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Cohort profile: An observational longitudinal study examining health in a cohort of female cancer survivors with a history of pelvic radiotherapy, a population-based cohort in the Western Region of Sweden

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BMJ Cohort profile

Cohort profile: An observational longitudinal study examining health in a cohort of female cancer survivors with a history of pelvic radiotherapy, a population-based cohort in the Western Region of Sweden

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BMJ Cohort profile

ABSTRACT

Purpose: In response to the need for more advanced and longitudinal data concerning long-term radiotherapy-induced late effects and states among female cancer survivors, the study “Health among women after pelvic radiotherapy”, was established.

Participants: Since 2011 and ongoing, participants are recruited from a population-based study-cohort including all female cancer patients over 18 years old, treated with pelvic radiotherapy with curative intent at Sahlgrenska University Hospital in Gothenburg, Sweden in the Western Region, covering 1.7 million of the Swedish population. The dataset here accounted for baseline data provided by 605 female cancer survivors and three-month follow-up data from 260 individuals with gynecological-, rectal- and anal cancer collected during a six-year period.

Findings to date: The data collected include self-reports of demographics, physical symptoms, and cancer-treatment details. The cohort is currently used for research projects in radiation-induced intestinal syndromes and late adverse effects affecting sexuality, urinary tract, lymphatic system, and physical activity. These projects include evaluation of interventions developed and provided in a nurse-led clinic. A recently published study report cancer survivors need support for additional rehabilitation when having fecal- and urinary-incontinence to increase physical activity levels.

Future plans: This cohort will be expanded to comprise the entire data collection from 2011-2020, including baseline data, data from the three months-, and the one-year follow-up data after interventions. The data will be used to study conditions and treatment-induced late-effects pre-, and post-interventions. The data collection and the cancer rehabilitation-model outlined in this paper have potential to contribute to the future development of treatment for radiotherapy-induced late effects among pelvic cancer survivors.

Keywords: *Female cancer survivors, Treatment-induced late-effects, Pelvic radiotherapy, Cancer rehabilitation, Nurse-led clinic*

Strengths and limitations

- The large dataset consists of a population-based cohort, which creates good conditions for studying cancer survivors without selection-induced problems.
- Results of this study will provide new information on a wide range of treatment-induced cancer survivorship diseases and states. The interventions outlined in this paper have the potential to contribute to understand manifestations of treatment-induced cancer survivorship diseases and states, and to the future development of evidence-based management strategies in pelvic cancer rehabilitation.
- Non-participation and loss to follow-up may affect the results.
- There is no information from study-participants’ reasons for drop-off.
- Our cohort includes data collected in Sweden, which may limit the generalizability to other populations.

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41 Introduction

42 An increasing number of individuals live longer after a cancer diagnosis than was common in the past, and more
43 and more patients are now living with treatment-induced late-effects, treatment-induced cancer survivorship
44 diseases, and survivorship states [1-3]. Pelvic radiotherapy affects the intestinal and urinary tract, the lymphatic
45 system, and sexual health [4-6]. In this video at [https://www.jostrust.org.uk/video/letstalk-pelvic-radiation-](https://www.jostrust.org.uk/video/letstalk-pelvic-radiation-disease-after-cervical-cancer)
46 [disease-after-cervical-cancer](https://www.jostrust.org.uk/video/letstalk-pelvic-radiation-disease-after-cervical-cancer), some of more than 20 million cancer survivors in Europe express how radiation-
47 induced impaired intestinal health affects them as cancer survivors. In Sweden, approximately 3500 women are
48 diagnosed with pelvic cancer (gynecological-, anal-, and rectal cancer) every year [7]. In 2011, we started a
49 nurse-led clinic focusing on treatment-induced late effects among pelvic cancer survivors with the intent to
50 develop self-care strategies and treatments. We have previously reported on the benefits of the clinic regarding
51 the resulting improved quality of life and psychosocial wellbeing among female pelvic-cancer survivors [8].

52 In this paper, we describe a study cohort in a continuous data collection procedure, and interventions performed
53 at a nurse-led clinic that have been ongoing since 2011. We collect data from female cancer survivors with a
54 history of pelvic radiotherapy in western Sweden, an area that includes 20 percent of the Swedish population.
55 The Swedish register-tradition offers good conditions for studying cancer survivors without selection-induced
56 problems. The dataset contains information on needs pre-intervention and post-intervention from women that
57 have received pelvic radiotherapy at Sahlgrenska University Hospital 2007-2016. Female cancer survivors
58 referred to the nurse-led clinic are also invited to participate in the study. This paper outlines the systematic
59 data-collection and the characteristics of the study participants, data and information that can be employed in
60 future analyses to then be reported.

61

62 Cohort description*63 Setting*

64 In 2009 the Swedish government proposed a new regulation: "A National Cancer Strategy" (SOU2009:1) [9]. In
65 collaboration with county councils and regions, six Regional Cancer Centers (RCC) were established. Based on
66 the national strategy proposals, the RCC in western Sweden finances a nurse-led clinic at Sahlgrenska
67 University Hospital. The nurse-led clinic was founded in 2011 by a physician senior consultant with a PhD
68 degree who has specialized in gynecological oncology, together with an oncology nurse with a PhD degree in

BMJ Cohort profile

oncology. Currently, the team consists of three clinical oncology nurses specially trained in understanding and working on issues concerning cancer survivorship. The cancer survivors receive education about radiotherapy-induced late-effects, basic anatomy and physiology and together with the nurse decide on actions for supportive care regarding medication, nutrition, and coping with sexual, psychological and social challenges. In case of specific needs, intercurrent diseases or suspected recurrence of cancer, the patient meets the medical senior consultant who has the primary medical responsibility for the clinic. The medical senior consultant meets the team regularly and discusses planning for medication with the staff member who will issue the prescriptions. The health-care program developed in the clinic is based on programs developed by others and on our previous studies in the area [4,10-16].

Participants

Study participants are recruited from two different cohorts; 1) a population-based study-cohort group including all female cancer patients treated with curative intent from 2007 and onwards continuously identified from medical records at Sahlgrenska University Hospital in Sweden and, 2) a referred patient group including all female patients referred to the rehabilitation clinic. Inclusion criteria are female cancer survivors with a history of pelvic radiotherapy, at least six months since completed radiotherapy. Exclusion criteria are: Recurrence of cancer, and women physically and cognitively unable to understand and answer the questionnaire or who do not understand Swedish at all.

Invited women

An introductory letter is sent to eligible study participants. Shortly after, a research secretary phones and gives them oral information, asks them if they are willing to participate in the study and to give permission to be sent a written informed consent and the questionnaire. When the baseline questionnaire is returned, the participant receives an invitation to come to the nurse-led clinic where individual healthcare interventions are performed. The code number from the questionnaire (followed throughout the data collection) is entered into the patient-database FileMaker Pro17 Advanced®, specifically designed to suit the study. Three and twelve months after the completed intervention, the study participant receives a follow-up questionnaire. In case questionnaires are delayed or missing, the research secretary who keeps track of each patient sends two reminders at time-points determined in advance, see figure 1.

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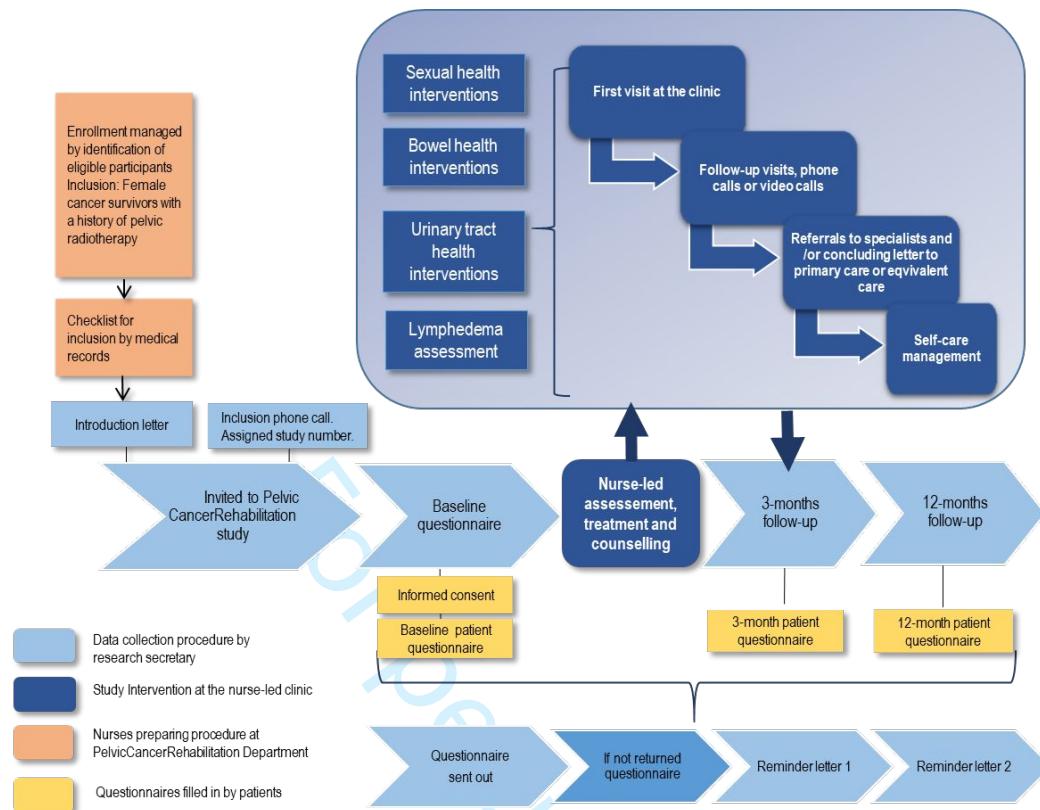


Figure 1. Flowchart of Pelvic cancer rehabilitation ongoing data collection procedure and the procedure for patient inclusion, contact with participants and the follow up points for questionnaires.

Referred patients

Patients referred from oncology health care providers, general practitioners and private referrals that meet inclusion criteria, are also invited to participate in the study. The data collection procedure followed the same principles as followed for the group of invited women.

Study-specific questionnaires

As shown in table 1, the baseline questionnaire consists of 175 questions, divided into eight main sections and one concluding chapter. Information about the frequency, intensity, duration, and quality of each symptom and the degree of the distress it causes is obtained. One question is cited here as an example: "How many times (approximately) have you had bowel movements per week, during the last six months?" with possible answers "About every other day", "Fewer than once a day", "Once a day", "Up to twice a day", "2-3 times per day", "3-4 times per day", "5 times or more, per day". To facilitate statistical analyses, the answers are coded into values, ranked and placed into groups. Variables such as age and number of children are categorized into groups.

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111 Table 1. The study-specific baseline questionnaire, divided into eight sections and one concluding section

Section	Question areas
Sociodemographic	Gender Age Marital status Children Level of education Employment status
Quality of life and wellbeing	Quality of life Depression Worrying Anxiety
Body-perception and self-image	Femininity Self-esteem Fertility Childbirth Vaginal and perianal injury related to childbirth or physical trauma
Intestinal and defecation habits	Loose stool Fecal incontinence Urgency to defecation Excessive gas Abdominal pain Having stoma Medical treatments related to intestinal symptoms
Micturition habits and urinary-tract symptoms	Urinary frequency Urgency to urinate Nocturia Having a urine catheter Medical treatment due to symptoms
Sexual health	Menopause Use of systemic hormone replacement therapy Use of topical estrogen Impaired lubrication Vaginal shortness Vaginal inelasticity Dyspareunia
Sexual abuse	Experienced sexual abuse Experience sexual harassment Age at sexual abuse or harassment To which extend the exposure affects sexual life
Lymphedema	Heaviness in legs, genitals and abdomen If diagnosed with lymphedema, current lymphedema treatment
Concluding chapter	Self-reported needs An offer to visit the nurse-led clinic for assessment and counselling

112 Several sections allow free comments

113 Additionally, the questionnaire addresses the extent to which the symptoms affect social functioning. In the
114 concluding section, participants are invited to visit the nurse-led clinic. Some questions serve to rank the
115 patients' most distressing symptoms. In the follow-up questionnaires the study-participants' health-status and
116 symptoms are measured, and interventions performed at the nurse-led clinic are evaluated.

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118 *Diagnostic and alleviative means*

119 At the first visit to the clinic, the questionnaire serves as a foundation for the interventions. The patient's current
120 health status reveals the needs that are in focus. Current symptoms and self-care strategies are discussed, and
121 new strategies suggested and decided on together with the patient. The duration of the contact and the number of
122 follow-ups varies from one month to one year, depending on the symptoms and the effect of treatments and
123 interventions. Cerna et al (17) observed in a study with an educational perspective that patients and nurses in
124 current settings can together create tailor-made solutions. The nurses focus on encouraging the patients' self-
125 reflection and keep up the patient's motivation to continue to engage in self-care.

126 *Intestinal health*

127 The assessment is based on five syndromes: urgency to defecate, fecal leakage, excessive gas production,
128 excessive mucus discharge and blood discharge [17]. Symptoms such as leakage of mucus and blood, abdominal
129 bloating, signs of bacterial overgrowth and bile-salt malabsorption are also assessed. Diagnostic means
130 including blood test, for example, routine blood screening, electrolytes, Vitamin B12 and serum Mg2 are taken
131 when indicated. An algorithm developed by the research group serves as a guide in the clinical setting [8]. A
132 mobile application has been developed that was specially designed for radiation-induced intestinal syndromes
133 and can show graphs of variation in intestinal health over time. The application serves as a complement to
134 existing methods for self-assessment and patients' self-management and helps to support the nurse- and
135 patient's conversation and decision-making [18,19]. The objective of the interventions is to restore or improve
136 intestinal health and includes medical treatment, pelvic-floor muscle training and techniques of cognitive
137 training to control the intestinal function. Details of these interventions can be accessed elsewhere [8,20].

138 *Sexual health*

139 The PLISSIT-model (Permission, Limited Information, Specific Suggestions, and Intensive Therapy) developed
140 by Annon [21] is used for addressing sexual-health concerns. The first three levels in the model are helpful for
141 most patients. When specific suggestions are not sufficient, the patient is recommended to take part in Intensive
142 Therapy, sometimes given in the current setting, at other times with a person named in a referral to a sexologist
143 or psychotherapist. Female sexual dysfunction is a complex condition including diverse aspects, definitions, and
144 classifications [22]. To assess and treat sexual dysfunction, previous sexual practices and experiences are
145 discussed with attention given to patients' integrity, special needs, and preferences. Structural information about
146 common physical late effects regarding vaginal changes and sexual problems is provided, as well as information

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on psychological issues influencing sexual health, in accordance with evidence-based knowledge and practice in the field [4,13,23-25,1]. Patients receive information about and instructions on use of vaginal dilator therapy and topical estrogen, and they are also given guidance and suggestions regarding a lack of desire. When requested, specific sexual devices, films, and literature are suggested to encourage and help the patient to regain sexual function as well as to regain body, self-esteem, and intimacy.

Sexual abuse

Cancer patients with a history of sexual abuse have an increased risk of sexual problems after cancer treatment and a large proportion of women with cervical cancer and dyspareunia post-cancer-treatment have been sexually abused [26]. In reported cases, experiences of sexual abuse are carefully discussed with the patient and in some cases, this leads to referral to psychologists or therapists.

Urinary-tract health

Symptoms of urgency, nocturia, urinary retention, urinary-tract infection, and pelvic pain are addressed. Diagnostic means includes evaluation of urinary frequency and of symptoms divided into irritative symptoms, obstructive symptoms, and bleeding. A 72-hour voiding diary including urine volume and fluid intake is a helpful resource for this discussion. Consulting and guidance are given by making recommendations about topical estrogen, pelvic floor muscle training, medical treatment, self-care modifications and behavioral interventions, in accordance with previous evidence-based knowledge [27,28]. In case of severe urinary-tract symptoms, referrals are sent to urotherapists, physiotherapists or urologists.

Lymphedema

Lower limb lymphedema is a common non-curable chronic complication with multi-factorial pathophysiology [29]. Early detection and treatment of lymphedema is essential in order to prevent complications. Self-reported or objectively assessed swelling or heaviness in the lower limbs leads to referral to a lymph-therapist. The primary therapy is the use of individually tailored compression garments and second-line therapy consists of manual lymphatic drainage with for example intermittent use of pumps and other self-care strategies [30,31].

Statistical analyses

Initially, data from the questionnaires were entered into EpiDataSoftware® version 3.1 (EpiData Association). Since only one answer is allowed for each question, the procedure was to enter the first choice every other time and the second choice the other time in case a question was marked with two answers. In order to make analysis

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of open-ended questions possible, the answers to these were transcribed in Microsoft Word (2016). R version 3.5.2. was used for statistical analysis of the data. The results will be reported in means, medians, and percentages.

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the regional ethics review board in Gothenburg (D 686-10) and with the 1964 Helsinki declaration and its later amendments. The research was approved by the Regional Ethics Review Board in Gothenburg (D 686-10), Gothenburg University. Written informed consent was obtained from all individual participants included in the study.

Findings to date

From January 2011 to June 2017, we identified a total of 791 patients in the population-based cohort that met the eligibility criteria. Of the total sample, 684 (86%) individuals gave oral consent to participate in the study and of these 464 (68%) completed the baseline questionnaire.

During the same period, 184 referred patients met the inclusion criteria and were invited to participate in the study. One-hundred-and-forty-one (76.6%) participants completed the baseline questionnaire and of these 131 (92 %) participants took part in interventions.

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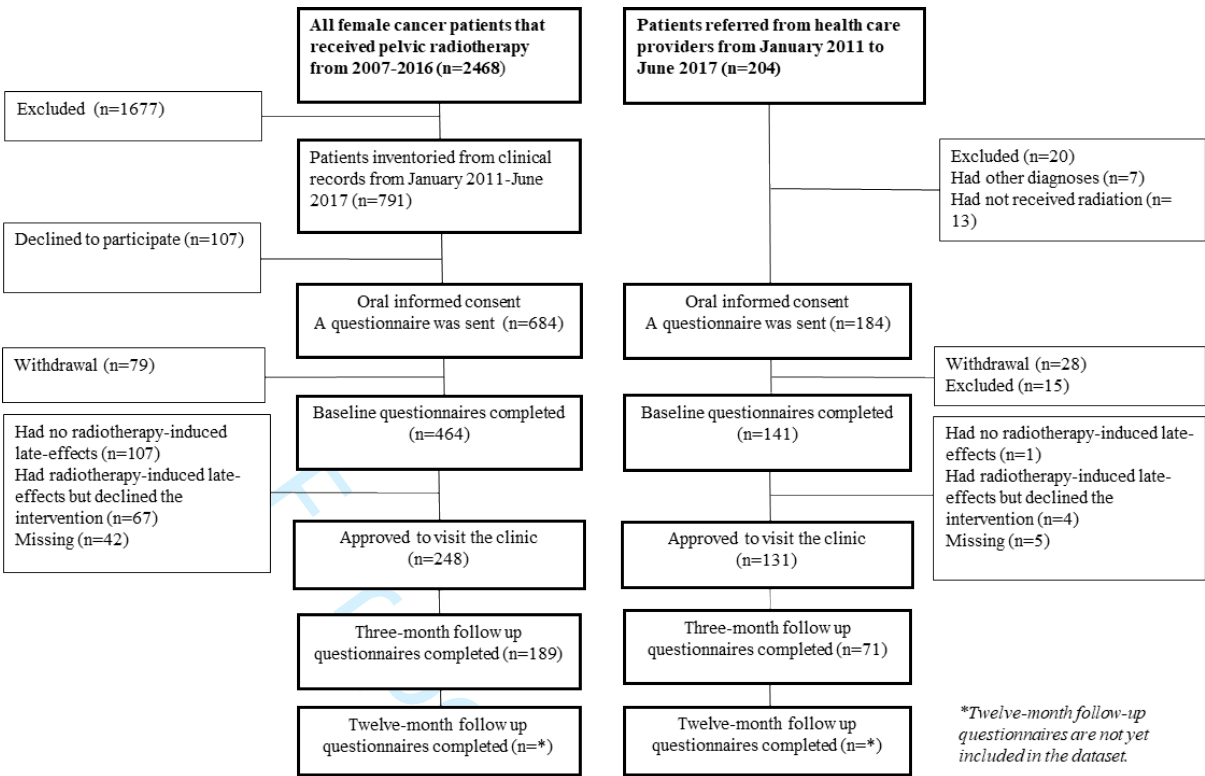


Figure 2. Schematic diagram of data collected from two different study-cohorts from January 2011 to June 2017; a population-based cohort and patients referred from oncology health care providers, general practitioners and private referrals that met the inclusion criteria. The diagram includes study response rate, completeness of questionnaires and reasons for loss of participants.

The responses and completeness of the questionnaires from both study groups are shown in the schematic diagram, see figure 2. In table 2, we present the baseline characteristics and demographics in the dataset that consists of 605 participants: 464 (76.7 %) from the invited cohort and 161 (23.3 %) from the referred cohort.

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Table 2. Characteristics of the study participants

Variable	Total	Invited	Referral
Participants, n (%)	605	464 (76.7)	141 (23.3)
Cancer type, n (%)			
Endometrial cancer	216 (35.7)	181 (39.0)	35 (24.8)
Cervical cancer	132 (21.8)	80 (17.2)	52 (36.9)
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)
Anal cancer	80 (13.2)	58 (12.5)	22 (15.6)
Rectal cancer	145 (24.0)	122 (26.3)	23 (16.3)
Other	4 (0.7)		4 (2.8)
Age in years			
Mean	64.5	66.5	57.6
SD	12.6	11.5	13.6
Missing, (%)	11	7 (1.5)	4 (2.8)
Years since radiotherapy, grouped			
0	35 (5.8)	6 (1.3)	29 (20.6)
1	219 (36.1)	166 (35.8)	53 (37.6)
2	98 (16.1)	86 (18.5)	12 (8.5)
3	139 (23.0)	131 (28.2)	8 (5.7)
≥4	105 (17.3)	69 (14.9)	36 (25.5)
Missing	9 (1.5)	6 (1.3)	3 (2.1)
Mean	2.6	2.2	3.9
SD	3.4	1.2	6.7
Cancer treatment, n (%)			
External radiotherapy, only	145 (24.0)	101 (21.8)	44 (31.2)
External radiotherapy and brachytherapy	20 (3.3)	16 (3.4)	4 (2.8)
External radiotherapy, brachytherapy and surgery	180 (29.7)	157 (33.8)	23 (16.3)
External radiotherapy and surgery	260 (43.0)	190 (40.9)	70 (49.6)
Marital status, n (%)			
Married or living with a partner	402 (66.4)	309 (66.6)	93 (66.0)
Widow	70 (11.6)	59 (12.7)	11 (7.8)
Has a partner but lives alone	30 (5.0)	15 (3.2)	15 (10.6)
Single	102 (17.0)	80 (17.2)	22 (15.6)
Missing	1 (0.2)	1 (0.2)	
Education level, n (%)			
Elementary school	173 (29.1)	150 (32.3)	23 (16.3)
Secondary school	227 (38.2)	169 (36.4)	58 (41.1)
Collage/University	194 (32.0)	135 (28.9)	59 (41.8)
Missing	11 (1.8)	10 (2.2)	1 (0.7)
Employment status, n (%)			
Student	4 (0.7)	3 (0.6)	1 (0.7)
Unemployed job seeker	12 (2.0)	10 (2.2)	2 (1.4)
Employed	162 (27.0)	116 (25.0)	46 (32.6)
Housewife	4 (0.7)	2 (0.2)	2 (1.4)
On sick leave	54 (9.0)	17 (3.7)	37 (26.2)
Disability pension	35 (5.7)	26 (5.6)	9 (6.4)
Retired	328 (54.7)	284 (61.2)	44 (31.2)
Missing	6 (1.0)	6 (1.3)	
Resident, n (%)			
In a big city	182 (30.6)	131 (28.2)	51 (36.2)
Small or medium sized city	309 (50.2)	244 (52.6)	61 (43.3)
On the countryside	116 (18.9)	87 (18.8)	29 (20.6)
Missing	2 (0.3)	2 (0.4)	
Smoking, n (%)			
Not smoking	448 (74.0)	339 (73.1)	109 (77.3)
Smoking	67 (11.0)	52 (11.2)	17 (12.1)
Missing	88 (14.5)	73 (15.7)	15 (10.6)

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

BMJ Cohort profile

The majority of the study participants had a history of gynecological cancer and had been treated with radiotherapy in combination with surgery. In the population-based study-cohort, the mean age was higher and twice as many were retired compared to the referred group. In the referred group, twice as many were on sick leave. In total, 379 (63 %) of 605 study participants were approved to visit the clinic, see table 3. Sixty-seven (14.4 %) of the women in the population-based study-group that declined to visit the clinic report that they had radiotherapy-induced late-effects.

Table 3. Number (N) and proportion (%) of study-participants that approved to visit the clinic

	Total N (%)	Invited N (%)	Referred N (%)
No, I have no late effects and do not need to visit the clinic	108 (17.8)	107 (23.1)	1 (0.7)
No, I have late effects, but I do not want to visit the clinic	71 (11.7)	67 (14.4)	4 (2.8)
Yes, I want to visit the clinic	379 (62.6)	248 (53.4)	131 (92.9)
Missing	47 (7.8)	42 (9.1)	5 (3.5)

Strengths and limitations

The data collection has generated a large dataset consisting of patient entries from six months to several years post pelvic radiotherapy treatment. Over a period of six and a half years, almost 1000 female pelvic cancer survivors were invited to participate in the study, and this dataset consists of 605 cancer survivors. In the population-based cohort-group, 68 % completed a baseline questionnaire. Treatment and interventions were offered from physical, psychosocial and sexual perspective to patients from both the population-based cohort and the referred cohort and were evaluated. As shown in table 3, 53.4 % of study participants in the study population cohort were approved to visit the clinic, which may indicate the proportion of cancer survivors' unmet needs. At present, improved self-care strategies, increased clinical knowledge, and development of technology enable the possibilities for helping cancer-survivors manage and treat late effects. By manifesting treatment-induced cancer survivorship diseases and states, we believe that it may be more likely that effective treatments can be developed.

Cancer survivorship issues have advanced from being neglected to gradually being given increasingly greater attention in healthcare practice as well as in research. That is reflected by the development of national

BMJ Cohort profile

guidelines, scientific conferences and national and international meetings in the area. Efforts are made to both understand the manifestation of treatment-induced late effects, as well as to find strategies to deal with late effects in pelvic cancer survivors. Twenty years have passed since researchers within our team [4] first observed that gynecological cancer patients suffer from vaginal changes affecting their sexual health. More recently, we have identified five syndromes impairing pelvic cancer survivors' intestinal health. The results published in 2017 [17] simplify the search for prevention, management, and for help in minimizing the occurrence and intensity of survivorship diseases. One promising ongoing study conducted by Schofield et al in Australia, evaluates a care program similar to ours [32,33]. Furthermore, in 2015 Andreyev et al [11] published a guide for management of intestinal problems, including an algorithm that in our opinion is a useful tool for clinicians to use. However, the pathophysiological changes, described in numerous previous studies are not yet fully understood [15-17]. Inflammatory and fibrotic processes in the gut wall are probably of importance in explaining the varying symptoms. The processes may relate to both the intestinal tract and other organs located in the pelvis. Hofsjö et al in our research group [34], recently studied vaginal changes and found morphological explanations for changes in the vaginal wall. Biopsies from the vaginal connective tissue affected by radiotherapy showed dense collagen and entangled elastin fibers, a finding that may explain common symptoms such as reduced vaginal elasticity during intercourse, reduced lubrication and dyspareunia.

In Sweden, promising steps are being taken towards developing a program of national coordination of cancer rehabilitation practice. The ongoing establishment of oncology nurse navigators [35] is also an initiative that has the potential to increase the supportive care to cancer survivors. In the 1980s, research in the psychological field [36] showed that patients have a high risk of anxiety related to oncology treatment. Recent studies report that patients have a lower risk of future anxiety and depression when addressing needs during treatment [37,38]. In our opinion, when planning future follow-up in clinical cancer care, these findings need to be taken into account, irrespective of the patients' cancer diagnosis. We suggest that healthcare in the future should provide advanced specialist expertise to handle severe treatment-induced late-effects.

Sexual concerns are generally not addressed or discussed as much as the patients would like [39], and patients generally wait for healthcare providers to bring up the topic [40]. In the current setting, sexual health conversations are integrated in clinical work, routines for assessment and treatment are created, and it becomes

BMJ Cohort profile

clearer when a patient should be referred to specialists and sexologists. The PLISSIT-model [21] has been used for addressing sexual health concerns in our as well as in other different clinical settings. Clinical experiences show that sexual functioning might improve and even return to pre-diagnosis level through frequent follow-up, observations that are consistent with results from previous studies [41]. Considering parts of WHO's definition; "sexual health requires a positive and respectful approach to sexuality and sexual relationships" [42], health care providers need to be able to talk openly about sexuality. To overcome common communication barriers, it has been suggested that health-care professionals should actively engage in training to improve their communication skills [43,44]. Our clinical experience reveals that several patients were relieved to be able to speak openly about sexual issues as well as about other private health issues. The baseline questionnaire seems to serve as a therapeutic tool that can be followed up in counseling.

268

In this study, we found it necessary for ethical reasons to offer all patients in the population the best available intervention. Hence, the observational study design was considered to be the best suited, a design previously shown to produce reasonably useful results [45]. We use self-reported data that are known to provide a wider range of responses than data collected using other data collection instruments [46]. To avoid information-related problems, we took preventive actions in advance by using questionnaires based on the clinometric method introduced, developed, used and described by us in previous research projects [4,6,47,5]. Furthermore, we employed epidemiological methods, as introduced into the survivor-field by a hierarchical step-model, to handle bias and confounding [48]. We consider that the wide range of time since completed treatment may be a weakness in the study but will probably also facilitate measurement of symptom progression in future analysis. The minor changes in the interventions made during the study carried out due to increased knowledge need to be considered in the analysis. Furthermore, the non-participation and loss to follow-up may affect the results. We can only speculate on the causes but possible reasons for the drop-offs may be lack of time, not being motivated or being unwilling to recall the experience of previously had cancer. Possible reasons for declining an offer to visit the clinic despite troublesome symptoms could be having too severe symptoms to travel to the clinic. Age-related problems and long-distance transportation can be other causes. The large number of population-based study participants is considered to be one of the strengths in this study since this creates good conditions for studying cancer survivors without selection-induced problems. The data collected from the referred patients will allow analysis of the prevalence of symptoms and unmet needs observed by other health-care providers. Since

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the data were collected in Sweden, we do not know to what extent our future analysis will be applicable to other populations.

Our and others' understanding of the complexity and pathophysiological mechanisms of symptoms and late effects has increased during the study. Through recurrent lectures for patients and professionals, and by implementation of treatment strategies directly to patients, we return the acquired knowledge to the clinic and to the cancer survivors themselves. Worth mentioning is that current rehabilitation clinic serves as a model for similar clinics in other regions of Sweden, which is part of the national strategy financed by the Swedish government. The current nurse-led clinic is possibly the beginning of a future tertiary center to develop interventions and treatments to cancer survivors.

We believe that the data collection outlined in this paper and the interventions that continually evaluates will contribute to understand manifestations of treatment-induced cancer survivorship diseases and states, and to future development of evidence-based management strategies in pelvic cancer rehabilitation. Further results from the interventions will be reported in future papers.

Collaboration

Requests for specific research projects and collaborative work are encouraged and can be addressed to the corresponding author.

Patient and public involvement

Results from future studies from the female cancer survivor population-based cohort will be submitted for publication in peer-reviewed journals and presented at relevant conferences.

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BMJ Cohort profile

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318

319 **Footnotes**

320 *Author's contributions:*

1. Guarantor of integrity of the entire study: Gunnar Steineck
2. Study concepts and design: Karin Bergmark, Gunnar Steineck, Gail Dunberger
3. Data analysis: Linda Akeflo, Gail Dunberger, Karin Bergmark, Eva Elmerstig, Gunnar Steineck
4. Statistical analysis: Viktor Skokic
5. Manuscript preparation: Linda Akeflo, Karin Bergmark, Gail Dunberger, Eva Elmerstig
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336

337 Abbreviations

338 N Number

339 PLISSIT Permission, Limited Information, Specific Suggestions and Intensive Therapy

340 RCC Regional Cancer Center

341 SD Standard Deviation

342 SOU Statens Offentliga Utredningar (Swedish: National Public Inquiries)

343 WHO World Health Organization

344

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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

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BMJ Cohort profile

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

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BMJ Cohort profile

ABSTRACT

Purpose: The study “Health among women after pelvic radiotherapy” was conducted in response to the need for more advanced and longitudinal data concerning long-term radiotherapy-induced late effects and chronic states among female cancer survivors. The objective of this paper is to detail the cohort profile and the study procedure in order to provide a sound basis for future analyses of the study cohort.

Participants: Since 2011, and still currently ongoing, participants have been recruited from a population-based study cohort including all female patients with cancer, over 18 years of age, treated with pelvic radiotherapy with curative intent at Sahlgrenska University Hospital in Gothenburg, in the Western Region of Sweden, which covers 1.7 million of the Swedish population. The dataset presented here consists of baseline data provided by 605 female cancer survivors and three-month follow-up data from 260 individuals with gynaecological-, rectal- or anal cancer, collected over a six-year period.

Findings to date: Data has been collected from 2011 onwards. To date, three studies have been published using the dataset reporting long-term radiation-induced intestinal syndromes and late adverse effects affecting sexuality, the urinary tract, the lymphatic system, and physical activity. These projects include the evaluation of interventions developed by and provided in a nurse-led clinic.

Future plans: This large prospective cohort offers the possibility to study health outcomes in female pelvic cancer survivors undergoing a rehabilitation intervention in a nurse-led clinic, and to study associations between demographics, clinical aspects and long-term late effects. Analysis focusing on the effect of the interventions on sexual health aspects, pre- and post-interventions, is currently ongoing. The cohort will be expanded to comprise the entire data collection from 2011-2020, including baseline data and data from three-month and one-year follow-ups after interventions. The data will be used to study conditions and treatment-induced late effects pre- and post-intervention.

Keywords: *Female cancer survivors, Treatment-induced late effects, Pelvic radiotherapy, Cancer rehabilitation, Nurse-led clinic*

Strengths and limitations

- The major strength of the study is the large representative population-based cohort (n=605)
- Uses a large longitudinal dataset consisting of female cancer survivors’ entries from six months to several years post-pelvic radiotherapy treatment
- Highlighting treatment-induced cancer survivorship diseases and chronic states improves the possibilities for developing further effective treatments

BMJ Cohort profile

- One limitation of the study is the reliance on self-reported data, which has the potential for response bias
- The interventions that were provided varied over the course of the study, which is considered a potential limitation

Introduction

An increasing number of individuals now live longer after a cancer diagnosis than was previously common, and more and more patients are living with treatment-induced late effects, treatment-induced cancer survivorship diseases, and survivorship chronic states [1-3]. Pelvic radiotherapy affects the intestinal and urinary tracts, the lymphatic system, and sexual health [4-10]. In a video at <https://www.jostrust.org.uk/video/letstalk-pelvic-radiation-disease-after-cervical-cancer>, some of more than 20 million cancer survivors in Europe describe how radiation-induced impaired intestinal health affects them. In Sweden, approximately 3,500 women are diagnosed with pelvic cancer (gynaecological, anal, or rectal cancer) every year [11]. In 2011, we started a nurse-led clinic focusing on treatment-induced late effects among pelvic cancer survivors with the intent of developing self-care strategies and treatments. We have previously reported on the benefits of the clinic regarding the resulting improved quality of life and psychosocial wellbeing among female pelvic cancer survivors [12].

We aim to describe a population-based cohort consisting of female cancer survivors treated with pelvic radiotherapy using a dataset from a longitudinal study that has been ongoing since 2011. A further aim is to describe the data collection procedure, the interventions provided in a nurse-led clinic, and the characteristics of the study cohort. In addition, a few basal empirical results will be presented to illustrate the study cohort. The objective of this paper is to detail the cohort profile and the study procedure in order to provide a sound basis for future analyses in the study cohort.

Cohort description

Setting

In 2009, the Swedish government proposed a new regulation: “A National Cancer Strategy” (SOU2009:1) [13]. In collaboration with the Swedish county councils and regions, six Regional Cancer Centres (RCC) were

BMJ Cohort profile

established. Based on the national strategy proposals, the RCC in western Sweden financed a nurse-led clinic at Sahlgrenska University Hospital. The nurse-led clinic was founded in 2011 by a senior consultant physician who has a PhD and is specialised in gynaecological oncology, and an oncology nurse with a PhD in oncology. The team currently consists of three clinical oncology nurses who are specially trained and clinically specialised in understanding and addressing issues concerning pelvic cancer survivorship late effects. The cancer survivors receive education about radiotherapy-induced late effects, basic anatomy and physiology and, together with the nurse, decide on supportive care actions regarding medication, nutrition, and coping with sexual, psychological, and social challenges. In cases with more specific needs, intercurrent diseases, or a suspected recurrence of cancer, the patient meets the senior medical consultant who has the primary medical responsibility for the clinic. The senior medical consultant meets regularly with the team and discusses plans for patients' medication with the staff member who will issue the prescriptions. The healthcare program developed in the clinic is based on programs developed by others and on our previous studies in this area [4,14-20].

Patient and Public Involvement

Patients and/or the public are not involved in the design, conducting, reporting, or dissemination plans in this research. Results from future studies from the cohort will be submitted for publication in peer-reviewed journals and presented at relevant conferences.

Participants

Study participants are recruited from two different cohorts: 1) a population-based study cohort group including all female patients with cancer treated with curative intent from 2007 onwards who are continuously identified from medical records at Sahlgrenska University Hospital in Sweden and 2) a referred patient group including all female patients with cancer referred to the rehabilitation clinic. Inclusion criteria are female cancer survivors who completed pelvic radiotherapy at least six months prior to inclusion. Exclusion criteria are cancer recurrence, inability to comprehend or answer the questionnaire, and poor proficiency in the Swedish language. Data are collected from female cancer survivors with a history of pelvic radiotherapy in western Sweden, an area that includes 20 percent of the Swedish population. The tradition of collecting registry data in Sweden offers good opportunities for studying cancer survivors without selection-induced problems. The dataset

BMJ Cohort profile

contains information about the pre-intervention and post-intervention needs of women who received pelvic radiotherapy at Sahlgrenska University Hospital between 2007 and 2016. Female cancer survivors referred to the nurse-led clinic are also invited to participate in the study.

Invited women

An introductory letter is sent to eligible study participants. Shortly after, a research secretary phones them and gives oral information about the study, asks if they are willing to participate and, if so, asks them to give permission to be sent a written informed consent and the questionnaire. When the baseline questionnaire is returned, the participant receives an invitation to attend the nurse-led clinic where individual healthcare interventions are conducted. The code number from the questionnaire (followed throughout the data collection) is entered into the patient-database FileMaker Pro17 Advanced® that was specifically designed to suit the study. The study participant receives a follow-up questionnaire three and twelve months after the completed intervention. The research secretary keeps track of each patient and, if case questionnaires are delayed or missing, sends two reminders at time points determined in advance, see Figure 1.

Referred patients

Patients referred from oncology healthcare providers, general practitioners, and through private referrals, who meet the inclusion criteria are also invited to participate in the study. The data collection procedure follows the same principles as for the invited women in the population-based cohort.

Study-specific questionnaires

As shown in Table 1, the baseline questionnaire consists of 175 questions, divided into eight main sections and one concluding chapter. Information is obtained about the frequency, intensity, duration, and quality of each symptom, and the degree of distress it causes the patient. An example of one question is: “How many times per week (approximately) have you had bowel movements during the past six months?” with possible answers: “About every other day”, “Less than once a day”, “Once a day”, “Up to twice a day”, “2-3 times per day”, “3-4

BMJ Cohort profile

times per day”, or “5 times or more per day”. To facilitate statistical analyses, the answers are coded into values, ranked, and placed into groups. Variables such as age and number of children are categorised into groups.

Table 1. The study-specific baseline questionnaire, divided into eight sections and one concluding chapter

Section	Question areas
Sociodemographic	Gender Age Marital status Number of children Level of education Employment status
Quality of life and wellbeing	Quality of life Depression Worry Anxiety
Body perception and self-image	Femininity Self-esteem Fertility Childbirth Vaginal and perianal injury related to childbirth or physical trauma
Intestinal and defecation habits	Loose stools Faecal incontinence Urgency to defecate Excessive gas Abdominal pain Having a stoma Medical treatment related to intestinal symptoms
Micturition habits and urinary tract symptoms	Urinary frequency Urgency to urinate Nocturia Having a urinary catheter Medical treatment due to symptoms
Sexual health	Menopause Use of systemic hormone replacement therapy Use of topical oestrogen Impaired lubrication Vaginal shortness Vaginal inelasticity Dyspareunia
Sexual abuse	Experience of sexual abuse Experience of sexual harassment Age when experienced sexual abuse or harassment Extent to which the experience affects sexual life
Lymphoedema	Heaviness in legs, genitals and abdomen If diagnosed with lymphoedema, current lymphoedema treatment
Concluding chapter	Self-reported needs Invite to visit the nurse-led clinic for assessment and counselling

Several sections allow free comments

The questionnaire also addresses the extent to which the symptoms affect social functioning. In the concluding chapter, the participants are invited to visit the nurse-led clinic. Some questions require the patients to rank their

BMJ Cohort profile

127 most distressing symptoms. In the follow-up questionnaires, the study participants' health status and symptoms
128 are measured, and the interventions conducted at the nurse-led clinic are evaluated.

129

130 *Diagnostic and alleviative means*

131 The questionnaire serves as a basis for the interventions conducted at the first visit to the clinic. The patient's
132 current health status reveals the areas that need to be focused on. Current symptoms and self-care strategies are
133 discussed. New strategies are then suggested and decided on together with the patient. The duration of the
134 contact and the number of follow-ups varies from one month to one year depending on the symptoms and the
135 effect of treatments and interventions.

136

137 *Intestinal health*

138 The assessment is based on five syndromes: urgency to defecate, faecal leakage, excessive gas production,
139 excessive mucus discharge, and blood discharge [21]. Symptoms, such as leakage of mucus and blood,
140 abdominal bloating, signs of bacterial overgrowth, and bile salt malabsorption, are also assessed. Diagnostic
141 means, including blood tests such as electrolytes, blood counts, vitamin B12 and serum magnesium, are taken
142 when indicated. An algorithm developed by the research group serves as a guide in the clinical setting [12]. A
143 mobile application has also been developed that was specially designed for radiation-induced intestinal
144 syndromes and which can show graphs of the variation in intestinal health over time. The application serves as a
145 complement to existing methods of patients' self-assessment and self-management, and helps to support the
146 nurse's and patient's conversation and decision-making [22,23]. The objective of the interventions is to restore
147 or improve intestinal health and includes medical treatment, pelvic floor muscle training, and techniques using
148 cognitive training to control intestinal function. Details of these interventions can be accessed elsewhere [12,24].

149

150 *Sexual health*

151 The PLISSIT-model (Permission, Limited Information, Specific Suggestions, and Intensive Therapy) developed
152 by Annon [25] is used to address sexual health concerns. The first three levels in the model are helpful for most
153 patients. When specific suggestions are not sufficient, the patient is recommended to take part in Intensive

BMJ Cohort profile

Therapy, which is sometimes given in the clinical setting and other times with a sexologist or psychotherapist after a referral is sent. Female sexual dysfunction is a complex condition, including diverse aspects, definitions, and classifications [26]. To assess and treat sexual dysfunction, previous sexual practices and experiences are discussed, with particular attention given to patients’ integrity, special needs, and preferences. Structured information about common physical late effects involving vaginal changes and sexual problems is provided as well as information concerning psychological issues influencing sexual health; all information given is in accordance with evidence-based knowledge and practice in the field [4,17,27-29,1]. Patients receive information about and instructions on the use of vaginal dilator therapy and topical oestrogen, and they are also given guidance and suggestions related to lack of sexual desire. When requested, specific sexual devices, films, and literature are suggested to encourage and help the patient to regain sexual function, which for some patients is helpful in managing issues of body image perception, self-esteem, and intimacy.

Sexual abuse

Patients with a history of sexual abuse have an increased risk of developing sexual problems after cancer treatment, and a large proportion of women with cervical cancer and those experiencing dyspareunia post-cancer treatment have been sexually abused [30]. In cases where this is reported, experiences of sexual abuse are carefully and sensitively discussed with the patient and, in some cases, this may lead to referral to a psychologist or therapist.

Urinary tract health

Symptoms of urgency, nocturia, urinary retention, urinary tract infection, and pelvic pain are addressed. The diagnostic methods used include evaluations of urinary frequency and of symptoms, which are divided into irritative symptoms, obstructive symptoms, and bleeding. Patients can keep a 72-hour voiding diary, including urine volume and fluid intake, which is a helpful resource for this discussion. Guidance and recommendations are given about topical oestrogen, pelvic floor muscle training, medical treatments, self-care modifications, and behavioural interventions, all in accordance with previous evidence-based knowledge [31,32]. In cases of severe urinary tract symptoms, referrals are sent to a urotherapist, physiotherapist, or urologist.

BMJ Cohort profile

182 *Lymphoedema*

183 Lower limb lymphoedema is a common non-curable chronic complication with multifactorial pathophysiology
184 [33]. Early detection and treatment of lymphoedema is essential in order to prevent complications. Self-reported
185 or objectively assessed swelling or heaviness in the lower limbs leads to referral for lymphatic therapy. The
186 primary therapy is the use of individually tailored compression garments and second-line therapy consists of
187 manual lymphatic drainage with intermittent use of pumps and other self-care strategies [34,35].

188

189 *Statistical analyses*

190 Initially, data from the questionnaires were entered into EpiDataSoftware® version 3.1 (EpiData Association).
191 Since only one answer to each question is allowed, in the event of two answers the procedure was to alternate
192 entering the first provided answer and the second provided answer. In order to facilitate the analysis of
193 responses to the open-ended questions, the answers to these questions were transcribed in Microsoft Word
194 (2016). R version 3.5.2. was used for statistical analysis of the data. The results will be reported in means,
195 medians, and percentages.

196

197 **Ethics**

198 All procedures in the study, which involved human participants, were in accordance with the ethical standards
199 of the Regional Ethics Review Board in Gothenburg (D 686-10) and with the 1964 Declaration of Helsinki and
200 its later amendments. The research was approved by the Regional Ethics Review Board in Gothenburg (D 686-
201 10), Gothenburg University. Written informed consent was obtained from all individual participants included in
202 the study.

203

204 **Findings to date**

205 Three studies based on the cohort have been published [12,36,37]. Two papers focused on gastrointestinal side
206 effects and one on sexual health aspects. It was found that the majority of the women reported a change in bowel
207 habits and, in almost half of them, the effect was considerable [12]. Women with faecal leakage were less likely
208 to practise physical activity than survivors without leakage, and survivors who practised weekly physical

BMJ Cohort profile

activity experienced better quality of life and were less frequently in a depressed mood than women not physical active [36]. Furthermore, a statistically significant increase in psychological distress and sexual health impairment was found among women with a history of sexual abuse compared to women without such experience [37].

Characteristics of study participants

From January 2011 to June 2017, we identified a total of 791 patients in the population-based cohort who met the inclusion criteria. Of the total sample, 684 (86%) individuals gave oral consent to participate in the study and of these, 464 (68%) completed the baseline questionnaire.

During the same period, 184 referred patients met the inclusion criteria and were invited to participate in the study. Of those invited to participate, 141 (76.6%) completed the baseline questionnaire and of these, 131 (92%) took part in interventions.

The responses and completeness of the questionnaires from both study groups are shown in the schematic diagram, see Figure 2. In Table 2, we present the baseline characteristics and demographics in the dataset, which consists of 605 participants: 464 (76.7%) from the invited cohort and 161 (23.3%) from the referred cohort.

Table 2. Characteristics of the study participants

Variable	Total	Invited	Referred
Participants, n (%)	605	464 (76.7)	141 (23.3)
Cancer type, n (%)			
Endometrial cancer	216 (35.7)	181 (39.0)	35 (24.8)
Cervical cancer	132 (21.8)	80 (17.2)	52 (36.9)
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)
Anal cancer	80 (13.2)	58 (12.5)	22 (15.6)
Rectal cancer	145 (24.0)	122 (26.3)	23 (16.3)
Other	4 (0.7)		4 (2.8)
Age in years			
Mean	64.5	66.5	57.6
SD	12.6	11.5	13.6
Missing, (%)	11	7 (1.5)	4 (2.8)
Years since radiotherapy, grouped			
0	35 (5.8)	6 (1.3)	29 (20.6)
1	219 (36.1)	166 (35.8)	53 (37.6)
2	98 (16.1)	86 (18.5)	12 (8.5)
3	139 (23.0)	131 (28.2)	8 (5.7)
≥4	105 (17.3)	69 (14.9)	36 (25.5)
Missing	9 (1.5)	6 (1.3)	3 (2.1)
Mean	2.6	2.2	3.9
SD	3.4	1.2	6.7

BMJ Cohort profile

Cancer treatment, n (%)

External radiotherapy, only	145 (24.0)	101 (21.8)	44 (31.2)
External radiotherapy and brachytherapy	20 (3.3)	16 (3.4)	4 (2.8)
External radiotherapy, brachytherapy and surgery	180 (29.7)	157 (33.8)	23 (16.3)
External radiotherapy and surgery	260 (43.0)	190 (40.9)	70 (49.6)

Marital status, n (%)

Married or living with a partner	402 (66.4)	309 (66.6)	93 (66.0)
Widow	70 (11.6)	59 (12.7)	11 (7.8)
Has a partner but lives alone	30 (5.0)	15 (3.2)	15 (10.6)
Single	102 (17.0)	80 (17.2)	22 (15.6)
Missing	1 (0.2)	1 (0.2)	

Education level, n (%)

Elementary school	173 (29.1)	150 (32.3)	23 (16.3)
Secondary school	227 (38.2)	169 (36.4)	58 (41.1)
College/University	194 (32.0)	135 (32.3)	59 (41.8)
Missing	11 (1.8)	10 (2.2)	1 (0.7)

Employment status, n (%)

Student	4 (0.7)	3 (0.6)	1 (0.7)
Unemployed job seeker	12 (2.0)	10 (2.2)	2 (1.4)
Employed	162 (27.0)	116 (25.0)	46 (32.6)
Housewife	4 (0.7)	2 (0.2)	2 (1.4)
On sick leave	54 (9.0)	17 (3.7)	37 (26.2)
Disability pension	35 (5.7)	26 (5.6)	9 (6.4)
Retired	328 (54.7)	284 (61.2)	44 (31.2)
Missing	6 (1.0)	6 (1.3)	

Resident, n (%)

In a big city	182 (30.6)	131 (28.2)	51 (36.2)
In a small or medium-sized city	309 (50.2)	244 (52.6)	61 (43.3)
In the countryside	116 (18.9)	87 (18.8)	29 (20.6)
Missing	2 (0.3)	2 (0.4)	

Smoking, n (%)

Does not smoke	448 (74.0)	339 (73.1)	109 (77.3)
Smokes	67 (11.0)	52 (11.2)	17 (12.1)
Missing	88 (14.5)	73 (15.7)	15 (10.6)

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

The majority of the study participants had a history of gynaecological cancer and had been treated with radiotherapy in combination with surgery. In the population-based study cohort, the mean age was higher and twice as many were retired compared to the referred group. In the referred group, twice as many were on sick leave. In total, 379 (63%) of the 605 study participants agreed to visit the clinic, see Table 3. Sixty-seven (14.4%) of the women in the population-based study group who declined to visit the clinic reported that they had radiotherapy-induced late effects.

Table 3. Number (N) and proportion (%) of study participants who agreed to visit the clinic

	Total N (%)	Invited N (%)	Referred N (%)
No, I have no late effects and do not need to visit the clinic	108 (17.8)	107 (23.1)	1 (0.7)

BMJ Cohort profile

235	No, I have late effects, but I do not want to visit the clinic	71 (11.7)	67 (14.4)	4 (2.8)
236	Yes, I want to visit the clinic	379 (62.6)	248 (53.4)	131 (92.9)
237	Missing	47 (7.8)	42 (9.1)	5 (3.5)
238	N (number) and proportion (%) of women is presented			

Strengths and limitations

In this paper, we describe the population-based cohort consisting of female cancer survivors treated with pelvic radiotherapy in the western region of Sweden. The data collection procedure, the interventions provided, and the characteristics of the study cohort are also outlined. In addition, a few basal empirical results are reported to illustrate the study population. The major strength of the study is the large population-based cohort, since it creates the possibility of studying cancer survivors without selection-induced problems and makes it representative of the reference population consisting of an increasing number of female cancer survivors treated with pelvic radiotherapy. The longitudinal study design enables future investigations of long-term treatment-induced late effects, diseases, and chronic states. Moreover, it will be possible to evaluate the long-term outcomes of interventions and the treatments provided.

The data collection has generated a large dataset consisting of patient entries from six months to several years post-pelvic radiotherapy treatment. Over a period of six and a half years, almost 1,000 female pelvic cancer survivors have been invited to participate in the study; the dataset consists of 605 cancer survivors. In the population-based cohort group, 68% completed a baseline questionnaire. Treatment and interventions concerning physical, psychosocial, and sexual issues were offered to patients in both the population-based cohort and the referred cohort, and these were evaluated. As shown in Table 3, 53.4% of the study participants in the population-based cohort agreed to visit the clinic, which may indicate the proportion of cancer survivors with unmet needs. Improved self-care strategies, increased clinical knowledge, and developments in technology currently provide healthcare professionals with possible methods to help cancer survivors manage and treat the late effects of pelvic radiotherapy treatment. We believe that highlighting treatment-induced cancer survivorship diseases and chronic states may increase the likelihood of further effective treatments being developed.

BMJ Cohort profile

Cancer survivorship issues have advanced from being neglected to gradually being given increasingly greater attention in healthcare practice as well as in research. This is reflected by the development of national guidelines and the organisation of national and international scientific conferences and meetings in this subject area. Efforts are being made to both understand how treatment-induced late effects manifest in pelvic cancer survivors and to find strategies to deal with these late effects. Twenty years have passed since researchers within our team [4] first observed that patients with gynaecological cancer suffered from vaginal changes affecting their sexual health. More recently, we have identified five syndromes impairing pelvic cancer survivors' intestinal health. Results published in 2017 [21] simplify the search for ways to prevent, manage, and help minimise the occurrence and intensity of survivorship diseases. One promising ongoing study being conducted by Schofield et al in Australia is evaluating a care program similar to ours [38,39]. Furthermore, in 2015 Andreyev et al [15] published a guide for the management of intestinal problems, including an algorithm that, in our opinion, is a useful tool for clinicians. However, the pathophysiological changes, which are described in numerous previous studies, are not yet fully understood [19-21]. Inflammatory and fibrotic processes in the gut wall are probably of importance in explaining the various symptoms. The processes may relate to both the intestinal tract and other organs located in the pelvis. Hofsjö et al in our research group [40] recently studied vaginal changes and found morphological explanations for changes in the vaginal wall. Biopsies from the vaginal connective tissue affected by radiotherapy showed dense collagen and entangled elastin fibres, a finding that may explain common symptoms such as reduced vaginal elasticity during intercourse, reduced lubrication, and dyspareunia.

In Sweden, promising steps are being taken towards developing a program for national coordination of cancer rehabilitation practice. Cerna et al [23], in a study concerning self-management from an educational perspective, observed that patients and nurses can together create tailor-made solutions. The nurses focus on encouraging the patients to self-reflect and on maintaining the patient's motivation to continue to engage in self-care. The ongoing establishment of oncology nurse navigators [41] is also an initiative that has the potential to increase the supportive care given to cancer survivors. In the 1980s, research in the psychological field [42] showed that patients have a high risk of anxiety related to oncology treatment. Recent studies report that patients have a lower risk of future anxiety and depression when their needs are addressed during treatment [43,44]. In our opinion, when planning future follow-up in clinical cancer care, these findings need to be taken into account,

BMJ Cohort profile

irrespective of the patient’s cancer diagnosis. We suggest that, in the future, healthcare should provide advanced specialist expertise in the management of severe treatment-induced late effects.

Sexual concerns are generally not addressed or discussed as much as patients would like [45], and patients generally wait for healthcare professionals to raise the subject [46]. In our clinical setting, sexual health conversations are integrated into the clinical work, routines for assessment and treatment have been created, and it becomes clearer when a patient should be referred to specialists and sexologists. The PLISSIT-model [25] has been used for addressing sexual health concerns in both our own clinical setting and in that of others. Clinical experience shows that sexual function might improve and even return to pre-diagnosis level through frequent clinical follow-up, which is consistent with results from previous studies [47]. Parts of WHO’s definition of sexual and reproductive health state that: “sexual health requires a positive and respectful approach to sexuality and sexual relationships” [48], so healthcare professionals need to be able to talk openly to patients about sexuality. It has been suggested that healthcare professionals should actively engage in training to improve their communication skills in order to overcome common communication barriers [49,50]. Our clinical experience has shown that several patients have felt relieved when being able to speak openly about sexual issues as well as other private health concerns. The baseline questionnaire seems to serve as a therapeutic tool that can be followed up in counselling.

One could argue that the observational study design is a limitation in this study and that a randomised clinical trial might provide data that are more reliable. However, for ethical reasons, we found it necessary to offer all patients in the population the best available intervention. Hence, we considered that the observational study design was best suited to this purpose, a design previously shown to produce reasonably useful results [51]. One important limitation of the study is the reliance on self-reported data, which has the potential for response bias. However, we considered self-reported data to provide a wider range of responses than data collected using other data collection instruments [52]. To avoid information-related problems, we took advance preventive action by using questionnaires based on the clinometric method that we have introduced, developed, used, and described in previous research projects [4,6,53,5]. We employed epidemiological methods, introduced into the cancer survivorship field by a hierarchical step-model, to manage bias and confounding [54]. This method was considered appropriate to measure causal relationship, and to examine different symptoms and characteristics in

BMJ Cohort profile

321 treatment-induced side effects. In short, the method comprises a quantitative pre-phase of semi-structured
322 interviews with persons suitable for the study. Thereafter, a face-to-face-validation is conducted to ensure
323 satisfactory internal consistency.

324

325 The wide range in length of time since completion of treatment may be considered a weakness in the study;
326 however, this will probably also facilitate measurement of symptom progression in future analyses. Another
327 potential limitation is that the interventions provided varied over the course of the study due to the increase in
328 both ours and others' understanding of the complexity and pathophysiological mechanisms of symptoms and
329 late effects. The minor changes in the interventions during the study need to be considered in future analysis.
330 The results may also be affected by non-participation and loss to follow-up. We can only speculate about the
331 reasons for these, such as patients not having time, not feeling motivated, or being unwilling to recall their
332 previous cancer experience. Possible reasons for patients declining an offer to visit the clinic despite having
333 troublesome symptoms could be due to the symptoms being too severe to enable travel to the clinic. Age-related
334 problems and long-distance transportation can be other reasons. The data collected from the referred patients
335 will allow analysis of the prevalence of symptoms and unmet needs observed by other healthcare providers.
336 Since the data were collected in Sweden, we do not know to what extent our analysis will be applicable to other
337 populations.

338

339 Through frequent lectures for patients and healthcare professionals, and the implementation of treatment
340 strategies directly to patients, we apply the knowledge we have acquired and use it in the clinic and with the
341 cancer survivors themselves. It is also worth mentioning that our rehabilitation clinic serves as a model for
342 similar clinics in other regions of Sweden that have been established as part of the national strategy financed by
343 the Swedish government. The current nurse-led clinic may serve as the beginning of a future tertiary centre to
344 develop interventions and treatments for cancer survivors.

345

346 The extent to which the interventions provided in the individualised nurse-led rehabilitation might improve
347 health in female cancer survivors treated with pelvic radiotherapy is currently unclear. The dataset from the 3-
348 month follow-up questionnaire was prepared and used in recently published studies, while preparation of the

BMJ Cohort profile

dataset from the one-year follow-up questionnaire is ongoing. To the best of our knowledge, our study cohort is one of only a few published population-based cohorts of female pelvic cancer survivors with treatment-induced late effects receiving individualised interventions with a focus on physical and sexual health after radiotherapy. The interventions developed, outlined, and provided will hopefully contribute to further development of evidence-based management strategies in pelvic cancer rehabilitation and will be reported in future papers.

Collaboration

Requests concerning possible specific research projects and collaborative work are encouraged and can be addressed to the corresponding author.

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Footnotes

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1. Guarantor of integrity of the entire study: Gunnar Steineck
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BMJ Cohort profile

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380 Data are available on reasonable request.

381

382 **Abbreviations**

383 N Number

384 PLISSIT Permission, Limited Information, Specific Suggestions and Intensive Therapy

385 RCC Regional Cancer Centre

386 SD Standard Deviation

387 SOU Statens Offentliga Utredningar (Swedish: National Public Inquiries)

388 WHO World Health Organization

389

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Figure legends

Figure 1. Flowchart of Pelvic Cancer Rehabilitation ongoing data collection procedure and the procedure for patient inclusion, contact with participants, and the follow-up points for questionnaires.

Figure 2. Schematic diagram of data collected from two different study cohorts from January 2011 to June 2017: a population-based cohort and patients referred from oncology healthcare providers, general practitioners, and through private referrals who met the inclusion criteria. The diagram includes study response rate, completeness of questionnaires, and reasons for loss of participants.

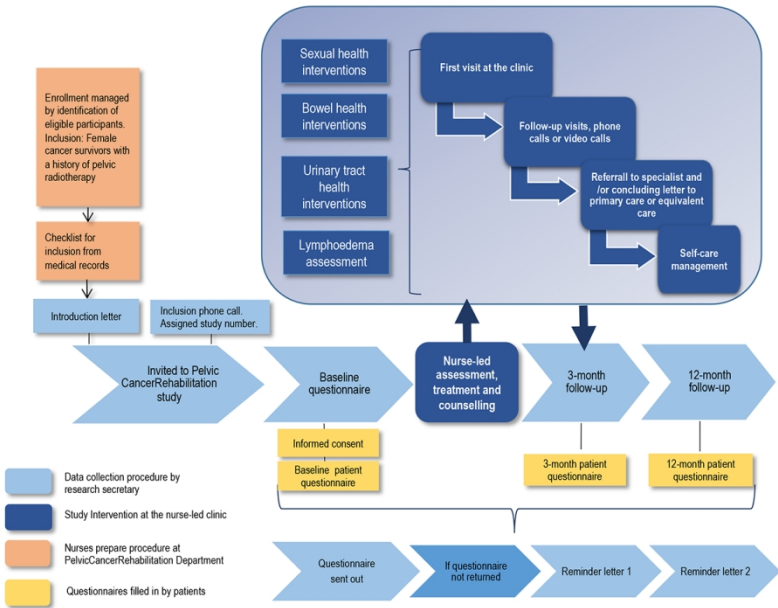


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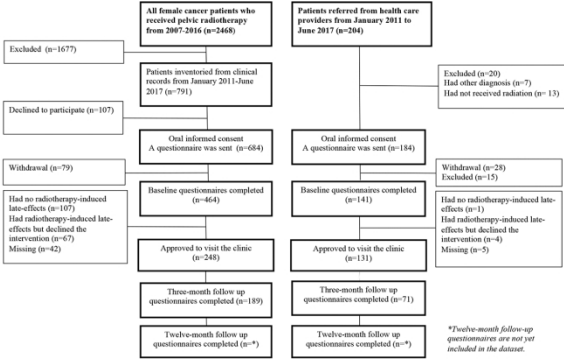


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STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study Design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study Size	10	Explain how the study size was arrived at	
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical Methods	12	(a) Describe all statistical methods, including those used to control for confounding	
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	Cohort study—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key Results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.