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ORIGINAL ARTICLE

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Late radiation-induced bowel syndromes, tobacco smoking, age at treatment and time since treatment – gynecological cancer survivors

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ABSTRACT

Background: It is unknown whether smoking; age at time of radiotherapy or time since radiotherapy influence the intensity of late radiation-induced bowel syndromes.

Material and methods: We have previously identified 28 symptoms decreasing bowel health among 623 gynecological-cancer survivors (three to twelve years after radiotherapy) and 344 matched population-based controls. The 28 symptoms were grouped into five separate late bowel syndromes through factor analysis. Here, we related possible predictors of bowel health to syndrome intensity, by combining factor analysis weights and symptom frequency on a person-incidence scale.

Results: A strong ($p < .001$) association between smoking and radiation-induced urgency syndrome was found with a syndrome intensity (normalized factor score) of 0.4 (never smoker), 1.2 (former smoker) and 2.5 (current smoker). Excessive gas discharge was also related to smoking ($p = .001$). Younger age at treatment resulted in a higher intensity, except for the leakage syndrome. For the urgency syndrome, intensity decreased with time since treatment.

Conclusions: Smoking aggravates the radiation-induced urgency syndrome and excessive gas discharge syndrome. Smoking cessation may promote bowel health among gynecological-cancer survivors. Furthermore, by understanding the mechanism for the decline in urgency-syndrome intensity over time, we may identify new strategies for prevention and alleviation.

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Introduction

New technologies make it possible for health care to increase its ambition to not only cure cancer but to cure with restored health. To use this new technology efficiently, we need to learn more about the unwanted effects of the therapy in the long term, and develop a radiation physiology [1]. The beams that converge on the tumor during radiotherapy inevitably pass through the normal tissue and may thereby induce pathophysiological processes [2]. For the cancer survivor, the joy of being cured from his or her cancer consequently is clouded by the fact that the life-saving beams may also induce lifelong survivorship diseases [3,4]. Concerning the diseases that decrease bowel health we have too few data to understand the extent to which smoking, age at the time of treatment and duration of follow-up modify their intensity [5–7].

We currently lack a nosology that combines symptom frequency and intensity, markers in blood and feces with x-ray and endoscopic findings to provide a measure of the intensity of the radiation-induced survivorship diseases. Up to now we are referred to study symptoms and group them to syndromes to reflect radiation-induced survivorship diseases. In prostate cancer, four different syndromes decreasing bowel health have been disentangled [8]. On the basis of atomized patient-reported outcomes (PROMs) and a modified factor analysis, we recently identified five different syndromes decreasing bowel health among gynecological cancer survivors [4]. These syndromes reflect a complex interaction between the function of the gut microbiota and radiation-induced inflammatory and fibrotic processes in the wall of the small bowel, colon and rectum [9]. In addition, muscles in the inner and outer anal sphincter may be replaced by connective tissue as a consequence of the irradiation [10]. The resulting fibrosis decreases the strength of the sphincters and compromises their capacity to hold the survivor continent [11].

We also lack a widely accepted terminology [12]; here we refer to the syndromes as radiation-induced leakage syndrome, radiation-induced urgency syndrome, radiation-induced excess mucus discharge, radiation-induced excess gas discharge and radiation-induced blood discharge. Toilet dependency, a need to always have a toilet within 2 minutes

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distance and sudden defecation into the clothes without forewarning, without feeling the need to go to the toilet, is two urgency-related symptoms included in the urgency syndrome. Continuous and intermittent leakage of loose and solid stools is included in the leakage syndrome.

Relying on atomized patient-reported symptoms [13], we have used as a crude metric of intensity of each syndrome a weighted score of symptom frequency. The weights arise from a previous factor analysis in which we interpret the factor loading of a specific symptom as a measure of the extent to which the symptom reflects the syndrome [4]. A symptom that reflects any one of the five syndromes to a larger extent than any of the other symptoms will get a higher weight than the others. Using this metric, and having data from a population-based group of gynecological cancer survivors followed up three to twelve years after radiotherapy [13], we investigated how smoking, age and time to follow-up affect the intensity of five different survivorship diseases decreasing bowel health.

Material and methods

Between 1991 and 2003, approximately 1800 women underwent radiotherapy for a gynecological malignancy at two oncological clinics in Sweden. Survivors born in 1927 or earlier were excluded, as were survivors illiterate in Swedish (Supplementary Figure, Demographics). Dunberger and coworkers describe details in the data collection [13].

Based on the clinical epidemiological tradition for atomized PROMs we constructed a study-specific questionnaire with a section focusing bowel health. The atomized questions were based on semi-structured interviews and have wordings as close as possible to those used by the survivors in the transcribed interviews. We use the term 'atomized' to depict that we asked for each phenomenon (symptom) directly, just as we do in the clinic (the clinimetric approach) [14,15]. We do not retrieve information about a phenomenon indirectly by summarizing items to a score (the psychometric approach).

Predictors

Concerning smoking we asked: 'Do you smoke?' The answering categories were 'No, I have never smoked', 'No, I quitted at the age of ___', 'Yes, occasionally', 'Yes, I smoke ___ cigarettes per 24 hours (or a corresponding amount of tobacco'). We classified the survivor as being a 'Current smoker' if she reported to smoke occasionally or some number of cigarettes. Time to follow-up was defined by the date of ending radiotherapy and the date the questionnaire was completed. Year of birth was asked for in the questionnaire. Age at receiving radiotherapy was determined by the year of birth and the date of the start of the radiotherapy.

Outcomes

Here, we utilized 28 different atomized symptoms related to bowel health (For details, see Figure 2 in the article Steineck and coworkers [4]). For example, concerning toilet dependency we asked: 'Have you planned ahead to always be in the vicinity of a toilet to avoid defecating in the clothes, the previous half year?' Answers were given on a person-incidence scale ('No', 'Yes, occasionally', 'Yes, at least once a month', 'Yes, at least once a week', 'Yes, at least three times a week', and 'Yes, at least once a day').

Data collection

After sending an introductory letter, we phoned the survivors and population controls. To those agreeing to consider participation we mailed the questionnaire. Three weeks later, we posted a thank-you-and-reminder-card. When appropriate, we made reminder telephone calls to those not responding. All actions were taken by a neutral third-party secretariat [16]. The data collectors had not been involved in the actual care. The ethical review board approved of the study.

Statistical analysis

A previous article described the assignment of symptoms to the five syndromes. For each syndrome, we weighed the answers concerning person-incidence for each symptom by a measure (factor loading) obtained from a previously described factor analysis [4]. We used the sum as a measure of syndrome intensity. We normalized the factor scores using the values for both survivors and controls, that is, since the mean is 0.0 in the normalized score negative numbers are assigned to subjects despite those having one or several symptoms in a specific syndrome.

For each group and syndrome, we calculated the mean of the values of syndrome intensity (mean of normalized factor scores) for the persons in the group. We also calculated the standard error of the means. To compare groups, we used Spearman correlation. To dichotomize (having or not having a specific syndrome), we used a cutoff value of the 85th percentile of the intensity (normalized factor score) among the population controls. In each group, we calculated the percentage of subjects having the syndrome and calculated percentage ratios (cited as relative risks) as a measure of the association, for example, between smoking and having the urgency syndrome. Log-binominal models modeled the adjusted relative risks and the calculations were made in SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Demography

As seen in Table 1, current smokers had a younger age at the time of treatment and at follow-up than former smokers and never-smokers. Employment status and place of residence were similar between smoking categories, while the percentage of smokers having a body mass index above 30 was somewhat less among smokers. Smokers more often reported that they never exercised. Cervical cancer and endometrial cancer dominated as targets for the radiotherapy and

Table 1. Demographic properties according to smoking status.

	Gynecological cancer survivors			Population controls		
	($N = 623$)			($N = 344$)		
	Smoking status			Smoking status		
	Never ($N = 278$)	Former ($N = 190$)	Current ($N = 141$)	Never ($N = 146$)	Former ($N = 108$)	Current ($N = 88$)
Age at follow-up						
Median	67.0	64.3	62.1	63.0	58.0	53.1
IQR[a]	60.7–73.6	57.8–71.0	54.6–68.6	47.0–72.1	48.1–68.0	47.0–62.0
Range[b]	29.6–79.1	33.8–79.0	27.6–79.1	35.9–79.7	37.0–79.6	37.0–78.1
Missing data	(# = 0)			(# = 2)		
Age at treatment						
Median	60.2	57.7	54.1	–	–	–
IQR[a]	53.6–66.8	51.2–63.9	46.9–61.1	–	–	–
Range[b]	26.4–75.5	25.6–75.6	18.5–74	–	–	–
Missing data	(# = 14)			(# = –)		
Marital status						
Married/partner	170 (61.4%)	106 (55.8%)	70 (50%)	94 (64.4%)	71 (65.7%)	53 (60.2%)
Widow	37 (13.4%)	26 (13.7%)	18 (12.9%)	21 (14.4%)	9 (8.3%)	7 (8%)
Partner but lives alone	16 (5.8%)	11 (5.8%)	9 (6.4%)	8 (5.5%)	7 (6.5%)	7 (8%)
Single	54 (19.5%)	47 (24.7%)	43 (30.7%)	23 (15.8%)	21 (19.4%)	21 (23.9%)
Missing data	(# = 2)			(# = 0)		
Education						
Elementary school	94 (33.9%)	51 (26.8%)	46 (32.6%)	33 (22.9%)	20 (18.5%)	16 (18.2%)
Secondary school	99 (35.7%)	73 (38.4%)	59 (41.8%)	52 (36.1%)	44 (40.7%)	48 (54.5%)
College or university	84 (30.3%)	66 (34.7%)	36 (25.5%)	59 (41%)	44 (40.7%)	24 (27.3%)
Missing data	(# = 1)			(# = 2)		
Body mass index						
$\leq$18.5	7 (2.7%)	4 (2.2%)	6 (4.4%)	1 (0.7%)	2 (1.9%)	2 (2.3%)
18.5–25	117 (44.7%)	85 (47.5%)	66 (48.5%)	64 (47.4%)	52 (50%)	47 (54.7%)
25–30	87 (33.2%)	63 (35.2%)	45 (33.1%)	51 (37.8%)	36 (34.6%)	27 (31.4%)
$\geq$30	51 (19.5%)	27 (15.1%)	19 (14%)	19 (14.1%)	14 (13.5%)	10 (11.6%)
Missing data	(# = 38)			(# = 17)		
Parity						
Never given birth	70 (25.2%)	46 (24.2%)	42 (29.8%)	22 (15.1%)	10 (9.3 %)	13 (14.8%)
1–3 children	188 (67.6%)	133 (70%)	83 (58.9%)	113 (77.4%)	93 (86.1%)	72 (81.8%)
>3 children	20 (7.2%)	11 (5.8%)	16 (11.3%)	11 (7.5%)	5 (4.6%)	3 (3.4%)
Missing data	(# = 0)			(# = 0)		
Caesarean section						
Yes	12 (4.4%)	10 (5.3%)	6 (4.3%)	13 (8.9%)	19 (17.9%)	8 (9.1%)
No	263 (95.6%)	177 (94.7%)	134 (95.7%)	133 (91.1%)	87 (82.1%)	80 (90.9%)
Missing data	(# = 7)			(# = 2)		
Anal injury[c]						
Yes	5 (1.8%)	6 (3.2%)	7 (5.1%)	8 (5.5%)	6 (5.7%)	3 (3.4%)
No	266 (98.2%)	180 (96.8%)	130 (94.9%)	138 (94.5%)	100 (94.3%)	85 (96.6%)
Missing data	(# = 19)			(# = 2)		
Irritable bowel syndrome						
Yes	7 (2.6%)	7 (3.7%)	9 (6.7%)	4 (2.8%)	5 (4.7%)	4 (4.8%)
No	264 (97.4%)	180 (96.3%)	126 (93.3%)	137 (97.2%)	101 (95.3%)	79 (95.2%)
Missing data	(# = 20)			(# = 12)		
Crohn's disease						
Yes	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No	274 (100%)	183 (99.5%)	137 (100%)	141 (100%)	106 (100%)	83 (100%)
Missing data	(# = 18)			(# = 12)		
Ulcerative colitis						
Yes	1 (0.4%)	2 (1.1%)	1 (0.8%)	3 (2.1%)	2 (1.9%)	2 (2.5%)
No	263 (99.6%)	182 (98.9%)	132 (99.2%)	137 (97.9%)	104 (98.1%)	77 (97.5%)
Missing data	(# = 33)			(# = 17)		
Diabetes mellitus						
Yes	26 (9.4%)	15 (8%)	11 (7.8%)	5 (3.5%)	6 (5.6%)	6 (6.8%)
No	252 (90.6%)	172 (92%)	130 (92.2%)	136 (96.5%)	101 (94.4%)	82 (93.2%)
Missing data	(# = 5)			(# = 6)		
Heart failure						
Yes	9 (3.3%)	10 (5.4%)	10 (7.1%)	4 (2.8%)	3 (2.8%)	1 (1.1%)
No	264 (96.7%)	175 (94.6%)	130 (92.9%)	140 (97.2%)	104 (97.2%)	87 (98.9%)
Missing data	(# = 13)			(# = 3)		
Cardiac infarction						
Yes	7 (2.6%)	5 (2.7%)	6 (4.3%)	1 (0.7%)	3 (2.8%)	1 (1.1%)
No	266 (97.4%)	180 (97.3%)	134 (95.7%)	143 (99.3%)	104 (97.2%)	87 (98.9%)
Missing data	(# = 13)			(# = 3)		
Angina pectoris						
Yes	12 (4.4%)	12 (6.5%)	7 (5%)	5 (3.5%)	4 (3.7%)	2 (2.3%)
No	261 (95.6%)	173 (93.5%)	133 (95%)	139 (96.5%)	103 (96.3%)	86 (97.7%)
Missing data	(# = 13)			(# = 3)		
Rheumatism						
Yes	18 (6.6%)	17 (9.2%)	5 (3.6%)	6 (4.2%)	6 (5.6%)	7 (8%)
No	254 (93.4%)	168 (90.8%)	135 (96.4%)	138 (95.8%)	101 (94.4%)	81 (92%)
Missing data	(# = 14)			(# = 3)		

(*continued*)

Table 1. Continued

	Gynecological cancer survivors (*N* = 623)			Population controls (*N* = 344)		
	Smoking status			Smoking status		
	Never (*N* = 278)	Former (*N* = 190)	Current (*N* = 141)	Never (*N* = 146)	Former (*N* = 108)	Current (*N* = 88)
Diagnosis						
Sarcoma uteri	16 (5.8%)	7 (3.7%)	7 (5%)	–	–	–
Vulvar cancer	0 (0%)	3 (1.6%)	3 (2.1%)	–	–	–
Vaginal cancer	3 (1.1%)	6 (3.2%)	5 (3.5%)	–	–	–
Cervical cancer	52 (18.7%)	41 (21.6%)	49 (34.8%)	–	–	–
Endometrial cancer	185 (66.5%)	106 (55.8%)	64 (45.4%)	–	–	–
Ovarian cancer	17 (6.1%)	19 (10%)	12 (8.5%)	–	–	–
Fallopian tube cancer	5 (1.8%)	8 (4.2%)	1 (0.7%)	–	–	–
Missing data	(# = 0)			(# = –)		
Prescribed to dose to tumor						
EBRT[d] (median)	44.8	40	44.9	–	–	–
EBRT[d] (IQR[a])	39.6–46	39.6–46	40–46.8	–	–	–
EBRT[d] (range[b])	14.4–67	28.8–67	10.8–70	–	–	–
Missing data	(# = 1)			(# = –)		
Prescribed to dose to tumor						
Brachy (median)	10	10	10	–	–	–
Brachy (IQR[a])	0–10	0–10	0–20	–	–	–
Brachy (range[b])	0–48	0–48	0–48.5	–	–	–
Missing data	(# = 168)			(# = –)		
Dose to anal-sphincter						
Mean (median)	33.8	35.0	37.1	–	–	–
Mean (IQR[a])	25.5–37.9	27.0–39.6	28.6–41.6	–	–	–
Mean (range[b])	3.0–64.1	3.2–64.0	1.9–63.6	–	–	–
Missing data	(# = 96)			(# = –)		
Max (median)	40.2	39.4	41.8	–	–	–
Max (IQR[a])	38.0–44.4	37.8–44.5	38.3–45.2	–	–	–
Max (range[b])	8.1–66.7	4.3–67.1	2.6–66.2	–	–	–
Missing data	(# = 96)			(# = –)		
Dose to rectum						
Mean (median)	43.8	40.5	43.5	–	–	–
Mean (IQR[a])	39.9–46.2	39.5–45.9	39.7–46.5	–	–	–
Mean (range[b])	9.5–66.8	8.1–68	10.8–68.3	–	–	–
Missing data	(# = 96)			(#=–)		
Max (median)	45.3	42.2	45.2	–	–	–
Max (IQR[a])	41.2–47.4	40.9–47.2	41.5–48.4	–	–	–
Max (range[b])	19.7–70.2	26.9–70.0	11.2–70.7	–	–	–
Missing data	(# = 96)			(# = –)		
Dose to sigmoid						
Mean (median)	40.7	40.7	41.5	–	–	–
Mean (IQR[a])	38.6–44.7	38.8–43.7	39.3–45.6	–	–	–
Mean (range[b])	19.5–61.2	23.5–59.5	10.8–60.7	–	–	–
Missing data	(# = 94)			(# =–)		
Max (median)	46.0	43.0	46.3	–	–	–
Max (IQR[a])	41.6–47.7	41.4–47.4	41.6–48.9	–	–	–
Max (range[b])	20.3–68.4	27.3–69.0	11.3–71.5	–	–	–
Missing data	(# = 94)			(# = –)		
Dose to small-intestines						
Mean (median)	40.6	40.8	42.2	–	–	–
Mean (IQR[a])	38.6–44.8	39.4–44.7	40–46.1	–	–	–
Mean (range[b])	19.5–57.3	26.2–59.0	11.0–66.1	–	–	–
Missing data	(# = 110)			(# = –)		
Max (median)	45.6	42.5	46.4	–	–	–
Max (IQR[a])	41.5–47.5	41.3–47.3		–	–	–
Max (range[b])	20.3–69.6	27.2–68.0	11.4–71.1	–	–	–
Missing data	(# = 110)			(# = –)		
Treatment modality						
Surgery + EBRT[d]	15 (5.4%)	16 (8.5%)	16 (11.3%)	–	–	–
Surgery + EBRTd + BT[e]	166 (59.7%)	97 (51.3%)	65 (46.1%)	–	–	–
Surgery + EBRTd + chemo[f]	21 (7.6%)	27 (14.3%)	15 (10.6%)	–	–	–
Surgery + EBRTd + BTe + chemo[f]	57 (20.5%)	36 (19%)	19 (13.5%)	–	–	–
EBRT[d]	0 (0%)	1 (0.5%)	1 (0.7%)	–	–	–
EBRT[d] + BT[e]	8 (2.9%)	7 (3.7%)	12 (8.5%)	–	–	–
EBRT[d] + Chemo[f]	2 (0.7%)	1 (0.5%)	4 (2.8%)	–	–	–
EBRT[d] + Chemo[f] + BT[e]	9 (3.2%)	4 (2.1%)	9 (6.4%)	–	–	–
Missing data	(# = 1)			(# = –)		

[a]IQR denotes inter quartile range.
[b]Range denotes interval between minimum and maximum value.
[c]Inflicted during delivery or at other occasion.
[d]EBRT denotes external beam radiation therapy.
[e]BT denotes brachytherapy.
[f]Chemo denotes chemo therapy.

most patients had undergone surgery in addition to radiotherapy as part of their therapy. The median dose to the delineated risk organs, anal sphincter, rectum, sigmoid and the small bowel, was somewhat higher for the smokers.

Mean factor scores

The factor scores are normalized to the values for all 967 (623 survivors and 344 matched controls) subjects. That is, the mean factor score, interpreted as the mean intensity of the syndrome, is set to 0.0 in each of the five syndromes. This explains the occurrence of negative numbers and that they denote the occurrence of the symptoms that are included in the respective syndrome.

Table 2 and Figure 1 showed a much higher intensity of the urgency syndrome among current smokers than among never-smokers (2.5 against 0.4) with former smokers being in between (1.2). Similarly, smoking is also associated with this syndrome among controls; the corresponding figures are 1.1, −2.1 and −2.6. A clearly statistically significant association was also found for excessive gas discharge (factor scores being 0.8, 0.4 and 0.0) among survivors. A p value below .05 was obtained for survivors and blood discharge but not for the leakage syndrome and excess mucus discharge.

Concerning age at the time of treatment, the highest intensities (mean factor scores) were found when the treatment was given early in life as compared to late in life (Table 2 and Figure 2), and the association was statistically significant for the urgency syndrome, excess gas discharge and blood discharge.

Only the urgency syndrome showed a statistically significant decline in intensity with increasing time of follow-up (Table 2 and Figure 3). The mean intensity increased with follow-up time for the leakage syndrome, but not in a statistically significant way. The intensity was by and large identical regardless of follow-up time for both excessive mucus discharge and blood discharge.

Table 2. Relation between factor scores and smoking among gynecological cancer survivors and population controls.

	Study population Survivors ($N = 623$), controls ($N = 344$)			
	Smoking status (#Missing; survivors = 14, controls = 2) Mean factor score (± SEM)			Spearman correlation Rho (p value)
Survivorship-diseases	Never Survivors, $N = 278$ Controls, $N = 146$	Former Survivors, $N = 190$ Controls, $N = 108$	Current Survivors, $N = 141$ Controls, $N = 88$	Correlation between factor scores and smoking
Urgency syndrome				
Survivors	0.4 (0.2–0.7)	1.2 (0.9–1.5)	2.5 (2.0–2.9)	.17 (<.001)
Controls	−2.6 (−2.8–−2.4)	−2.1 (−2.3–−1.9)	−1.1 (−1.5–−0.6)	.15 (.005)
Leakage syndrome				
Survivors	0.3 (0.1–0.5)	0.4 (0.2–0.6)	0.8 (0.5–1.1)	.05 (.243)
Controls	−0.9 (−1–−0.9)	−0.9 (−0.9–−0.8)	−0.4 (−0.7–−0.1)	.06 (.241)
Excessive gas discharge				
Survivors	0.0 (−0.1–0.1)	0.4 (0.3–0.6)	0.8 (0.6–1.1)	.13 (.001)
Controls	−0.7 (−0.8–−0.6)	−0.5 (−0.7–−0.4)	−0.3 (−0.6–−0.1)	.03 (.572)
Excessive mucus discharge				
Survivors	0.1 (0.0–0.3)	0.1 (0.0–0.2)	0.4 (0.2–0.6)	.05 (.201)
Controls	−0.4 (−0.4–−0.3)	−0.4 (−0.5–−0.3)	−0.1 (−0.3–0.1)	.02 (.660)
Blood discharge				
Survivors	0 (−0.1–0.1)	0.2 (0.1–0.4)	0.2 (0.0–0.3)	.10 (.015)
Controls	−0.4 (−0.4–−0.3)	0.1 (−0.2–0.3)	−0.3 (−0.4–−0.2)	.07 (.214)
	Age at treatment (#Missing; survivors = 14) Mean factor score (± SEM)			Spearman correlation Rho (p value)
	18–45 years Survivors, $N = 88$	45–60 years Survivors, $N = 262$	60–76 years Survivors, $N = 258$	Correlation between factor scores and age at treatment
Urgency syndrome	2.4 (1.9–2.9)	1.5 (1.3–1.8)	0.3 (0.1–0.6)	−.14 (<.001)
Leakage syndrome	0.5 (0.2–0.9)	0.5 (0.3–0.7)	0.3 (0.2–0.5)	0.01 (.86)
Excessive gas discharge	1.0 (0.7–1.3)	0.5 (0.3–0.6)	−0.1 (−0.2–0.0)	−.16 (<.001)
Excessive mucus discharge	0.5 (0.3–0.8)	0.2 (0.1–0.3)	0.1 (0.0–0.2)	−.14 (<.001)
Blood discharge	0.5 (0.3–0.8)	0.1 (0.0–0.2)	0.0 (−0.1–0.1)	−.13 (<.001)
	Time since treatment (#Missing; survivors = 14) Mean factor score (± SEM)			Spearman correlation Rho (p value)
	2–6 years Survivors, $N = 88$	6–10 years Survivors, $N = 262$	10–16 years Survivors, $N = 258$	Correlation between factor scores and time since treatment
Urgency syndrome	1.4 (1.2–1.7)	0.9 (0.6–1.3)	0.8 (0.4–1.2)	−.09 (.023)
Leakage syndrome	0.4 (0.2–0.5)	0.3 (0.1–0.5)	0.7 (0.4–1.0)	.04 (.30)
Excessive gas discharge	0.4 (0.3–0.5)	0.3 (0.1–0.5)	0.1 (−0.1–0.3)	−.05 (.24)
Excessive mucus discharge	0.2 (0.1–0.3)	0.1 (−0.1–0.2)	0.2 (0.1–0.4)	−.02 (.68)
Blood discharge	0.1 (0.0–0.2)	0.1 (0.0–0.2)	0.1 (−0.1–0.3)	−.03 (.44)

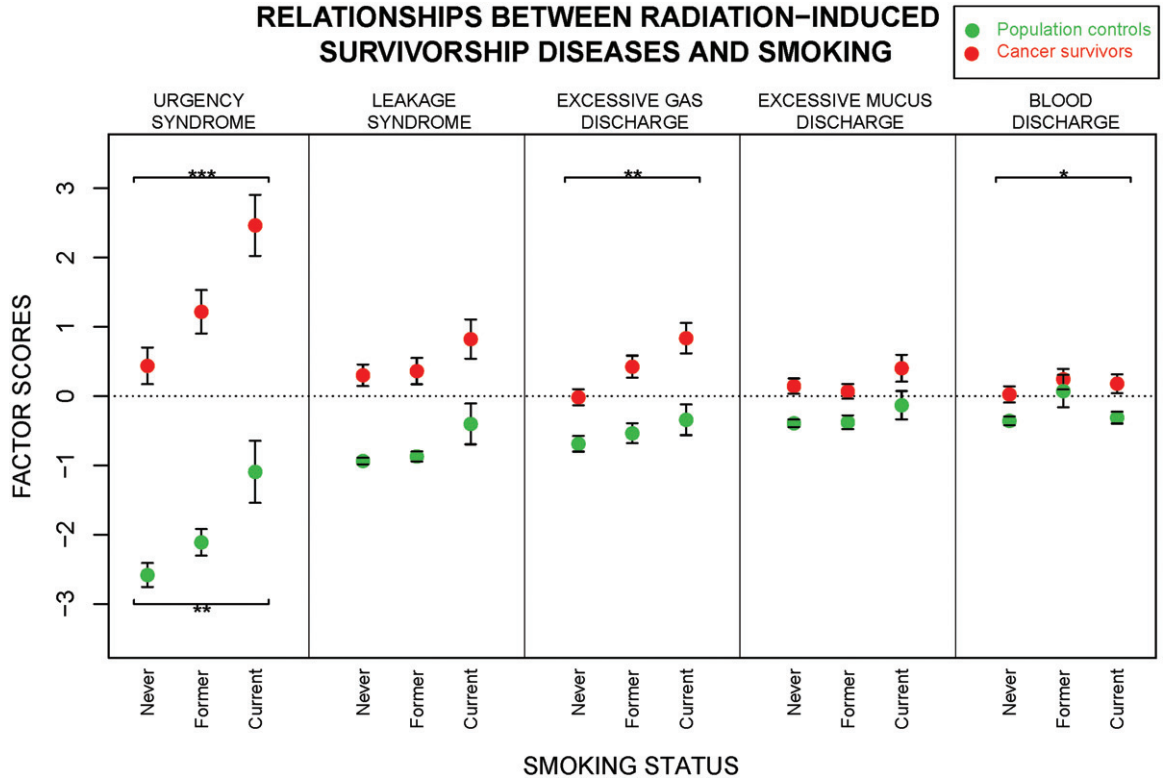

Figure 1. A graphical representation of the relations between smoking habits and the factor scores (disease intensities) of the five factors interpreted as the radiation-induced survivorship diseases *urgency syndrome*, *leakage syndrome*, *excessive gas discharge*, *excessive mucus discharge* and *blood discharge*. Solid red discs denote the estimated mean factor score of a certain radiation-induced survivorship disease within a certain smoking category. Green slid discs denote the corresponding values among population controls. The lines through the discs stretch plus minus the standard error of the mean from the means, once again for each pair of radiation-induced survivorship disease and smoking category. Asterisks encode the significance levels of the Spearman correlations between smoking and factor scores for the five radiation-induced survivorship diseases. Asterisks above the red discs correspond to the Spearman correlations between smoking and factor scores among the cancer survivors and asterisks below the green discs correspond to the Spearman correlations between smoking and factor scores among the population controls. The significance level encoding is given by ***: (−infinity, .001], **: (.001 and .01], *: (.01 and .05]. We see that there are significant Spearman correlations between smoking and factor score in the following cases: *urgency syndrome* (cancer survivors and population controls), *excessive gas discharge* (cancer survivors) and *blood discharge* (cancer survivors). In all cases are the Spearman correlations positive. For precise values see Table 2. For relative risks of developing the survivorship disease in different smoking categories, see Table 3.

In Table 3, we have dichotomized intensity factor scores at the 85th percentile among controls. Those survivors and controls that have a figure above that cutoff point are classified as having the syndrome and those below as not having the syndrome. Based on that calculation, we see that 40% of the smokers have the urgency syndrome and 21% the excessive mucus discharge. With dichotomized data we can form relative risks, which are seen in Supplementary Table. It shows that a statistically significant association (here indicated by a 95% confidence interval of the relative risk not covering 1.00) remains after adjusting for dose to risk organs, in addition to age at treatment and time since treatment, for the urgency syndrome and excessive gas discharge when current smokers are being compared to never smokers.

Discussion

Using a novel metric for intensity of five different syndromes [4], we investigated the association with smoking, age at the time of treatment and time to follow up. Information was retrieved from a population-based group of gynecological cancer survivors three to twelve years after radiotherapy as well as from population-based controls matched for age and residence [13]. We found a clear association between smoking and radiation-induced urgency syndrome and excessive gas discharge. While current smokers have the highest intensity for these syndromes, they have a somewhat lower intensity of blood discharge than former smokers. Moreover, a clear inverse relationship was observed between time to follow up and the urgency syndrome, while the relationship was directly opposite for the leakage syndrome. The results strengthen the notion that ionizing radiation induces several specific survivorship diseases with varying pathophysiological processes affecting bowel health in cancer survivors and having varying causes over time.

Available data from us and others indicate that smoking increases the occurrence of long-lasting bowel health-related syndromes among cancer survivors decreasing bowel health [6], Alsadius and coworkers studied 836 prostate-cancer survivors two to fifteen years after radiotherapy [5]. The following symptoms had a higher occurrence among current smokers as compared to never-smokers: diarrhea, abdominal cramps, defecation urgency at least once a week, sensation of bowel not being emptied after defecation and a sudden involuntary defecation into clothing without any prior warning of a need for going to the toilet. All these symptoms are urgency-related.

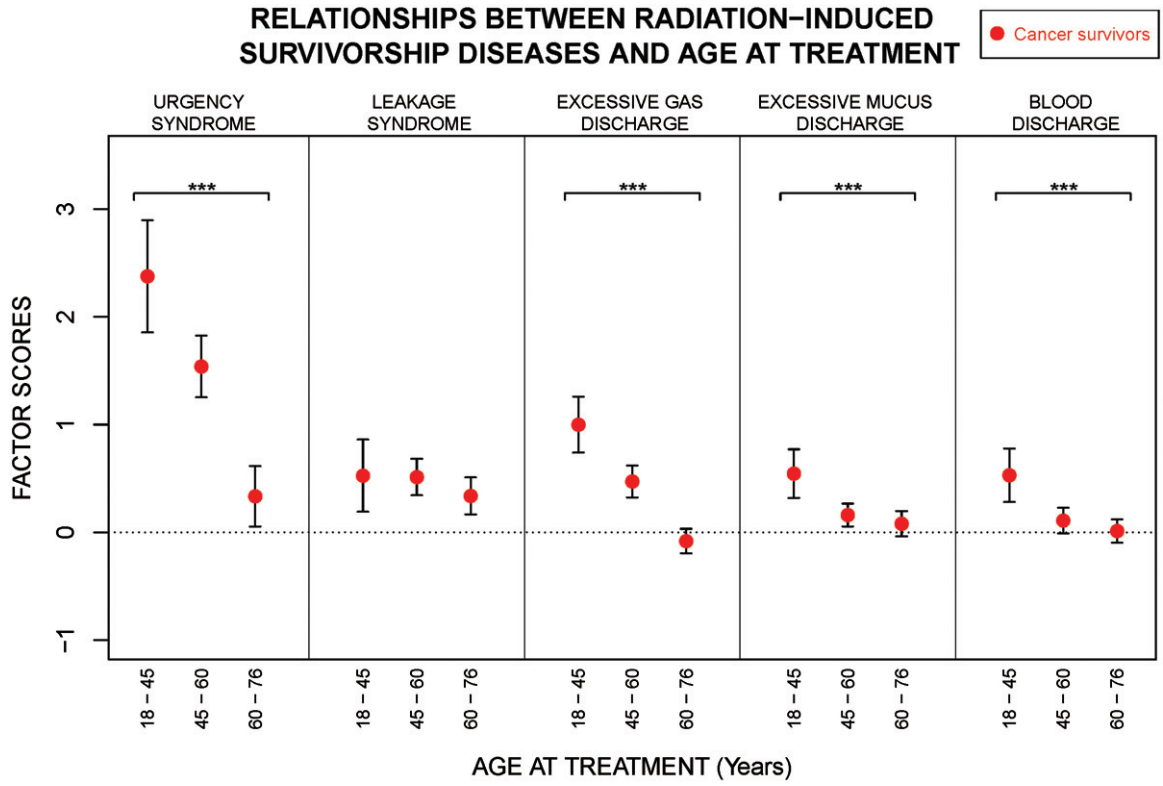

Figure 2. A graphical representation of the relations between age at treatment and the factor scores (disease intensities) of the five factors interpreted as the radiation-induced survivorship diseases *urgency syndrome*, *leakage syndrome*, *excessive gas discharge*, *excessive mucus discharge* and *blood discharge*. Solid red discs denote the estimated mean factor score of a certain radiation-induced survivorship disease within a certain interval of age at treatment. The lines through the discs stretch plus minus the standard error of the mean from the means, once again for each pair of radiation-induced survivorship disease and age at treatment interval. Asterisks encode the significance levels of the Spearman correlations between age at treatment and factor scores for the five radiation-induced survivorship diseases. The significance level encoding is given by ***: (−infinity, .001], **: (.001 and .01], *: (.01 and .05]. The intervals used were created manually as a compromise between the objectives of containing equal amounts of cancer survivors and having equal interval widths. We see that there are significant Spearman correlations between age at treatment and factor scores in the following cases: *urgency syndrome*, *excessive gas discharge*, *excessive mucus discharge* and *blood discharge*. In all cases are the Spearman correlations negative. For precise values see Table 2. The intervals used in this figure also formed the basis of the calculation of relative risks of survivorship disease development in different ranges of age at treatment. For relative risks, see Table 3.

Varying mechanisms have been proposed for the mechanism of smoking facilitating the processes that ultimately result in a radiation-induced survivorship disease. Radiation-induced damage to endothelial cells in small vessels of the gut wall may attract leukocytes [17]. The leucocytes may adhere to each other, and cause obstruction of small post-capillary vessels. The obstruction may lead to hypoxia and a subsequent gut-wall ischemia [18], which in turn may initiate inflammatory and fibrotic processes hindering the gut wall from healing after radiotherapy [11,19]. Inhaling smoke leads to a constriction of small blood vessels [20] and there may be a synergy between leucocyte-induced obstruction and smoking-related vessel constriction for the occurrence of hypoxia [17]. Moreover, certain markers of the general level of inflammation in the body are higher among current smokers than among never-smokers, indicating ongoing inflammatory processes [21]. Such general processes in the body may play a role for the specific inflammatory processes that prevent the gut wall from returning to normal function.

A strong inverse relation was found between time to follow-up and intensity of radiation induced urgency syndrome while the intensity of the leakage syndrome increased over time. We started the observation three years after the radiotherapy and possibly the patho-physiological processes leading to urgency-related symptoms at that time had reached a steady level or diminished. Taking drugs like sterculia gum, increasing stool consistency and skipping meals are, according to clinical experience, ways to decrease the intensity of the urgency syndrome [22]. Possibly a major reason for the decreased intensity is that the survivors learn to cope with their urgency-related symptoms by varying means. Leakage of bowel content, on the other hand, may increase over time since the gradual replacement of muscle with fibrotic tissue may be a lifelong process [11]. On top of that, muscles generally get weaker with increasing age.

We know little about the mechanisms involved for excess gas discharge and excess mucus discharge. The data presented here indicate that these syndromes may be the end result of pathophysiological processes other than those producing the urgency syndrome. Disturbances of the composition and function of the gut microbiota probably play a major role [9,23]. Blood discharge for many survivors depends on telangiectasias (spider veins) on the surface of a fibrotic wall [11], the normal protection by mucus may be absent when fibrotic tissue line the lumen. An obvious explanation for smoking decreasing the intensity of blood

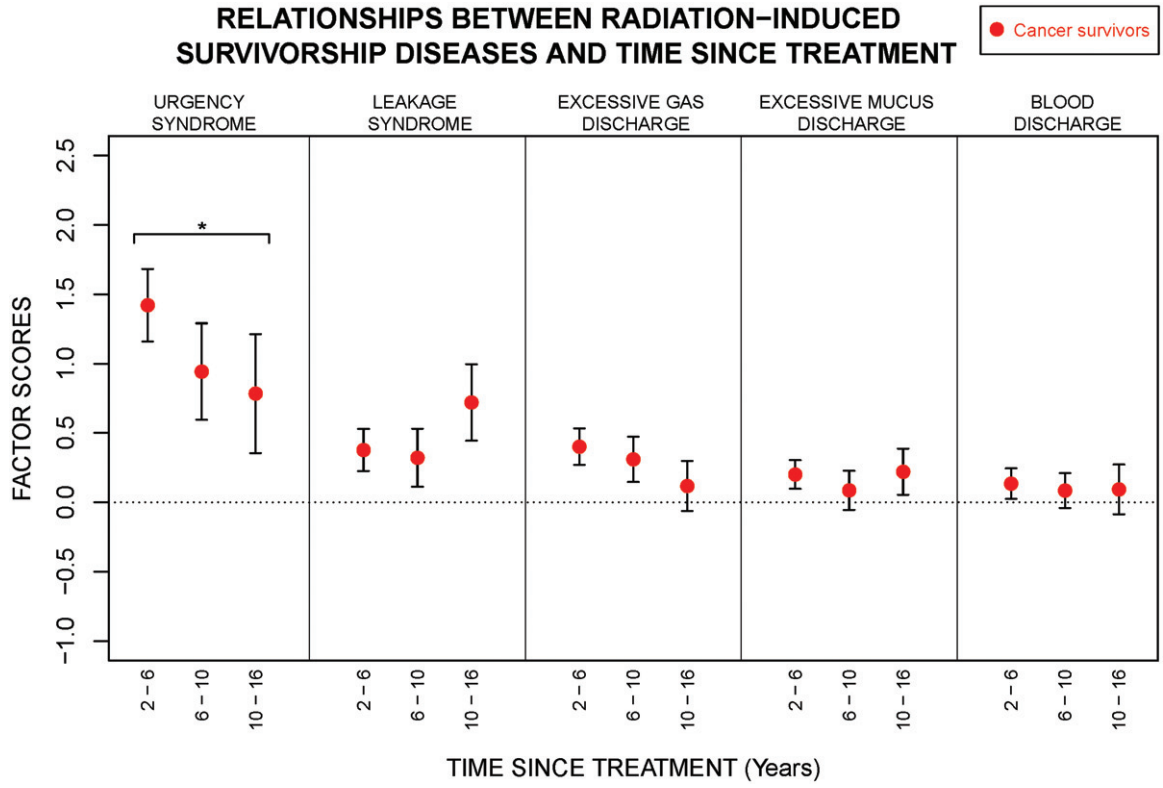

Figure 3. A graphical representation of the relations the since treatment and the factor scores (disease intensities) of the five factors interpreted as the radiation-induced survivorship diseases *urgency syndrome*, *leakage syndrome*, *excessive gas discharge*, *excessive mucus discharge* and *blood discharge*. Solid red discs denote the estimated mean factor score of a certain radiation-induced survivorship disease within a certain interval of time since treatment. The lines through the discs stretch plus minus the standard error of the mean from the means, once again for each pair of radiation-induced survivorship disease and time since treatment interval. Asterisks encode the significance levels of the Spearman correlations between time since treatment and factor scores for the five radiation-induced survivorship diseases. The significance level encoding is given by ***: (−infinity, .001], **: (.001 and .01], *: (.01 and .05]. The intervals used were created manually as a compromise between the objectives of containing equal amounts of cancer survivors and having equal interval widths. We see that there are significant Spearman correlations between time since treatment and factor scores in the case of *urgency syndrome*. In this case the Spearman correlation is negative. For precise values see Table 2. The intervals used in this figure also formed the basis of the calculation of relative risks of survivorship disease development in different ranges of time since treatment. For relative risks, see Table 3.

Table 3. Percentage having each specific late radiation-induced bowel syndrome among current, former and never smokers.

	Cancer survivors ($N = 623$)			Population controls ($N = 344$)		
	Smoking status			Smoking status		
	Never $N = 278$	Former $N = 190$	Current $N = 141$	Never $N = 146$	Former $N = 108$	Current $N = 88$
Urgency syndrome						
Disease counts *N* (%)	69 (24.8)	61 (32.1)	56 (39.7)	4 (2.7)	3 (2.8)	11 (12.5)
p Value[a]		.0064			.002	
Leakage syndrome						
Disease counts *N* (%)	83 (29.9)	63 (33.2)	53 (37.6)	8 (5.5)	6 (5.6)	7 (8.0)
p Value[a]		.28			.71	
Excessive gas discharge						
Disease counts *N* (%)	25 (9.0)	34 (17.9)	33 (23.4)	4 (2.7)	5 (6.4)	9 (10.2)
p Value[a]		.0002			.04	
Excessive mucus discharge						
Disease counts *N* (%)	47 (16.9)	32 (16.8)	29 (20.6)	7 (4.8)	4 (3.7)	8 (9.1)
p Value[a]		.60			.23	
Blood discharge						
Disease counts *N* (%)	24 (8.6)	20 (10.5)	19 (13.5)	7 (4.8)	8 (7.4)	3 (4.1)
p Value[a]		.31			.43	

[a]Chi-square test with trend.

discharge is the constriction of small vessels caused by smoking prevents telangiectasias from bleeding.

A strength of the study is that we use a novel metrics for the intensity of the specific syndromes reflecting specific radiation-induced survivorship diseases. Using these metrics instead of single symptoms or a score that nonspecifically reflects different radiation-induced survivorship diseases with varying pathophysiologies, we probably remove some noise that otherwise would have diluted the effect measures. Concerning the risk of confounding different causes, we have

no indication that another factor associated with smoking may confound the results for the urgency syndrome and excessive gas discharge. We cannot exclude, however, that the associations are different among survivors who did not participate. Concerning misclassification, it logically is low for age at follow-up and time to follow-up. The variable 'smoking' is certainly misclassified to some degree as compared to the real-life circumstances for each survivor; this misclassification leads to the data containing lower differences in intensity between the smoking categories than the true differences. The absolute levels of the intensity of the syndromes we studied reflect doses to the rectum, sigmoid and small bowel that were standard at that time in Sweden and may not reflect settings in which the doses to the bowel have another level or distribution. Moreover, in other populations than ours the prevalence of various effect-modifying factors may be different and these differences may influence the associations studied.

Studies aimed at finding means to prevent or alleviate radiation-induced survivorship diseases that decrease bowel health may benefit from clear metrics of syndrome intensity. Markers in blood and feces alongside with physical measurements and endoscopies can be added to atomized symptoms and clear-cut scales for occurrence. The crude metrics we used here, weighting together atomized late symptoms to syndromes, advance our understanding of the role of smoking and the trajectories of the survivorship diseases over time. Our study leaves no doubt that to restore bowel health after radiotherapy, cessation of smoking is crucial along with, for example, diminishing the dose of ionizing radiation to the risk organs. Moreover, the sharp decline in intensity of the urgency syndrome over time may indicate that survivors develop strategies to alleviate symptoms, perhaps by medication, modifying diet or skipping meals. There may be a body of knowledge among today's survivors; efforts to retrieve and put together such information could be fruitful for tomorrow's cancer survivors.

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Disclosure statement

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