Received: 18 January 2023 | Revised: 19 May 2023 | Accepted: 1 June 2023

DOI: 10.1002/ijc.34638

RESEARCH ARTICLE

Cancer Epidemiology

IJC INTERNATIONAL JOURNAL of CANCER

Second primary cancer among 217702 colorectal cancer survivors: An analysis of national German cancer registry data

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Abstract

With improvements in survival after colorectal cancer (CRC), more survivors are at risk of developing a second cancer, particularly in younger populations where CRC incidence is increasing. We estimated the incidence of second primary cancer (SPC) in CRC survivors and its potential risk factors. We identified CRC cases diagnosed between 1990 and 2011 and SPCs until 2013 from nine German cancer registries. Standardized incidence ratios (SIR) and absolute excess risk (AER) per 10 000 person-years were calculated and were stratified by index site: colon cancer (CC) and rectal cancer (RC), age and sex. Cox regression assessed potential SPC risk factors, including primary tumor-related therapy considering death as a competing risk. We included 217 202 primary CRC cases. SPC occurred in 18 751 CRC survivors (8.6%; median age: 69 years). Risk of cancer was significantly higher in CRC survivors than in the general population (SIR males 1.14, 95% confidence interval [CI] 1.12-1.17, AER = 24.7; SIR females 1.20, 95% CI 1.17-1.23, AER = 22.8). Increased risks of SPCs were observed for the digestive system, urinary system and female and male reproductive organs. CRC incidence increased in younger persons (<50 years) and SPC incidence was 4-fold in this group (SIR males 4.51, 95% CI 4.04-5.01, AER = 64.2; SIR females 4.03, 95% CI 3.62-4.48, AER = 77.0). Primary tumor-related factors associated with SPC risk were right-sided cancer and smaller primary tumor size. Treatment and risk of SPC differed for CC (no effect) and RC (lower risk after chemotherapy). CRC survivors have excess risk of developing SPC, with particular characteristics that could guide targeted surveillance.

KEYWORDS

cancer epidemiology, cancer registry data, colorectal cancer, second primary cancer

Abbreviations: AAPC, Average annual percent change; AER, Absolute excess risk; ASIR, Age-standardized incidence rates; CC, Colon cancer; CRC, Colorectal cancer; DCO, Death certificate only; gFOBT, Guaiac-based fecal occult blood testing; HNPCC, Hereditary non-polyposis colorectal cancer syndrome; HR, Hazard ratio; IACR, International Association of Cancer Registries; IARC, International Agency for Research on Cancer; ICD-10, International Classification of Disease 10th revision; ICD-O-3, International Classification of Disease for Oncology, third edition; RC, Rectal cancer; SEER, Surveillance, Epidemiology and End Results; SIR, Standardized incidence ratios; SPC, Second primary cancers; TLR4, Toll-like-receptor 4; ZfKD, German Centre for Cancer Registry Data (Zentrum für Krebsregisterdaten).

Linda A. Liang and Ying-Ju Tseng have contributed equally to this study.

What's new?

Colorectal cancer (CRC) survivors who were diagnosed with CRC before age 50 may be at increased risk of second primary cancer (SPC). Here, using data collected from cancer registries across Germany, the authors estimated SPC incidence after primary CRC. Analyses reveal a significant excess in risk of SPCs among CRC survivors, especially younger patients. Frequent SPC sites included the digestive tract, urinary tract and reproductive organs. SPC was associated with primary CRC-related characteristics, including tumor size and location and with treatment modality. The findings indicate that enhanced surveillance for SPCs may benefit some subgroups of CRC survivors.

1 | INTRODUCTION

Colorectal cancer (CRC) is the fourth most common cancer diagnosed globally[1] and incidence has declined or stabilized in older adults largely due to screening efforts.[2] In Germany, preventive screening of CRC via stool-based testing has been offered since 1977, and colonoscopy since 2002. As uptake in CRC screening increased[3] in parallel to advances in treatment, survival and quality of life also increased.[4] The relative 5-year survival rates in Germany are 62% and 63% in females and males, respectively, and have been increasing.[5] Despite these improvements in survival, an increase in subsequent cancers is anticipated, particularly in younger survivors where the early onset of CRC (below 50 years of age) is becoming more frequent,[2,6] and overall survival in this group is notably poorer possibly due to the development of multiple cancers.[7]

According to the International Agency for Research on Cancer (IARC) and the International Association of Cancer Registries (IACR), second primary cancers (SPC) are defined as a subsequent and separate cancer entity that occurs in cancer survivors. SPC exclude any extensions, recurrence or metastases of the index cancer diagnosed.[8] Lifestyle factors such as smoking and genetic susceptibility have been linked with CRC, indicating potential shared risk factors for SPC development.[9-11] Although CRC predominantly occurs beyond 65 years of age, the incidence of subsequent cancers following CRC diagnosis appears to be greater in younger survivors (<50 years) than among older persons compared with their respective general populations.[12,13] In addition, associations between SPC following radiotherapy of the index malignancy have been observed.[13,14] One study from Taiwan considered additional types of treatment of primary CRC such as surgery and chemotherapy but found no associations with SPCs.[15] Recent studies have also examined primary cancer characteristics such as tumor site and other potential risk factors of SPC to possibly stratify analyses according to risk for post-cancer surveillance.[16,17] These results are limited to U.S. Surveillance, Epidemiology, and End Results (SEER) data or state-based registries from Australia. To our knowledge, no studies so far have estimated incidence of SPC stratified by age groups, sex, tumor site (colon, rectum) and examined further additional risk factors of primary cancer-related characteristics and treatment modalities on the impact of SPC development.

We determined the risk of SPC by using detailed epidemiological cancer registry data encompassing over a third of the German adult population. We describe the incidence of CRC and SPC by younger and older age cohorts separately for primary colon (CC) and rectal cancer (RC). We also investigated the potential effects of primary cancer-related treatments and characteristics for SPC development, considering death as a competing risk.

2 | METHODS

This population-based registry study uses data from nine long-standing German cancer registries, which cover approximately 29.9 million inhabitants (~37% of the German population). The German Centre for Cancer Registry Data at the Robert Koch Institute (Zentrum für Krebsregisterdaten, ZfKD) collects incidence and survival data from all cancer registries across Germany for the adult population (≥18 years).[18] Vital status, site and date of cancer diagnoses, histological type, grading, TNM classification according to the Union for International Cancer Control and type of therapy of the primary cancer (radiotherapy, chemotherapy, immunotherapy and surgical intervention) were obtained. All cancers were coded according to the German modification of International Classification of Disease 10th revision (ICD-10) and International Classification of Disease for Oncology, third edition (ICD-O-3). Data on genetic cancer syndromes or lifestyle factors were not available from the cancer registries.

All primary CRC tumors (ICD-10 C18-C20) were included. We included primary CRC diagnosed between January 1, 1990 and December 31, 2011, and SPC cases until December 31, 2013. We excluded primary CRC diagnosed before age 20 and undeterminable tumors (Tx, T0). For our SPC analyses, we excluded primary CRC cases identified by death certificate only (DCO) or those with a survival time of <1 month. The end period for inclusion of primary CRC was 2011, while the end of SPC follow-up was 2013 to capture events (death, SPCs) that occurred after primary CRC diagnoses in the latter years. Non-melanoma skin SPCs (ICD-10 C44) were excluded.

All SPC were coded by the cancer registries according to the international rules for multiple primary cancers from the IARC and IACR, which are histologically different to the primary cancer and require some form of verification.[8] We also followed the IARC/IACR definition, which does not involve time dependency and therefore we allowed synchronous cancers (diagnoses <2 or <6 months after primary cancer). Synchronous and metachronous cancers potentially

TABLE 1 Demographics of primary colorectal cancers and second malignant neoplasms.

		Total n = 217 202	Primary CRC only n = 198 451	SPC development n = 18 751
Age at first cancer diagnosis: median (interquartile range)		70 (62-78)	70 (62-78)	69 (62-75)
Age group	20-29	427 (0.20)	408 (0.21)	19 (0.10)
	30-39	1972 (0.91)	1843 (0.93)	129 (0.69)
	40-49	8605 (3.96)	8071 (4.07)	534 (2.85)
	50-59	28 798 (13.26)	26 312 (13.26)	2486 (13.26)
	60-69	63 153 (29.08)	56 342 (28.39)	6811 (36.32)
	70-79	71 614 (32.97)	65 136 (32.82)	6478 (34.55)
	80-89	37 555 (17.29)	35 443 (17.86)	2112 (11.26)
	≥90	5078 (2.34)	4896 (2.47)	182 (0.97)
Sex	Male	114 684 (52.80)	103 290 (52.05)	11 394 (60.76)
	Female	102 518 (47.20)	95 161 (47.95)	7357 (39.24)
Follow-up period	Median years	3.67	3.71	3.42
	≤1 year	47 625 (21.93)	43 226 (21.78)	4399 (23.46)
	>1 to ≤5 years	82 712 (38.08)	75 183 (37.88)	7529 (40.15)
	>5 to ≤10 years	50 121 (23.08)	45 595 (22.98)	4526 (24.14)
	>10 years	36 744 (16.92)	34 447 (17.36)	2297 (12.25)
Calendar year	1990-1999	59 727 (27.50)	53 353 (26.88)	6374 (33.99)
	2000-2011	157 475 (72.50)	145 098 (73.12)	12 377 (66.01)
SPC diagnosis	Synchronous (≤6 months)	30 842 (14.20)	27 906 (14.06)	2936 (15.66)
	Metachronous (>6 months)	186 360 (85.80)	170 545 (85.94)	15 815 (84.34)
Primary tumor characteristics:				
Site	C18 Colon	134 760 (62.04)	123 284 (62.12)	11 476 (61.20)
	C19 Rectosigmoid junction	7642 (3.52)	6895 (3.47)	747 (3.98)
	C20 Rectum	74 800 (34.44)	68 272 (34.40)	6528 (34.81)
Sub-site[a]	Right colon	46 451 (21.39)	42 805 (21.57)	3646 (19.44)
	Transverse colon	10 308 (4.75)	9404 (4.74)	904 (4.82)
	Left colon	61 781 (28.5)	56 547 (28.49)	5324 (28.39)
	Unspecified/overlapping colon	16 130 (7.43)	14 528 (7.32)	1602 (8.54)
	Rectum	82 442 (38.0)	75 167 (37.88)	7275 (38.8)
T category (size)	T1	17 709 (8.15)	15 609 (7.87)	2100 (11.20)
	T2	28 194 (12.98)	25 063 (12.63)	3131 (16.70)
	T3	101 221 (46.60)	92 721 (46.72)	8500 (45.33)
	T4	29 510 (13.59)	28 000 (14.11)	1510 (8.05)
	Missing	40 568 (18.68)	37 058 (18.67)	3510 (18.72)
Histology	I. Carcinoma:			
	Ia. Epidermoid carcinoma	340 (0.16)	294 (0.15)	46 (0.25)
	Ib. Adenocarcinoma	195 997 (90.24)	179 140 (90.27)	16 857 (89.90)
	Ic. Other specified carcinoma	2932 (1.35)	2724 (1.37)	208 (1.11)
	Id. Carcinoma, NOS	10 968 (5.05)	9745 (4.91)	1223 (6.52)
	II. Leiomyosarcoma	52 (0.02)	48 (0.02)	4 (0.02)
	III. Melanoma	54 (0.02)	49 (0.02)	5 (0.03)
	IV. Unspecified	6631 (3.05)	6251 (3.15)	380 (2.03)
	V. All other types	154 (0.07)	134 (0.07)	20 (0.11)
	Missing	74 (0.03)	66 (0.03)	8 (0.04)
Radiotherapy	Yes	25 718 (11.84)	23 683 (11.93)	2035 (10.85)
	No	147 107 (67.73)	135 554 (68.31)	11 553 (61.61)

(Continues)

TABLE 1 (Continued)

		Total n = 217 202	Primary CRC only n = 198 451	SPC development n = 18 751
	Missing	44 377 (19.48)	39 214 (19.76)	5163 (27.53)
Chemotherapy	Yes	49 457 (22.77)	45 777 (23.07)	3680 (19.63)
	No	125 431 (57.75)	115 333 (58.12)	10 098 (53.85)
	Missing	42 314 (19.48)	37 341 (18.82)	4973 (26.52)
Immunotherapy	Yes	1808 (0.83)	1741 (0.88)	67 (0.36)
	No	148 531 (68.38)	137 059 (69.06)	11 472 (61.18)
	Missing	66 863 (30.78)	59 651 (30.06)	7212 (38.46)
Surgery	Yes	157 393 (72.46)	144 186 (72.66)	13 207 (70.43)
	No	26 354 (12.13)	24 906 (12.55)	1448 (7.72)
	Missing	33 455 (15.40)	29 359 (14.79)	4096 (21.84)

Abbreviations: CRC, colorectal cancer; SPC, second primary cancer.
[a]Right colon: cecum, ascending colon and hepatic flexure (ICD-O C18.0, C18.2, C18.3); Transverse colon: Transverse colon (ICD-O C18.4); Left colon (descending colon): splenic flexure, descending colon, sigmoid colon and rectosigmoid junction (ICD-O C18.5, C18.6, C18.7, C19); Unspecified/overlapping colon: malignant neoplasm of appendix, malignant neoplasm of overlapping sites of colon and colon unspecified (ICD-O C18.1, C18.8, C18.9); Rectum: Rectum (ICD-O C20).

share the same risk factors as the primary cancer and we instead stratified our results by follow-up period until SPC occurrence (<1 year, 1-5 years, 5-10 years and >10 years). Additionally, we conducted analyses stratified for CC (ICD-10 C18) and RC (ICD-10 C19 and C20). Of the TNM classification, only tumor size (T1-4) was included due to the high number of missing data on lymph node involvement (N) and metastasis (M).

2.1 | Statistical analyses

Age-standardized incidence rates (ASIR) of CRC from 1995 to 2011 were calculated using the European standard population (1976) and standard reference populations from the same registry regions (provided by ZfKD). These CRC cases included persons diagnosed with primary CRC, regardless of SPC development. We fitted joinpoint regression models to assess the incidence trends across the entire period 1995 to 2011 (average annual percent change, AAPC).

Standardized incidence ratios (SIR), the ratio of observed (O) SPC to the expected (E) number of cancer cases (O/E) were calculated to determine the risk of SPC among the CRC cohort compared with the general population.[19] Person-years at risk were calculated from the primary CRC diagnosis date until any of the following events occurred first: diagnosis of any SPC, death, or the end of follow-up. To calculate the expected number of cancer cases, cancer incidence rates from the general German population (provided by ZfKD) were taken for the corresponding region and period, including DCO cases. The number of expected cancers was calculated as the sum of the product of stratum-specific person-years at risk and corresponding stratum-specific (age, sex, federal state, cancer site) incidence rates. The 95% confidence intervals (95% CI) were estimated based on the Poisson distribution.[19] SPC sites were grouped based on the Cancer Incidence in Five Continents report.[20] In addition, we calculated the absolute excess risk (AER), the overall burden by subsequent cancers, defined as the difference between the observed and expected numbers of SPC per 10 000 person-years at risk.[21]

To identify risk factors considering death as a competing risk, we conducted cause-specific Cox regression adjusting for age, sex, primary cancer therapies and primary tumor stage for all CRC, CC and RC cases.[22] Cases who died before a documented SPC or who survived event-free were censored at the date of death and end of follow-up, respectively. As sensitivity analyses, we repeated SIR and AER calculations for six registries with high completeness (≥90%).[23] We used R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria), including the packages msSPChelpR[24] and survival[25], as well as the Joinpoint Regression Program (version 4.9.0.1, National Institute of Cancer) to conduct all inferential analyses.

3 | RESULTS

We identified 273 503 primary cases of CRC aged above 20 years and diagnosed between 1990 and 2011, regardless of SPC development. After further exclusion of cases with no survival time, T0 or Tx colorectal tumors and DCO diagnoses, 217 202 CRC cases were included. Among these, 18 751 cases developed a SPC (8.63%). The median age for all included cases was 70 years (interquartile range: 62-78) and among those with SPC, the median age was similar: 69 years (Table 1). CRC cases aged between 60 and 79 years comprised more than half the population (62.8%) while cases 20 to 49 years comprised 5.1% of the total included population. Among all cases, 52.8% were male, 62.0% were diagnosed with a primary tumor in the colon, and 46.6% were diagnosed with tumor size T3. The majority of diagnoses (90.2%) were adenocarcinomas. Median follow-up time of CRC survivors until death or end of study regardless of SPC was 3.67 years (range 1 month to 25.16 years). The median duration between primary CRC and SPC development was 3.41 years (range 1 month to 24.21 years). Survivors who were diagnosed with

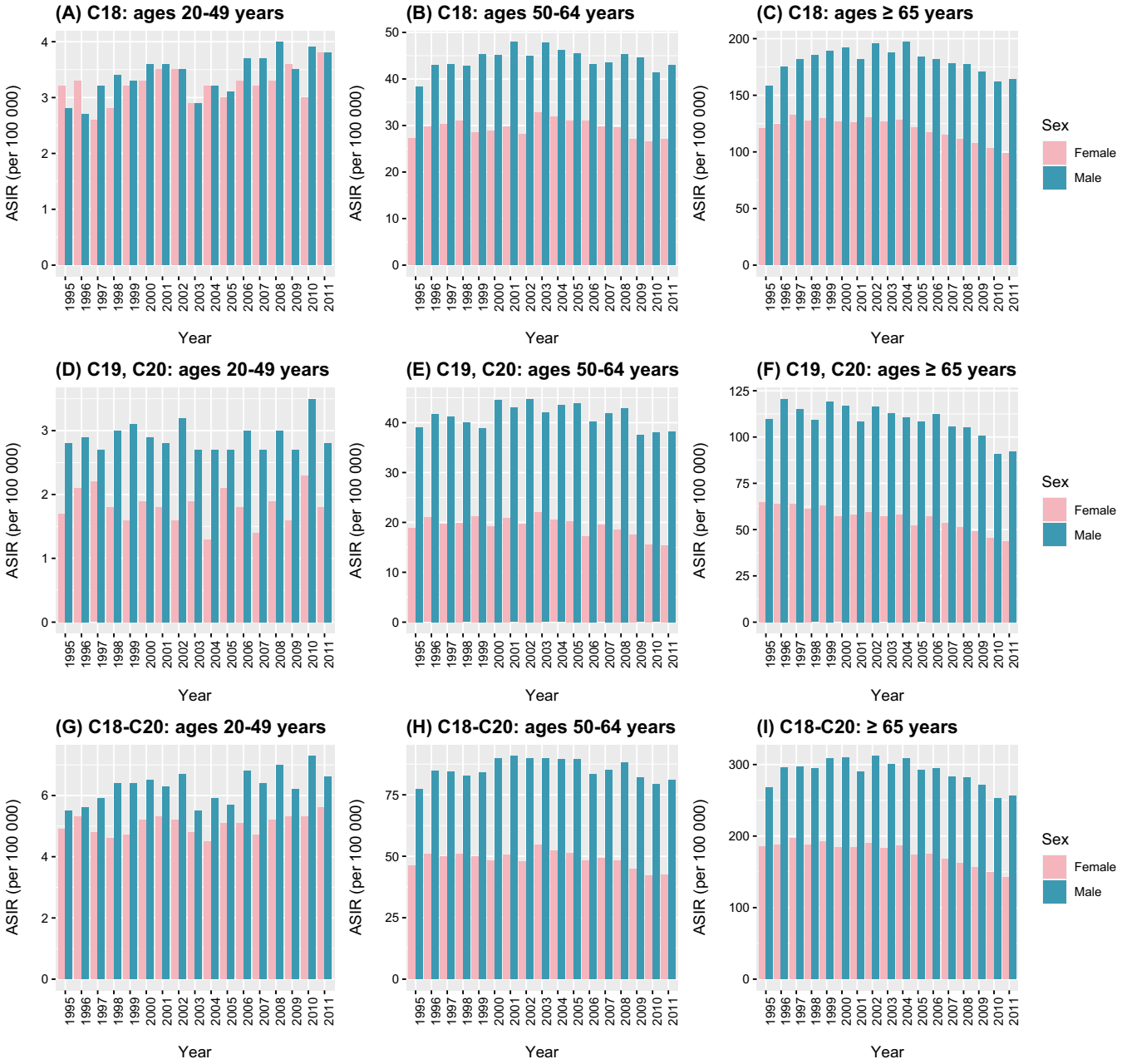

FIGURE 1 Age-standardized incidence rates of colon, rectal and colorectal cancer by age groups and stratified by sex for the years 1995 to 2011. ASIR, Age-standardized incidence rates using European reference population 1976; C18, colon cancer; C19, C20, rectal cancer; C18-C20, colorectal cancer.

SPC aged 20-49, 50-64 and ≥ 65 years had median latency durations of 4.08 years, 4.66 years and 3.0 years, respectively (Table S1). Among 50-64 year old survivors with SPC, the median latency duration was <3 years for SPCs in the small intestine, colon, rectum, female lower genital tract and male testis.

3.1 | Incidence of CRC and SPCs

Incidence of primary CRC (regardless of SPC) between 1995 and 2011 (Figure 1) appeared to increase among younger cohorts aged 20 to 49 years, for both sexes (Figure 1G). On average among this younger cohort, CRC increased annually by 1.6% (95% CI 1.1-2.2) in females and by 1.8% (95% CI 1.0-2.6) among males and this was contributed predominantly by cancers of the colon (Table S2). Marked sex differences of primary CRC (C18-C20) incidence were observed in older cohorts aged ≥50 years (Figure 1H, I) and for rectal cancer (C19, C20, Figure 1E, F), particularly for males with higher incidence than for females. In all age groups and sexes except for females aged 50 to 64 years, CRC increased significantly every year by between 0.7% and 1.9% (Supplementary Table S2).

TABLE 2 Standardized incidence ratio (SIR) of SPC by sex and patient characteristics.

	Males					Females				
	O	E	SIR	95% CI	AER[a]	O	E	SIR	95% CI	AER[a]
Overall	11 394	9957.67	1.14	1.12–1.17	24.65	7357	6119.33	1.20	1.17-1.23	22.84
Age (years)										
20-49	339	75.25	4.51	4.04-5.01	64.17	343	85.10	4.03	3.62-4.48	76.96
50-64	3493	2036.00	1.72	1.66-1.77	68.82	1874	1007.65	1.86	1.78-1.95	59.18
65-84	7277	7432.76	0.98	0.96-1.00	−4.91	4669	4309.19	1.08	1.05-1.12	11.09
≥85	285	413.66	0.69	0.61-0.77	−102.03	471	717.40	0.66	0.6-0.72	−65.90
Follow-up period (years)										
≤1	2652	1851.79	1.43	1.38-1.49	79.75	1747	1071.64	1.63	1.55-1.71	76.47
1 < to ≤5	4584	3913.98	0.97	0.95-1.00	−4.70	2945	2710.92	1.09	1.05-1.13	10.05
5 < to ≤10	2798	2450.36	1.14	1.1-1.18	23.25	1728	1589.92	1.09	1.04-1.14	9.51
>10	1360	947.20	1.44	1.36-1.51	60.56	937	746.84	1.25	1.18-1.34	25.22
Calendar year										
1990-1999	3646	2925.11	1.25	1.21-1.29	36.70	2728	2259.57	1.21	1.16-1.25	22.11
2000-2011	7748	7032.56	1.10	1.08-1.13	18.52	4629	3859.75	1.20	1.16-1.23	23.31
SPC diagnosis										
Synchronous (≤6 m)	1806	983.82	1.84	1.75-1.92	155.56	1130	574.26	1.97	1.85-2.09	118.55
Metachronous (>6 m)	9588	8973.8476	1.07	1.05-1.09	11.59	6227	5545.07	1.12	1.10-1.15	13.78
Primary tumor site										
C18 Colon	6730	5986.04	1.12	1.10-1.15	22.33	4746	4155.47	1.14	1.11-1.18	16.55
C19-C20 Rectum	4664	3971.62	1.17	1.14-1.21	27.74	2611	1963.86	1.33	1.28-1.38	34.97
Primary tumor sub-site[b]										
Right colon	1995	1815.66	1.10	1.05-1.15	18.52	1651	1600.22	1.03	0.98-1.08	3.99
Transverse colon	509	432.66	1.18	1.08-1.28	31.26	395	331.75	1.19	1.08-1.31	22.73
Left colon	3333	3101.02	1.07	1.04-1.11	13.28	1991	1741.06	1.14	1.09-1.19	15.68
Unspecified/overlapping colon	893	636.709	1.40	1.31-1.50	68.78	709	482.43	1.47	1.36-1.58	53.81
Rectum	4664	3971.62	1.17	1.14-1.21	27.74	2611	1963.86	1.33	1.28-1.38	34.97

Abbreviations: AER, absolute excess risk ([(O − E)/person years]*10 000); E, expected; O, observed; SIR, standardized incidence ratio (O/E); SPC, second primary cancer.

[a]Per 10 000 person years.

[b]Right colon: cecum, ascending colon and hepatic flexure (ICD-O C18.0, C18.2, C18.3); Transverse colon: Transverse colon (ICD-O C18.4); Left colon (descending colon): splenic flexure, descending colon and sigmoid colon (ICD-O C18.5, C18.6, C18.7); Unspecified/overlapping colon: malignant neoplasm of appendix, malignant neoplasm of overlapping sites of colon and colon unspecified (ICD-O C18.1, C18.8, C18.9); Rectum: Rectosigmoid junction and rectum (ICD-O C19, C20).

Compared with the general population, CRC survivors were overall at greater risk of developing another cancer (males: SIR 1.14, 95% CI 1.12-1.17; females: SIR 1.20, 95% CI 1.17-1.23; Table 2). In cases aged 20 to 49 years (n = 682), the risk of cancer was 4-fold greater, relative to the general population in both males (SIR: 4.51, 95% CI 4.04-5.01) and females (SIR: 4.03, 95% CI 3.62-4.48). The absolute excess risk was high (AER per 10 000 person-years males = 64.17; females = 76.96). The SIR in survivors aged 50 to 64 years were also significantly elevated with respect to the general population for both males and females and additionally in females aged 65 to 84 years (Table 2). Risk of subsequent cancer was markedly lower than expected in those diagnosed with CRC after age 85 years.

Regarding the follow-up period (Table 2), the incidence of cancer was in excess between 1-9 years following CRC diagnosis and differed by sex, particularly in the first 5 years (SPC SIR males: 0.97, 95% CI 0.95-1.00; females: 1.09, 95% CI 1.05-1.13). After 10 years, SIRs were in significant excess. Almost all the primary CRC sites and subsites, revealed an elevated risk, particularly in the rectum and overlapping sites of the colon.

3.2 | CC (C18) and SPCs

Following primary CC (Figure 2A), the incidence of cancer in males younger than 65 years (n = 2101) compared with the general

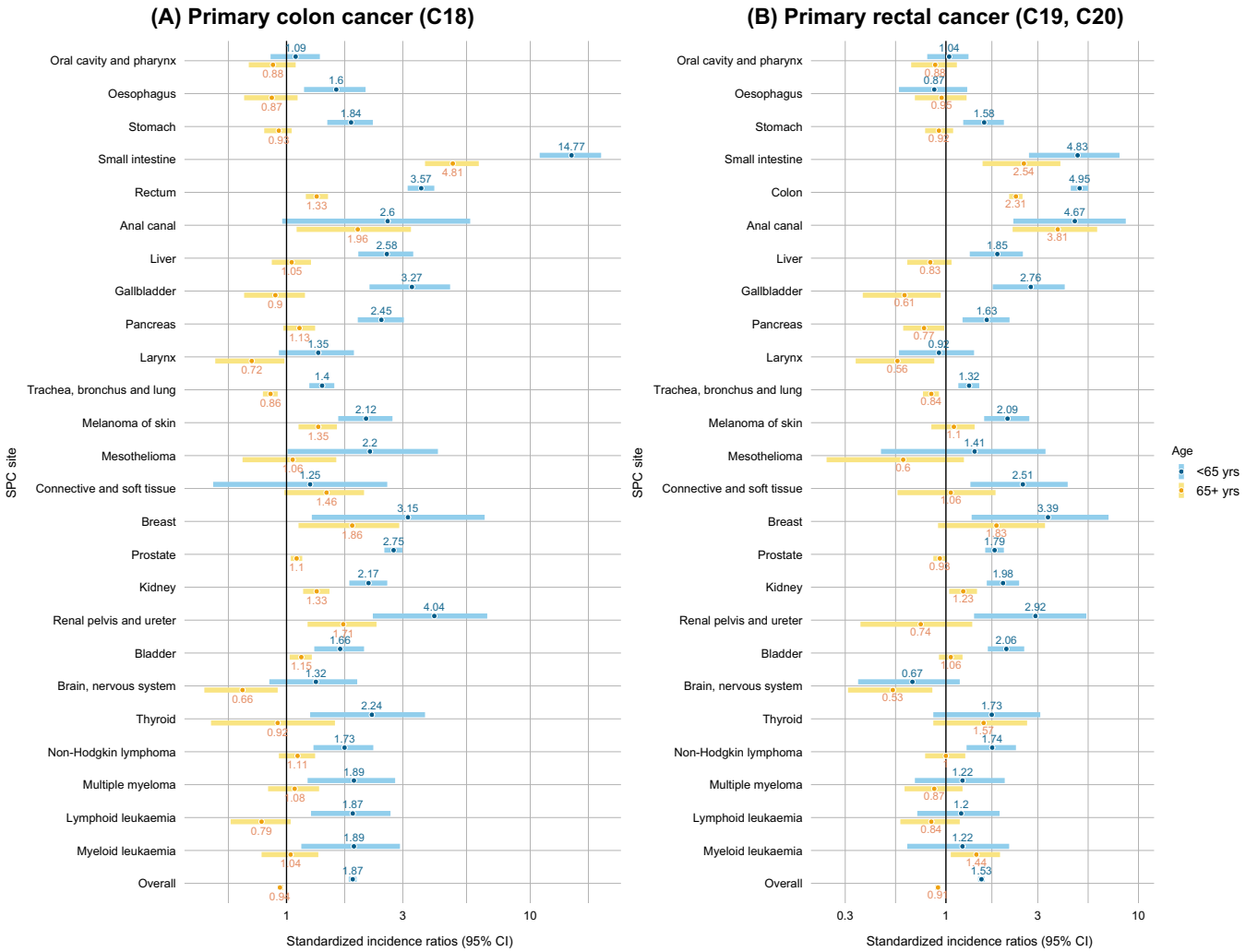

FIGURE 2 Standardized incidence ratio by SPC location following primary colon (A) or rectal (B) cancer among males by age group. Note: Sites with very low cases of SPCs are not presented in this figure. CI, confidence interval; SPC, second primary cancer.

population was markedly elevated (SPC SIR: 1.87, 95% CI 1.8-1.94), particularly in the stomach, rectum, kidney, prostate and respiratory tract. Cancer incidence in males older than 65 years (n = 4629; Figure 2A) was below the expected cancers (SPC SIR: 0.94, 95% CI 0.92-0.97). However, incidence was elevated at similar sites in younger men, except for the stomach, liver, pancreas and respiratory system. The excess burden of prostate cancers was particularly high (AER <65 yrs = 26.45; ≥65 years = 6.08; Table S3).

In females younger 65 years (n = 1299), the incidence of cancer after CC was increased overall (SPC SIR: 2.12, 95% CI 2.02-2.22, Figure 3A), especially in the rectum, as well as the breast, ovary and respiratory tract. Among older females ≥65 years (n = 3447), the risk of cancer was similar to the older female general population (SPC SIR: 1.00, 95% CI 0.97-1.03), but was in excess, particularly at the rectum, stomach, breast and ovary (Figure 3A). The highest burden of excess risk was observed at the breast (AER <65 yrs = 11.11; ≥65 yrs = 5.1; Table S4).

3.3 | RC (C19, C20) and SPCs

Among males younger than 65 years with primary RC (n = 1731), an increased incidence of cancer was observed (SPC SIR: 1.53, 95% CI 1.47-1.59; Figure 2B). Similar to CC, cancers following RC occurred in excess in the stomach, pancreas and liver, as well as the colon, respiratory tract and bladder. The incidence of cancer overall regardless of SPC site (SPC SIR: 0.91, 95% CI 0.88-0.94) was lower than expected among males ≥65 years compared with the general population (n = 2933; Figure 2B). The highest burden was observed in the colon for younger and older males (AER <65 yrs = 23.82; ≥65 yrs = 28.06; Table S5).

For females younger than 65 years (n = 918), the risk of cancer was twice that of the general population (SPC SIR: 2.00, 95% CI 1.89-2.12), and similar for CC, occurred in excess of expected cases in the stomach, bladder, corpus uteri and breast (Figure 3B). A markedly increased risk of cancer was observed in the colon (SPC SIR: 8.22, 95% CI 7.19-9.35). There was no increase in incidence among females

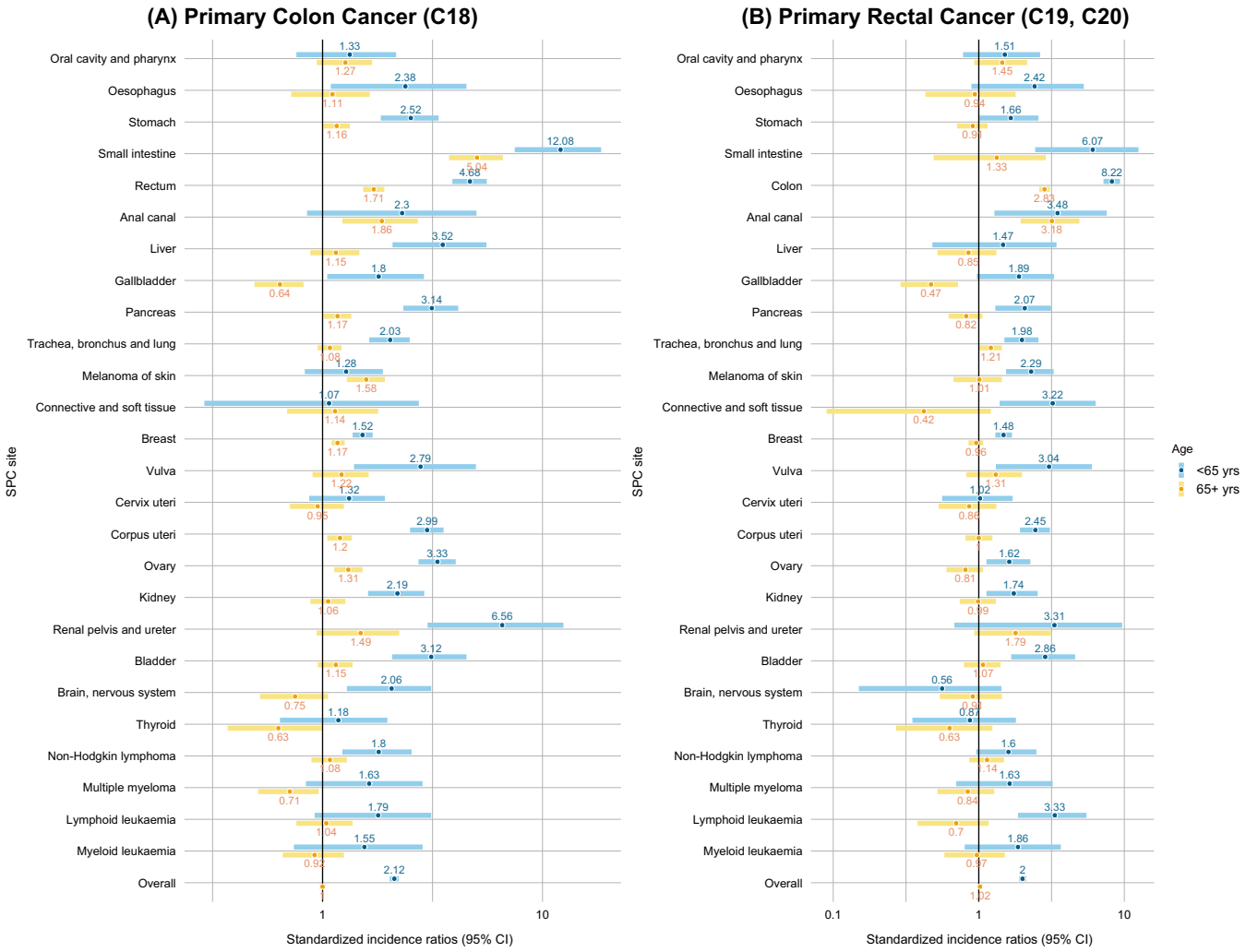

FIGURE 3 Standardized incidence ratio by SPC location following primary colon (A) or rectal (B) cancer among females by age group. Note: Sites with very low cases of SPCs are not presented in this figure. CI, confidence interval; SPC, second primary cancer.

older than 65 years (n = 1693) (SPC SIR: 1.02, 95% CI 0.98-1.07; Figure 3A). The highest excess burden following RC was similar to that following CC, observed for the colon (AER <65 yrs = 28.14; ≥65 yrs = 30.54; Table S6).

In young survivors aged 20 to 49 years following primary CC or RC, SPCs occurred in high excess of the expected cases for the digestive system, respiratory system, prostate for males and female reproductive organs (breast, corpus uteri, ovary; Figure S1). When analyzed by follow-up time, incidence of SPC within the first year and after 15 years was high (SIR>5) for both sexes and remained markedly elevated (from 2.5-fold to 4.8-fold) for SPC found within 1 to 15 years following a primary diagnosis (Table S7).

3.4 | Potential risk factors

Adjusted cause-specific Cox models revealed that the risk of SPC had increased significantly among males by 57% (hazard ratio [HR] 1.57; 95% CI 1.51-1.64) compared with females (Table 3). CRC survivors with primary left-sided CC or with RC were at lower risk of developing cancer than those with right-sided cancers, while a primary tumor size <T2 increased cancer risk by 23% and 12%, respectively (HR T1: 1.23; 95% CI 1.13-1.35; HR T2: 1.12, 95% CI 1.03-1.22) compared with CRC survivors with T4 (reference category). Therapy (chemotherapy, radiotherapy and immunotherapy) for primary CRC was not associated with the risk of SPC, even when considering primary CRC characteristics and death as a competing risk. Among primary CC cases, survivors with primary left-sided CC had lower cancer risk than those with right-sided CC (HR 0.90, 95% CI 0.85-0.95) and all colon tumor sizes T1 to T3 were significantly associated with SPC compared with T4 (reference category). Among primary RC cases, the risk of SPC was lower after chemotherapy compared with no chemotherapy (HR 0.91, 95% CI 0.83-1.00).

There were some variations in SIRs by cancer registry, with particularly high DCO cases for reported SPC diagnoses in Hamburg and North Rhine-Westphalia (Münster) (Table S8). Sensitivity analyses of highly

TABLE 3 Risk factors for SPC among primary CRC survivors.

	All CRC (C18-C20) n = 217 202						Primary Colon Cancer (C18) n = 134 760						Primary Rectal Cancer (C19, C20) n = 82 442					
	Univariate			Multivariable[a]			Univariate			Multivariable[a]			Univariate			Multivariable[b]		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age group (years)			<.0001[c]						<.0001[c]						<.0001[c]			
20-49	Ref			Ref			Ref			Ref			Ref			Ref		
50-64	1.66	1.53-1.81	<.0001	1.64	1.46-1.84	<.0001	1.62	1.46-1.79	<.0001	1.68	1.43-1.98	<.0001	1.70	1.50-1.92	<.0001	1.60	1.35-1.89	<.0001
≥65	1.99	1.84-2.16	<.0001	2.05	1.83-2.30	<.0001	1.84	1.66-2.03	<.0001	1.99	1.70-2.33	<.0001	2.17	1.93-2.45	<.0001	2.14	1.81-2.53	<.0001
Sex																		
Female	Ref			Ref			Ref			Ref			Ref			Ref		
Male	1.48	1.43-1.52	<.0001	1.57	1.51-1.64	<.0001	1.54	1.49-1.60	<.0001	1.60	1.51-1.69	<.0001	1.37	1.31-1.44	<.0001	1.54	1.44-1.64	<.0001
Primary tumor-related																		
Sub-site[d]																		
Right side	Ref			Ref			Ref			Ref			-	-	-	-	-	-
Left side	1.00	0.96-1.04	.9898	0.91	0.86-0.96	.0008	0.99	0.95-1.04	.757	0.90	0.85-0.95	.0002	-	-	-	-	-	-
Rectum	1.05	1.01-1.10	.0119	0.91	0.86-0.97	.0015	-	-	-	-	-	-	-	-	-	-	-	-
Tumor size			.0027[c]						.135[c]						.0008[c]			
T1	1.16	1.09-1.24	<.0001	1.23	1.13-1.35	<.0001	1.21	1.12-1.32	<.0001	1.35	1.20-1.51	<.0001	1.05	0.94-1.17	.4039	1.07	0.93-1.23	.3399
T2	1.05	0.99-1.12	.1100	1.12	1.03-1.22	.0075	1.08	1.00-1.17	.0558	1.20	1.08-1.33	.0010	0.97	0.88-1.08	.5639	1.00	0.88-1.14	.9783
T3	1.00	0.95-1.06	.8779	1.07	0.99-1.15	.0755	1.04	0.97-1.11	.2759	1.15	1.05-1.27	.0023	0.92	0.83-1.01	.0751	0.94	0.83-1.05	.2649
T4	Ref			Ref			Ref			Ref			Ref			Ref		
Chemotherapy																		
No	Ref			Ref			Ref			Ref			Ref			Ref		
Yes	0.88	0.85-0.92	<.0001	0.95	0.90-1.01	.0729	0.89	0.85-0.94	<.0001	0.98	0.92-1.05	.6127	0.89	0.84-0.94	<.0001	0.91	0.83-1.00	.0384
Radiotherapy																		
No	Ref			Ref			Ref			Ref			Ref			Ref		
Yes	0.92	0.88-0.97	.0007	1.00	0.93-1.08	.9339	1.27	1.07-1.50	.0050	1.12	0.86-1.46	.5919	0.93	0.88-0.98	.0093	1.04	0.95-1.13	.4207
Immunotherapy																		
No	Ref			Ref			Ref			Ref			Ref			Ref		
Yes	0.78	0.62-1.00	.0468	0.83	0.63-1.09	.1734	0.78	0.58-1.10	.107	0.79	0.55-1.13	.1938	0.78	0.53-1.17	.235	0.88	0.58-1.35	.5627

Abbreviations: CRC, colorectal cancer; HR, hazard ratio; SPC, second primary cancer; -, not relevant.

[a]Adjusted estimates for all confounders in the table.

[b]Adjusted estimates for all confounders in the table, except sub-site.

[c]Linear trend test.

[d]Right side: cecum, ascending colon and hepatic flexure (ICD-O C18.0, C18.2, C18.3); Left side (descending colon): splenic flexure, descending colon and sigmoid colon (ICD-O C18.5, C18.6, C18.7, C19); Rectum: Rectum (ICD-O C19, C20); Transverse colon: Transverse colon (ICD-O C18.4) and Unspecified/overlapping colon: malignant neoplasm of appendix, malignant neoplasm of overlapping sites of colon and colon unspecified (ICD-O C18.1, C18.8, C18.9) were excluded from analyses.

complete registries (>90%) showed similar patterns in incidence, however moving away from unity (Table S9). Excluding these registries (Berlin, Brandenburg, Saxony-Anhalt and Thuringia) and an additional registry with higher DCOs (Hamburg) showed more conservative estimates towards unity, but revealed similar trends (Table S10).

4 | DISCUSSION

We analyzed the incidence of SPC among CRC survivors using large epidemiological cancer registry data covering over a third of the German adult population. Similar to previous reports from other national cancer registries, we found an elevated risk of a second cancer after CRC, particularly in the digestive system, respiratory tract, urinary system and prostate in males, female reproductive organs[15,26-29] as well as second primary CRC.[17,27] This risk is pronounced in survivors <65 years of age, as previously observed.[7,12,13,17] The risk is especially high in younger survivors aged <50 years, where we also observed an increase in primary CC diagnoses between the years 1995 to 2011. This observation of increasing early-onset CRC rates are in concordance with recent estimates from Germany as well as other high-income populations.[2,6] Younger cohorts diagnosed with CRC are at increased risk of developing cancer compared with the general population of the same age.[12,13] As for risk factors in relation to SPC onset, index tumor location (right-sided) and smaller size are associated with the onset of subsequent cancer in agreement with previous studies.[16,17] Treatment modality of CC on the other hand was associated with development of SPC, similar to one study from Taiwan.[15] However, SPC risk appeared to be lower after treatment of RC.

The risk of subsequent cancer was significantly in excess of the expected incidence for CRCs diagnosed up to age 85 years; highest in the youngest cohort (ages 20-49 years), followed by the middle-aged cohort (50-64 years) and remaining markedly elevated for ages 65-84 years in females only. Several explanations may contribute to these findings. In Germany, CRC screening (in the form of guaiac-based fecal occult blood testing; gFOBT) was offered opportunistically to the general population aged 45 years and older from 1977 until 2002, when the age was raised to a minimum of 50 years.[3] From 2002 to 2017, gFOBT was offered annually to persons aged 50 to 54 years. From age 55, gFOBT was offered every two years with no upper age limit or alternatively, one colonoscopy every 10 years (two in total). The incidence of CRC diagnoses in this same period (1977 to 2012) increased by roughly 1.5-fold for both men and women following screening introduction, peaking around the early 2000s.[30] The increased SPC risk particularly in the age group 50-64 is possibly due to increased medical surveillance following cancer screening, which may lead to more incidental detection of subsequent cancers.[31] Although we observed a median latency period of 4.7 years between primary CRC and SPC for this age group, this was shortened for clinically relevant surveillance sites such as the colon and rectum where recurrence or second primary CRC are commonly found[17] and was longer (more than 5 years) for other sites where other cancer screenings are recommended, for example mammography.[32] Older age (above 65 years) is also associated with increased cancer risk owing to age-related cancers.[15,21,33] In our SIR observations, this effect for SPC incidence reverses among elderly cohorts (above 85 years), likely due to competing risks of comorbidities, worse survival and death not considered within our SIR calculations.[21]

4.1 | SPC incidence among younger cohorts

As for younger cohorts, persons diagnosed with primary CRC before age 50 are at significant risk of developing a subsequent cancer. In survivors aged 20 to 49 years who developed SPC, genetic predisposition, rather than longer follow-up duration (survival) or intensive medical follow-up may explain some of this excess risk.[13,21] For example, genetic susceptibility to malignancies such as hereditary non-polyposis colorectal cancer syndrome (HNPCC), Lynch syndrome and familial adenomatous polyposis (FAP), which may be responsible for the onset of primary CRC,[34] can lead to an increased risk of SPC at the adjacent organs[35] including the digestive system, reproductive organs and urinary system.[15,28,33] However, inherited CRC syndromes comprise less than half of early-onset CRC cases,[36] and only up to 35% of cases among those diagnosed before the age of 35.[37]

We also cannot exclude the possibility that the increased risks observed among younger cohorts may be a consequence of increased surveillance and monitoring for further tumors, as indicated by the high excess SPC risk in the first year of follow-up. Clinical guidelines in Germany for those with hereditary syndromes have remained rather thorough, recommending for example in addition to annual gynecological screening, transvaginal ultrasound for surveillance of ovarian and endometrial cancers following Lynch syndrome.[38] It is also recommended for those with first-degree relatives diagnosed with CRC to undergo screening at an earlier stage, which may further contribute to incidence. The increased risk of SPC among primary cancers diagnosed in the lung, breast and stomach among others is also notably high,[39] likely to due to intensified surveillance as part of clinical management. We observed that SPCs in the first years, particularly the first 12 months after primary CRC were substantially high and may support this hypothesis. Moreover, although this data was not available from the cancer registry data, host and lifestyle factors inducing chronic inflammation and comorbidities may contribute to increased SPC risk, particularly where the prevalence of obesity has increased.[40] This may explain our observation of remarkably high risk of SPC among younger cohorts, since the number of persons diagnosed with early-onset CRC (aged below 50 years) is increasing in Germany[6] and is strongly linked to obesity.[41] Thus, screening efforts, genetic predisposition to develop multiple cancers and the respective medical surveillance, as well as increasing CRC diagnoses among the younger cohorts may explain some of the excess SPC incidences observed.

4.2 | SPC sites

Independent of age, sites for SPC occurrence appear to be prominent across several organs such as the urinary bladder, kidney, upper

respiratory tract and reproductive organs. Previous SEER data suggest that the risk of second cancers particularly in the respiratory tract, reproductive system and urinary system are due to the shared origin of the endoderm-derived epithelia.[28] Other studies propose the role of inflammation with obesity and alteration of gut microbial ecology as contributing to cancer occurrence.[42] Lipopolysaccharide from the gut microbiota may activate toll-like-receptor 4 (TLR4) and induce tumor promotion, which leads to hepatocarcinogenesis.[43] Additionally, the increased risks of stomach, liver, respiratory tract and urinary tract cancers are possibly attributed to the same risk factors for CRC, including increased body size, tobacco smoking, alcohol and red meat intake.[9-11] Further investigations on the association of lifestyle factors are necessary to determine its contribution to SPC development.

4.3 | Associated risk factors with SPC

Treatment of the primary cancer is also a potential implicating factor. During endoscopic removal of the primary CRC, the potential seeding of primary tumor cells to new locations causing second primary CRC may occur.[44] However, mechanical tumor seeding is difficult to establish as a causal factor and recent advances to surgical technique have lowered this potential risk.[45] Cytotoxic effects from chemotherapy and radiotherapy may also induce second cancers.[21] After stratifying our results by follow-up period in order to distinguish more surveillance-related diagnoses from potential therapy-induced diagnoses, we observed marked elevated risk after 5 years, as previously reported.[33] Our regression results however found no association with SPC after exposure to both chemotherapy and radiotherapy, except in RC survivors where chemotherapy reduced the risk. These findings indicate that treatment cannot explain all the excess risk. Postoperative radiation therapy and adjuvant chemotherapy can also reduce cancer recurrence,[46] but radiotherapy was found to increase the risk of SPC in organs within or adjacent to the irradiated volume in patients with rectal cancer.[47] One recent SEER-based study also found increased risk of SPC following radiotherapy of primary CRC, however based among post-operative survivors.[48]

Furthermore, survivors with smaller tumors in our study had a higher risk of SPC compared with larger tumors, even after accounting for death as a competing risk factor where survival time may differ. During our observation period, advances in the treatment of early-stage CRC have led to significant improvements in survival.[49] Large CRC tumors (T4) often have worse prognoses where combined chemotherapy and radiotherapy are applied, while early-stage (smaller tumor) patients generally undergo surgical intervention. Survival of stage III CRC has been reported to be better than stage II, possibly due to these clinical management differences.[50] It is, however, possible that prognosis in patients with larger tumors (often later stages) is overall poorer so fewer SPCs developed, inflating the relative comparison somewhat or that monitoring for SPC is less intense due to poorer prognosis. These findings nevertheless point to the possibility of tailored surveillance and considerations in clinical decision-making based on disease status.

There are some limitations to our findings. First, the follow-up period and completeness of information varied across federal state registries, which could affect the magnitude of SIR estimates. These differences are due to historical and operational issues relating mostly to data delivery timeliness and different reporting practices.[23] Nevertheless, our sensitivity analyses of highly complete registries ($n = 5$) found robust estimates. Second, misclassification of metastases or recurrences and intensified surveillance of subsequent cancers could have occurred, especially in the first 6 months after primary CRC, resulting in overestimation. We stratified analyses based on follow-up period to observe SPC risk outside of this time frame. Third, data on potential behavioral and individual risk factors such as alcohol and tobacco use, obesity and genetic syndromes were not available. Large and long-standing prospective cohort studies with these data are scarce and often not sufficiently powered.[40] Although we obtained treatment information and could evaluate its impact on SPC occurrence, we did not have detailed information such as dose of radiotherapy, drugs for chemotherapy, sequence of treatment and concomitant medications. Additionally, immortal time bias could have occurred. As a result, the follow-up duration and person-years at risk may be longer and thus our SIR estimates may be underestimated.

Nonetheless, we analyzed a large sample size of primary CRC survivors covering 29.9 million inhabitants (37% of the German population) with a maximum follow-up period of 25 years. We presented the risks of SPC by sex, age, follow-up period and anatomic sites using high-quality and complete cancer registry data. Our analyses on potential risk factors for SPC adjusted for primary cancer-related characteristics and treatment, and also considered death as a competing risk. If our observations, which further contribute to the current body of evidence, can be unequivocally determined through prospective cohort data accounting for potentially associated individual and lifestyle factors described, then the clinical impact should be to consider potential adaptations to clinical guidelines on surveillance and decision-making following CRC survival.

5 | CONCLUSION

Overall our results found that: (1) risk of SPCs diagnosed after CRC is in excess compared with the general population; (2) risks of SPC, particularly for younger survivors (particularly below age 50) occurred in excess and at the respiratory tract, urinary system and reproductive organs among others, and (3) the potential primary tumor-related risk factors for developing SPC include right-sided CRC and smaller tumors. While we did not find an overall association for therapy with SPC development, the risk appears to differ between treatment of CC and RC. Early and targeted surveillance of particular sub-groups of colorectal cancer survivors should be enhanced and appropriate clinical guidelines for subsequent cancer surveillance could be updated specifically for patient characteristics and disease status. Future research on the genetic and environmental etiology of SPC occurrence in younger cohorts <50 years is warranted.

AUTHOR CONTRIBUTIONS

The work reported in the paper has been performed by the authors, unless clearly specified in the text. Stefanie J. Klug and Linda A. Liang: concept and design. Linda A. Liang, Ying-Ju Tseng and Luana F. Tanaka: data analysis and interpretation of data. Linda A. Liang and Ying-Ju Tseng: drafting of the manuscript. Luana F. Tanaka and Stefanie J. Klug: critical revision of the manuscript. All authors reviewed, edited and approved the final manuscript.

ACKNOWLEDGEMENTS

We thank the German Centre for Cancer Registry Data (ZfKD) at the Robert Koch Institute, particularly Dr. Klaus Kraywinkel. The study data originated from the following German cancer registries: Berlin, Brandenburg, Hamburg, Mecklenburg-Western Pomerania, North Rhine-Westphalia (Münster), Saarland, Saxony, Saxony-Anhalt and Thuringia. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

This research was supported solely by the Chair of Epidemiology's university budget. No external grant money was received for this research.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Due to legal restrictions, the individual level raw data used for this analysis is only available via request to the German Centre for Cancer Registry Data (ZfKD) that can provide a scientific use file. More information on the application process is provided on the ZfKD website: https://www.krebsdaten.de/Krebs/EN/Content/ScientificUseFile/scientificusefile_node.html. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

This study analyzed the scientific use file (SUF) of the German Centre for Cancer Registry Data (ZfKD). Data collection is mandated and regulated by the Federal Cancer Registry Data Act (BKRG) and secondary data analysis of the anonymous SUF, as used in this study, does not require ethics approval (§3 and §5 BKRG).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Liang LA, Tseng Y-J, Tanaka LF, Klug SJ. Second primary cancer among 217702 colorectal cancer survivors: An analysis of national German cancer registry data. *Int J Cancer*. 2023;153(8):1459-1471. doi:10.1002/ijc.34638