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Systematic Review

Risks of colorectal and extracolonic cancers following colorectal cancer: a systematic review and meta-analysis

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Abstract

Background: Colorectal cancer survivors face increased risks of developing new primary cancers in colorectum and other anatomical sites. This systematic review aimed to estimate primary colorectal and extracolonic cancers risks following colorectal cancer.

Methods: Peer-reviewed articles published before January 2025 were screened across 4 databases to identify studies using population cancer registry reporting standardized incidence ratios (SIRs) of primary cancers following colorectal cancer, compared with the general population. A meta-analysis was conducted to summarize the SIRs, and age-specific cumulative risks of primary cancers following colorectal cancer were estimated using the summarized SIRs and age-, sex-, calendar-, region-, and cancer-specific incidence data.

Results: Of 8254 articles identified, 57 were included in meta-analysis. The pooled SIRs (95% confidence interval) for any primary cancer, extracolonic cancer and colorectal cancer were 1.13 (1.06 to 1.20), 1.10 (1.03 to 1.17), and 1.55 (1.33 to 1.77), respectively. Increased risks were also observed for primary cancers of small intestine, ovary, uterus, testes, kidney, female breast, thyroid, and prostate overall, as well as for lung and urinary bladder cancer in recent studies. The cumulative risks of any primary cancer, extracolonic cancer, and colorectal cancer to age 75 years were 38.5%, 31.6%, and 8.24% in Australasia; 33.8%, 30.9%, and 4.77% in North America; 27.4%, 25.6%, and 8.01% in East Asia; and 33.4%, 28.8%, and 4.68% in Europe.

Conclusion: Colorectal cancer survivors have an increased risk of subsequent primary cancers, both extracolonic and colorectal, when compared with the general population. These findings underscore the necessity for tailored surveillance and prevention strategies to effectively identify and manage subsequent primary cancers in this population.

Introduction

Colorectal cancer remains a significant global challenge despite advancements in survival rates in developed nations. Globally, it ranks as the third most prevalent cancer diagnosis and the second leading cause of cancer-related mortality worldwide, with an estimated 1.93 million new cases and 903 859 deaths in 2022.[1] In developed nations, the implementation of early detection strategies through screening[2-4] and the development of advanced treatment options[5,6] have significantly enhanced the chances of surviving the disease, whereas developing countries face significant challenges in accessing cancer screening and early detection measures.[7] Approximately 95% of people diagnosed with early-stage colorectal cancer have a survival span exceeding 5 years.[3] The overall 5-year survival rate for colorectal cancer has witnessed an increase from 59.2% in 1985 to 65.0% in 2020 in the United States,[8] and from 54% in 1989-1993 to 71% in 2016-2020 in Australia.[9]

This increase in survival rate extends the duration at risk for the onset of another primary cancer, which is distinct from recurrences or metastases of the initial cancer. These can potentially manifest in the remaining large bowel or any other extracolonic sites. The likelihood of developing a primary cancer in the colorectum or any extracolonic site post curative surgical resections for the initial colorectal cancer is reported to be ~4.6%-20% over the course of their lives.[10-19]

Recent systematic reviews reported the risk of developing primary cancer following colorectal cancer varies site of the cancer, population, and the length of follow-up period. The risks of primary cancer following colorectal cancer were higher compared with the general population for cancers of the urinary bladder, female genital tract, kidney, thorax (lung, bronchus, and mediastinum), small intestine, stomach, thyroid, and melanoma.[20,21] The most common primary cancers following colorectal cancer are prostate (32.2%), lung and bronchus (11.6%), urinary bladder and kidney (10.8%), and melanoma of the skin (3.9%) for male survivors, and breast (25.8%), lung and bronchus (13.6%), uterus (8.2%), and urinary bladder and kidney (5.6%) for female survivors.[13] In addition to the site of cancer, the risk of another primary cancer also differs by geographic region with the most frequently diagnosed cancer after colorectal cancer in Asian countries being gastric cancer (1.6%-4.7%)[14-16,18] and in non-Asian countries being breast cancer (7.0%-14.2%) in women and prostate cancer (14.6%-22.0%) in men.[22-25] Furthermore, the longer the duration since the first colorectal cancer, the greater the risk of developing a subsequent primary cancer.[12,13,18]

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Some of the findings of the recent systematic reviews are inconclusive and some of the methods used are potentially flawed. Inclusions of clinics or hospitals-based studies could introduce detection bias, potentially leading to an overestimation of subsequent cancer occurrence in colorectal survivors relative to the general population. Although heterogeneity was evident, particularly with varying restrictions on the lag period between diagnoses of the first colorectal cancer and subsequent cancers, other sources of potential heterogeneity were not thoroughly explored. This highlights a gap in addressing variability across studies. Moreover, the individual studies included in the meta-analyses were not mutually inclusive across both reviews, limiting the validity of the findings.[20,21] Therefore, we conducted this systematic review restricted to studies using the highest quality population-based data and meta-analysis to assess the risks of developing different types of primary cancers following the first colorectal cancer, maximizing the validity of the estimates. In addition, we determined if these risks differed by cancer site, follow-up period, latency period, study years, geographic region, age at initial cancer diagnosis and sexes. Furthermore, we calculated age- and region-specific cumulative risks of primary cancers following colorectal cancer for North America, East Asia, Europe, and Australasia regions using the summary standardized incidence ratios (SIRs) and age-, sex-, region-, calendar-, and cancer-specific 5-year incidences for the general population. The findings of this study can inform clinical decision making, survivorship care, and future research on the prevention and early detection of subsequent primary cancers for colorectal cancer survivors.

Methods

We reported this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline,[26] and the predetermined study protocol registered on the International Prospective Register of Systematic Reviews (PROSPERO ID. CRD42023361707).

Literature sources and inclusions

We searched Medline, Embase, Cochrane Central Registry of Controlled Trials, and Web of Science on the Ovid platform to identify published and peer-reviewed literature that reported the risks of developing primary cancers following colorectal, colon or rectum cancer and published before January 6, 2025. We used both MeSH terms and other forms of controlled vocabularies by incorporating truncation operators for terms—"extracolonic cancers," "second primary cancers," "subsequent cancers," or "multiple primary cancers," in combination with "Colorectum," "Colon" or "Rectum," and "Risks" (Table S4). We also reviewed the reference lists of all relevant letters, articles, previous literature reviews, and meta-analyses to identify any articles not captured by the search strategy mentioned above. Automated notifications for publications after the search dates were established and continuously screened until the publication of this review to be able to include any recent and relevant articles.

We included all observational population-wide cancer registry studies with the study population of the colorectal cancer survivors; that defined subsequent primary cancers diagnosed at any time after the initial diagnosis or curative treatment for the colorectal cancer; and that reported the SIR for relative risks of developing subsequent cancers after the first colorectal cancer compared with that of the general population. We excluded studies that reported only synchronous colorectal cancers, recurrence, and/or metastasis from the first colorectal cancer; studies that focused on specific subpopulations, such as Lynch Syndrome patients with colorectal cancer; letters to the editors, conference abstracts, editorials, reviews of articles, commentaries, non–peer review studies and reports; and animal studies (Table S1). If data were duplicated in more than 1 study in terms of study population, study period and types of subsequent cancers, only the most recent was included. However, we included studies based on the same database that reported different subsequent types of cancer. Screening the study titles, abstracts, and full texts was conducted independently by 2 authors (Y.K.A and Y.Z) using the Covidence Web-based systematic review tool.[27] Any discrepancies were reviewed by the 2 authors for consensus. Unresolved discrepancies were decided by a third author (A.K.W).

Data extraction and risk of bias assessment

We extracted the following information from each study: study title, first author name, publication year, country of registry, name of data registry, study design, sample size, age at diagnosis of the first colorectal cancer, sex, site and number of subsequent cancers (except melanoma or nonmelanoma skin cancer), the interval between diagnoses of the first colorectal cancer and subsequent cancers (defined as latency period), observation time after diagnosis of the first colorectal cancer, the site within the bowel of the initial colorectal cancer, definition of subsequent cancers, SIRs and their 95% confidence interval (CI) with stratified estimates by sex, age, year of diagnosis of first colorectal cancer (if reported), *P*-values, and which covariates were standardized for incidence ratio calculations, using the Microsoft Excel version 16.7.

All included studies were critically evaluated for risk of bias using the Risk of Bias in Non-randomized Studies—of Exposure (ROBINs-E) tool.[28] All 7 domains were evaluated: risk of bias due to confounding, risk of bias arising from measurement of the exposure, risk of bias in selection of participants into the study, risk of bias due to postexposure interventions, risk of bias due to missing data, risk of bias arising from measurement of the outcome, and risk of bias in selection of the reported result. The data extraction and risk of bias assessment were primarily conducted by 1 author (Y.K.A) and independently checked by another author (Y.Z) to identify errors and inconsistencies in the data. Any disagreements between the 2 authors were resolved following the procedures mentioned above for article inclusion.

Data analysis

We conducted meta-analyses to generate pooled estimates of the SIRs for developing primary cancers following the diagnosis of colorectal cancer. If studies reported multiple SIRs for subgroups of subsequent cancer diagnoses without providing an overall estimate, we performed a within-study meta-analysis to obtain an overall estimate. For studies that did not report 95% confidence interval and/or the expected number of subsequent cancers, we calculated them from the available data reported in the article using the following formulas[29]:

$$\text{Expected number of subsequent cancer diagnoses} = \text{Total number of observed first colorectal cancer diagnoses}/\text{SIR}$$

$$\text{Standard error} = \text{square root of (total number of observed cancer diagnoses}/(\text{Expected number of subsequent cancer diagnoses})^2)$$

$$95\%\ \text{Confidence Interval} = \text{SIR} \pm (1.96 \times \text{standard error})$$

As the included studies varied by study population and cancer registry, we employed a random-effects model to combine the

estimates and tested the extent of heterogeneity between studies using I^2 statistics.[30] For the within-study meta-analysis, we applied a fixed-effects model if I^2 statistics were less than 50%, assuming low or moderate heterogeneity. We also investigated the sources of heterogeneity by conducting linear-fitted meta-regression models, for study characteristics—year of observation ended, study region, follow-up time, latency period, initial cancer sites, sex, age at initial cancer diagnosis, and the logarithm of individual SIR estimates. Means of follow-up time and latency period were primarily used. In cases where means were not reported, median values were used. Study countries were categorized into 4 regions: East Asia (Japan, South Korea, and Taiwan), Australia, the United States and Canada, and Europe. Where we identified heterogeneity, we performed stratified analyses for the study characteristics listed above that explained heterogeneity. For these stratified analyses, all continuous modifiers were categorized into a binary variable using the median values. For example, the year 2005 of the observations ended was selected as a median cutoff point.

To examine the influence of individual studies on the pooled estimates, sensitivity analyses were conducted by repeating the meta-analysis after removing 1 study at a time. Furthermore, funnel plots and Egger et al.'s linear regression test were performed to identify the existence of publication bias.[31] All analyses were conducted for the first initial site of colon/rectum/colorectum and each subsequent cancer. However, subgroup analysis and publication bias assessment were not conducted for outcomes reported by 5 or fewer studies. We used the "metan" command in STATA 14.0 to perform all meta-analyses.[32]

Age-specific cumulative risks of individual subsequent cancers for colorectal cancer survivors and the general population were calculated for 4 regions: North America (the United States and Canada), East Asia (Japan and South Korea), Europe (UK, Switzerland, Spain, Slovenia, Poland, Norway, Netherlands, Malta, Lithuania, Italy, Ireland, Iceland, Germany, France, Estonia, Denmark, Czech Republic, Cyprus, Croatia, Bulgaria, and Austria), and Australasia (Australia and New Zealand)[33] as follows. First, we calculated the annual cancer incidence rates per 100 000 people based on the 5-year incidence rates in the general population (0-4 years, 5-9 years, etc) from the International Agency for Research on Cancer. These cancer incidences were then added up to provide the cumulative cancer incidence rate in the general population and converted to age-specific cumulative risks using the formula: cumulative risk = 1−exp (−accumulated cumulative incidence).[34] Finally, the age-specific cumulative risks for subsequent cancer in those with a prior diagnosis of colorectal cancer were calculated by multiplying the cumulative risk for the general population by the respective SIR values from subgroup meta-analysis, either by the recent study end period or 4 different study regions if they showed significant modifiers. For example, we considered the pooled SIR for the United States to estimate age-specific cumulative risks in the North America population, whereas the pooled SIR for Australia applied to Australasia population. Otherwise, the overall pooled SIR with their corresponding 95% confidence intervals was used. One-sample proportional test was performed by making assumptions on the equality of proportions for cumulative risks of each cancer up to the age of 75 years between colorectal cancer survivors and general population.

Results

Study selection and study characteristics

A total of 8234 articles were identified through 4 electronic databases (2997 studies identified in Ovid Medline, 3181 in Embase, 113 in Cochrane Central Register of Controlled Trials, and 1943 in Web of Science Core Collection), and an additional 20 articles were found through a hand search. After removing 2977 duplicates and excluding 4942 articles deemed ineligible based on the title and abstract, 335 articles were retrieved for full text assessment. Finally, 57 articles[22-25,35-87] that reported the SIR for different primary cancers following the initial diagnosis of colorectal cancer were included in the meta-analysis (Figure 1). These studies represented population-wide registries from East Asia (Korea, Japan, and Taiwan), Australia (Queensland, South Australia, New South Wales, Victoria, and Tasmania), Europe (France, England, Italy, Germany, Sweden, Switzerland, Scotland, Netherlands, Austria, Finland, and Denmark), the United States (Connecticut and US SEER registries), and Canada. One study reported 2 different registries separately: Germany and Sweden,[39] and another study reported a pooled analysis of 13 population-wide multicountry registries from British Columbia, Manitoba, Saskatchewan in Canada, Singapore, Slovenia, Norway, Denmark, Scotland in the United Kingdom, New South Wales in Australia, Sweden, Finland, Iceland, and Zaragoza in Spain.[63] In total, these studies reported a combined cohort of 2 896 463 (potential duplicate cases because we included the same registries with different study periods, but overlaps in a few years, and different outcomes of subsequent cancers) colorectal cancer cases, aged at least 15 years at the diagnosis of the first colorectal cancer, within a maximum follow-up period of 38 years to assess the development of primary cancers following colorectal cancer over their lifetimes. However, 17 studies did not report the number of initial colorectal cancer cases included in the analysis[42,43,46,48,50,51,54,64,69,70,73-77,80,83] and, therefore, the size of the cohort is at least this large but of unspecified size (Table 1).

Risk of any primary cancer following colorectal cancer

People with a previous diagnosis of colorectal cancer were 13% more likely than the general population to be diagnosed with a subsequent primary cancer (pooled SIR = 1.13; 95% CI = 1.06 to 1.20) with a more than 2-time increased risk for colorectal cancer cases aged younger than 50 years (2.20; 1.63 to 2.67; $P < .001$). For studies with more than median or mean 4 years of follow-up, the increased risk was 22% (1.22; 1.12 to 1.32). The increased risk was 16% for females and 7% for males ($P = .016$). This increased risk also differed by region ($P = .0007$). The cumulative risks of any primary cancer up to the age of 75 years ranged from 27.4% to 38.5% by region, and were ~5% higher for colorectal cancer survivors compared with the general population, except in East Asia (P range = 0.04 to <0.001) (Figures 2-4, Figure S1).

Risk of any extracolonic cancer following colorectal cancer

There was a 10% increased risk of developing a primary cancer in extracolonic sites following colorectal cancer (1.10; 1.03 to 1.17) with a 2-time increased risk for colorectal cancer cases aged younger than 50 years (2.01; 1.35 to 2.67; $P = .004$). The increased risk was 13% for colon cancer cases, but no increased risk for rectal cancer cases ($P = .032$). The cumulative risks of any primary cancer in extracolonic sites up to the age of 75 years ranged from 25.6% to 31.6% by region and were ~3% higher following colorectal cancer compared with the general population ($P = .004$) (Figures 2-4 and Figure S1).

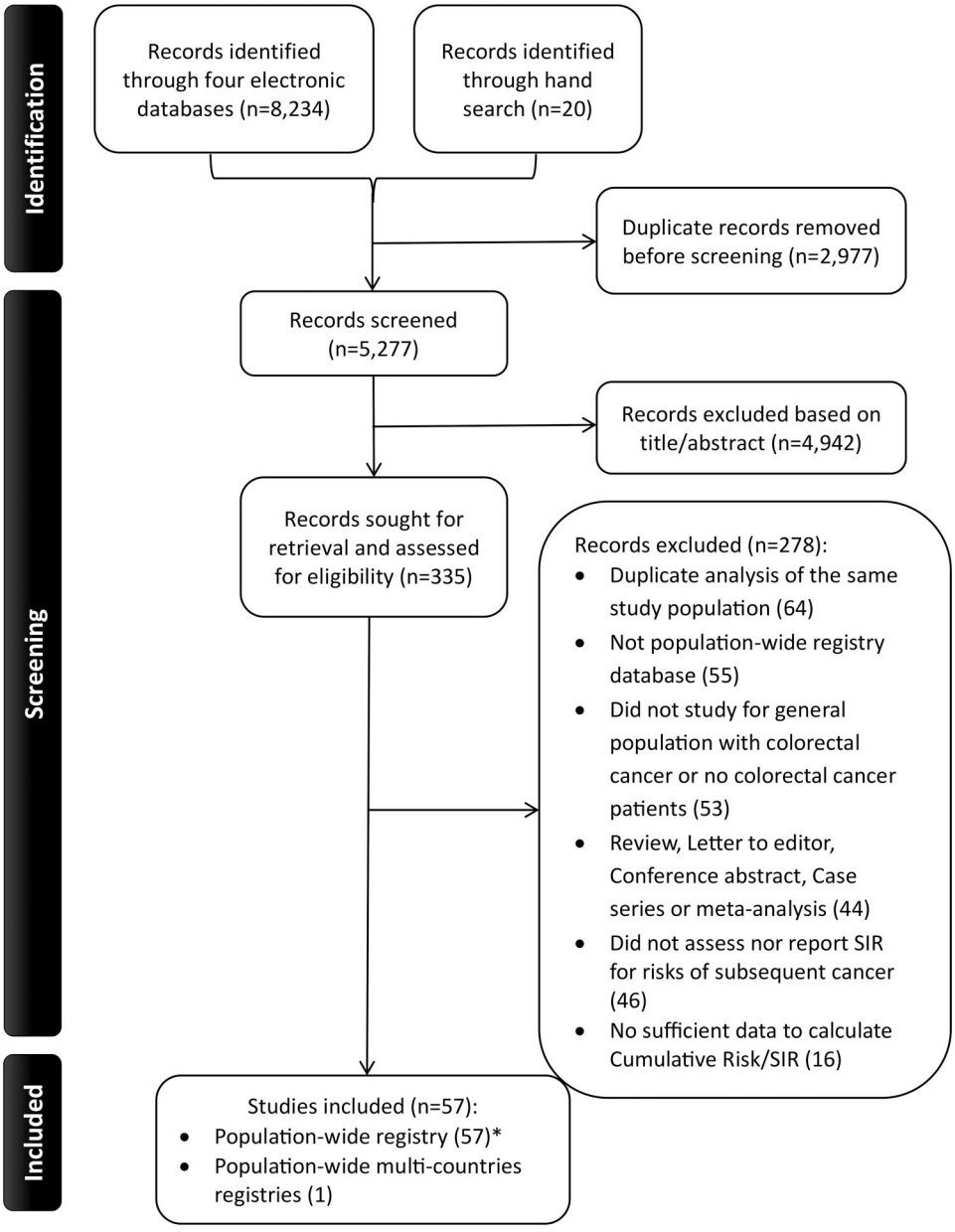

Figure 1. Flow diagram showing the study selection for the systematic review.* One study reported for 2 different registries; SIR = standardized incidence ratio.

Risk of primary colorectal cancer following colorectal cancer

There was a 55% increased risk of developing primary colorectal cancer following colorectal cancer (1.55; 1.33 to 1.77). This increased risk differed by region ($P = .009$): 2.12 (1.57 to 2.68) for Australia, 1.86 (1.11 to 2.62) for East Asia, 1.32 (0.97 to 1.66) for Europe, and 1.66 (1.61 to 1.70) for the United States. The increased risk was 4 times for those younger than age 50 years but no increased risk for those 50 years and older ($P < .001$). The cumulative risks of primary colorectal cancer up to the age of 75 years ranged from 4.68% to 8.24% by region and were ~3% higher for colorectal cancer survivors compared with the general population, except in Europe (P range = 0.04 to <0.001) (Figures 2-4 and Figure S1).

Risks of primary cancers at gastrointestinal tract (except colorectum) following colorectal cancer

People with a previous diagnosis of colorectal cancer were almost 4 times more likely than the general population to be diagnosed with a subsequent primary small intestine cancer (3.92; 2.88 to 4.96). This increased risk was more than 6 times higher for colon cancer cases but no increased risk for rectal cancer cases ($P = .016$). This increased risk also differed by region ($P = .003$). The cumulative risks of primary small intestine cancer up to the age of 75 years ranged from 0.57% to 0.82% by region and were ~0.5% higher for colorectal cancer survivors compared with the general population ($P < .001$) (Table S2 and Figure S2).

Table 1. Characteristics of the studies of the risks for primary cancers diagnosed after colorectal cancer.

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
1	Ahn, 2019, South Korea, Pancreas	The Korean National Health Insurance Claims Database	2005-2015	251 482	Mean 65.56 years	the date of the first cancer diagnosis	NR	NR	Pancreas (498)
2	Bouvier, 2008, France, European Journal Of Cancer	Population-based Cancer Registry in Burgundy	1976-2005	10 801	Median 71.1 (Interquartile 21.0–99.6) years	6 months after the first cancer diagnosis	Median 42.7 (Interquartile 6.5–270.6) months	Anastomotic recurrences: Colorectal cancers that had developed in the context of inflammatory bowel diseases, hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis; Anal cancers.	Colorectum (216)
3	Bright, 2019, United Kingdom, Lancet Oncol	English and Welsh Cancer Registrations	1971-2006	5805	Min 15-Max 39 years	5 years after the first cancer diagnosis	Median 16.8 (Interquartile 10.5–25.2) years	Individuals who had not survived 5 years from their first neoplasm; Individuals who had a previous childhood cancer included in the British Childhood Cancer Survivor Study: A subsequent primary neoplasm occurring in anatomical sites close to the first primary neoplasm; Any cancer in a contralateral paired organ.	any subsequent primary cancer excluding CRC (1290) Breast (179) Cervix (237) Central Nervous System (intracranial) (50) Leukemias (16) Lymphoma (183) Ovary (58) Sarcoma (46) Testis (206) Thyroid (33) Urinary Bladder (39)
4	Buiatti, 1997, Italy, European Journal Of Cancer	Three Italian Cancer Registries	1981-1989	5238	Mean 68.6 years	the date of the first cancer diagnosis	Mean 2.7 years (Min 2 months–Max NR)	A subsequent primary cancer occurring in the first 2 months after the first cancer diagnosis.	any subsequent primary cancer (163) Urinary Bladder (7) Breast (Female) (4) Colorectum (9) Gastric Cancer (4) Kidney (7) Lung (10) Ovary (5) Prostate (9) Small intestine (3)

(continued)

Table 1. (continued)

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
5a	Chen, 2015, Germany, Cancer Letters	German Cancer Registries	1997-2010	219 468	Median 65.8 (Interquartile 55.6–76.0) years	the date of the first cancer diagnosis	NR	Cancer patients who had a death certificate or autopsy only; Second concordant cancers; non-melanoma skin cancers.	any subsequent primary cancer excluding concordant cancers (11583)
5 b	Chen, 2015, Sweden, Cancer Letters	The Swedish Cancer Registry	1997-2010	69 774	Median 65.8 (Interquartile 55.6–76.0) years	the date of the first cancer diagnosis	NR	Cancer patients who had a death certificate or autopsy only; Second concordant cancers; non-melanoma skin cancers.	any subsequent primary cancer excluding concordant cancers (4022)
6	Cluze, 2009, France, European Journal of Cancer Prevention	French Cancer Registry	1989-2002	4944	Mean 68 (Males) Mean 70.6 years (Females)	the date of the first cancer diagnosis	Mean 2.9 years, Min 2 months-Max 5 years	Patients lost to follow-up at the date of their last contact; Synchronous cancers (diagnosed within 2 months after diagnosis of the first cancer).	Acute Myeloid Leukemia (3) any subsequent primary cancer (224) Bone (1) Central Nervous System-eye (3) Female Genitals (7) Gastric Cancer (5) Kidney (7) Liver-Hepatic Ducts (5) Esophagus (3) Pancreas (1) Prostate (38) Small intestine (5)
7	Coyte, 2014, United Kingdom, BMC cancer	The Scottish Cancer Registry	2000-2004	7225	Mean 69.9 (Min 46.5–Max 93.3) years	2 months after the first cancer diagnosis	Min 2 months-Max 15 years	Patients whose index cancer was diagnosed at date of death; Date of death was recorded as preceding date of incidence; Difficult to distinguish between synchronous and metachronous tumors during this period; non-melanoma skin cancer.	any subsequent primary cancer (324) any subsequent primary cancer excluding CRC (271)
8	Crocetti, 2001, Italy, European Journal Of Cancer	Eleven Italian Cancer Registries	1989-1995	NR	Mean 65.6 years	2 months after the first cancer diagnosis	Mean 2.6 years, (Min 2 months–Max NR)	Cases diagnosed by death certificate.	Ovary (32)

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Table 1. (continued)

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
9	Crocetti, 2021, Italy, Cancer Medicine	28 Italian Cancer Registries	1998-2012	NR	Min 0-Max 84 years	2 months after the first cancer diagnosis	Median < 7 years, Min 2 months-Max 15 years	Non-melanoma skin cancer; Cases detected at autopsy; Cases known from death certificate only or with follow-up time equal to zero; Third or subsequent malignant tumors; Cases diagnosed at the age of 85 years or more; Second primary cancers diagnoses <2 months after the first one.	Thyroid (230)
10	Dasgupta, 2012, Australia, Cancer Causes Control	The Queensland Cancer Registry	1996-2007	15 775	Mean 64 years, Min 20-Max 79 years	2 months after the first cancer diagnosis	Median 4.2 years, Interquartile range 2.2-7.3 years	New malignancies diagnosed within the first 2 months of follow-up; Another invasive cancer prior to their first CRC diagnosis.	any subsequent primary cancer (1615) any subsequent primary cancer excluding CRC (1342) Breast (Female) (113) Colorectum (273) Gastric Cancer (38) Kidney (57) Lung (202) Lymphoid Leukemia (21) Myeloma (21) Non-Hodgkin Lymphoma (42) Pancreas (33) Prostate (265) Small intestine (20) Urinary Bladder (73) Uterine Body (25)
11	Dong, 2001, Sweden, International Journal Of Cancer	The Swedish Family-Cancer Database	1958-1996	67 899	NR	One month after the first cancer diagnosis	Median 2 years (Males) Median 3 years (Female), Min 1 month-Max 38 years	Patients lost to follow-up at the date of their last contact; Synchronous cancers diagnosed within 2 months after diagnosis of the first cancer.	any subsequent primary cancer (6197) Colon[a] (719)

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Table 1. (continued)

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
12	Evans, 2002, United Kingdom, Gut	The Thames Cancer Registry in Southeast England	1961-1995	127 281	NR	the date of the first cancer diagnosis	NR	Non-melanoma skin cancers; Non-malignant tumors; Patients without a date of birth; Patients with a cancer at a different site, diagnosed on the same day as colorectal cancer.	any subsequent primary cancer (4317) any subsequent primary cancer excluding CRC (3804) Brain (32) Breast (Female) (513) Buccal cavity, Pharynx (8) Cervix (69) Colorectum (513) Gallbladder (18) Gastric Cancer (234) Kidney (103) Larynx (37) Leukemias (111) Liver (21) Lymphoma (112) Myeloma (48) Esophagus (109) Ovary (207) Pancreas (127) Prostate (950) Small intestine (20) Testis (8) Thyroid (19) Urinary Bladder (319) Uterine Body (106)
13	Feller, 2020, Switzerland, BMC cancer	Nine Swiss Cancer Registries	1981-2014	35 949	Median 70 years (Males), Median 73 years (Females)	6 months after the first cancer diagnosis	Median 6.0 (Interquartile 2.1–10.9) years	Synchronous primary cancers diagnosed within 6 months after first diagnosis; Patients with less than 6 months of follow-up.	any subsequent primary cancer (4441)
14	Heard, 2004, Australia, Cancer Causes and Control	The South Australian Cancer Registry	1997-2001	NR	NR	One month after the first cancer diagnosis	NR	People with more than 2 primary cancers.	Breast (Female) (145) Colorectum (344) Gastric Cancer (64) Kidney (64) Leukemias (64) Lung (152) Lymphoma (54) Ovary (38) Pancreas (37) Prostate (321) Urinary Bladder (55) Uterine Body (25)

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Table 1. (continued)

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
15	Hemminki, 2001, Sweden, Cancer Epidemiology, Biomarkers & Prevention	The Swedish Cancer Registry	1958-1996	68 104	Mean 66.15 years (Males), Mean 64.84 years (Females)	One month after the first cancer diagnosis	NR	NR	Brain (113) Breast (Female) (445) Leukemias (130) Lung (339) Lymphoma (165) Myeloma (57) Small intestine (110) Thyroid (45) Ovary (143)
16	Hemminki, 2001, Sweden[b], Int. J. Cancer	The Swedish Cancer Registry	1958-1996	34 577	NR	NR	NR	NR	Buccal Cavity, Pharynx (46) Cervix (13) Female Genital Tract (15) Esophagus (14) Rectum (56)
17	Hemminki, 2003, Sweden, Int. J. Cancer	The Swedish Cancer Registry	1958-1998	NR	NR	the date of the first cancer diagnosis	NR	NR	Pancreas (404)
18	Hoar, 1985, United States of America, National Cancer Institute Monograph	The Connecticut Tumor Registry	1935-1982	42 264	NR	2 months after the first cancer diagnosis	NR	All persons who survived less than 2 months after the diagnosis of their first primary cancer; All patients who developed a simultaneous cancer during this period; First primary cancers diagnosed only at autopsy or death certificate area.	any subsequent primary cancer (2268) any subsequent primary cancer excluding Colon/Rectum (2693) Bone (4) Brain (27) Breast (Female) (323) Buccal Cavity, Pharynx (93) Cervix (32) Colorectum (953) Female Genitals (262) Gastric Cancer (122) Hematologic Malignancies (186) Larynx (33) Leukemias (81) Lung (322) Lymphoma (68) Myeloma (37) Esophagus (39) Ovary, Fallopian Tubes (99) Pancreas (76) Prostate (392) Testis (1) Thyroid (11) Uterine Body (116)

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Table 1. (continued)

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
19	Jegu, 2014, France, BMC Cancer	Ten French Cancer Registries	1989-2007	NR	Mean 64.2 years	2 months after the first cancer diagnosis	Median 4.0 years (Min 2.0 months–Max NR)	Non-melanoma skin cancers; Extensions, recurrences or metastases; A synchronous second cancer (<61 days of follow-up); Third and subsequent primary cancers.	any subsequent primary cancer excluding the first primary cancer (2931) Urinary Bladder (136) Breast (Female) (297) Colorectum (272) Lung, Bronchus, and Trachea (279) Uterine Body (66)
20	Kok, 2013, Netherlands, Cancer Epidemiology	The Netherlands Cancer Registry	1989-2008	NR	Median 70 years, Interquartile range 64-76 years	the date of the first cancer diagnosis	Median 2.3 years, Min 1 day-Max 19 years	Non-invasive cancers; Patients with a first and second primary cancer diagnosed on the same day; Patients diagnosed with cancer found during autopsy; Patients with a first primary prostate cancer.	Prostate (1770)
21	Lee, 2015, Taiwan, Medicine	The Taiwan National Health Insurance Database	1996-2011	98 876	Median 67.0 (Interquartile 56.0–75.0) years	1 year after the first cancer diagnosis	Median 4.03 (Interquartile 2.14–7.49) years	Participants who were followed <1 year; Synchronous primary malignancies diagnosed within the first year after diagnosis of CRC; Neoplasms of the small intestine to avoid misclassification; Second primary CRCs.	any subsequent primary cancer excluding CRC (4259) Bone and Soft Tissue (45) Breast (275) Cervix (92) Female Genital Tract (257) Gastric Cancer (299) Hematologic Malignancies (226) Kidney (191) Liver and Biliary Tract (636) Lung and Mediastinum (843) Esophagus (77) Ovary (59) Pancreas (100) Prostate (455) Thyroid (73) Urinary Bladder (259) Uterine Body (106)

(continued)

Table 1. (continued)

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
22	Levi, 1993, Switzerland, British Journal Of Cancer	The Vaud Cancer Registry	1974-1989	NR	NR	2 months after the first cancer diagnosis	Min 2 months-Max 14 years	Tumors occurring synchronously.	Prostate (25)
23	Levi, 2012, Switzerland, International Journal Of Cancer	The Vaud Cancer Registry	1974-2008	9389	Min 20 years–Max NR	2 months after the first cancer diagnosis	Mean 4.7 years	Cases diagnosed at death and of those with a second primary occurring 2 or less months since the first primary.	Colorectum (136)
24	Liang, 2015, Taiwan, Japanese Journal Of Clinical Oncology	The Taiwan Cancer Registry	1995-2009	65 648	Median 66 years	2 months after the first cancer diagnosis	Median 4.4 years (Min 2 months–Max NR)	Patients with missing clinical data or those who died within 2 months after CRC diagnosis; A local recurrence considered if the reported second cancers developed at the same site as the first primary cancer.	any subsequent primary cancer (3810) Colorectum (900) Lymphoma (49) Oropharynx (82) Small intestine (56)
25	Lynge, 1985, Denmark, National Cancer Institute Monograph	The Danish Cancer Registry	1943-1980	56 087	NR	2 months after the first cancer diagnosis	NR	All persons who survived less than 2 months after the diagnosis of their first primary cancer; All patients who developed a simultaneous cancer during this period; First primary cancers diagnosed only at autopsy or death certificate area.	any subsequent primary cancer (2257) any subsequent primary cancer excluding Colon/Rectum (2147) Bone (3) Brain (32) Breast (Female) (234) Buccal cavity, Pharynx (54) Cervix (51) Colorectum (308) Female Genitals (288) Gastric Cancer (173) Hematologic malignancies (142) Larynx (28) Leukemias (76) Lung (295) Lymphoma (49) Myeloma (17) Esophagus (22)

(continued)

Table 1. (continued)

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
									Ovary, Fallopian Tubes (123) Pancreas (86) Prostate (100) Testis (4) Thyroid (10) Uterine Body (94)
26	Malmer, 2000, Sweden, Int. J. Cancer	The Swedish Cancer Registry	1958-1994	156 872	Median 72 years	6 months after the first cancer diagnosis	Mean 81.3 months, Median 81 months	NR	All primary brain tumors (224)
27	McCredie, 1997, Australia, American Association For Cancer Research Inc.	The New South Wales Central Cancer Registry	1972-1991	42 509	Mean 67.1 years	2 months after the first cancer diagnosis	Mean 4.1 years	Second primary cancer within the first 2 months.	any subsequent primary cancer excluding Skin and Colon (2098) Breast (Female) (218) Buccal cavity, Pharynx (45) Cervix (21) Colorectum (202) Gastric Cancer (76) Kidney (85) Larynx (16) Leukemias (60) Lung (244) Lymphoma (90) Esophagus (27) Ovary (62) Pancreas (47) Prostate (372) Small intestine (15) Thyroid (16) Urinary Bladder (99) Uterine Body (52)
28	Moot, 2003, Australia, ANZ Journal Of Surgery	The Victorian Cancer Registry	1982-1995	8289	Mean 67 years	2 months after the first cancer diagnosis	Mean 7.2 years	Second primary cancers diagnosed on the same date as the index cancers.	Colorectum (276) Prostate (216)
29	Mulder, 2012, Netherlands, Diseases Of The Colon And Rectum	The Rotterdam Cancer registry	1995-2006	10 283	Median 70 years, Interquartile range 62-77 years	6 months after the first cancer diagnosis	Mean 3.9 years	Patients who were not treated by resection for their first colorectal cancer; Those with a diagnosis of metastatic disease;	Colorectum (135)

(continued)

Table 1. (continued)

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
								Patients who underwent a total colectomy for their primary colorectal cancer; Patients with less than 6 months of follow-up, because of death, or those who received a diagnosis after June 2006; Patients known with predisposing conditions, such as Lynch syndrome and familial adenomatous polyposis; Single colorectal cancer cases and patients with synchronous colorectal cancer.	
30	Preyer, 2017, Austria, BMC Cancer	Austrian Cancer Registries	1988-2010	7138	Min 15 years–Max NR	2 months after the first cancer diagnosis	Median 5.7 years, Interquartile range 1.4-10.3 years	Non-melanoma skin cancers; Death certificate only cases; Cases with a survival of less than 2 months; Life status could not be assessed; Second primary cancers found at the same time of diagnosis of the first primary cancer (synchronous cancers) or occurring within 2 months after the first primary cancer diagnoses; Third or subsequent primary cancers.	any subsequent primary cancer (614)

(continued)

Table 1. (continued)

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
31	Ringland, 2009, Australia, Annals Of Oncology	The New South Wales Central Cancer Registry	1987-2004	29 471	Min 30 years–Max NR	2 months after the first cancer diagnosis	Mean 5.1 years, Median 3.7 years, Interquartile range 1.4-10.7 years	Patients <30 years of age at diagnosis of first primary to avoid a major bias towards selection of patients with inherited CRC syndromes such as familial adenomatous polyposis or hereditary non-polyposis colon cancer; Patients died within 2 months of first diagnosis.	Colorectum (660)
32	Rombouts, 2017, Netherlands[b], Annals Of Oncology	The Netherlands Cancer Registry	1989-2014	29 027	Mean 66 years, Min 14—Max 95 years (radiation therapy cohort), Mean 70 years, Min 19-Max 98 years (non-radiation therapy cohort)	One day after the first cancer diagnosis	Median 8.1 years (radiation therapy cohort), Median 7.1 years (non-radiation therapy cohort), Min 0-Max 27 years (Both cohorts)	Patients who had clinical or pathological evidence of metastatic disease at the time of the primary cancer; Patients with a follow-up of zero days.	any subsequent primary cancer (4965)
33	Shen, 2006, Multiple countries, American Journal Of Epidemiology	13 Multi-countries Cancer Registries	0-2000	494 966	NR	the date of the first cancer diagnosis	NR	Third and subsequent primary neoplasms; non-melanoma skin cancer.	Pancreas (850)
34	Tabuchi, 2012, Japan, Cancer Science	The Osaka Cancer Registry	1985-2005	NR	Min 0-Max 79 years	3 months after the first cancer diagnosis	Mean 3.9 years, Median 2.5 years, Min 3 months-Max 10 years	In situ carcinomas, benign intracranial tumors, and any third or fourth (or more) primaries; Both the observed and expected numbers of second primary cancer in the same site as the first cancer.	any subsequent primary cancer excluding CRC (2470) Hematologic Malignancies (108) Larynx (29) Breast (Female) (91) Gallbladder (58) Gastric Cancer (558) Liver (352) Lung (410) Mouth/Pharynx (47) Esophagus (95) Ovary (34) Pancreas (109) Prostate (107) Thyroid (42) Uterine Body (50)

(continued)

Table 1. (continued)

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
35	Tanaka, 1991, Japan, Japanese Journal Of Cancer Research	The Osaka Cancer Registry	1966-1986	14 235	NR	the date of the first cancer diagnosis	NR	Simultaneous primary cancers occurring within 3 months from the date of dx of the initial cancer.	any subsequent primary cancer (416) Cervix (8) Leukemias (6) Lymphoma (4) Urinary Bladder (11)
36	Teppo, 1985, Finland, Journal Of The National Cancer Institute	The Finnish Cancer Registry	1953-1973	21 122	Min 15 years–Max NR	1 year after the first cancer diagnosis	Min 1-Max 15 years	Subsequent new tumors (both the observed and expected ones) at the same site.	any subsequent primary cancer excluding Colon (329) Breast (Female) (31) Cervix (2) Colorectum (32) Gallbladder, Bile Ducts (4) Gastric Cancer (45) Lung (30) Prostate (23) Urinary Bladder (8) Uterine Body (21)
37	Tiritilli, 2022, United States of America, Digestive Diseases And Sciences	The US SEER 9 Registries	1975-2017	356 899	Min 20 years–Max NR	6 months after the first cancer diagnosis	NR	Individuals with unknown age at diagnosis; Cases diagnosed by death certificate or autopsy only.	any subsequent primary cancer (37043)
38	Trama, 2022, Italy, Cancer	34 Italian Cancer Registries	1976-2021	1885	NR	the date of the first cancer diagnosis	Median 8 years, Min 1-Max 37 years	Non-melanoma skin tumors; Benign and in situ tumors of the central nervous system (CNS); Recurrences or progressive disease from multiple primary cancers; Synchronous multiple tumors.	any subsequent primary cancer (89) Colorectum (10) Female Genital Tract (17) Lung and Tracheal Tumors (7) Uterine Body (14)
39	Tsukuma, 1994, Japan, Japanese Journal Of Cancer Research	The Osaka Cancer Registry	1966-1989	NR	Min 0-Max 79 years	3 months after the first cancer diagnosis	Mean 3.7 years, Min 3 months-Max 9 years	In situ carcinomas, and any third or fourth (or more) primaries; A second primary cancer within 3 months (synchronous second primaries);	any subsequent primary cancer excluding colon (1143) Colorectum (45) Gastric Cancer (68) Liver (13) Ovary (9)

(continued)

Table 1. (continued)

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
								Patients who did not survive for 3 months or more after diagnosis of the first cancer.	
40	Utada, 2014, Japan, Japanese Cancer Association	The Nagasaki Prefecture Cancer Registry	1985-2008	NR	NR	the date of the first cancer diagnosis	Mean 4.3 years, Median 1.8 years	Third or subsequent primary cancers; Any cancers in the same site as second primary cancers unless their histological type differs from that of the first primary cancer; Second primary cancers in the same site as the first primary cancer.	any subsequent primary cancer excluding CRC (2997) Gastric Cancer (751) Ovary (34) Pancreas (137)
41	Van Der Meer, 2022, Netherlands, International Journal Of Colorectal Disease	The Netherlands Cancer Registry	1989-2017	140 403	Mean 70.6 years	the date of the first cancer diagnosis	NR	Tumors located in the appendix (C18.1) and neuroendocrine tumors were excluded.	Ovary (410)
42	Ye, 2018, Australia, American Cancer Society	The Tasmanian Cancer Registry	1980-2013	7567	Mean 63.4 years, Median 66.2 years	2 months after the first cancer diagnosis	Mean 6.9 years, Median 4.8 years, Interquartile range 1.2-10.2 years	Second primary cancers occurring within 2 months of the date of the first cancer diagnosis; Cases of benign tumors; Cancers in situ, or of uncertain behavior; non-melanoma skin cancers.	any subsequent primary cancer (827) Lung (121) Prostate (182)
43	Zhang, 2009, Sweden, British Journal Of Cancer	The Swedish Cancer Registry	1978-2004	NR	NR	the date of the first cancer diagnosis	NR	NR	Prostate (92)
44	Zheng, 2021, Sweden, Clinical Epidemiology	The Swedish Cancer Registry	1990-2015	NR	Median 69 years, Min 59-Max 78 years	the date of the first cancer diagnosis	NR	NR	Gallbladder (44) Liver (117)
45	Zheng, 2021, Sweden, Clinical Epidemiology	The Swedish Cancer Registry	1990-2015	NR	NR	the date of the first cancer diagnosis	NR	NR	Gastric Cancer (288)

(continued)

Table 1. (continued)

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
46	Zheng, 2021, Sweden, European Association Of Urology	The Swedish Cancer Registry	1990-2015	NR	NR	the date of the first cancer diagnosis	NR	Cancers for which 1-year survival was less than 50%.	Kidney (303)
47	Zheng, 2021, Sweden, Cancer Reports	The Swedish Cancer Registry	1990-2015	NR	NR	the date of the first cancer diagnosis	NR	Cancers for which 1-year survival was less than 50%.	Urinary Bladder (704)
48	Chen, 2023, United States of America, Frontiers in Oncology	The Kentucky Cancer Registry	2000-2019	15 333	Median 62.6 years	Five years after the first primary cancer diagnosis	Mean 5.6 years	Non-melanoma skin cancer	any SPC (1808) any SPC excluding CRC (1548) Colorectum (260)
49	Choi, 2024, Democratic People's Republic of Korea, JMIR PUBLIC HEALTH AND SURVEILLANCE	The South Korea Health Insurance Review and Assessment (HIRA) database	2008-2019	22 008	Mean 60.8 years (Males), Mean 61.9 years (Females)	Five years after the first primary cancer diagnosis	Mean 3.8 years, Median 4.3 years	Same-type cancers to minimize the bias from misclassification of the first cancer recurrence.	any SPC excluding CRC (1465) Bladder (71) Brain (33) Breast (Female) (63) Cervix (14) Esophagus (31) GB-biliary (73) Hodgkin lymphoma (1) Kidney (32) Larynx (15) Leukemia (25) Liver (130) Lung (293) Multiple myeloma (15) Non-Hodgkin lymphoma (37) Ovary (13) Pancreas (80) Prostate (189) Stomach (231) Thyroid (55) Uterus (35)
50	Kang, 2023, Democratic People's Republic of Korea, Ann Hepatobiliary Pancreat Surg	The Korea Central Cancer Registry	1993-2017	NR	Mean 58.5 years	Two months after the first cancer diagnosis	Mean 5.3 years	Recurrence or metastasis	Pancreas (exocrine) (724)

(continued)

Table 1. (continued)

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
51	Liang, 2023, Germany, International Journal of Cancer	German Cancer Registries	1990-2013	217 202	Median 70 years, Interquartile range 62-78 years	the date of the first cancer diagnosis	Median 3.67 years	Primary colorectal cancer diagnosed before age 20 and undeterminable tumors (Tx, T0); Cases identified by death certificate only or those with a survival time of <1 month; Non-melanoma skin cancer (ICD-10 C44).	any SPC (18751) Bladder (671) Brain, nervous system (165) Breast (Female) (1741) Cervix uteri (113) Colon (1758) Corpus uteri (526) Gallbladder (237) Kidney (631) Larynx (112) Liver (384) Lymphoid leukaemia (224) Multiple myeloma (227) Myeloid leukaemia (216) Non-Hodgkin lymphoma (524) Esophagus (232) Oral cavity and pharynx (384) Ovary (369) Pancreas (691) Prostate (2869) Rectum (2124) Renal pelvis and ureter (384) Small intestine (233) Stomach (891) Testis (268) Thyroid (99) Trachea, bronchus and lung (2248)
52	McGuire, 2024, United States of America, Cancer Causes & Control	The US SEER 11 Registries	1992-2015	19 491	Mean 64.3-67.9 years (varied by Races)	Two months after the first cancer diagnosis	NR	NR	Bladder (524) Breast (1122) Colorectum (4709) Lung (3554) Prostate (1919) Uterine body (634)

(continued)

Table 1. (continued)

Study Serial Number	First Author, Year, Country, Name of Journal	Name of Population-wide Registries	Study period (Recruitment-Last Follow-up)	Total number of the first cancer patients	Age at diagnosis of the first cancer, year	Latency period between diagnoses of the first and subsequent cancers	Length of Follow-up	Exclusions in each study	Type of Subsequent Primary Cancers included in the meta-analysis (number of individuals diagnosed with a subsequent primary cancer)
53	van der Meer, 2024, Netherlands, ESMO Open	The Netherlands Cancer Registry	1989-2018	NR	Median 32 years, Min 26-Max 36 years	Six months after the first cancer diagnosis	Median 8.85 years	Survivors with a follow-up <6 months after first primary cancer diagnosis	any SPC (194)
54	Warkentin, 2024, Canada, CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION	The Alberta Cancer Registry	2004-2020	22 600	Mean 65 years (Males), Mean 66.7 years (Females)	Six months after the first cancer diagnosis	Mean 4.9 years	All stage 0 cancers (in situ)	any SPC (1675)
55	Yang, 2023, United States of America, International Journal of Colorectal Disease	The US SEER 8 Registries	1990-2019	152 402	Mean 68 years	Six months after the first cancer diagnosis	NR	Patients with distant stage, in situ or missing value; Cause of death was missing; Latency period less than 6 months; Second chance proven by autopsy only or death certificate.	any SPC (23816) Colorectum (4572) Corpus Uteri (NR) Esophagus (NR) Floor of mouth (NR) Kidney (734) Lung and bronchus (4156) Small intestine (NR) Stomach (NR)
56	Youlden, 2023, Australia, JOURNAL OF ADOLESCENT AND YOUNG ADULT ONCOLOGY	The Queensland Cancer Registry	1982-2018	1854	Min 15-Max 39 years	Six months after the first cancer diagnosis	Median 14 years, Interquartile 7.2-22.5 years	Synchronous primary cancers diagnosed within 6 months of the first primary cancer; Third or subsequent primary cancers.	any SPC (125) Breast (Female) (18) Colorectum (26)
57	Zuo, 2024, United States of America, Scientific reports	The US SEER Registries	2000-2018	331 491	Mean 58 years, Median 64 years	Six months after the first cancer diagnosis	NR	Survival time of zero; Unknown race and marital status; Unknown specific cause of death classification; History of other malignancies; and Patients certified only by autopsy or death.	Thyroid (883)

Abbreviations: CRC = colorectal cancer; NR = not reported.
[a] This study included only the first colon cancer cases.
[b] This study included only the first rectal cancer cases.

Risks of primary cancers in female reproductive organs following colorectal cancer

There were higher increased risks of developing primary cancers in female reproductive organs following colorectal cancer, with a 11% higher risk at the breast (1.11, 1.04 to 1.18), an 80% higher risk at the ovaries (1.80, 1.48 to 2.11), and a 80% higher risk at the uterine body (1.80, 1.47 to 2.13). The increased risk of primary breast cancer differed by region ($P = .007$): 1.22 (1.10 to 1.34) for Australia, 1.20 (1.09 to 1.32) for East Asia, 1.07 (0.97 to 1.18) for Europe, and 1.01 (0.86 to 1.16) for the United States (Figures 2 and 3, Figure S1). The cumulative risks of primary breast cancer up to age 75 years ranged from 3.97% to 6.45% and were ~1% higher for colorectal survivors only in East Asia and Australasia compared with the general population ($P < .001$) (Table S2 and Figure S2). Moreover, the increased risk of primary ovarian cancer was more than 2 times higher during the first 4 years and 45% after 4 years ($P = .004$), and for primary uterine cancer, the increased risk was 41% during the 2-6-month latency period and 4 times higher after 6-month latency period ($P = .007$) (Figures 2 and 3, Figure S1). This increased risk of uterine cancer also differed by region ($P = .006$). The cumulative risks of primary ovarian and uterine cancers for colorectal survivors compared with the general population are presented in Table S2 and Figure S2.

Risk of primary cancer in male genital organs following colorectal cancer

People with a previous diagnosis of colorectal cancer were 11% and 66% more likely than the general population to be diagnosed

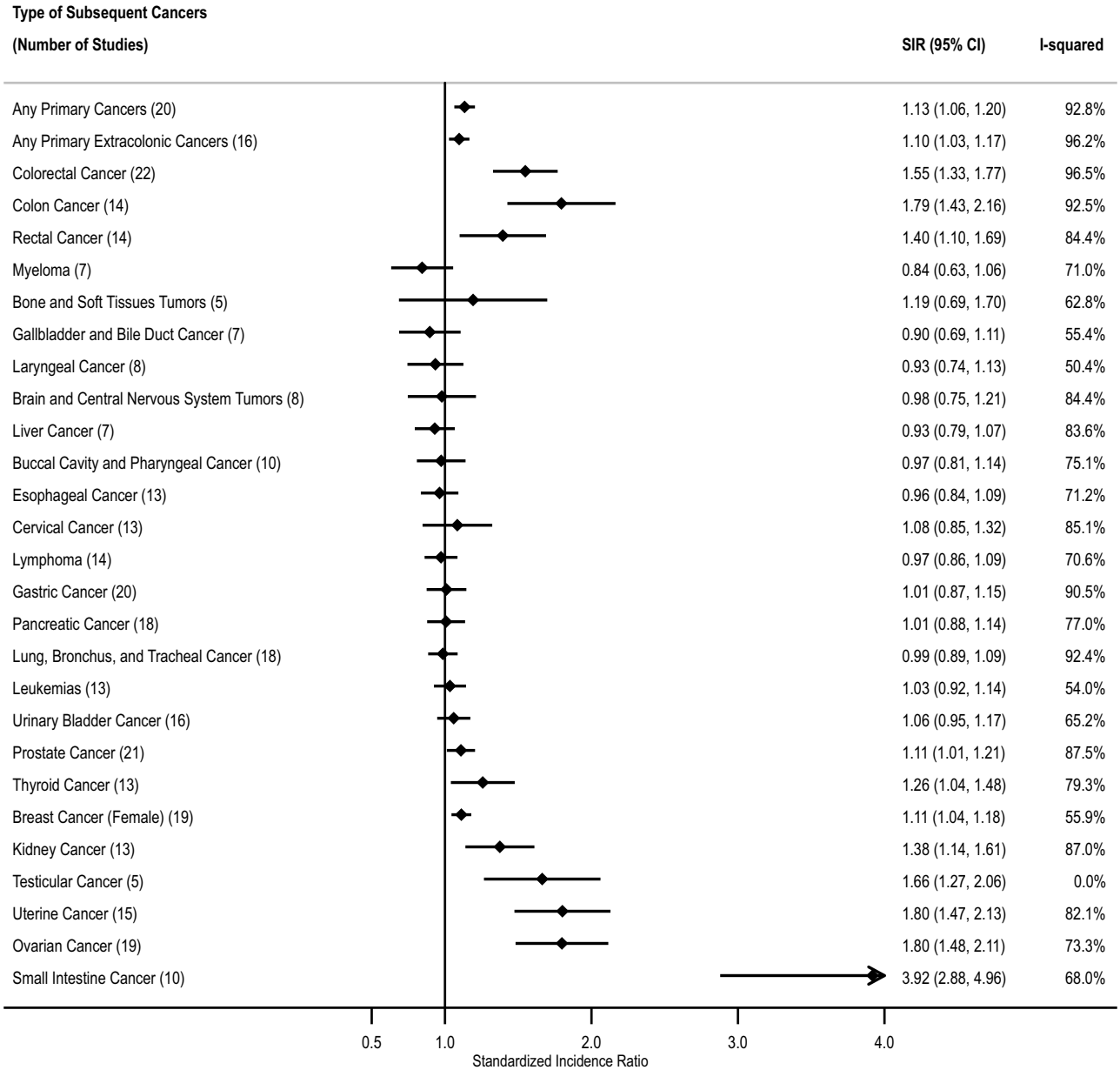

Figure 2. Forest plot displaying pooled SIR of subsequent primary cancers by site for colorectal cancer survivors. SIR = standardized incidence ratio; CI = confidence interval; I-squared statistic from the random-effects models for testing heterogeneity between studies.

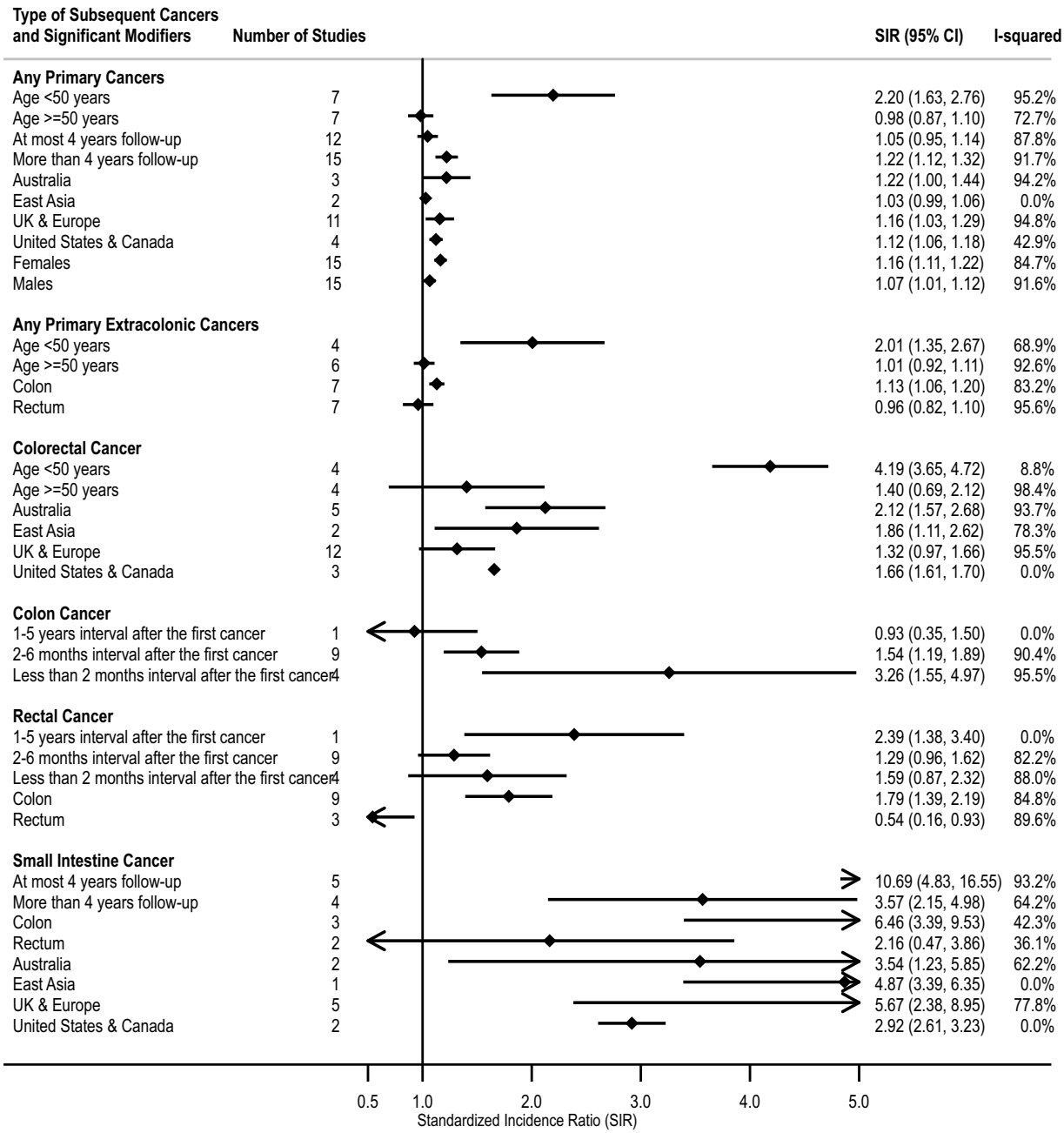

Figure 3. Forest plot displaying pooled SIR of subsequent primary cancers for colorectal cancer survivors from subgroup meta-analyses stratified by significant modifiers. SIR = standardized incidence ratio; CI = confidence interval; I-squared statistic from the random-effects models for testing heterogeneity between studies.

with subsequent primary prostate cancer (1.11; 1.01 to 1.21) and testicular cancer (1.66; 1.27 to 2.06), respectively. The increased risk of primary prostate cancer differed by region ($P = .0003$): 1.24 (1.14 to 1.33) for Australia, 1.16 (1.02 to 1.30) for East Asia, 0.98 (0.97 to 1.08) for Europe, and 1.08 (0.65 to 1.50) for the United States (Figures 2 and 3, Figure S1). The cumulative risks of primary prostate cancer up to age 75 years ranged from 2.63% to 7.56% by region and were ~1% higher for colorectal cancer survivors only in East Asia and Australasia compared with the general population (P range = 0.02 to <0.001) (Table S2 and Figure S2). The increased risk for primary testicular cancer did not differ by the potential modifiers ($P > .050$).

Risks of other primary extracolonic cancers following colorectal cancer

Moreover, colorectal cancer survivors encountered significantly higher risks of subsequent cancers at other extracolonic sites. These included kidney cancer (1.38; 1.14 to 1.61) and thyroid cancer (1.26; 1.04 to 1.48). The increased risk of primary kidney cancer differed by region ($P = .0003$): 1.62 (1.39 to 1.86) for Australia, 1.12 (0.47 to 1.78) for East Asia, 1.42 (0.96 to 1.87) for Europe, and 1.08 (1.01 to 1.15) for the United States (Figures 2 and 3, Figure S1). The cumulative risks of primary kidney cancer up to age 75 years ranged from 0.77% to 1.70% by region and were ~0.4% higher for colorectal cancer survivors in North America and

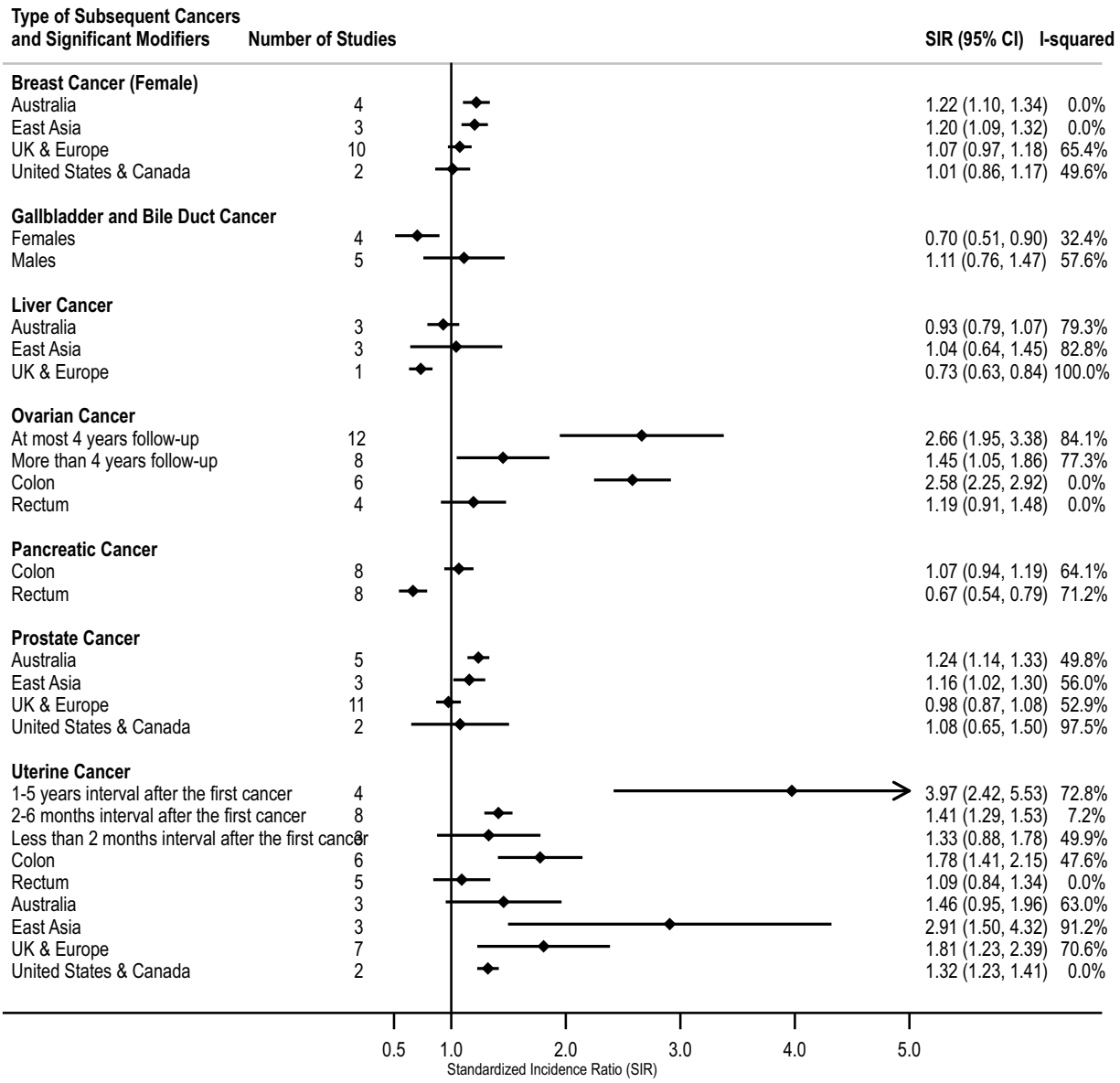

Figure 3. Continued.

Australasia compared with the general population (*P* range = 0.02 to <0.001) (Table S2 and Figures S2). The increased risk for primary thyroid cancer did not differ by the potential modifiers (*P* > .050).

There was no overall increased risk of developing primary lung cancer (including bronchus and trachea) following colorectal cancer (0.99; 0.89 to 1.09). However, the recent studies after 2005 showed a 13% increased risk of primary lung cancer (1.13; 1.03 to 1.24). Likewise, the increased risk of primary urinary bladder cancer following colorectal cancer was 19% (1.19; 1.08 to 1.31) after the study period of 2005 and 19% (1.19; 1.04 to 1.35) for 1-5 years latency period (Figures 2 and 3, Figure S1). However, there were no significant risks of developing subsequent cancers at the following sites: stomach (1.01; 0.87 to 1.15), gallbladder and bile duct (0.90; 0.69 to 1.11), liver (0.93; 0.79 to 1.07), buccal cavity and pharynx (0.97; 0.81 to 1.14), esophagus (0.96; 0.84 to 1.09), larynx (0.93; 0.74 to 1.13), brain and central nervous system (0.98; 0.75 to 1.21), pancreas (1.01; 0.88 to 1.14), leukemias (1.03; 0.92 to 1.14), lymphoma (0.97; 0.86 to 1.09), myeloma (0.84; 0.63 to 1.06), cervix (1.08; 0.85 to 1.32), and bone and soft tissues (1.19; 0.69 to 1.70) (Figure 2 and Figure S1).

Sensitivity analyses and publication biases

The sensitivity analyses indicated there was no evidence that the pooled estimates were due to any single study. Furthermore, there was no evidence of publication biases for the major outcomes for subsequent primary cancer, as indicated by Egger's test with a *P* value > .05. However, asymmetrical funnel plots and a *P* value < .05 in Egger et al.'s linear regression test revealed some evidence of publication biases for the outcomes of subsequent primary ovarian cancer, gastric cancer, and leukemias (Figure 5 and Figure S3).

Risk of bias assessment

Thirty-five out of 57 studies were considered to have a low risk of bias because they fulfilled all the requirements using the ROBINE tool. The design of population-wide studies itself included all cancer patients without selection bias and International

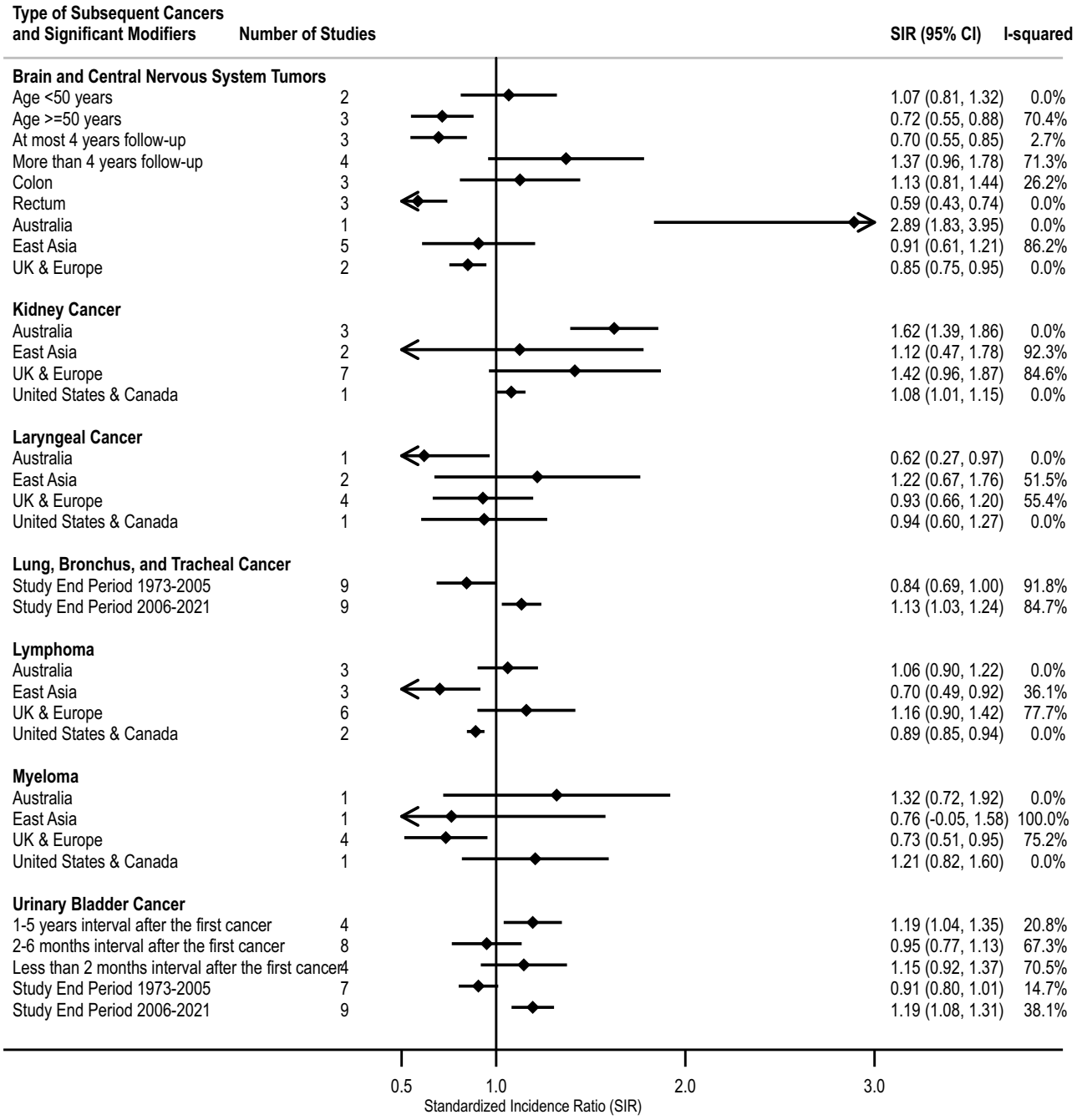

Figure 3. Continued.

Classification of Diseases (ICD) codes were consistently applied in recording the primary and subsequent cancers despite some adjustment for updated ICD codes reported by the studies. However, 14 studies provided no information or considered no latency period between diagnoses of the first colorectal cancer and subsequent cancers, hence the possibility that recurrent or metastatic or synchronous cancers could have been misclassified.[23,24,39,47,51,56,58,63,70,73-77] In addition, 3 studies did not provide adequate information to assess data completeness quality.[24,56,70] The outcomes for site of subsequent cancers were selectively reported in 7 studies although no potential effect could occur on the reported risk estimates.[42,50,54,55,69,70,72] In addition, 4 studies did not report which variables were standardized in the analysis despite SIRs being reported.[24,56,71,85] These studies were considered as having "some concern" for risks of bias (Table S3).

Discussion

This systematic review and meta-analysis provide new and significant insights into the extent to which the risk of cancer is elevated after being diagnosed with colorectal cancer. We have identified that age at initial colorectal cancer diagnosis, sex, site of initial cancer, the calendar year, geographic region, latency period, and time since colorectal cancer diagnosis are important modifiers for the increased risk of specific primary cancers after

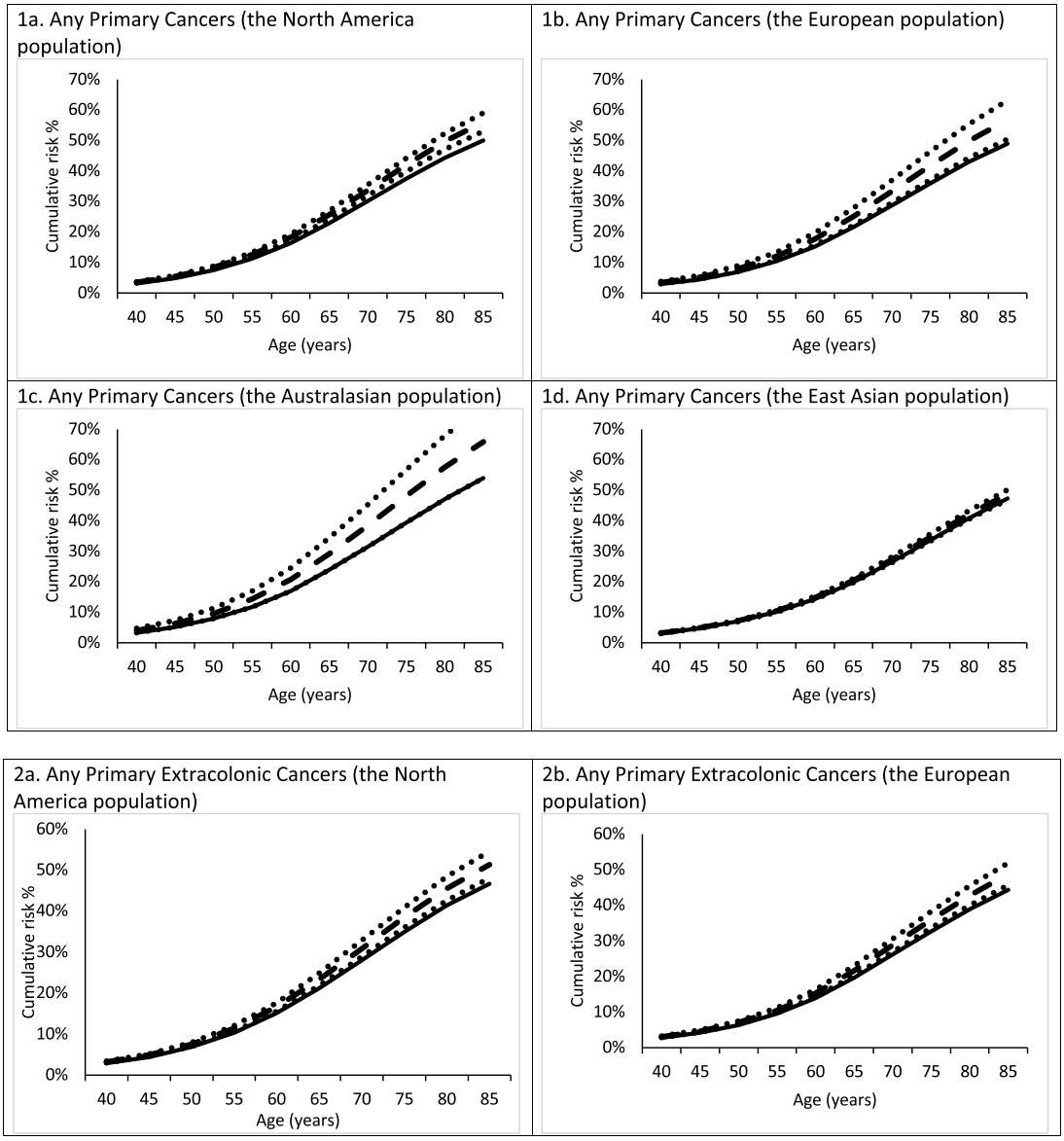

Figure 4. Age-specific cumulative risk of any subsequent primary cancers (**1a**–**1d**), any subsequent primary extracolonic cancers (**2a**–**2d**) and subsequent colorectal cancer (**3a**–**3d**) for colorectal cancer survivors (black dashed line) and corresponding confidence intervals (black dotted lines) compared with that of primary cancer for the general population (black solid line) by four geographic regions.

colorectal cancer. To the best of our knowledge, this is the first study to estimate age-specific cumulative risks of primary cancers following colorectal cancer by specific cancer sites and geographic regions, which is potentially important to inform clinical decision-making on surveillance strategies for colorectal cancer survivors.

Our finding shows the evidence for increased risk of primary cancer at any site, any extracolonic site and concordant site following colorectal cancer. The strength of evidence substantially increased among the early onset colorectal cancer survivors aged younger than 50 years. The highest increased risk of primary cancer after colorectal cancer was cancer of the small intestine (almost 4 times more common than for the general population), cancer of female and male reproductive organs (almost twice as often for ovary and uterus for women and testicular cancer for men, and 11% increased risk for female breast and prostate cancer), cancer of kidney (38% increase) and thyroid (26% increase). We did not find evidence for elevated risks of subsequent cancers of the gallbladder and bile duct, or the bone and soft tissues, despite these being reported by previous systematic reviews.[20,21]

We have not investigated the potential causes for primary cancer after colorectal cancer, so we can only speculate here on the reasons for their increased risk following colorectal cancer. One possible explanation for this observation is that there have been recent improvements in cancer screening and surveillance strategies applied more intensively for survivors with prior colorectal cancer compared with the general population. For example, the American Society of Clinical Oncology has endorsed a clinical practice guideline that defines follow-up care, surveillance protocols, and prevention measures for individuals who have survived colorectal cancer. This recent guideline recommends pelvic computed tomography (CT) scans every 6-12 months for individuals who have rectal cancer and annual or semi-annual abdominal and chest CT scans for those considered at high risk of cancer recurrence. Therefore, CT scans can help not only identify recurrent cancer and metastasis but also detect primary cancers in

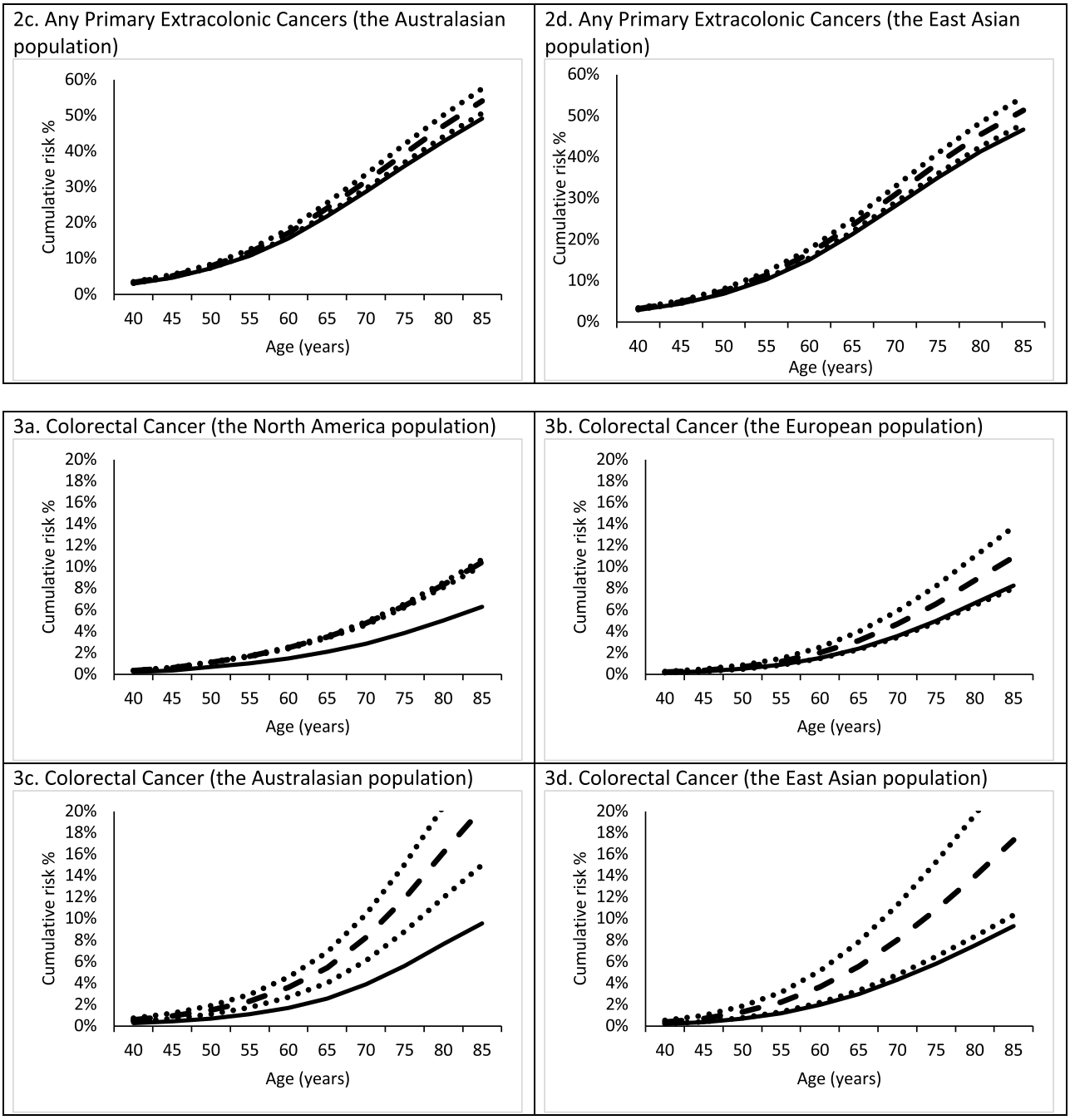

Figure 4. Continued.

high-risk areas of the abdomen and chest following colorectal cancer treatment.[88]

These increased risks may also be attributed to shared clinical factors for both primary and subsequent cancers such as obesity, tobacco use, alcohol intake, changes in diet, or underlying genetic manifestations. Carriers of MMR gene mutations with a primary colorectal cancer are at increased risks of subsequent cancer, including breast and prostate cancers, compared with the general population.[89] The treatments for the first colorectal cancer, such as radiotherapy, could trigger the development of cancers, particularly in the lower abdomen. This hypothesis is consistent with our observation of increased risks of cancer in female genital organs.[90] However, the relationship between therapeutic radiation and cancer risk could be complex—it is also possible that cancer could be reduced by radiation as a precancer could inadvertently be destroyed. For example, the diagnosis of cancer of the prostate could be reduced by pelvic radiotherapy for colorectal cancer destroying pre-malignant prostate disease.[62,91-94] Other potential common environmental factors, that could be more prevalent in colorectal cancer survivors, such as lack of physical activity, a sedentary lifestyle, or poor diet, may also contribute to developing subsequent cancers, given they are known risk factors for primary colorectal cancer.[95-104]

The findings of the study suggest that there are regional differences in subsequent cancer risks for colorectal cancer survivors. The risks of any subsequent cancers were observed only for Australian, European, and North American colorectal cancer survivors, whereas there was no evidence of increased risk for Asian

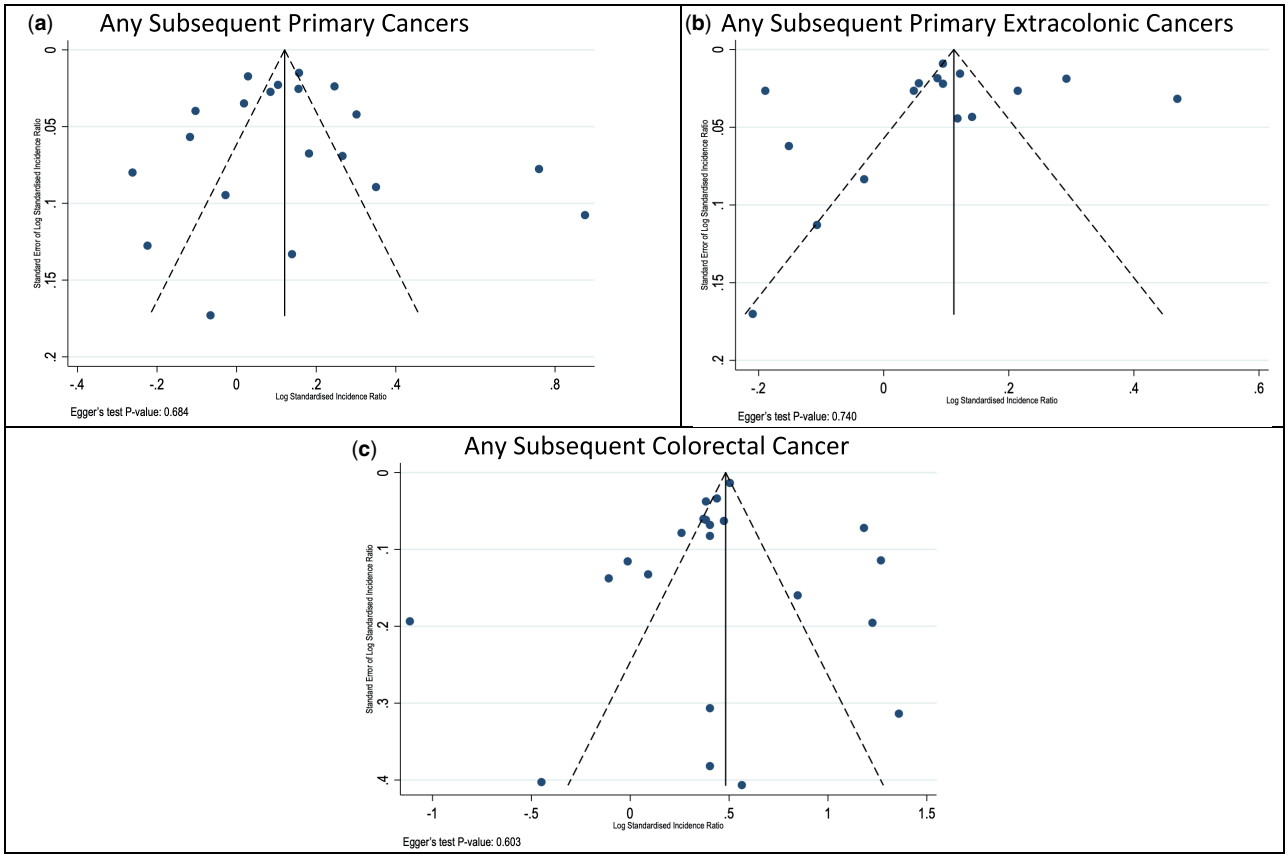

Figure 5. Funnel plots with pseudo 95% confidence limits of the studies included in the meta-analysis: (**a**) any subsequent primary cancers, (**b**) any subsequent primary extracolonic cancers, (**c**) subsequent colorectal cancer.

survivors. The Australian and East Asian survivors were at increased risks of female breast and prostate cancer, whereas the risk of the subsequent kidney cancer was observed only for the Australian and North American. In contrast, there were decreased risks of subsequent liver and myeloma only for European survivors and decreased risks of lymphoma for East Asian and North American survivors compared with the respective general population. Despite the possibility of a chance finding due to the large number of comparisons made in the original studies, further exploration of the potential underlying reasons for these regional differences is needed. This will also help develop effective screening and prevention strategies that are tailored to the specific needs of colorectal cancer survivors in different regions.

We also found that the risk of any primary cancer after primary colorectal cancer only increased above that of the general population after a median follow-up period of 4 years. However, the risk of ovarian cancer was substantially elevated in the first 4 years of the follow-up period. In addition, the risks of uterine cancer and urinary bladder cancer increased considerably among the survivors with the latency period of 1-5 years. This suggests the need for a high level of surveillance, which may vary depending on the types of subsequent cancers and the length of follow-up or latency period. Female survivors should be particularly attentive to surveillance within the first 4 years of diagnosis of the first colorectal cancer to detect subsequent ovarian cancer early.

Although we identified some evidence of the effects of measured potential factors for heterogeneity on the pooled estimates, there is still some degree of heterogeneity due to differences in the study population regarding age distribution, sex, family history of cancer, sites of the primary colorectal cancer, and treatment for the primary colorectal cancer. Therefore, further studies are suggested to examine potential factors that may influence the risks of subsequent cancers for colorectal cancer survivors.

The strengths of this study include the inclusion of only population-based cancer registry studies, which reduces detection bias and classification error and increases the precision of estimates given the large sample of at least 2.89 million colorectal cancer cases worldwide. We have avoided detection bias that is often observed in clinics/hospitals-based studies because cancer patients under more extensive medical care have a higher chance of having subsequent cancers detected than the general population. In addition, all studies were reported for data completeness and underwent a data checking process to ensure high-quality data, except for 3 studies that did not adequately describe data quality in the methods.[24,56,70] However, the study has limitations, such as incomplete information about follow-up and latency periods in some studies,[23,24,39,49,51,56,58,63,70,73-77] which should also be addressed. The lack of a definition for latency periods could introduce bias in the possibility of misclassifying recurrent, metastatic, or synchronous cancers as independent subsequent cancers. Nevertheless, we conducted a meta-regression analysis for the group with no information of the latency period and did not identify any potential impact on the pooled estimates. To minimize time and workload, data extraction and risk of bias assessment were primarily conducted by a

single author and independently verified by another author, although PRISMA guidelines recommend that both processes would ideally be completed independently by 2 or more authors. Nevertheless, this approach did not compromise the study's quality, as both reviewers had extensive experience in conducting systematic reviews.

In conclusion, our study provides evidence that the risk of subsequent primary cancers for colorectal cancer patients is substantially higher than that for the general population without prior colorectal cancer. The risk is highest for cancers in the same organ as the colorectum and extracolonic sites such as the small intestine, ovary, uterus, kidney, thyroid, female breast, testes, and prostate. The risks of subsequent female breast and prostate cancers are highest in Australia and East Asia, whereas the risks of any primary cancer, uterine cancer and urinary bladder cancer increase with longer follow-up or latency periods. Therefore, the findings of this study can inform clinical decision making on surveillance strategies for colorectal cancer survivors and highlight the need for personalized screening and surveillance strategies based on regional differences, the type of subsequent cancers, age at initial cancer diagnosis, and the duration of follow-up periods.

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Author contributions

Ye Kyaw Aung (Conceptualization, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing—original draft, Writing—review & editing), Ye Zhang (Investigation, Methodology, Validation, Writing—review & editing), Mark Jenkins (Conceptualization, Supervision, Validation, Writing—review & editing), and Aung Ko Win (Conceptualization, Supervision, Validation, Writing—review & editing)

Supplementary material

Supplementary material is available at *JNCI Cancer Spectrum* online.

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Conflicts of interest

The authors declare that they have no competing interests.

Data availability

All the data analyzed or generated are included in this article and its supplementary information files.

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