

CT colonography screening in extracolonic cancer survivors: impact on rates of colorectal and extracolonic findings by cancer type

Matthew E. Larson,¹ and Perry J. Pickhardt¹

¹Department of Radiology, E3/311 Clinical Science Center, University of Wisconsin School of Medicine Public Health, 600 Highland Ave., Madison, WI 53792-3252, USA

Abstract

Purpose: To compare the rates of colorectal and extracolonic findings at CT colonography (CTC) screening between patients with and without a personal prior history of other.

Methods: Over a 160-month interval, 349 adults (mean age, 60.3 years; 67% female) with a positive history of extracolonic cancer [Ca(+)], excluding 271 patients with isolated non-melanoma skin cancers, underwent CTC screening. This study cohort was compared against 8859 controls (mean age, 57.0 years; 53% female) without a prior cancer history [Ca(-)]. Primary outcome measures included the rates of relevant colorectal (C-RADS C2–C4) and extracolonic (C-RADS E3–E4) findings at CTC. Wilcoxon rank sum test was used to test for statistical significance with post-hoc analysis by relative rate (RR).

Results: Both colorectal (C2–C4) and extracolonic (E3–E4) findings were significantly increased in the Ca(+) group versus Ca(-) control group ($p = 0.0283$ and 0.0236 , respectively). Positive colorectal findings were most notably increased among survivors of non-small cell lung cancer (RR 3.1), head/neck cancers (RR, 3.4), and bladder cancers (RR 2.2). The proportion of C2–C4 patients undergoing intervention in the Ca(+) cohort was not significantly different than the Ca(-). Potentially relevant extracolonic findings (E3) were increased in survivors of hematogenous malignancies (RR 2.0), while likely important extracolonic findings (E4) were increased in survivors of female gynecological malignancies (RR 3.4).

Conclusions: Relevant colorectal and extracolonic findings at CTC screening are increased in patients with a previous extracolonic cancer history, particularly among certain cancer subsets. These results may have important implications for choice of colorectal test in these patients.

Key words: CT colonography—Cancer history—Colorectal cancer—Cancer screening

Colorectal cancer is one of the most common cancers among both men and women and is responsible for nearly 50,000 deaths in the United States annually [1]. As such, the United States Preventative Services Task force recommends routine screening for all patients starting at age 50 [2]. However, these guidelines do not specifically provide guidance on screening algorithms in patients with increased risk.

While many of the risk factors for colorectal cancer have been well defined, such as increased age, male sex, and family history, a few studies have hinted at increased incidence of colorectal cancer in patients with a history of other cancers. An analysis of new primary malignancies among cancer survivors in the SEER registries, containing over two million patients, suggests an increased prevalence of colorectal cancer among survivors of many cancer types, including survivors of Hodgkin lymphoma and oropharyngeal cancers [3]. Similarly, a retrospective cohort study of second primary malignancy in over 23,000 Australian cancer survivors suggests an overall increase in colorectal cancers among all cancer survivors [4]. However, neither of these studies specifically addresses the issue in the context of colorectal cancer screening, thereby demonstrating a probable linkage between cancer types but leaving a gap in clinically useful knowledge unfilled.

Here, we examine the results of CT colonography (CTC), an imaging-based colorectal cancer screening test that also provides information regarding disease outside the colon [5] in extracolonic cancer survivors. We aim to define populations of cancer survivors that may be at greater risk for positive colorectal findings such as colorectal cancer. We also aim to define which cancer survivors are at increased risk of positive extracolonic

findings in order to identify populations in which CT colonography may be useful in monitoring non-colorectal disease. Finally, we analyzed the relative rate at which cancer survivors plan intervention following CT colonography in order to determine whether or not cancer survivors undergo intervention at a greater rate than the general population.

Materials and methods

Patient population

All individuals undergoing CTC at our institution provide a brief medical history, including their personal history of cancer, during a brief pre-screening interview. In this study, subjects with no reported history of cancer comprise the main Ca(−) control group. Subjects with a reported history of cancer comprise the Ca(+) cohort. Subjects with history of colorectal cancer were considered separately from the Ca(+) group, as history of this malignancy already puts them into a high risk category and would likely inflate the relative proportion of colorectal findings. In addition, patients with reported non-melanoma skin cancer (NMSC), including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) were also excluded from the Ca(+) cohort, as the relatively large size of this population would dominate cohort results, and the likelihood of these cancers being invasive is relatively small. Likewise, BCC and SCC are not reportable to SEER, so inclusion of these individuals to the Ca(+) cohort would make it difficult to compare our results to other population based studies.

Consecutive patients undergoing initial CTC at our institution from April 2004–August 2017 (160 months) were included in this study ($N = 9487$). Cohort demographics, including age and gender, are summarized in Table 1, along with subcohorts defined by organ system and specific malignancy. Gender-specific subcohorts are included as well. Patients with a prior history of multiple malignancies are considered within each applicable sub-cohort, as well as within the multiple malignancy sub-cohort.

CTC technique and interpretation

The CTC technique used at our institution has evolved only slightly over time and has been described in detail elsewhere [6, 7]. In summary, patients undergo a low-volume bowel preparation on the day prior to CTC using a cathartic cleansing agent; magnesium citrate or sodium phosphate was employed in over 95% of cases, with PEG utilized in most of the remaining cases [8]. Oral contrast material tagging was achieved with 2.1% w/v barium sulfate and water-soluble iodinated contrast [9]. During the CTC examination, colorectal insufflation was main-

tained using room air or automated continuous low-pressure carbon dioxide delivered through a small flexible rectal catheter [10]. Patients were routinely scanned in both supine and prone positions, with additional decubitus positioning as needed [11]. Images were acquired on 16- to 64-multidetector-row CT scanners using 1.25-mm collimation, 1-mm reconstruction interval, 120 kV_p, and 50–75 mAs or tube-current modulation (range 30–300 mA).

All CTC examinations were prospectively interpreted by one of 12 experienced board-certified radiologists practicing within our abdominal imaging section. The interpreting radiologists were not blinded to the personal cancer history data. Radiologist interpretation of CTC examinations was performed using three-dimensional endoluminal fly-through for initial polyp detection and two-dimensional cross-sectional images for secondary detection and polyp confirmation [6, 12]. All studies were interpreted using a dedicated CTC software system (Vi-atronix V3D Colon). For all studies positive for non-diminutive lesions (≥ 6 mm) detected at CTC, the lesion size, segmental location, morphology (sessile, pedunculated, flat, mass), and diagnostic confidence (3 = most, 1 = least) [13] were prospectively recorded. Patient-level C-RADS categorization for colorectal and extracolonic findings was also recorded [14]. In general, patients are referred for polypectomy for all large CTC-detected polyps (≥ 10 mm) and masses (≥ 3 cm) (C-RADS C3 and C4, respectively). For patients with one or two small (6–9 mm) polyps (C-RADS C2), patients are given the alternative of CTC surveillance if they prefer to avoid OC [15]. The initial treatment plan is thus recorded in the database and recommendations shared via the imaging report. In instances where OC may be needed or recommended, the initial plan may be discussed between interpreting radiology and/or radiology staff with the referring provider and/or patient. For extracolonic evaluation, C-RADS E3 findings are considered likely of no great importance but may be indeterminate and may require an additional test, whereas E4 findings are likely to be of clinical significance.

Statistical analysis

Initial comparisons of C-RADS colorectal and extracolonic rates between Ca(+) and Ca(−) groups were done using Wilcoxon Rank Sum test in MatLab (R2015a, The Mathworks). For colorectal findings, C1–C4 each comprised a different grouping variable. For extracolonic findings, E1 and E2 findings were pooled for the Wilcoxon Rank Sum test, as they generally do not represent a differential level of clinical concern. C-RADS C0 or E0 findings were excluded from analysis; the former is rare ($< 1\%$ of cases) and the latter category is not

Table 1. Population and cohort demographics

	Total	Age (StDev)	Male (%)	Female (%)
Total population	9487	57.2 (7.5)	4375 (46)	5112 (54)
No cancer history [Ca(-)]	8859	57.0 (7.3)	4134 (47)	4725 (53)
Positive cancer history [Ca(+)]*	349	60.3 (9.3)	115 (33)	234 (67)
Melanoma	57	57.7 (8.2)	21 (37)	36 (63)
Head and Neck	9	61.8 (9.9)	6 (67)	3 (33)
Throat/Mouth	5	64.7 (11.5)	3 (60)	2 (40)
Salivary Gland	4	58.0 (7.3)	3 (75)	1 (25)
Lung	11	67.7 (10.6)	6 (55)	5 (45)
Lung—non-small cell	10	68.3 (10.9)	5 (50)	5 (50)
Lung—small cell	1	61.5	1 (100)	0 (0)
GI non-CRC	6	62.2 (3.8)	1 (17)	5 (83)
Anal	4	60.3 (2.7)	0 (0)	4 (100)
Stomach	1	67.8	1 (100)	0 (0)
Bile duct	1	64.2	0 (0)	1 (100)
Urinary system	24	65.3 (10.9)	16 (67)	8 (33)
Bladder	14	67.4 (13.6)	8 (57)	6 (43)
Kidney/renal cell	10	62.5 (4.8)	8 (80)	2 (20)
Hematogenous	27	60.3 (9.9)	14 (52)	13 (48)
Lymphoma—non-Hodgkin's	7	59.2 (8.1)	4 (57)	3 (43)
Lymphoma—Hodgkin's	6	62.6 (14.3)	4 (67)	2 (33)
Leukemia—CLL	5	63.9 (10.9)	3 (60)	2 (40)
Leukemia—AML	3	58.3 (8.9)	1 (33)	2 (67)
Leukemia—CML	3	57.4 (9.9)	1 (33)	2 (67)
Multiple myeloma	3	57.2 (8.2)	1 (33)	2 (67)
CNS	6	61.1 (7.2)	1 (17)	5 (83)
Brain-meningioma	4	62.2 (6.9)	1 (25)	3 (75)
Brain-glial	2	58.9 (10.0)	0 (0)	2 (100)
Endocrine	14	57.1 (6.1)	5 (36)	9 (64)
Thyroid	13	57.0 (6.3)	5 (38)	8 (62)
Adrenal	1	59.5	0 (0)	1 (100)
Sarcoma	3	54.5 (6.6)	2 (67)	1 (33)
Breast	101	59.7 (8.6)	1 (1)	100 (99)
Female breast	100	59.5 (8.5)	0 (0)	100 (100)
Male breast	1	76.3	1 (100)	0 (0)
Male GU	50	65.6 (11.4)	50 (100)	0 (0)
Prostate	44	66.9 (11.2)	44 (100)	0 (0)
Testicular	5	53.2 (5.8)	5 (100)	0 (0)
Male GU-other	1	71.2	1 (100)	0 (0)
Female GYN	62	59.1 (8.5)	0 (0)	62 (100)
Uterine/endometrial	24	63.5 (9.9)	0 (0)	24 (100)
Cervical	23	55.8 (5.5)	0 (0)	23 (100)
Ovarian	15	59.0 (11.5)	0 (0)	15 (100)
Choriocarcinoma	1	56.3	0 (0)	1 (100)
Vaginal/vulvar	1	58.8	0 (0)	1 (100)
Multiple cancers*	22	69.2 (11.9)	8 (36)	14 (64)
Men, Ca(-)	4134	57.2 (7.4)	4,134 (100)	0 (0)
Men, Ca(+)*	115	62.7 (10.1)	115 (100)	0 (0)
Women, Ca(-)	4725	56.8 (7.2)	0 (0)	4,725 (100)
Women, Ca(+)*	234	59.1 (8.6)	0 (0)	234 (100)
Isolated non-melanoma skin cancer	271	59.3 (8.7)	123 (45)	148 (55)
Colorectal cancer	8	77.6 (12.4)	3 (38)	5 (63)

*Colorectal cancer and isolated non-melanoma skin cancer excluded

employed our practice. Relative rates, along with 95% confidence intervals (CIs), were calculated in Excel (Microsoft). 95% CIs not containing 1 are considered statistically significant at the $p = 0.05$ level. Subcohorts comprised of gender specific cancers (female breast, all female gynecological, and all male urological) were compared only to Ca(-) patients of the same gender for the sake of relative rate calculation. In subcohorts where a zero value interfered with calculation of RR or CI, 0.5

was added to each applicable component during calculation.

Results

Proportion of C-RADS findings among major groups and subcohorts is shown in Table 2 and compared visually in Fig. 1 (colorectal findings) and Fig. 2 (extracolonic findings). Initial statistical comparisons between Ca(-) and Ca(+) were performed using the Wilcoxon

Table 2. Summary of population and cohort findings on initial CT colonography exam

	C1 (%)	C2 (%)	C3 (%)	C4 (%)	E1 and E2 (%)	E3 (%)	E4 (%)
Total population	7880 (83)	903 (10)	566 (6)	76 (<1)	8247 (87)	1054 (11)	185 (2)
No cancer history [Ca(-)]	7380 (83)	837 (9)	521 (6)	63 (<1)	7727 (87)	965 (11)	166 (2)
Positive cancer history [Ca(+)]*	276 (79)	35 (10)	27 (8)	8 (2)	290 (83)	50 (14)	9 (3)
Melanoma	47 (82)	5 (9)	3 (5)	2 (4)	47 (82)	8 (14)	2 (4)
Head and Neck	4 (44)	2 (22)	2 (22)	1 (11)	8 (89)	1 (11)	0 (0)
Throat/mouth	2 (40)	1 (20)	1 (20)	1 (20)	5 (100)	0 (0)	0 (0)
Lung	5 (45)	2 (18)	3 (27)	1 (9)	10 (91)	1 (9)	0 (0)
Lung—non-small cell	5 (50)	2 (20)	2 (20)	1 (10)	9 (90)	1 (10)	0 (0)
GI non-CRC	4 (67)	1 (17)	1 (17)	0 (0)	6 (100)	0 (0)	0 (0)
Urinary system	19 (79)	1 (4)	3 (13)	1 (4)	21 (87)	3 (13)	0 (0)
Bladder	9 (64)	1 (7)	3 (21)	1 (7)	13 (93)	1 (7)	0 (0)
Kidney/renal cell	10 (100)	0 (0)	0 (0)	0 (0)	8 (80)	2 (20)	0 (0)
Hematogenous	22 (81)	0 (0)	4 (15)	0 (0)	20 (74)	6 (22)	1 (4)
Lymphoma—non-Hodgkin's	6 (86)	0 (0)	0 (0)	0 (0)	5 (71)	2 (29)	0 (0)
Lymphoma—Hodgkin's	4 (67)	0 (0)	2 (33)	0 (0)	5 (83)	1 (17)	0 (0)
Leukemia—CLL	5 (100)	0 (0)	0 (0)	0 (0)	3 (60)	2 (40)	0 (0)
CNS	6 (100)	0 (0)	0 (0)	0 (0)	6 (100)	0 (0)	0 (0)
Endocrine	11 (79)	3 (21)	0 (0)	0 (0)	14 (100)	0 (0)	0 (0)
Thyroid	10 (77)	3 (23)	0 (0)	0 (0)	13 (100)	0 (0)	0 (0)
Breast	81 (80)	10 (10)	8 (8)	1 (< 1)	83 (82)	15 (15)	3 (3)
Female breast	80 (80)	10 (10)	8 (8)	1 (1)	83 (83)	15 (15)	2 (2)
Male GU	34 (68)	11 (22)	5 (10)	0 (0)	43 (86)	7 (14)	0 (0)
Prostate	28 (64)	11 (25)	5 (11)	0 (0)	38 (86)	6 (14)	0 (0)
Testicular	5 (100)	0 (0)	0 (0)	0 (0)	4 (80)	1 (20)	0 (0)
Female GYN	54 (87)	3 (5)	1 (2)	2 (3)	50 (81)	8 (13)	4 (6)
Uterine/endometrial	19 (79)	2 (8)	1 (4)	1 (4)	22 (92)	2 (8)	0 (0)
Cervical	21 (91)	1 (4)	0 (0)	0 (0)	18 (78)	4 (17)	1 (4)
Ovarian	14 (93)	0 (0)	0 (0)	1 (7)	11 (73)	1 (7)	3 (20)
Multiple cancers*	15 (68)	3 (14)	3 (14)	0 (0)	21 (95)	0 (0)	1 (5)
Men, Ca(-)	3329 (81)	454 (11)	299 (7)	27 (<1)	3651 (88)	405 (10)	77 (2)
Men, Ca(+)*	82 (71)	17 (15)	14 (12)	1 (<1)	97 (84)	17 (15)	1 (<1)
Women, Ca(-)	4051 (86)	383 (8)	222 (5)	36 (<1)	4076 (86)	560 (12)	89 (2)
Women, Ca(+)*	194 (83)	18 (8)	13 (6)	7 (3)	193 (82)	33 (14)	8 (3)
Isolated non-melanoma skin cancer	218 (80)	29 (11)	18 (7)	5 (2)	223 (82)	39 (14)	9 (3)
Colorectal cancer	6 (75)	2 (25)	0 (0)	0 (0)	7 (88)	0 (0)	1 (13)

*Colorectal cancer and isolated non-melanoma skin cancer cases excluded

rank sum test in order to compare the overall distribution of colorectal and extracolonic findings between groups. For both colorectal and extracolonic findings, this test demonstrated a statistically significant difference in distribution ($p = 0.028$ and $p = 0.024$, respectively) between cohorts. Mean ranks for both colorectal and extracolonic findings are greater in the Ca(+) group than the Ca(-) group, indicating that cancer survivors tend to have both higher graded colorectal and extracolonic findings at initial screening CTC.

To better characterize these differences in a clinically intuitive manner, relative rates (RR) were calculated for each subcohort with 5 or more patients (Table 3). RR was calculated two ways for both colorectal and extracolonic findings in order to highlight subtle differences in clinical questions that this study was designed to answer. For colorectal findings, RR is reported by any positive CTC result (C2–C4 vs. C1) and also by concerning CTC result (C3–C4 vs. C1–C2). For extracolonic findings, RR is reported by any potentially relevant finding (E3–E4 vs. E1–E2) and by likely concerning findings (E4 vs. E1–E3). While RR of C3–C4 results was increased in Ca(+) cohort (RR = 1.5, 95% CI 1.1–2.1), the most striking re-

sults were that of head and neck cancer survivors (RR = 5.0, 95% CI 2.0–12.7), especially throat/mouth cancer survivors (RR = 6, 95% CI 2.1–17.7), and bladder cancer survivors (RR = 4.3, 95% CI 1.9–9.9). As an example, a C3 finding of large cecal polyp in a bladder cancer survivor is shown in Figure 3. Standouts among potentially concerning extracolonic findings (E3–E4) include survivors of hematogenous malignancy (RR = 2.0, 95% CI 1.1–3.9), especially those with CLL (RR = 3.1, 95% CI 1.1–9.2). RR of concerning extracolonic finding (E4 alone) were elevated in survivors of female gynecologic malignancies (RR = 3.4, 95% CI 1.3–9.0), especially those with ovarian cancer (RR = 10.6, 95% CI 3.8–29.8). As an example, an E4 finding of a breast mass in a female gynecologic (cervical) cancer patient is illustrated in Figure 4. RR in any category among those with multiple prior cancers (CRC and NMSC excluded) was not significantly different from the Ca(-) cohort.

Finally, we compared the rates of planned intervention (including optical colonoscopy, flexible sigmoidoscopy, and surgery) for C2, C3, and C4 findings between Ca(+) and Ca(-) cohorts. Within each cate-

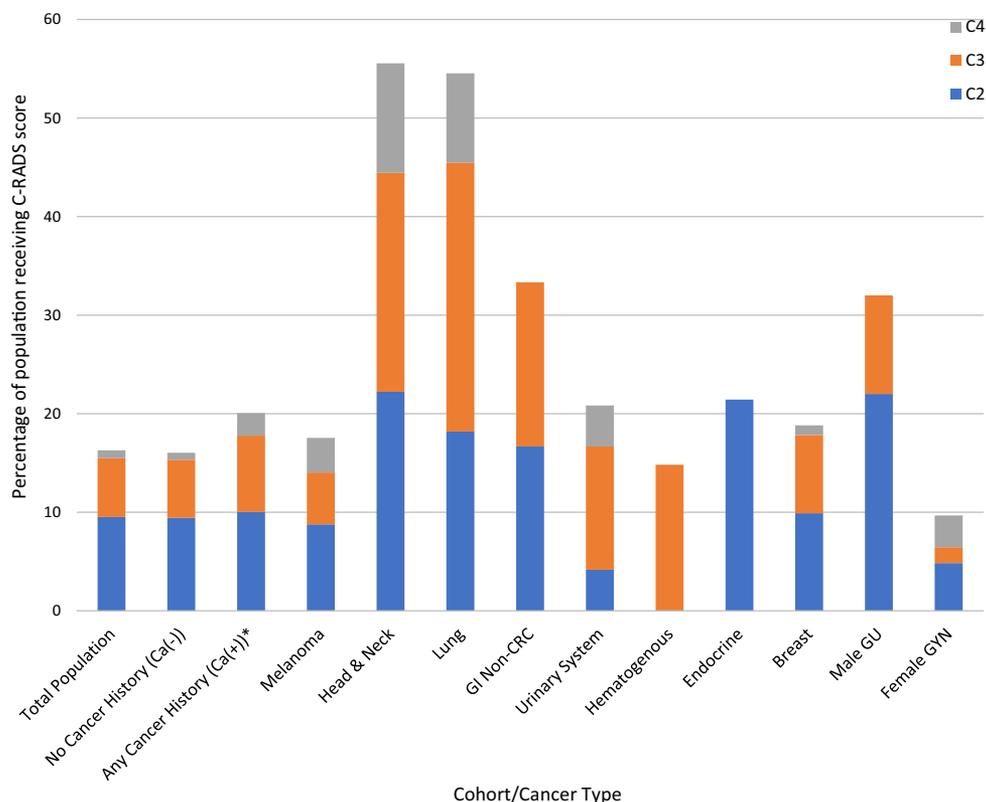


Fig. 1. Rate of positive colorectal C-RADS findings at CT colonography by patient cancer history. (*Colorectal cancer and isolated non-melanoma skin cancer cases excluded).

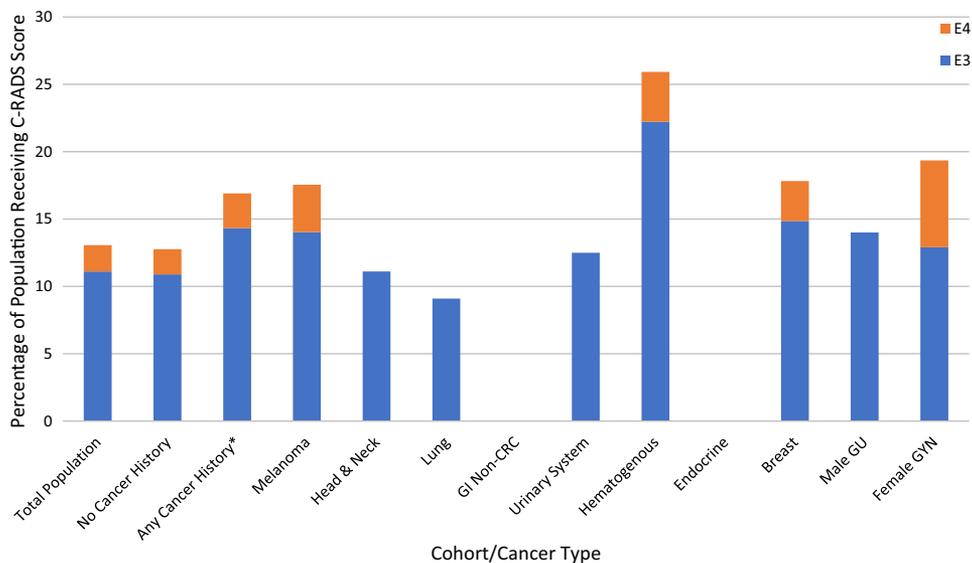


Fig. 2. Rate of positive extracolonic C-RADS findings at CT colonography by patient cancer history. (*Colorectal cancer and isolated non-melanoma skin cancer cases excluded).

gory, the proportion of patients planning for intervention based on CTC findings was less in the Ca(+) category than in the Ca(-) category (Figure 5). However, analysis of relative rate revealed no significant difference between the groups (Table 4).

Discussion

Colorectal findings

While rate of colorectal findings is generally increased within the entire Ca(+) cohort, a few specific cancer

Table 3. Relative risk of colorectal and extracolonic findings at CT colonography in patients with a past history of cancer vs. patients without a history of cancer

	Relative risk (95% CI) by C-RADS score			
	C2–C4	C3–C4	E3–E4	E4
Positive cancer history [Ca(+)]*	1.3 (1.0, 1.6)	1.5 (1.1, 2.1)	1.3 (1.0, 1.7)	1.4 (0.7, 2.7)
Melanoma	1.1 (0.6, 1.9)	1.3 (0.6, 3.1)	1.4 (0.8, 2.4)	1.9 (0.5, 7.4)
Head and neck	3.4 (1.9, 6.2)	5.0 (2.0, 12.7)	0.9 (0.1, 5.5)	2.7 (0.2, 39.8)
Throat/mouth	3.7 (1.8, 7.6)	6.0 (2.1, 17.7)	0.7 (0.0, 9.3)	4.4 (0.3, 63.3)
Lung	3.4 (2.0, 5.8)	5.5 (2.5, 12.0)	0.7 (0.1, 4.6)	2.2 (0.1, 33.6)
Lung—non-small cell	3.1 (1.7, 5.8)	4.5 (1.7, 11.7)	0.8 (0.1, 5.0)	2.4 (0.2, 36.4)
GI non-CRC	2.1 (0.7, 6.4)	2.5 (0.4, 15.1)	0.6 (0.0, 8.1)	3.8 (0.3, 55.2)
Urinary system	1.3 (0.6, 2.8)	2.5 (1.0, 6.2)	1.0 (0.3, 2.8)	1.1 (0.1, 16.6)
Bladder	2.2 (1.1, 4.5)	4.3 (1.9, 9.9)	0.6 (0.1, 3.7)	1.8 (0.1, 27.2)
Kidney/renal cell	0.3 (0.0, 4.2)	0.7 (0.0, 10.3)	1.6 (0.5, 5.4)	2.4 (0.2, 36.4)
Hematogenous	1.0 (0.4, 2.4)	2.3 (0.9, 5.7)	2.0 (1.1, 3.9)	2.0 (0.3, 13.6)
Lymphoma—non-Hodgkin's	0.4 (0.0, 6.4)	1.1 (0.1, 15.6)	2.2 (0.7, 7.2)	3.3 (0.2, 48.9)
Lymphoma—Hodgkin's	2.1 (0.7, 6.4)	5.0 (1.6, 15.6)	1.3 (0.2, 7.8)	3.8 (0.3, 55.2)
Leukemia—CLL	0.5 (0.0, 7.3)	1.3 (0.1, 17.9)	3.1 (1.1, 9.2)	4.4 (0.3, 63.3)
CNS	0.4 (0.0, 6.4)	1.1 (0.1, 15.6)	0.6 (0.0, 8.1)	3.8 (0.3, 55.2)
Endocrine	1.3 (0.5, 3.6)	0.5 (0.0, 7.7)	0.3 (0.0, 4.0)	1.8 (0.1, 27.2)
Thyroid	1.4 (0.5, 3.9)	0.5 (0.0, 8.2)	0.3 (0.0, 4.3)	1.9 (0.1, 29.0)
Breast	1.2 (0.8, 1.8)	1.4 (0.7, 2.5)	1.4 (0.9, 2.1)	1.6 (0.5, 4.9)
Female breast	1.4 (0.9, 2.1)	1.7 (0.9, 3.1)	1.2 (0.8, 1.9)	1.1 (0.3, 4.3)
Male GU	1.7 (1.1, 2.5)	1.3 (0.5, 2.9)	1.2 (0.6, 2.4)	0.5 (0.0, 8.3)
Prostate	1.9 (1.3, 2.8)	1.4 (0.6, 3.3)	1.2 (0.6, 2.5)	0.6 (0.0, 9.4)
Testicular	0.4 (0.0, 6.2)	1.0 (0.1, 14.9)	1.7 (0.3, 9.9)	4.4 (0.3, 63.7)
Female GYN	0.7 (0.3, 1.6)	0.9 (0.3, 2.8)	1.4 (0.8, 2.4)	3.4 (1.3, 9.0)
Uterine	1.3 (0.5, 3.1)	1.6 (0.4, 6.0)	0.6 (0.2, 2.3)	1.1 (0.1, 16.5)
Cervical	0.3 (0.0, 2.3)	0.4 (0.0, 6.1)	1.6 (0.7, 3.4)	2.3 (0.3, 15.9)
Ovarian	0.5 (0.1, 3.2)	1.2 (0.2, 8.1)	1.9 (0.8, 4.5)	10.6 (3.8, 29.8)
Multiple cancers*	1.8 (0.9, 3.5)	2.2 (0.8, 6.2)	0.4 (0.1, 2.4)	2.4 (0.4, 16.6)
Men, Ca(–)	1.2 (1.1, 1.3)	1.2 (1.0, 1.4)	0.9 (0.8, 1.0)	1.0 (0.8, 1.3)
Men, Ca(+)*	1.5 (1.1, 2.0)	1.7 (1.0, 2.7)	1.3 (0.9, 2.1)	0.5 (0.1, 3.3)
Women, Ca(–)	0.8 (0.8, 0.9)	0.8 (0.7, 1.0)	1.1 (1.0, 1.2)	1.0 (0.8, 1.3)
Women, Ca(+)*	1.2 (0.9, 1.6)	1.6 (1.0, 2.4)	1.3 (1.0, 1.7)	1.8 (0.9, 3.7)
Isolated non-melanoma skin cancer	1.2 (0.9, 1.5)	1.3 (0.9, 1.9)	1.4 (1.1, 1.8)	1.8 (0.9, 3.4)
Colorectal cancer	1.5 (0.5, 5.1)	0.8 (0.1, 12.4)	1.0 (0.2, 6.1)	6.7 (1.1, 42.0)

*Colorectal cancer and isolated NMSC excluded

Statistically significant values ($p < 0.05$) are highlighted in bold

types appear to be more prominent. Those with head and neck cancers (specifically mouth/throat) are substantially more likely to have positive CTC findings, consistent with the correlation between head and neck cancer and colorectal cancer reported in the NIH monograph for the whole population [16] and for men only by Youlden et al. [4]. To the best of our knowledge, the specific relationship between these malignancies has never been addressed. However, tobacco and alcohol use are proposed as risk factors for both malignancies. While these risk factors have never been examined in a CTC screening population, they have been shown to be major risk factors for advanced neoplasia found at screening optical colonoscopy and may prove to be fruitful avenues of future research.

Similarly, Our study also identified increased colonic findings in patients with a past history of lung cancer. Again, this finding is consistent with the NIH monograph [3, 17], which found a significant increase in colorectal cancer among survivors of lung cancer. Again, no specific link is proposed between these malignancies, and

common risk factors such as smoking are likely a major factor. In malignancies where smoking is a proposed common etiology, it may also prove interesting to examine whether or not specific polyp types that seem more common among smokers (serrated polyps [18]) account for the marginal increase in colorectal findings.

Our study also identified an increased rate of colorectal findings among bladder cancer survivors. Interestingly, this relationship is not echoed by the NIH monograph [19] (and is not addressed in Youlden et al [4]). However, the NIH monograph carries with it an average age of 69 for patients diagnosed with bladder cancer as an initial primary malignancy. Therefore it is difficult to compare our study population to theirs, as patients in their cohort may have had limited CRC screening after primary diagnosis due to the more advanced age at bladder cancer diagnosis. Again, we are aware of no defined connection between these two malignancies. Smoking is again a risk factor for both malignancies. However, the location of the bladder near

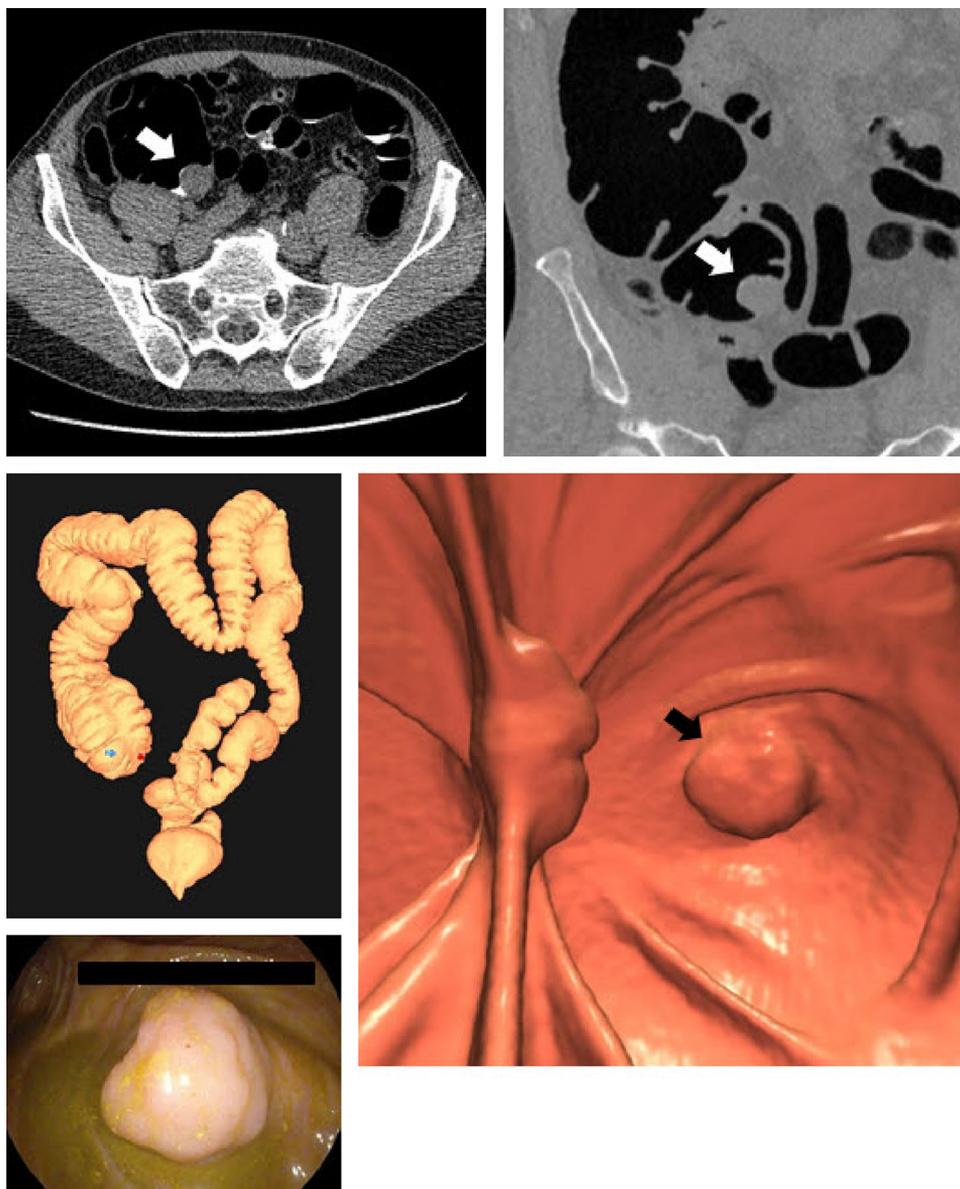


Fig. 3. Large cecal polyp (arrows) on CT colonography, a C-RADS C3 finding, noted in a 66-year-old man with past medical history of bladder cancer. This 2.3-cm polyp proved

to be a tubulovillous adenoma at surgical pathology after same-day colonoscopic resection.

the colon raises the possibility of a more direct etiology, such as treatment-related change.

We did also identify an increased rate of colorectal findings among survivors of Hodgkin Lymphoma. Interestingly, this correlates with the findings in the NIH monograph [3, 20] as well as previously published studies [21]. One prior study [21] found an increase in both colonic and rectal tumors among Hodgkin Lymphoma survivors, and suggested that radiotherapy was a major risk factor for the increased incidence of rectal tumor development.

Extracolonic findings

The significance of extracolonic findings at CTC and how they influence clinical decision-making following screening have been the subject of much debate in the literature [5]. In the population of cancer survivors, extracolonic findings have the potential to convey potentially ominous news – local recurrence of their disease, metastatic disease, or even a new primary. As demonstrated in this study, all cancer survivors are at increased risk of extracolonic findings, and should thus

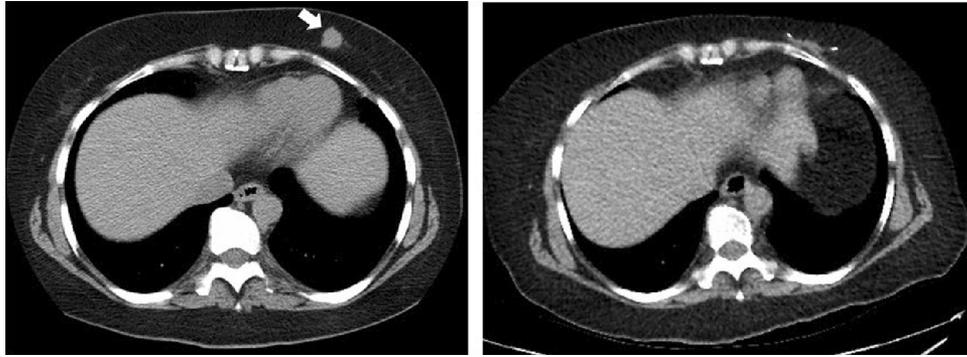


Fig. 4. Left breast mass (arrow), a C-RADS E4 finding, noted in a 50-year-old woman with a past history of gynecologic (cervical) cancer. This 2-cm lesion was missed on screening mammography three months earlier but

confirmed on subsequent diagnostic mammography. This lesion proved to be a primary breast adenocarcinoma after additional work-up. Subsequent CTC screening over 5 years later shows lumpectomy changes.

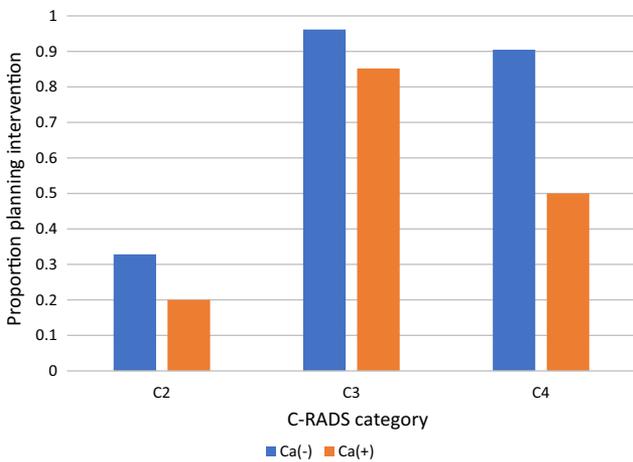


Fig. 5. Proportion of population planning intervention following positive colorectal findings on CT colonography. Ca(–)-Patients with no past medical history of cancer. Ca(+)-Patients with a past medical history of cancer. (*Colorectal cancer and isolated non-melanoma skin cancer cases excluded).

Table 4. Relative rate of planned intervention (optical colonoscopy, flexible sigmoidoscopy, or surgery) following positive CT colonography findings in patients with a past history of cancer (colorectal cancer and isolated non-melanoma skin cancer excluded) vs. patients without a past history of cancer

	Relative rate (95% CI)
C2	0.6 (0.3, 1.2)
C3	0.9 (0.8, 1.0)
C4	0.6 (0.3, 1.1)

be counseled appropriately before screening. Moreover, this relationship was most apparent in women with gynecological malignancies. This group is of particular interest as there are several known pathways that link female gynecologic cancers into syndromes of multiple

primary cancers, most notably BRCA1. In this way, CTC provides an additional route by which to monitor those at risk for recurrence or second primary malignancy, and should be considered by referring providers after careful consultation with the patient.

Relative interventional rate

One of the major advantages of CTC is that it prevents unnecessary invasive procedures. However, one relative disadvantage is that polyps seen on CTC cannot be immediately intervened upon. While a number of studies have aimed to stratify polyp risk by appearance on CTC, we sought to quantify the way by which cancer survivors react to positive colorectal CTC findings relative to those without a cancer history. To do this, we examined the rate of planned intervention for positive CTC findings among cancer survivors versus those without a cancer history, a metric that weighs both professional counseling and patient preference. Our initial hypothesis was that cancer survivors might be more likely to opt for intervention, as they would be less tolerant of any risk associated with unresected pre-cancerous lesions. If anything, we found the opposite to be true, suggesting that these patients may have a better understanding of the benign nature of smaller polyps, and are willing to undergo in vivo surveillance with CTC. The proportions of cancer survivors undergoing intervention was less across the board, with no significant difference in relative rate. This indicates that use of CTC among cancer survivors does not lead to any excess in duplicated screening efforts.

Limitations

While this study was adequately powered to show several trends among cancer survivors, there were many promising trends that did not reach statistical significance. We opted to include these data within our

tables (along with appropriate confidence intervals), along with raw data for these smaller groups because, to the best of our knowledge, no similar data exist in the published literature. Best clinical judgment should be exercised when incorporating these data into clinical decisions.

We also acknowledge that there is potential for bias in the CTC population. For screening studies, the population is certainly biased by the ethnic makeup of the patient population of our institution, as well as by those insurance plans that are willing to cover CTC [22]. There is also possible selection bias in the analysis of intervention rate, as patients undergoing CTC may be intrinsically less likely to opt for invasive procedures when given the opportunity. Finally, all personal history of cancer was by self report. As such, there is potential for recall bias within the study.

Conclusions

CT Colonography provides a powerful tool for colorectal cancer screening. Among the vulnerable population of cancer survivors, we have demonstrated a small but measurable increase in colorectal findings that should be considered when referring patients for screening and considering screening interval. Likewise, we demonstrated an increase in extracolonic findings at CTC that may hold particular significance to cancer survivors, and strongly recommend that referring providers counsel patients as to the possibility of these findings before screening and consider using CTC as an adjunct to their current disease surveillance regimen. Finally, we showed that cancer survivors are no more likely to opt for intervention following positive CTC results than control, indicating that using CTC in this group does not lead to unnecessary duplication of screening resources.

Acknowledgements MEL was supported by Ruth L Kirschstein National Research Service Award F30CA189673 from the National Cancer Institute, and by T32GM008692 from the National Institute of General Medical Sciences awarded to the University of Wisconsin-Madison Medical Scientist Training Program.

Compliance with ethical standards

Disclosure of potential conflicts of interest Dr. Pickhardt is co-founder of VirtuoCTC; shareholder in Elucent, SHINE, Collectar Biosciences; and advisor to Bracco.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

References

- Noone A, Howler N, M K, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis D, Chen H, Feuer E, Cronin K (2018) SEER Cancer Statistics Review 1975–2015, National Cancer Institute. https://seer.cancer.gov/csr/1975_2015/.
- Bibbins-Domingo K, Grossman DC, Curry SJ, et al. (2016) Screening for colorectal cancer US preventive services task force recommendation statement. *JAMA* 315(23):2564–2575. <https://doi.org/10.1001/jama.2016.5989>
- Curtis R, Freedman D, Ron E, Ries L, Hacker D, Edwards B, Tucker M, Faumeni J (2006) New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000, vol NIH Publ. No. 05-5302. National Cancer Institute, Bethesda, MD
- Youlten DR, Baade PD (2011) The relative risk of second primary cancers in Queensland, Australia: a retrospective cohort study. *Bmc Cancer* . <https://doi.org/10.1186/1471-2407-11-83>
- Pooler BD, Kim DH, Pickhardt PJ (2017) Extracolonic findings at screening CT colonography: prevalence, benefits, challenges, and opportunities. *Am J Roentgenol* 209(1):94–102. <https://doi.org/10.2214/ajr.17.17864>
- Pickhardt PJ (2007) Screening CT colonography: how I do it. *AJR Am J Roentgenol* 189(2):290–298
- Kim DH, Pickhardt PJ, Taylor AJ, et al. (2007) CT colonography versus colonoscopy for the detection of advanced neoplasia. *N Engl J Med* 357(14):1403–1412
- Borden ZS, Pickhardt PJ, Kim DH, et al. (2010) Bowel preparation for CT colonography: blinded comparison of magnesium citrate and sodium phosphate for catharsis. *Radiology* 254(1):138–144
- Johnson B, Hinshaw JL, Robbins JB, Pickhardt PJ (2016) Objective and subjective inpatient comparison of iohexol versus diatrizoate for bowel preparation quality at CT colonography. *Am J Roentgenol* 206(6):1202–1207. <https://doi.org/10.2214/ajr.15.15373>
- Shinners TJ, Pickhardt PJ, Taylor AJ, Jones DA, Olsen CH (2006) Patient-controlled room air insufflation versus automated carbon dioxide delivery for CT colonography. *Am J Roentgenol* 186(6):1491–1496
- Buchach CM, Kim DH, Pickhardt PJ (2011) Performing an additional decubitus series at CT colonography. *Abdom Imaging* 36(5):538–544. <https://doi.org/10.1007/s00261-010-9666-9>
- Pickhardt PJ, Lee AD, Taylor AJ, et al. (2007) Primary 2D versus primary 3D polyp detection at screening CT Colonography. *Am J Roentgenol* 189(6):1451–1456
- Pickhardt PJ, Choi JR, Nugent PA, Schindler WR (2004) The effect of diagnostic confidence on the probability of optical colonoscopic confirmation of potential polyps detected on CT colonography: prospective assessment in 1339 asymptomatic adults. *Am J Roentgenol* 183(6):1661–1665
- Zalis ME, Barish MA, Choi JR, et al. (2005) CT colonography reporting and data system: a consensus proposal. *Radiology* 236(1):3–9
- Pickhardt PJ, Kim DH, Pooler BD, et al. (2013) Assessment of volumetric growth rates of small colorectal polyps with CT colonography: a longitudinal study of natural history. *Lancet Oncol* 14(8):711–720
- Brown L, McCarron P, Freedman D (2006) New Malignancies Following Cancer of the Buccal Cavity and Pharynx. In: *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000*, vol Publ. No. 05-5302. National Cancer Institute, Bethesda, MD
- Caporaso N, Dodd K, Tucker M (2006) New Malignancies Following Cancer of the Respiratory Tract. In: *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000*, vol NIH Publ. No. 05-5302. National Cancer Institute, Bethesda, MD
- Figueiredo JC, Crockett SD, Snover DC, et al. (2015) Smoking-associated risks of conventional adenomas and serrated polyps in the colorectum. *Cancer Causes Control* 26(3):377–386. <https://doi.org/10.1007/s10552-014-0513-0>
- Wilson R, Silverman D, Fraument J, Curtis R (2006) New Malignancies Following Cancer of the Urinary Tract. In: *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000*, vol NIH Publ. No. 05-5302. Cancer Institute, Bethesda, MD

20. Dores G, Coté T, Travis L (2006) New Malignancies Following Hodgkin Lymphoma, Non-Hodgkin Lymphoma, and Myeloma. In: *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000*, vol NIH Publ. No. 05-5302. National Cancer Institute, Bethesda, MD
21. Dores GM, Metayer C, Curtis RE, et al. (2002) Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. *J Clin Oncol* 20(16):3484–3494. <https://doi.org/10.1200/jco.2002.090038>
22. Smith MA, Weiss JM, Potvien A, et al. (2017) Insurance coverage for CT colonography screening: impact on overall colorectal cancer screening rates. *Radiology* 284(3):717–724. <https://doi.org/10.1148/radiol.2017170924>