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Scientific Article

Intra-abdominal Surgery and Intestinal Syndromes After Pelvic Radiation Therapy

Cecilia Bull, PhD,[a,*] Amelie Toft Morén, MD,[a] Viktor Skokic, MSc,[a,b] Ulrica Wilderäng, PhD,[a] Dilip Malipatlolla, PhD,[a] Eleftheria Alevronta, PhD,[a] Gail Dunberger, PhD,[c] Fei Sjöberg, PhD,[a,d] Karin Bergmark, MD, PhD,[a] and Gunnar Steineck, MD, PhD[a]

[a]Division of Clinical Cancer Epidemiology, Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg, Sweden; [b]Division of Clinical Cancer Epidemiology, Department of Oncology and Pathology, Karolinska Institute, Stockholm, Sweden; [c]Department of Health Care Sciences, Marie Cederschiöld University, Stockholm, Sweden; and [d]Department of Infectious Diseases at the Institute of Biomedicine, Sahlgrenska Academy at the University of Gothenburg, Sweden

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Purpose: To determine the effects of intra-abdominal surgery on the intensities of 5 radiation-induced intestinal syndromes in survivors of pelvic cancer.

Methods and Materials: The analysis included 623 women born in 1927 or later who had survived cancer. They all had received external radiation therapy toward the pelvic area to treat gynecologic cancers. Information from 344 women who did not undergo irradiation, matched for age and residency, was also included. Main outcome measures after the surgical procedures were the intensity scores for 5 radiation-induced intestinal syndromes: urgency-tenesmus syndrome, fecal-leakage syndrome, excessive mucus discharge, excessive gas discharge, and blood discharge. The scores were based on symptom frequencies obtained from patient-reported outcomes and on factor loadings obtained from a previously reported factor analysis. Follow-up was 2 to 15 years after radiation therapy.

Results: Among survivors of cancer, intra-abdominal surgery increased the intensity of the urgency-tenesmus syndrome, the fecal-leakage syndrome, excessive gas discharge, and blood discharge but had a negligible effect on mucus discharge. Intra-abdominal surgery had an especially negative effect on the urgency-tenesmus syndrome. Although the combination of appendectomy with 1 or more other intra-abdominal surgeries resulted in the highest score for all syndromes, appendectomy alone had weak to no effect. In women who did not undergo irradiation, a similar pattern was seen, albeit with much lower scores.

Conclusions: We found intra-abdominal surgery to be a risk factor among survivors of gynecologic cancer, increasing the intensity score of 4 out of 5 radiation-induced intestinal syndromes. During radiation therapy, it may be worthwhile to pay extra attention to the dose of unwanted ionizing radiation to the intestines if the patient previously has undergone intra-abdominal surgery.

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Introduction

In the ambition to tailor radiation therapy for a specific patient ("personalized medicine"), the patient's medical history is an essential source of information. Concerning irradiation of a tumor in the pelvic cavity, a previous

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*Corresponding author: Cecilia Bull, PhD; email: cecilia.bull@gu.se

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surgery, particularly an intra-abdominal procedure, has been suggested to increase the risk of irradiation-induced intestinal complications.[1-3] Moreover, it has been proposed that an appendectomy would be more harmful than other intra-abdominal surgeries.[4] More information is needed on the relation between a previous intra-abdominal surgery and the late effects of radiation therapy on intestinal health.

Surgical procedures and inflammatory processes in the abdomen may lead to intra-abdominal adhesions, preventing organ movement. Imaging for treatment planning is used to locate the tumor and to minimize the exposure of ionizing radiation to the tissues at risk. During the course of radiation therapy, the organs will move, and thereby the tissues may receive a lower dose than calculated. The opposite may be true for patients with adhesions, resulting in higher toxicity and additional deterioration of intestinal health.[2]

Adhesions among women with a history of intra-abdominal surgery could be triggered by various mechanisms. Even minimally invasive surgery (laparoscopy) will produce adhesions when manipulating the intestines and removing diseased and/or inflamed tissue.[5] Intra-abdominal procedures may introduce pathogens into the body cavity or trigger immunologic mechanisms that could have a long-lasting impact on healing after a second insult, such as irradiation.[6] Lasting changes in blood cytokine profiles after intra-abdominal surgery can alter the immune response after radiation therapy, possibly aggravating injury.[7] Another possible mechanism involves the homeostasis of the endogenous microbiota. This is of particular interest when it comes to appendectomy. The appendix has a plethora of microbes,[8,9] and its unique constellation of lymphocytes indicates a specialized, albeit unknown, immunologic function.[10] Data collected after infection by *Clostridium difficile*[11] suggest that the appendix serves as an important reservoir for the microbiota. Logically, such a reservoir could promote intestinal healing after irradiation by supporting fast microbial repopulation. Frequent loose stools during and after radiation therapy may disturb the microbiota to such an extent that microbial repopulation is needed; removing the appendix could then reduce the ability to recover from pelvic radiation therapy.

It was previously found that radiation-induced bowel symptoms can be grouped into 5 syndromes (symptom clusters) with various pathophysiology. The syndromes were labeled "urgency-tenesmus syndrome," "fecal-leakage syndrome," "excessive mucus discharge," "excessive gas discharge," and "blood discharge' and are manifestations of what is termed radiation-induced cancer survivorship diseases[12] or pelvic radiation disease[13] in the literature. Based on a modified factor analysis, by weighting factor loadings and symptom frequencies to a factor score, a metric of the intensity of a specific syndrome can be obtained.[12] Lifestyle factors such as diet and tobacco smoking modify the intensity of the syndromes.[14,15] In this study, we analyzed whether an intra-abdominal procedure (other than the cancer surgery itself) affected the intensity of each of the 5 radiation-induced intestinal syndromes. We also examined whether such an effect, if found, was particularly large among those having undergone an appendectomy and whether tobacco smoking and citrus intake would influence the outcomes. Our setting was a population-based group of survivors of gynecologic cancer who were followed up at 2 to 15 years after radiation therapy.

Methods and Materials

The study was approved by the regional ethical review board (2005/1424-31/4), Stockholm, Sweden. We identified 1800 patients who had been treated with external radiation therapy toward the pelvic area for gynecologic cancers between the years 1991 and 2003 at Radiumhemmet, Karolinska University Hospital, Stockholm, or Sahlgrenska University Hospital, Gothenburg, Sweden. Of these, 823 cancer survivors met the following eligibility criteria: (1) born in 1927 or later, (2) Swedish literacy, and (3) no recurrence of malignancy after completion of treatment. As seen in Fig. 1, an introduction letter was sent to the 823 eligible participants. Of these, 731 gave informed oral consent and were provided with a questionnaire; 650 completed the questionnaire. Participants who had answered "yes" to having undergone an ostomy or having a history of inflammatory bowel disease (Crohn's disease, ulcerative colitis) or irritable bowel syndrome were excluded in further analysis. A total of 623 individuals who had survived cancer were part of the final analysis. The mean follow-up time was 7.0 years, with a range of 2.3 to 15.0 years. Three-dimensional conformal radiation therapy (3D-CRT) was used during this period. The radiation therapy treatment regimen with the doses that were typically given are described in a previous publication.[16]

To control for whether intra-abdominal surgery by itself induced any of the 5 syndromes, 486 healthy participants, matched for age and residency, were identified using the Swedish Population Registry. Of those, 344 healthy individuals completed the study and provided data to the analysis.

Statistical analysis

The individual syndrome intensities were based on a factor analysis of 28 identified bowel symptoms, such as stools containing blood, immediate need to defecate, loose stools, and abdominal bloating. A complete list of the 28 symptoms and details on the statistical methods used to identify the factors and determine the bowel symptoms' factor loadings was provided by Steineck et al.[12] In short,

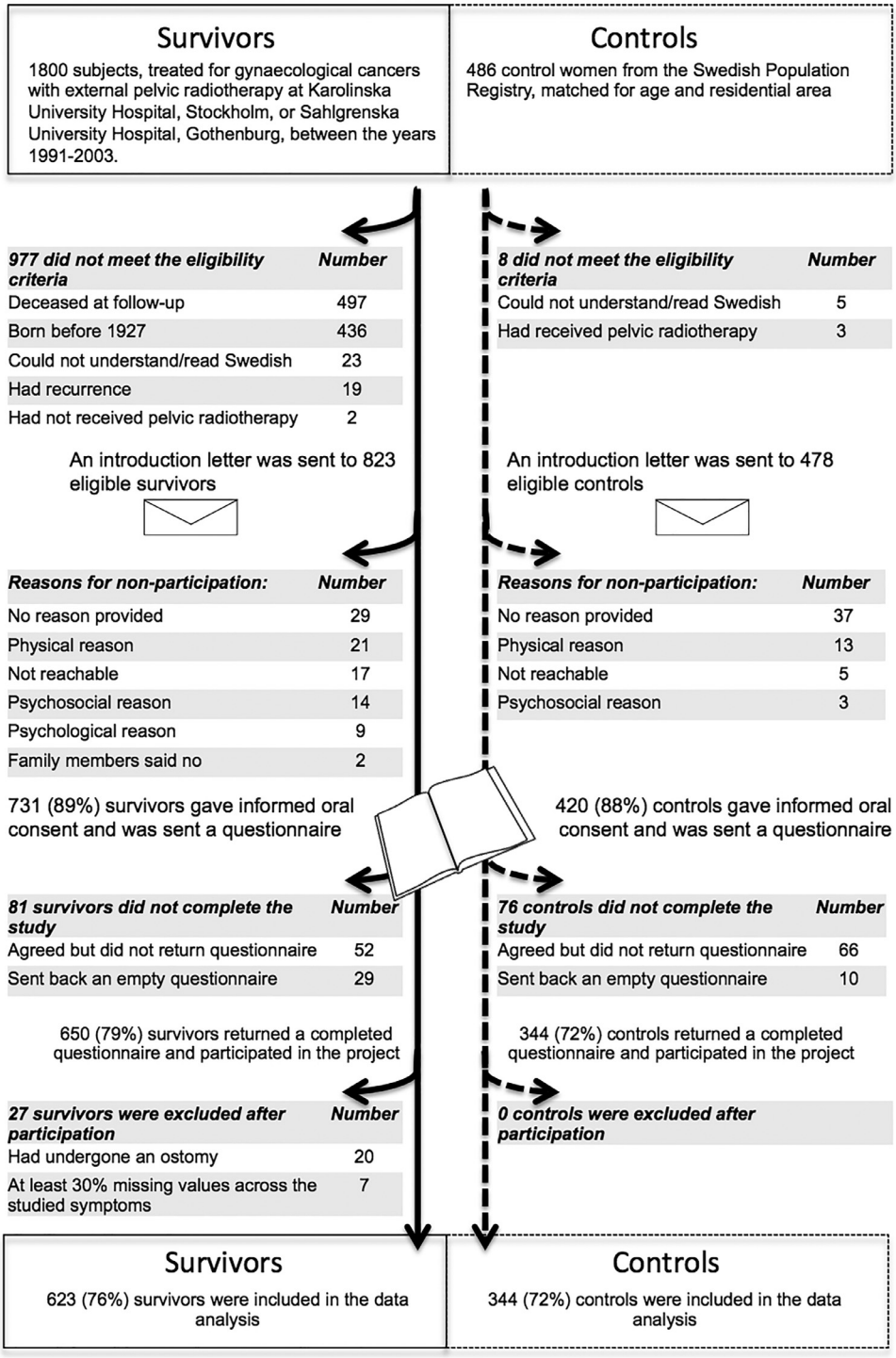

Figure 1 Flowchart for the data collection process. Overview of the data collection from gynecologic cancer survivors and matched women not irradiated. The inclusion and exclusion criteria and questionnaire response rate are presented.

to uncover patterns in the initially large data set with the identified symptoms in the individuals who had survived cancer, the data were modelled using exploratory factor analysis with Spearman correlations as input. To determine the appropriate number of factors, which in this analysis would reflect syndromes (clusters of symptoms), both parallel analysis and a nonparametric bootstrap version of the Kaiser rule were used, and both suggested 6 factors. Depending on the symptoms loading into the factors, the factors were referred to as "urgency syndrome," "leakage syndrome," "excessive gas discharge," "excessive mucus discharge," "blood discharge," and "constipation".

For clarity, "urgency syndrome" and "leakage syndrome" were later changed to "urgency-tenesmus syndrome" and "fecal-leakage syndrome". Maximum likelihood estimation was used to estimate the values of the factor loadings. Varimax rotation was used to improve the interpretability of the results and to filter out variables with a weak loading. Factor-specific cutoffs on the factor loadings were calculated based on parametric bootstrapping (the variable cutoff method described in the statistical appendix of Steineck et al.[12]). One factor (constipation) was removed in the current analysis because this factor was not specifically associated with being a survivor of cancer compared with individuals who had not had cancer. To be able to compare factor scores (syndrome intensities) between individuals, data were standardized by rescaling to mean 0 and marginal variances of 1. Factor scores were then calculated as linear combinations of the symptom intensity values of an individual across the 28 symptoms studied and the factor-specific factor loadings.

The distributions of the intensities of the 5 radiation-induced survivorship syndromes among individuals having undergone intra-abdominal surgery and those not having undergone intra-abdominal surgery within the studied group of cancer survivors who had undergone irradiation were compared using the Kruskal-Wallis test. An analogous comparison was performed among the individuals who had not undergone irradiation. Furthermore, the individuals having undergone intra-abdominal surgery were subsequently divided into those having undergone only appendectomy and those having undergone intra-abdominal surgery excluding appendectomy. Examples of common intra-abdominal surgeries were ectopic pregnancy, cholecystectomy, caesarian section, and removal of ovarian cysts. Surgeries that were performed as part of the cancer treatment were not included. Additionally, we added those who had undergone both an appendectomy and 1 or more other intra-abdominal surgeries. These subgroups were compared using Kruskal-Wallis tests followed by the Dunn post hoc test. To investigate the presence of possible effect modification from lifestyle factors, smoking status and citrus intake were selected for analysis based on the results of previous studies exploring the relationships between the syndrome intensities and demographical information.[14,15] Spearman correlation analysis was used to disclose potential associations between syndrome intensity and smoking status or citrus intake. Furthermore, using *t* tests, 95% confidence intervals on the difference in mean syndrome intensity between cancer survivors having and not having undergone intra-abdominal surgery within the extreme categories of the potential effect modifiers were calculated (*never* and *current* for smoking and *weekly* and *daily* for citrus intake). In a conservative approach to detect deviations from additivity of the effect of intra-abdominal surgery on syndrome intensities across potential confounder categories, the confidence intervals were examined for nonoverlap, but no such situations occurred.

Lastly, since many (but not all) of the participants reported that they had given birth, anal-sphincter damage was assessed as a possible effect-modifying factor.

Results

The demographics and clinical characteristics are presented in Table E1. Overall, there was relatively large homogeneity between the groups. The mean age was slightly higher among cancer survivors with a history of intra-abdominal surgery and cancer survivors with a history of appendectomy alone compared with the group with no surgery. The survivors who had undergone appendectomy alone had a lower level of education compared with the survivors who had undergone intra-abdominal surgery other than an appendectomy or who had not undergone intra-abdominal surgery.

Table E6 shows comparisons between cancer survivors and participants who had not undergone irradiation with regard to demographics and the subgroups, with *P* values provided for each subgroup comparison. The difference in mean age between cancer survivors and participants who had not undergone irradiation was 6.2 years, with the participants who had not undergone irradiation slightly younger than the cancer survivors.

Syndrome-intensity scores

We investigated the intensity scores of 5 radiation-induced intestinal syndromes: urgency-tenesmus syndrome, fecal-leakage syndrome, excessive mucus discharge, excessive gas discharge, and blood discharge. To assess whether intra-abdominal surgery could exacerbate these syndromes, all individuals who had undergone intra-abdominal surgery (including appendectomy) were analyzed regarding syndrome intensity score (Fig. 2, Table E2).

Among cancer survivors participants who had undergone irradiation, individuals who had undergone intra-abdominal surgery reported higher intensities of 4 syndromes (urgency-tenesmus syndrome [$P \leq .001$], fecal-leakage syndrome [$P \leq .001$], excessive gas discharge [$P = .04$], excessive mucus discharge [$P \leq .86$], and blood discharge [$P = .01$]).

The reported occurrence of 1 of the symptoms (sudden defecation urgency requiring lavatory) loaded into the urgency-tenesmus syndrome is shown in Fig. E1 (Table E5). Urgency-tenesmus syndrome was the syndrome most affected by an intra-abdominal surgery. Intra-abdominal surgery did not have any significant impact on the intensity score of mucus discharge. In the participants who had not undergone irradiation, no statistically significant differences in intensity scores between

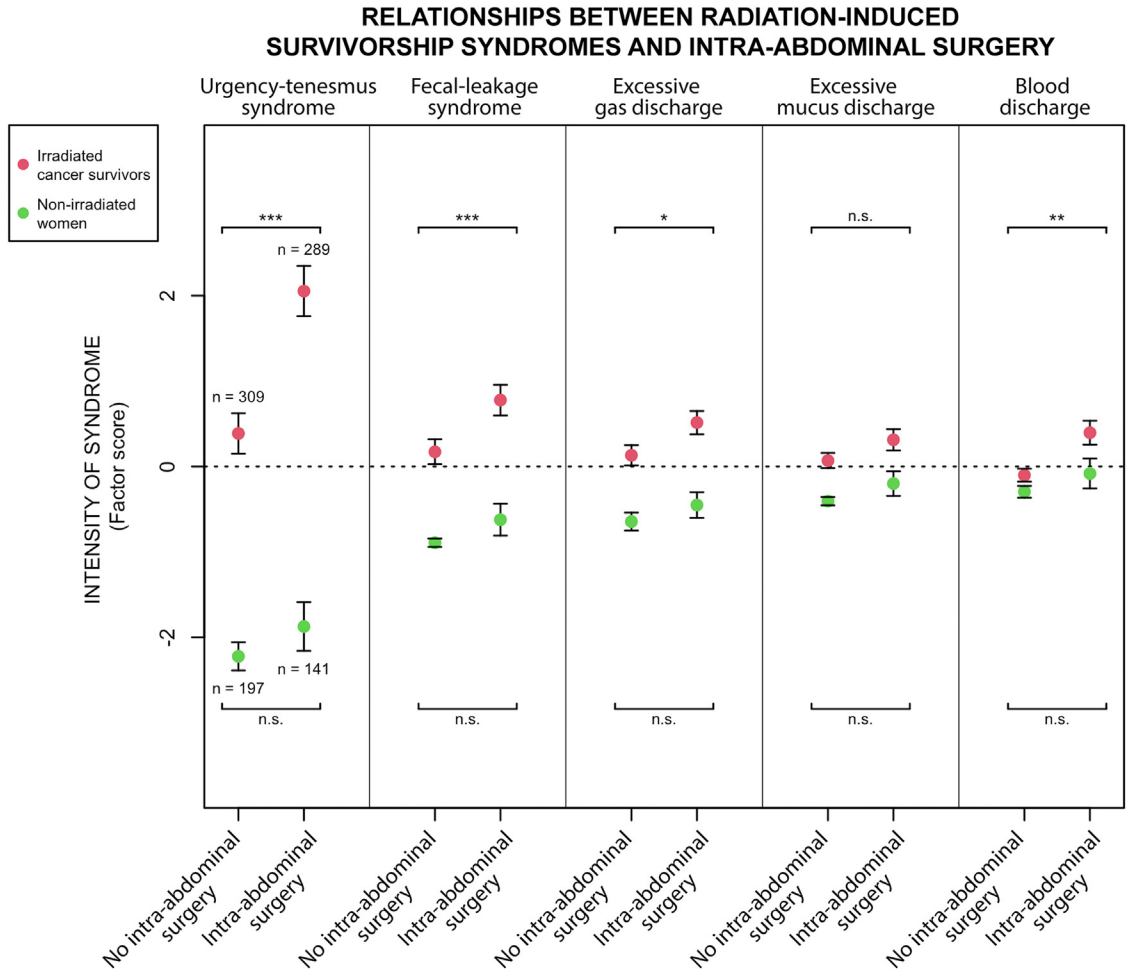

Figure 2 Main analysis. Relationships between the intensity scores of radiation-induced intestinal syndromes and intra-abdominal surgery (including appendectomy) among irradiated cancer survivors and women not irradiated. *Abbreviation:* n.s. = nonsignificant. *$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.

those who had undergone intra-abdominal surgery and those who had not was found for any of the syndromes.

Those who had undergone intra-abdominal surgery (280 in the irradiated group and 136 in the nonirradiated group) were divided into those who had appendectomy only (74 in the irradiated group and 49 in the nonirradiated group), those having undergone intra-abdominal surgery other than an appendectomy (146 in the irradiated group and 55 in the nonirradiated group), and those who had undergone both an appendectomy and 1 or more other intra-abdominal surgeries (60 in the irradiated group and 32 in the nonirradiated group) (Fig. 3 and Table E3).

If there was a statistically significant overall effect (Kruskal-Wallis; significance illustrated with asterisks), a Dunn post hoc test was performed. Participants who had survived cancer with a history of only appendectomy appeared to be at a slightly higher risk for increased intensity of urgency-tenesmus syndrome compared with individuals who had not undergone intra-abdominal surgery, although this was not statistically significant. Intra-abdominal surgery, excluding appendectomy, was found to increase the intensity of urgency-tenesmus syndrome among cancer survivors ($P = .002$), whereas the intensity scores for the other syndromes showed no significant difference. Individuals having undergone both appendectomy and other intra-abdominal surgery had the highest mean intensities of all 5 syndromes, with statistically significantly higher values for 3 of the syndromes (urgency-tenesmus syndrome [$P = .0001$], fecal-leakage syndrome [$P < .0001$], and blood discharge [$P = .004$]) compared with the individuals who had not undergone intra-abdominal surgery.

In convergence, the data suggest a dose-effect relationship, with the lowest score for no intra-abdominal surgery, followed by appendectomy only, intra-abdominal surgery excluding an appendectomy, and having undergone both an appendectomy and another intra-abdominal procedure. However, when inspecting the mean values among women who had not undergone irradiation, the

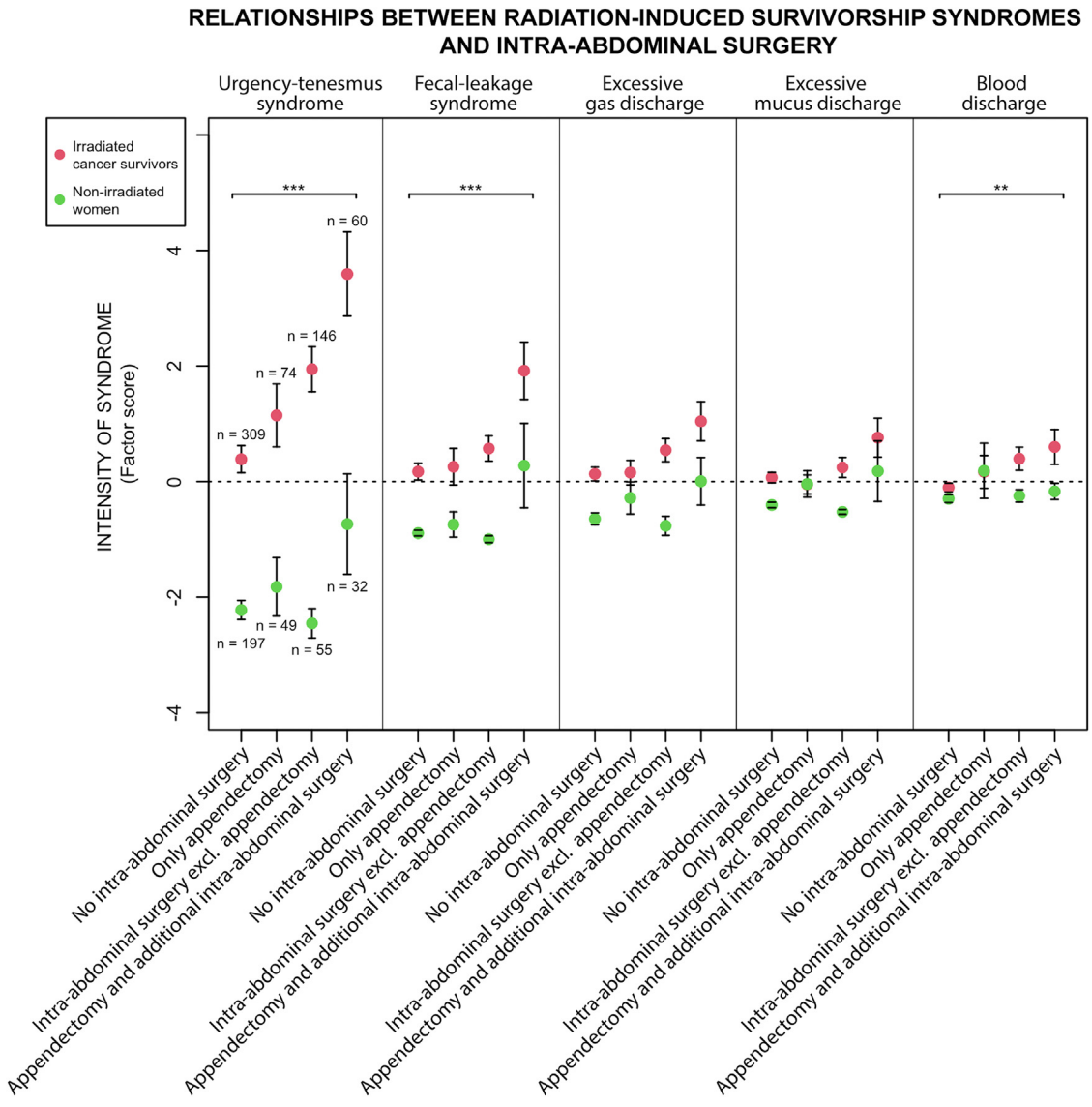

Figure 3 In-depth analysis. Intensity of the 5 syndromes in irradiated cancer survivors and women not irradiated, divided into those having had no intra-abdominal surgery, only appendectomy, intra-abdominal surgery excluding appendectomy, or appendectomy and additional intra-abdominal surgery. *Abbreviation:* n.s. = nonsignificant. $^{*}P \leq .05$; $^{**}P \leq .01$; $^{***}P \leq .001$.

individuals having undergone appendectomy tended to have a higher mean intensity score than those who had undergone intra-abdominal surgery only.

Smoking and citrus intake influenced the score intensity

We further investigated whether smoking and citrus intake affected the intensity of the urgency-tenesmus syndrome in cancer survivors with a history of intra-abdominal surgery (Fig. 4 and Table E4). No or weak signs of effect modifications were found.

Anal-sphincter damage increased the severity scores

Anal sphincter rupture can occur during child delivery and may produce symptoms similar to those included in the syndromes we studied. Because the study population consisted of women, we assessed whether anal-sphincter rupture was a confounding factor concerning the intensity of the syndromes (Fig. E2). An effect modification was found in which the intensity scores were higher than average in cancer survivors with a history of intra-abdominal surgery and anal sphincter rupture, but removing these participants (n = 18) and their matched participants in

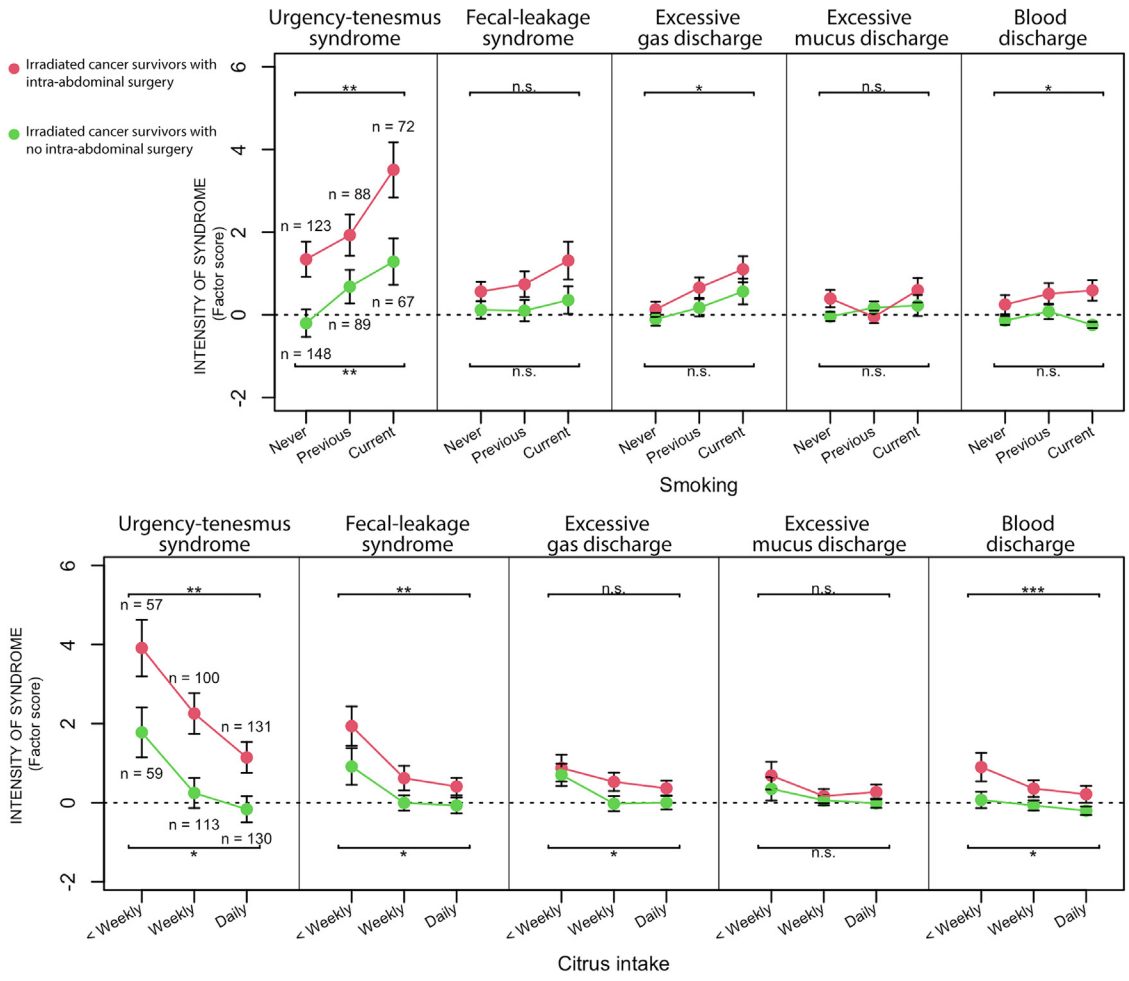

Figure 4 Confounders. Spearman correlation analysis for association between syndrome intensity and smoking status or citrus intake among cancer survivors with or without intra-abdominal surgery. *Abbreviation:* n.s. = nonsignificant. $^{*}P \leq .05$; $^{**}P \leq .01$; $^{***}P \leq .001$.

the control group (n = 18) (Fig. E3) did not change the outcome of the original analysis (Fig. 2).

Discussion

Modern advances in radiation therapy are used to limit the unwanted dose to healthy tissue. But to increase survival rates, the technology is also used to increase the dose to the tumor, and undesirable levels of radiation to normal tissue remains a major issue. Using a weighting of symptom frequency–based factor loadings,[12] we investigated to what extent an intra-abdominal surgery influenced the intensity of 5 radiation-induced intestinal syndromes: urgency-tenesmus syndrome, fecal-leakage syndrome, excessive mucus discharge, excessive gas discharge, and blood discharge. We found a statistically significant association between intra-abdominal surgery and the intensity of 4 of the 5 investigated syndromes, with the association with urgency-tenesmus syndrome being the most pronounced. We found the negative impact of appendectomy on the intensity scores to be weaker than that of other intra-abdominal surgeries (P = .906 vs P = .0024, respectively), arguing against the hypothesis that removing the appendix in particular would hamper intestinal recovery after radiation therapy. However, the intensity scores of all 5 syndromes were the highest for participants who had undergone a combination of appendectomy and another intra-abdominal surgery.

It has been suggested previously that intra-abdominal surgery reduces the chances of restored intestinal health in survivors of pelvic cancer.[4,7,17] There are no data to support any specific pathophysiological processes that could explain the link between intra-abdominal surgery and poor intestinal health. It is known that both the disease that precedes the surgical procedure and the procedure itself could lead to an increased risk of adhesions, reducing the motility of the intestine. The reduced motility results in a greater dose of ionizing radiation to certain parts of the intestines and may result in more severe late effects. However, with regard to the role of the appendix in restoring the preradiation composition and function of

the microbiota, very little is known. There is evidence that diet modifies the frequency and intensity of the late effects after pelvic radiation therapy.[18] A growing number of researchers are studying probiotics in this context, with the aim to promote the diversity of the microbiota and improve the intestinal barrier to prevent bacteria from migrating into the intestinal wall. In line with the data emerging from these studies and evidence that the appendix facilitates recovery after intestinal infections, we hypothesized that the lack of a reservoir for microbiota owing to an appendectomy may compromise the recovery of intestinal health after irradiation. We cannot confirm that hypothesis, because our data provide evidence that having only had an appendectomy had no effect or a weak effect on intestinal health after radiation therapy. It can also be speculated that other types of surgeries, such as cholecystectomy, may disrupt the intestinal homeostasis in various ways and increase certain intensity scores.

Intake of citrus fruits has been shown to decrease the intensity of the urgency-tenesmus syndrome, while smoking increases it.[14,15] A possible explanation is that dietary components high in fiber, such as citrus fruits, have a positive effect on the microbiota and mucus protection,[19] whereas it is known that tobacco smoking reduces tissue healing. We investigated whether the intake of citrus fruits and smoking may be effect-modifying factors for the relationship between intra-abdominal surgery and the intensity of the urgency-tenesmus syndrome. Daily smoking appeared to increase the intensity of the urgency-tenesmus syndrome more in cancer survivors who had undergone an intra-abdominal surgery, but only weakly. The intensity scores tended to decrease in line with higher citrus intake but in a similar manner regardless of having undergone an intra-abdominal surgery or not. Unfortunately, we only have data on the intake of citrus fruits and smoking status from when participants were filling out the questionnaire, not during radiation therapy, intra-abdominal surgery, or other time points during follow-up.

Our study's strengths include the large number of individuals studied and weighing together the symptoms that reduce intestinal health into a clinometric that considers both the symptoms and their relation to the underlying pathogenesis. Almost all women treated for gynecologic cancer in the geographic areas of the 2 cancer clinics at the time of recruitment were irradiated at the clinics where our study was conducted. Therefore, we avoided selection-induced problems in this truly population-based setting. Moreover, weighting together symptoms to an index probably reduced the noise that generally is inevitable when studying symptoms one by one. Comparison of the demographics between participants who had not undergone irradiation and the cancer survivors indicated some differences between these 2 populations when divided into the 4 treatment subgroups but not in both main subgroups (no intra-abdominal surgery and intra-abdominal surgery) for the same variable. One exception was the variable "employed." That the parameter "employed" consistently differed between cancer survivors and participants who had not undergone irradiation could probably be attributed to the combination of a slightly higher age among cancer survivors (6.2 years' difference in mean age between cancer survivors and nonirradiated participants) and an increased incidence of disability pension among cancer survivors. However, these factors should not undermine the conclusions presented in the paper.

We do not know whether the conclusions drawn from the current data with cancer survivors treated with 3D-CRT can be extrapolated directly onto cancer survivors receiving modern intensity modulated radiation therapy (IMRT). Comparative studies have investigated the occurrence of radiation-induced bowel symptoms among patients treated with 3D-CRT and IMRT, and while it appears that the modern radiation techniques result in less bowel toxicity both early and late after radiation therapy,[20,21] some studies reported inconclusive findings or suggested that the advantages concerning bowel health might diminish over time.[22,23] With modern radiation therapy techniques, the distal part of the colorectum still receives very high radiation doses when treating patients with gynecologic cancer. The radiation oncologist may also take advantage of the high-precision radiation therapy by increasing the dose to the tumor to increase local control and the chances of curing the patient. This reduces the tissue-sparing effect. At this time, we can only speculate that patterns of reduced bowel health similar to those observed with 3D-CRT might be found when IMRT is combined with abdominal surgery, albeit perhaps less pronounced.

A major weakness of this study includes the lack of some important information. For example, the time of intra-abdominal surgery in relation to cancer treatment is unknown. Also, the time since surgery could be a confounding factor when comparing appendectomy, usually performed at a younger age, with other intra-abdominal surgeries. In addition, some participants may have had their appendix removed during the cancer surgery and have therefore not been classified correctly. Taken together, there is a possibility of misclassification, but such misclassifications should rather dilute the results and cannot explain the found differences.

Conclusion

Our present findings suggest it may be particularly important to fully take advantage of modern technology to continuously redefine the target volume and apply resource-demanding replanning when the patient previously has undergone an intra-abdominal surgical procedure. If a specific part of the intestine is found to have decreased motility, it may be sensible to delineate it as an

organ at increased risk when planning radiation therapy. With the growing knowledge of factors that modify the unwanted late effects of radiation therapy, we come closer to genuinely personalized medicine.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101303.

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