 (28). Women with dyspareunia and a history of sexual abuse report a higher psychological distress level and lower sexual functioning than women without a history of abuse (29). Early life sexual abuse is associated with an increased risk of endometriosis (30), one of the main causative factors of deep dyspareunia (31). For gynecological cancer survivors treated with pelvic radiotherapy, dyspareunia is frequently reported and is associated with radiation-induced impaired vaginal elasticity (32).

Furthermore, sexual dysfunction is more likely among women with a history of sexual abuse and/or cancer. However, most women with sexual dysfunctions, such as dyspareunia, do not have a history of sexual abuse or cancer (15).

This thesis investigates in what proportion and with what level of severity women with a history of sexual abuse treated with pelvic radiotherapy for cancer suffer from sexual dysfunction and associated conditions such as depression and anxiety. The thesis hypothesizes that those female cancer survivors treated with pelvic radiotherapy having a history of sexual abuse will have more symptoms related to sexual dysfunction than women treated with pelvic radiotherapy with no experience of sexual abuse.

BACKGROUND

1:1 SEXUAL VIOLENCE

1:1:1 Definition, risks and consequences

WHO estimates women's exposure to either physical and/or sexual violence as 35.6% globally defining sexual violence as: *“any sexual act, attempt to obtain a sexual act unwanted sexual comments or advances, or acts to traffic, or otherwise directed, against a person's sexuality using coercion, by any person regardless of their relationship to the victim, in any setting, including but not limited to home and work”*. The definition includes sexual abuse, harassment, and humiliation as sexual violence (33).

The prevalence of reported sexual violence in the world lies between 6 and 59% (34). In Nordic countries, the lifetime prevalence of sexual abuse among patients seeking gynecological care was 17-33% (35). In a national Swedish prevalence study from 2014, 38% of women reported a history of exposure to sexual violence. In Sweden, current measures indicate that 1 in 4 women in Sweden has experienced intimate partner violence, including sexual violence and 30.000 police reports are done every year of intimate partner violence. However, the estimates are that 80% of intimate partner violence is not reported in Sweden, and less than 40% actively search for help (36). Intimate partner violence and its immediate and long-term health consequences escalate public health problems globally due to the COVID-19 pandemic (37).

Sexual violence is not only a global problem. Sexual abuse is compounded by social injustice resulting from unequal and exploitative relationships sustained and nurtured by the social structures (38). An ecological framework has been established to identify the risk and preventative factors associated with interpersonal violence against women (39). The model is based on evidence that no single factor can explain sexual violence - it is the outcome of a

interaction between risks at the individual, interpersonal, community, and societal levels (40). Exposure to prior abuse (41), low socioeconomic status, and drug/alcohol abuse (42) are examples of risk factors for sexual violence.

In 2020, The Public Health Authority in Sweden issued a report stating the importance of providing healthcare services for victims of sexual abuse to provide conditions to maintain equal sexual health for all (43). In 2003, WHO provided clear guidelines for the healthcare of victims of sexual abuse with the background of the gap between the healthcare services provided for victims of sexual abuse and their healthcare needs (44). Through the Istanbul convention, the EU has urged its members to provide strategic and specialist care for victims of sexual abuse (45). In Sweden, victims of sexual abuse are directed to primary healthcare for help. However, in 2020, the Swedish Association of Local Authorities and Regions highlighted a gap between the needs of help for victims of sexual abuse and current healthcare services regarding accessibility and availability (46). Overall, the healthcare system has a fundamental role in assuring everyone's right to equal sexual health by screening for experience for sexual abuse. Over the years, several national guidelines for healthcare providers have been developed to screen for sexual violence in the health care setting by National Centre for Women's Justice (47).

According to a study by Rajan et al. (2021), the meantime in Stockholm between being a victim of sexual abuse to first disclosure to healthcare providers estimates to be 15.9 years. The time between exposure to abuse to disclosure for healthcare professionals has been explained by multiple internal and external gatekeeping barriers (Appendix 1). Altogether, the long meantime is due to the lack of facilities currently provided by Swedish health care, with only two specialist emergency wards for victims of sexual abuse and one primary care directed towards specialty care for abuse victims (48).

The short and/or middle to long-term health consequences of sexual violence are direct and indirect physical, reproductive, psychological symptoms, together with manifestations of health risk behaviour and potentially fatal outcomes (49). Somatization among victims of sexually abused women is common. Lifetime diagnoses of gastrointestinal disorders, chronic nonspecific pain, psychogenic non-epileptic seizure disorder, and chronic pelvic pain are significantly associated with victims of sexual violence (50). Diagnoses of drug and alcohol abuse, post-traumatic stress disorder, psychotic, bipolar, stress anxiety disorders, depression, attention-deficit hyperactivity disorder, and somatic pain are more prevalent among individuals with a history of sexual abuse than individuals without such a history (51). Sexual victimization can be a pathway to criminality for women (52), usually through the development of mental illness, substance abuse, and repeated exposure to interpersonal trauma (53). The risk factors and consequences of sexual violence are interacting vicious cycles; poverty contributes to sexual violence, leading to criminal behavior and low socioeconomic class risk.

1:1:2 Sexual Violence and Cancer

A correlation is reported between cancer development and a combination of adverse childhood events (ACE), including sexual abuse (54). The literature indicates a high rate of current or history of abuse among women with some cancer types (55), especially cervical cancer (56).

The prevalence of cervical cancer is ten times higher among women with a history of sexual abuse than for the general population (57,58). The risk of invasive cervical cancer is increased when associated with a history of adult exposure to forced sex or childhood exposure to sexual abuse (59). Furthermore, victims of any type of intimate partner violence are more than

twice as likely to have abnormal pap smear results, 60% more likely to have cervical dysplasia, and 4.5 times more likely to have cervical cancer than women with no intimate partner violence (60).

Methodological differences between studies limit the evidence for the association between sexual violence and increased cancer risk. Study populations (61), varying measures to assess abuse (62), underreporting of sexual violence - both in the general care (63) and gynecological setting (64) – limits generalization of results.

1.1.3 Mechanisms behind sexual violence leading to cancer

Different theories suggest direct and indirect mechanisms linking abuse to cervical cancer development, even though the pathway is most likely multifactorial (65) (Figure 1). Direct mechanisms for the development of cervical cancer include sexual transmission of human papillomavirus (HPV) during abuse. Women with a history of sexual abuse are more likely to be exposed to genital high-risk oncogenic human papillomavirus (HR-HPV), while on average, exposure at a younger age than for women who acquire HPV via a non-abusive sexual transmission (66). HPV is a necessary precursor to cervical dysplasia and cancer (67).

Sexually victimized women tend to engage in high-risk sexual behavior and are at higher risk of sexually transmitted infections (68) - including HIV (68). For women infected with HIV, cervical cancer is one of the most common cancers (69) - more likely in advanced stages and usually responding poorly to treatment (70). Women living with HIV have a higher prevalence and persistence (71) of HR-HPV infection, leading to a higher risk of cervical intraepithelial neoplasia lesions (72, 73). The evidence that HIV facilitates the persistence of HR-HPV also holds for the development of anal cancer. HIV-positive men who have sex with

men show to have a higher prevalence of anal HPV infection and anal cancer incidence than HIV-negative men who have sex with men (74).

HIV infection appears to play a multifactorial oncogenic role in cervical cancer development through interferences with immune function and direct cancer growth promotion (75). A recent study demonstrates that women living with HIV and antiretroviral treatment are less susceptible to HR-HPV than those not on antiretroviral treatment. Antiretroviral treatment is associated with a reduction in invasive cervical cancer incidence (76). HIV is associated with multiple indirect multifactorial factors for developing cervical cancer, such as lower economic status, multiple sexual partners, earlier sexual debut, and smoking (77).

Increased persistent HPV-infection rates lead to cervical cancer in other groups of systemic immunocompromised patients, such as organ transplant recipients (78) and women with Hodgkin's disease undergoing immunosuppressive therapy (79). Since the immune state of the individual seems to be related to the persistence of the HPV, stress (80) associated with higher cortisol levels (81) may affect cervical neoplasia risk by decreasing a women's immune competence (82-83).

Indirect mechanisms of sexual violence leading to cancer include smoking, drinking, and drug use (84), as well as lower adherence to preventative screening, delays or non-compliance to treatment (85), plus an increase in cancer high-risk behavior (86). Among other mechanisms, these effects lead back to increased stress responsiveness, dysfunctional regulation of the hypothalamic-pituitary-adrenal (HPA) axis (87), and dysregulation in central serotonergic responses (88), leading to negative health-risk coping strategies among victims of sexual violence.

Non-compliance to pap-smear screening for cervical cancer has been reported for individuals who have experienced adverse childhood events (ACE) such as sexual violence (89). Non-compliance is aggravated when combined with low socioeconomic status, resulting in fewer early cervical cancer diagnoses (90). Screening tests for detecting both breast and cervical cancer may be perceived as invasive and re-traumatizing to sexual abuse victims (21, 91-93)-61). To sum up, psychosocial caused by the experience of sexual violence, high sexual and healthrisk behavior, and non-compliance to screening may be linked to cervical neoplasia (Figure 1).

1:2 THE VAGINA AND SEXUAL FUNCTION

1.2.1 Anatomy

In medical literature, the vagina is often described and explained in terms of its reproductive functions, where the ovaries, cervix, uterus, uterine tubes, and vagina make up the internal organs of reproduction in the female. The cervix fits into the vagina, and a circular structure is formed around it (fornix). The vagina is an elastic, fibromuscular tube approximately 8-10 cm long with a mucosal lining of stratified epithelium. The vaginal walls usually lie close together; under sexual stimulation, the walls moving apart (94). The vagina is supplied by all branches of the inter iliac arteries - the vaginal arteries, branches of the uterine artery, middle rectal artery, and internal pudendal artery. The vessels from the vaginal veins drain into the internal iliac veins and are under control by autonomic innervation. An interplay between sufficient blood flow and innervation is important for orgasmic function.

1.2.2 Histology

The vaginal wall consists of the mucosa (epithelium and lamina propria), the smooth muscle layer, and the adventitia. The mucosa of the vagina lacks glands; secretory activity during sexual stimulation derives from a transudate of plasma from the cervix's local capillaries and glands (96). Hofsjö et al. (2019) found that in survivors of cervical cancer, external radiation reduces the estrogen receptor α and androgen receptor protein expression in the vaginal mucosa, indicating that the vaginal changes in irradiated cervical cancer survivors and the lack of response to hormonal treatment could be due to the decreases in sex steroid hormone receptor expressions (97).

The muscularis of the vagina consists of autonomically innervated smooth muscle fibers arranged into an outer longitudinal and inner circular layer. The smooth muscle layers contain a great variety of transmitters. Some of them are 5HT, nor-epinephrine, acetylcholine, dopamine, and oxytocin (98). Orgasm frequency and pleasure are relatively unaffected in women who have undergone radiation therapy for cervical cancer (99). Intracavitary brachytherapy is usually one of the ground pillars for radiotherapy treatment for cervical cancer in high-income countries. The narrower radiation field of brachytherapy can maintain an intact pelvic floor and an undisturbed blood supply to erectile tissue, so the clitoris is intact, which leaves the orgasmic function undisturbed.

1.2.3 Innervation

The pelvic and pelvic floor's innervation contains nerve fibers from all parts of the peripheral nervous system. The autonomic efferent innervation to the *upper parts* of the vagina is through the uterovaginal plexus, which contains both sympathetic and parasympathetic fibers.

The autonomic afferent fibers from the upper part of the vagina travel through the pelvic splanchnic nerves to sacral spinal cord segments. The hypogastric nerves innervate the upper two-thirds of the vaginal mucosa and control lubrication of blood flow essential for genital swelling during sexual arousal (100).

The autonomic efferent and afferent innervation to the *lower part* of the vagina are carried through the pudendal nerve, made up of somatic branches of the sacral plexus (S2-4) (101).

The pudendal nerve's location in the pelvis makes it prone to injury during pelvic surgeries and parturition. Damage to the sacral nerves and their peripheral branches can be associated with dyspareunia, pelvic pain, and affected sensation in the lower genital tract (102).

1.3 CANCER AND PELVIC RADIOTHERAPY

1:3:1 Treatment with Pelvic Radiotherapy

Pelvic radiotherapy remains a crucial - often primary - part of multi-modal treatment for tumors affecting rectal, anal, and gynecological areas (103). The incidence of rectal cancer in Sweden years 2007-2011 was 25/100.000 for males and 17/100.000 for women (104). In 2016 approximately 1308 men and 845 women were diagnosed with rectal cancer (105). Together with colon cancer, rectal cancer is the third most common cancer form globally and in Sweden (74). Screening for colorectal cancer is established in many parts of the world, and colorectal cancer screening is now implemented in Sweden (106).

Anal cancer is a rare but increasingly more common cancer diagnosis in Sweden, affecting both males and females with a slightly higher incidence rate for females. Anal cancer accounts for 1-2% of all gastrointestinal tumors in Sweden, with 150 cases each year (107).

Anal intraepithelial neoplasia is very similar to cervical intraepithelial neoplasia in terms of etiology; they are related to persistent HR-HPV infection (108), with an increased risk of HPV/HIV co-infection (109-110).

Malignant tumors originating in the female reproductive organs, including the cervix, ovaries, uterus, fallopian tubes, vagina, vulva, and trophoblastic tumors from the placenta, are classified as gynecological cancers (111). Gynecological malignancies account for 10% of all cancer in women, with 3000 cases reported per year in Sweden. The three most common are corpus, ovarian and cervical cancer (112), which in 2018 accounted for 1373, 544, and 543 cases, respectively. In low and middle-income countries, cervical cancer is common, and it ranks fourth for both incidence and mortality for cancer among women globally (113).

The outcome of cervical cancer is multifactorial but depends largely on the health sector's ability to detect and treat the malignancies. Death from cervical cancer is mostly preventable. Despite this, most countries in low to middle-income regions cannot afford effective cervical cancer screening (113). In Sweden, The National Board of Health and Services have guidelines from 2019 giving the fundament of the screening program in terms of method, age limit, and intervals. Overall, cervical cancer incidence has declined since the 1960s due to the screening program and most cervical cancer cases in Sweden failed to participate in the screening program (114). In light of the COVID-19 pandemic, self-swab at home will be initiated in some regions in Sweden as a primary cervical cancer screening method for women aged 23-70 (115).

1:3:2 Modalities

Cancer is a leading cause of morbidity and mortality in the world. Treatment modalities compromise radiation therapy, surgery, chemotherapy, and hormonal therapy to control and/or kill malignant cells. Radiation dosage depends partly on the different kinds of interactions between radiation and body tissue. The goal of radiation therapy is to maximize the dose at the tumor location while minimizing the surrounding body tissue exposure. There is a continuous development of new radiation methods to protect normal tissue without compromising cure rate and survival (116). Radiation therapy can include both external and internal radiation therapy. An example of external radiation therapy is charged particle exposure by accelerator beams (Linac, cyclotron, e.g.). Examples of internal radiation therapy are brachytherapy often used for cervical cancer treatment in high-income countries using long-lived radioactive sources in close vicinity of the tumor, radio-immunotherapy, and peptide receptor radionuclide therapy (117).

1:3:3 Side effects and vaginal changes

Pelvic radiotherapy and the associated side effects affect many people every year. Radiotherapy is both psychologically and physically demanding for both patients and relatives. General side effects of all radiotherapy, regardless of the area of radiation, are fatigue, hair loss, skin changes, nausea, and vomiting. Specific pelvic radiotherapy-induced symptoms are bladder and gastrointestinal dysfunction, chronic diarrhea/constipation, bloating excess gas, and changes in bowel habits such as harder, looser, or more urgent stools than average (118).

For female patients, irradiation of ovaries leads to early menopause or menopausal symptoms, causing infertility (119). Vaginal changes are expected and manifest in symptoms such as

drying and thinning of the vaginal lining, fibrosis, shortening, narrowing of the vagina, decreased elasticity, reduction of lubrication, and diminishment of the size and number of blood vessels in the vagina (120). The vaginal changes are associated with vaginal stenosis, defined as abnormal inelasticity, tightening, and shortening of the vagina due to the formation of fibrosis (121). Vaginal fibrosis is the formation of excess fibrous connective tissue in the vagina; one study shows that 97% of cervical cancer survivors treated with pelvic radiotherapy have fibrosis. The histology of the vaginal wall between irradiated cervical cancer survivors and controls is significantly different (9). Vaginal changes resulting in fibrosis and vaginal stenosis can lead to discomfort in everydaylife. Changes in body perception and pain during sexual activity and gynecological examination all affect the general and sexual health of the cancer survivor (122).

1:4 SEXUAL HEALTH

1:4:1 Definition and socio-cultural context

Sexuality is one of our fundamental needs, together with food, water, air, and sleep. WHO defines sexual health as” *the integration of the somatic, emotional, intellectual and social aspects of sexual being, in ways that are positively enriching and that enhance personality, communication and love*” (123). The Sexual Health Model extends the above definition by stating that “*sexual health has a communal aspect, reflecting not only self-acceptance and respect but also respect and appreciation for individual differences and diversity, as well as a feeling of belonging to and involvement in one’s sexual culture(s)*” (124). Sexual health means the absence of disease, dysfunction, or infirmity and the possibility to have positive, pleasurable, and safe sexual experiences free of discrimination and violence.

The individual's physiology or biological sex, together with sociocultural norms, creates a gender role that may not correspond to the person's internal and individual experience of gender. Gender identity – the genuine feeling of one's internal experience of gender absent from biological, sociocultural, or juridical terms – should be encouraged in sexual health counseling. Sexuality is a central aspect of being human throughout life and encompasses sex, gender identities, roles, sexual orientation, eroticism, pleasure, intimacy, and reproduction (125).

Sexology is the scientific study of human sexuality, sexual interests, behaviors, and functions and is an interdisciplinary field questioning old traditions in periods of political and ideological shifts (127). Sexology states that concepts such as sexually normal/abnormal, natural/unnatural change over time, and is dependent on the socio-cultural context and its values (126). Socio-cultural factors which influence a patient's experience of sexual identity, roles, and practices concerning sexual dysfunction symptoms present both opportunities and challenges to health care practitioners for improving sexual health care services (128).

Physical and psychological bodily changes can predispose conditions for sexual dysfunction, including decreased, low or no sexual desire, superficial and deep dyspareunia, difficulty reaching orgasm, and vaginismus. The perception of being affected by sexual dysfunction is a subjective experience (129). When the conditions are chronic and cause distress, it may classify as sexual dysfunction. According to the scientific perspective on sexual dysfunction, the classification and appellation for sexual dysfunction are dynamic and changing over time. The symptoms could be part of the normal sexual variation but may be classified either by the affected individual or the healthcare provider as a dysfunction influenced by current socio-cultural norms of what normal sexual function is. The notion of sexual dysfunction should be from the patient's perspective – both in terms of chronicity and distress it causes.

1:4:2 Sexual health in cancer rehabilitation

WHO states that every individual has the right to sexual health on fair and equal terms. In 2014, a new National health care program was launched in Sweden addressing all patients' right to cancer rehabilitation before, during, and after treatment (131). The program is continuously under revision with the latest recommendations from 2021.

Sexual dysfunction after cancer is prevalent and sexual health should have a prominent role in the pelvic cancer rehabilitation setting. The survival rate for cancer increases, and consequently, an increasing number of individuals are living with chronic sexual dysfunctions as a radiation-induced side effect (132). Also, as irradiation of pelvic radiotherapy can cause infertility early in the process, initiating the dialogue of eventually oocyte cryopreservation for fertility preservation should be addressed to premenopausal women (133). The success of the sexual adaptation process is partly dependent on individual and relationship factors, where health care professionals in the cancer rehabilitation setting can facilitate through support and information (134).

Finally, sexual health requires an open-mindedness towards sexuality and sexual practice in consultation with patients in health care. Especially pre, during, and after treatment in the oncology setting. The vaginal changes may be perceived – due to socio-cultural norms – by either the patient, partner, or healthcare professional as something to be “treated.” The patient's view of sexuality, personal perception, and implication of sexual health in response to vaginal changes should steer the management plan for cancer rehabilitation (135,136).

AIM OF THE THESIS

The thesis aims to examine sexual and general health among female cancer survivors with a history of pelvic radiotherapy. Further, additional aim was to assess the proportion and the level of severity of women with a history of sexual abuse who have undergone pelvic radiotherapy with curative intent for gynecological, anal, and rectal cancer suffer from sexual dysfunction compared to women not reporting sexual abuse.

METHODS

3:1 Study participants

This is a longitudinal, qualitative questionnaire-based study with participants recruited from a population based-cohort and from a referred patient group. All participants – both from the population-based cohort and the referred patient group – were female cancer survivors treated with pelvic radiotherapy with a curative intent. The population-based study cohort included all female cancer patients over 18 years old, treated with pelvic radiotherapy during 2007-2016 at Sahlgrenska University Hospital. The referred patient group included women treated with pelvic radiotherapy with curative intent referred to the pelvic rehabilitation clinic from other health care providers in the Western Coast region of Sweden. The inclusion criteria were female cancer survivors with a history of pelvic radiotherapy alone or as part of their oncologic treatment, six months or more since the end of radiotherapy. Exclusion criteria were a recurrence of cancer, multi diseased, not understanding the Swedish language, or physically or cognitively unable to participate in the survey (Figure 2). An introductory letter was sent to participants meeting the inclusion criteria. After that, a research secretary phoned and gave oral information about the study and asked for participation.

3:2 Measurements

The baseline study-specific questionnaire was sent out to participants enrolling in the study meeting the inclusion criteria. The survey is used to identify radiotherapy-induced side-effects at baseline and to evaluate further healthcare interventions performed at the pelvic rehabilitation department with three-month and one-year follow-up questionnaires. For this thesis, 570 responses from the first baseline study-specific questionnaire were analyzed. The self-reported questionnaire is based on previously validated questionnaires conducted according to a clinimetric methodology developed by Steineck et al. (137, 138). The method requires an initial quantitative phase of semi-structured interviews, consisting of study

participants relevant for the study. In this case women with a history of pelvic radiotherapy for gynecological, rectal and anal cancer. Afterward, face-to-face validation is essential to confirm internal consistency for the questionnaire.

The baseline questionnaire consists of 175 questions divided into eight sections and designed to address relevant symptoms which the cancer treatment may have induced. The sections include sociodemographic variables, quality of life and well-being, body perception and self-image, intestinal and defecation habits, urinary tract symptoms, sexual health variables, sexual abuse and harassment, and lymphedema variables. The follow-up questionnaire (3-month after the first visit to the pelvic rehabilitation clinic included the same sections except for sexual abuse.

In total, there are five questions in the questionnaire addressing sexual abuse and harassment variables, and forty problems focused on sexuality and sexual function.

The section on sexual abuse starts with a brief description of the prevalence and eventual synergistic impact sexual abuse may have on the already established side-effects of radiation.

The questions regarding sexual abuse are phrased to include all types of sexual abuse – including sexual harassment and humiliation - consistent with the WHO definition (44).

Exposure to sexual abuse was assessed by asking, “Have you been exposed to any sexual abuse? Try to grade the level of abuse to you, not in juridical terms” with the answer alternatives “No never,” “Yes, I have been a bit sexually abused” “Yes, I have been moderately sexually abused” and “Yes, I have been severely sexually abused.” Following questions assessing sexual abuse were “Have you been exposed to repeated abuse?” with alternatives “Not relevant,” “Yes,” “No,” and “Have you been exposed to incest?” “No,” “Yes.” Here, only the answer “No” and “Not relevant” on any of these questions were

classified as non-exposure to sexual abuse (unsure data analyzes was made both with and without not relevant as variable).

Sexual dysfunction was assessed through variables such as reduced sexual interest, vaginal shortness and inelasticity; dyspareunia; the frequencies of intercourse and orgasm; and orgasmic pleasure. The questions address each symptom's characteristics (frequency, intensity, duration, and quality of each symptom) and the degree of the distress it caused. For example, the question "*For some women the vagina can feel inelastic during intercourse. Have you suffered from this during intercourse?*" had the following possible answers: "Not relevant," "No, not at all" "Yes, A little," "Yes, Moderately" and "Yes, A lot." The corresponding distress was assessed on a verbal scale of intensity with the question: "*If your vagina feels short or inelastic during intercourse and if this were to persist, how would you feel about it?*" The possible answers were "Not relevant," "It does not distress me at all," "It distresses me a little," "It distresses me moderately," and "It distresses me a lot."

Furthermore, four questions at the end of the survey addressed questions about the need for support at the intervention clinic with symptoms related to sexual dysfunction. To assess the condition for help for vaginal stenosis, the question "*Do you wish help with vaginal shortening?*" had the following answer options "No," "Yes, I need help, and my need is "A little," "Moderate," "A lot."

Well-being and quality of life were assessed using a 7-point numeric scale to assess psychological well-being, anxiety, depression, energy level, and physical well-being. Here the value 1 describes a low or nonexistent prevalence or intensity, and 7 describes a high or constant prevalence or intensity of the state or condition, corresponding to the lowest and the best possible well-being.

3:3 Terminology

Terms describing female genital pain in current literature are inconsistent, and definitions vary. Superficial and deep dyspareunia are clinical terms defining pain depending on the localization and origin, usually in vaginal sexual activity. For this thesis, dyspareunia's terms are explained in the background to give a brief literature review in its role in defining sexual dysfunction.

However, the sexual activity includes a wide variety of sexual practices, which not historically may have been considered in the clinical term dyspareunia. Moreover, the topic of female sexuality has been tabooed for decades, - leading to cancer-related sexual problems often remain unidentified despite patients' wishes for help (119). Genital pain during sexual activity should include vulvar (clitoral, labia, vulvar, and vestibule) pain and vaginal pain during penetration and/or orgasm. Vaginal intercourse was the term used when the questionnaire used for this study was developed; however, throughout this thesis, we use deep and superficial genital pain during vaginal sex to broaden the perspective of female genital pain.

3:4 Statistical analysis

Data was entered in Epidata Software 3.1 (Epidata associations) – later added in Microsoft Excel and transferred to the statistical program R version 3.5.2 that was used for statistical analysis of the data. Data compilation covered the whole section of sexual harassment and abuse variables (Table 1), 21 of 40 questions of sexual health aspects (Table 3) and 8 out of 11 on sociodemographic characteristics, including estrogen treatment (Table 1) and 5 out of 13 on QOL, anxiety, and self-esteem (Table 2). The responses for the relevant variables were dichotomized or trichotomized to facilitate data analysis.

A subgroup of participants with experience of sexual abuse was identified. The Chi-square test was applied when feasible to investigate the associations between a reported history of sexual abuse and outcomes with more than two categories. Otherwise, Fisher's exact test was used for comparing categorical variables between the sub-groups. Associations between a reported history of sexual abuse and outcomes with two categories were analyzed in terms of relative risks as estimated by the log-binomial model, implemented in the R function `glm()`. Ninety-five percent confidence intervals and the likelihood ratio test were used for inference.

The statistical significance of the differences in demographical characteristics with respect to a reported history of sexual abuse was assessed using ANOVA in the cases of continuous variables and the chi-square or Fisher's exact test was used in the cases of categorical variables. For the bivariable analysis (Table 4, 5) the Fisher's Exact Test was used. Group differences were considered significant if their associated p values were strictly less than 0.05. The estimated relative risks (RR) were calculated and associated 95% confidence intervals using the Mantel-Haenszel method presented in tables. The results are presented descriptively by means, medians, percentages, and relative risks.

3:5 Ethical considerations

All procedures performed in studies involving human participants followed the regional ethics review board's ethical standards in Gothenburg (D 686-10) and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

RESULTS

4:1 Characteristics of the study sample

Of all 570 women who participated in the study, 62 (10.9 %) experienced sexual abuse (Table 1). Women that had experienced sexual abuse were on average younger (57.2 years vs. 64.9 years, $p < 0.001$), stated to a higher proportion that they had a partner but lived alone (16.1 % vs. 3.7 %, $p = < 0.001$), and were more likely to be on sick leave (16.7 % vs. 8.5 %, $p = 0.024$), compared to women without the experience of sexual abuse. More women than without experience of sexual abuse had cervical (32.3 % vs. 21.5 %, $p = 0.063$) and anal (17.7% vs. 12.4%, $p = 0.063$) cancer with no statistically significant difference between the groups. The 62 women ranked the degree of abuse as “mild” by 33 (53.2 %), “moderate” by 11 (17.7 %), and “severe” by 18 (29 %). The mean age of first sexual abuse was 13.6 years with a range of 4-35 years.

Table 1. Demographics and clinical characteristics of female pelvic cancer survivors with and without experience of sexual abuse

Characteristics	Experience of sexual abuse, N= 570		P-value
	No 508 (89.1)	Yes 62 (10.9)	
Age, in years			<0.001
Mean (IQR*)	64.94 (58-74)	57.21 (51-68)	
SD**	12.4	12.3	
Min-max	27-94	26-76	
Marital status, N (%)			<0.001
Has a partner but lives alone	19 (3.7)	10 (16.1)	
Married or living with a partner	346 (68.1)	39 (62.9)	
Single	81 (15.9)	13 (21)	
Widow	62 (12.2)	0 (0)	
Employment status, N (%)			0.024
Disability pension	26 (5.1)	6 (10)	
Employed	137 (27.1)	21 (35)	
Housewife	4 (0.8)	0 (0)	
On sick leave	43 (8.5)	10 (16.7)	
Retired	282 (55.8)	21 (35)	
Student	3 (0.6)	1 (1.7)	
Unemployed job seeker	10 (2)	1 (1.7)	
Smoking, N (%)			0.760
Not smoking	380 (87.4)	51 (85)	
Smoking	55 (12.6)	9 (15)	
Cancer type, N (%)			0.063
Cervical cancer	109 (21.5)	20 (32.3)	
Endometrial cancer	187 (36.8)	16 (25.8)	
Vulvar cancer	19 (3.7)	1 (1.6)	
Rectal cancer	126 (24.8)	12 (19.4)	
Anal cancer	63 (12.4)	11 (17.7)	

Other	4 (0.8)	2 (3.2)	<i>N=Numbers,</i>
Cancer treatment, N (%)			0.955
External radiotherapy with and without brachytherapy	133 (88.7)	17 (11.3)	
Surgery with external radiotherapy with and without brachytherapy	375 (89.3)	45 (10.7)	
Degree of sexual abuse***			
A little		33 (53.2)	
Moderate		11 (17.7)	
Severe		18 (29)	
Repeated sexual abuse		N (%)	
No		44 (71)	
Yes		17 (27.4)	
Not relevant		1 (1.6)	
Incest			
No		56 (90.3)	
Yes		6 (9.7)	
Age at first sexual abuse		Years (IQR)	
Mean		13.6 (8.2-17)	
SD		6.6	
Min-Max		4-35	
Exposure to sexual abuse has affected sexual life		N (%)	
Moderate or a lot		20 (32.3)	
Not at all or a little		34 (54.8)	
Not relevant		5 (8.1)	

IQR=Interquartile range, **SD=Standard deviation, *Experience of sexual abuse subjectively assessed by the study participants with the range: a little, moderate-severe. Note Internal dropouts' range: 0-14.55%.*

Table 1-4 are retrieved from publication 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 May 18.

4:2 Aspects of well-being and self-esteem

A higher proportion of women with a history of sexual abuse reported “always in a depressed mood” (19.4% vs. 9%, $p=0.007$) and “always anxious” (22.6% vs. 11.8 %, $p=0.007$) the last six months compared to women without a history of sexual abuse which showed statistically significant (Table 2). Fewer women with experience of sexual abuse reported a very high quality of life (17.7% vs. 29.9% $P=0.134$) compared to women without experience of sexual abuse without any statistical significance between the groups. Both women with and without experience of sexual abuse reported decreased self-esteem (70% vs. 68%). A significant proportion of women compared to those without experience of sexual abuse reported increased self-esteem after cancer treatment (28% vs. 15.9%, $p=0.009$).

Table 2. Self-reported aspects of well-being and self-esteem in female cancer survivors with and without sexual abuse

Aspects assessed	Experience of sexual abuse		P-value
	No N=499	Yes N=62	
Level of QoL*, N (%)			0.134
No QoL at all or very low	46 (9.2)	7 (11.3)	
Moderate	303 (60.8)	44 (71)	
Very high	149 (29.9)	11 (17.7)	
How often feeling depressed**, N (%)			0.007
Always	45 (9)	12 (19.4)	
Sometimes	243 (48.7)	34 (54.8)	
Never	211 (42.3)	16 (25.8)	
How often feeling worried or anxious**, N (%)			0.007
Always	59 (11.8)	14 (22.6)	
Sometimes	240 (48.2)	34 (54.8)	
Never	199 (40)	14 (22.6)	
Self-esteem*, N (%)			0.285
Low	33 (6.9)	6 (9.7)	
Moderate	294 (61.3)	42 (67.7)	
High	153 (31.9)	14 (22.6)	
Change in self-esteem after cancer and cancer treatment* N (%)			0.009
Not relevant	39 (13.5)	2 (4)	
Yes, decreased	204 (70.6)	34 (68)	
Yes, increased	46 (15.9)	14 (28)	

N=Numbers, QoL=Quality of life. *Patient-reported answers with the range 1-7 and classified as follows: 1-2 "Low"; 3-5 "Moderate"; 6-7 "High".

**Patient-reported answers with a range 1-7 classified as follows: 1-2 "Never"; 3-5 "Sometimes"; 6-7 "Always".

Note Internal dropouts' range: 0-6.61%.

4:3 Sexual health aspects

Fewer women in the sexual abuse group had natural menopause before cancer treatment (61.7% vs. 79% $P=0.004$), possibly correlating to a younger age. More women with than without sexual abuse used local estrogen (21.1 % vs. 34.5 %, $p=0.100$) and had noticed “moderate or a lot” short vagina during vaginal sex (34.6% vs. 51.6%, $p=0.073$, RR 1.49, CI 0.96-2.14) with no statistically significant difference between the groups (Table 3). A statistically significant proportion of women with experience of sexual abuse was less satisfied with the partner as a friend/fellow (14.6% vs. 4.2% $p=0.010$) compared to women without the experience of sexual abuse, whereas there was no statistically significant difference between the groups with less satisfaction with the partner as a lover (11.2% vs. 12.5% $p=0.768$)

Deep genital pain during vaginal sex was reported by twice as many for women with an experience of sexual abuse compared to women without sexual abuse (52 % vs. 25.1 %, $p=0.011$, RR 2.07, CI 1.24-3.16). There was no significant difference between the women with a history of sexual abuse compared to women without regarding “moderate to a lot” of distress if genital pain during vaginal sex would persist (93.3 % vs. 85.4 %, $p=0.379$).

A statistically significant proportion of women with an experience of sexual abuse use lubricant during vaginal sex (69% vs. 44.9% $p=0.025$, RR=1.54, CI 1.10-1.99).

Slightly fewer women with experience of sexual abuse reported pleasurable experience of orgasm (72.2% vs. 77% $p=0.550$), more women with experience of sexual abuse reported a higher frequency of weekly vaginal sex (16.1% vs. 10.3% $p=0.246$), less satisfaction with sexual life (68% vs. 62.9% $p=0.612$), and more distress if overall current problems with sexual life persisted (74.5% vs. 71.5% $p=0.881$) compared to the group with no experience of sexual abuse.

Table 3. Self-reported sexual health aspects in women with and without experience of sexual abuse

Aspects assessed	Experience of sexual abuse, N (%)		P-value	RR (CI)
	No	Yes		
The onset of natural menopause before cancer treatment, N (%)			0.004	
No	104 (21)	23 (38.3)		
Yes	391 (79)	37 (61.7)		
Use of hormone replacement (estrogen), N (%)			0.100	
No	342 (70.1)	32 (58.2)		
Yes, systemic hormone therapy	40 (8.2)	4 (7.3)		
Yes, local estrogen	106 (21.7)	19 (34.5)		
Feeling of sexually attractiveness, N (%)			0.720	1.04 (0.90-1.15)
Not at all or a little	383 (80.5)	50 (83.3)		
Moderate or a lot	93 (19.5)	10 (16.7)		
Satisfied with partner as a friend/fellow human being, N (%)			0.010	3.45 (1.37-7.86)
Not at all or a little	14 (4.2)	7 (14.6)		
Moderate or a lot	317 (95.8)	41 (85.4)		
Satisfied with partner as a lover, N (%)			0.769	1.12 (0.35-2.64)
Not at all or a little	27 (11.2)	4 (12.5)		
Moderate or a lot	215 (88.8)	28 (87.5)		
Frequency of arousal in sexual situations, N (%)			0.877	0.92 (0.53-1.40)
About or more often than half of the times	131 (59.3)	20 (62.5)		
Less often than half of the times	90 (40.7)	12 (37.5)		
Satisfied with the feeling of arousal in sexual situations N (%)			0.597	1.1 (0.75-1.47)
Moderate or a lot	99 (48.8)	14 (43.8)		
Not at all or a little	104 (51.2)	18 (56.2)		
Noticed genital swelling during arousal, N (%)			0.772	0.92 (0.47-1.55)
About half or more of the times	105 (67.3)	21 (70)		
Less often than half of the times	51 (32.7)	9 (30)		
How easy to orgasm N (%)			0.504	1.14 (0.76-1.58)
Very easy or easy	124 (58.2)	21 (52.5)		
Difficult or very difficult	89 (41.8)	19 (47.5)		
Satisfied with the ability to orgasm N (%)			0.994	0.99 (0.63-1.41)
Moderate or a lot	124 (57.9)	24 (58.5)		
Not at all or a little	90 (42.1)	17 (41.5)		
How pleasurable was the experience of orgasm			0.550	1.21 (0.62-2.08)
Moderate or a lot	127 (77)	26 (72.2)		
Not at all or a little	38 (23)	10 (27.8)		

Noticed vaginal shortness during vaginal sex			0.073	1.49 (0.96-2.14)
Moderate or a lot	65 (34.6)	16 (51.6)		
Not at all or a little	123 (65.4)	15 (48.4)		
Noticed vaginal inelasticity during vaginal sex			0.282	1.28 (0.87-1.27)
Moderate or a lot	65 (35.5)	15 (45.5)		
Not at all or a little	118 (64.5)	18 (54.5)		
Use of lubricant during vaginal sex			0.025	1.54 (1.10-1.99)
Not at all or occasionally	113 (55.1)	9 (31)		
Sometimes or always	92 (44.9)	20 (69)		
Superficial genital pain during vaginal sex, N (%)			0.614	1.2 (0.70-1.82)
Moderate or a lot	62 (35.8)	12 (42.9)		
Not at all or a little	111 (64.2)	16 (57.1)		
Deep genital pain during vaginal sex, N (%)			0.011	2.07 (1.24-3.16)
Moderate or a lot	42 (25.1)	13 (52)		
Not at all or a little	125 (74.9)	12 (48)		
Level of distress if genital and sexual pain persists, N (%)			0.205	1.03 (0.97-1.23)
Moderate or a lot	134 (85.4)	28 (93.3)		
Not at all or a little	23 (14.6)	2 (6.9)		
How often vaginal sex, N (%)			0.246	0.6 (0.29-1.32)
Never, a few times or less than 1-2 times a month	409 (89.7)	52 (83.9)		
About 1-2 times a week	47 (10.3)	10 (16.1)		
Level of distress if current problems with vaginal sex persist, N (%)			0.418	1.1 (0.90-1.29)
Moderate or a lot	160 (72.4)	32 (80)		
Not at all or a little	61 (27.6)	8 (20)		
Overall satisfaction with sexual life, N (%)			0.612	1.08 (0.85-1.31)
Moderate or a lot	93 (37.1)	15 (31.9)		
Not at all or a little	158 (62.9)	32 (68.1)		
Level of distress if overall problems with sexual life persist, N (%)			0.881	1.04 (0.84-1.23)
Moderate or a lot	173 (71.5)	35 (74.5)		
Not at all or a little	69 (28.5)	12 (25.5)		

*N=Numbers, RR=Relative risk, 95 % Confidence interval (CI). *Patient-reported answers were dichotomized as follows: "No, not at all; Yes, a little" as indicating No, and "Yes, moderate; Yes, a lot" as indicating Yes. Note Internal dropouts' range: 23.48-24.9%.*

4:4 Genital pain and associations with physical aspects and well-being

Superficial genital pain was more common among rectal cancer survivors (27 %) than among women with other diagnoses, while deep genital pain was more common among cervical cancer survivors (41.8 % vs. 20.4% p=0.016) (Table 4). Deep genital pain was more prevalent among cervical cancer survivors (41.8 % vs. 20.4% p=0.016) (Table 4) compared to the other diagnoses. Superficial genital pain was more common among rectal cancer survivors (27%) than among women with other diagnoses.

Table 4. Bivariable analysis of possible predictors for genital pain during vaginal sex among women treated with pelvic radiotherapy

	Superficial genital pain*, N=205, (%)		P-value	Deep genital pain*, N=226, (%)		P-value
	Yes n=74 (36.6)	No n=128 (63.4)		Yes n=55 (28.6)	No n=137 (71.4)	
Diagnosis			0.122			0.016
Anal cancer	16 (21.6)	14 (10.9)		9 (16.4)	21 (15.3)	
Cervical cancer	18 (24.3)	34 (26.6)		23 (41.8)	28 (20.4)	
Endometrial cancer	17 (23)	46 (35.9)		9 (16.4)	47 (34.3)	
Rectal cancer	20 (27)	31 (24.2)		12 (21.8)	37 (27)	
Vulvar cancer	3 (4.1)	2 (1.6)		2 (3.6)	2 (1.5)	
Other	0 (0)	1 (0.8)		0 (0)	2 (1.5)	
Local estrogen use			0.101			0.071
Yes	28/74 (37.8)	33/128 (25.7)		37(38.6)	17 (61.4)	
No	46/74 (62.1)	95/128 (74.2)		35 (24.4)	102 (75.6)	
Vaginal shortness			0.031			<0.001
Yes	31/66 (47.7)	34/114 (29.8)		37/54 (68.5)	29/127 (22.8)	
No	34/66 (51.5)	80 /114(70.2)		17/54 (31.4)	103/124 (83)	
Vaginal inelasticity			<0.001			<0.001
Yes	45/66 (68.1)	22/118 (18.6)		36/54 (66.6)	26/129 (20.2)	
No	21/66 (31.8)	96/118 (81.3)		18/54 (33.3)	103/129 (79.9)	

N (number) and proportion (%) of women are presented and include only women who had practiced vaginal sex. P-values in bold print.

*Patient-reported answers were dichotomized as follows: "No, not at all; Yes, a little" as indicating No, and "Yes, moderate; Yes, a lot" as indicating Yes. Note Internal dropouts' range: 23.48-24.9%.

More than half of anal cancer survivors (21.6% vs. 10.9% p=0.122) compared to endometrial cancer (23% vs. 35.6% p=0.122) reported superficial genital pain. All women with vaginal inelasticity –

both with and without sexual abuse – reported both superficial genital pain (68.1 % vs. 31.8 %, p=0.001) and deep genital pain (66.6 % vs. 33.3 %, p=0.001). Similarly, a statistically significantly higher proportion of women with than without vaginal shortness reported both superficial (47.7% vs. 29.8%, p= 0.031) and deep (68.5% vs. 22.8%, p=0.001) genital pain compared to women not reporting vaginal shortness (Table 4). Overall, deep genital pain was significantly associated with women reporting depressed mood compared to women not reporting depressed mood (70.9% vs. 29.1% p=0.017) (Table 5).

Table 5. Bivariable analysis of genital pain and depressed mode

	Depressed mode* N=534 (%)		P-value
	Never N= (%)	Sometimes/Always N=(%)	
Superficial vulvar or genital pain**			0.834
Yes, n=74 (13.8)	27 (36.5)	47 (63.5)	
No, n=128 (23.9)	52 (40.6)	76 (59.4)	
Deep genital pain**			0.017
Yes n=55 (10.3)	16 (29.1)	39 (70.9)	
No, n=137 (25.7)	67 (48.9)	70 (51.1)	

N=numbers and proportion (%) of women are presented and includes only women who had practiced vaginal sex. P-values in bold print.

**Patient-reported answers were dichotomized as follows for aspects on genital pain: “No, not at all; Yes, a little” as indicating No, and “Yes, moderate; Yes, a lot” as indicating Yes Note. Internal dropout range 2.48%.*

**Patient-reported answers with a range 1-7 on the self-reported experience of depression were dichotomized as follows: 1-3= “Never,” 4-7 “Sometimes or always.” Note Internal dropout range 10.25-25 %.*

DISCUSSION

5:1 Methods – Limitations and Strengths

Even though the subgroup analysis consists of a small number of participants with a history of sexual abuse N=65 (10.9%), it portrays the relative proportion of women exposed to sexual abuse in the general European population (139). However, as the prevalence of sexual abuse varies due to underreporting (61-64), and self-reported disclosure of sexual abuse may vary between different countries, both factors limit the data collection's generalizability in this thesis.

Gender equality is a dominant factor in the disclosure of sexual abuse. The Gender Equality Index is a tool to measure the progress of gender equality developed by The European Institute for Gender Equality. It measures six core domains; work, money, knowledge, time, power, and health, together with two additional domains, violence against women and intersecting inequalities, to get a gender equality index score for each specific country.

In Sweden, regarded as one of the most gender-equal countries in Europe (gender equality index 83.8), the prevalence of physical and sexual violence is 46%. In Poland, the prevalence of physical and sexual violence is 19%, and gender equality index is one of the lowest in Europe, scoring 55.8; thus, societal norms play an essential role (139-140). Globally, women in low- middle income countries are more exposed to sexual violence, increasing due to the COVID- 19 pandemic (37). Sexual violence combined with the global burden of HIV– where the estimated death rate of HIV-related conditions is estimated to increase by 10 percent due to the pandemic - is higher in low-middle income countries, contributing to a significantly increased risk of cervical cancer (33, 113, 141).

Sexual and reproductive health resources are limited in many parts of the world, and there is a need for efficient screening interventions for both HR-HPV and HIV is for cancer preventative

work. In the context of limited prevention and treatment options of cancer, such as limited radiotherapy and cancer rehabilitation in low- middle income countries, this thesis's findings are primarily generalizable to high-income countries.

The internal dropouts in terms of "not relevant"-answers in the questionnaire may affect the results' consistency. We do not know why the participants did not respond. Both women with and without experience of sexual abuse might find the questions intrusive, and factors such as age, culture, and norms may be involved. Recall bias, both considering eventual exposure to childhood sexual abuse and symptoms from acute side effects when only a short time has passed since completed radiotherapy, may threaten internal validity. The self-reported questionnaire should benefit from questions concerning sexual health aspects, not focusing on vaginal sex. In the average population, spontaneous superficial genital pain during daily activities vulvodynia-, is the most common type of vulvar pain (142). The extent to which participants are affected by vulvodynia would be of interest for future studies since vulvodynia has shown more prevalence among victims of sexual abuse (143). As some patient are from a referred patient group and the other from a population-based cohort may influence the results further discussed under clinical implications.

All of the above limitations in the data collection for this thesis are relevant for the methodological development of future studies. The observational study design enabled an exploration of the total population-based cohort, enabling sub-group analysis performance. Self-reported data is a strength to gain a wide range of responses than other instruments (144). The clinmetric method with face-face validation used for this thesis and other research projects (8, 111, 118, 122, 137-138) provides high validity

5:2 Results

The results indicate that more women with than without experience of sexual abuse suffer from symptoms of sexual dysfunction such as superficial and deep genital pain during vaginal sex. Women with a history of sexual abuse reported lower quality of life and decreased well-being than women without such an experience. Women with a history of sexual abuse are to a higher extent affected by anxiety and depressive symptoms. The results confirm previous results by Bergmark et al. (24), which showed a statistically significant higher risk of genital pain during vaginal sex among cervical cancer survivors with a history of pelvic radiotherapy and sexual abuse compared to healthy controls with a history of sexual abuse.

Moreover, the sexual abuse group requested help for sexual dysfunctions, such as genital pain and vaginal shortness, to a greater extent, compared to women not reporting a history of sexual abuse. (Figure 3). The marginal higher frequency of vaginal sex could be a confounding factor in the results both for the higher distress reported for genital pain and, thus, the higher amount requesting help for these symptoms.

This thesis confirms that women with experience of sexual abuse at an average are at a younger age compared to women with no experience of sexual abuse, indicating a link between sexual abuse and the development of HPV-induced neoplasia cancer at an earlier age (15, 54-59, 66). In our study, the mean age for exposure for the first abuse was 13.6 years. Of these, almost one-third of the women reported exposure to repeated sexual abuse. HPV infection is common in young women with initial sexual relations (66-67), but other co-factors such as immunological aspects are necessary for developing neoplasia (78-83). It is estimated that half of the high-risk HPV infection that develops into cancer is acquired by age by the age of 21, 75 % by the age of 31, and more than 85 % by 40 (145). While invasive

cancer over many years, chronic infection and pre-cancer establishes within 5-10 years (67). HPV-induced progressive infection with the pre-cancer state can relate to a history of sexual abuse in some cases (16). There was no difference between the groups regarding smoking which is considered one of the risk factors for cervical neoplasia. We do not have any data on, for instance, drug use and other potential maladaptive coping strategy for PTSD symptoms among young women with experience of sexual abuse potentially linked with the development of cervical neoplasia through the stress theory model (86-89). The HPV-related diagnosis, which is anal and cervical cancer in our data, was higher in the sexual abuse group than the non-sexual abuse group, supporting the HR-HPV theory.

For all women in the study self-reported symptoms of vaginal shortness were associated with genital pain, previously reported by Hofsjö et al. (9), as caused by radiotherapy-induced fibrosis. The causes of genital pain have similarities between women both with and without a history of pelvic radiotherapy. The complex conditions of female and genital pain, vestibulodynia, vaginismus, vulvovaginitis, pelvic floor dysfunction, genitourinary syndrome of menopause, orgasm difficulties should be understood the context of female sexual response.

Previous research of sexuality notes that disruption at any point of the response cycle can contribute to and cause genital pain (146-147). To treat vaginal pain, estrogen use recommendations, dilator therapy, and relaxation treatment of pelvic floor muscles are similar irrespective of the origin of pain. Furthermore, it is crucial to have open communication in the relationship, plus educational interventions to understand the anatomy and physiology changes and support exploring sexual practices.

Although the well-being was lower in the sexual abuse group, all women's overall well-being

in the data collection was low. Decreased self-esteem after cancer treatment was reported by most women, like previous studies (148). We found that one-third of the women with experience of sexual abuse reported increased self-esteem, which may be explained by that positive feelings might follow surviving a life-threatening disease. Due to a previous study some patients seem to be capable of taking something positive from the cancer experience, increasing strength and confidence (149).

The findings indicate that sexual abuse may lead to impaired sexual health and well-being in female cancer survivors, which urges these women's supportive care. Healthcare professionals need continuing education to stress the importance of necessary resources and skills in consultation since the magnitude of sexual and general health is considerable. Poor intestinal and urinary tract health is another aspect that needs to be considered for radiotherapy-induced diseases since it may negatively affect sexual health and general health among female cancer survivors.

5:3 Clinical Implications

Victims of sexual abuse need easily accessible, immediate, straightforward short and long-term treatment for abuse and prevention measures to avoid increased cancer risk. Providing self-sampling HPV for individuals that may be at higher risk for cervical neoplasia due to recent or past experiences of sexual abuse and/or for individuals affected by HIV could be an intervention for prevention. Especially with implications in low-middle income countries as sexual violence estimates to increase while HPV and HIV preventative interventions are lacking due to the pandemic (141). Overall, there is limited data on cancer rehabilitation regarding sexual and general health in low-middle income countries.

The result also emphasizes the importance of identifying women with a history of sexual abuse in the general healthcare setting. In this material some women were referred from other health care providers. We do not investigated further if the reported history of sexual abuse was different between the referred patient group and the population-based cohort. For future studies this would be of importance as it may influence the outcome of the study as well as giving implication if the referred patient group eventually reported more severe symptoms of sexual dysfunction and general well-being compared to the population-based cohort group. As identification of sexual abuse can be made either by a questionnaire – as used in this study – or by clinicians duiring actively about exposure to sexual abuse. If a history of sexual abuse was more common in the referred patient group the clinical implication of identification of abuse emphasizes the importance of actively asking of a history of sexual abuse among all health- care providers.

This thesis and other studies suggest that screening for sexual abuse is important to offer treatment of sexual abuse, for an eventual police report, and to encourage individuals to participate in cervical cancer screening programs. Early detection and treatment of sexual

abuse can limit the individual and societal economic burden of sexual violence. However, strategies prevent sexual abuse are the most essential in the first place. Further, the importance lies in healthcare professionals to prevent retraumatization in the treatment procedures.

Impaired sexual and general health after pelvic radiotherapy – shown in this thesis – reflects some of the long-term consequences of sexual abuse. These underly the importance of developing individually targeted rehabilitation for oncology patients with a previous experience of sexual abuse. Multidisciplinary teamwork with physicians, nurses, sexologists, and trauma-therapists would improve supportive care and prevent retraumatization among affected women. Sexual health needs to be addressed as an aspect of general wellbeing to give appropriate support and treatment both in and outside the pelvic rehabilitation.

To fulfill the Istanbul convention, to give victims of sexual abuse rights to treatment, and bridge the gap of the current health care access for victims of sexual abuse, we suggest implementing routine screening methods for sexual violence in the oncology and healthcare settings overall. Thus, to optimize the sexual and general health conditions for victims of sexual abuse, the healthcare system has a responsibility to provide: 1) appropriate abuse treatment, 2) prevent an eventual HPV-related cancer, and 3) tailor individualized needs and support throughout cancer treatment and rehabilitation

CONCLUSION

Victims of sexual abuse suffer from life-long consequences. Previous exposure to sexual abuse is an additional factor besides pelvic radiotherapy, potentially increasing radiotherapy's negative effect on sexual health aspects and general wellbeing after cancer treatment. Women exposed to sexual abuse suffer from more symptoms of sexual dysfunction such as dyspareunia and vaginal inelasticity compared to women without such a history.

POPULAR SCIENTIFIC SUMMARY – SWEDISH

Kvinnor som varit utsatta för sexuellt våld rapporterar en betydande nedsatt sexuell hälsa och generellt välmående. Sexuella övergrepp kan öka risken för cancer; särskilt livmoderhals- samt anal-cancer som är associerade till hög-risktyperna av humana papillomvirus (HR- HPV). Tidigare studier rapporterar sämre välmående under och efter cancerbehandling hos individer som tidigare varit utsatta för sexuella övergrepp jämfört med kvinnor som inte varit utsatta. Det finns begränsad forskning om hur den sexuella hälsan påverkas hos kvinnor som tidigare varit utsatta för sexuella övergrepp och som genomgått strålbehandling mot bäckenet för gynekologisk-, anal- och rektal-cancer. En tidigare studie har hittat en signifikant synergistisk effekt mellan sexuella övergrepp och livmoderhalscancer för yttlig genital smärta under vaginala samlag.

Syftet med denna populationsbaserade kohortstudie var att 1) undersöka sexuell hälsa och välbefinnande hos kvinnor som strålbehandlats mot bäckenet och, 2) fastställa till vilken grad tidigare utsatthet för sexuella övergrepp påverkar sexuell hälsa och välbefinnande efter strålbehandling mot bäckenet.

Mellan 2011–2017 rekryterades studiedeltagare från två grupper; 1) en populationsbaserad kohortstudie som inkluderar alla kvinnor som genomgått strålbehandling mot bäckenet mellan 2007–2016 på Sahlgrenska Universitets Sjukhus; samt 2) en patientgrupp som behandlats med strålbehandling mot bäckenet som remitterats till Bäckencancerrehabiliteringen via andra vårdinstanser i Västra Götalands regionen.

Studiedeltagare fyllde i ett formulär med frågor rörande aspekter på sexuell hälsa, sexuella övergrepp samt generellt välmående. Studiepopulationen delades in i två grupper; en med och en utan tidigare erfarenhet av mild/måttlig/svår grad av sexuella övergrepp eller kränkning samt upprepade övergrepp och/eller incest. Aspekter rörande sociodemografisk, typ av cancerdiagnos, sexuell hälsa,

välstånd hos de kvinnor som utsatts för sexuella övergrepp jämfördes med de som rapporterade icke sexuell utsatt. Resultaten rapporterades deskriptivt i form av medelvärde, median och relativa risker. Signifikans nivån sattes på $p < 0.05$.

Av 570 kvinnor rapporterade 62 (11%) tidigare erfarenhet av sexuella övergrepp eller kränkning. Fler kvinnor som varit utsatta för sexuella övergrepp rapporterade depressiva symptom (19% vs. 9%, $p=0.007$), led av ångest (23% vs. 12%, $p=0.007$) och hade vaginalsmärta under sexuell aktivitet jämfört med de kvinnor som inte rapporterade tidigare erfarenhet av sexuella övergrepp. Vaginal smärta under sexuell aktivitet var statistiskt signifikant associerat med vaginal förkortning (68 % vs. 31 % $p < 0.001$) samt vaginal oelasticitet (67 % vs. 33 %, $p < 0.001$). 73% av alla deltagande kvinnor i kohorten rapporterade majoriteten att de skulle vara mycket berörda om problem med den sexuella hälsan skulle kvarstå.

Sexuella övergrepp har en avgörande betydelse för den sexuella hälsan såväl som andra aspekter på välbefinnande hos kvinnliga canceröverlevare som genomgått strålbehandling mot bäckenet. Det behövs rutiner och tydliga riktlinjer för att fråga om sexuellt våld inom onkologin. Detta före, under och efter cancerbehandling för att identifiera kvinnor som är eller har varit utsatta för sexuella övergrepp. Detta för att utveckla individanpassade åtgärder för att motverka ytterligare eventuell traumatisering och tillhandahålla rätt form av stöd och interventioner inom cancerrehabilitering samt vidare innan och under cancer behandling.

FIGURES

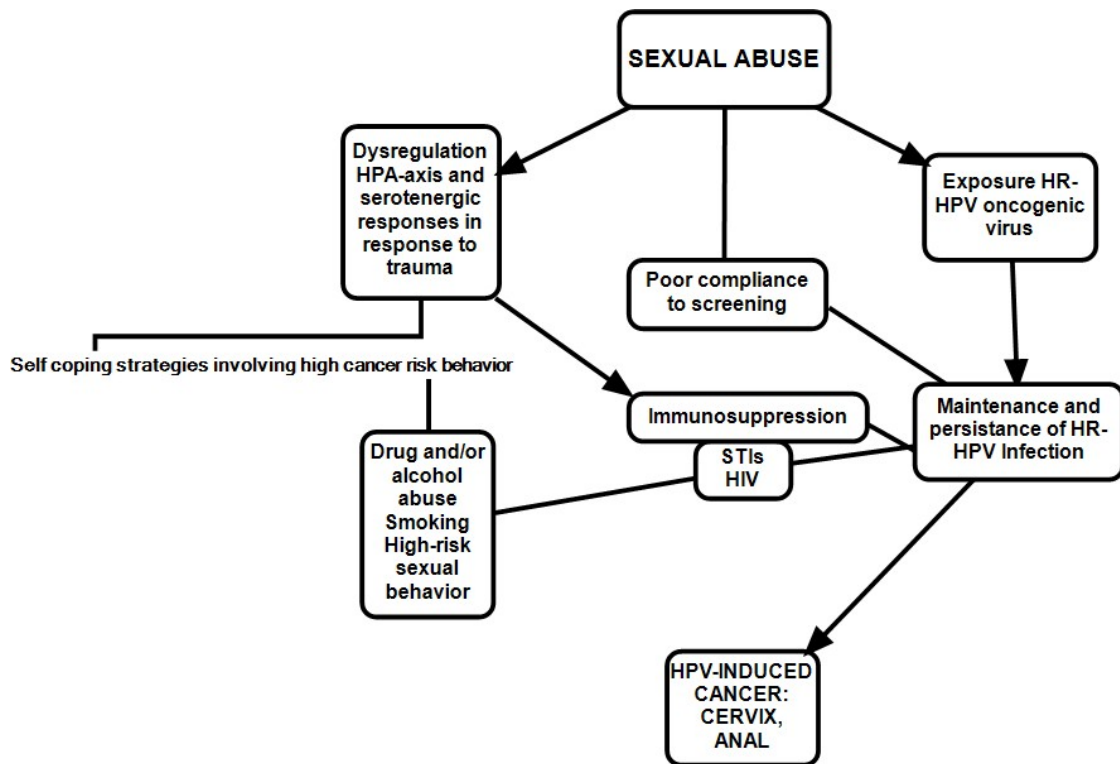


Figure 1. Flow chart of a potential model highlighting the direct and indirect mechanisms of sexual abuse leading to high-risk human papilloma virus (HR-HPV) associated cancers

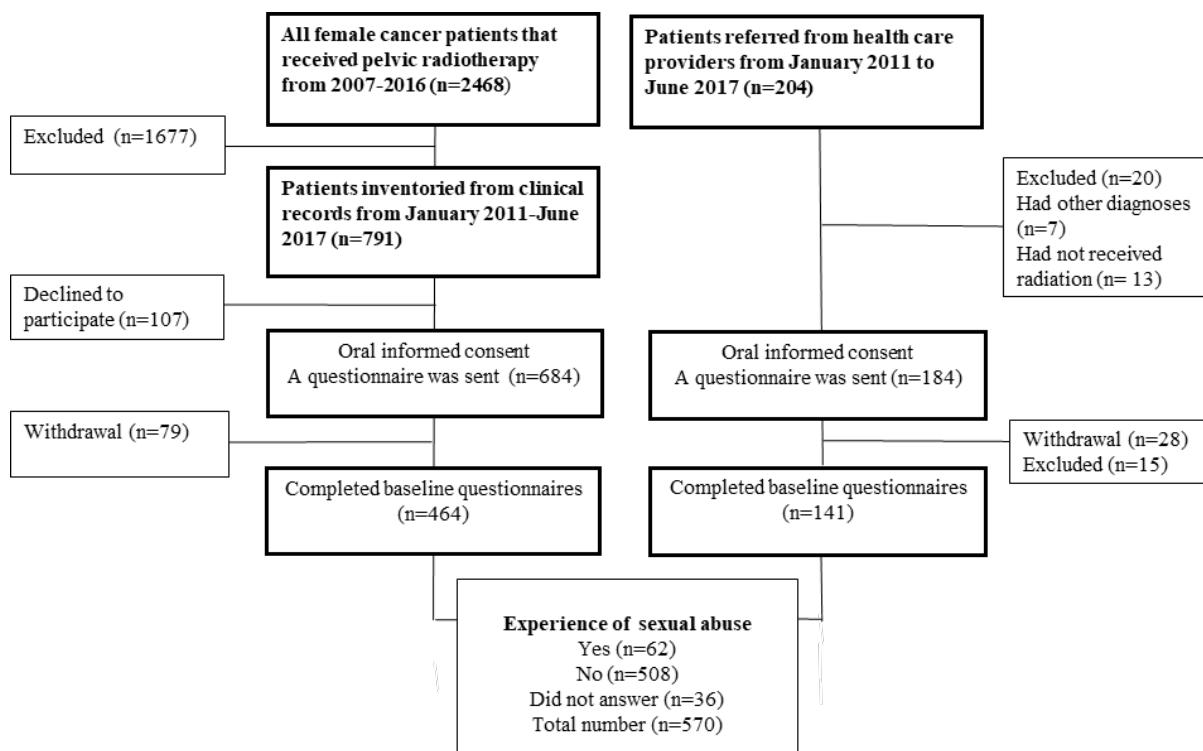


Figure 2. Data-collection diagram including study response rate, reasons for loss of participation, the number of completed baseline questionnaires, and study participants reporting experience of sexual abuse previously

Figure 2 is retrieved from publication 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 May 18.

APPENDICES

	External dimension (within the healthcare system)	Internal dimension (within the patient)
Competence related gatekeeper	<ul style="list-style-type: none"> • Insufficient knowledge of prevalence • Insufficient knowledge of health consequences • Insufficient knowledge of disclosure processes • Insufficient recognition of the importance of compassion and empowerment 	<ul style="list-style-type: none"> • Insufficient knowledge and understanding of the symptoms and difficulties experienced
Emotional related gatekeeper	<ul style="list-style-type: none"> • Insufficient emotional preparedness to receive narratives of disclosure • Insufficient emotional preparedness to accept SA as a plausible origin of the symptoms presented. • Insufficient emotional preparedness to confirm and communicate SA as a plausible origin of the symptom, to the patient 	<ul style="list-style-type: none"> • Feelings and emotional preparedness to disclose: <ul style="list-style-type: none"> - High levels of feelings of shame, disgust or guilt - Fear of not being believed by healthcare professionals - Fear not to receive adequate help
Organizational related gatekeeper	<ul style="list-style-type: none"> • Healthcare systems being organized according to symptoms rather than to etiology • Healthcare systems organized according to treatment methods, not recognizing the importance of compassion and empowerment 	<ul style="list-style-type: none"> • Altered brain functions and abilities due to trauma <ul style="list-style-type: none"> - Alexithymia - Dissociative amnesia - Levels of hyperarousal inhibiting organized verbal narrative - Dissociative Identity Disorder

Appendix 1. *A possible model for gatekeeping mechanisms. The model is applicable for healthcare systems and professionals (external dimension) and healthcare-seeking SA (internal dimension) victims. The text in the boxes are examples of factors that may work as gatekeeping mechanisms to healthcare access for victims of SA.*

SA Sexual abuse*

The appendix is from Figure 1 retrieved from Rajan, Gita et al. "Delayed healthcare access among victims of sexual abuse, understood through internal and external gatekeeping mechanisms." *Nordic Journal of Psychiatry* (2021): 1-8.

APPENDICES

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