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Colorectal cancer: Incidence, risk factors, and detection

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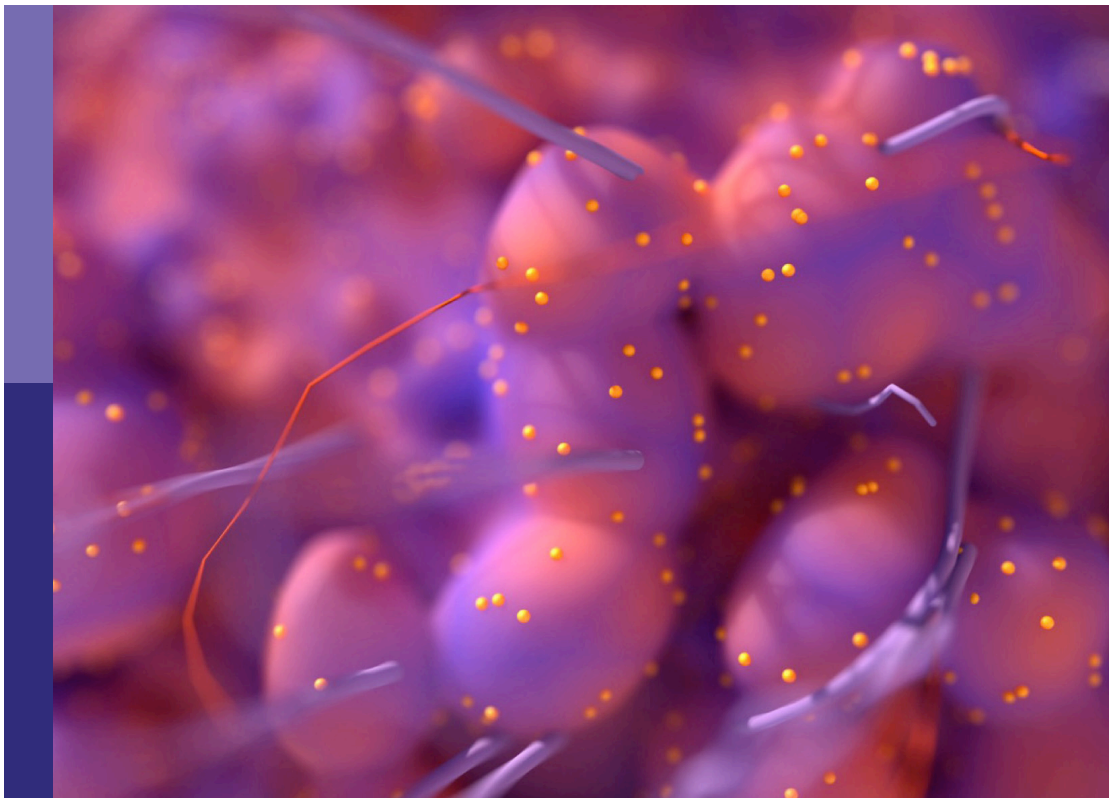

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Colorectal cancer: Incidence, risk factors, and detection

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Determinants of Participation and Detection Rate of Colorectal Cancer From a Population-Based Screening Program in China

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Colorectal cancer (CRC) screening has been widely implemented in Europe and the USA. However, there is little evidence of participation and diagnostic yields in population-based CRC screening in China. The participation rate and detection of colorectal lesions in this program were reported and related factors were explored. The analysis was conducted in the context of the Cancer Screening Program in Urban China, which recruited 282,377 eligible participants aged 40–74 years from eight cities in Henan province from 2013 to 2019. A total of 39,834 participants were evaluated to be high risk for CRC by an established risk score system and were subsequently recommended for colonoscopy. Of 39,834 with high risk for CRC, 7,454 subjects undertook colonoscopy (participation rate of 18.71%). We found that 50–64 years, high level of education, marriage, former smoking, current alcohol drinking, low levels dietary intake of vegetables, high levels dietary intake of processed meat, lack of physical activity, fecal occult blood test positive result, history of colonic polyp, history of colorectitis, and family history of CRC were associated with increased participation of colonoscopy screening. Overall, 17 CRC (0.23%), 95 advanced adenoma (1.27%), 478 non-advanced adenomas dysplasia (6.41%), 248 hyperplastic polyp (3.33%), and 910 other benign lesions (12.21%) were detected. The findings from the study will provide important references for designing effective population-based CRC screening strategies in the future. Given the relatively low participation rate, there was room for improvement in the yield of CRC screening.

Keywords: adherence, colorectal cancer, lesion, early detection, colonoscopy

INTRODUCTION

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers worldwide, with an age-standardized incidence rate of 19.4 per 100,000 and an age-standardized mortality rate of 8.9 per 100,000, in 2018 (1). In recent years, the incidence of CRC is increasing in China owing to the improvement of living standards,

lifestyle changes, and the growing number of elderly population (2). In China, the world standardized incidence and mortality of CRC were 19.4 and 9.0 per 100,000, respectively. A total of 521,490 new cases and 247,563 deaths were estimated in 2018 in China, which accounted for 28.2 and 28.1% of all the world cases (1).

More than 90% CRCs are developed from colonic polyps, especially adenomatous polyps (3). Studies have shown that it takes about 7–12 years to progress from adenomatous polyps to early CRC. If the treatment is performed at the stage of adenomatous polyps, it can be completely cured and prevent canceration, and the 5-year survival rate can exceed 90% (4). However, the 5-year survival rate for advanced cases is <10% (4). Colonoscopy with biopsies for histologic confirmation has been shown to significantly reduce CRC mortality through early detection of cancer or removal of adenomatous polyps (5). However, colonoscopy is an invasive procedure requiring a high level of expertise, with a high cost (6, 7). In countries with moderate or low CRC incidence and limited medical resources, it is recommended to use a risk stratification scoring system to select high-risk patients for colonoscopy (8, 9). However, there is still evidence that in population-based screening programs, the strategy of combining risk stratification with subsequent colonoscopy remains ineffective. Since October 2012, the Chinese government has launched a population-based Cancer Screening Program in Urban China (CanSPUC). Except for CRC, lung cancer, female breast cancer, liver cancer, esophageal cancer, and gastric cancer were all targeted (10). Henan started this program in 2013. Qualified participants were recruited from the community in the study area and were invited to undergo cancer screening for free. Participants are first invited to conduct cancer risk assessment through the established Clinical Cancer Risk Scoring System. It is recommended that participants who are assessed as high risk for specific types of cancer undergo appropriate screening interventions in accordance with the research protocol. For CRC screening, it is recommended that people at high risk of CRC follow a procedure and go to a designated tertiary hospital for colonoscopy.

In this study, we report the CRC screening results conducted in the first 6 years (from 2013 to 2019) of the program in Henan Province of China. Our aim is to provide evidence of colonoscopy participation and diagnosis in a timely manner. Research on high-risk populations in China provides an important reference for designing effective CRC screening strategies in the future.

METHODS

Study Design and Population

We carried out a cross-sectional study within the framework of CanSPUC. CanSPUC is an ongoing national cancer screening program launched in October 2013 in Henan province of China. Study methods have been described elsewhere (10). In short, social media and community advertising were used to raise public awareness about the cancer screening process. After then, trained staff provided convocation and appointment services to residents aged 40–74 years who lived in selected communities of participating cities by phone and personal contact. All qualified participants (40–74 years) were interviewed to collect information about their exposure to risk factors by a trained staff, and after signing a written informed consent, their cancer risk was measured using a defined Clinical Cancer Risk Score System. To improve the detection rate of CRC and optimize the use of limited medical resources in this screening program, it is recommended that only participants who are assessed as high risk of CRC to undergo colonoscopy in a tertiary hospital are designated and free of charge. All participants provided a written informed consent, and the study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College.

In this analysis, we used data from the first 6 years of the CRC screening program in Henan Province, from October 2013 to October 2019. This province covers eight cities (Zhengzhou, Zhumadian, Anyang, Luoyang, Nanyang, Jiaozuo, Puyang, and Xinxiang). Overall, 282,377 eligible participants were recruited. After excluding non-CRC high-risk groups ($N = 242{,}542$) and participants with ineffective risk assessment results ($N = 1$), the study included 39,834 remaining participants. **Figure 1** shows the flowchart for recruiting the population sample of the study.

Risk Assessment

Participants were asked to perform a risk assessment before performing a colonoscopy. The basic principle of the development of the cancer risk scoring system is based on the Harvard Risk Index (11), but it also includes risk factors, relative risks, and exposure rates of risk factors for the Chinese population. Smoking (at least one cigarette a day for more than 6 months), alcohol drinking (at least once a week for more than 6 months), tea drinking (at least 3 times a week for more than 6 months), dietary intake of pickled food, hot drink or hot food diet, high-salt diet, more-dry diet, body mass index (BMI), indoor soot exposure in the past 10 years, history of intestinal polyps, history of chronic colorectitis, and family history of CRC in first-degree relatives are included in the risk scoring system. The panel of experts assigned each risk factor a score based on the degree of association with CRC. The cumulative risk score was calculated and then divided by the average risk score in the general population to get the final individual relative risk. Individuals whose relative risk exceeds 1.50 were defined as high risk of CRC.

Clinical Procedures

All colonoscopy tests were performed in a total of nine tertiary hospitals (one in each city, except for two in Zhengzhou) by experienced gastroenterologists (physicians with at least 5 years of experience in performing colonoscopy). The abnormal findings found during the colonoscopy were carefully examined in accordance with standard clinical procedures, and biopsy samples were collected for further pathological diagnosis. Any findings during the colonoscopy were recorded in photographs. Clinical information such as morphological features, macroscopic diagnosis, and size were collected and recorded in a data system.

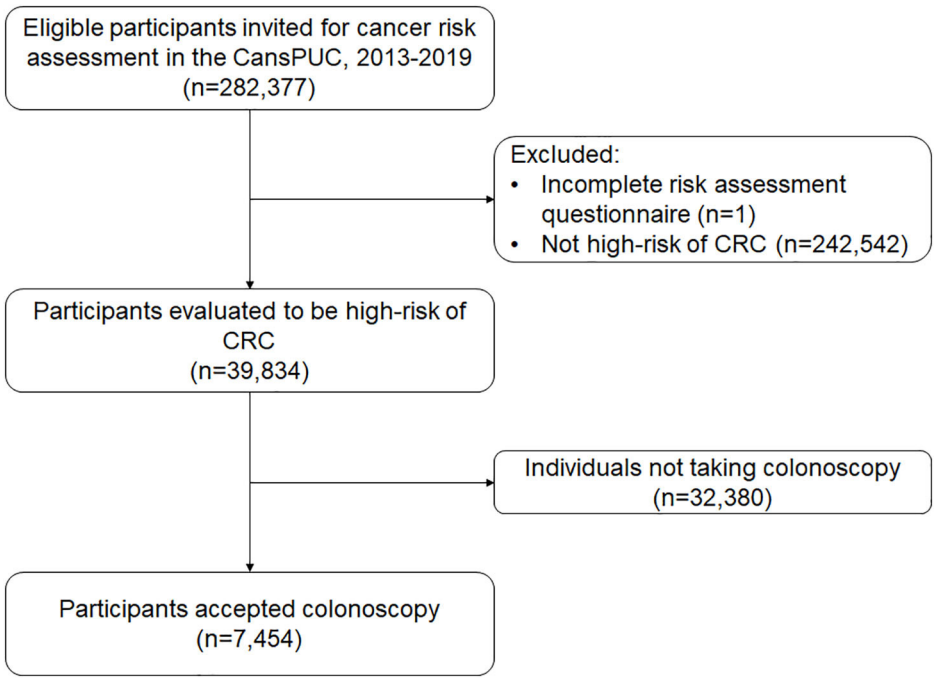

FIGURE 1 | Flow diagram of participant recruitment in CanSPUC, 2013–2019.

Outcome Ascertainment and Quality Control

Pathological examination was used for all abnormal findings found during colonoscopy by following the latest clinical guidelines. Pathological results were collected from highly standardized forms filled in by pathologists. For difficult cases with difficult or uncertain pathological diagnosis, the expert team of the National Cancer Center of China conducted consultation, and the report of the consultation results was forwarded to the respective doctors.

In this study, advanced adenomas are defined as at least one adenoma with villous components or at least one adenoma ≥10 mm or high-grade dysplasia.

Data Acquisition

Trained staff and physicians collect standardized paper documents (epidemiological questionnaires, colonoscopy reports, and pathology reports). Trained study staff checked the validity of forms and entered it into the data management system. If an inconsistency was found during the consistency check, the error was corrected by retrieving the original record. A unique identifier was used for each participant to track all relevant document forms of the individual. All data were transferred to the central data management team from the National Cancer Center of China, where the database was established and analyzed.

Statistical Analysis

In addition to the descriptive analysis of the characteristics of the study population, the overall participation rate and specific group participation rate owing to public factors were calculated, and a 95% CI was reported by Clopper–Pearson exact test. Chi-square test was used to compare differences in participation rates between groups. Associations between factors, including age (categorized into 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and 70–74 years), sex (male, female), BMI (<18.5, 18.5–24.0, 24.0–28.0, and ≥28.0 kg/m^2), waist (male: <85 and ≥85 cm; female: <80 and ≥80 cm), marriage status (unmarried or divorce or widowed, married), educational background (primary school or below, junior or senior high school, undergraduate or over), smoking status (never, current, former), alcohol drinking (never, current, former), dietary intake of vegetables (<2.5 kg/week, ≥2.5 kg/week), dietary intake of fruit (<1.25 kg/week, ≥1.25 kg/week), dietary intake of processed meat (<0.35 kg/week, ≥0.35 kg/week), physical activity (<3 times/week, ≥3 times/week), past fecal occult blood test (FOBT) (no, negative result, positive result, unknown result), history of colonic polyp (no, yes), history of colorectitis (no, yes), family history of CRC (no, yes), and colonoscopy participation rate were quantified by non-conditional logistic regression models and two-level logistic regression models with ORs and their 95% CIs. For two-level logistic regression model, the first level was the individual level (age, sex, BMI, waist, education background, marriage, smoking, alcohol drinking, dietary intake of vegetable, dietary intake of fruit, dietary intake of processed meat, physical activity, past FOBT, history of colonic polyp, history of colorectitis, and family history of CRC) and the second level was the geographical level (study sites). The diagnostic rate of colonoscopy was calculated, including the detection of CRC, and the detection rate of age and gender. The yield per

TABLE 1 | Characteristics of the study population and participation rates between different groups.

Factors	Participants at high risk for CRC (%)	Participants undertaking colonoscopy (%)	Participation rate (%)	χ^2	*P*-value*
Age (years)				98.74	<0.001
40–44	4,255 (10.68)	760 (10.20)	17.86		
45–49	6,982 (17.53)	1,317 (17.67)	18.86		
50–54	8,011 (20.11)	1,636 (21.95)	20.42		
55–59	6,714 (16.85)	1,372 (18.41)	20.43		
60–64	7,044 (17.68)	1,331 (17.86)	18.90		
65–69	5,113 (12.84)	827 (11.09)	16.17		
70–74	1,715 (4.31)	211 (2.83)	12.30		
Sex				7.39	0.007
Male	17,901 (44.94)	3,455 (46.35)	19.30		
Female	21,933 (55.06)	3,999 (53.65)	18.23		
BMI (kg/m^2)				30.46	<0.001
<18.5	533 (1.34)	99 (1.33)	18.57		
18.5–24.0	14,314 (35.93)	2,814 (37.75)	19.66		
24.0–28.0	17,175 (43.12)	3,240 (43.47)	18.86		
≥28.0	7,812 (19.61)	1,301 (17.45)	16.65		
Waist (cm)				6.75	0.009
<85 (male)/<80 (female)	13,887 (34.86)	2,695 (36.16)	19.41		
≥85 (male)/≥80 (female)	25,947 (65.14)	4,759 (63.84)	18.34		
Educational background				219.28	<0.001
Primary school or below	6,176 (15.50)	940 (12.61)	15.22		
Junior/senior high school	25,883 (64.98)	4,627 (62.07)	17.88		
Undergraduate or over	7,775 (19.52)	1,887 (25.32)	24.27		
Marriage				10.21	0.001
Unmarried/divorce/widowed	1,579 (3.96)	344 (4.61)	21.79		
Married	38,255 (96.04)	7,110 (95.39)	18.59		
Smoking				34.38	<0.001
Never	24,723 (62.07)	4,479 (60.09)	18.12		
Current	12,262 (30.78)	2,332 (31.29)	19.02		
Former	2,849 (7.15)	643 (8.63)	22.57		
Alcohol drinking				59.91	<0.001
Never	23,090 (57.97)	4,027 (54.02)	17.44		
Current	14,607 (36.67)	3,010 (40.38)	20.61		
Former	2,137 (5.36)	417 (5.59)	19.51		
Dietary intake of vegetables				65.31	<0.001
<2.5 kg/week	26,221 (65.83)	5,205 (69.83)	19.85		
≥2.5 kg/week	13,613 (34.17)	2,249 (30.17)	16.52		
Dietary intake of fruit				45.88	<0.001
<1.25 kg/week	29,004 (72.81)	5,662 (75.96)	19.52		
≥1.25 kg/week	10,830 (27.19)	1,792 (24.04)	16.55		
Dietary intake of processed meat				0	0.959
<0.35 kg/week	19,623 (49.26)	3,674 (49.29)	18.72		
≥0.35 kg/week	20,211 (50.74)	3,780 (50.71)	18.70		
Physical activity				33.70	<0.001
<3 times/week	25,475 (63.95)	4,984 (66.86)	19.56		
≥3 times/week	14,359 (36.05)	2,470 (33.14)	17.20		
Past FOBT				54.76	<0.001
No	32,879 (82.54)	6,071 (81.45)	18.46		
Yes (negative result)	3,379 (8.48)	580 (7.78)	17.16		

(Continued)

TABLE 1 | Continued

Factors	Participants at high risk for CRC (%)	Participants undertaking colonoscopy (%)	Participation rate (%)	χ^2	*P*-value*
Yes (positive result)	1,981 (4.97)	490 (6.57)	24.73		
Yes (unknown result)	1,595 (4.00)	313 (4.20)	19.62		
History of colonic polyp				438.14	<0.001
No	32,915 (82.63)	5,542 (74.35)	16.84		
Yes	6,919 (17.37)	1,912 (25.65)	27.63		
History of colorectitis				303.71	<0.001
No	18,758 (47.09)	2,833 (38.01)	15.10		
Yes	21,076 (52.91)	4,621 (61.99)	21.93		
Family history of CRC				585.68	<0.001
No	33,587 (84.32)	5,600 (75.13)	16.67		
Yes	6,247 (15.68)	1,854 (24.87)	29.68		

CRC, colorectal cancer; BMI, body mass index; FOBT, fecal occult blood test.

10,000 invitees and the number of colonoscopy used to detect a colorectal lesion were also calculated. Statistical software SAS version 9.4 (SAS Institute, Cary, NC) and STATA 14.0 were used for all statistical analyses. All tests are double-sided tests, and $p \leq 0.05$ are considered statistically significant.

RESULTS

Characteristics of the Study Population and Participation Rates

Table 1 lists the characteristics of people at high risk of CRC. Overall, more women (55.06%) were included in the study. The average age was 55.44 ± 8.36 years, and most (72.17%) were between 45 and 64 years old. About 63% of the participants (N = 24,987) were overweight or obese, and about 65% of them (N = 25,947) had abdominal obesity (present with waist). About 65% of the participants (N = 25,883) graduated from junior/senior high school, and most of them (96%, N = 38,255) were married. About 38% of the participants (N = 15,111) were current smokers or past smokers, and about 42% of them (N = 16,744) are current or past alcohol drinkers. About 66% of the participants (N = 26,221) had a dietary intake of vegetables with <2.5 kg/week, and about 73% of them (N = 29,004) had a dietary intake of fruit with <1.25 kg/week. About 51% of the participants (N = 20,211) had a dietary intake of processed meat with more than 0.35 kg/week, and about 64% of them (N = 25,475) participated in physical activity <3 times a week. About 17% of the high-risk population received FOBT previously and 28.48% of them (N = 1,981) had positive FOBT results. About 17% of the participants (N = 6,919) had a history of colonic polyp, and about 53% of them (N = 21,076) had a history of colorectitis. About 17% of the participants (N = 6,247) had a family member diagnosed with CRC. Of the 39,834 high-risk CRC participants, 7,454 of them underwent colonoscopy according to our research recommendations. The overall participation rate was 18.71% (95% CI 18.08–18.72%). Overall, the participation rate of men was slightly higher than that of women (19.30 vs. 18.23%, p = 0.007). They were also higher among participants in the 45–64 age group. Univariate analyses showed that participants who had a normal BMI (18.5–24.0 kg/m^2), had a smaller waist, had a high educational background, were unmarried/divorce/widowed, were current or former smokers, were current or former alcohol drinkers, had low levels of dietary intake of vegetables, had low levels of dietary intake of fruit, physical inactivity, had positive FOBT results, had a history of colonic polyp, had a history of colorectitis, or had a family history of CRC had relatively higher participation rates.

Multivariable Analysis for Factors Related to Participation Rate

As shown in **Table 2**, we also conducted a multivariable logistic regression model and a two-level logistic regression model to explore potential factors related to the participation rate. After adjusting for potential influencing factors, we found that age, education background, marriage, smoking, alcohol drinking, dietary intake of vegetables, dietary intake of processed meat, physical activity, FOBT results, history of colonic polyp, history of colorectitis, and family history of CRC were associated with participation rate. For instance, the odds of a participant with a history of colonic polyp undertaking screening colonoscopy was 0.53-fold higher than for a participant with no history of colonic polyp (OR 1.53, 95% CI 1.43–1.63). Similarly, the odds of a participant with a family history of CRC undertaking screening colonoscopy was 0.69-fold higher than for a participant with no family history of CRC (OR 1.69, 95% CI 1.58–1.81). After changing to the two-level logistic regression model in model II, the respective ORs did not change much (**Table 2**).

Colorectal Findings Under Screening Colonoscopy

Table 3 presents the diagnostic yield of colonoscopy in our screening program. Overall, there were 17 CRC, 95 advanced adenoma, 478 non-advanced adenomas dysplasia, 248 hyperplastic polyp, and 910 other benign lesions. This

TABLE 2 | Odds ratios of factors associated with participation rate of colonoscopy in the screening program.

Factors	Model I[§]		Model II[¶]	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age (years)				
40–44	1.00		1.00	
45–49	1.09 (0.99–1.21)	0.094	1.09 (0.99–1.21)	0.092
50–54	1.25 (1.14–1.38)	<0.001	1.25 (1.14–1.38)	<0.001
55–59	1.30 (1.17–1.44)	<0.001	1.30 (1.17–1.44)	<0.001
60–64	1.20 (1.08–1.33)	0.001	1.20 (1.08–1.33)	0.001
65–69	1.03 (0.92–1.15)	0.624	1.03 (0.92–1.16)	0.611
70–74	0.73 (0.61–0.86)	<0.001	0.73 (0.61–0.86)	<0.001
Sex				
Male	1.00		1.00	
Female	0.95 (0.88–1.02)	0.171	0.95 (0.88–1.02)	0.178
BMI (kg/m^2)				
<18.5	1.00		1.00	
18.5–24.0	1.03 (0.82–1.29)	0.806	1.03 (0.82–1.29)	0.806
24.0–28.0	1.00 (0.80–1.26)	0.984	1.00 (0.80–1.26)	0.983
≥28.0	1.01 (0.79–1.28)	0.961	1.01 (0.79–1.28)	0.958
Waist (cm)				
<85 (male)/<80 (female)	1.00		1.00	
≥85 (male)/≥80 (female)	0.98 (0.92–1.05)	0.578	0.98 (0.92–1.05)	0.575
Educational background				
Primary school or below	1.00		1.00	
Junior/senior high school	1.05 (0.97–1.14)	0.200	1.06 (0.97–1.14)	0.190
Undergraduate or over	1.45 (1.32–1.59)	<0.001	1.45 (1.32–1.59)	<0.001
Marriage				
Unmarried/divorce/widowed	1.00		1.00	
Married	0.83 (0.73–0.94)	0.003	0.83 (0.73–0.94)	0.003
Smoking				
Never	1.00		1.00	
Current	0.84 (0.78–0.92)	<0.001	0.84 (0.78–0.92)	<0.001
Former	1.20 (1.07–1.34)	0.002	1.20 (1.07–1.34)	0.002
Alcohol drinking				
Never	1.00		1.00	
Current	1.13 (1.05–1.21)	0.001	1.13 (1.05–1.21)	0.001
Former	1.04 (0.92–1.17)	0.558	1.04 (0.92–1.17)	0.553
Dietary intake of vegetables				
<2.5 kg/week	1.00		1.00	
≥2.5 kg/week	0.88 (0.82–0.94)	<0.001	0.88 (0.82–0.94)	<0.001
Dietary intake of fruit				
<1.25 kg/week	1.00		1.00	
≥1.25 kg/week	0.98 (0.91–1.05)	0.523	0.98 (0.91–1.05)	0.509
Dietary intake of processed meat				
<0.35 kg/week	1.00		1.00	
≥0.35 kg/week	1.12 (1.06–1.18)	<0.001	1.12 (1.06–1.18)	<0.001
Physical activity				
<3 times/week	1.08 (1.02–1.15)	0.007	1.08 (1.02–1.14)	0.008
≥3 times/week	1.00		1.00	
Past fecal occult blood test				
No	1.00		1.00	
Yes (negative result)	0.91 (0.82–1.00)	0.055	0.91 (0.83–1.00)	0.058
Yes (positive result)	1.24 (1.11–1.38)	<0.001	1.24 (1.11–1.38)	<0.001

(Continued)

TABLE 2 | Continued

Factors	Model I[§]		Model II[¶]	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Yes (unknown result)	0.99 (0.87–1.13)	0.915	0.99 (0.87–1.13)	0.915
History of colonic polyp				
No	1.00		1.00	
Yes	1.53 (1.43–1.63)	<0.001	1.53 (1.43–1.63)	<0.001
History of colorectitis				
No	1.00		1.00	
Yes	1.58 (1.50–1.67)	<0.001	1.58 (1.49–1.67)	<0.001
Family history of CRC				
No	1.00		1.00	
Yes	1.69 (1.58–1.81)	<0.001	1.69 (1.58–1.80)	<0.001

[§]*Odds ratios were adjusted for factors including study sites, age, sex, BMI, waist, education background, marriage, smoking, alcohol drinking, dietary intake of vegetable, dietary intake of fruit, dietary intake of processed meat, physical activity, past FOBT, history of colonic polyp, history of colorectitis, and family history of CRC in the non-conditional logistic regression model.*

[¶]*The model included the individual level (age, sex, BMI, waist, education background, marriage, smoking, alcohol drinking, dietary intake of vegetable, dietary intake of fruit, dietary intake of processed meat, physical activity, past FOBT, history of colonic polyp, history of colorectitis, and family history of CRC) and the geographical level (study sites). All models were controlled for year of recruitment.*

yielded the detection rates for CRC, advanced adenoma, non-advanced adenomas dysplasia, hyperplastic polyp, and other benign lesions at 0.23, 1.27, 6.41, 3.33, and 12.21%, respectively. In addition, based on the gender and age-adjusted detection rate for the Chinese standard population (1982), we calculated the number of colonoscopy tests required to detect one CRC, one advanced adenoma, one non-advanced adenomas dysplasia, one hyperplastic polyp, and one other benign lesions as 1840.7, 365.9, 71.3, 127.6, and 34.7, respectively. In terms of diagnostic yield per invitee, 4.3 CRC, 23.8 advanced adenomas, 119.9 non-advanced adenomas, 62.2 hyperplastic polyp, and 228.4 other benign lesions could be detected per 10,000 invitees.

As shown in **Figure 2**, the detection rates for advanced neoplasms, non-advanced adenomas, and any neoplasms increased with age and were higher for male than for female. The detection rate was highest in the group aged 65–69.

DISCUSSION

This study used CRC screening data obtained in the CanSPUC from 2013 to 2019. The study population covered 40,000 people in eight cities across Henan province. The study found that the overall participation rate of colonoscopy screening for high-risk populations in urban areas was relatively low (18.71%, 95% CI 18.08–18.72%), and there were certain regional differences. In this study, the identification of high-risk populations for colonoscopy screening through the evaluation of a high-risk cancer risk questionnaire is one of the screening strategies recommended in the existing consensus on screening for colorectal cancer in China, which can well find out colorectal cancer and precancerous lesions (12). In Europe and the USA, colonoscopy screening is usually recommended for people at average risk of 50 years and older. Preliminary analysis of a randomized controlled trial (RCT) underway in Europe revealed that the participation rate of colonoscopy screening in four participating countries (Norway, Sweden, Poland, and the Netherlands) was 22.9–60.7% (12). Another RCT in Italy reported a colonoscopy screening participation rate of 24.6% in the average-risk population (13). It can be seen that the poor population compliance of colonoscopy screening is a common problem in many countries.

This study found that people who had previously performed a FOBT test and who tested positive were more likely to undergo colonoscopy screening, which is consistent with findings from other studies (9). For instance, in a RCT conducted in Spain, the participation rates of colonoscopy group and fecal immunochemical test (FIT) group were 34.2 and 24.6%, respectively ($p < 0.001$) (14). A recent study from England reported that the participation rate using FOBT even increased to 66.4% in the National Health Service Bowel Cancer Screening Programme (15). FOBT is one of the common screening methods for colorectal cancer screening recommended by current screening guidelines (16). Compared with colonoscopy, FOBT has higher population compliance and lower cost in population screening (17). In terms of diagnostic ability, the newly developed FIT has shown good diagnostic sensitivity and specificity for CRC, but its diagnostic sensitivity for precancerous lesions is still poor (18). Therefore, how to play the role of FOBT in the organizational screening of the population—both to improve the compliance of the screening and to ensure a higher detection rate of cancer and precancerous lesions—needs to be further explored in future research.

History of colonic polyp, history of colorectitis, and family history of CRC are all important risk factors for CRC that have been confirmed by research (19). This study found that people

TABLE 3 | Colonic lesions detected by colonoscopy in the screening program.

Findings	Participants taking screening colonoscopy (%)	Yield per 10,000 invitees	Number of colonoscopies to detect one lesion[&]
Colorectal cancer	17 (0.23)	4.3	1,840.7
Advanced adenoma	95 (1.27)	23.8	365.9
≥10 mm	34 (0.46)	8.5	1,002.1
Non-advanced adenomas dysplasia	478 (6.41)	119.9	71.3
Hyperplastic polyp	248 (3.33)	62.2	127.6
Other benign lesions	910 (12.21)	228.4	34.7

[&] *Calculation was based on the age-specific and sex-specific detection rate adjusted by China Standard Population (1982).*

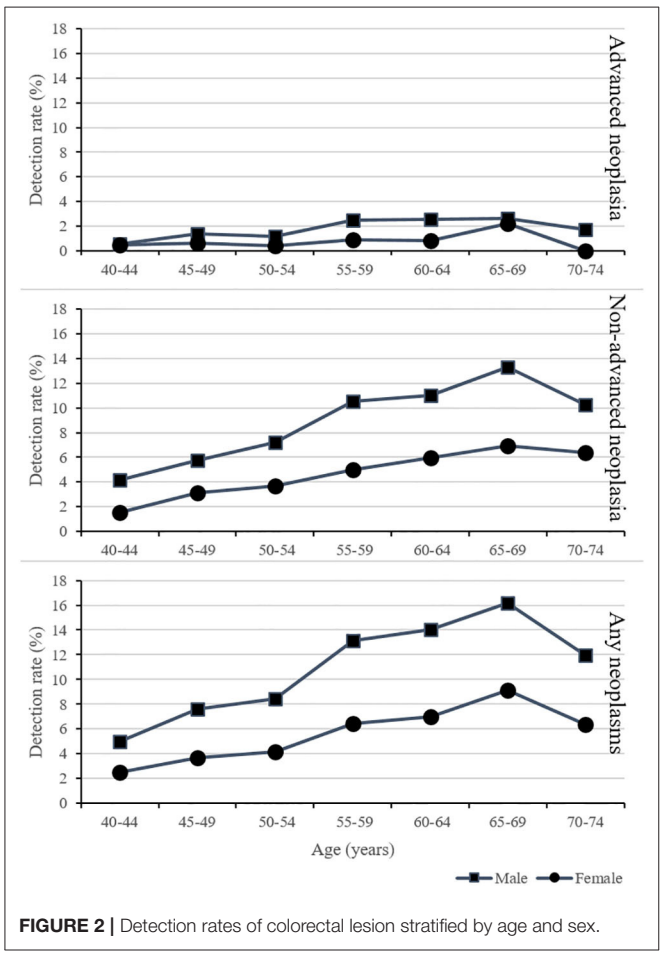

FIGURE 2 | Detection rates of colorectal lesion stratified by age and sex.

with these characteristics have better colonoscopy screening compliance. From the clinical point of view, the diagnosis of colonic polyp and colorectitis usually requires colonoscopy to confirm the diagnosis, and doctors will recommend regular colonoscopy review in this high-risk group, and those with a family history of CRC may have a higher recognition of the importance of CRC screening.

This study also found that the participation rate of colonoscopy screening among people aged 40–49 years and with lower education level was lower, which is consistent with the findings of the previous research (20). The analysis may be related to weak health awareness in those groups of people. Therefore, in future screenings, active, and effective health education for these characteristic populations, and raising their awareness of the meaning of CRC screening, will have positive significance for improving compliance with CRC screening.

We also found that the participation rate of colonoscopy screening among people with a history of smoking, alcohol drinking, low level of dietary intake of vegetables, high level of dietary intake of processed meat, and who lack physical activity was higher. A possible explanation to this rate includes that these people may have realized that their unhealthy lifestyle affected their health and thus increase compliance with colonoscopy (9). It needs to be verified in future research.

Through screening, it was found that the detection rate of CRC in urban residents was 0.23%, and the detection rate of advanced adenoma was 1.27%, which is at a low level, lower than the previously reported 0.25 and 3.07% (21). The detection rate in males was higher than in females, which is consistent with the characteristics of CRC incidence in males higher than females (22). With the increase of age, the detection rate of advanced neoplasms, non-advanced adenomas, and any neoplasms increased both for males and females, suggesting that CRC screening is more effective in the elderly population (23). However, the detection rate in the 70–74 age group decreased significantly, which is inconsistent with the trend of CRC in China (24). We noticed that the 70–74 age group had the lowest compliance with colonoscopy (12.30%), and compliance may be an important reason for restricting the detection rate (25). Therefore, improving the screening compliance of the elderly is especially important.

When interpreting our results, we should pay special attention to its strengths and limitations. One of the main advantages of this study is that our analysis comes from a large population-based cancer screening program in China.

In addition, well-trained researchers collected detailed patient information in a standardized manner, including epidemiological questionnaires and clinical examination data (colonoscopy and pathology) to ensure data quality. Each year, a team conducts competency training and conducts a centralized review of colonoscopy and pathology reports to improve the consistency and accuracy of clinical diagnosis. However, this study has some limitations. First, the percentage of the population undergoing endoscopic evaluation was very low (less than one-fifth), limiting the implications of the sample to the larger populations. Second, although we selected a population sample from eight cities, our study cannot represent the total population of Henan Province, so selection bias cannot be ruled out. Third, in view of the continuing follow-up of patients diagnosed with CRC, clinical disease information has not been fully obtained. Therefore, our study did not report tumor staging information. Finally, the information, such as on diet, were obtained through a questionnaire survey and not based on nutrition surveys, which might lead to information bias.

CONCLUSIONS

In summary, the participation rate of colonoscopy screening in high-risk urban populations in China is low. Taking effective interventions for subgroups with corresponding characteristics may improve the compliance of CRC screening in future population screening.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

LG, SZ, and JZ: conception and design. LG and LZ: statistical analyses. LG, HX, MJ, SZ, SL, JY, LZ, QC, XC, and YQ: data acquisition and data interpretation. JZ: drafting of the article. All authors: revised the manuscript and approved the final version of the manuscript.

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REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. (2019) 144:1941–53. doi: 10.1002/ijc.31937
2. Guo L, Chen H, Wang G, Lyu Z, Feng X, Wei L, et al. Development of a risk score for colorectal cancer in Chinese males: a prospective cohort study. *Cancer Med*. (2020) 9:816–23. doi: 10.1002/cam4.2734
3. Sung J. Does fecal occult blood test have a place for colorectal cancer screening in China in 2006? *Am J Gastroenterol*. (2006) 101:213–5. doi: 10.1111/j.1572-0241.2006.00485.x
4. UK CR. *Bowel Cancer Survival Statistics*. (2020). Available online at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/survival. (accessed March 23, 2020).
5. Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American cancer society, the US multi-society task force on colorectal cancer, and the American college of radiology. *CA Cancer J Clin*. (2008) 58:130–60. doi: 10.3322/CA.2007.0018
6. Huang HY, Shi JF, Guo LW, Bai YN, Liao XZ, Liu GX, et al. Expenditure and financial burden for the diagnosis and treatment of colorectal cancer in China: a hospital-based, multicenter, cross-sectional survey. *Chin J Cancer*. (2017) 36:41. doi: 10.1186/s40880-017-0209-4
7. Shi J, Liu G, Wang H, Mao A, Liu C, Guo L, et al. Medical expenditures for colorectal cancer diagnosis and treatment: a 10-year high-level-hospital-based multicenter retrospective survey in China, 2002–2011. *Chin J Cancer Res*. (2019) 31:825–37. doi: 10.21147/j.issn.1000-9604.2019.05.12
8. Yeoh KG, Ho KY, Chiu HM, Zhu F, Ching JY, Wu DC, et al. The Asia-Pacific colorectal screening score: a validated tool that stratifies risk for colorectal advanced neoplasia in asymptomatic Asian subjects. *Gut*. (2011) 60:1236–41. doi: 10.1136/gut.2010.221168
9. Chen H, Li N, Ren J, Feng X, Lyu Z, Wei L, et al. Participation and yield of a population-based colorectal cancer screening programme in China. *Gut*. (2018) 68:1450–7. doi: 10.1136/gutjnl-2018-317124
10. Guo L, Zhang S, Liu S, Zheng L, Chen Q, Cao X, et al. Determinants of participation and detection rate of upper gastrointestinal cancer from population-based screening program in China. *Cancer Med*. (2019) 8:7098–107. doi: 10.1002/cam4.2578
11. Colditz GA, Atwood KA, Emmons K, Monson RR, Willett WC, Trichopoulos D, et al. Harvard report on cancer prevention volume 4: harvard cancer risk index. *Cancer Causes Control*. (2000) 11:477–88. doi: 10.1023/A:1008984432272
12. Bretthauer M, Kaminski MF, Løberg M, Zauber AG, Regula J, Kuipers EJ, et al. Population-based colonoscopy screening for colorectal cancer: a randomized clinical trial. *JAMA Intern Med*. (2016) 176:894–902. doi: 10.1001/jamainternmed.2016.0960
13. Quintero E, Castells A, Bujanda L, Cubiella J, Salas D, Lanas Á, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. *N Engl J Med*. (2012) 366:697–706. doi: 10.1056/NEJMoa1108895
14. Multicentre Australian Colorectal-neoplasia Screening G. A comparison of colorectal neoplasia screening tests: a multicentre community-based study of the impact of consumer choice. *Med J Aust*. (2006) 184:546–50. doi: 10.1186/1741-7015-4-19
15. Senore C, Inadomi J, Segnan N, Bellisario C, Hassan C. Optimising colorectal cancer screening acceptance: a review. *Gut*. (2015) 64:1158–77. doi: 10.1136/gutjnl-2014-308081

16. Moss S, Mathews C, Day TJ, Smith S, Seaman HE, Snowball J, et al. Increased uptake and improved outcomes of bowel cancer screening with a faecal immunochemical test: results from a pilot study within the national screening programme in England. *Gut*. (2017) 66:1631–44. doi: 10.1136/gutjnl-2015-310691
17. Force USPST, Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, et al. Screening for colorectal cancer: US preventive services task force recommendation statement. *JAMA*. (2016) 315:2564–75. doi: 10.1001/jama.2016.5989
18. Armaroli P, Villain P, Suonio E, Almonte M, Anttila A, Atkin WS, et al. European code against cancer, 4th edition: cancer screening. *Cancer Epidemiol*. (2015) 39 (Suppl. 1):S139–52. doi: 10.1016/j.canep.2015.10.021
19. Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. *Ann Intern Med*. (2014) 160:171. doi: 10.7326/M13-1484
20. Imperiale TF, Ransohoff DF, Itzkowitz SH, Levin TR, Lavin P, Lidgard GP, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med*. (2014) 370:1287–97. doi: 10.1056/NEJMoa1311194
21. Brenner H, Kloor M, Pox CP. Colorectal cancer. *Lancet*. (2014) 383:1490–502. doi: 10.1016/S0140-6736(13)61649-9
22. Pulusu SSR, Lawrance IC. Dysplasia and colorectal cancer surveillance in inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol*. (2017) 11:711–22. doi: 10.1080/17474124.2017.1327347
23. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. (2016) 66:115–32. doi: 10.3322/caac.21338
24. Kurani SS, McCoy RG, Lampman MA, Doubeni CA, Finney Rutten LJ, Inselman JW, et al. Association of neighborhood measures of social determinants of health with breast, cervical, and colorectal cancer screening rates in the US midwest. *JAMA Netw Open*. (2020) 3:e200618. doi: 10.1001/jamanetworkopen.2020.0618
25. Abualkhair WH, Zhou M, Ahnen D, Yu Q, Wu XC, Karlitz JJ. Trends in incidence of early-onset colorectal cancer in the United States among those approaching screening age. *JAMA Netw Open*. (2020) 3:e1920407. doi: 10.1001/jamanetworkopen.2019.20407

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Patients With Chronic Hepatitis C Virus Infection Are at an Increased Risk of Colorectal Cancer: A Nationwide Population-Based Case-Control Study in Taiwan

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Aim: Studies evaluating colorectal cancer (CRC) risk associated with chronic hepatitis C virus (HCV) infection are limited.

Methods: In this case-control study, we identify 67,670 CRC cases newly diagnosed from 2005 to 2011 and randomly selected 67,670 controls without HCV and CRC from the same database, frequency matched by age and sex of cases.

Results: Results of logistic regression analysis revealed that the adjusted odds ratio (aOR) of CRC was 1.16 (95% confidence interval [CI] = 1.08–1.24, $p < 0.001$) in association with chronic HCV. The CRC risk was slightly greater for women than for men. The risk decreased with age, with the aOR decreased from 2.26 (95% CI = 1.32–3.87, $p = 0.003$) in patients under 45 years old to 1.31 (95% CI = 1.10–1.55, $p = 0.03$) in patients aged 50–59, and 1.10 (95% CI = 1.00–1.22, $p = 0.061$) in patients aged over 70.

Conclusions: Our findings suggested that patients with chronic HCV infection are at an elevated risk of developing CRC. Our data also imply that the CRC prevention programs are needed to target younger HCV patients.

Keywords: hepatitis C virus, colorectal cancer, population-based, case-control study, insurance data

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INTRODUCTION

Near 20% of worldwide malignancy strain can be associated to various virulent bodies. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV), Epstein Barr virus, human papilloma virus, and *Helicobacter pylori* may contribute to 1,200,000 annual cancer incident cases globally (1). HBV and/or HCV patients are at higher odds of developing liver tumor. However, cancer development requires not only oncoviruses but also several years of continuous infection accompanying chronic inflammation or immune-mediated suppression (2).

The prevalence of anti-HCV ranges from 1.7 to 2.8% in adults worldwide (3, 4). More than 184 million of people in the world have been diagnosed with the chronic infection of HCV in 2005. Both HBV and HCV are the most important causes of hepatocellular carcinoma (HCC) worldwide (4).

HCV infection is prevalent in Asian and African populations, may range from 4.4 to 15% (5, 6). With 4.4% of people aged ≥20 years living with HCV, Taiwan is one of areas with a high HCV infection rate, which increases with age (5).

An inadequate cultural desire of intravenous injections for common cold or fatigue and other minor conditions, and reusing syringes without adequate sterilization were the common causes of HCV infection in Taiwan, as disposable needles and syringes were not commonly available before 1980. And in earlier, unlicensed health care personnel might provide medical care in rural areas (5, 6). An earlier genotype study in hyperendemic areas in Taiwan found that genotype 1b was the most prevalent (47.0 to 76.9%), followed by genotypes 2a and 2b, in 1,164 patients positive for serum HCV antibodies and HCV RNA (ribonucleic acid). The genotype 1b HCV was more prevalent in older age groups, whereas the genotype 2a was more prevalent in younger people (7). A recent study in a southern Taiwan hospital found 18.3% of serum samples tested were genotype 6 among 1,147 patients with hepatitis C viremia (8).

In addition to being a vital risk factor for HCC, HCV infection has been commonly associated with other manifestations. The infection has also been associated with developing type 2 diabetes, lymphoma, neurological disorders, and even extrahepatic cancers and intrahepatic cholangiocarcinoma (9, 10). The extrahepatic malignancy progression in patients with HCV infection is not fully understood, such as the development of colorectal cancer (CRC) (10).

CRC is a highly prevalent cancer in the world and has become the third leading deaths among cancers (11). The CRC incidence rate has drastically increased in the recent decades in Oriental countries, namely Korea, Japan, and China (12). In Taiwan, there was a 30% of increase in CRC incidence rate during 2000–2016, with the second highest incidence and mortality among cancers in 2016 (13). Age, hereditary factors, lifestyle determinants (such as sedentary lifestyle, obesity, red meat consumption, smoking, and alcohol consumption), and long-term bowel inflammation have been associated with CRC in etiologic studies (14). Using colonoscopy to screen 233 participants with chronic HCV infection and 466 controls without HCV infection, the US study found that individuals with chronic HCV were at a 2-fold higher risk of colorectal adenoma in the distal colon than did those without HCV (15). However, limited studies have revealed a discrepancy in the association between CRC and HCV infection (16–20). People in Taiwan have been prevalent with both CRC and HCV infection. We therefore took the advantage of using a large nationwide population-based insurance claims data available to evaluate whether patients with chronic HCV infection are at an increased risk to develop CRC.

Abbreviations: aOR, Adjusted OR; CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; DM, diabetes mellitus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICD-9-CM, international classification of diseases, ninth revision, clinical modification; LHID, longitudinal health insurance database; NHI, national health insurance; NHIRD, national health insurance research database; NT$, new Taiwan dollar; OR, odds ratio; RCIP, registry for catastrophic illness patient; RNA, ribonucleic acid; ROS, reactive oxygen species; RR, relative risk; SIR, standardized incidence ratio; SRR, standardized rate ratio.

MATERIALS AND METHODS

Data Source

This population-based case-control study is conducted by using data obtained from the National Health Insurance (NHI) Research Database (NHIRD) of Taiwan. The NHIRD data were claims data medical providers submitted to the nationalized insurance program that started from 1995 to offer affordable, good-quality, and extensive health care services to Taiwanese residents (21). The insurance program covers nearly 99% of the Taiwanese citizens (22). Detailed information of the program is available in our previous studies (23, 24). This research was approved by the Institutional Review Board of China Medical University and Hospital Research Ethics Committee (Institutional Review Board approval number: CMU-REC-101-012).

Study Population

The International Classification of Diseases, Tenth Revision (ICD-10) has not been nationally implemented until January 2016, we used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) to identify diseases in the claims data. Patients with a diagnosis of CRC (153–154) from 2005 to 2011 were acknowledged from the Registry for Catastrophic Illness Patient (RCIP) database. The RCIP, an expansion program of the NHI program of Taiwan, was designed for look after people with serious diseases from financial crisis. The NHI program pays for expenses generated for the treatment of the disease when the patient with intractable disease is eligible to register in the RCIP (25). CRC is a NHI-recognized catastrophic illness. For patients with newly diagnosed CRC to be eligible for a catastrophic illness certificate, it is mandatory for the NHI administration to approve after reviewing imaging, clinical, and laboratory information provided by the primary care physician.

The present research evaluated the relationship between CRC risk and chronic HCV infection (coded as ICD-9-CM 070.41, 070.44, 070.51, 070.54, and V02.62). Patients with human immunodeficiency virus (HIV) infection (ICD-9-CM 042, 043, 044, and V08) or HBV infection (coded as ICD-9-CM 070.2,

070.3, and V02.61) were excluded. Anti-HCV antibody and hepatitis B surface antigen were characteristic plasma markers for HCV and HBV infection, correspondingly. Furthermore, data that lacked sex- and age-related information were excluded. Finally, we recruited 67,670 subjects with CRC after excluding three patients infected with HIV, 4,111 patients of HBV carriers, and 64 subjects with lost information on age and sex.

Controls were identified randomly from 1 million general population that randomly selected from the NHIRD with claims data between 2000 and 2011. The controls were selected at random from insured population without the history of HIV, HBV, or CRC or with missing data during 2005–2011, frequently matched by age and sex. The age of individual patient was defined as the difference between the index date and the date of birth. Among 866,326 eligible controls, 67,670 were selected. **Figure 1** shows the flowchart for selecting CRC cases and controls from the RCIP database and the 1-million database.

Statistical Analysis

The distribution of baseline demographic characteristics and comorbidities were compared between CRC cases and controls and examined with Chi-square test. In addition to liver cirrhosis, comorbidities considered as associated covariates included cardiovascular disorders of coronary artery disease (CAD), hyperlipidemia and hypertension, and renal disease, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and obesity ascertained during 2005–2011.

We used logistic regression analysis to calculate odds ratios (ORs) of CRC and 95% confidence intervals (CIs) associated with HCV. The overall relationship was evaluated first and the adjusted OR (aOR) was estimated after controlling for significant covariates using the multivariable analysis. Potential covariates included age, sex, geographical region, occupation, urbanization level, monthly income, DM, hypertension, hyperlipidemia, CAD, renal disease, COPD, obesity, and liver cirrhosis. In addition, we used stratification to differentiate the risk of CRC by covariates. Interactions between chronic HCV infection and covariates on colorectal cancer risk were evaluated using the likelihood ratio test. The 95% CI was used to define the significance of the relationship. Data analyses were performed by using SAS statistical software (version 9.4 for Windows; SAS Institute, Inc., Cary, N.C., USA).

RESULTS

Demographic Characteristics

Table 1 compared the demographic characteristics between CRC cases (N = 67,670) and controls (N = 67,670) identified from

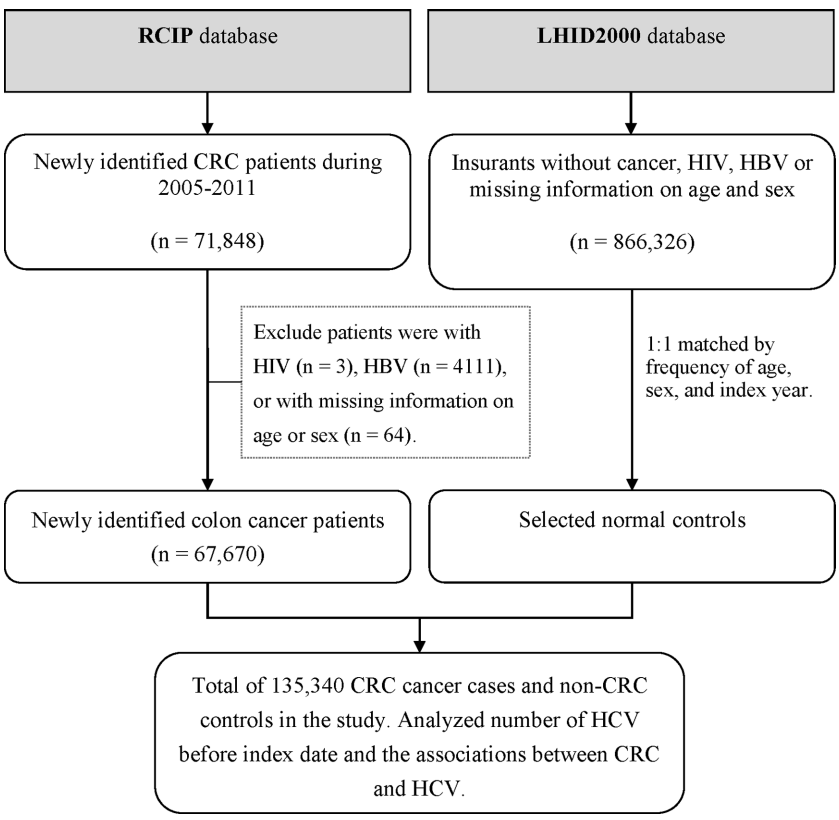

FIGURE 1 | Flow chart for study patients. Patients having colorectal cancer (CRC) were selected from the Registry for Catastrophic Illness Patient (RCIP) database and controls were selected from the Longitudinal Health Insurance Database 2000 (LHID2000) in Taiwan.

TABLE 1 | Demographic characteristics and comorbidities compared between colorectal cancer cases and controls during 2005–2011.

Variables	Controls (N = 67,670)		Cases (N = 67,670)		*P* value*
	n	(%)	n	(%)	
Sex					1.000
Women	29,208	(43.2)	29,208	(43.2)	
Men	384,62	(56.8)	38,462	(56.8)	
Age, years					1.000
<20	37	(0.05)	37	(0.05)	
20–29	466	(0.69)	466	(0.69)	
30–39	2,079	(3.07)	2,079	(3.07)	
40–49	5,867	(8.67)	5,867	(8.67)	
50–59	13,841	(20.5)	13,841	(20.5)	
60–69	16,035	(23.7)	16,035	(23.7)	
70–79	18,230	(26.9)	18,230	(26.9)	
≥80	11,115	(16.4)	11,115	(16.4)	
Geographical region					<0.001
Northern	28,606	(42.3)	28,726	(42.5)	
Central	13,717	(20.3)	13,512	(20.0)	
Southern	21,413	(31.6)	22,139	(32.7)	
Eastern and islands	3,934	(5.81)	3,293	(4.87)	
Occupation					<0.001
White collar	30,932	(45.7)	32,389	(47.9)	
Blue collar	28,631	(42.3)	28,016	(41.4)	
Retired and others	8,107	(12.0)	7,265	(10.7)	
Urbanization level					<0.001
Urban	18,155	(26.8)	18,669	(27.6)	
Suburban	30,176	(44.6)	30,880	(45.6)	
Rural	19,339	(28.6)	18,121	(26.8)	
Monthly income, NT$					0.020
<15,840	21,316	(31.5)	21,474	(31.7)	
15,841–25,000	32,534	(48.1)	32,054	(47.4)	
≥25,001	13,820	(20.4)	14,142	(20.9)	
Comorbidities					
DM	16,333	(24.1)	18,817	(27.8)	<0.001
Hypertension	36,060	(53.3)	37,593	(55.0)	<0.001
Hyperlipidemia	21,536	(31.8)	21,349	(31.6)	0.275
CAD	19,768	(29.2)	19,236	(28.4)	0.001
Renal disease	10,878	(16.1)	10,883	(16.1)	0.971
COPD	26,535	(39.2)	24,304	(35.9)	<0.001
Obesity	969	(1.43)	1,003	(1.48)	0.441
Liver cirrhosis	15,567	(23.0)	15,047	(22.2)	<0.001

**Chi-square test.*

2005 to 2011, matched by age and sex. Statistically significant differences were observed in geographical regions and urbanization levels ($p < 0.001$), occupation categories ($p < 0.001$), and monthly incomes ($p = 0.020$) between the two groups. Hypertension, liver cirrhosis, COPD, CAD, and DM were more prevalent among patients with CRC than among controls ($p \leq 0.001$).

Colorectal Cancer Risk in Patients With Chronic Hepatitis C Virus Infection

The prevalence of chronic HCV infection was higher in CRC cases than in controls (2.55 *vs.* 2.30%), with an aOR of 1.16 (95% CI = 1.08–1.24, $p < 0.001$) after controlling for age, sex, geographical region, occupation, urbanization level, monthly income, DM, hypertension, CAD, COPD, and liver cirrhosis in the multivariable logistic regression model (**Figure 2**). Sensitivity analysis was also performed by subdividing CRC into colon cancer and rectal cancer groups. Results showed that chronic HCV infection was positively linked with the risk of colon cancer (aOR = 1.13, 95% CI = 1.04–1.24, $p = 0.007$) as well as rectal cancer (aOR = 1.22, 95% CI = 1.08–1.37, $p = 0.001$) (**Supplementary Table 1**).

Sex-Specific Colorectal Cancer Risk in Patients With Chronic Hepatitis C Virus Infection

The HCV infection prevalence was higher in CRC cases than in controls for both females (2.79 *vs.* 2.43%) and males (2.49 *vs.* 2.30%). The sex-specific aORs of CRC associated with HCV infection were 1.21 (95% CI = 1.09–1.34, $p < 0.001$) in women and 1.12 (95% CI = 1.01–1.23, $p = 0.025$) in men (**Figure 3**). Further data analysis failed to show a significant interaction between gender and the HCV status on the CRC risk ($p = 0.461$).

Age-Specific Colorectal Cancer Risk in Patients With Chronic Hepatitis C Virus Infection

The aOR of CRC declined from 2.26 (95% CI = 1.32– 3.87, $p = 0.003$) for HCV patients <45 years old to 1.51 (95% CI = 1.00–2.77, $p = 0.050$) for HCV patients 45–49 years old, to 1.31 (95% CI = 1.10–1.55, $p = 0.003$) for HCV patients 50–59 years old, to 1.08 (95% CI = 0.95–1.24, $p = 0.252$) for HCV patients 60–69 years old, and to 1.10 (95% CI = 1.00–1.22, $p = 0.061$) for HCV patients ≥70 years old (**Figure 4**). Further data analysis showed a strong interaction between age and the HCV status on CRC risk ($p = 0.007$). **Supplementary Table 2** showed young HCV patients aged <45 years were at the highest elevated risks of both colon cancer (aOR = 1.99, 95% CI = 1.05–3.77, $p = 0.035$) and rectal cancer (aOR = 3.27, 95% CI = 1.18–9.03, $p = 0.022$).

The analyses of CRC risk in patients with chronic HCV infection stratified by geographical region, occupation, urbanization level, monthly income, DM, hypertension, CAD, COPD, and liver cirrhosis were illustrated in the **Supplementary Figures 1–9**.

DISCUSSION

Our population-based case-control study included 67,670 CRC patients and 67,670 controls in an endemic area of chronic HCV infection. Results showed that the HCV infection was higher in CRC cases than in control with an OR of 1.16 (95% CI = 1.08–1.24, $p < 0.001$). The risk was greater in younger patients. Limited studies have investigated HCV infection in patients with CRC, and the role of HCV infection in CRC development remains unclear. An earlier US study found chronic HCV infection is associated 2-fold higher risk of colorectal adenoma in the distal colon (15). Hurtado-Cordovi and colleagues found an increased incidence of colorectal adenoma (26.3 *vs.* 20.2%) in patients with HCV than controls without HCV, but not significant (26). Moreover, a retrospective chart review study conducted by Prakash et al. showed that patients with HCV had a higher incidence of colorectal adenoma detected from screening

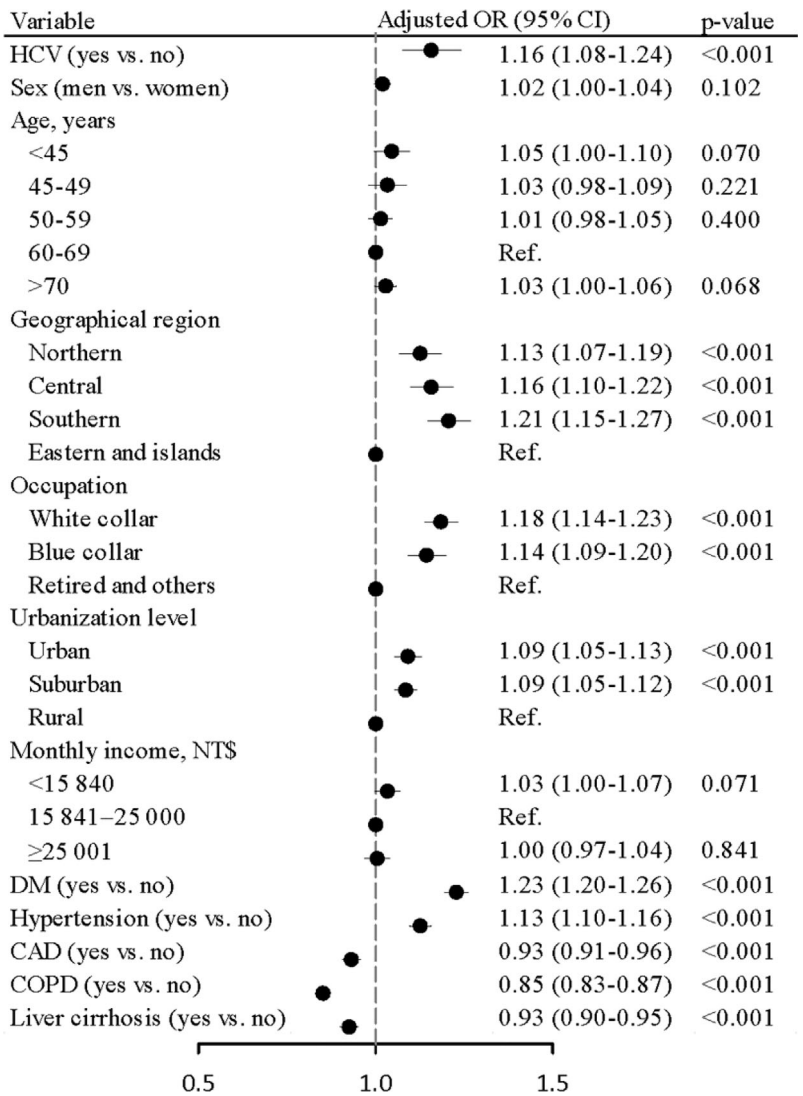

FIGURE 2 | Odds ratios and 95% confidence intervals of colorectal cancer associated with chronic hepatitis C virus infection adjusted for age, sex, geographical region, occupation, urbanization level, monthly income, DM, hypertension, CAD, COPD, and liver cirrhosis.

colonoscopy than did the general population (27). However, these studies were conducted with small sample sizes, it is difficult to draw a solid conclusion. Another case-control study conducted by Malaguarnera and his colleagues showed a significantly increased prevalence ($p < 0.005$) of anti-HCV in 66 elderly patients with CRC (35.5%) compared with 300 controls (10.5%) (28). A US retrospective cohort study with 145,210 HCV patients and 13,948,826 individuals without HCV found an increased CRC risk for HCV patients with a relative risk of 1.93 (95% CI = 1.65–2.27) (20). The US Chronic Hepatitis Cohort Study demonstrated that patients with chronic HCV infection had a significantly increased incidence of rectal cancer (standardized rate ratio [SRR] = 2.1; 95% CI = 1.3–2.8) but not colon malignancy (SRR = 0.4; 95% CI = 0.3–0.6). They also found an elevated risk of mortality from rectal cancer (RR = 2.6; 95% CI = 2.5–2.7) (16). Pol et al. suggested that cancer in patients with HCV infection occur frequently at a young age with poor prognosis (10). An Australian cancer registry study suggested that colon and rectal malignancy occurrence rates was not increased in HCV patients (standardized incidence ratio [SIR] = 0.6, 95% CI = 0.5–0.9 and SIR = 0.3, 95% CI = 0.2–0.6, respectively) (17). Likewise, no increased occurrence of rectal and colon cancers was seen in one nationwide, population-based cohort study conducted in Denmark (SIR = 1.0, 95% CI = 0.2–2.9 and SIR = 1.8, 95% CI = 0.4–5.4, respectively) (18). Furthermore, Swart et al. reported no raised occurrence of CRC in HCV patients (SIR = 0.9, 95% CI = 0.4–1.8) (19).

Drug abuse related injection uses are the predominant mode of HCV transmission in Australia, Europe, and United States (29). By contrast, intravenous injections for minor conditions driven by a cultural desire, inadequate sterilization and reuse of syringes, and lack of licensed medical providers were the main

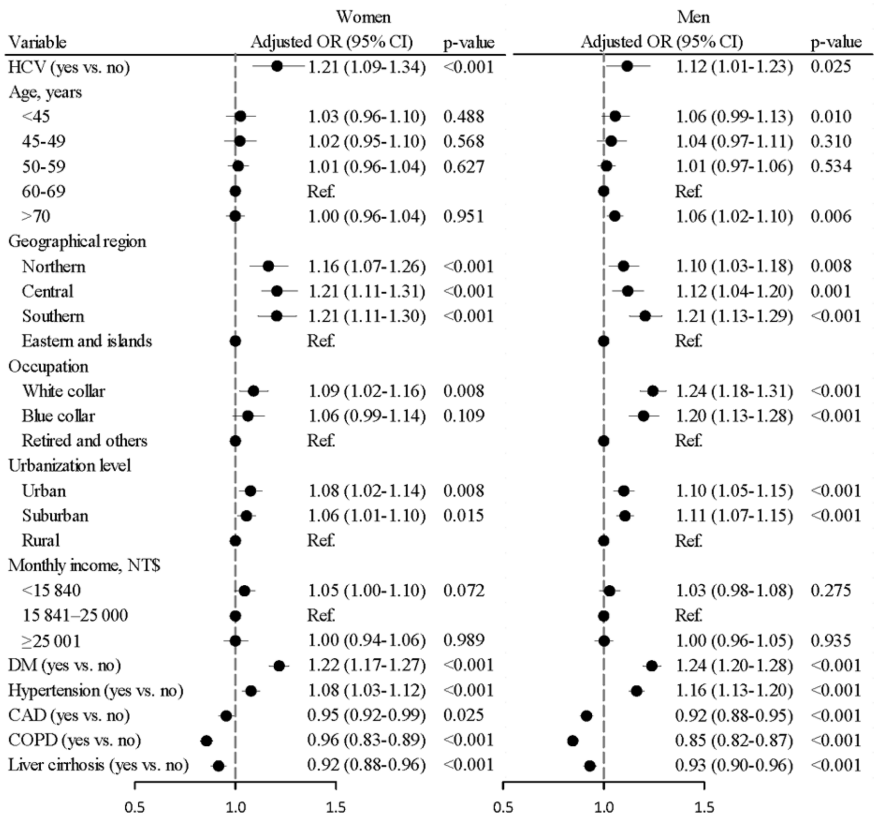

FIGURE 3 | Odds ratios and 95% confidence intervals of colorectal cancer associated with chronic hepatitis C virus infection stratified by sex. (Adjusted for age, geographical region, occupation, urbanization level, monthly income, DM, hypertension, CAD, COPD, and liver cirrhosis) (p for interaction was 0.461).

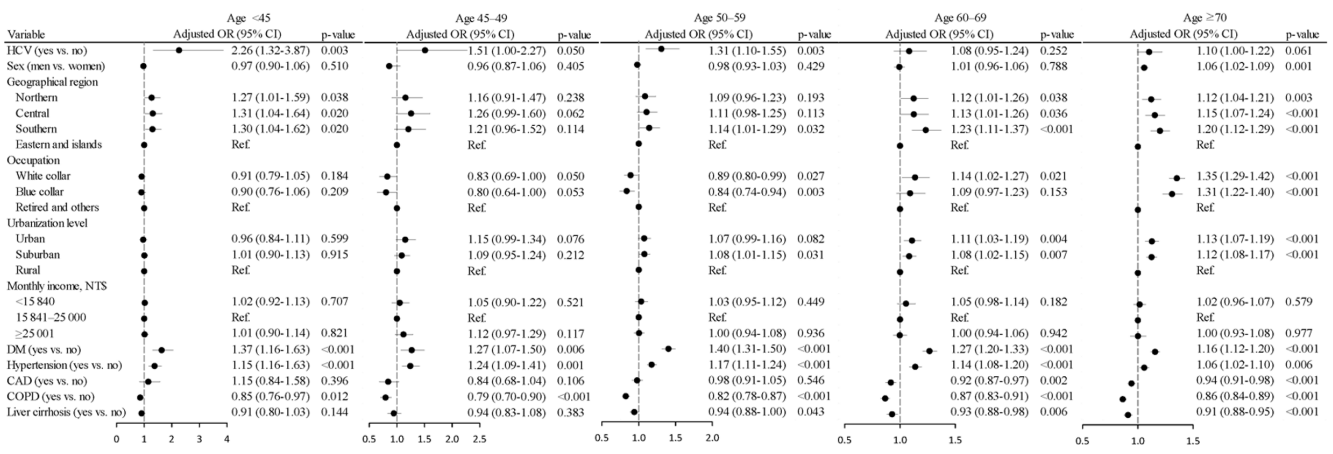

FIGURE 4 | Odds ratios and 95% confidence intervals of colorectal cancer associated with chronic hepatitis C virus infection stratified by age. (Adjusted for sex, geographical region, occupation, urbanization level, monthly income, DM, hypertension, CAD, COPD, and liver cirrhosis) (p for interaction was 0.007).

causes of HCV infection in Taiwan decades ago (5, 6). Taiwanese people could have thus exposed to HCV decades ago. Cancer may develop after several years (normally after 20–30 years) of continuous infection accompanying chronic inflammation or immune-mediated suppression (2). Hence, the positive association between CRC and chronic HCV infection is evident in Taiwan as a long period of infection promotes the carcinogenic process of the microorganism.

No epidemiological study has analyzed the role of different HCV genotypes in CRC development. HCV subtypes vary among populations. Types 1a and 1b are the most common in population in the United States and Europe (30). In Australia, genotype 1 accounts for 50–55% of HCV cases and genotype 3 accounts for 35–40% (31, 32). The Denmark population are prevalent with genotypes 1a (43%), 3a (39%), and 1b (11%) (33). In Taiwan, the most common genotypes of HCV are 1b, 2a, and 2b. The prevalence rate of genotype 1b is greater in older population (7). In recent years, genotype 6 has been more prevalent in the general Taiwanese population (8). In our study, the odds of HCV infection declined as age increased in both CRC and control groups. Therefore, HCV genotypes associating with developing CRC in Taiwan are unlikely to be subtypes 1a and 1b, which are the most common in the United States and Europe.

The exact mechanism by which chronic HCV infection leads to CRC development remains unknown. Yi and Yuan reviewed several possible mechanisms of HCV-induced hepatocarcinogenesis (34). HCV and its proteins/components trigger oxidative stress and inflammation-signaling cascades and in turn produce reactive oxygen species (ROS). ROS can lead to host genetic mutation and inflammation, consequently causing liver injury. Moreover, HCV disturbs lipid metabolism, which in turns contributes to steatosis. In addition, HCV regulates the cellular proliferation signaling pathway as well as facilitate TGF-β production. Subsequently, TGF-β promotes hepatic stellate cells to secrete excess extracellular matrix, which subsequently leads to liver fibrosis and inflammation causing tumor initiation and progression. Liver damage resulting from the aforementioned cascades may induce repeated hepatocyte generation. Finally, disease progenitors with abnormal proliferation form a "cancer field" and develop into carcinoma (34).

Studies have suggested that HCV and its particles can present in various extrahepatic organs or tissues (35), including intestinal tissues (36). Extrahepatic carcinogenesis of chronic HCV infection is potentially caused by indirect actions of the organism and probably not by the direct viral cytopathic effect (35). Thus, the hepatocarcinogenic mechanisms of chronic HCV contribute partially to CRC formation. Zhang et al. suggested that HCV activates the Ras/Raf/MEK/ERK pathway, resulting in cell proliferation (37). In addition, the core protein, NS5A, of HCV inhibits the tumor suppressor gene p53 and induces the transcription factor NF-κB (38, 39). The over expression of p53 is associated with the formation of advanced, large-sized adenoma, villous histology, and high-grade dysplasia (40). The induction of the NF-κB pathway is correlated with the malignant progression of colon cells (41).

In Taiwan, the Health Promotion Administration has started to subsidize citizens aged 50–69 years for CRC screening every 2 years since January 2004. In 2013, the age range has been expanded to aged 74 years. The screening program for CRC consists of two phases. First, the stool occult blood test is utilized for mass screening. In the second phase, subjects with a positive stool occult blood test are referred for confirmatory colonoscopy. In our study, we found that the risk of CRC decreased with age of patients with chronic HCV infection, with the adjusted OR decreased from 2.26 for aged <45 years to 1.31 for aged 45–49 years and 1.10 for patients aged ≥70 years. We suggested that the screening program for CRC prevention should be considered for younger HCV patients aged in their early 40s (42).

This study has several limitations. First, asymptomatic HCV carriers might not be identified for this study if they had not sought any medical attention. Therefore, in this study, these patients may be misclassified into the control group with no HCV. This misclassification may lead to estimated ORs toward null values and weaken the risk estimation. Second, ICD-10 is a better diagnostic classification system than ICD-9-CM is. However, ICD-10 has not been introduced to the NHI program in Taiwan till January 2016. Using ICD-9-CM codes to identify diseases may have few common coding variants. However, HCV and cancers are well known important disorders to population in Taiwan. Cancers are considered as catastrophic illnesses requiring certificates approval from physicians and the NHI program. The certificate may benefit the patients with lower payments generate by the disease. Hence, the CRC population in Taiwan is represented by these patients. Using ICD-9 might not accurately detect chronic HCV cases. In addition to anti-HCV, HCV RNA needs to be positive. Hence, using ICD-9 cannot provide the status of the patient's HCV viremia and treatment. However, previous Taiwanese community epidemiological studies showed that more than 70% of Taiwanese adults with serum anti-HCV positivity were positive to HCV RNA (43–46). Prior to year 2011, less than 10 percentages of the estimated 400,000 Taiwanese HCV with positive RNA cases have successfully reached sustained viral response (SVR) after completing their HCV interferon therapy (47). As result, we feel ICD-9 can provide relatively representative status of HCV prevalence in Taiwan. Third, in this study, information on other potential risk factors was unavailable in the database, including diet, lifestyle, obesity, and family history of CRC (14). Therefore, in the data analysis, we controlled for COPD, CAD, hypertension, obesity, liver cirrhosis, and hyperlipidemia as they may be the result of poor lifestyle modification. Fourth, HCV-infected patients might have more clinic visits leading to more detection of colorectal cancer. However, since January 2004, the Taiwanese national cancer screening program initiated by the Health Promotion Administration has started to subsidize citizens aged 50–69 years for colorectal cancer screening every 2 years. The age range was expanded to 50–74 years in June 2013 (42). Hence, detection bias in the association between HCV infection and colorectal cancer can be minimized by this nationwide screening intervention. Fifth, the HCV transmission route in Taiwan might be different from that in other ethnic groups. Hence, the results of this study should be cautiously interpreted before generalizing to other racial/ethnic groups.

CONCLUSIONS

Our study suggests that patients with chronic HCV infection are at significant risk of developing CRC. The CRC risk could be

greater for the younger individuals with HCV infection. It is necessary to conduct in other regions or for other ethnic population to clarify the relationship between CRC risk and chronic HCV infection in addition to the underlying pathophysiological mechanisms.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Information were gathered from the NHIRD of Taiwan and request can be made by sending a formal proposal to the NHI. Requests to access these datasets should be directed to nhird.nhri.org.tw.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of China Medical University and Hospital Research Ethics Committee (Institutional Review Board approval number: CMU-REC-101-012). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

F-HS, C-CY, and F-CS conceptualized the study. F-HS, C-HB, TL, F-CS, and C-CY contributed to the methodology. F-HS, C-HM, S-NC, F-CS, and C-CY conducted the formal analysis. F-HS, C-HB, TL, C-HM, AT, F-CS, and C-CY conducted the investigation. F-HS, TL, and C-CY wrote the original draft. F-HS, C-HB, AT, F-CS, and C-CY reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.561420/full#supplementary-material

REFERENCES

1. zur Hausen H, de Villiers EM. Cancer "causation" by infections–individual contributions and synergistic networks. *Semin Oncol* (2014) 41:860–75. doi: 10.1053/j.seminoncol.2014.10.003
2. Mesri EA, Feitelson MA, Munger K. Human viral oncogenesis: a cancer hallmarks analysis. *Cell Host Microbe* (2014) 15:266–82. doi: 10.1016/j.chom.2014.02.011
3. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol* (2014) 61:S45–57. doi: 10.1016/j.jhep.2014.07.027
4. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* (2013) 57:1333–42. doi: 10.1002/hep.26141
5. Chen CH, Yang PM, Huang GT, Lee HS, Sung JL, Sheu JC. Estimation of seroprevalence of hepatitis B virus and hepatitis C virus in Taiwan from a large-scale survey of free hepatitis screening participants. *J Formos Med Assoc* (2007) 106:148–55. doi: 10.1016/S0929-6646(09)60231-X
6. Sievert W, Altraif I, Razavi HA, Abdo A, Ahmed EA, Alomair A, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. *Liver Int* (2011) 31:61–80. doi: 10.1111/j.1478-3231.2011.02540.x
7. Yu ML, Chuang WL, Chen SC, Dai CY, Hou C, Wang JH, et al. Changing prevalence of hepatitis C virus genotypes: molecular epidemiology and clinical implications in the hepatitis C virus hyperendemic areas and a tertiary referral center in Taiwan. *J Med Virol* (2001) 65:58–65. doi: 10.1002/jmv.2001
8. Chen JJ, Tung HD, Lee PL, Kuo HT, Sheu MJ, Cheng CT, et al. High prevalence of genotype 6 hepatitis C virus infection in Southern Taiwan using Abbott genotype assays. *J Formos Med Assoc* (2020) 119:413–19. doi: 10.1016/j.jfma.2019.07.021
9. Gill K, Ghazinian H, Manch R, Gish R. Hepatitis C virus as a systemic disease: reaching beyond the liver. *Hepatol Int* (2016) 10:415–23. doi: 10.1007/s12072-015-9684-3
10. Pol S, Vallet-Pichard A, Hermine O. Extrahepatic cancers and chronic HCV infection. *Nat Rev Gastroenterol Hepatol* (2018) 15:283–90. doi: 10.1038/nrgastro.2017.172
11. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* (2015) 65:87–108. doi: 10.3322/caac.21262
12. Sung JJY, Chiu HM, Jung KW, Jun JK, Sekiguchi M, Matsuda T, et al. Increasing Trend in Young-Onset Colorectal Cancer in Asia: More Cancers in Men and More Rectal Cancers. *Am J Gastroenterol* (2019) 114:322–9. doi: 10.14309/ajg.0000000000000133
13. Health Promotion Administration. *Cancer Registry Annual Report* (2016). Available at: https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=269&pid=10227 (Accessed January 20, 2019).
14. Kuipers EJ, Grady WM, Lieberman D, Seufferlein T, Sung JJ, Boelens PG, et al. Colorectal cancer. *Nat Rev Dis Primers* (2015) 1:15065. doi: 10.1038/nrdp.2015.65
15. Rustagi T, Zarookian EI, Qasba O, Diez LF. Chronic hepatitis C as a risk factor for colorectal adenoma. *Int J Colorectal Dis* (2014) 29:75–80. doi: 10.1007/s00384-013-1763-0

16. Allison RD, Tong X, Moorman AC, Ly KN, Rupp L, Xu F, et al. Increased incidence of cancer and cancer-related mortality among persons with chronic hepatitis C infection, 2006-2010. *J Hepatol* (2015) 63:822–8. doi: 10.1016/j.jhep.2015.04.021
17. Amin J, Dore GJ, O'Connell DL, Bartlett M, Tracey E, Kaldor JM, et al. Cancer incidence in people with hepatitis B or C infection: a large community-based linkage study. *J Hepatol* (2006) 45:197–203. doi: 10.1016/j.jhep.2006.02.014
18. Omland LH, Farkas DK, Jepsen P, Obel N, Pedersen L. Hepatitis C virus infection and risk of cancer: a population-based cohort study. *Clin Epidemiol* (2010) 2:179–86. doi: 10.2147/clep.s10193
19. Swart A, Burns L, Mao L, Grulich AE, Amin J, O'Connell DL, et al. The importance of blood-borne viruses in elevated cancer risk among opioid-dependent people: a population-based cohort study. *BMJ Open* (2012) 2: e001755. doi: 10.1136/bmjopen-2012-001755
20. Nyberg AH. Increased cancer rates in patients with chronic hepatitis C: an analysis of the cancer registry in a large US health maintenance organization. *J Hepatol* (2015) 62:S220.
21. Wu TY, Majeed A, Kuo KN. An overview of the healthcare system in Taiwan. *London J Prim Care* (2010) 3:115–9. doi: 10.1080/17571472.2010.11493315
22. Fanchiang C. *Current issue: New IC health insurance card expected to offer many benefits. Taiwan Today, January 2nd 2004.* Available at: http://www.taiwantoday.tw/ct.asp?xItem520439&CtNode5122 (Accessed on 5 January 2019).
23. Su FH, Chang SN, Chen PC, Sung FC, Su CT, Yeh CC. Association between chronic viral hepatitis infection and breast cancer risk: a nationwide population-based case-control study. *BMC Cancer* (2011) 11:495. doi: 10.1186/1471-2407-11-495
24. Su FH, Le TN, Muo CH, Te SA, Sung FC, Yeh CC. Chronic hepatitis B virus infection associated with increased colorectal cancer risk in Taiwanese population. *Viruses* (2020) 12:E9. doi: 10.3390/v12010097
25. Bureau of National Health Insurance Taiwan. *Regulations for Exempting NHI Insured Persons from the Co-Payment*. Available at: http://www.nhi.gov.tw/English/webdata/webdata.aspx?menu=11&menu_id=295&WD_ID=295&webdata_id=2431 (Accessed January 25, 2019).
26. Hurtado-Cordovi J, Davis-Yadley AH, Lipka S, Vardaros M, Shen H. Association between chronic hepatitis C and hepatitis C/HIV co-infection and the development of colorectal adenomas. *J Gastrointest Oncol* (2016) 7:609–14. doi: 10.21037/jgo.2016.03.11
27. Prakash R, Shah N, Mullen K. Chronic hepatitis C patients have larger colonic adenomas. *Am J Gastroenterol* (2009) 104:S138.
28. Malaguarnera M, Gargante MP, Risino C, Ranno S, Berretta M, Cannizzaro MA, et al. Hepatitis C virus in elderly cancer patients. *Eur J Intern Med* (2006) 17:325–9. doi: 10.1016/j.ejim.2006.02.004
29. Alter MJ. Epidemiology of hepatitis C virus infection. *World J Gastroenterol* (2007) 13:2436–41. doi: 10.3748/wjg.v13.i17.2436
30. Thrift AP, El-Serag HB, Kanwal F. Global epidemiology and burden of HCV infection and HCV-related disease. *Nat Rev Gastroenterol Hepatol* (2017) 14:122–32. doi: 10.1038/nrgastro.2016.176
31. Bowden DS, Berzsenyi MD. Chronic hepatitis C virus infection: genotyping and its clinical role. *Future Microbiol* (2006) 1:103–12. doi: 10.2217/17460913.1.1.103
32. Thompson AJ. Australian recommendations for the management of hepatitis C virus infection: a consensus statement. *Med J Aust* (2016) 204:268–72. doi: 10.5694/mja16.00106
33. Johansen IS, Weis N, Christensen PB. Viral hepatitis in Denmark. *Viral Hepat J* (2014) 20:43–8. doi: 10.4274/vhd.02411
34. Yi Z, Yuan Z. Hepatitis C Virus-Associated Cancers. *Adv Exp Med Biol* (2017) 1018:129–46. doi: 10.1007/978-981-10-5765-6_8
35. Fiorino S, Bacchi-Reggiani L, de Biase D, Fornelli A, Masetti M, Tura A, et al. Possible association between hepatitis C virus and malignancies different from hepatocellular carcinoma: A systematic review. *World J Gastroenterol* (2015) 21:12896–953. doi: 10.3748/wjg.v21.i45.12896
36. Yan FM, Chen AS, Hao F, Zhao XP, Gu CH, Zhao LB, et al. Hepatitis C virus may infect extrahepatic tissues in patients with hepatitis C. *World J Gastroenterol* (2000) 6:805–11. doi: 10.3748/wjg.v6.i6.805
37. Zhang Q, Wei L, Yang H, Yang W, Yang Q, Zhang Z, et al. Bromodomain containing protein represses the Ras/Raf/MEK/ERK pathway to attenuate human hepatoma cell proliferation during HCV infection. *Cancer Lett* (2016) 371:107–16. doi: 10.1016/j.canlet.2015.11.027
38. McGivern DR, Lemon SM. Tumor suppressors, chromosomal instability, and hepatitis C virus-associated liver cancer. *Annu Rev Pathol* (2009) 4:399–415. doi: 10.1146/annurev.pathol.4.110807.092202
39. Fung J, Lai CL, Yuen MF. Hepatitis B and C virus-related carcinogenesis. *Clin Microbiol Infect* (2009) 15:964–70. doi: 10.1111/j.1469-0691.2009.03035.x
40. Einspahr JG, Martinez ME, Jiang R, Hsu CH, Rashid A, Bhattacharrya AK, et al. Associations of Ki-ras proto-oncogene mutation and p53 gene overexpression in sporadic colorectal adenomas with demographic and clinicopathologic characteristics. *Cancer Epidemiol Biomarkers Prev* (2006) 15:1443–50. doi: 10.1158/1055-9965.EPI-06-0144
41. Simiantonaki N, Kurzik-Dumke U, Karyofylli G, Jayasinghe C, Kirkpatrick CJ. Loss of E-cadherin in the vicinity of necrosis in colorectal carcinomas: association with NFkappaB expression. *Inter J Oncol* (2007) 31:269–75. doi: 10.3892/ijo.31.2.269
42. Health Promotion Administration Taiwan. *Taiwan Breast cancer, Oral cancer, and Colorectal Cancer Screening Programs*. Available at: https://www.hpa.gov.tw/EngPages/Detail.aspx?nodeid=1051&pid=5957 (Accessed May 25, 2019).
43. Lee MH, Yang HI, Jen CL, Lu SN, Yeh SH, Liu CJ, et al. Community and personal risk factors for hepatitis C virus infection: a survey of 23,820 residents in Taiwan in 1991-2. *Gut* (2011) 60:688–94. doi: 10.1136/gut.2010.220889
44. Yu ML, Dai CY, Huang CF, Lee JJ, Yeh M, Yeh SM, et al. High hepatitis B virus surface antigen levels and favorable interleukin 28B genotype predict spontaneous hepatitis C virus clearance in uremic patients. *J Hepatol* (2014) 60:253–59. doi: 10.1016/j.jhep.2013.09.023
45. Huang JF, Dai CY, Hwang SJ, Ho CK, Hsiao PJ, Hsieh MY, et al. Hepatitis C viremia increases the association with type 2 diabetes mellitus in a hepatitis B and C endemic area: an epidemiological link with virological implication. *Am J Gastroenterol* (2007) 102:1237–43. doi: 10.1111/j.1572-0241.2007.01181.x
46. Chang IC, Huang SF, Chen PJ, Chen CL, Chen CL, Wu CC, et al. The Hepatitis Viral Status in Patients With Hepatocellular Carcinoma: a Study of 3843 Patients From Taiwan Liver Cancer Network. *Medicine* (2016) 95:e3284. doi: 10.1097/MD.0000000000003284
47. Ministry of Health and Welfare Taiwan. *Taiwan Hepatitis C Policy Guideline 2018-2025*. Available at: https://www.mohw.gov.tw/dl-53889-508908e3-203b-450c-9dc5- 3c3f7994e282.html (Accessed January 25, 2019).

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The Impact of Diabetes Mellitus on the Second Primary Malignancies in Colorectal Cancer Patients

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Introduction: All colorectal cancer (CRC) survivors have an increased risk of developing second primary malignancies (SPMs). The association between diabetes mellitus (DM) and the risk of cancer is well known. However, the role of DM and its therapy in the development of SPMs in CRC patients is not well described.

Methods: In this single-institutional retrospective analysis we identified 1,174 colorectal carcinoma patients, median follow-up 10.1 years, (median age 63 years, 724 men). All patients over 18 years with histologically confirmed CRC who were admitted in the period 1.1. 2003- 31.12.2013 and followed-up till 31.12. 2018 at the Masaryk Memorial Cancer Institute (MMCI) were screened for eligibility. The exclusion criteria were CRC diagnosed at autopsy, lost to follow-up and high risk of development of SPMs due to hereditary cancer syndrome. Tumours are considered multiple primary malignancies if arising in different sites and/or are of a different histology or morphology group. Comparisons of the basic characteristics between the patients with SPM and the patients without SPM were performed as well as comparison of the occurrence of SPMs by the site of diagnosis between the DM and non-DM cohorts and survival analyses.

Results: A SPM was diagnosed in 234 (20%) patients, DM in 183 (15%) patients. DM was diagnosed in 22.6% of those with SPM vs. in 13.8% of those without SPM (p=0.001). The most common types of SPMs in DM patients were other CRC, kidney, lung, bladder and nonmelanoma skin cancer, but only carcinoma of the liver and bile duct tracts was significantly more common than in the group without DM. Although breast cancer was the second most common in the group with DM, its incidence was lower than in the group without DM, as well as prostate cancer. A significantly higher incidence of SPMs was found in older CRC patients (≥ 65 years) and in those with lower stage colon cancer and DM. No significant difference in DM treatment between those with and without a SPM was observed including analysis of type of insulin.

Conclusion: CRC patients with diabetes mellitus, especially those with older age, and early stages of colon cancer, should be screened for second primary malignancies more often than the standard population. Patients without DM have longer survival. According to the occurrence of the most common second malignancies, a clinical examination, blood count, and ultrasound of the abdomen is appropriate, together with standard breast and colorectal cancer screening, and lung cancer screening under certain conditions, and should be recommended in CRC survivors especially in patients with intercurrent DM, however the necessary frequency of screening remains unclear.

Keywords: diabetes mellitus, second primary malignancies, second primary neoplasms, multiple primary neoplasms, colorectal cancer, cancer survivors

INTRODUCTION

Colorectal carcinoma (CRC) is one of the most common malignant tumors in all western countries. Due to the success of personalized therapy and screening, mortality from this disease has been reduced in recent times. In 2015, its prevalence in the Czech Republic (third rank in incidence within Europe) reached 64 126 persons and increased by almost 40% in comparison with 2005 (1). However, the increasing number of people being cured carries the risk of development of another type of cancer. In Western countries, 17% of all cancer patients experience second primary malignancy (SPM) during their lifetime (2). CRC patients after curative resection are thought to have an additional tumor risk of up to 40% (3). For this reason, it is necessary to focus attention on the early diagnosis of other malignancies in patients with complete remission and adapt the type and timing of screening for SPMs. Primary malignancies are associated with lifestyle, environmental risk factors, and hereditary factors, in secondary tumours, treatment of previous cancer is additionally added.

The associations between diabetes mellitus (DM) and the risk of cancer is well known (4), nevertheless, the factors responsible for this relationship remain unclear. Insulin is a growth factor and major regulator of cell metabolism. Stimulation of growth is facilitated by the insulin receptor which is expressed on cancer cells in an A isoform, known by its predominant mitogenic effect which can stimulate neoplastic proliferation (5). Other factors responsible for cancer development are hyperglycemia accompanying insulin resistance leading to hyperinsulinemia, insulin-like growth factor 1, oxidative stress, and inflammation (6). Obesity which is linked to diabetes mellitus type II is responsible for an increased risk of cancer as well (7). It is hypothetized, that the type of DM treatment also plays an important role in the development of cancer (8, 9). Peroral antidiabetics (PADs) and insulin are long-term standards of care for patients with diabetes mellitus. Previously used animal insulin is currently replaced by recombinant human insulins produced by recombinant DNA technology, which use Escherichia Coli or Saccharomyces cerevisiae. In recent years, insulin glargine has acquired much attention in cancer patients. Insulin glargine (GlyA21, ArgB31, ArgB32 human insulin) is insulin produced by recombinant DNA technology using E. coli, substituting asparagine at position 21 in the A chain with glycine and adding two arginine residues to the B chain at positions 31 and 32 (10). In a large German study, a higher cancer incidence was associated with administration of glargine compared to human insulin. On the other hand, the opposite was described in other retrospective trials and a metaanalysis (11–16). It seems that observational studies describing insulin glargine as a risk factor for developing cancer have important methodological bias (17) and, thus, the importance of insulin glargine in the development of cancer remains unclear (18, 19). There is no robust evidence describing the influence of the type of production of insulin on the development of SPMs or risk of cancer.

In addition to insulin, oral antidiabetic drugs (PAD) are also used to treat diabetes with metformin being one of the most commonly prescribed. Metformin is an antihyperglycemic drug with a hypoglycemic effect without hyperglycemia, it improves insulin resistance (20) and decreases circulating insulin levels through activation of the adenosine monophosphate-activated protein kinase (AMPK) pathway (21). Antiproliferative potential is demonstrated by reduced prevalence and number of metachronous adenomas or polyps after polypectomy (22) and, thus, it is considered as a protective factor in colorectal adenomas and subsequent carcinomas (23). In multiple studies, metformin has also been identified as a drug with anticancer activity, especially in CRC (24–30).

A metaanalysis of 24 metformin studies demonstrates that metformin usage decreases cancer risk in diabetes mellitus type II patients (8) and that metformin could have a protective effect (29, 31). However, no large studies evaluating the risk of development of SPMs and type of treatment of diabetes mellitus in CRC patients are currently available.

The aim of this single-institutional retrospective analysis is the identification of SPMs in colorectal cancer patients and description of the potential relationship between the occurrence of DM, its treatment and the development of SPMs.

MATERIAL AND METHODS

Patients Selection

After approval by the institutional ethics committee (2019/1827/MOU), all patients over 18 years with histologically confirmed

CRC who were admitted in the period 1.1. 2003- 31.12.2013 and followed-up till 31.12. 2018 at the Masaryk Memorial Cancer Institute (MMCI) in Brno, Czech Republic, were screened for eligibility after signing their informed consent enabling use of their personal data in the research. All patients who did not meet the exclusion criteria were included. The exclusion criteria were as follows: CRC diagnosed at autopsy, lost to follow-up and high risk of development of SPMs due to hereditary cancer syndrome (e.g., BRCA1,2, Lynch syndrome, or familial adenomatous polyposis). Basic diagnostic and treatment data including the laterality of CRC were retrieved from electronic medical records. Additional data about the type of DM, type of treatment of DM, and type of PAD or insulin therapy were obtained in patients with a diagnosis of DM. The diagnosis of DM had to precede the first malignancy.

Second Primary Malignancies

For epidemiological studies, tumors are considered multiple primary malignancies if arising in different sites and/or are of a different histology or morphology group (32). In our study, criteria according to the SEER definition of multiple primary tumors were used: 1) tumors with ICD-O-3 histology codes that are different at the first, second or third number are multiple primaries; 2) tumors with ICD-O-3 topography codes that are different at the second and/or third characters are multiple primaries (33).

Synchronicity and multiplicity were qualified according to the rules of the International Agency for Research on Cancer (IARC) which suggest synchronous tumours to be diagnosed in an interval of less than 6 months (or metachronous if more than 6 months) and if arising in different sites (34).

Statistical Analysis

Comparisons of the basic characteristics between the patients with SPM and the patients without SPM were summarized with counts and frequencies and tested with the Fisher exact test in case of categorical characteristics. For countinuous characteristics median, 5%–95% percentile and the Mann-Whitney test was used. The Fisher exact test was also used to test the relationship between the occurrence of SPMs on one side and the presence of DM, DM therapy, and the laterality of colorectal cancer on the other side.

Comparison of the occurrence of SPMs by the site of diagnosis between the DM and non-DM cohorts was performed by the N-1 chi-squared test. SPMs with an unknown date of diagnosis were not included in the analysis (7 cases). The national cancer registry of the Czech Republic (35) was used to compare the frequencies of sites of diagnosis in our study with the frequencies in the entire Czech population.

Kaplan-Meier curves were utilized to display the survival of the patients with colorectal cancer stratified by the occurrence of SPM and DM. 15-year survival was used as the primary endpoint. Observations with 15 or more years of follow-up were censored at 15 years. The Breslow test was used to compare the differences in survival between defined groups of patients with respect to the presence of DM and the occurrence of SPM.

RESULTS

Second Primary Malignancies

In total, 1174 patients were identified and enrolled in this study. The median follow-up was 10.1 years, median age 63 years and 724 of the patients were men (62%). The other basic characteristics are summarized in **Table 1** in respect to occurance of SPM, which was diagnosed in 234 (20%) patients (**Table 2**). One secondary neoplasm was found overall in 190 (16.2%) patients, 36 (3.1%) patients suffered from two SPMs and 8 (0.7%) were treated with three SPMs (**Table 2**). A significantly higher incidence of SPMs was observed in older CRC patients and also in patients with a lower stage of CRC reflecting their better overall survival.

Diabetes Mellitus

Diabetes mellitus was diagnosed in 183 (15.5%) patients. DM was diagnosed in 22.6% of those with SPM vs. in 13.8% of those without SPM (p=0.001). The type of DM treatment is summarized in **Table 3**. Oral antidiabetic drugs (PADs) alone or in combination with insulin were taken by 127 patients. No significant difference in DM treatment between those with and without SPM was observed including analysis of type of insulin and its production.

CRC patients with diabetes mellitus had a higher incidence of SPMs than those without DM, especially another CRC, liver and intrahepatic bile ducts, lung, nonmelanoma tumors of the skin, kidney, bladder, non-Hodgkin disease, and leukemia (**Table 4**),

TABLE 1 | Characteristics of colorectal cancer patients (C18–C20) stratified by the occurrence of second primary malignancies.

	No SPM (N = 940)	With SPM (N = 234)	p-value
Gender			
Men	590 (62.8%)	134 (57.3%)	0.133[1]
Women	350 (37.2%)	100 (42.7%)	
Age at CRC diagnosis			
0–44	79 (8.4%)	14 (6.0%)	0.001[1]
45–54	153 (16.3%)	21 (9.0%)	
55–64	296 (31.5%)	58 (24.8%)	
65–74	278 (29.6%)	93 (39.7%)	
75+	134 (14.3%)	48 (20.5%)	
Median (5%–95% percentile)	63 (55–70)	67 (60–73)	< 0.001[2]
Clinical stage			
Complete records	906 (96.4%)	221 (94.4%)	0.012[1]
Stage I + in situ	249 (27.5%)	68 (30.8%)	
Stage II	218 (24.1%)	67 (30.3%)	
Stage III	260 (28.7%)	61 (27.6%)	
Stage IV	179 (19.8%)	25 (11.3%)	
Occurrence of DM			
No	810 (86.2%)	181 (77.4%)	0.001
Yes	130 (13.8%)	53 (22.6%)	

[1]Fischer exact test; [2]Mann-Whitney test; SPM, second primary malignancy; CRC, colorectal cancer.

TABLE 2 | Second primary malignancies in patients with colorectal cancer (C18–C20).

Patients with CRC	Men (N = 724)	Women (N = 450)	Total (N = 1 174)
No SPM	590 (81.5%)[1]	350 (77.8%)[1]	940 (80.1%)
With SPM	134 (18.5%)[1]	100 (22.2%)[1]	234 (19.9%)
Two primary neoplasms	112 (15.5%)	78 (17.3%)	190 (16.2%)
Three primary neoplasms	18 (2.5%)	18 (4.0%)	36 (3.1%)
Four primary neoplasms	4 (0.6%)	4 (0.9%)	8 (0.7%)

[1]p-value of Fisher exact test: 0,133. SPM, second primary malignancy; CRC, colorectal cancer.

but except for liver and intrahepatic bile duct cancer (4.6% with DM vs. 0.5% without DM, p=0.014), a higher incidence of other SPMs was not statistically significant (**Figure 1**). Although breast cancer is the second most common in the group with DM, its incidence is lower than in the group without DM, as well as prostate cancer. Statistical significance of a group of other malignant neoplasms is biased by multiple diagnostic units and is listed in **Table 5**.

According to the date of diagnosis of SPMs, patients were divided into three groups (before the development of CRC, synchronous and metachronous SPM). These and individual SPMs according to DM are summarized in **Table 6**. In patients with DM, there was a statistically significant difference in laterality of initial CRC cancer between the SPM and non-SPM groups (**Table 7**). In the SPM group, a higher proportion of cancer of the righ colon and left colon and, conversely, a lower proportion of rectal cancer compared to the group without SPM was observed (p= 0.014). Patients with rectal cancer and DM had the smallest probability of developing SPM. The transverse colon (C18.4) was excluded from the laterality assessment, due to the difficult assignment into the group for the right or left colon, only by ICD-O-3 topography codes.

Overall survival (OS) differed according to the occurence of SPM and DM (Breslow test p=0.001). Patients without SPMs and with DM have shorter OS (median 4.7 years) than patients with SPMs and DM (median 7.8 years). Patients without SPMs have shorter survival, probably because of the poor prognosis of primary CRC in combination with DM than those with SPMs and DM, who have early stages of CRC, longer survival, and a higher probability of development SPMs. Patients without DM have longer survival, than those with DM. DM seems to be an important factor for survival. Patients without DM have a similar survival estimation for both groups (with or without SPMs) during the first 5 years, after which patients without diabetes and SPMs live longer (**Figure 2** and **Table 8**).

DISCUSSION

In patients with CRC and a history of DM, a higher incidence of second primary malignancies compared with CRC patients without DM was observed in this large retrospective study with more than a 10 year follow up. Identifying the group of patients with CRC at higher risk of developing a SPM, and analyzing their type and timing is essential for clinical practice and development of long-term management, especially with increasing prevalence associated with better treatment and screening programes. This group of patients with SPMs is usually excluded from clinical trials, and available information about their OS or other related factors are limited. Recently, an online competing-risk nomogram was released (http://biostat.fudan.edu.cn/crc) (36), however, without DM listed as a risk factor.

Considering the general biology of carcinogenesis, each primary malignancy is associated with the occurrence of secondary malignancies, but the type of SPMs does not have to be the same. For example, breast cancer survivors often developed secondary breast cancer and colorectal cancer (37) and lung cancer is associated with the occurrence of other tumors of the lung, head and neck and the genitourinary tract (38). According to Jia et al., CRC survivors with an older age, male sex, with localized disease, and treatment with surgery are at high risk of developing SPMs (36, 39). A high incidence of the SPM in older patients is probably due to the long exposition of toxic substances in the environment during the longer life of these people. Also in patients with DM there was a higher incidence of SPMs, and DM was an independent risk factor for the occurrence of SPMs in gastric cancer patients (40). The higher incidence of liver and intrahepatic bile duct cancer in our analysis is in contrast with Broman et al´s. study, where the incidence of these tumors was lower than expected, it is probably

TABLE 3 | Relationship between treatment of diabetes mellitus and risk of second primary malignancy in patients with colorectal cancer (C18–C20).

Therapy of DM	No SPM (N = 130)	With SPM (N = 53)	p-value
Diet	32 (24.6%)	12 (22.6%)	0.737
PAD	65 (50.0%)	30 (56.6%)	
PAD/Insulin	25 (19.2%)	7 (13.2%)	
Insulin	8 (6.2%)	4 (7.5%)	
Therapy of DM - PAD	**No SPM (N = 90)**	**With SPM (N = 37)**	**p-value**
Metformin	74 (82.2%)	33 (89.2%)	0.427
Other PAD	16 (17.8%)	4 (10.8%)	
Therapy of DM - insulin	**No SPM (N = 33)**	**With SPM (N = 11)**	**p-value**
Glargine	6 (18.2%)	2 (18.2%)	1.000
Other insulin	27 (81.8%)	9 (81.8%)	
Insulin made by recombinant DNA technology in Escherichia coli	8 (24.2%)	2 (18.2%)	1.000
Insulin made by recombinant DNA technology in Saccharomyces cerevisiae	25 (75.8%)	9 (81.8%)	

SPM, second primary malignancy; DM, diabetes mellitus; PAD, oral antidiabetics.

TABLE 4 | Second primary malignancies by the site of diagnosis stratified by the occurrence of diabetes mellitus.

	No diabetes mellitus (N = 214)	With diabetes mellitus (N = 65)	All malignant neoplasms according to NOR (N = 2,367,973)
Oral cavity and pharynx (C00–C14)	6 (2.8%)	1 (1.5%)	47,097 (2.0%)
Esophagus (C15)	1 (0.5%)	0 (0.0%)	16,943 (0.7%)
Stomach (C16)	5 (2.3%)	1 (1.5%)	84,738 (3.6%)
Colon and rectum (C18–C20)	42 (19.6%)	17 (26.2%)	268,753 (11.3%)
Liver and intrahepatic bile ducts (C22)	1 (0.5%)	3 (4.6%)	30,775 (1.3%)
Gallbladder and biliary tract (C23, C24)	0 (0.0%)	0 (0.0%)	39,697 (1.7%)
Pancreas (C25)	2 (0.9%)	0 (0.0%)	65,789 (2.8%)
Larynx (C32)	2 (0.9%)	0 (0.0%)	21,055 (0.9%)
Lung, bronchus and trachea (C33, C34)	5 (2.3%)	4 (6.2%)	249,926 (10.6%)
Malignant melanoma of skin (C43)	12 (5.6%)	1 (1.5%)	56,372 (2.4%)
Other malignant neoplasms of skin (C44)	4 (1.9%)	3 (4.6%)	532,199 (22.5%)
Soft tissues (C47, C49)	0 (0.0%)	1 (1.5%)	10,358 (0.4%)
Breast (C50)	41 (19.2%)	8 (12.3%)	199,562 (8.4%)
Cervix uteri (C53)	7 (3.3%)	0 (0.0%)	43,373 (1.8%)
Uterus (C54, C55)	5 (2.3%)	1 (1.5%)	66,192 (2.8%)
Ovary (C56)	5 (2.3%)	0 (0.0%)	42,593 (1.8%)
Prostate (C61)	24 (11.2%)	4 (6.2%)	142,994 (6.0%)
Testis (C62)	4 (1.9%)	0 (0.0%)	14,440 (0.6%)
Kidney (C64)	18 (8.4%)	7 (10.8%)	85,270 (3.6%)
Bladder (C67)	10 (4.7%)	4 (6.2%)	69,826 (2.9%)
Central nervous system (C70–C72)	0 (0.0%)	0 (0.0%)	27,516 (1.2%)
Thyroid gland (C73)	4 (1.9%)	0 (0.0%)	23,545 (1.0%)
Hodgkin's disease (C81)	1 (0.5%)	0 (0.0%)	12,082 (0.5%)
Non-Hodgkin's lymphoma (C82–C86)	4 (1.9%)	2 (3.1%)	41,122 (1.7%)
Multiple myeloma (C90)	1 (0.5%)	0 (0.0%)	17,252 (0.7%)
Leukemia (C91–C95)	4 (1.9%)	2 (3.1%)	46,717 (2.0%)
Other malignant neoplasms	6 (2.8%)	6 (9.2%)	111,787 (4.7%)

Only SPMs with known date of diagnosis were considered (date of diagnosis was not available for seven SPMs).
SPM, second primary malignancy; CRC, colorectal cancer, NOR, national cancer registry (1977–2017).

due to our detailed information from source documentation, where hepatic lesions are well diagnosed which is not the case in Broman´s analysis, where possible misclassification of primary liver tumors as colorectal metastases in patients with a history of CRC were admitted (41). Relationship between diabetes and risk of second primary contralateral breast cancer was described in the study Li et al. Women with DM had a 2.2-fold increased risk of contralateral breast cancer than non-diabetics patients (42). Diabetes mellitus was identified as a potential risk factor for development of SPMs in cholangiocarcinoma patients (43).

The risk of development of a SPM is inherently associated with survival after treatment of a primary malignancy which is limited in a more advanced local tumor or even in primarily metastatic disease. In concordance with our results, an analysis by Jia et al. (36) shows that patients with SPMs have better OS in the first 10 years and thereafter, they had worse survival than patients without SPMs. In our study OS was better in the first 7 years for patients with SPMs and DM but, thereafter was worse than SPMs without DM, patients without SPMs and with DM had the worst OS.

In addition to DM itself, its treatment, antidiabetic therapy, was described as a risk factor for developing cancer and it seems that antidiabetic treatment may also play a role in carcinogenesis. In previously published literature, insulin use has been associated with increased and metformin with decreased incidence of colorectal cancer (44). Among insulin users, an increased risk of breast cancer was reported (45). Patients treated with metformin have no lower probability of SPMs incidence in our group of patients. In concordance with our results, in head and neck cancer metformin does not show a protective effect on the development of SMPs (46), on the other hand, in the development of primary pancreatic cancer this relationship was significant (47). Although long-term use of metformin appears to have the effect of reducing the incidence of CRC and its progression (48), it appears to have no effect on the incidence of secondary malignancies in CRC patients, as we have shown. In one previous study users of insulin glargine and users of other insulin analogs had a lower risk of cancer in general than those using human insulin (49), but on the other hand, an increased risk of breast cancer in users of insulin glargine in comparison with users of human insulin was found (50). For users of glargine insulin compared to users of non-glargine insulin, a decreased risk of colon cancer, as well as a marginally significant increased risk of breast cancer and prostate cancer, was observed (9, 51). However, in some studies, the effect on cancer development has not been confirmed (14). It has even been previously described that serum of patients treated by insulin glargine is more mitogenic to a breast cancer cell than those treated by other types of insulins (52). Recently, a higher risk of development of cancer was not found in a patient treated by insulin glargine or detemir compared with human insulin (53) and according to our results, insulin glargine was not associated with a higher risk of SPMs in our group of patients.

An inherent limitation of this study is related to its retrospective nature, which is similar to all other studies dealing with this issue.

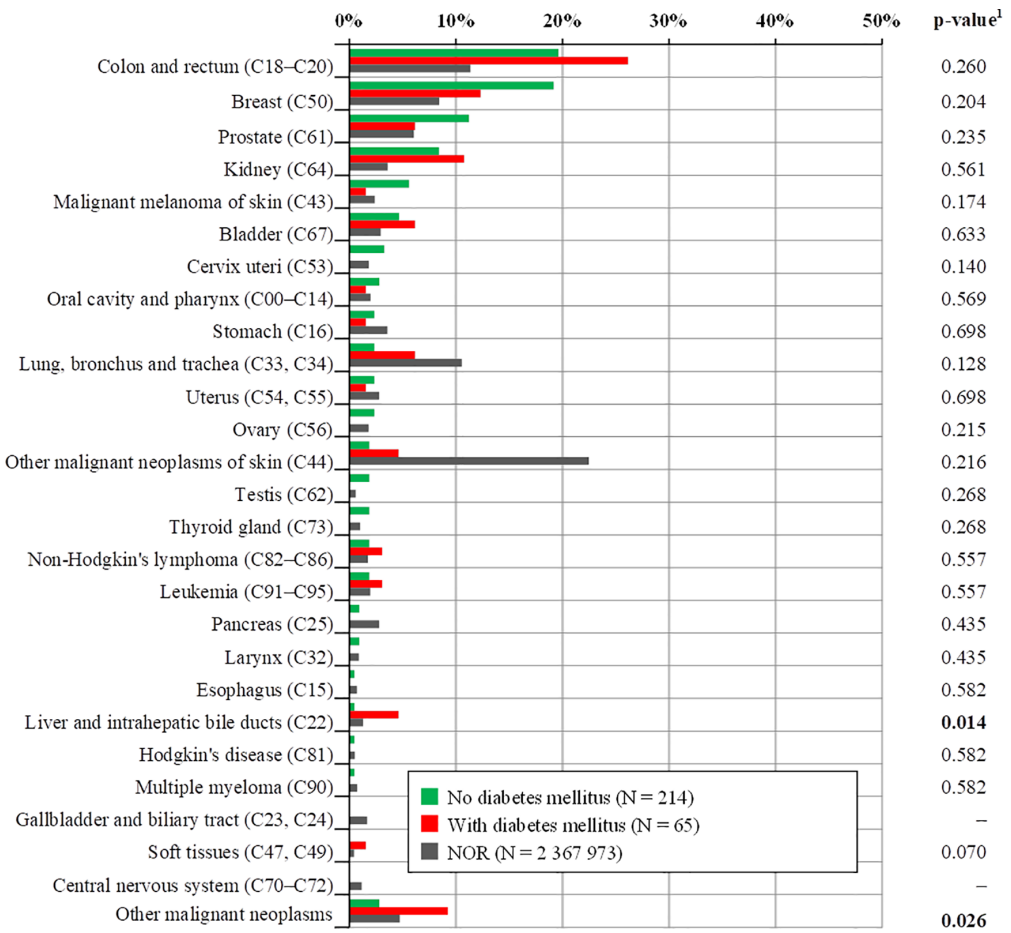

FIGURE 1 | Comparison of the occurrence of total second primary malignancies with respect to diabetes mellitus. Only SPMs with known date of diagnosis were considered (date of diagnosis was not available for seven SPMs). [1]p-value of N-1 Chi-squared test for group no diabetes mellitus and group with diabetes mellitus. SPMs, second primary malignancies; CRC, colorectal cancer, NOR, national cancer registry (1977–2017).

The same reason limits availability of some other data which may be related to the risk of SPM, such as obesity, which increases the risk of malignancy (54) as well as information on alcohol use, smoking, diet, sports activity, and lifestyle (55, 56). Although one may assume that patients with DM have mostly uniform diet, this and other information was not available for the majority of our patient´s cohort and has a significant impact on cancer development. Due to the length of follow-up and changes in the treatment strategy for both CRC and diabetes mellitus, patients with a more recent diagnosis of CRC could survive longer, and their SPMs may not have been detected yet, despite the long follow-up of our group of patients. The strengths of our study include use of a well-characterized and population-based cohort of CRC survivors, patient characteristics, and treatment with extensive follow-up, detailed information on the incidence of SPMs in CRC patients from the source documentation, review of medical charts, and detailed information about antidiabetic medication of patients.

TABLE 5 | Other malignant neoplasms as second primary malignancies in detail.

	No diabetes mellitus (N = 6)	With diabetes mellitus (N = 6)
Small intestine (C17)	2 (33.3%)	3 (50.0%)
Anus and anal canal (C21)	1 (16.7%)	1 (16.7%)
Thymus (C37)	0 (0.0%)	1 (16.7%)
Penis (C60)	1 (16.7%)	1 (16.7%)
Eye and adnexa (C69)	1 (16.7%)	0 (0.0%)
Malignant immunoproliferative diseases (C88)	1 (16.7%)	0 (0.0%)

The better identification of risk groups of patients is important for clinicians, health care providers, and health insurance companies. From our analysis it has arisen that CRC patients stage I or II with diabetes mellitus have a higher incidence of SPMs, especially second colon and rectal cancer, liver and intrahepatic bile ducts, lung, nonmelanoma tumors of the skin, kidney, bladder, non-Hodgkin lymphoma, and leukemia. Liver and intrahepatic bile duct cancer is even more common than in the group without DM. On the other hand, although breast cancer is the second most common in the group with DM, its incidence is lower than in the group without DM, as well as prostate cancer.

TABLE 6 | Second primary malignancies by the site of diagnosis stratified by the occurrence of diabetes mellitus.

	No diabetes mellitus (N = 214)				With diabetes mellitus (N = 65)				All malignant neoplasms according to NOR (N = 2,367,973)
	SPM before[1] the first CRC (N = 82)	SPM synchronously[2] with the first CRC (N = 59)	SPM after[3] the first CRC (N = 73)	Total SPM (N = 214)	SPM before[1] the first CRC (N = 22)	SPM synchronously[2] with the first CRC (N = 27)	SPM after[3] the first CRC (N = 16)	Total SPM (N = 65)	
Oral cavity and pharynx (C00–C14)	3 (3,7%)	1 (1,7%)	2 (2,7%)	6 (2,8%)	0 (0,0%)	0 (0,0%)	1 (6,3%)	1 (1,5%)	47,097 (2.0%)
Esophagus (C15)	0 (0,0%)	0 (0,0%)	1 (1,4%)	1 (0,5%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	16,943 (0.7%)
Stomach (C16)	1 (1,2%)	1 (1,7%)	3 (4,1%)	5 (2,3%)	0 (0,0%)	1 (3,7%)	0 (0,0%)	1 (1,5%)	84,738 (3.6%)
Colon and rectum (C18–C20)	0 (0,0%)	28 (47,5%)	14 (19,2%)	42 (19,6%)	0 (0,0%)	13 (48,1%)	4 (25,0%)	17 (26,2%)	268,753 (11.3%)
Liver and intrahepatic bile ducts (C22)	0 (0,0%)	1 (1,7%)	0 (0,0%)	1 (0,5%)	0 (0,0%)	1 (3,7%)	2 (12,5%)	3 (4,6%)	30,775 (1.3%)
Gallbladder and biliary tract (C23, C24)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	39,697 (1.7%)
Pancreas (C25)	1 (1,2%)	1 (1,7%)	0 (0,0%)	2 (0,9%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	65,789 (2.8%)
Larynx (C32)	2 (2,4%)	0 (0,0%)	0 (0,0%)	2 (0,9%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	21,055 (0.9%)
Lung, bronchus and trachea (C33, C34)	0 (0,0%)	0 (0,0%)	5 (6,8%)	5 (2,3%)	2 (9,1%)	2 (7,4%)	0 (0,0%)	4 (6,2%)	249,926 (10.6%)
Malignant melanoma of skin (C43)	5 (6,1%)	3 (5,1%)	4 (5,5%)	12 (5,6%)	1 (4,5%)	0 (0,0%)	0 (0,0%)	1 (1,5%)	56,372 (2.4%)
Other malignant neoplasms of skin (C44)	2 (2,4%)	1 (1,7%)	1 (1,4%)	4 (1,9%)	0 (0,0%)	2 (7,4%)	1 (6,3%)	3 (4,6%)	532,199 (22.5%)
Soft tissues (C47, C49)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	1 (4,5%)	0 (0,0%)	0 (0,0%)	1 (1,5%)	10,358 (0.4%)
Breast (C50)	26 (31,7%)	6 (10,2%)	9 (12,3%)	41 (19,2%)	8 (36,4%)	0 (0,0%)	0 (0,0%)	8 (12,3%)	199,562 (8.4%)
Cervix uteri (C53)	6 (7,3%)	1 (1,7%)	0 (0,0%)	7 (3,3%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	43,373 (1.8%)
Uterus (C54, C55)	4 (4,9%)	0 (0,0%)	1 (1,4%)	5 (2,3%)	1 (4,5%)	0 (0,0%)	0 (0,0%)	1 (1,5%)	66,192 (2.8%)
Ovary (C56)	1 (1,2%)	0 (0,0%)	4 (5,5%)	5 (2,3%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	42,593 (1.8%)
Prostate (C61)	12 (14,6%)	6 (10,2%)	6 (8,2%)	24 (11,2%)	1 (4,5%)	1 (3,7%)	2 (12,5%)	4 (6,2%)	142,994 (6.0%)
Testis (C62)	4 (4,9%)	0 (0,0%)	0 (0,0%)	4 (1,9%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	14,440 (0.6%)
Kidney (C64)	1 (1,2%)	8 (13,6%)	9 (12,3%)	18 (8,4%)	1 (4,5%)	3 (11,1%)	3 (18,8%)	7 (10,8%)	85,270 (3.6%)
Bladder (C67)	2 (2,4%)	1 (1,7%)	7 (9,6%)	10 (4,7%)	1 (4,5%)	2 (7,4%)	1 (6,3%)	4 (6,2%)	69,826 (2.9%)
Central nervous system (C70–C72)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	27,516 (1.2%)
Thyroid gland (C73)	1 (1,2%)	0 (0,0%)	3 (4,1%)	4 (1,9%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	23,545 (1.0%)
Hodgkin's disease (C81)	1 (1,2%)	0 (0,0%)	0 (0,0%)	1 (0,5%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	12,082 (0.5%)
Non-Hodgkin's lymphoma (C82–C86)	3 (3,7%)	1 (1,7%)	0 (0,0%)	4 (1,9%)	2 (9,1%)	0 (0,0%)	0 (0,0%)	2 (3,1%)	41,122 (1.7%)
Multiple myeloma (C90)	1 (1,2%)	0 (0,0%)	0 (0,0%)	1 (0,5%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	17,252 (0.7%)
Leukemia (C91–C95)	2 (2,4%)	0 (0,0%)	2 (2,7%)	4 (1,9%)	1 (4,5%)	0 (0,0%)	1 (6,3%)	2 (3,1%)	46,717 (2.0%)
Other malignant neoplasms	4 (4,9%)	0 (0,0%)	2 (2,7%)	6 (2,8%)	3 (13,6%)	2 (7,4%)	1 (6,3%)	6 (9,2%)	111,787 (4.7%)

Only SPMs with known date of diagnosis were considered (date of diagnosis was not available for seven SPMs).

[1]diagnosed 6 or more months before the first CRC in the patient.

[2]diagnosed within 6 months before or after the first CRC in the patient.

[3]diagnosed 6 or more months after the first CRC in the patient.

SPM, second primary malignancy; CRC, colorectal cancer, NOR, national cancer registry (1977–2017).

TABLE 7 | Relationship between second primary malignancies and laterality of colorectal cancer stratified by the occurrence of diabetes mellitus excluding patients with C18.4 (transverse colon).

Laterality	No diabetes mellitus (N = 955)			With diabetes mellitus (N = 174)		
	No SPM (N = 810)	With SPM (N = 181)	p-value of Fisher exact test	No SPM (N = 130)	With SPM (N = 53)	p-value of Fisher exact test
Right colon (C18.0–C18.3)	137 (17.5%)	35 (20.2%)	0.651	19 (15.3%)	15 (30.0%)	**0.014**
Left colon (C18.5–C19)	216 (27.6%)	48 (27.7%)		34 (27.4%)	18 (36.0%)	
Rectum (C20)	429 (54.9%)	90 (52.0%)		71 (57.3%)	17 (34.0%)	

SPM, second primary malignancy.
Bold values emphasize statistical significance.

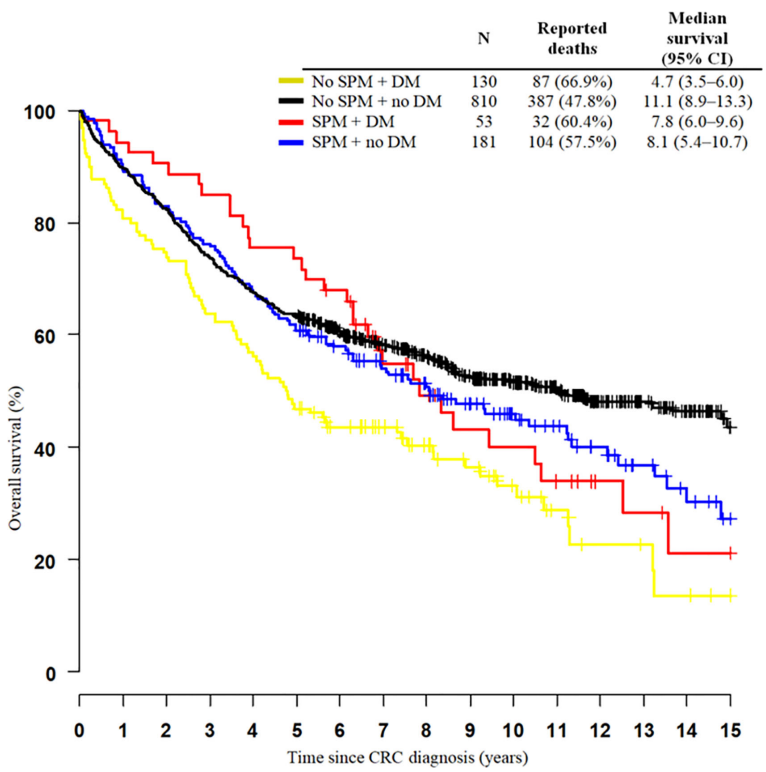

FIGURE 2 | Kaplan-Meier curves of 15-year survival among colorectal cancer patients (C18–C20) stratified by the occurrence of multiple primary neoplasms and diabetes mellitus. SPM, second primary neoplasm; DM, diabetes mellitus; CI, confidence interval.

TABLE 8 | P-values of Breslow test for colorectal cancer patients (C18–C20) stratified by the occurrence of second primary malignancy and diabetes mellitus.

	No SPM + DM	No SPM + no DM	SPM + DM	SPM + no DM	Overall comparison
No SPM + DM	–	**<0.001**	**0.009**	**0.007**	**0.001**
No SPM + no DM	**<0.001**	–	0.721	0.468	
SPM + DM	**0.009**	0.721	–	0.438	
SPM + no DM	**0.007**	0.468	0.438	–	

SPM, second primary malignancy; DM, diabetes mellitus.
Bold values emphasize statistical significance.

CONCLUSION

In conclusion, this single-institution population-based study shows that CRC patients in complete remission have an increased risk of development of SPMs, especially patients ≥65years of age, with stage I and II primary colon cancer and those with diabetes mellitus. These patients should be frequently and regularly screened for second primary malignancies. This screening should be cheap and without increased radiation load. According to the occurrence of the most common second malignancies, clinical examination, blood

count, and ultrasound of the abdomen are appropriate, together with standard breast and colorectal cancer screening, and lung cancer screening under certain conditions, but the frequency of the screening remains unclear.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of Masaryk Memorial Cancer Institute. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization: JH and MS. Data curation: JH and LP. Formal analysis: JH, LP, and TK. Funding acquisition: JH, RD, RG, SK, and TK. Investigation: JH. Methodology: JH, OS, IK, LP, and LB. Project administration: JH. Writing—original draft: JH, TK, and LP. Writing—review and editing: JH, TK, RD, OS, IK, and MS. Supervision, MS. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Dusek L, Pavlík T, Májek O, Büchler T, Muzik J, Maluskova D, et al. Estimating Cancer Incidence, Prevalence, and the Number of Cancer Patients Treated With Antitumor Therapy in 2015 and 2020 - Analysis of the Czech National Cancer Registry. *Klin Onkol* (2015) 28(1):30–43. doi: 10.14735/amko201530
2. Donin N, Filson C, Drakaki A, Tan HJ, Castillo A, Kwan L, et al. Risk of Second Primary Malignancies Among Cancer Survivors in the United States, 1992 Through 2008. *Cancer* (2016) 122(19):3075–86. doi: 10.1002/cncr.30164
3. Raj KP, Taylor TH, Wray C, Stamos MJ, Zell JA. Risk of Second Primary Colorectal Cancer Among Colorectal Cancer Cases: A Population-Based Analysis. *J Carcinog* (2011) 10:6. doi: 10.4103/1477-3163.78114
4. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and Cancer. *Endocr Relat Cancer* (2009) 16(4):1103–23. doi: 10.1677/ERC-09-0087
5. Vigneri R, Goldfine ID, Frittitta L. Insulin, Insulin Receptors, and Cancer. *J Endocrinol Invest* (2016) 39(12):1365–76. doi: 10.1007/s40618-016-0508-7
6. Home P. Insulin Therapy and Cancer. *Diabetes Care* (2013) 36 Suppl 2(Suppl 2):S240–4. doi: 10.2337/dcS13-2002
7. Gallagher EJ, LeRoith D. Obesity and Diabetes: The Increased Risk of Cancer and Cancer-Related Mortality. *Physiol Rev* (2015) 95(3):727–48. doi: 10.1152/physrev.00030.2014
8. Thakkar B, Aronis KN, Vamvini MT, Shields K, Mantzoros CS. Metformin and Sulfonylureas in Relation to Cancer Risk in Type II Diabetes Patients: A Meta-Analysis Using Primary Data of Published Studies. *Metabolism* (2013) 62(7):922–34. doi: 10.1016/j.metabol.2013.01.014
9. Colmers IN, Bowker SL, Tjosvold LA, Johnson JA. Insulin Use and Cancer Risk in Patients With Type 2 Diabetes: A Systematic Review and Meta-Analysis of Observational Studies. *Diabetes Metab* (2012) 38(6):485–506. doi: 10.1016/j.diabet.2012.08.011
10. Vajo Z, Fawcett J, Duckworth WC. Recombinant DNA Technology in the Treatment of Diabetes: Insulin Analogs. *Endocr Rev* (2001) 22(5):706–17. doi: 10.1210/edrv.22.5.0442
11. Bordeleau L, Yakubovich N, Dagenais GR, Rosenstock J, Probstfield J, Chang Yu P, et al. The Association of Basal Insulin Glargine and/or n-3 Fatty Acids With Incident Cancers in Patients With Dysglycemia. *Diabetes Care* (2014) 37 (5):1360–6. doi: 10.2337/dc13-1468
12. Rosenstock J, Fonseca V, McGill JB, Riddle M, Hallé JP, Hramiak I, et al. Similar Risk of Malignancy With Insulin Glargine and Neutral Protamine Hagedorn (NPH) Insulin in Patients With Type 2 Diabetes: Findings From a 5 Year Randomised, Open-Label Study. *Diabetologia* (2009) 52(9):1971–3. doi: 10.1007/s00125-009-1452-2
13. Fagot JP, Blotière PO, Ricordeau P, Weill A, Alla F, Allemand H. Does Insulin Glargine Increase the Risk of Cancer Compared With Other Basal Insulins?: A French Nationwide Cohort Study Based on National Administrative Databases. *Diabetes Care* (2013) 36(2):294–301. doi: 10.2337/dc12-0506
14. Peeters PJ, Bazelier MT, Leufkens HG, Auvinen A, van Staa TP, de Vries F, et al. Insulin Glargine Use and Breast Cancer Risk: Associations With Cumulative Exposure. *Acta Oncol* (2016) 55(7):851–8. doi: 10.3109/0284186X.2016.1155736
15. Ghosal S, Stephens J, Van Deventer A, Mital V, Jayasinghe P, Khan M, et al. Critical Appraisal of the Recent Data Published on the Link Between Insulin and Cancer. *Diabetes Metab Syndr* (2011) 5(4):211–3. doi: 10.1016/j.dsx.2012.03.004
16. Home PD, Lagarenne P. Combined Randomised Controlled Trial Experience of Malignancies in Studies Using Insulin Glargine. *Diabetologia* (2009) 52 (12):2499–506. doi: 10.1007/s00125-009-1530-5
17. Wu JW, Filion KB, Azoulay L, Doll MK, Suissa S. Effect of Long-Acting Insulin Analogs on the Risk of Cancer: A Systematic Review of Observational Studies. *Diabetes Care* (2016) 39(3):486–94. doi: 10.2337/dc15-1816
18. Rendell M, Akturk HK, Tella SH. Glargine Safety, Diabetes and Cancer. *Expert Opin Drug Saf* (2013) 12(2):247–63. doi: 10.1517/14740338.2013.770469
19. Sciacca L, Vella V, Frittitta L, Tumminia A, Manzella L, Squatrito S, et al. Long-acting Insulin Analogs and Cancer. *Nutr Metab Cardiovasc Dis* (2018) 28(5):436–43. doi: 10.1016/j.numecd.2018.02.010
20. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and Molecular Mechanisms of Metformin: An Overview. *Clin Sci (Lond)* (2012) 122(6):253–70. doi: 10.1042/CS20110386
21. Gonzalez-Angulo AM, Meric-Bernstam F. Metformin: A Therapeutic Opportunity in Breast Cancer. *Clin Cancer Res* (2010) 16(6):1695–700. doi: 10.1158/1078-0432.CCR-09-1805
22. Higurashi T, Hosono K, Takahashi H, Komiya Y, Umezawa S, Sakai E, et al. Metformin for Chemoprevention of Metachronous Colorectal Adenoma or Polyps in Post-Polypectomy Patients Without Diabetes: A Multicentre Double-Blind, Placebo-Controlled, Randomised Phase 3 Trial. *Lancet Oncol* (2016) 17(4):475–83. doi: 10.1016/S1470-2045(15)00565-3
23. Kim YH, Noh R, Cho SY, Park SJ, Jeon SM, Shin HD, et al. Inhibitory Effect of Metformin Therapy on the Incidence of Colorectal Advanced Adenomas in Patients With Diabetes. *Intest Res* (2015) 13(2):145–52. doi: 10.5217/ir.2015.13.2.145
24. Najafi M, Cheki M, Rezapoor S, Geraily G, Motevaseli E, Carnovale C, et al. Metformin: Prevention of Genomic Instability and Cancer: A Review. *Mutat Res Genet Toxicol Environ Mutagen* (2018) 827:1–8. doi: 10.1016/j.mrgentox.2018.01.007
25. Alcusky M, Keith SW, Karagiannis T, Rabinowitz C, Louis DZ, Maio V. Metformin Exposure and Survival in Head and Neck Cancer: A Large Population-Based Cohort Study. *J Clin Pharm Ther* (2019) 44(4):588–94. doi: 10.1111/jcpt.12820

26. Tseng CH. Metformin and Lung Cancer Risk in Patients With Type 2 Diabetes Mellitus. *Oncotarget* (2017) 8(25):41132–42. doi: 10.18632/oncotarget.17066
27. Tseng CH. Use of Metformin and Risk of Kidney Cancer in Patients With Type 2 Diabetes. *Eur J Cancer* (2016) 52:19–25. doi: 10.1016/j.ejca.2015.09.027
28. Liu F, Yan L, Wang Z, Lu Y, Chu Y, Li X, et al. Metformin Therapy and Risk of Colorectal Adenomas and Colorectal Cancer in Type 2 Diabetes Mellitus Patients: A Systematic Review and Meta-Analysis. *Oncotarget* (2017) 8 (9):16017–26. doi: 10.18632/oncotarget.13762
29. Coyle C, Cafferty FH, Vale C, Langley RE. Metformin as an Adjuvant Treatment for Cancer: A Systematic Review and Meta-Analysis. *Ann Oncol* (2016) 27(12):2184–95. doi: 10.1093/annonc/mdw410
30. Ding L, Liang G, Yao Z, Zhang J, Liu R, Chen H, et al. Metformin Prevents Cancer Metastasis by Inhibiting M2-like Polarization of Tumor Associated Macrophages. *Oncotarget* (2015) 6(34):36441–55. doi: 10.18632/oncotarget.5541
31. Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, Bonanni B, et al. Metformin and Cancer Risk in Diabetic Patients: A Systematic Review and Meta-Analysis. *Cancer Prev Res (Phila)* (2010) 3(11):1451–61. doi: 10.1158/1940-6207.CAPR-10-0157
32. Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T, et al. Multiple Primary Tumours: Challenges and Approaches, a Review. *ESMO Open* (2017) 2 (2):e000172. doi: 10.1136/esmoopen-2017-000172. eCollection 2017.
33. SEER Training Modules. *Multiple primary neoplasms*. U. S. National Institutes of Health: National Cancer Institute. Available at: https://training.seer.cancer.gov/. [Retrieved June 10, 2020]
34. Working Group Report. International Rules for Multiple Primary Cancers (ICD-0 Third Edition). *Eur J Cancer Prev* (2005) 14(4):307–8. doi: 10.1097/00008469-200508000-00002
35. Institute of Health Information and Statistics of the Czech Republic. National Health Information System (NHIS), Czech National Cancer Registry (CNCR). http://www.uzis.cz/en/czech-nationalcancer-registry-cncr. [Retrieved June 10, 2020]
36. Jia H, Li Q, Yuan J, Sun X, Wu Z. Second Primary Malignancies in Patients With Colorectal Cancer: A Population-Based Analysis. *Oncologist* (2020) 25 (4):e644–50. doi: 10.1634/theoncologist.2019-0266
37. La Francis IE, Cooper RB. Second Primary Malignancies Associated With Primary Female Breast Cancer: A Review of the Danbury Hospital Experience. *Conn Med* (1992) 56(8):411–4.
38. Duchateau CS, Stokkel MP. Second Primary Tumors Involving Non-Small Cell Lung Cancer: Prevalence and Its Influence on Survival. *Chest* (2005) 127 (4):1152–8. doi: 10.1378/chest.127.4.1152
39. Lee YT, Liu CJ, Hu YW, Teng CJ, Tzeng CH, Yeh CM, et al. Incidence of Second Primary Malignancies Following Colorectal Cancer: A Distinct Pattern of Occurrence Between Colon and Rectal Cancers and Association of Co-Morbidity With Second Primary Malignancies in a Population-Based Cohort of 98,876 Patients in Taiwan. *Medicine (Baltimore)* (2015) 94(26): e1079. doi: 10.1097/MD.0000000000001079
40. Takeuchi D, Koide N, Komatsu D, Okumura M, Suzuki A, Miyagawa S. Relationships of Obesity and Diabetes Mellitus to Other Primary Cancers in Surgically Treated Gastric Cancer Patients. *Int J Surg* (2014) 12(6):587–93. doi: 10.1016/j.ijsu.2014.04.012
41. Broman KK, Bailey CE, Parikh AA. Sidedness of Colorectal Cancer Impacts Risk of Second Primary Gastrointestinal Malignancy. *Ann Surg Oncol* (2019) 26(7):2037–43. doi: 10.1245/s10434-019-07326-7
42. Li CI, Daling JR, Tang MT, Malone KE. Relationship between diabetes and risk of second primary contralateral breast cancer. *Breast Cancer Res Treat* (2011) 125(2):545–51. doi: 10.1007/s10549-010-1035-4
43. Zhuang L, Yan X, Meng Z. Second primary malignancy in patients with cholangiocarcinoma: a population-based study. *Cancer Manag Res* (2019) 11:1969–83. doi: 10.2147/CMAR.S187614
44. González N, Prieto I, Del Puerto-Nevado L, Portal-Nuñez S, Ardura JA, Corton M, et al. 2017 Update on the Relationship Between Diabetes and Colorectal Cancer: Epidemiology, Potential Molecular Mechanisms and Therapeutic Implications. *Oncotarget* (2017) 8(11):18456–85. doi: 10.18632/oncotarget.14472
45. Morden NE, Liu SK, Smith J, Mackenzie TA, Skinner J, Korc M. Further Exploration of the Relationship Between Insulin Glargine and Incident Cancer: A Retrospective Cohort Study of Older Medicare Patients. *Diabetes Care* (2011) 34(9):1965–71. doi: 10.2337/dc11-0699
46. Kwon M, Roh JL, Song J, Lee SW, Kim SB, Choi SH, et al. Effect of Metformin on Progression of Head and Neck Cancers, Occurrence of Second Primary Cancers, and Cause-Specific Survival. *Oncologist* (2015) 20(5):546–53. doi: 10.1634/theoncologist.2014-0426
47. Zhou PT, Li B, Liu FR, Zhang MC, Wang Q, Li YY, et al. Metformin Is Associated With Survival Benefit in Pancreatic Cancer Patients With Diabetes: A Systematic Review and Meta-Analysis. *Oncotarget* (2017) 8 (15):25242–50. doi: 10.18632/oncotarget.15692
48. Bradley MC, Ferrara A, Achacoso N, Ehrlich SF, Quesenberry CPJr, Habel LA. A Cohort Study of Metformin and Colorectal Cancer Risk Among Patients With Diabetes Mellitus. *Cancer Epidemiol Biomarkers Prev* (2018) 27(5):525–30. doi: 10.1158/1055-9965.EPI-17-0424
49. Dankner R, Balicer R, Boffetta P, Boker LK, Wallenstein S, Freedman L, et al. Diabetes, Glucose Control, Glucose Lowering Medications, and Cancer Risk: A 10-year Population-Based Historical Cohort. *BMC Cancer* (2012) 12:364. doi: 10.1186/1471-2407-12-364
50. Ruiter R, Visser LE, van Herk-Sukel MP, Coebergh JW, Haak HR, Geelhoed-Duijvestijn PH, et al. Risk of cancer in patients on insulin glargine and other insulin analogs in comparison with those on human insulin: results from a large population-based follow-up study. *Diabetologia* (2012) 55:51–62. doi: 10.1007/s00125-011-2312-4
51. Karlstad O, Starup-Linde J, Vestergaard P, Hjellvik V, Bazelier MT, Schmidt MK, et al. Use of Insulin and Insulin Analogs and Risk of Cancer - Systematic Review and Meta-Analysis of Observational Studies. *Curr Drug Saf* (2013) 8 (5):333–48. doi: 10.2174/15680266113136660067
52. Mayer D, Chantelau E. Treatment With Insulin Glargine (Lantus) Increases the Proliferative Potency of the Serum of Patients With type-1 Diabetes: A Pilot Study on MCF-7 Breast Cancer Cells. *Arch Physiol Biochem* (2010) 116 (2):73–8. doi: 10.3109/13813451003631439
53. But A, De Bruin ML, Bazelier MT, Hjellvik V, Andersen M, Auvinen A, et al. Cancer Risk Among Insulin Users: Comparing Analogues With Human Insulin in the CARING Five-Country Cohort Study. *Diabetologia* (2017) 60 (9):1691–703. doi: 10.1007/s00125-017-4312-5
54. Gibson TM, Park Y, Robien K, Shiels MS, Black A, Sampson JN, et al. Body Mass Index and Risk of Second Obesity-Associated Cancers After Colorectal Cancer: A Pooled Analysis of Prospective Cohort Studies. *J Clin Oncol* (2014) 32(35):4004–11. doi: 10.1200/JCO.2014.56.8444
55. Morais S, Castro C, Antunes L, Peleteiro B, Bento MJ, Lunet N. Second Primary Cancers and Survival in Patients With Gastric Cancer: Association With Prediagnosis Lifestyles. *Eur J Cancer Prev* (2019) 28(3):159–66. doi: 10.1097/CEJ.0000000000000447
56. Wood ME, Vogel V, Ng A, Foxhall L, Goodwin P, Travis LB. Second Malignant Neoplasms: Assessment and Strategies for Risk Reduction. *J Clin Oncol* (2012) 30(30):3734–45. doi: 10.1200/JCO.2012.41.8681

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Characteristics and Absolute Survival of Metastatic Colorectal Cancer Patients Treated With Biologics: A Real-World Data Analysis From Three European Countries

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Introduction: Biologics were approved for the treatment of advanced colorectal cancer (CRC) based on favorable benefit-risk-assessments from randomized controlled trials (RCTs), but evidence on their use in the real-world setting is scarce. Based on descriptive analyses we therefore aimed to assess characteristics and survival of CRC patients treated with biologics using large healthcare databases from three European countries (Netherlands, Italy, Germany).

Methods: We included CRC patients treated with a biologic in 2010 or 2014 and characterized them regarding age, sex, comorbidities, and absolute survival.

Results: Among 4,758 patients, the mean age ranged from 64.8 to 66.8 years, the majority was male, and comorbidities used as exclusion criteria in RCTs were coded in up to 30% of these patients. The proportion of bevacizumab users decreased between 2010 (72–93%) and 2014 (63–85%). In 2014, the absolute 12-month survival in new users was 64% (95% CI 51–77%), 56% (30–80%), and 61% (58–63%) in the Dutch, Italian, and German database, respectively, varying by age and comorbidity.

Conclusions: Our study suggests that in the real-world setting, CRC patients treated with biologics are older and less selected regarding comorbidities compared to patients in RCTs, potentially explaining the relatively low 12-month survival we found. Treatment decisions in the real-world setting may require careful evaluation given that the risk-benefit ratio may vary depending on age and co-existing conditions.

Keywords: colorectal cancer, biologics, survival, Europe, real-world data

INTRODUCTION

Several randomized controlled trials (RCTs) have shown that biologic drugs, called "biologic" because they are produced by living organisms, may improve survival in patients with advanced colorectal cancer (CRC) (1–4). One example is the pivotal study on bevacizumab published in 2004. Bevacizumab was one of the first biologic drugs developed for treating metastatic CRC.

The study showed a 12-month survival of 74.3% for patients combining bevacizumab and chemotherapy, as compared to 63.4% for patients receiving chemotherapy alone (5). With respect to adverse events the incidence of grade 3 or 4 adverse events in the bevacizumab group was 10 percentage points higher (statistically significant difference) and the incidence of hospitalizations due to adverse events was five percentage points higher (5). A positive assessment of the risk-benefit ratio and confirmatory results from further RCTs led to the approval by the European Medicines Agency of bevacizumab for the treatment of advanced CRC in 2005 (6).

However, the risk-benefit ratio observed in clinical trials conducted under controlled conditions and in selected study populations is not necessarily similar to the risk-benefit ratio in the real-world setting. In particular, a poorer health status overall or a higher prevalence of certain comorbidities could negatively affect this ratio (7). Monitoring the use of these drugs in the real-world setting is thus urgently needed.

So far, available studies using real-world data such as administrative claims are often based on data from the United States (8–10). To our knowledge, real-world evidence based on routinely collected data on utilization of biologics in CRC patients from Europe is limited to two studies from the Czech Republic using data from a specific drug registry, one study from the Netherlands using data from a regional cancer registry, and one from Italy based on five regional cancer registries (11–14). Large claims or medical record databases from Europe have thus not been used for this purpose so far.

To shed further light on this topic, we aimed to explore the potential of large European healthcare databases for real-world monitoring of biologics in the treatment of CRC. Based on descriptive analyses we assessed the general characteristics, treatment patterns, and overall survival of patients using one or more of the three biologics available for CRC treatment during the study period, namely the vascular endothelial growth factor (VEGF)-inhibitor bevacizumab, slowing the growth of new blood vessels, and the two epidermal growth factor receptor (EGFR)-inhibitors cetuximab and panitumumab, inhibiting cell growth and division.

METHODS

Data Sources

We conducted a retrospective cohort study based on healthcare databases from three European countries [Netherlands: PHARMO Database Network (PHARMO); Italy: Caserta Local Health Unit (Caserta LHU); Germany: German Pharmacoepidemiological Research Database (GePaRD)]. A detailed description of these databases is provided in the (**Supplementary Material 1**). In brief, the PHARMO is a population-based network of electronic healthcare databases currently covering over 6 million persons out of 17 million inhabitants of the Netherlands (15). It combines anonymous data from different primary and secondary healthcare settings in the Netherlands. For this study, we used data from the Hospital Database, the In-patient Pharmacy Database, and the Out-patient Pharmacy Database, linked on a patient level through validated algorithms.

Caserta LHU contains claims data from several databases since 2009. It covers ∼1.2 million residents of Caserta (Italy) from 2009 to 2014. It includes, amongst others, information on drug dispensing in the outpatient setting, hospitalizations, outpatient diagnostic tests, and specialists' visits (16–19).

GePaRD is based on claims data from four statutory health insurance providers in Germany and currently includes information on ∼25 million persons who have been insured with one of the participating providers since 2004 or later. In addition to demographic data, GePaRD contains information on drug dispensings, outpatient, and inpatient services and diagnoses (20).

Study Design and Study Population

In each database, we aimed to include CRC patients exposed to biologics in 2014 (cohort 2014) and for comparison also CRC patients exposed to biologics in 2010 (cohort 2010, available in GePaRD and PHARMO only). Exposure to biologics was defined as at least one in- or outpatient dispensing of any relevant biologic (bevacizumab, cetuximab, panitumumab; see **Supplementary Material 2** for a list of ATC codes) in the respective year. We selected the cohorts in a two-step process. First, we identified all persons with such a dispensing in the respective year and defined the day of their first dispensing as cohort entry. Second, we limited the cohorts to patients with a CRC diagnosis (PHARMO and GePaRD: ICD-10: C18-20; Caserta LHU: ICD-9: 153*, 154*). In GePaRD, a previously developed algorithm was used to identify CRC cases (21). We considered CRC diagnoses during a preobservation period of 1 year before and on the day of cohort entry. Comorbidities and the presence of metastases were identified by ICD-10 and ICD-9 codes, respectively, and database-specific algorithms. We defined the cohort exit as the end of follow-up or death, whichever came first.

Data Analyses

We characterized the patients regarding age, sex, presence of codes for metastases, and length of follow-up. Furthermore, we assessed the prevalence of comorbidities during the preobservation period, which were defined as exclusion criteria in the pivotal study by Hurwitz et al., namely cardio-vascular diseases, ascites, metastases of the central nervous system, bleeding diatheses, and coagulopathy (see **Supplementary Material 3** for a list of ICD-10 and ICD-9 codes) (5).

For each cohort, we determined the type of biologic drug leading to cohort entry as well as the number of different biologic drugs dispensed during a follow-up of 12 and 30 months. We used Kaplan-Meier survival analyses to describe absolute survival after cohort entry. We restricted these analyses to new users of biologics defined as persons without a dispensation of biologics in the 12 months before cohort entry. This helped to avoid the comparison of patients in different phases of treatment with biologics and also ensured a better comparability with clinical trials, which typically report the survival for

TABLE 1 | Characteristics of colorectal cancer patients using biologics in 2010 and 2014.

	2010		2014		
	GePaRD (Germany)	**PHARMO (Netherlands)**	**GePaRD (Germany)**	**PHARMO (Netherlands)**	**Caserta LHU (Italy)**
Number of patients	2,162	112	2,362	73	49
Sex male [percent]	54.7[a]	62.5	53.2[a]	63.0	65.3
Mean age (SD) [years]	65.7 (10.0)	65.8 (8.9)	66.8 (10.4)	64.8 (9.0)	66.4 (11.9)
Median age (Q1, Q3) [years]	67 (60, 73)	68 (61, 72)	68 (60, 74)	65 (61, 72)	68 (58, 75)
<60 years [percent]	24.8	23.2	23.5	24.6	
60–75 years [percent]	60.0	58.9	56.0	61.6	
>75 years [percent]	15.4	17.9	20.5	13.7	
Presence of distant metastases [percent]	90.3	66.1	92.3	72.6	81.6
Comorbidities [percent]					
Cardio-vascular diseases	28.5	2.7	29.8	5.5	22.4
Ascites	1.9	0.0	3.3	0.0	2.0
CNS metastases	1.3	0.0	1.2	0.0	0.0
Bleeding diatheses	0.7	0.0	0.6	0.0	0.0
Coagulopathy	1.0	0.0	1.6	0.0	0.0

[a]*In one of the health insurances providing data of about 6 million insured persons to GePaRD, the proportion of women 50 years old or older is substantially higher as compared to the general population (32.1 vs. 22.5%). This explains the unexpected gender distribution among patients with CRC in GePaRD.*

TABLE 2 | Type and number of biologics used by colorectal cancer patients.

	2010		2014		
	GePaRD (Germany) ***N* = 2,162**	**PHARMO (Netherlands)** ***N* = 112**	**GePaRD (Germany)** ***N* = 2,362**	**PHARMO (Netherlands)** ***N* = 73**	**Caserta LHU (Italy)** ***N* = 49**
Biologics used during 30 months of follow-up[a] [percent]					
Bevacizumab	80.5	92.9	76.3	84.9	81.6
Cetuximab	39.1	1.8	32.7	4.1	24.5
Panitumumab	19.7	16.1	24.1	28.8	6.1
Number of different biologics used during 30 months follow-up [percent]					
One	69.9	89.3	78.2	82.2	87.8
Two	23.3	10.7	19.4	17.8	12.2
More than two	6.8	0.0	2.4	0.0	0.0

[a]*Since use of multiple drugs per patient was possible, numbers may add up to more than 100%.*

persons initiating treatment with biologics. In GePaRD, we also assessed overall survival among new users stratified by age group and in the subgroup of new users with the above-mentioned comorbidities. In a subsample of GePaRD containing new users from one participating statutory health insurance which provides information on the number of cytostatic agents used in in- and outpatient chemotherapy, we assessed the number of new users having received chemotherapy within 30 days before or after cohort entry including the number of cytostatic agents used. All analyses were conducted in SAS (22).

RESULTS

Characteristics of the Study Population

Overall, we identified 2,274 CRC patients exposed to biologics in 2010 and 2,484 patients in 2014. **Table 1** shows the number of included patients and their characteristics stratified by database and year. GePaRD contributed the largest proportion of patients both in 2010 and 2014 (95%). The mean age ranged from 64.8 to 66.8 years and the proportion of males ranged from 53.2 to 65.3%. In the majority of patients, there were codes for metastases with some variation between databases. In the data from GePaRD and from Caserta LHU, there were codes for cardiovascular disease in more than 20% of patients, while this proportion was lower in PHARMO. Other comorbidities used as exclusion criteria in the study by Hurwitz et al. such as ascites were coded mainly in GePaRD among 0.6–3.3% of patients.

Type and Number of Biologics Used

Table 2 shows the type of biologic and the number of different biologics used during a follow-up period of 30 months. In GePaRD, the proportion of patients using bevacizumab and

TABLE 3 | 12-month absolute survival of colorectal cancer patients using biologics overall (all databases) and stratified by age and presence of selected comorbidities (GePaRD only).

	2010		2014		
	GePaRD (Germany)	PHARMO (Netherlands)	GePaRD (Germany)	PHARMO (Netherlands)	Caserta LHU (Italy)
Users of biologics, 12-month survival (95% CI) [percent]					
All	60.4 (58.3–62.4)	65.2 (56.2–74.5)	60.7 (58.7–62.7)	63.0 (50.9–74.0)	63.3 (48.3–76.6)
New users of biologics, 12-month survival (95% CI) [percent]					
All	60.7 (58.4–63.0)	68.9 (55.7–80.1)	61.8 (59.1–64.5)	64.4 (50.9–76.5)	56.3 (29.9–80.3)
Stratified by age in years					
<60	62.5 (57.8–67.1)		67.8 (62.2–73.0)		
60–75	61.5 (58.5–64.5)		63.5 (59.9–67.1)		
>75	54.9 (48.8–61.0)		50.2 (44.0–56.4)		
New users of bevacizumab, 12-month survival (95% CI) [percent]					
All	59.5 (56.3–62.6)		62.1 (58.4–65.7)		
Stratified by age in years					
<60	60.2 (53.2–66.9)		71.2 (63.2–78.4)		
60–75	61.3 (57.2–65.3)		62.5 (57.5–67.4)		
>75	52.2 (44.2–60.0)		52.8 (44.8–60.7)		
New users of biologics with selected comorbidities[a], 12-month survival (95% CI) [percent]					
All	56.4 (52.2–60.5)		56.9 (52.2–61.5)		
Stratified by age in years					
<60	50.0 (38.6–61.4)		53.2 (38.1–67.9)		
60–75	59.8 (54.5–65.0)		61.5 (55.5–67.2)		
>75	51.1 (42.4–59.7)		48.0 (39.0–57.1)		

[a]*We considered comorbidities that often led to exclusion of patients from randomized controlled trials investigating biologics in colorectal cancer patients: cardio-vascular diseases, ascites, CNS metastases, bleeding diatheses, and coagulopathy (for a list of the respective ICD-9 and ICD-10 codes see* ***Supplementary Material 3****).*

cetuximab decreased between 2010 and 2014: For bevacizumab, it decreased from 81% in 2010 to 76% in 2014, for cetuximab it increased from 39% in 2010 to 33% in 2014. During the same time, the proportion of patients using panitumumab increased from 20% in 2010 to 24% in 2014. In PHARMO, the proportion of patients using bevacizumab was 93% in 2010 and decreased to 85% in 2014. For cetuximab, the proportion was 2% (2010) and 4% (2014) and for panitumumab, it increased from 16% in 2010 to 29% in 2014. In the database from Caserta LHU (data from 2014 only), the proportion of patients using bevacizumab (82%) was similar to PHARMO in 2014, while for cetuximab, the proportion was 25% and thus similar to GePaRD in 2014.

Across all databases, 11–30% of patients received two or more different biologics relevant regarding CRC during 30 months of follow-up. In both years, this proportion was highest in GePaRD where it decreased from 30% in 2010 to 22% in 2014. Only patients from GePaRD received more than two different biologic drugs (7% in 2010 and 2% in 2014).

In the subsample of GePaRD containing new users from the (only) statutory health insurance that provides data on the number of cytostatic agents used in in- and outpatient chemotherapy ($n = 2{,}417$), 95% received chemotherapy within 30 days before or after cohort entry. Of these patients, 19% were treated with one cytostatic agent, 66% received two different cytostatic agents, and 15% received three or more different cytostatic agents.

Description of Survival

Table 3 shows the absolute 12-month survival among CRC patients treated with biologics. In GePaRD, about 40% of the patients died within 12 months after cohort entry in both years. This applied to all patients as well as to new users of biologics, i.e., those without a dispensing of biologics in the 12 months before cohort entry. In the other databases, the point estimates of this proportion varied from 31 to 44% and had a large confidence interval that included the point estimates of GePaRD. As illustrated in **Figures 1**, **2**, the probability of dying among new users of biologics increased to about 70% within 24 months in GePaRD and tended to be lower in PHARMO (with non-overlapping 95% confidence intervals, i.e., statistical significance at the 0.05 level). Compared to GePaRD, the probability of dying was also lower for patients from the Caserta LHU database, but the confidence intervals were large and included the point estimates observed in GePaRD and PHARMO.

Stratified by age group (GePaRD only), the 12-month survival among new users of biologics was 7–18% lower in CRC patients of the oldest age group (>75 years) compared to the two younger age groups (<60 and 60–75 years) (**Table 3**). As shown in **Figure 3**, the survival curves of the oldest age group started to diverge from the younger age groups after 3 months. The respective confidence intervals were non-overlapping (which corresponds to statistically significant differences) from month 10 onwards. After 24 months, the probability of dying was 61% in

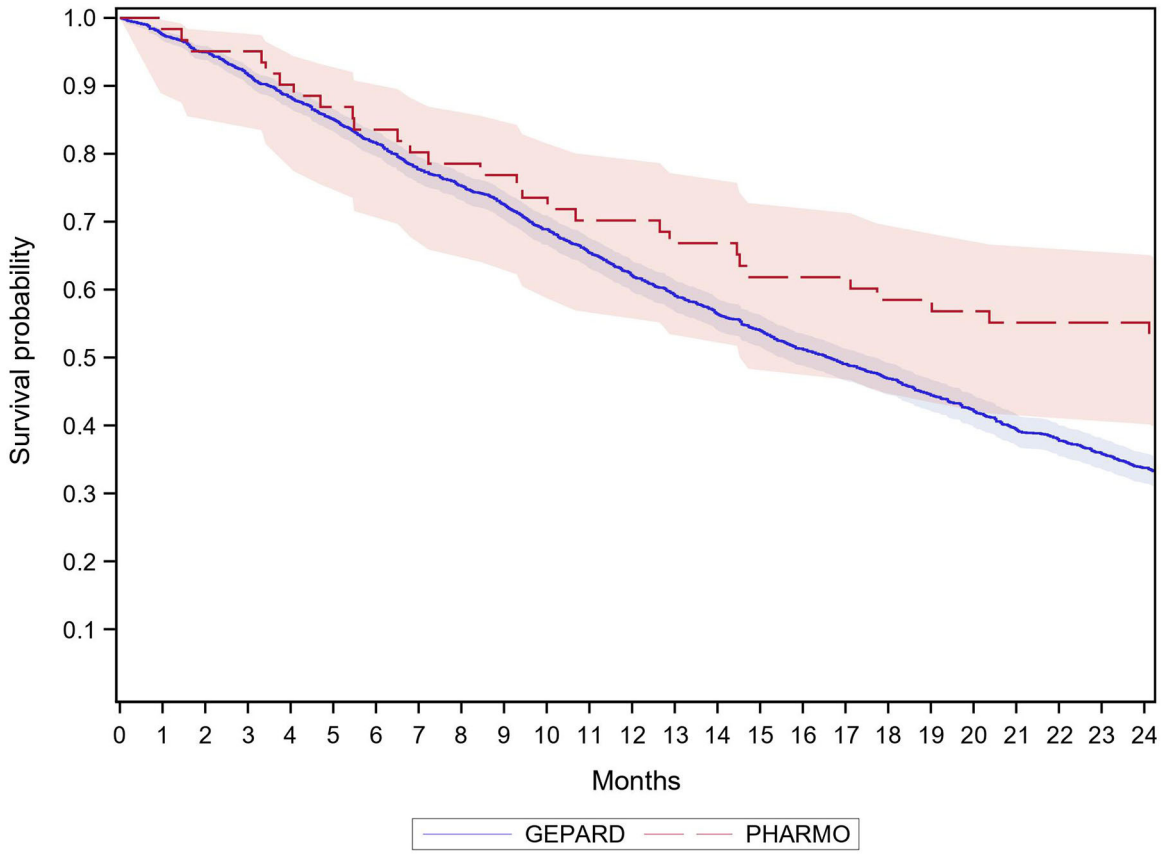

FIGURE 1 | Survival of new users of biologics with colorectal cancer by database 2010.

the youngest age group (<60 years), 65% in the age group 60–75 years, and 77% in the oldest age group (>75 years).

Figure 4 shows the results of age-stratified survival analyses restricted to new users of biologics with selected comorbidities (see methods section). In the youngest age group (<60 years), the 12-month survival was 53% and thus 14% lower compared to the survival observed in the unrestricted group of patients aged <60 years (**Table 3**). The 12-month survival in the youngest age group (<60 years) was similar to the oldest age group (>75 years) and lower compared to age group 60–75 years. Between months 6 and 12, the differences in the survival curves between the youngest age group and the age group 60–75 years were statistically significant (non-overlapping 95% confidence intervals). After 12 months, the survival probability in the youngest age group approached the survival probability in the age group 60–75 years. After 24 months, the survival probabilities were 32% in the two younger age groups (<60 years and 60–75 years) and 20% in the oldest age group (>75 years).

DISCUSSION

This observational population-based study of more than 4,500 CRC patients from three European countries showed that CRC patients treated with biologics in the real-world setting differ substantially from those included in pivotal RCTs of those drugs. In particular, the CRC patients in the real-world setting were older and had comorbidities used as exclusion criteria in the RCTs. This might explain the relatively poor absolute survival observed in our study. Furthermore, we observed different patterns regarding utilization of the EGFR-inhibitors cetuximab vs. panitumumab between countries.

In GePaRD, where survival probability could be estimated more precisely than in the other databases, a 12-month absolute survival of 60–62% was observed among new users of biologics, also in analyses restricted to new users of bevacizumab (**Table 3**). By contrast, the 12-month survival in the RCT by Hurwitz et al. was 74% for bevacizumab users (**Figure 5**) and thus considerably higher than in GePaRD (5). Also, a review of 17 RCTs investigating the role of biologics combined with standard chemotherapy as first-line treatment of CRC reported 12-month survival rates higher to our findings for the vast majority of studies: Survival was higher in 16 RCTs, and in one RCT it was either higher or similar, depending on the respective chemotherapy (3). The difference in survival—as assessed by indirect comparison—would have even been larger if the sex distribution in GePaRD (unusually high proportion of female CRC patients) had been similar to the RCTs, keeping in mind that partly higher relative survival rates

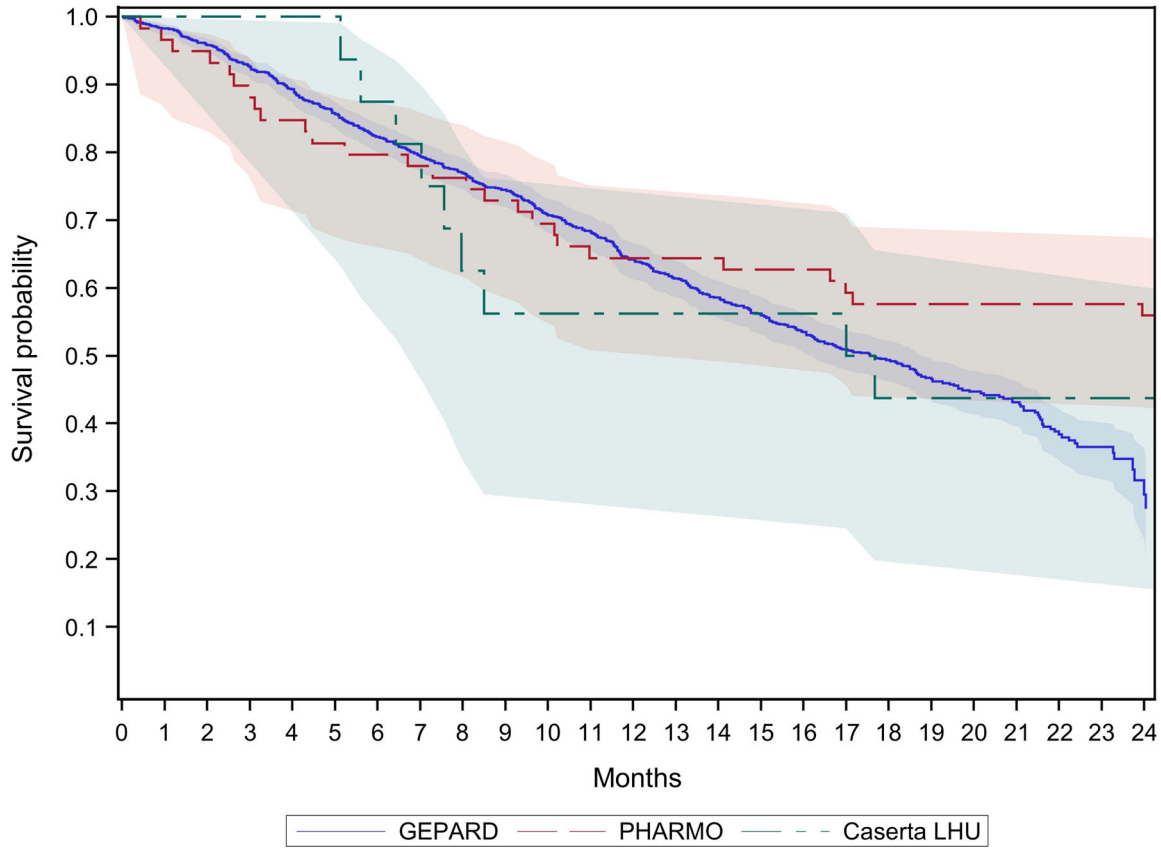

FIGURE 2 | Survival of new users of biologics with colorectal cancer by database 2014.

have been reported for female CRC patients compared to male patients (23).

To explore potential reasons for the observed survival rates, further factors need to be taken into account. The patients in our study were about 6 years older as compared to the patients of the pivotal RCT on bevacizumab (5). Also, most of the other RCTs reviewed by Mahipal and Grothey reported a lower median age compared to our study population. Not surprisingly, our analyses stratified by age showed the lowest absolute survival for the oldest age group (>75 years). Similarly, a study analyzing data from four RCTs found a lower 12-month survival for patients >70 years compared to younger patients (24). Thus, the age structure is likely an important factor explaining the relatively poor 12-month survival observed in our study. Interestingly, our subgroup analysis focusing on CRC patients <60 years with comorbidities showed a 12-month survival of only 50%, suggesting that presence of comorbidities is another important predictor of 1-year mortality among CRC patients treated with biologics. Half of the 17 RCTs reviewed by Mahipal and Grothey, including Hurwitz et al., excluded a priori patients with an Eastern Cooperative Oncology Group (ECOG) performance status of ≥2. We could not assess the ECOG performance status in our study but there were patients in our cohort with comorbidities often used as exclusion criteria in the RCTs. Given these comorbidities and the older age in our cohort, we assume that the ECOG status in the real-world setting is worse than in RCTs. Furthermore, the use of biologics as first vs. second line therapy may be considered in the interpretation of our findings. While all RCTs reviewed by Mahipal and Grothey investigated the effectiveness of biologics as first line therapy, studies published in 2013 also suggested a benefit as second line therapy (i.e., continuation beyond first tumor progression) (25). This may have influenced clinical practice, but we did not find differences in survival between the cohorts 2010 vs. 2014, nor did we observe a relevant difference between new users of biologics vs. prevalent users. Overall, it seems that CRC patients receiving biologics in the real-world setting mainly differ from those enrolled in RCTs of biologics with respect to the presence of comorbidities and age distribution.

The comparison of our findings to other studies using real-world data from Europe is hampered regarding studies using certain criteria to select patients, e.g., if they excluded patients with early disease progression (11, 12) or focused on patients with metachronous metastases (13). A study from the UK based on medical records, which included unselected patients with advanced CRC ($N = 714$) similar to our approach, confirmed our findings. They found a 12-month survival of ∼66% in patients

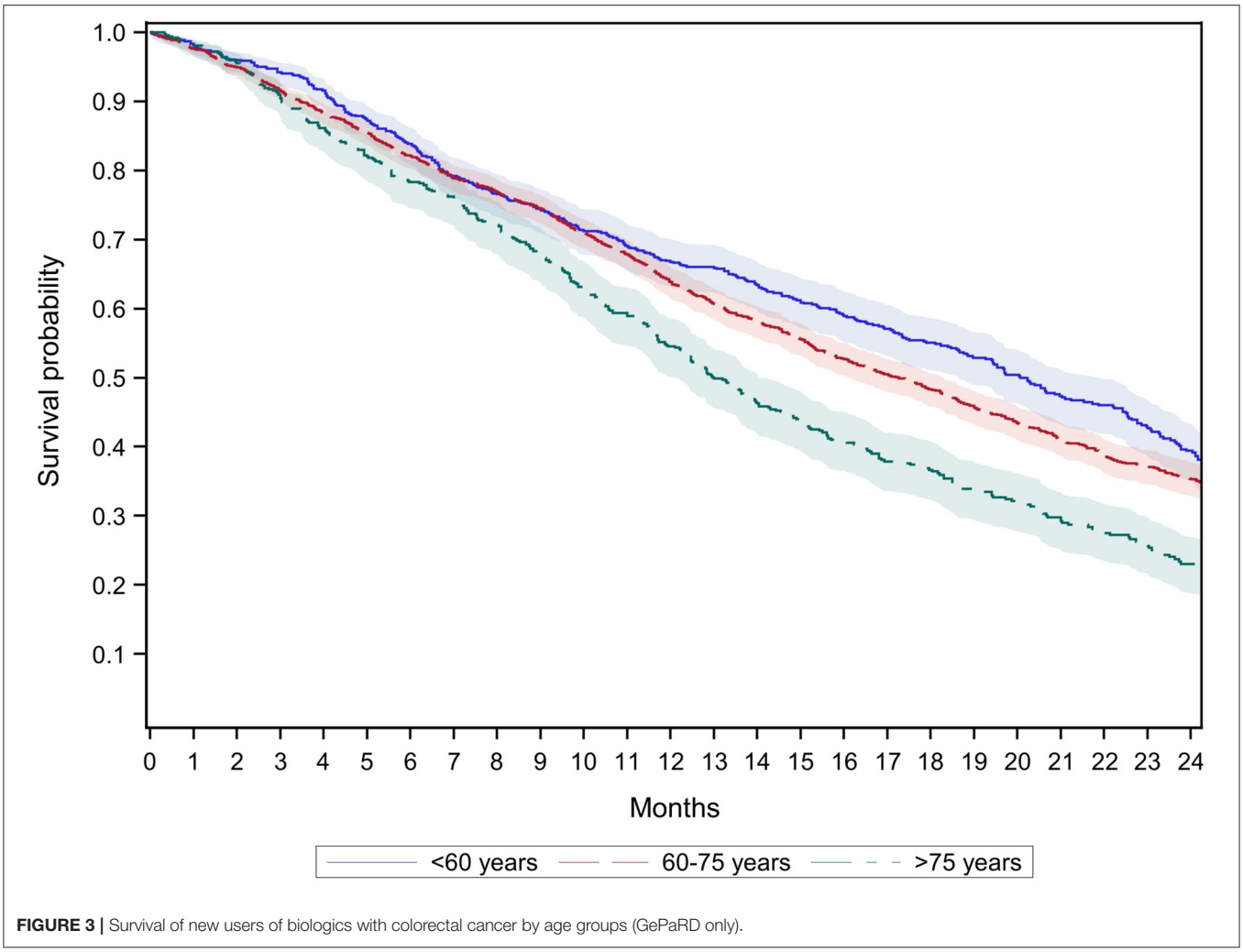

FIGURE 3 | Survival of new users of biologics with colorectal cancer by age groups (GePaRD only).

who received bevacizumab with the first-line chemotherapy (26). The median age of the study population was similar to our study population and the authors reported comorbidities such as hypertension in 21–34% of the patients and cardiac disorders in 3–7%. Future research focusing on the comparison of patients' characteristics in different countries would be of great interest.

Interestingly, we observed some differences between countries in our analyses. Survival of CRC patients in the German database (GePaRD) was partly statistically significantly lower as compared to the Dutch database (PHARMO), which could not be explained by differences in the age and sex distribution. The prevalence of comorbidities was lower in Dutch patients than in German patients. In part, we assume this resulted from differences in the coding practice but it might also indicate a less selective use of biologics in Germany than in the Netherlands. In other words, as compared to Dutch CRC patients, German patients might be more likely to receive biologics despite an already very poor prognosis or an increased risk of biologic-related adverse reactions due to comorbidities. There were also differences in utilization patterns between countries. Unlike in the German or Italian database, the EGFR-inhibitor cetuximab hardly played a role in the Netherlands, while panitumumab, another EGFR-inhibitor, was used in about one quarter of patients in the Netherlands and in Germany in 2010 but hardly played a role in Italy. Given that all drugs are authorized by the European Medicines Agency, these differences cannot be explained by marketing authorizations. Instead, country-specific reimbursement practices, costs, marketing strategies, or different clinical practices might explain the observed patterns.

It is beyond the scope or the possibilities of our study to judge whether the current use of biologics in the real-world setting is appropriate and clinically justified in all patients receiving biologics. It should still be noted that the risk-benefit ratio of these drugs, as investigated in RCTs, could easily get out of balance if comorbidities increased the risk of severe adverse events or if advanced age or poor prognosis (i.e., terminal illness) lowered the potential benefit on survival. Indeed, our study's findings regarding age, comorbidity, and survival among users of biologics in the real-world setting support concerns that the risk-benefit ratio might be less favorable than in RCTs. Of note, this does not question the efficacy of the drugs regarding tumor progression but solely refers to the selection of patients receiving

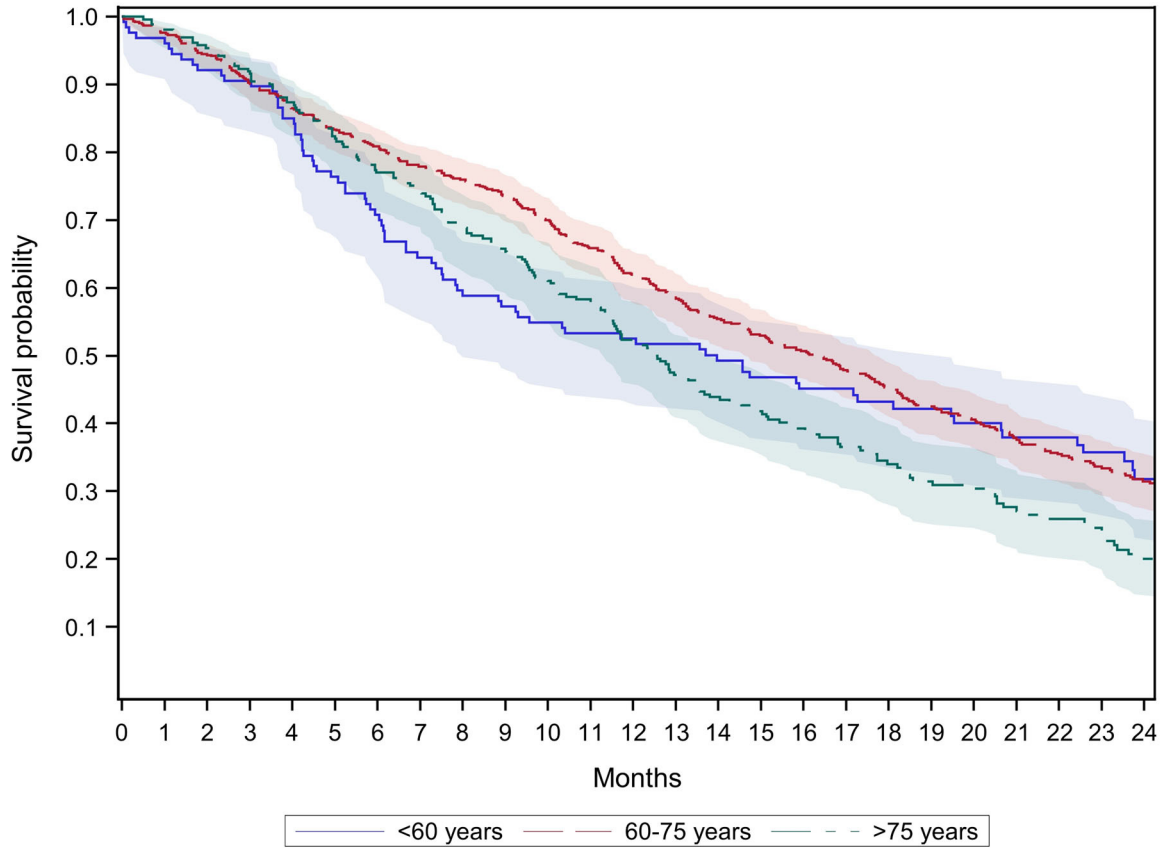

FIGURE 4 | Survival of new users of biologics with colorectal cancer and selected comorbidities† by age groups (GePaRD only). †We considered comorbidities that often led to exclusion of patients from randomized controlled trials investigating biologics in colorectal cancer patients: cardio-vascular diseases, ascites, CNS metastases, bleeding diatheses, and coagulopathy (for a list of the respective ICD-9 and ICD-10 codes see **Supplementary Material 3**).

these drugs. Critical evaluation of treatment decisions regarding biologic use in CRC patients is therefore required, also taking into account ethical issues, e.g., prescribing drugs to patients with poor prognosis where risks may outweigh benefits.

To the best of our knowledge, this is the largest study providing real-world evidence on CRC patients using biologics in Europe and the only study conducting parallel analyses based on databases from different European countries. The study illustrates that large source populations are indeed needed to address research questions on this rare exposure. The sample size in the Dutch and the Italian database was still relatively small but patterns in utilization could be assessed anyhow. The confidence intervals of survival estimates were rather large in these two databases but still partly non-overlapping (e.g., survival curves in PHARMO vs. GePaRD). The databases used for our study also have limitations. The coding of diagnoses is often suboptimal in such databases and coding practices could differ between countries. We assume that this explains the heterogeneous and partly low proportion of CRC patients with codes for metastases as it is very unlikely that these drugs are used "off-label" in non-metastatic CRC patients. Also with respect to comorbidities there was variation in the prevalence between databases, which may in part be explained by these coding issues. Information on molecular subtypes, especially regarding the KRAS status, would have been interesting for additional analyses but was not available in the data used for this study. The same applies to information on the concomitant treatment with chemotherapy. The role of specific cytostatic agents investigated in trials, e.g., the use of capecitabin and bevacizumab in elderly patients in the real-world setting could thus not be assessed in our study (27). We could only do some analysis on concomitant chemotherapy. For example, an analysis in a subsample of new users of GePaRD for whom information on the number of cytostatic agents was available suggested a very high proportion of patients receiving concomitant chemotherapy. In addition, we focused on patterns of use and absolute survival in our study while studies based on primary data often additionally assessed progression-free survival. Although progression-free survival might be assessable with secondary data as well, there is more uncertainty as compared to absolute survival. Also, the follow-up in our data was limited in the 2014 cohorts due to the lag in data availability. Finally, it was beyond our scope to assess treatment regimens (duration, dose, treatment lines) of biologics, which would have required further assumptions and would have been difficult to harmonize across databases. Our study was merely descriptive and focused on patients receiving biologics.

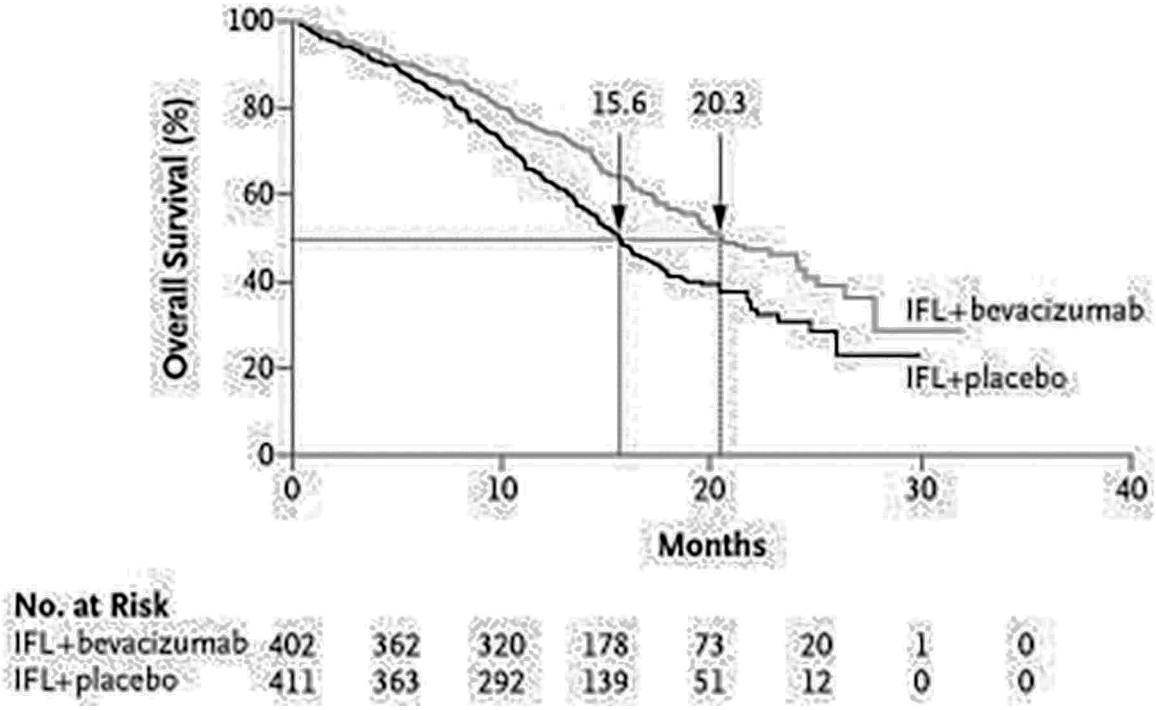

FIGURE 5 | For comparison: Survival of users of standard chemotherapy and bevacizumab and survival of users of standard chemotherapy alone as found in the RCT by Hurwitz et al. (5).

Comparison of survival to a control group not receiving biologics would be highly problematic due to confounding by indication and unmeasured confounders.

In conclusion, our study illustrated the potential of European healthcare databases for the real-world monitoring of biologics in the treatment of CRC. These databases do not represent the ideal of a homogeneous and complete European cancer registry with detailed, high-quality data on patient- and tumor-related factors and treatment. As long as such a registry does not exist, we feel it is important to use the specific potential of existing databases in order to allow the various pieces of evidence to complement each other. Consistently across databases, our findings suggest that in the real-world setting, CRC patients treated with biologics are older and have a higher burden of comorbidities as compared to CRC patients enrolled in RCTs of biologics. This may explain the relatively poor 12-month survival rate observed in our study. Our findings highlight the importance of carefully evaluating and reflecting clinical decision making when treating CRC patients with biologics in the real-world setting given that the risk-benefit ratio may vary depending on age and co-existing conditions.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because PHARMO: The datasets generated and/or analyzed during the current study are not publicly available due to privacy reasons. University of Messina/Caserta LHU: The datasets generated and/or analyzed during the current study are not publicly available due to privacy reasons. GePaRD: In accordance with German data protection regulations, access to the data of this study may only be given to third parties within the realm of collaborations with BIPS and after signing an agreement for guest researchers. As we are not the owners of the data, we are not legally entitled to grant access to GePaRD. Requests to access the datasets should be directed to Katja A. Oppelt, oppelt@leibniz-bips.de.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KO, JK, YI, VI, RH, GT, and UH have made substantial contributions to conception and design of the study and interpretation of data. MT (Caserta LHU), UH (GePaRD), and RH (PHARMO) have made substantial contributions to the acquisition of data. KO, JK, YI, and VI have made substantial contributions to the analysis of data. KO and UH have been involved in drafting the manuscript. JK, YI, VI, RH, MT, GT, and UH have critically revised the manuscript for important intellectual content. All authors have given final approval of the version to be published and agreed to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.630456/full#supplementary-material

REFERENCES

1. Sobrero A. A tribute to biologics in advanced colorectal cancer treatment. *Ann Oncol.* (2016) 27:1372–4. doi: 10.1093/annonc/mdw245
2. Noel MS. Biologics in bowel cancer. *J Gastrointest Oncol.* (2017) 8:449–56. doi: 10.21037/jgo.2017.05.03
3. Mahipal A, Grothey A. Role of Biologics in first-line treatment of colorectal cancer. *J Oncol Pract.* (2016) 12:1219–28. doi: 10.1200/JOP.2016.018382
4. EMA. *Biological Medicine.* (2021). Available online at: https://www.ema.europa.eu/en/glossary/biological-medicine (accessed January 31, 2021).
5. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.* (2004) 350:2335–42. doi: 10.1056/NEJMoa032691
6. EMA. *Avastin: EMA.* (2019). Available online at: https://www.ema.europa.eu/en/medicines/human/EPAR/avastin (accessed August 27, 2019).
7. Batra A, Cheung WY. Role of real-world evidence in informing cancer care: lessons from colorectal cancer. *Curr Oncol.* (2019) 26(Suppl. 1):S53–s6. doi: 10.3747/co.26.5625
8. Raouf S, Bertelli G, Ograbek A, Field P, Tran I. Real-world use of bevacizumab in metastatic colorectal, metastatic breast, advanced ovarian and cervical cancer: a systematic literature review. *Future Oncol.* (2019) 15:543–61. doi: 10.2217/fon-2018-0480
9. Houts AC, Ogale S, Sommer N, Satram-Hoang S, Walker MS. Treatment patterns and outcomes in patients with KRAS wild-type metastatic colorectal cancer treated in first line with bevacizumab- or cetuximab-containing regimens. *J Gastrointest Cancer.* (2019) 50:69–77. doi: 10.1007/s12029-017-0027-6
10. Hess LM, Cui ZL, Mytelka DS, Han Y, Goodloe R, Schelman W. Treatment patterns and survival outcomes for patients receiving second-line treatment for metastatic colorectal cancer in the USA. *Int J Colorectal Dis.* (2019) 34:581–8. doi: 10.1007/s00384-018-03227-5
11. Buchler T, Chloupkova R, Poprach A, Fiala O, Kiss I, Kopeckova K, et al. Sequential therapy with bevacizumab and EGFR inhibitors for metastatic colorectal carcinoma: a national registry-based analysis. *Cancer Manag Res.* (2019) 11:359–68. doi: 10.2147/CMAR.S183093
12. Fiala O, Veskrnova V, Chloupkova R, Poprach A, Kiss I, Kopeckova K, et al. Impact of delayed addition of Anti-EGFR monoclonal antibodies on the outcome of first-line therapy in metastatic colorectal cancer patients: a retrospective registry-based analysis. *Target Oncol.* (2018) 13:735–43. doi: 10.1007/s11523-018-0597-7
13. Razenberg LG, van Gestel YR, de Hingh IH, Loosveld OJ, Vreugdenhil G, Beerepoot LV, et al. Bevacizumab for metachronous metastatic colorectal cancer: a reflection of community based practice. *BMC Cancer.* (2016) 16:110. doi: 10.1186/s12885-016-2158-8
14. Franchi M, Barni S, Tagliabue G, Ricci P, Mazzucco W, Tumino R, et al. Effectiveness of first-line bevacizumab in metastatic colorectal cancer: the observational cohort study GRETA. *Oncologist.* (2019) 24:358–65. doi: 10.1634/theoncologist.2017-0314
15. Kuiper JG, Bakker M, Penning-van Beest FJA, Herings RMC. Existing data sources for clinical epidemiology: the PHARMO database network. *Clin Epidemiol.* (2020) 12:415–22. doi: 10.2147/CLEP.S247575
16. Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, Tari DU, et al. How much are biosimilars used in clinical practice? A retrospective Italian population-based study of erythropoiesis-stimulating agents in the years 2009-2013. *BioDrugs.* (2015) 29:275–84. doi: 10.1007/s40259-015-0132-7
17. Ingrasciotta Y, Giorgianni F, Marcianò I, Bolcato J, Pirolo R, Chinellato A, et al. Comparative effectiveness of biosimilar, reference product and other Erythropoiesis-Stimulating Agents (ESAs) still covered by patent in chronic kidney disease and cancer patients: an italian population-based study. *PLoS ONE.* (2016) 11:e0155805. doi: 10.1371/journal.pone.0155805
18. Marcianò I, Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, et al. How did the introduction of biosimilar filgrastim influence the prescribing pattern of granulocyte colony-stimulating factors? Results from a multicentre, population-based study, from five Italian centres in the Years 2009-2014. *BioDrugs.* (2016) 30:295–306. doi: 10.1007/s40259-016-0175-4
19. Marcianò I, Ingrasciotta Y, Giorgianni F, Ientile V, Chinellato A, Tari DU, et al. Pattern of use of biosimilar and originator somatropin in Italy: a population-based multiple databases study during the years 2009-2014. *Front Endocrinol.* (2018) 9:95. doi: 10.3389/fendo.2018.00095
20. Pigeot I, Ahrens W. Establishment of a pharmacoepidemiological database in Germany: methodological potential, scientific value and practical limitations. *Pharmacoepidemiol Drug Saf.* (2008) 17:215–23. doi: 10.1002/pds.1545
21. Oppelt KA, Luttmann S, Kraywinkel K, Haug U. Incidence of advanced colorectal cancer in Germany: comparing claims data and cancer registry data. *BMC Med Res Methodol.* (2019) 19:142. doi: 10.1186/s12874-019-0784-y
22. SAS Institute. *The SAS systems for Windows. Release 9.3.* Cary, NC: SAS Inst (2011).
23. Majek O, Gondos A, Jansen L, Emrich K, Holleczek B, Katalinic A, et al. Sex differences in colorectal cancer survival: population-based analysis of 164,996 colorectal cancer patients in Germany. *PLoS ONE.* (2013) 8:e68077. doi: 10.1371/journal.pone.0068077
24. Cassidy J, Saltz LB, Giantonio BJ, Kabbinavar FF, Hurwitz HI, Rohr UP. Effect of bevacizumab in older patients with metastatic colorectal cancer: pooled analysis of four randomized studies. *J Cancer Res Clin Oncol.* (2010) 136:737–43. doi: 10.1007/s00432-009-0712-3
25. Bennouna J, Sastre J, Arnold D, Österlund P, Greil R, Van Cutsem E, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol.* (2013) 14:29–37. doi: 10.1016/S1470-2045(12)70477-1
26. Khakoo S, Chau I, Pedley I, Ellis R, Steward W, Harrison M, et al. ACORN: observational study of bevacizumab in combination with first-line chemotherapy for treatment of metastatic colorectal cancer in the UK. *Clin Colorectal Cancer.* (2019) 18:280–91.e5. doi: 10.1016/j.clcc.2019.07.003

27. Cunningham D, Lang I, Marcuello E, Lorusso V, Ocvirk J, Shin DB, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol.* (2013) 14:1077–85. doi: 10.1016/S1470-2045(13)70154-2

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Trends in Colorectal Cancer Incidence Rates in Saudi Arabia (2001–2016) Using Saudi National Registry: Early- Versus Late-Onset Disease

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Early-onset (<50 years old) colorectal cancer (CRC) has been increasing worldwide and is associated with poor outcomes. Over 85% of the Saudi population are <50 years old, which put them at heightened risk of early-onset CRC. No study assessed the trends in CRC incidence rates among the Saudis. The Joinpoint Regression software by the Surveillance, Epidemiology, and End Results (SEER) program was used to estimate the magnitude and direction of CRC incidence trends by age and gender. The annual percentage change (APC) and the average annual percentage change (AAPC) between 2001 and 2016 were computed. In a sensitivity analysis, we also assessed trends using various age groups. Between 2001 and 2016, the early-onset CRC incidence (per 10^5) increased from 1.32 (95% CI: 1.11, 1.54) to 2.02 (95% CI: 1.83, 2.22) with AAPC (2.6, 95% CI: -0.4, 5.7). At same period, the late-onset incidence increased from 3.54 (95% CI: 3.10, 3.97) to 9.14 (95% CI: 8.62, 9.66) with AAPC (6.1, 95% CI: 3.5, 8.8). Among early-onset CRC patients, age 40–49 has the highest rates and women in this age group has higher rate than men. Our national data showed a gradual increase in CRC incidence rates, which reflect the global concern of early-onset CRC. Further research is needed to understand the etiology of early-onset CRC. Primary health care providers must be alerted about the increasing rate of early-onset CRC. To reduce the future burden of the disease, initiating CRC screening before age 50 is warranted.

Keywords: colorectal cancer, Saudi Arabia, registry, incidence rate, population-based

HIGHLIGHTS

Given the global concern of increasing incidence rates of early-onset colorectal cancer, this cross-sectional analysis of data between 2001 and 2016 showed an increase the CRC incidence rate in Saudis including the early-onset colorectal cancer. This finding raise questions about the importance of initiating screening in individuals younger than 50 years old.

INTRODUCTION

Colorectal cancer (CRC) is the third most diagnosed cancer globally with more than 1.9 million incident cases in 2020 (1). While the global incidence rates have been decreasing in the screening-eligible age group (50–75) due to the adoption of CRC screening and reduction in risk factors such as smoking, there have been global reports of increasing rates in the younger population (<50), with the highest annual percentage change (APC) among the age group 20–39 (2, 3). These reports bring about the discussion about the appropriate age to initiate the screening, with some reports advocating for starting at age 45 and others as early as the age of 40, after considering the benefit-risk profile of screening at younger age (4–6).

Unlike other international studies, investigating the trends of CRC among the Saudi population is critical for several reasons. First, the Saudi population is young with 35% in the age group 20–39 and 86% younger than 50 years old (7). Second, obesity is common among the Gulf Cooperation Council (GCC) countries, and Saudi Arabia is no exception. In 2016, 35% of Saudi adults and one in five adolescents are considered obese (8). Both, a young population with a high proportion of obesity are characteristics that engender the development of early-onset CRC. Studies from the US, Canada, the UK, Australia, and New Zealand showed an association between the childhood obesity epidemic and the rise in early-onset CRC (9). For instance, women with BMI ≥ 23 at age 18 had a 63% higher risk of early-onset CRC compared to women with a BMI of 18.5–20.9 (10). Third, there is currently no population-based screening for CRC in Saudi Arabia, leading to delayed CRC detection, increased late-stage diagnosis, and poor survival across all age groups (11–13).

In Saudi Arabia, CRC is the most diagnosed cancer in men and third in women with 1659 cases reported in 2016, representing almost 13% of all diagnosed cancers (14). The age-standardized incidence rates per 10^5 people during 2016 were 12.9 and 9.5 in males and females. It is, nevertheless, unknown if the incidence rates have been increasing similarly across all age groups, and no study has investigated changes in incidence rates by age at diagnosis. While approximately 13% of early-onset CRC develops from germline mutations in genes causing hereditary CRC syndromes, the majority of early-onset CRC are sporadic, poorly differentiated, with mucinous adenocarcinoma and are diagnosed at late stage (15, 16).

On May 18, 2021 and in an effort to detect the disease at early stages, the United State Preventive Services Task Force (USPSTF) recommended CRC screening in adults aged 45–49 years with a grade "B" recommendation (17). While the recommendation recognizes the aggressive nature of early-onset CRC (4, 6), it also reflects the implications of early-onset CRC in terms of the choice of therapies and prognosis. Accordingly, it is imperative to characterize age groups with the heightened risk of early-onset CRC in the Saudi population and to investigate CRC trends in this young population. Therefore, the specific aims of the present study were to assess the average annual incidence rates for the years 2012–2016, to assess the time-weighted average annual percentage change (AAPC) during the recent 10 years (2007–2016) and 5 years (2012–2016), and to compare the incidence rates by age, gender, and subsites.

MATERIALS AND METHODS

Study Design and Data Source

The Saudi Cancer Registry (SCR) was used in this study. The SCR is a population-based cancer registry that was established in 1992 and

TABLE 1 | Characteristics of the Saudi population and the population-based colorectal cancer cases, Saudi Arabia, 2016.

Characteristics	Saudi population, 2016 (n = 20,064,970)		CRC cases, 2016 (n = 1654)	
	N	%	N	%
Age				
<20	7849953	39.12	2	0.12
20–29	3888427	19.38	28	1.69
30–39	3219098	16.04	120	7.26
40–49	2314483	11.53	270	16.32
50–54	838595	4.18	237	14.33
55–59	644701	3.21	212	12.82
60–64	471268	2.35	218	13.18
65–69	315851	1.57	148	8.95
70–74	211897	1.06	154	9.31
75+	310697	1.55	265	16.02
Gender				
Male	10225650	50.96	950	57.44
Female	9839320	49.04	704	42.56
Region				
Asir	1719950	8.57	148	8.96
Baha	376204	1.87	21	1.27
Jazan	1187284	5.92	32	1.94
Madinah	1353102	6.74	92	5.57
Hail	529012	2.64	35	2.12
Qassim	991032	4.94	77	4.66
Najran	430711	2.15	11	0.67
Jouf	373662	1.86	21	1.27
Tabuk	710699	3.54	28	1.70
Northern region	285486	1.42	14	0.85
Riyadh	4579570	22.82	501	30.35
Makkah	4440571	22.13	359	21.74
Eastern province	3087687	15.39	312	18.90

Abbreviations: APC, Annual Percent Change; AAPC, Average Annual Percent Change; CRC, Colorectal Cancer; GCC, Gulf Cooperation Council; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; SCR, Saudi Cancer Registry; SEER, Surveillance, Epidemiology, and End Results; UAE, United Arab Emirates; USPSTF, United State Preventive Services Task Force.

collects all cancer cases in Saudi Arabia. The registry gathers information using CanReg that meets high-quality cancer registration set by the International Agency for Research on Cancer (IARC). For the current study, we retrieved all CRC cases diagnosed between 2001 and 2016. Data were retrieved from patients' medical records using clinical and histopathological diagnoses through trained cancer registrars. To ensure completeness and validity of the data, the tumor's information is reviewed, coded using the International Classification of Diseases for Oncology 3rd Edition (ICD-O-3), and then linked from various regions. Census data of the Saudi population were obtained from the General Authority for Statistics.

Covariates and Outcome Variables

The primary outcome was the average annual incidence rates during 2001–2016, 2007–2016, and 2012–2016. The incidence rates were stratified by age at diagnosis and categorized as <50 (early-onset CRC) or ≥50 years (other younger age categories were also reported). The subsite for CRC was also categorized according to the ICD-10 codes with colon cancer (code C18) and rectal cancer (code C19 and C20). The 13 regional areas of Saudi Arabia have also been retrieved from the Saudi Authority of Statistics as well as the SCR and were used in the calculation of rates.

Sensitivity Analysis

According to Jacobs et al. (18), there is a distinction between the early-onset colon (20–44 years) and rectal cancers (≤54 years). Based on this difference, the authors suggest different definitions for eligibility criteria among early-onset colon and rectal cancer patients. Therefore, we categorize the CRC patients based on the authors' suggestions. Additionally, to compare our results with

TABLE 2 | Colorectal cancer age-adjusted incidence rates by age group and year, Saudi Arabia, 2001–2016.

Year	<50 years		50+ years		All ages	
	ASR	95% CI	ASR	95% CI	ASR	95% CI
2001	1.32	(1.11, 1.54)	3.54	(3.10, 3.97)	4.86	(4.38, 5.35)
2002	1.44	(1.22, 1.66)	3.98	(3.53, 4.42)	5.41	(4.92, 5.91)
2003	1.35	(1.14, 1.56)	5.22	(4.70, 5.74)	6.57	(6.01, 7.13)
2004	1.56	(1.33, 1.78)	5.77	(5.23, 6.31)	7.33	(6.74, 7.92)
2005	1.79	(1.56, 2.03)	6.66	(6.09, 7.23)	8.45	(7.84, 9.07)
2006	1.58	(1.37, 1.79)	7.58	(6.93, 8.22)	9.15	(8.47, 9.83)
2007	1.96	(1.73, 2.19)	6.89	(6.34, 7.45)	8.86	(8.26, 9.46)
2008	1.80	(1.58, 2.02)	6.82	(6.28, 7.36)	8.62	(8.03, 9.20)
2009	2.13	(1.89, 2.37)	8.40	(7.80, 9.00)	10.53	(9.89, 11.17)
2010	1.99	(1.76, 2.22)	7.55	(6.99, 8.11)	9.54	(8.94, 10.14)
2011	2.01	(1.79, 2.22)	8.08	(7.53, 8.63)	10.09	(9.49, 10.68)
2012	1.85	(1.65, 2.05)	8.23	(6.69, 8.78)	10.08	(9.50, 10.67)
2013	1.74	(1.56, 1.92)	7.67	(7.19, 8.14)	9.41	(8.89, 9.92)
2014	1.64	(1.46, 1.82)	7.56	(7.08, 8.04)	9.20	(8.69, 9.71)
2015	1.64	(1.46, 1.82)	8.29	(7.79, 8.78)	9.93	(9.40, 10.45)
2016	2.02	(1.83, 2.22)	9.14	(8.62, 9.66)	11.17	(10.61, 11.72)

TABLE 3 | Age-standardized colorectal cancer incidence rates during the most recent years by gender, Saudi Arabia.

Age	Men		Women		Both	
	2007–2016 Incidence rate (95% CI)	2012–2016 Incidence rate (95% CI)	2007–2016 Incidence rate (95% CI)	2012–2016 Incidence rate (95% CI)	2007–2016 Incidence rate (95% CI)	2012–2016 Incidence rate (95% CI)
<20	0.02 (0.02, 0.03)	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	0.02 (0.01, 0.04)	0.04 (0.03, 0.05)	0.04 (0.03, 0.05)
20–29	0.14 (0.13, 0.16)	0.13 (0.10, 0.16)	0.13 (0.11, 0.14)	0.12 (0.09, 0.15)	0.27 (0.25, 0.28)	0.26 (0.23, 0.27)
30–39	0.39 (0.37, 0.41)	0.39 (0.34, 0.43)	0.41 (0.38, 0.42)	0.41 (0.35, 0.45)	0.79 (0.76, 0.82)	0.80 (0.75, 0.82)
40–49	1.23 (1.18, 1.28)	1.25 (1.11, 1.31)	1.40 (1.30, 1.42)	1.31 (1.17, 1.38)	2.58 (2.52, 2.63)	2.56 (2.41, 2.58)
50–54	1.13 (1.09, 1.18)	1.17 (1.07, 1.28)	1.15 (1.10, 1.20)	1.16 (1.06, 1.27)	2.28 (2.23, 2.34)	2.34 (2.26, 2.41)
55–59	1.36 (1.31, 1.42)	1.51 (1.38, 1.63)	1.12 (1.06, 1.18)	1.15 (1.04, 1.26)	2.49 (2.42, 2.55)	2.65 (2.57, 2.74)
60–64	1.65 (1.58, 1.73)	1.77 (1.61, 1.93)	1.44 (1.36, 1.51)	1.53 (1.38, 1.67)	3.09 (3.01, 3.17)	3.30 (3.19, 3.40)
65–69	1.82 (1.74, 1.89)	1.69 (1.52, 1.85)	1.26 (1.18, 1.33)	1.33 (1.19, 1.47)	3.08 (2.99, 3.16)	3.02 (2.91, 3.13)
70–74	1.48 (1.42, 1.55)	1.73 (1.57, 1.89)	1.01 (0.95, 1.07)	1.04 (0.91, 1.16)	2.49 (2.42, 2.57)	2.77 (2.67, 2.87)
75+	1.66 (1.60, 1.71)	1.81 (1.67, 1.95)	1.06 (1.01, 1.12)	1.09 (0.99, 1.20)	2.72 (2.66, 2.78)	2.90 (2.81, 2.99)
0–75+	10.89 (10.44, 11.35)	11.42 (10.38, 12.46)	8.94 (8.48, 9.40)	9.12 (8.18, 10.06)	19.84 (19.32, 20.35)	20.54 (19.84, 21.24)
20–49	1.76 (1.68, 1.84)	1.73 (1.55, 1.91)	1.88 (1.80, 1.96)	1.80 (1.61, 1.98)	3.64 (3.54, 3.74)	3.52 (3.40, 3.65)
<50	1.78 (1.70, 1.87)	1.75 (1.56, 1.94)	1.90 (1.81, 1.99)	1.82 (1.63, 2.02)	3.68 (3.58, 3.79)	3.57 (3.43, 3.71)
50+	9.11 (8.74, 9.48)	9.67 (8.82, 10.53)	7.04 (6.67, 7.41)	7.30 (6.55, 8.04)	16.15 (15.74, 16.57)	16.97 (16.41, 17.54)

global research (3, 19), we have also investigated the trends in incidence rate among the age group 20–49.

Statistical Analysis

Incidence rates were computed annually and were averaged over the entire study period to examine changes over time. The rates were computed by dividing the age-specific number of incident CRC cases by the appropriate age-specific person-years at risk, as determined from the General Authority for Statistics stratified by gender. The exact Poisson 95% confidence intervals for these rates were calculated in SAS version 9.4 (SAS Institute, Cary, NC). The rates are reported per 10^5 population and were age-standardized using the world standard population.

The time-weighted AAPC was also computed using the Surveillance, Epidemiology, and End Results Program (SEER) Joinpoint regression analysis. The method fits joined straight lines to the observed age-adjusted incidence rates on a logarithmic scale (20). The method tests the null hypothesis of a zero joinpoint against the alternative hypothesis of maximum joinpoints. The maximum joinpoints are determined by the total number of years available in the registry. If the AAPC is statistically significantly different from zero ($p < 0.05$), then trends are considered increasing or decreasing; otherwise, they are considered stable trends.

RESULTS

Table 1 shows the characteristics of the Saudi population and CRC cases from the most recent available data during the year 2016. The majority (39%) of the population is younger than 20 years old, about 86% is younger than 50 years old, and mostly reside in regions of Riyadh, Makkah, and Eastern province. Almost one-third of the CRC cases are among age groups 40–54, are predominantly males, and reside in the three most populated regions. While there has been an increase in the age-standardized rates across all age groups, the steepest increase was among patients age 50 years or older (**Table 2**).

Table 3 displays the average age-standardized incidence rates during the years 2007–2016 and the years 2012–2016. Overall, the incidence rates are similar in the most recent 5 years (2012–2016) and the past 10 years (2007–2016). In general, men have higher rates than women except in the age groups 40–49, where women have higher rates than men. Among patients with early-onset CRC (<50), those in the age group 40–49 have the highest rates and even higher than those 50–54 and 55–59, especially among women.

As shown in **Table 4** (and **Figures 1**, **2**), both early-onset CRC patients (<50) and those 50+ have shown increased AAPC during the study period. Specifically, in the latest 5 and 10 years of data, colon cancer has shown consistent increase in 50+ patients, while it was either increasing or stable in rectal cancer patients across all age groups.

While the most pronounced increase in AAPC was among those 50+, early-onset patients have consistent AAPC increase especially among patients diagnosed with colon cancer. The highest increase in AAPC among 50+ was for men diagnosed with colon cancer (AAPC, 8.0 (95% CI 5.0, 11.2)), and the

TABLE 4 | Trends in colorectal cancer incidence rates by gender, age, and subsite, Saudi Arabia, 2001–2016.

Gender	Subsite	Age	Trend 1		Trend 2		Trend 3		AAPC (95% CI)	
			Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	2001–2016	2007–2016
Male	Colon	<50	–	–	–	–	–	–	2.56 (0.8,4.3)	1.07 (-2.2,4.5)
		50+	2001–2005	22.1 (8.9, 36.9)	2005–2016	3.3 (1.8, 4.8)	–	–	8.0 (5.0, 11.2)	3.62 (1.8, 5.5)
	Rectum	<50	–	–	–	–	–	–	1.53 (-0.5, 3.6)	-0.96 (-5.1, 3.4)
		50+	2001–2004	28.1 (5.3, 55.9)	2004–2016	1.3 (-0.2, 2.8)	–	–	6.20 (2.3, 10.1)	1.87 (-.40, 4.1)
	CRC	<50	–	–	–	–	–	–	1.92 (0.3, 3.6)	-0.15 (-3.4, 3.2)
		50+	2001–2004	28.6 (8.9, 51.9)	2004–2016	2.7 (1.5, 4.0)	–	–	7.5 (4.2, 10.8)	2.90 (1.1, 4.8)
Female	Colon	<50	2001–2007	11.0 (3.3, 19.3)	2007–2016	-1.2 (-4.0, 1.6)	–	–	3.5 (0.4, 6.6)	-1.53 (-4.0, 1.0)
		50+	2001–2006	12.7 (4.3, 21.9)	2006–2016	2.5 (0.7, 4.3)	–	–	5.8 (3.1, 8.5)	2.48 (0.40, 4.6)
	Rectum	<50	–	–	–	–	–	–	0.47 (-1.4, 2.4)	-1.66 (-5.6, 2.4)
		50+	2001–2006	14.6 (5.0, 25.1)	2006–2016	0.2 (-1.8, 2.3)	–	–	4.8 (1.8, 7.8)	0.39 (-1.8, 2.6)
	CRC	<50	2001–2009	5.7 (2.4, 9.2)	2009–2016	-2.4 (-5.4, 0.6)	–	–	1.8 (-0.2, 3.9)	-1.61 (-3.2, 0)
		50+	2001–2006	13.5 (5.9, 21.9)	2006–2016	1.6 (-0.01, 3.3)	–	–	5.5 (3.1, 7.9)	1.70 (-0.3, 3.7)
All	Colon	<50	2001–2007	9.1 (2.8, 15.7)	2007–2016	-0.6 (-2.8, 1.7)	–	–	3.2 (0.7, 5.7)	-0.65 (-2.5, 1.3)
		50+	2001–2006	14.7 (7.4, 22.5)	2006–2016	2.5 (1.0, 4.0)	–	–	6.4 (4.1, 8.7)	2.81 (1.1, 4.6)
	Rectum	<50	–	–	–	–	–	–	0.81 (-1.1, 2.8)	-1.54 (-5.6, 2.7)
		50+	2001–2004	27.5 (7.2, 51.6)	2004–2016	1.0 (-0.3, 2.4)	–	–	5.8 (2.5, 9.3)	0.92 (-1.1, 3.0)
	CRC	<50	2001–2010	5.3 (3.1, 7.5)	2010–2014	-6.7 (-14.7, 2.0)	2014-2016	10.54 (-7, 31.3)	2.6 (-0.4, 5.7)	-1.20 (-3.4, 1.1)
		50+	2001–2005	18.6 (7.5, 30.8)	2005–2016	1.9 (0.6, 3.3)	–	–	6.1 (3.5, 8.8)	2.06 (0.3, 3.9)

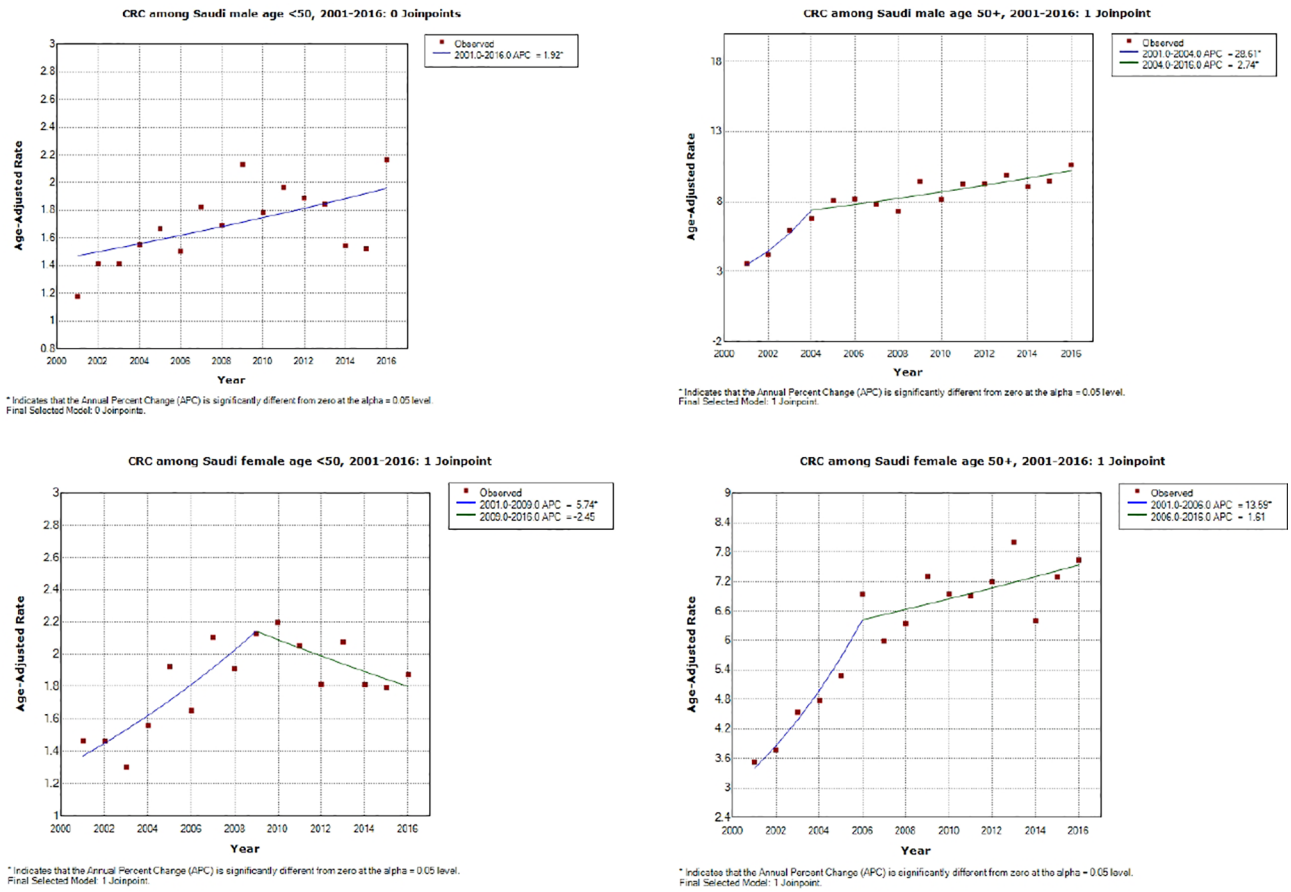

FIGURE 1 | Colorectal cancer incidence trends during the study period (2001–2016) by age and gender. *APC is statistically significantly different from zero using a two-sided test based on the permutation method.

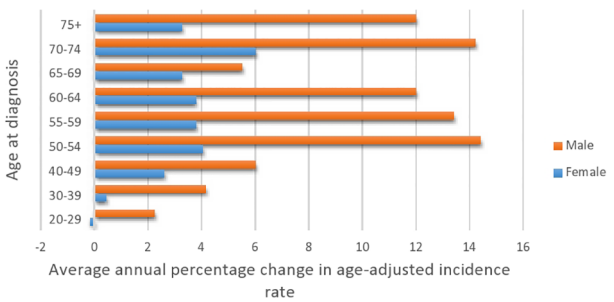

FIGURE 2 | Average annual percentage change in colorectal cancer by age at diagnosis and gender (2001–2016).

highest increase in AAPC among early-onset was for women diagnosed with colon cancer (AAPC, 3.50 (95% CI 0.4, 6.6)).

Table 5 presents the AAPC during different periods and across various age groups. Among the early-onset CRC patients, one can notice the persistent increase in the AAPC among the age group 40–49 and males in the age group 30–39. One can also observe the increase in the AAPC among males in almost all age groups. In general, men have a higher increase in AAPC than women (**Table 5** and **Figure 2**), with the highest increase observed in men aged 50–54. Lastly, **Figure 3** shows the geographic distribution of age-standardized incidence rates across Saudi Arabia. The region of Riyadh and the Eastern province had the highest rates, while the regions of Jizan and Najran had the lowest rates in 2016.

Lastly, the supplementary materials show the comparison in incidence rate trends between colon and cancer patients by age at diagnosis (<50 *vs.* 50+ years old). Overall, there has been a significant increase in the rates of colon cancer especially in 50+ years old patients, with a slower increase in patients with rectal cancer diagnosis (**Supplementary Figures**).

DISCUSSION

The present study was designed to elucidate the magnitude and direction of CRC incidence rate trends by age and gender in the Saudi population. We found that both the early- and late-onset CRC incidence rates have been increasing during the past years,

TABLE 5 | The average annual percentage change in colorectal cancer incidence rates, number of cases, and population at risk of colorectal cancer by gender and age, Saudi Arabia, 2001–2016.

Age group	2001–2016			2007–2016			2012–2016		
	AAPC, (95% CI)	Cases	At risk	AAPC, (95% CI)	Cases	At risk	AAPC (95% CI)	Cases, n	At risk, n
20–29									
Male	2.24 (-2.6, 7.3)	213	19496153	-5.97 (-10.62, -1.09)	166	12770676	-10.86 (-12.74, -8.95)	79	6698712
Female	-0.15 (-3.9, 3.7)	203	26917804	-1.51 (-8.98, 6.58)	140	17983467	-0.15 (-3.85, 3.69)	71	9394870
Total	0.61 (-2.4, 3.7)	417	46413957	-3.94 (-7.90, 0.20)	306	30754143	-6.30 (-23.79, 15.20)	150	16093582
30–39									
Male	4.16 (2.6, 5.7)	614	18202883	2.45 (0.20, 4.75)	451	11787983	3.11 (-7.92, 15.46)	247	6118127
Female	0.44 (-1.4, 2.3)	655	20040987	0.14 (-2.85, 3.21)	465	13849503	0.44 (-1.43, 2.35)	256	7622327
Total	0.85 (-0.7, 2.4)	1268	38243870	-0.18 (-2.05, 2.47)	916	25637486	6.05 (0.83, 11.53)	503	13740454
40–49									
Male	6.0 (4.8, 7.2)	1340	16503235	5.59 (3.19, 8.05)	998	10642711	6.04 (0.43, 11.95)	557	5249650
Female	2.6 (1.1, 4.2)	1391	13315700	-1.95 (-3.80, -0.06)	1057	9388325	2.62 (1.08, 4.18)	565	5328800
Total	3.3 (0.6, 6.0)	2731	29818935	-1.17 (-4.17, 1.93)	2055	20031036	1.11 (-12.15, 16.38)	1122	10578450
50–54									
Male	14.40 (6.0, 23.6)	971	14271149	18.85 (6.78, 32.29)	786	9353314	38.84 (0.59, 91.63)	468	4284658
Female	4.04 (1.4, 6.8)	946	4565216	1.48 (-2.48, 5.61)	762	3313250	4.04 (1.38, 6.78)	441	1893713
Total	5.9 (-1.8, 14.2)	1917	18836365	1.96 (-1.65, 5.69)	1548	12666564	5.52 (-8.83, 22.12)	909	6178371
55–59									
Male	13.40 (4.4, 23.2)	1117	13134994	20.49 (15.20, 26.02)	899	9041816	33.27 (-7.81, 92.66)	581	4329919
Female	3.79 (1.8, 5.9)	873	3425455	1.47 (-2.12, 5.19)	691	2465862	3.79 (1.76, 5.85)	413	1439765
Total	6.6 (1.4, 12.0)	1990	16560449	2.79 (0.74, 4.87)	1590	11507678	3.63 (-3.02, 10.74)	994	5769684
60–64									
Male	12.0 (3.6, 21.2)	1054	11542310	20.67 (13.05, 28.81)	794	7912660	44.62 (-19.98, 161.35)	492	3892314
Female	3.78 (1.9, 5.7)	873	2636916	3.42 (0.29, 6.64)	660	1837727	3.78 (1.88, 5.72)	402	1054044
Total	6.1 (2.0, 10.4)	1927	14179226	2.91 (0.80, 5.06)	1454	9750387	5.40 (-4.62, 16.47)	894	4946358
65–69									
Male	5.5 (-0.6, 11.9)	1030	9740352	9.20 (-4.30, 24.61)	773	6821321	41.35 (-25.54, 168.35)	403	3390723
Female	3.27 (-0.1, 6.8)	725	1879501	2.07 (-1.986.29),	557	1327576	3.27 (-0.12, 6.77)	334	753261
Total	5.2 (1.8, 8.8)	1755	11619853	-0.97 (-3.81, 1.96)	1330	8148897	1.13 (-6.23, 9.07)	737	4143984
70–74									
Male	14.2 (6.5, 22.5)	933	8233623	23.88 (18.66, 29.34)	713	5744946	56.25 (-30.29, 250.22)	436	2921751
Female	6.0 (2.5, 9.6)	601	1399651	0.07 (-3.51, 3.78)	468	926243	6.01 (2.52, 9.63)	267	514943
Total	8.5 (5.1, 12.1)	1534	9633274	3.83 (1.71, 6.0)	1181	6671189	-0.02 (-6.99, 7.46)	703	3436694
75+									
Male	12.0 (5.1, 19.5)	1374	7002390	17.22 (9.06, 25.99)	1081	4860583	48.44 (-21.01, 178.93)	633	2515466
Female	3.27 (0.7, 5.9)	914	1884621	0.74 (-4.03, 5.75)	705	1323235	3.27 (0.75, 5.86)	397	726320
Total	7.0 (2.6, 11.6)	2288	8887011	2.45 (-1.14, 6.18)	1786	6183818	4.53 (-10.71, 22.36)	1030	3241786

with the steepest increase in the age group 40–49. While there is a lack of local and regional incidence rate trends data, one study estimated the APC during 1999 and 2003 in the Saudi population (21). Authors found significant increases in APC among males (20.5% during 1999–2003) and a non-significant increase among females (6.06% during 2001–2003). Our regression models showed comparable results in males (18.01% during 2001–2005) and females (12.30% during 2001–2006). Taken together, local data suggest increases in all age groups with a more pronounced increase in males.

Similarly, international studies have shown increases in CRC incidence rates among the younger age group. Although CRC is frequently diagnosed in the elderly population (22), data from different countries have shown an alarming increase in the incidence of early-onset CRC amongst men and women (23–25). Between 2008 and 2012, the AAPC in the incidence of early-onset CRC was documented at 4, 2.8, 2.8, and 2.2% in New Zealand, Canada, Australia, and the USA, respectively (3). As indicated above, there is limited data reported on this subject in the GCC countries. For instance, a limited analysis of 387 CRC cases in the United Arab Emirates (UAE) diagnosed in 2015 reported that 41.9% were diagnosed at an age younger than 50 years (26). Only less than one-third of the population from this analysis were UAE nationals. Given the small number of patients, and the heterogeneity of the reported population, it may be difficult to draw conclusions about the trends of early-onset CRC.

Unlike other countries where the incidence of late-onset CRC has declined or remained stable (27), we have shown that the incidence of late-onset CRC in Saudi Arabia continued to rise. Moreover, less than one-third of Saudi patients were diagnosed with localized disease (14). This is likely related to the lack of an effective national screening program for CRC. Our analysis showed that there is an incremental increase of both early- and late-onset CRC. The AAPC of early-onset CRC in our report is comparable to western populations.

As we have shown, increases in incidence rates amongst young individuals (<50 years) have not been the same between the colon and rectal cancer cases in Saudi Arabia. The degree of increase has been less for rectal cancer when compared with colon cancer cases (**Supplementary Figures**). This is, in part, maybe due to differences

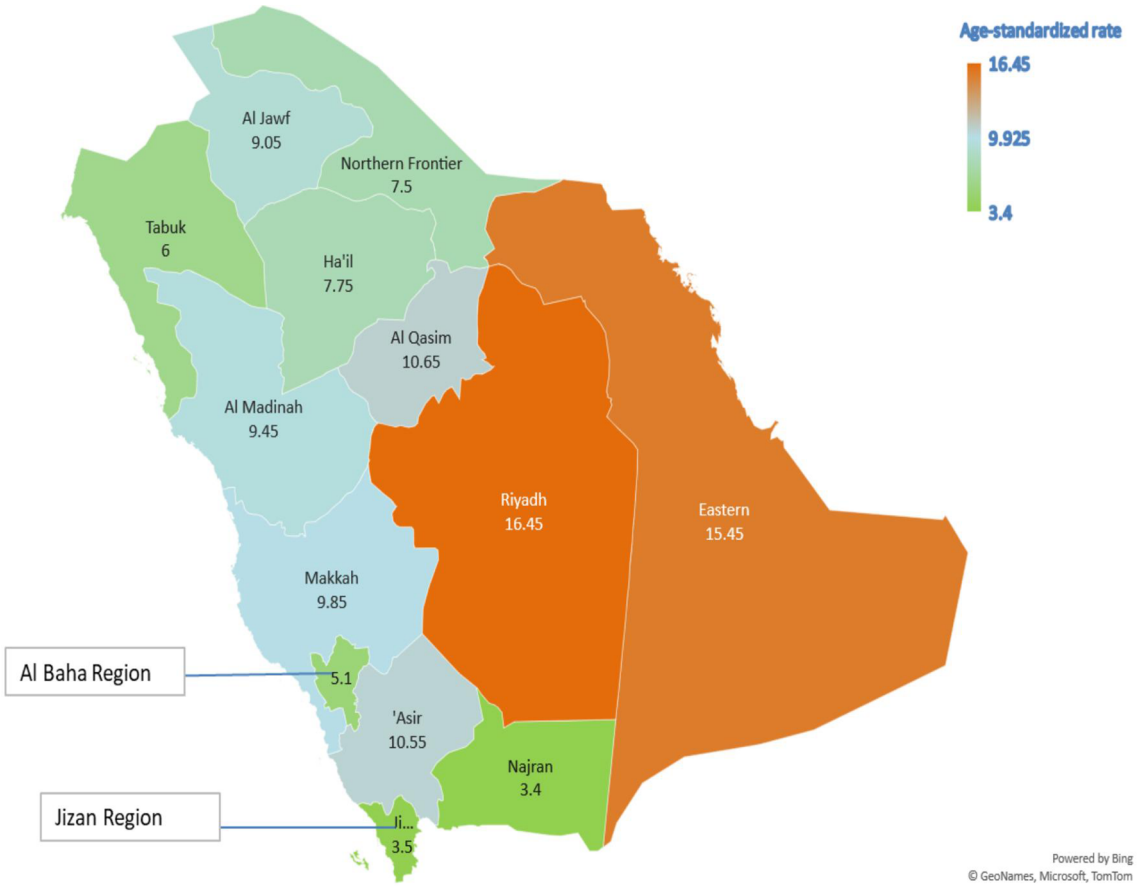

FIGURE 3 | The geographic distribution of the age-standardized incidence rates per 10^5 population, Saudi Arabia 2016.

in risk factors with certain ones affecting colon rather than rectal cancer. Dietary changes, lack of physical activity, and alcohol intake are known and established risk factors for colon cancer, but not for rectal cancer (28). Obesity was also shown in a meta-analysis to be a risk factor for colon cancer; however, this association was not seen in women with rectal cancer (29). Obesity during childhood has been associated with the increase in early-onset CRC (30). Furthermore, the observation of differences between colon and rectal cancer rates was also reported by a large study on a European population by Vuik and colleagues (19).

Trends in CRC incidence rates in Saudi Arabia reported in this study are in line with what has been reported by other studies in USA (31), Europe (19), and the UAE (26). These results have major implications on our population, healthcare system, and other involved stakeholders. This increase in early-onset CRC resulted in major oncology societies like the American Cancer Society, in 2018, lowering the age for screening for CRC to the age of 45 years (32). The results of their modeling assumed that screening those between the ages of 45–50 would have a preventive effect just as screening those above 50 years of age. Their analyses showed that this will result in a reduction in incidence and mortality, and that benefit-burden balance is favoring screening this younger group. More recently, the USPSTF recommended that adults from the age of 45 years get screened for CRC. Targeting this younger population is therefore important in our population.

Moving forward with establishing a national screening program with a special focus on young-onset CRC is essential. A large survey of more than 1000 young-onset CRC patients reported that more than half were diagnosed at a later stage (stages III & IV), needed more time to be diagnosed, and visited more than two physicians before a correct diagnosis of CRC was made (33). Therefore, education of health care providers on being vigilant and aware of signs and symptoms of CRC regardless of age is crucial. This needs engagement from health agencies, medical societies, and perhaps media in a collaborative national effort to address the needs of this vulnerable group of young-onset CRC patients. Studying and, more importantly, addressing modifiable risk factors of early-onset CRC such as obesity, diet, and lack of exercise are needed. Furthermore, a comprehensive survivorship cancer care and availability of genetic testing are needed to improve the care of young patients with CRC.

One of the strengths of the present study is the use of SCR, which is based on all regions of Saudi Arabia and is therefore

representative and generalizable to the Saudi population. Moreover, the current study leveraged the lengthy period of data collection which includes all CRC cases in Saudi Arabia and thus utilized the latest available 16 years of CRC data, the longest studied period in CRC Saudi patients. In addition to the strengths, several limitations should be considered when interpreting the results of our study. First, the current study lacks tumor-sidedness data which has prognostic value, and also lacks molecular characterization of tumors. These variables are not available in the original data source and therefore were not investigated. Second, we were unable to assess patient-level information, which includes variables such as education, income, and other sociodemographic variables because our analysis was based on aggregate data. Nonetheless, aggregate data are very useful for assessing trends in cancer rates (34). Third, patients, especially residents of remote/rural areas, are referred to a tertiary hospital in major cities for cancer care and could be a potential source of referral bias, which might result in underestimation of cases in remote areas. Nevertheless, this kind of selection bias is less likely to affect the findings of the present study given the case ascertainment method implemented by the SCR (35). Fourth, we lack contemporary data (2017–2019) in this study because the year 2016 is the latest available year reported by the SCR. Lastly, our data show an increase in CRC during the year 2016 compared to earlier years. The sudden increase in incidence rate could be due to the implementation of opportunistic CRC (*vs.* organized or population-based) screening, after the initial publication of CRC guidelines in 2015 (36).

CONCLUSION

Both early-onset and late-onset CRC are increasing in Saudi Arabia. For early-onset CRC, primary health care providers must be alerted about the increasing rate and should possibly investigate the cancer family history in the younger population, especially in Saudis aged 30–49 years who had the highest increase in CRC incidence. Additionally, national efforts directed to prevention measures such as CRC screening are warranted.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://nhic.gov.sa/eServices/Pages/TumorRegistration.aspx.

AUTHOR CONTRIBUTIONS

MeA designed the study, analyzed the data, discussed the results, and wrote the manuscript. MoA and KA discussed the results, searched the literature, wrote the manuscript, and collected data. All authors approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.730689/full#supplementary-material

REFERENCES

1. International Agency for Research on Cancer. *Globocan 2020: Cancer Fact Sheets — Colorectal Cancer*. IARC (2020). Available at: https://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf.
2. Wang DY, Thrift AP, Zarrin-Khameh N, Wichmann A, Armstrong GN, Thompson PA, et al. Rising Incidence of Colorectal Cancer Among Young Hispanics in Texas. *J Clin Gastroenterol* (2017) 51:34–42. doi: 10.1097/MCG.0000000000000563
3. Siegel RL, Torre LA, Soerjomataram I, Hayes RB, Bray F, Weber TK, et al. Global Patterns and Trends in Colorectal Cancer Incidence in Young Adults. *Gut* (2019) 68:2179–85. doi: 10.1136/gutjnl-2019-319511
4. Ahnen DJ, Wade SW, Jones WF, Sifri R, Silveiras JM, Greenamyer J, et al. The Increasing Incidence of Young-Onset Colorectal Cancer: A Call to Action. *Mayo Clin Proc* (2014) 89:216–24. doi: 10.1016/j.mayocp.2013.09.006
5. Bailey CE, Hu CY, You YN, Bednarski BK, Rodriguez-Bigas MA, Skibber JM, et al. Increasing Disparities in the Age-Related Incidences of Colon and Rectal Cancers in the United States, 1975-2010. *JAMA Surg* (2015) 150:17–22. doi: 10.1001/jamasurg.2014.1756
6. Abdelsattar ZM, Wong SL, Regenbogen SE, Jomaa DM, Hardiman KM, Hendren S. Colorectal Cancer Outcomes and Treatment Patterns in Patients Too Young for Average-Risk Screening. *Cancer* (2016) 122:929–34. doi: 10.1002/cncr.29716
7. General Authority for Statistics. *Demographic Survey*. Riyadh, Saudi Arabia: General Authority for Statistics (2016). Available at: https://www.stats.gov.sa/sites/default/files/en-demographic-research-2016_2.pdf.
8. World Health Organization. *World Health Organization - Noncommunicable Diseases (Ncd) Country Profiles, 2018*. Geneva, Switzerland: World Health Organization (2018). Available at: https://www.who.int/nmh/countries/sau_en.pdf?ua=1.
9. Keum N, Giovannucci E. Global Burden of Colorectal Cancer: Emerging Trends, Risk Factors and Prevention Strategies. *Nat Rev Gastroenterol Hepatol* (2019) 16:713–32. doi: 10.1038/s41575-019-0189-8
10. Liu PH, Wu K, Ng K, Zauber AG, Nguyen LH, Song M, et al. Association of Obesity With Risk of Early-Onset Colorectal Cancer Among Women. *JAMA Oncol* (2019) 5:37–44. doi: 10.1001/jamaoncol.2018.4280
11. Alyabsi M, Ramadan M, Algarni M, Alshammari K, Jazieh AR. The Effect of Marital Status on Stage at Diagnosis and Survival in Saudis Diagnosed With Colorectal Cancer: Cancer Registry Analysis. *Sci Rep* (2021) 11:8603. doi: 10.1038/s41598-021-88042-9
12. Alyabsi M, Sabatin F, Jazieh AR. The Outcome of Unscreened Population in Colorectal Cancer: The Impact of Sex and Other Determinants on Cancer Stage. *Cancer Manag Res* (2020) 12:12319–27. doi: 10.2147/CMAR.S268823
13. Alyabsi M, Alhumaid A, Allah-Bakhsh H, Alkelya M, Aziz MA. Colorectal Cancer in Saudi Arabia as the Proof-of-Principle Model for Implementing Strategies of Predictive, Preventive, and Personalized Medicine in Healthcare. *EPMA J* (2020) 11(1):119–31. doi: 10.1007/s13167-019-00186-x

14. Almatroudi A. The Incidence Rate of Colorectal Cancer in Saudi Arabia: An Observational Descriptive Epidemiological Analysis. *Int J Gen Med* (2020) 13:977–90. doi: 10.2147/IJGM.S277272
15. Crosbie AB, Roche LM, Johnson LM, Pawlish KS, Paddock LE, Stroup AM. Trends in Colorectal Cancer Incidence Among Younger Adults-Disparities by Age, Sex, Race, Ethnicity, and Subsite. *Cancer Med* (2018) 7:4077–86. doi: 10.1002/cam4.1621
16. Ballester V, Rashtak S, Boardman L. Clinical and Molecular Features of Young-Onset Colorectal Cancer. *World J Gastroenterol* (2016) 22:1736–44. doi: 10.3748/wjg.v22.i5.1736
17. U.S. Preventive Services Task Force. *Final Recommendation Statement: Colorectal Cancer: Screening*. United States: U.S. Preventive Services Task Force (2021). Available at: https://uspreventiveservicestaskforce.org/uspstf/recommendation/colorectal-cancer-screening.
18. Jacobs D, Zhu R, Luo J, Grisotti G, Heller DR, Kurbatov V, et al. Defining Early-Onset Colon and Rectal Cancers. *Front Oncol* (2018) 8:504. doi: 10.3389/fonc.2018.00504
19. Vuik FE, Nieuwenburg SA, Bardou M, Lansdorp-Vogelaar I, Dinis-Ribeiro M, Bento MJ, et al. Increasing Incidence of Colorectal Cancer in Young Adults in Europe Over the Last 25 Years. *Gut* (2019) 68:1820–6. doi: 10.1136/gutjnl-2018-317592
20. US Department of Health and Human Services. *National Cancer Institute. Joinpoint Trend Analysis Software*. (2019). Available at: https://surveillance.cancer.gov/joinpoint/ Accessed on May 23, 2021.
21. Ibrahim EM, Zeeneldin AA, El-Khodary TR, Al-Gahmi AM, Sadiq BMB. Past, Present and Future of Colorectal Cancer in the Kingdom of Saudi Arabia. *Saudi J Gastroenterol* (2008) 14:178. doi: 10.4103/1319-3767.43275
22. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, et al. Colorectal Cancer Statistics, 2020. *CA: Cancer J Clin* (2020) 70(3):145–64. doi: 10.3322/caac.21590
23. Lui RN, Tsoi KK, Ho JM, Lo CM, Chan FC, Kyaw MH, et al. Global Increasing Incidence of Young-Onset Colorectal Cancer Across 5 Continents: A Joinpoint Regression Analysis of 1,922,167 Cases. *Cancer Epidemiol Prev Biomarkers* (2019) 28:1275–82. doi: 10.1158/1055-9965.EPI-18-1111
24. El Din KS, Loree JM, Sayre EC, Gill S, Brown CJ, Dau H, et al. Trends in the Epidemiology of Young-Onset Colorectal Cancer: A Worldwide Systematic Review. *BMC Cancer* (2020) 20:1–14. doi: 10.1186/s12885-020-06766-9
25. Meester RG, Mannalithara A, Lansdorp-Vogelaar I, Ladabaum U. Trends in Incidence and Stage at Diagnosis of Colorectal Cancer in Adults Aged 40 Through 49 Years, 1975-2015. *Jama* (2019) 321:1933–4. doi: 10.1001/jama.2019.3076
26. Humaid O, Al-Shamsi AAA, Hassan A, Abu-Gheida I, Alrawi S. Early Onset Colorectal Cancer in the United Arab Emirates, Where do We Stand? *Acta Sci Med Sci* (2020) 4:24–7. doi: 10.31080/ASCB.2020.04.0267
27. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. Colorectal Cancer Incidence Patterns in the United States, 1974–2013. *JNCI: J Natl Cancer Institute* (2017) 109(8). doi: 10.1093/jnci/djw322
28. Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, et al. Comparison of Risk Factors for Colon and Rectal Cancer. *Int J Cancer* (2004) 108:433–42. doi: 10.1002/ijc.11540
29. Larsson SC, Wolk A. Obesity and Colon and Rectal Cancer Risk: A Meta-Analysis of Prospective Studies. *Am J Clin Nutr* (2007) 86:556–65. doi: 10.1093/ajcn/86.3.556
30. Keum N, Giovannucci E. Global Burden of Colorectal Cancer: Emerging Trends, Risk Factors and Prevention Strategies. *Nat Rev Gastroenterol Hepatol* (2019) 16(12):713–32. doi: 10.1038/s41575-019-0189-8
31. Siegel RL, Jakubowski CD, Fedewa SA, Davis A, Azad NS. Colorectal Cancer in the Young: Epidemiology, Prevention, Management. *Am Soc Clin Oncol Educ Book* (2020) 40:1–14. doi: 10.1200/EDBK_279901
32. Macrae FA. Colorectal Cancer: Epidemiology, Risk Factors, and Protective Factors. *Uptodate com [ažurirano 9. lipnja 2017* (2016).
33. Yarden RI, Newcomer KL, Board NTYA. Young Onset Colorectal Cancer Patients are Diagnosed With Advanced Disease After Multiple Misdiagnoses. *AACR Annu Meeting* (2019). doi: 10.1158/1538-7445.AM2019-3347
34. Ingram DD, Malec DJ, Makuc DM, Kruszon-Moran D, Gindi RM, Albert M, et al. National Center for Health Statistics Guidelines for Analysis of Trends. *Vital Health Stat 2 Data Eval Methods Res* (2018) (179):1–71.
35. Saudi Cancer Registry. *Annual Report* (2016). Available at: https://nhic.gov.sa/en/eServices/Documents/2016.pdf.
36. Alsanea N, Almadi MA, Abduljabbar AS, Alhomoud S, Alshaban TA, Alsuhaibani A, et al. National Guidelines for Colorectal Cancer Screening in Saudi Arabia With Strength of Recommendations and Quality of Evidence. *Ann Saudi Med* (2015) 35:189–95. doi: 10.5144/0256-4947.2015.189

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The Incidence Rate and Risk Factors of Malignancy in Elderly-Onset Inflammatory Bowel Disease: A Chinese Cohort Study From 1998 to 2020

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Background: Patients suffering from inflammatory bowel disease (IBD) have an increased risk of cancer. However, the risk of malignancy in patients with elderly-onset IBD (≥60 years) remains controversial. Hence, we aimed to identify and compare the dissimilarities in morbidity and related risk factors between patients with elderly-onset and adult-onset (18–59 years) IBD in a Chinese cohort.

Methods: Patients with confirmed IBD, diagnosed at age ≥18 years, between January 1998 and December 2020 at the Peking Union Medical College Hospital were enrolled. The yearly incidence rates (IRs) for cancer were calculated, and the characteristics were analyzed in these patients.

Results: A total of 1,480 patients suffering from adult-onset IBD and 129 patients suffering from elderly-onset IBD with a median follow-up period of 4.9 years and 4.8 years, respectively, were included. Patients in the elderly-onset IBD group demonstrated an increased overall incidence of cancer than that demonstrated by patients in the adult-onset group (IR 26.9 versus 9.51, respectively, per 1,000 person-years; relative risk [RR], 2.83). Colorectal cancer was the most common malignancy in the two groups, and patients suffering from elderly-onset IBD demonstrated a higher incidence of the malignancy (IR, 7.07 versus 3.34, respectively, per 1,000 person-years; RR, 2.12). Among the extraintestinal cancers, hematological malignancies and urinary tract cancers (including renal and urinary bladder carcinoma) were common in the elderly-onset group (IR, 4.24 and 4.24 per 1,000 person-years, respectively), whereas thyroid cancer was more common in the adult-onset group (IR, 1.36 per 1,000 person-years). Analysis of clinical characteristics revealed that patients with elderly-onset IBD who developed cancer were more likely to have diabetes and urinary lithiasis (p = 0.041 and 0.035, respectively). In addition, patients in the elderly-onset group had a shorter course from IBD to cancer, less exposure to immunosuppressants, less extraintestinal manifestations, and higher cancer-related mortality. Cox proportional risk regression

analysis in the elderly-onset IBD group revealed that diabetes was an independent risk factor for the progression to cancer (hazard ratio [HR], 12.53 [2.379–65.994], $P = 0.003$).

Conclusion: The risk of malignancy in patients suffering from elderly-onset IBD increased significantly as compared with those with adult-onset disease. Therefore, cancer monitoring should be initiated earlier for patients in the elderly-onset group.

Keywords: elderly-onset inflammatory bowel disease, incidence rate, malignancies, risk factor, cohort study

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is widely accepted as a chronic inflammatory disorder of the intestine. IBD has a bimodal age of onset, with one peak between 20 and 40 years of age and another between 60 and 70 years. Diagnosis at age ≥60 years is considered elderly-onset IBD and constitutes 10%–15% of the total number of IBD cases (1). The incidence rate of elderly-onset IBD has been reported as 4–8/100,000 person-years (2). However, with the aging population in China, the burden and incidence of elderly-onset IBD continue to rise. Data obtained from Hong Kong revealed that the incidence of elderly-onset UC increased from 0.1 per 100,000 persons (before 1991) to 1.3 per 100,000 persons after 2010 (3, 4). In addition, it is known that the clinical characteristics of the patients suffering from elderly-onset and adult-onset IBD (18–59 years) are not always consistent. However, sufficient attention has not been paid to elderly-onset IBD owing to its relatively lower incidence in China.

IBD, as a chronic disease, is prone to be associated with various comorbidities and/or complications throughout its course. A study conducted in Canada reported that 785.6 per 100,000 patients with IBD developed malignancies each year (5). The factors associated with IBD-related malignancies include the location of the lesion, duration, medications, and special comorbidities. Patients with IBD are especially at an elevated risk of developing colitis-associated cancers, which are related to the extent of inflammation, severity, and course of the disease (6). Studies have demonstrated that chronic inflammatory conditions can lead to malignancies even in other organs (7). In addition, IBD-related therapeutic drugs may alter the immune status, which in turn has a profound impacts on tumorigenesis. For example, azathioprine and anti-TNFα biologics have been mentioned to be a risk factor for hematologic malignancies in patients suffering from IBD (8, 9). Recent studies have shown that certain comorbidities including primary sclerosing cholangitis, chronic kidney disease, respiratory disease, and diabetes mellitus are associated with carcinogenesis in IBD patients (HR, 2.43; OR = 1.29, 1.07, and 1.06, respectively) (5, 10). The high risk of malignancy in patients with IBD has been reported as SIR of 1.2–1.6 (11–13). Data obtained from Hong Kong revealed a significant increase in the incidence of colorectal cancer in patients of elderly-onset UC as compared with those of non-elderly onset UC (0.9% versus 3.2%, respectively, $p = 0.033$) (3). There is evidence that clinical characteristics including complications and medications used differ between patients suffering from elderly-onset and non-elderly-onset IBD. In addition, a study reported that later onset of IBD was associated with a higher risk of early colorectal cancer (14). However, recent cohort studies conducted in the Western populations have shown that elderly-onset IBD only leads to an increased risk of extraintestinal tumors (7, 15), and there is no difference in the risk of colorectal cancer compared to patients with adult-onset disease. Furthermore, studies have shown that corticosteroids increase the cancer risk in patients of elderly-onset IBD (16, 17).

IBD is an emerging disease, the incidence of which is increasing rapidly in China, and several patients are developing complications, including cancer. It is known that elderly patients are vulnerable to cancer. Therefore, research on the incidence and risk factors of malignancy in China is essential to develop preventive strategies and contribute to the global data. The differentiation between elderly patients with IBD and those with elderly-onset IBD has been suboptimal in previous studies. Here, we attempted to identify the dissimilarities in the incidence of cancer between patients with elderly-onset IBD and adult-onset IBD in a Chinese cohort. We aimed to provide information to develop cancer-monitoring strategies in patients of elderly-onset IBD.

METHODS

Study Design

All data for this cohort study were obtained from the medical documents, telephonic follow-up records, and the National Central Cancer Registry database from January 1998 to December 2020 of patients diagnosed with or hospitalized for the treatment of IBD at the Peking Union Medical College Hospital. The Ethics Review Committee of the Peking Union Medical College Hospital approved this study.

Study Population

Inclusion criteria: (1) patients diagnosed with IBD (UC and CD) based on the third European Crohn's and Colitis Organization consensus guidelines and (2) IBD diagnosed at age ≥18 years.

Exclusion criteria: (1) patients with a history of malignancy before the diagnosis of IBD; (2) patients with a previous history of a specific autoimmune disease; the reason for exclusion was baseline claims for biologics, immunomodulators, or corticosteroids; (3) patients with unclassified IBD were excluded owing to unclassified disease severity and extent; and (4) patients without ≥1 day of follow-up. Patients were regularly (at least once a year for

most patients) followed up, from the date of diagnosis of IBD until the outcome occurrence, death, or terminal point of the study (June 2021).

Data Collection

Patients with cancer occurring after the diagnosis of IBD and during follow-up were included. The retrospectively collected data at diagnosis included sex, age at IBD diagnosis, type of IBD, disease extent, the behavior of CD, intestinal complications (including fistula, stenosis, obstruction, perforation, bleeding, abdominal abscess, perianal lesions, and toxic megacolon), extraintestinal manifestations (oral ulcers, skin lesions, joint lesions, ocular lesions, fatty liver, cholelithiasis, and thrombotic disease), comorbidities (diabetes mellitus, urolithiasis, hypertension, coronary heart disease, myocardial infarction, and heart failure), and a history of alcohol abuse and smoking. The data recorded during follow-up included drug exposure (5-aminosalicylic acid, glucocorticoids, azathioprine, methotrexate, thalidomide, and biologics), the outcome of cancer, age at diagnosis of cancer, and cause of death.

Outcome Measures

The time to the diagnosis of cancer was the primary outcome measure. The diagnosis of cancer was based on pathological features. The date of diagnosis, type of cancer, affected organ, and histological type were recorded.

The incidence of cancer and mortality was estimated as the incidence densities, which were calculated as the number of new cancer cases or death divided by the number of patient-years (18). The incidence of cancer between 1998 and 2008 has been presented as the accumulated incidence rate considering the small number of enrolled cases and cancer cases. The annual incidence of cancer for the entire cohort was the ratio of the number of new cancer cases (from January 1 to December 31 of each year) to the number of person-years at risk (5), which were calculated for the eligible patients from January 1 to the last data collection, cancer occurrence, death, or endpoint of the year (December 31) (18). Poisson regression was used to measure the annual incidence rates of cancer in the adult-onset and elderly-onset groups, which have been presented graphically as 3-year centered moving averages from 2009 to 2019 (5).

Statistical Analysis

Data are presented as means and standard deviations (SD), medians and interquartile ranges (IQRs), or frequencies and percentages. IBM SPSS version 21 (Armonk, NY, USA) and GraphPad Prism version 7.0 (San Diego, CA, USA) were used for data analyses. The Mann–Whitney *U* test or Fisher's exact test was performed to analyze differences between the two groups. Cox regression and logistic regression analysis were used for multivariate analysis.

RESULTS

Cohort Description

A total of 1,863 patients with confirmed IBD from January 1998 to December 2020 were identified, and 254 cases were excluded according to the aforementioned criteria (**Figure 1**). Finally, 1,609 patients were included (1,065 with UC and 544 with CD), and the total follow-up summation was 8,799.94 person-years. Patients were categorized into the adult-onset IBD (18–59 years) or elderly-onset IBD (≥60 years) group based on their age at diagnosis, with the median follow-up of 4.9 years and 4.8 years, respectively, and the total follow-up duration of 8,092.9 years and 707.1 years, respectively. Among the 1,480 patients with adult-onset disease (966 with UC and 514 with CD) and 129 patients with elderly-onset disease (99 with UC and 30 with CD), the mean age at diagnosis of IBD was 35.5 (SD, 11.4) years and 65.2 (SD, 5.63) years ($p < 0.0001$), respectively, and men accounted for 59.1% and 65.1% of the cases, respectively. Moreover, 17.1% of the patients with elderly-onset IBD had a long-term history of smoking (>35 years), and 13.2% had a history of heavy drinking (>50 g/day on average for men and >25 g/day for women). Diabetes, hypertension, and coronary heart disease were more common among patients in the elderly-onset IBD ($p = 0.001$, <0.0001, and <0.0001, respectively), as shown in **Table 1**.

Incidence Trends of Malignancy in Patients With Elderly-Onset and Adult-Onset IBD

A total of 96 cancer cases occurred during the study (10.9 per 1,000 person-years; 95% confidence interval [CI], 8.9 to 13.3 per 1,000 person-years), including 77 cases in the adult-onset and 19 cases in the elderly-onset IBD groups. The incidence was significantly higher among patients in the elderly-onset group than in the adult-onset group (26.9 versus 9.51 per 1,000 person-years, respectively; RR, 2.83). Among the intestinal tumors, the incidence of colorectal cancer in the elderly-onset group was also higher than that in the adult-onset group (7.07 versus 3.34 per 1,000 person-years, respectively; RR, 2.12). In terms of extraintestinal cancers, thyroid cancer was the most common in patients with adult-onset IBD (14.3%, 1.36 per 1,000 person-years; 95% CI, 0.8–2.5 per 1,000 person-years), followed by hematological tumors and cervical malignancies (including cervical and endometrial cancers; 9.10%, 0.87 per 1,000 person-years; 95% CI, 0.4–1.8 per 1,000 person-years). However, hematological and urinary tract tumors (including kidney and bladder cancer) were the most common among patients in the elderly-onset IBD group (15.8%, 4.24 per 1,000 person-years; 95% CI, 1.4–12.3 per 1,000 person-years), as shown in **Table 2**. As no malignancy was recorded among patients with elderly-onset IBD from 1998 to 2008 (shown in **Supplementary Table 1**), the incidence rate of cancer between 1998 and 2008 has been presented as the accumulated incidence rate and annual incidence of malignancy in the two groups were analyzed from 2009 to 2019. As shown in **Figure 2**, the overall annual incidence of tumors in the elderly-onset IBD group was always above the morbidity in the adult-onset group. Further stratification of tumors showed that the incidence of extraintestinal cancers in the elderly-onset group was also beyond that of the adult-onset group (except in 2014) and showed an increasing trend after 2016. However, the incidence of intestinal tumors gradually decreased from 2015. The incidence of extraintestinal tumors in the adult-onset group

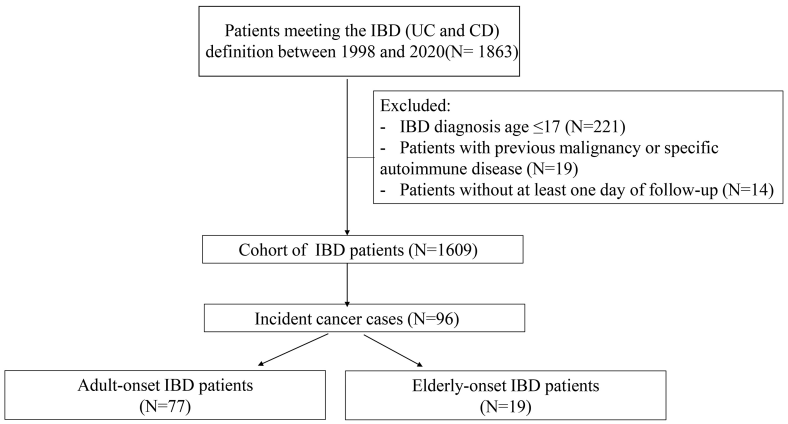

FIGURE 1 | Cohort definition and flowchart.

showed a decreasing trend; however, that of intestinal tumors showed an increasing trend after 2017, as shown in **Figure 3**.

Characteristics of IBD Patients Who Developed Malignancies

Univariate analysis of IBD and cancer cases revealed that the time from IBD onset to tumor development in the elderly-onset group was significantly shorter than that in the adult-onset group (4.28 ± 4.15 versus 12.1 ± 8.75, respectively, $p < 0.0001$). In addition, the cancer-related mortality rate was higher in the elderly-onset group than in the adult-onset group (8.45 versus 0.865 per 1,000 person-years; 31.5% versus 9.72%, respectively; $p = 0.007$). Patients with cancer in the elderly-onset IBD group had a long-term history of smoking (>35 years) than those in the adult-onset group (26.3% versus 5.2%, respectively, $p = 0.03$). Regarding comorbidities, the proportion of sufferers with diabetes or urinary calculi in the elderly-onset group was distinct compared with the adult-onset group (15.8% versus 2.6%, respectively; $p = 0.041$; 78.9% versus 53.2%, respectively; $p = 0.035$). Moreover, cancer cases in the elderly-onset group showed a significantly lower rate of

TABLE 1 | Patient characteristics of the cohort.

	Adult-onset IBD (Age 18–59)	Elderly-onset IBD (Age ≥60)	*p*-value
Total patients (*N*)	1,480	129	0.007
UC	966 (65.3)	99 (76.7)	
CD	514 (34.7)	30 (23.3)	
Sex, *N* (%)			0.219
Male	874 (59.1)	84 (65.1)	
Female	606 (40.9)	45 (34.9)	
Age at IBD diagnosis			<0.0001
Mean (SD)	35.5 (11.4)	65.2 (5.63)	
Follow-up time, years			0.985
Mean (SD)	5.46 (4.18)	5.46 (4.28)	
Median (IQR)	4.85 (5.36)	4.79 (6.19)	
Smoke duration, *N* (%)			<0.0001
Never	1,107 (74.8)	76 (58.9)	
<15 years	174 (11.8)	6 (4.65)	
15–35 years	163 (11.0)	25 (19.4)	
>35 years	36 (2.4)	22 (17.1)	
Drink, *N* (%)			<0.0001
Never	1,077 (72.8)	78 (60.5)	
Mild	271 (18.3)	25 (19.4)	
Moderate	65 (4.40)	9 (6.98)	
Severe	67 (4.50)	17 (13.2)	
Appendectomy history, *N* (%)	111 (7.50)	7 (5.43)	0.372
Comorbidities, *N* (%)			
Diabetes	63 (4.30)	14 (10.9)	0.001
Hypertension	125 (8.45)	55 (42.6)	<0.0001
Coronary disease	38 (2.57)	22 (17.1)	<0.0001
Urolithiasis	840 (56.8)	83 (64.3)	0.123

TABLE 2 | Distribution and incidence rates of malignancy among adult-onset and elderly-onset groups.

	Adult-onset IBD (Age 18–59)		Elderly-onset IBD (Age ≥60)	
	N (%)	Per 1,000 PYs [95% CI]	*N* (%)	Per 1,000 PYs [95% CI]
GI malignancies	32 (41.6)	3.95 [2.80–5.60]	8(42.1)	11.3 [5.70–22.1]
Colorectal cancer	27 (35.1)	3.34 [2.30–4.80]	5(26.3)	7.07 [3.00–16.5]
SBA	1 (1.30)	0.12 [0–0.70]	0	0
Appendiceal mucinous neoplasms	2 (2.60)	0.25 [0–0.80]	0	0
Hepatobiliary malignancy	2 (2.60)	0.25 [0–0.80]	3(15.8)	4.24 [1.4–12.3]
Lung cancer	5 (6.49)	0.62 [0.3–1.4]	2(10.5)	2.83 [0.80–10.2]
Urinary tract malignancy	5 (6.49)	0.62 [0.3–1.4]	3(15.8)	4.24 [1.4–12.3]
Hematological malignancy	7 (9.10)	0.86 [0.4–1.8]	3(15.8)	4.24 [1.4–12.3]
Thyroid cancer	11 (14.3)	1.36 [0.8–2.5]	0	0
Genital malignancy				
Female breast cancer	5 (6.49)	0.62 [0.3–1.4]	1(5.26)	1.41 [0.20–7.90]
Prostate cancer	1 (1.30)	0.12 [0–0.70]	2(10.5)	2.83 [0.80–10.2]
Uterus malignancy	7 (9.10)	0.87 [0.4–1.8]	0	0
Ovarian cancer	2 (2.60)	0.25 [0–0.80]	0	0
Others	2 (2.60)	0.25 [0–0.80]	0	0
Total	77 (100)	9.51 [7.6–11.9]	19(100)	26.9 [17.3–41.6]

PYs, patient-years; SBA, small bowel adenocarcinoma.

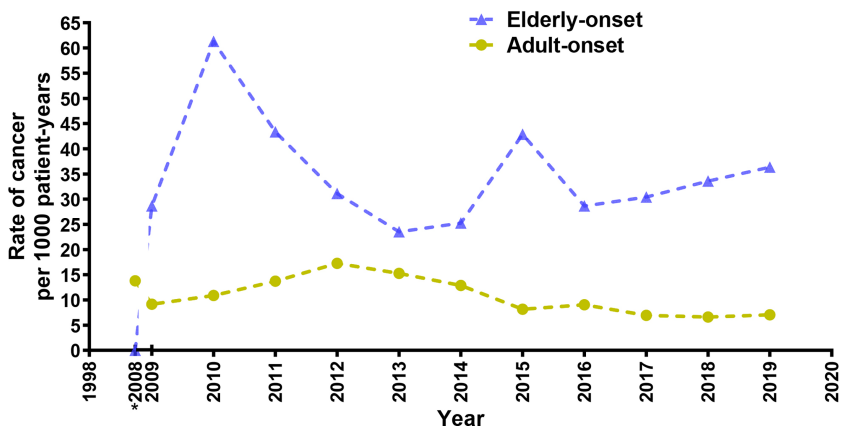

FIGURE 2 | Annual incidence rate of cancer for elderly-onset IBD and adult-onset IBD as a function of calendar time presented as 3-year moving averages from 2009 to 2019. *Accumulated incidence rate of cancer from 1998 to 2008.

extraintestinal manifestations, including joint pain and oral ulcers (0 versus 23.4%, respectively; $p = 0.003$; 0 versus 24.7%, respectively; $p = 0.002$), and the incidence of perianal lesions and intestinal obstruction was also significantly lower (0 versus 15.6%, respectively; $p = 0.017$; 0 versus 14.3%, respectively, $p = 0.03$). Regarding the medication history, the use of glucocorticoids, azathioprine, and thalidomide among cancer patients in the elderly-onset IBD group was not common ($p = 0.027$, 0.003, and 0.030, respectively), and the exposure rates of three or more IBD drugs were 0% versus 27.6%, respectively ($p = 0.001$), as shown in **Table 3**.

Risk Factors for Malignancy in Patients With Elderly-Onset IBD

We further explored the risk factors for malignancy among patients in the elderly-onset IBD using Cox regression analysis as well as multivariable logistic regression analysis adjusted for age, gender, and duration. As shown in **Figure 4** and **Supplementary Figure 1**, diabetes was a risk factor for the progression of elderly-onset IBD to malignancy (Adjusted HR, 12.53 [2.379–65.994], $p = 0.003$), whereas glucocorticoid use and the course of disease were protective factors against cancer (Adjusted HR, 0.194 [0.052–0.716], $p = 0.014$ and 0.764 [0.639–0.914], $p = 0.003$).

DISCUSSION

The present study focused on the incidence of malignancy in an IBD cohort in mainland China and presented several important findings. First, patients in the elderly-onset IBD group demonstrated a higher incidence of overall cancer development

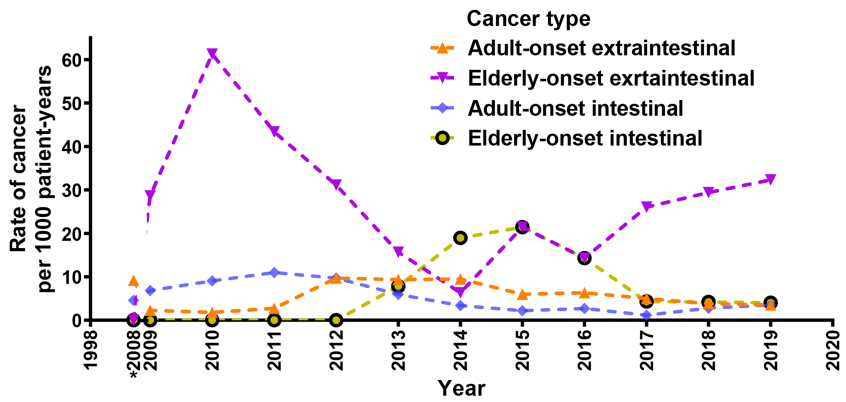

FIGURE 3 | Crude rates of elderly-onset IBD and adult-onset who developed intestinal or extra-intestinal cancers presented as 3-year moving averages from 2009 to 2019. *Accumulated incidence rate of cancer from 1998 to 2008.

as compared with those in the adult-onset group, especially for colorectal cancer, which was the most common malignancy in the two groups. Among the extraintestinal cancers, lymphoproliferative or myeloproliferative disorders and urinary tract cancers were the common malignancies among elderly-onset group, whereas thyroid cancer was more common in the adult-onset group. Second, the progression of elderly-onset IBD to malignancy demonstrated a shorter course and was associated with higher tumor-related mortality. Third, diabetes mellitus was an independent risk factor for elderly-onset IBD leading to malignancy, whereas glucocorticoid use was a protective factor. Therefore, considering the aging population in China, it is necessary to initiate tumor surveillance earlier in patients with elderly-onset IBD.

In this study, the overall morbidity of malignancies in the IBD cohort from 1998 to 2020 was 10.9 per 1,000 person-years (95% CI, 8.9–13.3 per 1,000 person-years), which is higher (2.85 per 1,000 person-years) than that reported in the Hong Kong cohort (2000–2016) (13). In addition, the incidence was marginally higher than that reported by Brassard P et al. in the Western IBD population (7.86 per 1,000 person-years; 95% CI, 7.54–8.19 per 1,000 person-years) (5). To determine whether elderly-onset IBD patients had an increased risk of developing cancer compared with non-IBD elderly population, standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) were calculated. Based on the national incidence rates from NCCR, we calculated the expected number of cancer cases according to gender, age, and calendar period in 1-year intervals, and compared it with the observed cancer cases from 1998 to 2020. Finally, we obtained the standardized incidence rate (SIR = 1.86 [1.063–3.021], $p = 0.031$), which further verified the role of elderly-onset IBD in increasing the overall incidence of cancer. Considering that the present study was conducted at one single center and was a hospital-based cohort, the incidence of IBD-associated malignancies could have been overestimated owing to selection bias. Therefore, a larger multicenter cohort study is required for further verification of the results. Following stratification by tumor type, IBD-related colorectal cancer constituted 33.3% of the cases, with an overall incidence of 3.6 per 1,000 person-years, which is similar to that reported in the Western countries (3.5 per 1,000 person-years) (19). Regarding extraintestinal tumors, hematological malignancies and thyroid cancer were the most common, and the high incidence of hematological malignancies in IBD is consistent with that reported in Denmark (20). Interestingly, in this cohort, all patients who developed thyroid cancer belonged to the adult-onset group. A previous large case–control study suggested that age was a protective factor against the progression of IBD to thyroid cancer (21). Radiation exposure at an early age has long been considered an independent risk factor for thyroid cancer (22). Therefore, the method of optimizing radiographical examination and reducing the incidence of thyroid cancer in young patients with IBD required further investigation. Previous studies in Western populations have reported an increased risk of extraintestinal cancers, especially prostate cancer, hematological malignancies, and skin cancer, in elderly patients with IBD (7, 15). However, the increased risk of colorectal cancer is controversial (14, 23). Our study suggested that the overall morbidity of cancer, including colorectal cancer and extraintestinal tumors (hematological, urinary, hepatobiliary, lung, prostate, and breast carcinomas), was greater in elderly-onset IBD than in adult-onset disease group (IR, 26.9 versus 9.51 per 1,000 person-years, respectively; RR, 2.83). Further analysis of the annual incidence of intestinal and extraintestinal carcinomas in both groups revealed that the incidence of parenteral tumors was higher in the elderly-onset group than in the adult-onset group. In terms of intestinal cancer, the incidence of colorectal cancer was also higher in the elderly-onset IBD group from 2013. However, the incidence started to decline after 2015 and gradually became similar to that in the adult-onset group in the last 3 years. The reason may be that colitis-associated colorectal cancer is related to the course of IBD, and the risk of malignancy in patients with adult-onset IBD is higher than that in elderly-onset patients. Therefore, the

TABLE 3 | Patient characteristics of adult-onset and elderly-onset IBD patients who developed a malignancy.

	Adult-onset IBD (Age 18–59)	Elderly-onset IBD (Age ≥60)	*p*-value
Total patients (*N*)	77	19	
Sex, *N* (%)			0.071
Male	39 (51.9)	14 (73.7%)	
Female	38 (48.1)	5 (26.3%)	
IBD diagnosis, *N* (%)			0.279
UC	61 (79.2)	17 (89.5)	
CD	16 (20.8)	2 (10.5)	
Age at IBD diagnosis			<0.0001
Mean (SD)	37.5 (10.6)	66.6 (4.06)	
Median(IQR)	37 (17.00)	66 (5.0)	
Duration of disease to cancer, years			<0.0001
Mean (SD)	12.1 (8.75)	4.28 (4.15)	
Median(IQR)	11.3 (12.3)	3.53 (3.39)	
Death, *N* (%)	8 (11.1)	7 (36.8)	0.007
Cancer-related death	7 (9.72)	6 (31.5)	
Others	1 (1.39)	1 (5.26)	
Family history of cancer	22 (28.6)	4 (21.1)	0.5
Smoke duration, *N* (%)			0.03
Never	61 (79.2)	13 (68.4)	
<15 years	7 (9.1)	0	
15–35 years	5 (6.5)	1 (5.3)	
>35 years	4 (5.2)	5 (26.3)	
Drink, *N* (%)	16 (20.8)	5 (26.3)	0.437
Appendectomy history, *N* (%)	6 (7.8)	0	0.098
Comorbidities, *N* (%)			
Diabetes	2 (2.6)	3 (15.8)	0.041
Hypertension	20 (26.3)	8 (42.1)	0.187
Coronary disease	6 (7.8)	4 (21.1)	0.117
Urolithiasis	41 (53.2)	15 (78.9)	0.035
IBD-related surgery, *N* (%)	12 (15.6)	4 (21.1)	0.576
Extra-intestinal manifestation			
Arthralgia	18 (23.4)	0	0.003
Oral ulcer	19 (24.7)	0	0.002
Eye lesion	4 (5.2)	0	0.179
Fatty liver	7 (7.8)	2 (10.5)	0.850
Cholelithiasis	6 (7.8)	2 (10.5)	0.707
Complication			
Bleeding	11 (14.3)	1 (5.3)	0.246
Perforation	4 (5.2)	0	0.179
Obstruction	11 (14.3)	0	0.03
Skin lesion, *N* (%)	4 (5.2)	0	0.179
Perianal lesion, *N* (%)	12 (15.6)	0	0.017
Medication exposure (ever exposed)			
5-ASA	71 (92.2)	18 (94.7)	0.694
Steroids	46 (59.7)	6 (31.6)	0.027
Thiopurines	18 (23.4)	0	0.003
Methotrexate	5 (6.50)	0	0.132
Thalidomide	10 (13.0)	0	0.030
Biologics	3 (3.90)	0	0.246
Multi-medication exposure*			0.001
0 medication	4 (5.2)	1 (5.3)	
1–2 medications	47 (65.5)	18 (93.3)	
3+ medications	26 (27.6)	0	

incidence of intestinal tumors in patients with younger-onset IBD may gradually increase with a longer follow-up period. Furthermore, we compared the incidence of cancer between patients in the young-onset (18–40 years old) and middle-age-onset (41–59 years old) groups; however, there was no significant difference (IR, 8.42 versus 11.8 per 1,000 person-years, respectively; $p = 0.164$) in the overall occurrence, as shown in **Supplementary Table 2**.

Analysis of clinical characteristics in the 96 cancer cases revealed that the time from IBD diagnosis to the development of malignancy was shorter, and the all-cause mortality was higher among patients in the elderly-onset group compared with that in the adult-onset group. Inflammation and aging are known to promote the development of tumors, and this synergistic effect is more significant in elderly patients with IBD, which leads to the rapid progression of carcinomas. Another interesting finding was

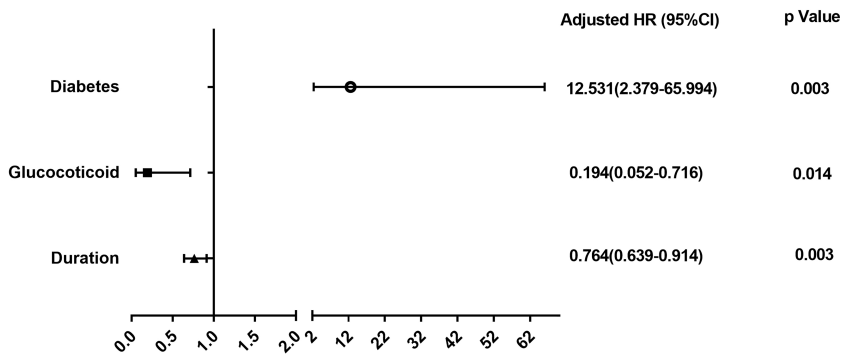

FIGURE 4 | Risk factors for overall cancer in elderly-onset IBD.

that the proportion of diabetes mellitus in the cancer cases from elderly-onset group was significantly higher than that in the cancer cases of adult-onset IBD. The analysis of risk factors in elderly patients with IBD showed that diabetes mellitus was an independent risk factor for the progression of IBD to cancer. A recent Canadian study also suggested that diabetes mellitus could increase the incidence of IBD-related cancer (OR = 1.06; 95% CI, 1.01–1.11) (5). The underlying mechanism may be related to inflammatory mediators including IL-6, IL-1α, and TNF-α, which not only promote epithelial–mesenchymal transition through activation of the Janus kinase/signal transducer and activator of trans-ions pathway but also increase the risk of type 2 diabetes (24). This partly explains the increased risk of colorectal cancer in patients suffering from elderly-onset IBD; however, more evidence is required to support the association between diabetes, IBD, and colorectal cancer. Previously, several studies focused on the role of drug use in the cancer risk of patients with IBD and reported that glucocorticoids increased the risk of cancer (18) and azathioprine increased the risk of lymphoproliferative or myeloproliferative disorders (9). However, our study found that glucocorticoid use was a protective factor against the progression of IBD to malignancy in the elderly-onset IBD group. We hypothesize that the treatment period and dose of glucocorticoids may account for the difference. In addition, our data revealed a lower utilization rate of immunosuppressive agents (including azathioprine and thalidomide) in the elderly IBD population; therefore, the role of azathioprine in promoting the occurrence of tumors in patients with elderly-onset IBD needs to be discussed further.

To the best of our knowledge, the current work is a large sample cohort study of tumorigenesis in patients with elderly-onset IBD in mainland China, which provides an in-depth and detailed analysis of tumor incidence and related risk factors. Our study supports the view that patients with elderly-onset IBD are at a greater risk of developing cancer as compared with those with a younger-onset disease. In addition, our study indicates that early tumor onset and higher tumor-related mortality occur in this population, providing strong evidence for early surveillance in patients suffering from elderly-onset IBD. In this study, Cox regression was used for multivariate analysis. In general, multivariate analysis can be conducted by logistic regression and Cox regression. So, we used the multivariable logistic regression analysis for further verification (shown in **Supplementary Figure 1**). Not surprisingly, both statistical methods confirmed that diabetes was a risk factor for cancer in elderly-onset IBD, whereas glucocorticoid use and the course of disease were protective factors. Considering that this is a dynamic cohort, the results obtained from Cox regression analysis are displayed in **Figure 4**. The chief limitation of this study lies in the single-center design, which was limited to the inpatients treated in the Peking Union Medical College Hospital. The included patients had a relatively wide range of lesions and severe disease activity, which may have led to selection bias. Therefore, the analysis of risk factors (such as diabetes) needs to be further verified in larger multi-center cohort studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Review Committee of the Peking Union Medical College Hospital (Ethics Review Number S-K1781). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

ZW finished the data collection, analyzed the data, and wrote the main manuscript. JQ designed the study and revised the manuscript. HZ, HY, and MZ participated in the data

collection and provided valuable suggestions. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.788980/full#supplementary-material

REFERENCES

1. Gisbert JP, Chaparro M. Systematic Review With Meta-Analysis: Inflammatory Bowel Disease in the Elderly. *Aliment Pharmacol Ther* (2014) 39(5):459–77. doi: 10.1111/apt.12616
2. Katz S, Pardi DS. Inflammatory Bowel Disease of the Elderly: Frequently Asked Questions (FAQs). *Am J Gastroenterol* (2011) 106(11):1889–97. doi: 10.1038/ajg.2011.271
3. Shi HY, Chan FK, Leung WK, Li MK, Leung CM, Sze SF, et al. Natural History of Elderly-Onset Ulcerative Colitis: Results From a Territory-Wide Inflammatory Bowel Disease Registry. *J Crohns Colitis* (2016) 10(2):176–85. doi: 10.1093/ecco-jcc/jjv194
4. Jeuring SF, van den Heuvel TR, Zeegers MP, Hameeteman WH, Romberg-Camps MJ, Oostenbrug LE, et al. Epidemiology and Long-Term Outcome of Inflammatory Bowel Disease Diagnosed at Elderly Age-An Increasing Distinct Entity? *Inflamm Bowel Dis* (2016) 22(6):1425–34. doi: 10.1097/MIB.0000000000000738
5. Loo SY, Vutcovici M, Bitton A, Lakatos PL, Azoulay L, Suissa S, et al. Risk of Malignant Cancers in Inflammatory Bowel Disease. *J Crohns Colitis* (2019) 13(10):1302–10. doi: 10.1093/ecco-jcc/jjz058
6. Danese S, Malesci A, Vetrano S. Colitis-Associated Cancer: The Dark Side of Inflammatory Bowel Disease. *Gut* (2011) 60(12):1609–10. doi: 10.1136/gutjnl-2011-300953
7. Cheddani H, Dauchet L, Fumery M, Charpentier C, Marie Bouvier A, Dupas JL, et al. Gower-Rousseau C. Cancer in Elderly Onset Inflammatory Bowel Disease: A Population-Based Study. *Am J Gastroenterol* (2016) 111(10):1428–36. doi: 10.1038/ajg.2016.304
8. Yadav S, Singh S, Harmsen WS, Edakkanambeth Varayil J, Tremaine WJ, Loftus EVJr. Effect of Medications on Risk of Cancer in Patients With Inflammatory Bowel Diseases: A Population-Based Cohort Study From Olmsted County, Minnesota. *Mayo Clin Proc* (2015) 90(6):738–46. doi: 10.1016/j.mayocp.2015.03.024
9. Khan N, Abbas AM, Lichtenstein GR, Loftus EVJr, Bazzano LA. Risk of Lymphoma in Patients With Ulcerative Colitis Treated With Thiopurines: A Nationwide Retrospective Cohort Study. *Gastroenterology* (2013) 145(5):1007–15.e3. doi: 10.1053/j.gastro.2013.07.035
10. Trivedi PJ, Crothers H, Mytton J, Bosch S, Iqbal T, Ferguson J, et al. Effects of Primary Sclerosing Cholangitis on Risks of Cancer and Death in People With Inflammatory Bowel Disease, Based on Sex, Race, and Age. *Gastroenterology* (2020) 159(3):915–28. doi: 10.1053/j.gastro.2020.05.049
11. Sifuentes H, Kane S. Monitoring for Extra-Intestinal Cancers in IBD. *Curr Gastroenterol Rep* (2015) 17(11):42. doi: 10.1007/s11894-015-0467-8
12. Axelrad JE, Lichtiger S, Yajnik V. Inflammatory Bowel Disease and Cancer: The Role of Inflammation, Immunosuppression, and Cancer Treatment. *World J Gastroenterol* (2016) 22(20):4794–801. doi: 10.3748/wjg.v22.i20.4794
13. Mak JWY, So J, Tang W, Yip TCF, Leung WK, Li M, et al. Cancer Risk and Chemoprevention in Chinese Inflammatory Bowel Disease Patients: A Population-Based Cohort Study. *Scand J Gastroenterol* (2020) 55(3):279–86. doi: 10.1080/00365521.2020.1731760
14. Baars JE, Kuipers EJ, van Haastert M, Nicolaï JJ, Poen AC, van der Woude CJ. Age at Diagnosis of Inflammatory Bowel Disease Influences Early Development of Colorectal Cancer in Inflammatory Bowel Disease Patients: A Nationwide, Long-Term Survey. *J Gastroenterol* (2012) 47(12):1308–22. doi: 10.1007/s00535-012-0603-2
15. Hou JK, Feagins LA, Waljee AK. Characteristics and Behavior of Elderly-Onset Inflammatory Bowel Disease: A Multi-Center US Study. *Inflamm Bowel Dis* (2016) 22(9):2200–5. doi: 10.1097/MIB.0000000000000849
16. Khan N, Pernes T, Weiss A, Trivedi C, Patel M, Xie D, et al. Incidence of Infections and Malignancy Among Elderly Male Patients With IBD Exposed to Vedolizumab, Prednisone, and 5-ASA Medications: A Nationwide Retrospective Cohort Study. *Adv Ther* (2021) 38(5):2586–98. doi: 10.1007/s12325-021-01713-x
17. Khan N, Vallarino C, Lissoos T, Darr U, Luo M. Risk of Malignancy in a Nationwide Cohort of Elderly Inflammatory Bowel Disease Patients. *Drugs Aging* (2017) 34(11):859–68. doi: 10.1007/s40266-017-0498-y
18. Swain S, Sarmanova A, Mallen C, Kuo CF, Coupland C, Doherty M, et al. Trends in Incidence and Prevalence of Osteoarthritis in the United Kingdom: Findings From the Clinical Practice Research Datalink (CPRD). *Osteoarthritis Cartilage* (2020) 28(6):792–801. doi: 10.1016/j.joca.2020.03.004
19. Sebastian S, Hernández V, Myrelid P, Kariv R, Tsianos E, Toruner M, et al. Colorectal Cancer in Inflammatory Bowel Disease: Results of the 3rd ECCO Pathogenesis Scientific Workshop (I). *J Crohns Colitis* (2014) 8(1):5–18. doi: 10.1016/j.crohns.2013.04.008
20. Kappelman MD, Farkas DK, Long MD, Erichsen R, Sandler RS, Sørensen HT, et al. Risk of Cancer in Patients With Inflammatory Bowel Diseases: A Nationwide Population-Based Cohort Study With 30 Years of Follow-Up Evaluation. *Clin Gastroenterol Hepatol* (2014) 12(2):265–73.e1. doi: 10.1016/j.cgh.2013.03.034
21. Wadhwa V, Lopez R, Shen B. Crohn's Disease Is Associated With the Risk for Thyroid Cancer. *Inflamm Bowel Dis* (2016) 22(12):2902–6. doi: 10.1097/MIB.0000000000000963
22. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, et al. Thyroid Cancer After Exposure to External Radiation: A Pooled Analysis of Seven Studies. *Radiat Res* (1995) 141(3):259–77. doi: 10.2307/3579003
23. Mak JWY, Lok Tung Ho C, Wong K, Cheng TY, Yip TCF, Leung WK, et al. Epidemiology and Natural History of Elderly-Onset Inflammatory Bowel Disease: Results From a Territory-Wide Hong Kong IBD Registry. *J Crohns Colitis* (2021) 15(3):401–8. doi: 10.1093/ecco-jcc/jjaa181
24. Jurjus A, Eid A, Al Kattar S, Zeenny MN, Gerges-Geagea A, Haydar H, et al. Inflammatory Bowel Disease, Colorectal Cancer and Type 2 Diabetes Mellitus: The Links. *BBA Clin* (2015) 5:16–24. doi: 10.1016/j.bbacli.2015.11.002

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Linear Skeletal Muscle Index and Muscle Attenuation May Be New Prognostic Factors in Colorectal Carcinoma Treated by Radical Resection

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Objective: This study evaluated the association between body composition and clinical parameters and prognosis in patients with colorectal cancer (CRC) treated by radical resection.

Methods: Baseline data on patient age, body mass index (BMI), bowel obstruction and tumor-related factors were collected retrospectively. Body composition parameters such as visceral fat area (VFA), total abdominal muscle area (TAMA), muscle attenuation (MA), posterior renal fat thickness (PPNF) and intermuscular fat area (IMF) are measured using Computed tomography (CT) scans. We also propose a new predictor of linear skeletal muscle index (LSMI) that can be easily measured clinically at CT. Follow-up endpoints were disease-free survival and all-cause death. We follow up with patients in hospital or by telephone. Univariate and multifactorial Cox proportional hazards analyses were performed to identify risk factors associated with prognosis. Survival analysis was performed using the Kaplan-Meier method and a nomogram was established to predict survival.

Results: A total of 1761 patients (median age 62 years) with CRC were enrolled in our study, of whom 201 had intestinal obstruction and 673 had a BMI > 24.0. Among all patients, the 3- and 5-year disease-free survival rates were 84.55% and 68.60% respectively, and the overall survival rates were 88.87% and 76.38%. Overall survival was significantly correlated with MA, LSMI, SMI, Tumor size, N stage, metastasis and adjuvant therapy by Cox regression analysis ($p < 0.05$). The risk of tumor progression was significantly associated with MA, VFA, LSMI, SMI, Male, N stage, metastasis and adjuvant therapy ($p < 0.05$). In addition, based on the Chinese population, we found that female patients with MA < 30.0 HU, LSMI < 18.2, and SMI < 38.0 had a worse prognosis, male patients with MA < 37.6 HU, LSMI < 21.9, and SMI < 40.3 had a poorer prognosis.

Conclusion: Our findings suggest that linear skeletal muscle index and MA can be used as new independent predictors for colorectal cancer patients treated with radical surgery, and that baseline data such as body composition parameters, LSMI and tumor-related factors can collectively predict patient prognosis. These results could help us to optimize the management and treatment of patients after surgery.

Keywords: colorectal carcinoma, linear skeletal muscle index, body composition parameters, tumor-related factors, prognostic factors, computed tomography.

INTRODUCTION

Colorectal cancer is the third most common cancer worldwide, with a total of 935,173 deaths from colorectal cancer in 2020 (1). In China, the incidence and mortality of colorectal cancer are increasing simultaneously, which is one of the worst among the three models proposed by Arnold et al. for the recent trend of colorectal cancer prevalence in the world (2).

Studies have reported that a higher BMI is associated with a series of endocrine and metabolic changes related to cancer development (3). However, in patients with gastric cancer (4) and colorectal cancer (5), a higher BMI at diagnosis is not associated with a higher risk of death, resulting in an obvious "obesity paradox". BMI is an imprecise body composition. It cannot distinguish between muscle and adipose tissue, nor can it describe the different proportions of adipose tissue and lean tissue (6), and cannot represent obesity well, thus confusing the health consequences of morbidity and mortality (7–9). Recent observational studies have shown that adipose tissue and muscle distribution are risk factors for postoperative complications and overall survival in cancer patients (10, 11). Furthermore, body composition may be further aggravated by cancer and cancer treatment, highlighting the importance of body composition in oncology (12, 13).

Body composition is not only associated with disease prognosis but also with the risk of surgical complications, e.g. Sarcopenic obesity has been used to predict postoperative pancreatic fistula (POPF) after pancreaticoduodenectomy (PD) (14, 15) and visceral obesity increases the risk of postoperative complications in colon cancer (16, 17). In recent years, body composition parameters have been extensively explored and have been found to affect the prognosis of colorectal cancer patients. SMI and MA have been found to be related to patient prognosis. Dolan, Ross D et al. (18) found that SMI [hazard ratio (HR) 1.50, 95% confidence interval (CI) 1.04–2.18, P = 0.031] was independently associated with overall survival and van Wijk, Laura et al. (19) found that overall survival was lower in patients with both muscle quantity and quality loss compared to other categories. However, relevant studies are still limited, and it is difficult to measure every patient clinically because of the complexity of SMI measurement.

Therefore, in the present study, we propose new clinically easy to measure at CT new predictors of linear skeletal muscle index (LSMI), retrospectively analyzed for oncology-related factors and individual body composition parameters, associated with prognosis in patients with colorectal cancer after radical surgery treatment.

MATERIALS AND METHODS

Study Population

We selected data related to patients admitted to the colorectal cancer surgery ward of the Second Affiliated Hospital of Harbin Medical University from January 2012 to August 2016, including patients who were pathologically diagnosed with colon or rectal cancer and underwent radical surgery at our hospital. We excluded patients with severe systemic disease (eg: severe sepsis, septic shock, hypotension, and multiple organ dysfunction syndrome), other malignancies and those lacking key information (eg: follow-up). Baseline data collected included gender, age, BMI, diagnosis of ileus and diabetes mellitus, body composition parameters, receipt of adjuvant therapy (the standard XELOX, consisting of eight cycles of capecitabine and eight cycles of oxaliplatin) and various tumor characteristics (T and N stage, maximum diameter, presence of metastases, etc.). In this study, the met7astatic location included lung, liver, peritoneum, bone and brain. Based on the previous studies, prognostic factors had been determined (3, 18). All potential prognostic factors were considered as baseline information and calculated after diagnosis and before treatment. As this study was retrospective, we did not obtain relevant information on smoking, alcohol consumption and exercise.

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Harbin Medical University.

Body Composition and Linear Skeletal Muscle Index Measurements

The CT scan results of the 64-slice multi-detector CT scanner (Somatom Definition Flash, Siemens AG, Erlangen, Germany) for each patient were obtained from our center's database. Volume was used to segment CT data to measure body composition parameters. At the same time, the maximum diameter of paravertebral muscle group in horizontal direction (Ll, cm) and vertical direction (L2, cm) were further measured in the cross section of the third lumbar midpoint. The product of the transverse and longitudinal diameter of the paravertebral muscle group was L1×L2 **(Figure 1)**. In this study, we defined Ll×L2(cm^2)/height squared (m^2) as linear Skeletal muscle index (LSMI).

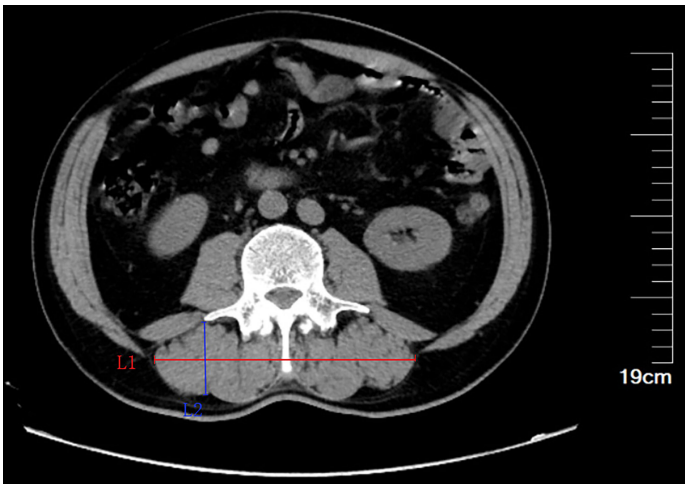

FIGURE 1 | Diagram of transverse and longitudinal diameter of the third lumbar paravertebral muscle group. LI, maximum diameter in horizontal direction; L2, maximum diameter in vertical direction.

CT values for muscle tissue were in the range of -29 ~ 150 Hounsfield units; CT values for adipose tissue were in the range of -150 ~ -50 Hounsfield units (20). We measured total psoas muscle area (TPA), total abdominal muscle area (TAMA), subcutaneous fat area (SFA) and visceral fat area (VFA). Posterior renal fat thickness (PPNF) and perirenal fat area (PFA) were measured at the level of the renal vein (21–23), while subcutaneous fat thickness (SCF) was measured at the level of the umbilicus (24, 25). We also measured intermuscular adipose tissue and mean muscle attenuation (MA) at the level of the inferior endplate of L3 (26–28).

Data Standardization and Outcome Events

We derived highly normalized indices (reported as cm^2/m^2) for psoas muscle (PMI) and skeletal muscle (SMI) using the data collected. For example, PMI is total lumbar muscle area (TPA) divided by height squared, and SMI is total abdominal muscle area (TAMA) divided by height squared.

The endpoints of our study were disease-free survival (DFS) and overall survival (OS), defined as all-cause mortality.

Follow-Up Assessments

Patients were followed up according to NCCN guidelines after radical resection of colorectal cancer (29). The last follow-up was in October 2021. For high-risk patients, physical examinations, CEA and CA19-9, biochemistry, abdominal and pelvic ultrasound were examined every 3 months, and colonoscopy, thoracoabdominal and pelvic CT or MRI were examined every 6 months during the first 2 years after surgery. For other patients, physical examinations, CEA and CA19-9, biochemistry, and abdominal and pelvic ultrasound were reviewed every 3-6 months, and colonoscopy, thoracoabdominal and pelvic CT or MRI were reviewed annually during the first 2 years after surgery. Three to five years after surgery, all patients underwent physical examination, CEA and CA19-9 monitoring, biochemical examination and abdominal and pelvic ultrasound every 6 months, colonoscopy and chest and abdominal and pelvic CT or MRI examinations every year. For all patients, physical examinations, CEA and CA19-9, biochemistry, abdominal pelvic ultrasound, colonoscopy, and thoracoabdominal pelvic CT or MRI were reviewed annually 5 years after surgery.

Statistical Analysis

Statistical analyses were performed using R version 4.1.2 (R Project for Statistical Computing, Vienna, Austria) and SPSS statistics version 25.0 (IBM, Armonk, NY). X-tile is used to determine the cut-off values. Categorical data was expressed as frequencies (%) and continuous data was expressed as median (min-max). We also used the Kaplan-Meier method to analyze patient survival. In survival analysis, disease-free survival (DFS) and overall survival (OS) were analyzed using standard Cox regression analysis based on the proportional risk assumption. Furthermore, univariate Cox proportional risk models were used to analyze categorical data as well as continuous data, and all univariate significant variables were included in the multivariate Cox proportional risk analysis ($p < 0.05$).

RESULTS

Patient Characteristics

The characteristics of the 1761 post-radical colorectal cancer patients were shown in **Table 1**. Their median age was 62 years (range 23 - 90) and according to the BMI classification, 673 patients were considered as overweight (BMI > 24) and 148 patients were considered as obese (BMI > 28). In these populations, the prevalence of intestinal obstruction, hypertension, diabetes and anaemia were 11.41%, 24.36%, 11.65% and 11.41% respectively. There were slightly more

TABLE 1 | Baseline characteristics of study cohort.

	N (%)/Median (Min-Max)
	N (%)
Gender	
Male	1082 (61.44%)
Female	679 (38.56%)
Diabetes mellitus	
Yes	205 (11.64%)
No	1556 (88.36%)
Hypertension (≥130/85mmHg)	
Yes	429 (24.36%)
No	1332 (75.64%)
Anemia	
Yes	346 (19.65%)
No	1415 (80.35%)
Ileus	
Yes	201 (11.41%)
No	1560 (88.59%)
Primary site	
Multiple primary	4 (0.23%)
Right-sided colon	425 (24.13%)
Left-sided colon	436 (24.76%)
Rectum	896 (50.88%)
Tumor size	
>5cm	906 (51.45%)
≥5cm	855 (48.55%)
T stage	
T1	45 (2.56%)
T2	136 (7.72%)
T3	635 (36.06%)
T4	945 (53.66%)
N stage	
N0	1141 (64.79%)
N1	375 (21.29%)
N2	245 (13.92%)
Metastasis	
M0	1637 (92.96%)
M1	124 (7.04%)
Adjuvant therapy	
No	866 (49.18%)
Yes	895 (50.82%)
	Median (Min-Max)
Age	62.00 (23.00-90.00)
BMI	23.05 (12.35-37.03)
MA (Muscle attenuation)	45.41 (2.31-58.90)
IMF (intermuscular)	10.24 (0.90-19.21)
TPA	25.04 (12.20-40.63)
TAMA	129.06 (72.22-196.76)
VFA	105.13 (7.36-186.32)
PFA	21.97 (5.16-30.27)
SFA	108.97 (7.57-209.81)
Abdominal wall fat thickness	2.38 (0.53-4.23)
PPNF	2.15 (0.13-4.23)
VD (visceral fat density)	-91.39 (-115.06-66.72)
SD (subcutaneous fat density)	-92.22 (-118.60-66.61)
PMI	8.93 (3.85-16.62)
LSMI (linear skeletal muscle index)	24.30 (10.02-33.76)
SMI	47.80 (25.82-64.96)

males (n=1082) than females (n=679). All patients had a pathological diagnosis of malignancy, which included 635 patients with T3 and 945 patients with T4 stage **(Table 1)**.

Survival Analysis

The Kaplan-Meier analysis showed that the 3- and 5-year overall survival rates were 88.87% and 76.38%, respectively **(Figure 2A)**; the disease-free survival rates were 84.55% and 68.60%, respectively **(Figure 2B)**. At follow-up, we identified 553 patients who developed resurgence of diseases after radical colorectal cancer surgery and 416 patients who died during the five-year period.

Prognostic Factors

A total of 27 factors were included in univariate Cox proportional hazard analysis **(Table 2)**. After that, the significant prognostic factors in univariate COX regression analysis were included in multivariate COX proportional risk analysis. Finally, multivariate COX proportional risk analysis showed that MA, LSMI, SMI, Tumor size, N stage, Metastasis, and postoperative adjuvant therapy were significantly correlated with OS ($P < 0.05$; **Table 3**). MA, VFA, LSMI, SMI, gender, Tumor size, N stage, Metastasis, and postoperative adjuvant therapy were significantly associated with DFS ($P < 0.05$; **Table 4**).

We further found that patients with higher MA, LSMI and SMI values had a lower risk of all-cause mortality, while patients with tumor size ≥5cm, higher N stage, presence of distant metastases and no postoperative adjuvant chemotherapy had a higher risk of all-cause mortality. And patients with higher MA, LSMI and SMI values had a lower risk of tumor progression, while patients with higher VFA, male patients, tumor size ≥5 cm, higher N stage, presence of distant metastases and no postoperative adjuvant chemotherapy had a higher risk of tumor progression.

Cut-Off Values for Prognostic Factors

Based on the overall survival (OS), we found that female patients with MA <30.0HU (**Figure 3A**), LSMI <18.2 (**Figure 3B**), and SMI <38.0 (**Figure 3C**) had a poorer prognosis; male patients with MA <37.6HU (**Figure 3D**), LSMI <21.9 (**Figure 3E**), and SMI <40.3 (**Figure 3F**), male patients had a worse prognosis.

Nomograms Construction and Clinical Performance

Based on overall survival, we constructed a nomogram using seven independent predictors including MA, LSMI, SMI, tumor size, N stage, metastasis and adjuvant therapy after multivariate COX regression analysis **(Figure 4)**. The calibration curves at 3 and 5 years were close to 45 degrees **(Figure 5)**, indicating that the nomogram has good calibration ability. DCA curves at 3 and 5 years showed that the model had good clinical performance **(Figure 6)**. The ROC was used in this study to determine the predictive effect of the model. The 3-year and 5-year AUC values for this nomogram were 0.835 (95% CI, 0.818 - 0.852) and 0.748 (95% CI, 0.733 - 0.763) **(Figure 6)**.

DISCUSSION

In patients with colorectal cancer, quantitative calculation of skeletal muscle area by abdominal CT images is the recognized gold standard for the diagnosis of sarcopenia (30). However,

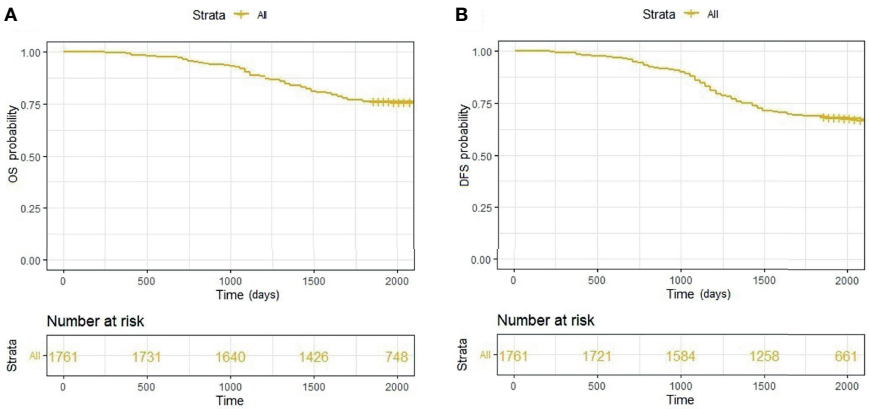

FIGURE 2 | **(A)** Overall survival of all patients; **(B)** Disease-free survival of all patients.

because this method requires a lot of time for each patient to use software to perform manual segmentation, it is currently not clinically conditions to diagnose sarcopenia for each patient (31). This study is the first to find that the product of the transverse and longitudinal diameter of the paraspinal muscle group/square of the height (Linear Skeletal muscle index) on abdominal CT images of the third lumbar spine can be used as a new prognostic factor for colorectal cancer. This method has the advantages of saving time and being easy to measure. When LSMI <18.2 in female patients, and LSMI <21.9 in male patients, the prognosis of patients is worse.

At the same time, we found that few studies have examined muscle and fat tissues among Chinese people. To our knowledge, this is the first time that a combination of muscle and adipose-related parameters, linear Skeletal Muscle Index (LSMI), and oncological parameters has been used to determine survival outcomes in CRC patients undergoing radical surgery. We found that skeletal muscle mass index (SMI), muscle attenuation (MA), linear skeletal muscle index (LSMI), tumor size, N stage, metastasis, and postoperative adjuvant therapy were significantly correlated with the survival rate of colorectal cancer patients after radical resection.

Skeletal muscle is the largest organ in non-obese individuals and it accounts for 40% of body mass (32). Muscle and fat are two important components of the body and a reliable method of assessing the amount and distribution of muscle and fat in the body is clinical imaging and CT scan analysis at the level of the third lumbar vertebra is considered to be the gold standard for measuring body composition parameters. There may be some amount of skeletal muscle loss, either during cancer radiotherapy or malignancy development (33–35), and loss of muscle mass or quality may shorten overall survival (36). The amount and distribution of adipose tissue affects clinical outcomes differently in different types of tumors (10, 11).

SMI is used to measure body muscle mass and is often used as a standard indicator to diagnose sarcopenia, while MA is used to measure muscle quality (37). Skeletal muscle is the largest protein storage site in the body, and it secretes hundreds of myostatin peptides that affect immune function, adipose tissue oxidation, insulin sensitivity and systemic metabolism. Studies have shown that sarcopenia can be mediated through mechanisms such as autophagy (38), disturbances in adipose tissue metabolism (39), oxidative stress (40) and systemic inflammation (41). Loss of MA and SMI is associated with poor prognosis in patients with a variety of solid tumors, such as bladder cancer, lung cancer, breast cancer and gastric cancer (42–45).

Low MA is associated with physical inactivity, obesity and muscle atrophy, which often results in metabolic disturbances, severe postoperative complications and a systemic inflammatory response (46). Inflammation and oxidative stress activate the ubiquitin-proteasome system and apoptosis-inducing proteins, and inhibit insulin-like growth factors (47). Studies have found that skeletal muscle attenuation density is negatively correlated with muscle fibre fat content, and muscle mass and strength are positively correlated (48).

Research demonstrating that muscle mass and quantity are associated with mortality could be used as a framework to test the hypothesis that targeted interventions for muscle status may provide clinical benefit in this population. In this framework, measures of muscle mass and quantity could be used as therapeutic targets (i.e. biomarkers) to guide the development of early treatment. For example, resistance training combined with exercise, nutrition and medication might improve muscle status.

Most of the pathological types of colorectal cancer are adenocarcinoma, which contains a large number of lipid droplets. Therefore, lipid metabolism may play an important role in colorectal cancer. Adipose tissue is an endocrine organ with high metabolic activity, with visceral adipose tissue (VAT) being the most metabolically active (49). Environmental and genetic factors lead to abnormal fat distribution in the body. The accumulation of VAT does not necessarily correlate positively with BMI and patients with low BMI may have higher than normal levels of visceral adipose tissue. Visceral adipose tissue releases adipokines such as IL-6, TNF-a, VEGF, and fibrinogen

TABLE 2 | Univariate cox proportional hazard analysis for risk factors of patients' prognosis.

Characteristics		OS		DFS	
		HR (95%CI)	*P value*	HR (95%CI)	*P value*
Gender	Male	1.0 (ref)	P<0.001	1.0 (ref)	P<0.001
	Female	0.51 (0.41,0.64)		0.59 (0.49,0.71)	
Diabetes mellitus	No	1.0 (ref)	P=0.776	1.0 (ref)	P=0.604
	Yes	0.96 (0.71,1.30)		0.93 (0.72,1.21)	
Hypertension (≥130/85mmHg)	No	1.0 (ref)	P=0.377	1.0 (ref)	P=0.592
	Yes	0.9 (0.72,1.13)		0.95 (0.78,1.15)	
Anemia	No	1.0 (ref)	P=0.565	1.0 (ref)	P=0.638
	Yes	1.07 (0.85,1.36)		1.05 (0.86,1.29)	
Ileus	No	1.0 (ref)	P=0.012	1.0 (ref)	P=0.118
	Yes	1.41 (1.08,1.86)		1.22 (0.95,1.55)	
Primary site	Multiple primary	1.0 (ref)	P=0.296	1.0 (ref)	P=0.265
	Right-sided colon	1.16 (0.16,8.31)		0.68 (0.17,2.73)	
	Left-sided colon	0.99 (0.14,7.06)		0.63 (0.16.2.56)	
	Rectum	0.93 (0.13,6.61)		0.56 (0.14,2.27)	
Tumor size	<5cm	1.0 (ref)	P<0.001	1.0 (ref)	P<0.001
	≥5cm	2.77 (2.25,3.41)		2.09 (1.76,2.47)	
T stage	T1	1.0 (ref)	P<0.001	1.0 (ref)	P<0.001
	T2	1.14 (0.42,3.09)		1.13 (0.56,2.28)	
	T3	2.00 (0.82,4.88)		1.22 (0.65,2.31)	
	T4	2.89 (1.19,6.99)		1.84 (0.98,3.45)	
N stage	N0	1.0 (ref)	P<0.001	1.0 (ref)	P<0.001
	N1	1.89 (1.50,2.37)		2.12 (1.75,2.56)	
	N2	2.76 (2.17,3.50)		2.67 (2.16,3.30)	
Metastasis	M0	1.0 (ref)	P<0.001	1.0 (ref)	P<0.001
	M1	5.57 (4.42,7.03)		6.95 (5.61,8.62)	
Adjuvant therapy	No	1.0 (ref)	P<0.001	1.0 (ref)	P<0.001
	Yes	0.20 (0.16,0.22)		0.40 (0.34,0.48)	
Age		1.00 (0.99,1.01)	P=0.839	1.00 (0.99,1.01)	P=0.592
BMI		0.99 (0.97,1.02)	P=0.665	1.00 (0.97,1.02)	P=0.757
MA (Muscle attenuation)		0.92 (0.91,0.93)	P<0.001	0.94 (0.93,0.94)	P<0.001
IMF (intermuscular)		0.99 (0.97,1.01)	P=0.355	1.00 (0.98,1.02)	P=0.904
TPA		1.00 (0.99,1.01)	P=0.720	1.00 (0.99,1.01)	P=0.755
TAMA		0.93 (0.93,0.94)	P<0.001	0.95 (0.95,0.96)	P<0.001
VFA		1.00 (1.00,1.01)	P=0.054	1.00 (1.00,1.01)	P=0.001
PFA		0.97 (0.95,0.98)	P<0.001	0.98 (0.97,0.99)	P<0.001
SFA		1.00 (1.00,1.01)	P=0.880	1.00 (0.99,1.00)	P=0.962
Abdominal wall fat thickness		1.05 (0.96,1.15)	P=0.268	1.04 (0.96,1.12)	P=0.322
PPNF		1.00 (0.93,1.09)	P=0.922	1.02 (0.95,1.09)	P=0.603
VD (visceral fat density)		1.00 (0.99,1.01)	P=0.924	1.00 (1.00,1.01)	P=0.647
SD (subcutaneous fat density)		1.00 (1.00,1.01)	P=0.609	1.00 (0.99,1.00)	P=0.606
PMI		0.96 (0.92,0.99)	P=0.009	0.99 (0.96,1.02)	P=0.054
LSMI (linear skeletal muscle index)		0.78 (0.76,0.79)	P<0.001	0.82 (0.81,0.83)	P<0.001
SMI		0.80 (0.78,0.81)	P<0.001	0.85 (0.84,0.86)	P<0.001

activator inhibitor-1 that are involved in inflammation and angiogenesis, while decreasing lipocalin expression (50). Meanwhile, many studies have reported that reduced serum lipocalin levels are associated with an increased incidence of common malignancies, including breast, colon and prostate cancers (51, 52). Visceral obesity is one of the manifestations of abnormal body fat distribution under the influence of multiple genetic and environmental factors.

Visceral obesity increases the burden of endoplasmic reticulum, triggers an endoplasmic reticulum stress response and impairs insulin signaling pathways. These factors lead to chronic inflammatory response and insulin resistance, magnifying surgical stress and aggravating surgical complications (17). Polyunsaturated fatty acids (PUFA) have also been found to intervene in the development and progression of colorectal cancer (53). Meanwhile, our results also suggest that visceral fat area (VFA), a fat parameter measured in the third lumbar spine, may significantly influence the invasion and development of colorectal cancer.

The current study has some limitations, and we need to acknowledge that the present study did not retrospectively obtain data on important diagnostic factors related to sarcopenia, such as walking speed and patient self-report on the SARC-F questionnaire (54). Additionally, we did not obtain parameters related to tumor nutrition, such as grip strength, triceps skinfold thickness and the PG-SGA score patient self-assessment scale (55), because some body composition parameters are directly affected by the patient's nutritional

TABLE 3 | Multivariate cox proportional hazard analysis for risk factors of patients' prognosis (OS).

Characteristics		OS	
		HR (95%CI)	***P value***
Gender	Male	1.0 (ref)	P=0.433
	Female	0.89 (0.68,1.18)	
Ileus	No	1.0 (ref)	P=0.365
	Yes	1.14 (0.86,1.52)	
Tumor size	<5cm	1.0 (ref)	P=0.034
	≥5cm	1.28 (1.02,1.61)	
T stage	T1	1.0 (ref)	P=0.568
	T2	1.61 (0.59,4.42)	
	T3	1.61 (0.65,3.96)	
	T4	1.42 (0.58,3.51)	
N stage	N0	1.0 (ref)	P<0.001
	N1	1.31 (1.03,1.67)	
	N2	1.89 (1.46,2.46)	
Metastasis	M0	1.0 (ref)	P<0.001
	M1	4.55 (3.46,5.97)	
Adjuvant therapy	No	1.0 (ref)	P<0.001
	Yes	0.43 (0.33,0.56)	
MA (Muscle attenuation)		0.96 (0.95,0.97)	P<0.001
TAMA		1.00 (0.99,1.01)	P=0.931
VFA		1.00 (1.00,1.01)	P=0.502
PFA		1.00 (0.98,1.01)	P=0.679
PMI		0.97 (0.94,1.01)	P=0.141
LSMI (linear skeletal muscle index)		0.91 (0.89,0.93)	P<0.001
SMI		0.89 (0.86,0.93)	P<0.001

status. In addition, the relatively small cohort and retrospective nature of data collection are potential sources of bias. Future research should focus on validating and refining these results.

Besides, we consider providing some commentary on the next steps for this line of research. In the future, we plan to examine these indicators compared to sarcopenia or other independent prognostic factors for colorectal cancer and explore whether imaging is the most cost-effective tool in this setting. Moreover, we will determine if there are ways to assess proxies for skeletal muscles (e.g., exercise behavior, nutrition, walking pace) in the real-world.

TABLE 4 | Multivariate cox proportional hazard analysis for risk factors of patients' prognosis (DFS).

Characteristics		DFS	
		HR (95%CI)	***P value***
Gender	Male	1.0 (ref)	P=0.001
	Female	0.67 (0.53,0.84)	
Tumor size	<5cm	1.0 (ref)	P=0.020
	≥5cm	1.25 (1.04,1.51)	
T stage	T1	1.0 (ref)	P=0.080
	T2	1.63 (0.80,3.31)	
	T3	1.13 (0.54,1.95)	
	T4	1.11 (0.53,1.93)	
N stage	N0	1.0 (ref)	P<0.001
	N1	1.43 (1.16,1.75)	
	N2	1.64 (1.31,2.06)	
Metastasis	M0	1.0 (ref)	P<0.001
	M1	4.04 (3.19,5.12)	
Adjuvant therapy	No	1.0 (ref)	P=0.033
	Yes	0.80 (0.65,0.98)	
MA (Muscle attenuation)		0.97 (0.97,0.98)	P<0.001
TAMA		1.00 (0.99,1.01)	P=0.828
VFA		1.01 (1.00,1.01)	P<0.001
PFA		1.00 (0.99,1.01)	P=0.902
PMI		1.00 (0.96,1.03)	P=0.801
LSMI (linear skeletal muscle index)		0.93 (0.91,0.95)	P<0.001
SMI		0.93 (0.90,0.96)	P<0.001

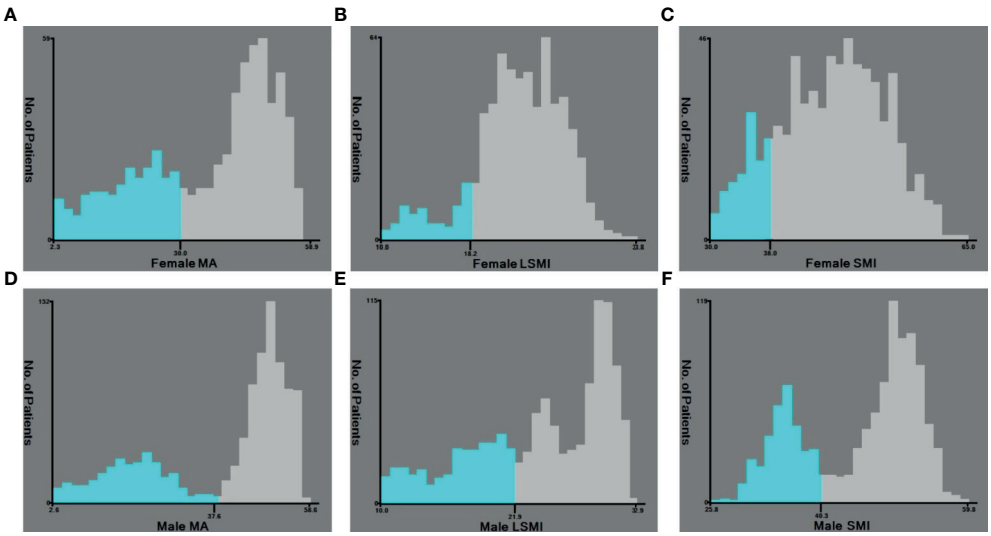

FIGURE 3 | **(A)** Cut-off values of Female MA; **(B)** Cut-off values of Female LSMI; **(C)** Cut-off values of Female SMI; **(D)** Cut-off values of Male MA; **(E)** Cut-off values of Male LSMI; **(F)** Cut-off values of Male MA.

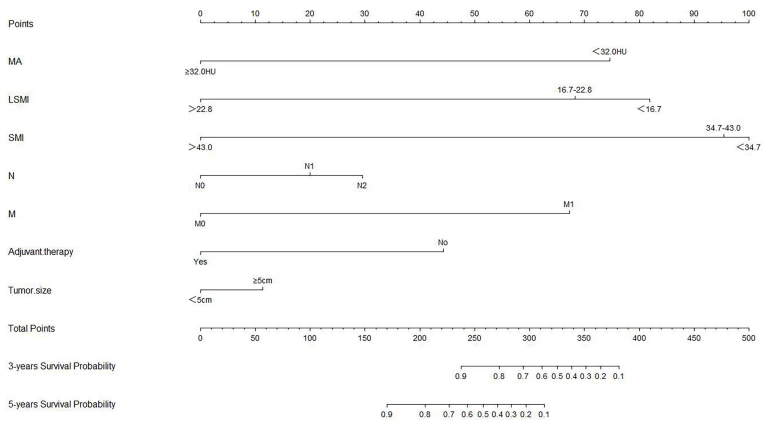

FIGURE 4 | Nomogram for predicting overall survival in colorectal cancer patients.

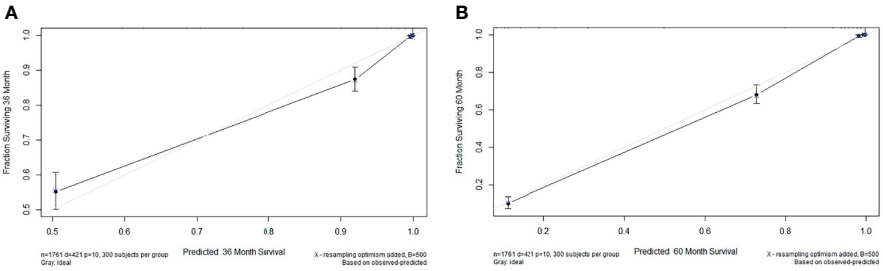

FIGURE 5 | **(A)** The calibration plots of the nomogram for 3-year overall survival. **(B)** The calibration plots of the nomogram for 5-year overall survival.

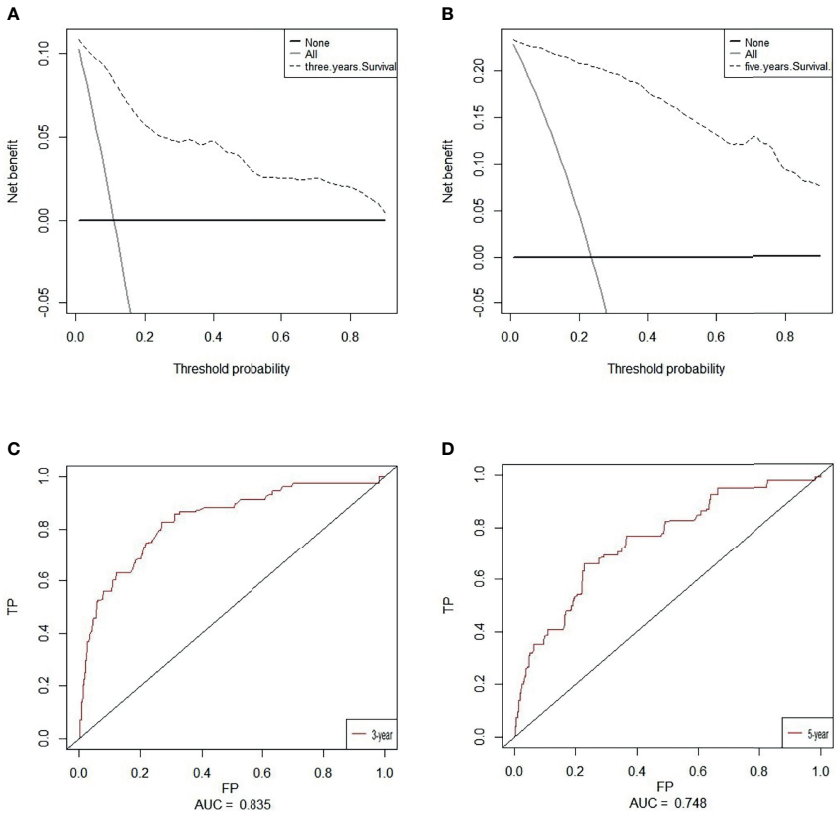

FIGURE 6 | Decision curve analysis (DCA) of the nomogram of based on 3-year **(A)** and 5-year **(B)** overall survival. The x-axis and the y-axis were the threshold probability and the net benefit, respectively. Receiver operating characteristic (ROC) analyses of the nomogram based on 3-year **(C)** and 5-year **(D)** overall survival.

CONCLUSION

We demonstrate for the first time that linear skeletal muscle index is an independent and powerful prognostic factor for patients with colorectal cancer, and furthermore we find that more refined body composition parameters than BMI combined with oncology-related parameters may provide a more comprehensive assessment of patient prognosis. Our results may provide a reference in their postoperative management.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

This study was reviewed and approved by the Research Ethics Committee of the Second Affiliated Hospital of Harbin Medical University, China. Patients/participants provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YW: conceptualization, data capture, investigation, writing-original, formal analysis. YLMW and HZ: formal analysis, software, validation and writing-review and editing. LA: software, visualization and data capture. ZW and XJ: data collection, data management and software. YL: formal analysis and investigation. GY: visualization and data capture. HX: writing-review and editing. GL: software, investigation, supervision and writing-revision. CW: investigation and methodology. GW: supervision, validation and project management. ML: supervision, project management, funding acquisition. All authors of this article made significant contributions and approved the submitted version.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660
2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Patterns and Trends in Colorectal Cancer Incidence and Mortality. *Gut* (2017) 66(4):683–91. doi: 10.1136/gutjnl-2015-310912
3. Caan BJ, Cespedes Feliciano EM, Kroenke CH. The Importance of Body Composition in Explaining the Overweight Paradox in Cancer-Counterpoint. *Cancer Res* (2018) 78(8):1906–12. doi: 10.1158/0008-5472.CAN-17-3287
4. Chen HN, Chen XZ, Zhang WH, Yang K, Chen XL, Zhang B, et al. The Impact of Body Mass Index on the Surgical Outcomes of Patients With Gastric Cancer: A 10-Year, Single-Institution Cohort Study. *Medicine (Baltimore)* (2015) 94(42):e1769. doi: 10.1097/MD.0000000000001769
5. Schlesinger S, Siegert S, Koch M, Walter J, Heits N, Hinz S, et al. Postdiagnosis Body Mass Index and Risk of Mortality in Colorectal Cancer Survivors: A Prospective Study and Meta-Analysis. *Cancer Causes Control* (2014) 25 (10):1407–18. doi: 10.1007/s10552-014-0435-x
6. Prado CM, Heymsfield SB. Lean Tissue Imaging: A New Era for Nutritional Assessment and Intervention. *JPEN J Parenter Enteral Nutr* (2014) 38(8):940–53. doi: 10.1177/0148607114550189
7. Antonopoulos AS, Oikonomou EK, Antoniades C, Tousoulis D. From the BMI Paradox to the Obesity Paradox: The Obesity-Mortality Association in Coronary Heart Disease. *Obes Rev* (2016) 17(10):989–1000. doi: 10.1111/obr.12440
8. Goossens GH. The Metabolic Phenotype in Obesity: Fat Mass, Body Fat Distribution, and Adipose Tissue Function. *Obes Facts* (2017) 10(3):207–15. doi: 10.1159/000471488
9. Strulov Shachar S, Williams GR. The Obesity Paradox in Cancer-Moving Beyond BMI. *Cancer Epidemiol Biomarkers Prev* (2017) 26(1):13–6. doi: 10.1158/1055-9965.EPI-16-0439
10. Hopkins JJ, Sawyer MB. A Review of Body Composition and Pharmacokinetics in Oncology. *Expert Rev Clin Pharmacol* (2017) 10 (9):947–56. doi: 10.1080/17512433.2017.1347503
11. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic Value of Sarcopenia in Adults With Solid Tumours: A Meta-Analysis and Systematic Review. *Eur J Cancer* (2016) 57:58–67. doi: 10.1016/j.ejca.2015.12.030
12. Henderson TO, Ness KK, Cohen HJ. Accelerated Aging Among Cancer Survivors: From Pediatrics to Geriatrics. *Am Soc Clin Oncol Educ Book* (2014) 34:e423–30. doi: 10.14694/EdBook_AM.2014.34.e423
13. Hurria A, Jones L, Muss HB. Cancer Treatment as an Accelerated Aging Process: Assessment, Biomarkers, and Interventions. *Am Soc Clin Oncol Educ Book* (2016) 35:e516–22. doi: 10.1200/EDBK_156160
14. Nishida Y, Kato Y, Kudo M, Aizawa H, Okubo S, Takahashi D, et al. Preoperative Sarcopenia Strongly Influences the Risk of Postoperative Pancreatic Fistula Formation After Pancreaticoduodenectomy. *J Gastrointest Surg* (2016) 20(9):1586–94. doi: 10.1007/s11605-016-3146-7
15. Linder N, Schaudinn A, Langenhan K, Krenzien F, Hau HM, Benzing C, et al. Power of Computed-Tomography-Defined Sarcopenia for Prediction of Morbidity After Pancreaticoduodenectomy. *BMC Med Imaging* (2019) 19 (1):32. doi: 10.1186/s12880-019-0332-6
16. Ozoya OO, Siegel EM, Srikumar T, Bloomer AM, DeRenzis A, Shibata D. Quantitative Assessment of Visceral Obesity and Postoperative Colon Cancer Outcomes. *J Gastrointest Surg* (2017) 21(3):534–42. doi: 10.1007/s11605-017-3362-9
17. Cakir H, Heus C, van der Ploeg TJ, Houdijk AP. Visceral Obesity Determined by CT Scan and Outcomes After Colorectal Surgery; a Systematic Review and Meta-Analysis. *Int J Colorectal Dis* (2015) 30(7):875–82. doi: 10.1007/s00384-015-2174-1
18. Dolan RD, Almasaudi AS, Dieu LB, Horgan PG, McSorley ST, McMillan DC. The Relationship Between Computed Tomography-Derived Body Composition, Systemic Inflammatory Response, and Survival in Patients Undergoing Surgery for Colorectal Cancer. *J Cachexia Sarcopenia Muscle* (2019) 10(1):111–22. doi: 10.1002/jcsm.12357
19. van Wijk L, van Duinhoven S, Liem MSL, Bouman DE, Viddeleer AR, Klaase JM. Risk Factors for Surgery-Related Muscle Quantity and Muscle Quality Loss and Their Impact on Outcome. *Eur J Med Res* (2021) 26(1):36. doi: 10.1186/s40001-021-00507-9
20. Gill TS, Varghese BA, Hwang DH, Cen SY, Aron M, Aron M, et al. Juxtatumoral Perinephric Fat Analysis in Clear Cell Renal Cell Carcinoma. *Abdom Radiol (NY)* (2019) 44(4):1470–80. doi: 10.1007/s00261-018-1848-x
21. Dariane C, Le Guilchet T, Hurel S, Audenet F, Beaugerie A, Badoual C, et al. Prospective Assessment and Histological Analysis of Adherent Perinephric Fat in Partial Nephrectomies. *Urol Oncol* (2017) 35(2):39.e9–17. doi: 10.1016/j.urolonc.2016.09.008
22. Davidiuk AJ, Parker AS, Thomas CS, Leibovich BC, Castle EP, Heckman MG, et al. Mayo Adhesive Probability Score: An Accurate Image-Based Scoring System to Predict Adherent Perinephric Fat in Partial Nephrectomy. *Eur Urol* (2014) 66(6):1165–71. doi: 10.1016/j.eururo.2014.08.054
23. Kocher NJ, Kunchala S, Reynolds C, Lehman E, Nie S, Raman JD. Adherent Perinephric Fat at Minimally Invasive Partial Nephrectomy Is Associated With Adverse Peri-Operative Outcomes and Malignant Renal Histology. *BJU Int* (2016) 117(4):636–41. doi: 10.1111/bju.13378
24. Goldenberg L, Saliba W, Hayeq H, Hasadia R, Zeina AR. The Impact of Abdominal Fat on Abdominal Aorta Calcification Measured on Non-Enhanced CT. *Medicine (Baltimore)* (2018) 97(49):e13233. doi: 10.1097/MD.0000000000013233
25. Han Y, Kwon EY, Yu MK, Lee SJ, Kim HJ, Kim SB, et al. A Preliminary Study for Evaluating the Dose-Dependent Effect of D-Allulose for Fat Mass Reduction in Adult Humans: A Randomized, Double-Blind, Placebo-Controlled Trial. *Nutrients* (2018) 10(2):160. doi: 10.3390/nu10020160
26. Barbalho ER, Gonzalez MC, Bielemann RM, da Rocha IMG, de Sousa IM, Bezerra RA, et al. Is Skeletal Muscle Radiodensity Able to Indicate Physical Function Impairment in Older Adults With Gastrointestinal Cancer? *Exp Gerontol* (2019) 125:110688. doi: 10.1016/j.exger.2019.110688
27. Hayashi N, Ando Y, Gyawali B, Shimokata T, Maeda O, Fukaya M, et al. Low Skeletal Muscle Density Is Associated With Poor Survival in Patients Who Receive Chemotherapy for Metastatic Gastric Cancer. *Oncol Rep* (2016) 35 (3):1727–31. doi: 10.3892/or.2015.4475
28. Lu J, Zheng ZF, Li P, Xie JW, Wang JB, Lin JX, et al. A Novel Preoperative Skeletal Muscle Measure as a Predictor of Postoperative Complications, Long-Term Survival and Tumor Recurrence for Patients With Gastric Cancer After Radical Gastrectomy. *Ann Surg Oncol* (2018) 25(2):439–48. doi: 10.1245/s10434-017-6269-5
29. Benson AB, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK, et al. NCCN Guidelines Insights: Colon Cancer, Version 2.2018. *J Natl Compr Canc Netw* (2018) 16(4):359–69. doi: 10.6004/jnccn.2018.0021
30. Brown JC, Caan BJ, Meyerhardt JA, Weltzien E, Xiao J, Cespedes Feliciano EM, et al. The Deterioration of Muscle Mass and Radiodensity Is Prognostic of Poor Survival in Stage I-III Colorectal Cancer: A Population-Based Cohort Study (C-SCANS). *J Cachexia Sarcopenia Muscle* (2018) 9(4):664–72. doi: 10.1002/jcsm.12305
31. Tandon P, Raman M, Mourtzakis M, Merli M. A Practical Approach to Nutritional Screening and Assessment in Cirrhosis. *Hepatology* (2017) 65 (3):1044–57. doi: 10.1002/hep.29003
32. Frontera WR, Ochala J. Skeletal Muscle: A Brief Review of Structure and Function. *Calcif Tissue Int* (2015) 96(3):183–95. doi: 10.1007/s00223-014-9915-y
33. Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA, den Braver NR, Berkhof J, Langius JA, et al. Loss of Muscle Mass During Chemotherapy Is Predictive for Poor Survival of Patients With Metastatic Colorectal Cancer. *J Clin Oncol* (2016) 34(12):1339–44. doi: 10.1200/JCO.2015.63.6043
34. Daly LE, Ni Bhuachalla EB, Power DG, Cushen SJ, James K, Ryan AM. Loss of Skeletal Muscle During Systemic Chemotherapy Is Prognostic of Poor Survival in Patients With Foregut Cancer. *J Cachexia Sarcopenia Muscle* (2018) 9(2):315–25. doi: 10.1002/jcsm.12267
35. Grossberg AJ, Chamchod S, Fuller CD, Mohamed AS, Heukelom J, Eichelberger H, et al. Association of Body Composition With Survival and Locoregional Control of Radiotherapy-Treated Head and Neck Squamous Cell Carcinoma. *JAMA Oncol* (2016) 2(6):782–9. doi: 10.1001/jamaoncol.2015.6339
36. Huang X, Ma J, Li L, Zhu XD. Severe Muscle Loss During Radical Chemoradiotherapy for Non-Metastatic Nasopharyngeal Carcinoma Predicts Poor Survival. *Cancer Med* (2019) 8(15):6604–13. doi: 10.1002/cam4.2538
37. Heymsfield SB, Gonzalez MC, Lu J, Jia G, Zheng J. Skeletal Muscle Mass and Quality: Evolution of Modern Measurement Concepts in the Context

of Sarcopenia. *Proc Nutr Soc* (2015) 74(4):355–66. doi: 10.1017/S0029665115000129
38. Paul PK, Kumar A. TRAF6 Coordinates the Activation of Autophagy and Ubiquitin-Proteasome Systems in Atrophying Skeletal Muscle. *Autophagy* (2011) 7(5):555–6. doi: 10.4161/auto.7.5.15102
39. Kir S, White JP, Kleiner S, Kazak L, Cohen P, Baracos VE, et al. Tumour-Derived PTH-Related Protein Triggers Adipose Tissue Browning and Cancer Cachexia. *Nature* (2014) 513(7516):100–4. doi: 10.1038/nature13528
40. Tezze C, Romanello V, Desbats MA, Fadini GP, Albiero M, Favaro G, et al. Age-Associated Loss of OPA1 in Muscle Impacts Muscle Mass, Metabolic Homeostasis, Systemic Inflammation, and Epithelial Senescence. *Cell Metab* (2017) 25(6):1374–89.e6. doi: 10.1016/j.cmet.2017.04.021
41. Feliciano EMC, Kroenke CH, Meyerhardt JA, Prado CM, Bradshaw PT, Kwan ML, et al. Association of Systemic Inflammation and Sarcopenia With Survival in Nonmetastatic Colorectal Cancer: Results From the C SCANS Study. *JAMA Oncol* (2017) 3(12):e172319. doi: 10.1001/jamaoncol.2017.2319
42. Mayr R, Gierth M, Zeman F, Reiffen M, Seeger P, Wezel F, et al. Sarcopenia as a Comorbidity-Independent Predictor of Survival Following Radical Cystectomy for Bladder Cancer. *J Cachexia Sarcopenia Muscle* (2018) 9 (3):505–13. doi: 10.1002/jcsm.12279
43. Kim EY, Kim YS, Park I, Ahn HK, Cho EK, Jeong YM. Prognostic Significance of CT-Determined Sarcopenia in Patients With Small-Cell Lung Cancer. *J Thorac Oncol* (2015) 10(12):1795–9. doi: 10.1097/JTO.0000000000000690
44. Hacker UT, Hasenclever D, Linder N, Stocker G, Chung HC, Kang YK, et al. Prognostic Role of Body Composition Parameters in Gastric/Gastroesophageal Junction Cancer Patients From the EXPAND Trial. *J Cachexia Sarcopenia Muscle* (2020) 11(1):135–44. doi: 10.1002/jcsm.12484
45. Cespedes Feliciano EM, Chen WY, Bradshaw PT, Prado CM, Alexeeff S, Albers KB, et al. Adipose Tissue Distribution and Cardiovascular Disease Risk Among Breast Cancer Survivors. *J Clin Oncol* (2019) 37(28):2528–36. doi: 10.1200/JCO.19.00286
46. Boer BC, de Graaff F, Brusse-Keizer M, Bouman DE, Slump CH, Slee-Valentijn M, et al. Skeletal Muscle Mass and Quality as Risk Factors for Postoperative Outcome After Open Colon Resection for Cancer. *Int J Colorectal Dis* (2016) 31(6):1117–24. doi: 10.1007/s00384-016-2538-1
47. Bowen TS, Schuler G, Adams V. Skeletal Muscle Wasting in Cachexia and Sarcopenia: Molecular Pathophysiology and Impact of Exercise Training. *J Cachexia Sarcopenia Muscle* (2015) 6(3):197–207. doi: 10.1002/jcsm.12043
48. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and Clinical Implications of Sarcopenic Obesity in Patients With Solid Tumours of the Respiratory and Gastrointestinal Tracts: A Population-Based Study. *Lancet Oncol* (2008) 9(7):629–35. doi: 10.1016/S1470-2045(08)70153-0
49. Tewari N, Awad S, Macdonald IA, Lobo DN. Obesity-Related Insulin Resistance: Implications for the Surgical Patient. *Int J Obes (Lond)* (2015) 39(11):1575–88. doi: 10.1038/ijo.2015.100
50. Fasshauer M, Bluher M. Adipokines in Health and Disease. *Trends Pharmacol Sci* (2015) 36(7):461–70. doi: 10.1016/j.tips.2015.04.014
51. Parida S, Siddharth S, Sharma D. Adiponectin, Obesity, and Cancer: Clash of the Bigwigs in Health and Disease. *Int J Mol Sci* (2019) 20(10):2519. doi: 10.3390/ijms20102519
52. Angel CZ, Iguacel I, Mullee A, Guha N, Wasson R, McKenna DJ, et al. Appetite-Regulating Hormones-Leptin, Adiponectin and Ghrelin-and the Development of Prostate Cancer: A Systematic Review and Exploratory Meta-Analysis. *Prostate Cancer Prostatic Dis* (2020) 23(1):11–23. doi: 10.1038/s41391-019-0154-1
53. Hofmanova J, Hyrslova Vaculova A, Kozubik A. Regulation of the Metabolism of Polyunsaturated Fatty Acids and Butyrate in Colon Cancer Cells. *Curr Pharm Biotechnol* (2013) 14(3):274–88. doi: 10.2174/1389201011314030004
54. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: Revised European Consensus on Definition and Diagnosis. *Age Ageing* (2019) 48(1):16–31. doi: 10.1093/ageing/afy169
55. Mendes NP, Barros TA, Rosa COB, Franceschini S. Nutritional Screening Tools Used and Validated for Cancer Patients: A Systematic Review. *Nutr Cancer* (2019) 71(6):898–907. doi: 10.1080/01635581.2019.1595045

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Prognostic Factors in Stage IV Colorectal Cancer Patients With Resection of Liver and/or Pulmonary Metastases: A Population-Based Cohort Study

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Importance: Currently, surgical resection of distant metastatic lesions has become the preferred treatment for select colorectal cancer (CRC) patients with liver metastasis (LM) and/or pulmonary metastasis (PM). Metastasectomy is the most common curative method. However, evidence of the factors affecting the prognosis of CRC patients after resection of LM and/or PM is still insufficient.

Objective: To explore the prognostic factors of CRC patients with LM and/or PM who have undergone resection of metastatic tumors and to provide reliable selection factors for surgical treatment in patients affected by LM and/or PM from CRC.

Methods: The SEER database was used to identify eligible CRC LM and/or PM patients who underwent resection of the primary tumor and distant metastases from January 1, 2010, to December 31, 2018. The Kaplan–Meier method was used to calculate survival, and comparisons were performed using the log-rank test for univariate analysis. A Cox proportional hazards regression model was used to identify prognostic factors for the multivariate analysis. The outcomes included overall survival (OS) and cancer-specific survival (CSS).

Results: A total of 3,003 eligible colorectal cancer patients with LM and/or PM were included in this study. The 3-year and 5-year OS rates were 53% and 33.6%, respectively, and the 3-year and 5-year CSS rates were 54.2% and 35.3%, respectively. In the adjusted

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multivariate analysis, age < 65 years (OS: p=0.002, CSS: p=0.002) was associated with better long-term outcomes, and primary tumors located on the left side of the colon (OS: p=0.004, CSS: p=0.006) or rectum (OS: p=0.004, CSS: p=0.006), T3 stage (OS: p<0.001, CSS: p<0.001), number of regional lymph nodes examined ≥ 12 (OS: p<0.001, CSS: p=0.001), and CRC LM (OS: p<0.001, CSS: p<0.001) were positive prognostic factors for survival after resection of metastatic tumors.

Conclusion: Age < 65 years is associated with better long-term outcomes in colorectal cancer patients with LM and/or PM, analogously to the left sided primary tumor, T3 stage, number of regional lymph nodes examined ≥ 12 and liver metastases.

Keywords: colorectal cancer, liver metastases, pulmonary metastases, surgical resection, prognostic factors

INTRODUCTION

Approximately 149,500 cases of colorectal cancer (CRC) are diagnosed each year in the United States (1). Over half will develop distant metastases, and the liver and lung are the dominant metastatic sites. In the past decade, with the advent of new drugs and the advancement of medical technologies, survival for metastatic CRC has significantly improved. However, surgical resection is still the most likely curative method for patients with potentially resectable liver metastasis (LM). In previous surgical case series, the five-year survival rates of CRC LM patients after resection ranged from 24%-58%, with an average of 40%, and surgical mortality rates were generally<5% (2–4). There is increasing evidence that pulmonary metastasectomy can also improve the outcomes of CRC pulmonary metastasis (PM) patients (5–7). A study that included 785 CRC PM patients undergoing resection of PM with curative intent found that the 5-year overall survival rate was 68% (8), and the 5-year survival rate for patients who were treated with chemotherapy alone was at most 20% (9). Currently, surgical resection has become the preferred treatment for many appropriately selected CRC LM and/or PM patients.

Nevertheless, many factors may affect the prognosis of CRC LM and/or PM patients after surgical resection, such as age, sex, race, comorbidities, primary tumor location, primary tumor size, TNM staging, extent of distant metastasis, preoperative or postoperative chemotherapy, and radiotherapy. Identifying the clinical factors that influence patient prognosis is important for formulating reasonable treatment plans, assessing prognosis and improving the survival rate. This population-based cohort study is the first to use the SEER (The Surveillance, Epidemiology, and End Results) database to explore the prognostic factors of CRC patients with LM and/or PM who underwent resection of distant metastases with the aim of providing reliable selection factors for surgical treatment in patients affected by LM and/or PM from CRC.

MATERIALS AND METHODS

Patients and Data Sources

This is a population-based cohort study investigating the prognostic factors of CRC patients with LM and/or PM who underwent resection of LM and/or PM. All data were obtained from the SEER database [Incidence-SEER Research Data, 18 Registries, Nov 2020 Sub (2000-2018)]. The following inclusion criteria were used: 1) stage IV CRC patients with LM and/or PM who had primary tumors and metastatic tumors resected from January 1, 2010, to December 31, 2018; 2) malignant tumor confirmed by postoperative pathology to be histological type code 8140/3 (adenocarcinoma); 3) distant metastasis proven by postoperative pathology; and 4) complete postoperative follow-up data. Exclusion criteria were as follows: 1) age <18 years; 2) a second primary cancer; and 3) distant metastases at sites other than the liver and lung, such as peritoneal, bone and brain metastases. Because the SEER database is a public database, institutional ethical approval and informed consent were not required.

Data Collection

Demographic data included age, sex, race, primary tumor location, T stage, N stage, primary tumor size, number of primary tumor regional lymph nodes examined, distant metastatic sites, survival status, cause of death and follow-up time. Patients were categorized according to age (<65 years and ≥ 65 years), primary tumor size (≤40 mm and >40 mm), primary tumor location (right side of the colon, left side of the colon, and rectum), the number of regional lymph nodes examined (<12, 12-20, and > 20), and the presence of LM, PM, or both. All the above variables were considered important factors that may affect the outcome of CRC patients with LM and/or PM after surgical resection. After statistical analysis, the relationship between these variables and patient prognosis was explored.

Outcomes and Statistical Analysis

The outcome endpoints included overall survival (OS) and cancer-specific survival (CSS). OS was defined as the time from resection of CRC LM and/or PM until death from any cause, and CSS was defined as the interval from resection of CRC LM and/or PM until death from cancer cause. Complete follow-up information about vital status in the SEER database was available up to December 31, 2018. Final study analyses were performed on December 01, 2021.

The survival analysis was performed using the Kaplan–Meier method, and comparisons were made using the log-rank test for univariate analysis. Variables with $p < 0.1$ were included in the multivariable analysis. A Cox proportional hazards regression model for multivariate analysis was used to identify prognostic factors, and a P value < 0.05 was considered a significant difference. All analyses were performed using R statistical software version 3.4.1.

RESULTS

A total of 85,568 cases were retrieved initially through the SEER database. According to our inclusion and exclusion criteria, the data of 3,003 eligible cases with IV stage CRC LM and/or PM were ultimately analyzed (**Figure 1**) . All patients underwent surgical resection of the primary tumor and metastatic tumor from January 1, 2010, to December 31, 2018. The characteristics of the patients involved in the study are shown in **Table 1**. The median follow-up time after liver and/or pulmonary metastasectomy was 21 months. Patient age ranged from 18 to 85 years old. Sixty-five percent (1950) were younger than 65 years, and thirty-five percent (1053) were 65 years or older, with 44.5% of patients being female (1336). Patients with only liver metastases accounted for 88.4%, only lung metastases accounted for 3.9%, and both liver and lung metastases accounted for 7.7%. Patients with synchronous or metachronous metastases were included in the analysis.

Overall survival and cancer-specific survival curves are shown in **Figure 2**. The 3-year and 5-year OS rates were 53% and 33.6%, respectively, and the 3-year and 5-year CSS rates were 54.2% and 35.3%, respectively. In univariate analysis, age, sex, primary tumor location, T stage, number of regional lymph nodes examined, and distant metastatic sites were significant prognostic factors (**Table 2**). All these variables were included in the multivariate analysis.

In the adjusted multivariate analysis, age, primary tumor location, number of regional lymph nodes examined, and distant metastatic sites were important prognostic factors for survival (**Table 3**). An age< 65 years was associated with better long-term outcomes (OS: HR=1.173, 95% CI 1.062 to 1.295, p=0.002 and CSS: HR=1.182, 95% CI 1.067 to 1.31, p=0.002). Patients with left-sided colon (OS: HR=0.845, 95% CI 0.754 to 0.946, p=0.004 and CSS: HR=0.861, 95% CI 0.765 to 0.969, p=0.006) and rectal tumors (OS: HR=0.787, 95% CI 0.677 to 0.916, p=0.004, and CSS: HR=0.786, 95% CI 0.67 to 0.921, p=0.006) who underwent surgical resection of metastatic tumors had a better prognosis than those with right-sided colon tumors. Patients with stage T3 disease had better long-term survival outcomes (OS: HR=0.291, 95% CI 0.234 to 0.363, p<0.001 and CSS: HR=0.284, 95% CI 0.225 to 0.358, p<0.001). The number of regional lymph nodes examined appeared to be positively correlated with long-term outcomes (OS: HR=0.829,

TABLE 1 | Characteristics of the patients.

Variable	No. (%)
Age (yr.)	
<65	1950 (64.94)
≥65	1053 (35.06)
Sex	
Female	1336 (44.50)
Male	1667 (55.50)
Race	
Black	393 (13.08)
White	2318 (77.20)
Others	292 (9.72)
Primary tumor location	
Right side of colon	789 (26.28)
Left side of colon	1505 (50.11)
Rectum	486 (16.20)
N/A	223 (7.42)
T stage	
T1-2	124 (4.12)
T3	1467 (48.86)
T4	652 (21.71)
N/A	760 (25.31)
N stage	
N0	466 (15.53)
N1	995 (33.12)
N2	826 (27.52)
N/A	716 (23.83)
Primary tumor size (mm)	
≤40	321 (10.69)
>40	581 (19.35)
N/A	2101 (69.97)
Regional nodes examined	
<12	454 (15.11)
≥12, <20	1364 (45.41)
≥20	1185 (39.48)
Metastasis	
Lung	118 (3.94)
Liver	2654 (88.37)
Both	231 (7.69)

N/A Not Applicable, missing values or not specially stated.

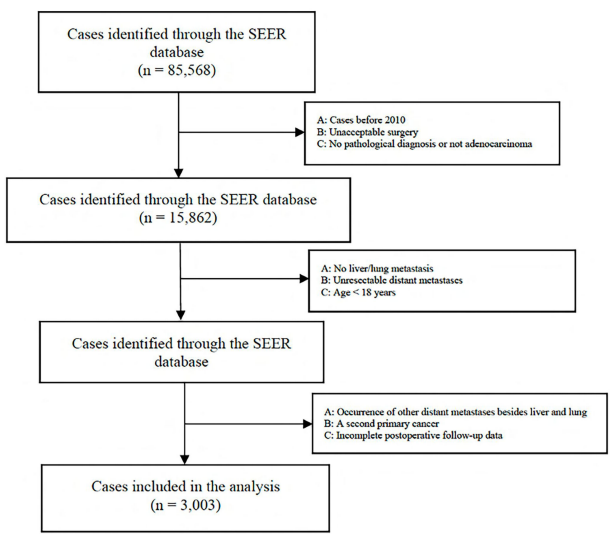

FIGURE 1 | Flowchart of the patient selection.

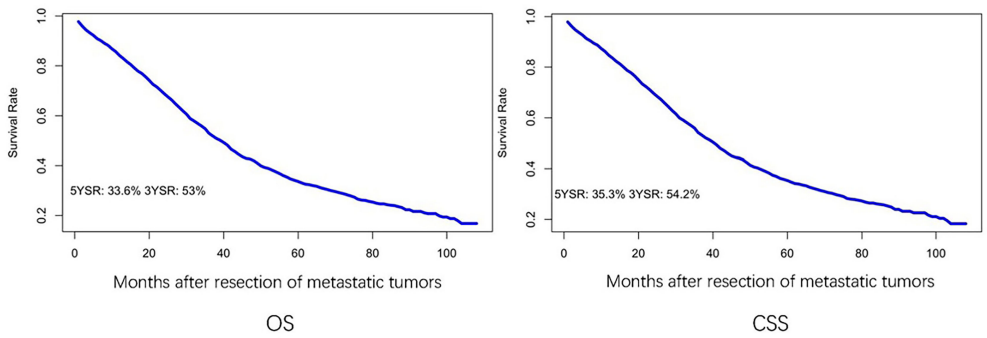

FIGURE 2 | Kaplan–Meier curve of OS and CSS after resection of LM and/or PM in CRC. YSR, year survival rate.

TABLE 2 | Univariate analysis of the prognostic factors of OS and CSS after resection of LM and/or PM in CRC.

Variable	OS			CSS		
	HR	95%CI	P Value	HR	95%CI	P Value
Age (yr.)						
<65	1	Reference	0.002	1	Reference	0.001
≥65	1.171	1.058-1.295		1.18	1.062-1.311	
Sex						
Female	1	Reference	0.072	1	Reference	0.046
Male	0.917	0.832-1.009		0.905	0.819-0.999	
Race						
Black	1	Reference	0.402	1	Reference	0.766
White	0.911	0.789-1.053		0.954	0.819-1.11	
Others	0.902	0.737-1.103		0.931	0.755-1.147	
Primary tumor location						
Right side of colon	1	Reference	0.002	1	Reference	0.006
Left side of colon	0.847	0.753-0.953		0.863	0.763-0.975	
Rectum	0.79	0.68-0.918		0.788	0.674-0.922	
T stage						
T1-2	1	Reference	<0.001	1	Reference	<0.001
T3	0.305	0.216-0.43		0.298	0.207-0.428	
T4	0.619	0.433-0.886		0.619	0.424-0.903	
N stage						
N0	1	Reference	0.1	1	Reference	0.125
N1	1	0.873-1.146		1.002	0.87-1.154	
N2	1.121	0.972-1.293		1.122	0.967-1.3	
Primary tumor size						
≤40	1	Reference	0.159	1	Reference	0.146
>40	1.159	0.935-1.437		1.173	0.939-1.465	
Regional nodes examined						
<12	1	Reference	<0.001	1	Reference	<0.001
≥12, <20	0.868	0.764-0.986		0.875	0.766-0.999	
≥20	0.811	0.711-0.925		0.805	0.702-0.924	
Metastasis						
Lung	1	Reference	<0.001	1	Reference	<0.001
Liver	0.539	0.442-0.658		0.532	0.433-0.653	
Both	3.33	1.983-5.591		3.433	2.002-5.887	

95% CI 0.725 to 0.949, p<0.001). Compared with PM only or both PM and LM, patients with LM only had a better long-term prognosis (OS: HR=0.56, 95% CI 0.447 to 0.657, p<0.001 and CSS: HR=0.284, 95% CI 0.225 to 0.358, p<0.001). In addition, male sex was a favorable factor for a prolonged CSS (CSS: HR=0.904, 95% CI 0.818 to 0.998, p=0.047).

DISCUSSION

This study is the first to use the SEER database to explore the prognostic factors of CRC patients with LM and/or PM who underwent resection of metastatic tumors. The current study showed that age, primary tumor location, T stage, number of

TABLE 3 | Multivariate analysis of the prognostic factors of OS and CSS after resection of LM and/or PM in CRC.

Variable	OS Multivariate Analysis			CSS Multivariate Analysis		
	5-y, %	HR (95%CI)	P Value	5-y, %	HR (95%CI)	P Value
Age (yr.)						
<65	36	1[Reference]	0.002	37	1[Reference]	0.002
≥65	30	1.173 (1.062-1.295)		31	1.182 (1.067-1.31)	
Sex						
Female	32	1[Reference]	0.073	33	1[Reference]	0.047
Male	35	0.916 (0.832-1.008)		37	0.904 (0.818-0.998)	
Primary tumor location						
Right side of colon	29	1[Reference]	0.004	31	1[Reference]	0.006
Left side of colon	30	0.845 (0.754-0.946)		30	0.861 (0.765-0.969)	
Rectum	35	0.787 (0.677-0.916)		37	0.786 (0.67-0.921)	
T stage						
T1-2	4	1[Reference]	<0.001	5	1[Reference]	<0.001
T3	40	0.291 (0.234-0.363)		42	0.284 (0.225-0.358)	
T4	15	0.607 (0.483-0.763)		16	0.607 (0.477-0.771)	
Regional nodes examined						
<12	27	1[Reference]	<0.001	28	1[Reference]	0.001
≥12, <20	33	0.829 (0.725-0.949)		35	0.843 (0.732-0.971)	
≥20	37	0.752 (0.654-0.866)		39	0.748 (0.646-0.867)	
Metastasis						
Lung	15	1[Reference]	<0.001	38	1[Reference]	<0.001
Liver	37	0.56 (0.477-0.657)		0	0.549 (0.466-0.647)	
Both	0	4.059 (3.114-5.29)		16	4.22 (3.217-5.537)	

regional lymph nodes examined, and distant metastatic sites are the most important prognostic factors. Compared with elderly patients (≥65 years), younger patients (<65 years) have better long-term outcomes. However, there is still a substantial proportion of elderly patients who have favorable long-term survival. Patients with primary tumors located in the left colon or rectum can obtain better CSS and OS after resection of metastatic tumors. It should be noted that preoperative T stage was found to be correlated with prognosis in the study; however, when the primary tumor was stage T3, patients achieved better long-term outcomes. In addition, the number of regional lymph nodes examined appears to be positively correlated with prognosis. When the number of regional lymph nodes examined is not less than 12, this may indicate a favorable prognosis. Finally, the prognosis of patients varies significantly depending on distant metastatic site. Compared with CRC patients with PM only or both PM and LM, patients with only LM have better long-term outcomes.

Previous studies have shown that age is an important factor affecting the prognosis of patients after resection of LM and PM, and advanced age (≥65 years) will increase the risk of death associated with surgery (4, 10–12). Despite this, there are still a significant number of elderly patients who can benefit from surgical resection and achieve good long-term survival. Advanced age is not an absolute contraindication for patients with CRC LM (10, 12, 13). Based on the results of our study, for elderly patients with CRC LM and/or PM, a detailed evaluation should be carried out before resection of metastatic tumors to minimize the risks of surgery and to provide elderly patients with the most appropriate treatment plan. The evidence supports the use of preemptive surgery for the management of highly selected metastatic CRC elderly patients.

The results of this study suggested that patients with a primary tumor located on the left side of the colon or rectum have a better prognosis than those with a primary tumor on the right side of the colon, which is consistent with the results of previous studies. A retrospective study by Corsini et al. aiming to study the effect of primary colorectal cancer tumor location on survival after pulmonary metastasectomy showed that left-sided colon and rectal cancer was associated with prolonged survival in patients after resection of PM (14). Yu et al. (15), using the Korean National Health Insurance database to study the prognostic factors of patients with colorectal cancer after PM resection, reported that the presence of distally located colon and rectal cancer is a positive factor for survival and prognosis. Yi, Chenghao (11) and Engstrand (16) also found that compared with the proximal colon, the distal colon and rectum were associated with better long-term survival after resection of metastatic tumors. All these results show that the primary tumor site has a good predictive effect on the outcome of patients after surgical resection. This discrepancy may be related to differences in the anatomical characteristics of the colorectal segments (17). More importantly, differences in molecular and pathological features reported in patients with right-sided and left-sided colon cancer may lead to different clinical features; for example, patients with metastatic right-sided cancer are more likely to have signet ring cell features, higher pathological T stage and grade, KRAS mutation, and microsatellite instability, which may also contribute to a worse prognosis of right-sided colon cancer (18–20). Currently, the

TNM staging system is recommended for predicting the prognosis of CRC patients. In our study, patients with T1-2 stage disease had worse OS and CSS rates than those with T3 stage disease, which may be related to the pathological characteristics of the tumor itself or bias in the results due to the small sample of cases with stage T1-2 disease. Further clinical studies should be designed to study the association between T stage and prognosis in colorectal cancer patients with LM and/or PM.

Lymph node examination plays an important role in evaluating the quality of surgery and for pathological examination, which is associated with accurate staging and adjuvant treatment performance (21). Currently, the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommend that at least 12 lymph nodes be examined. The current study also demonstrated that the number of regional lymph nodes examined is closely related to patient prognosis. When the number of regional lymph nodes examined is 12-20 or >20, the postoperative outcome of patients with LM and/or PM is significantly improved. Thus, surgeons should remove as many regional lymph nodes as possible to improve the prognosis of patients when resecting the primary tumor. Of course, we must also consider that more lymph node removal means greater surgical trauma. Importantly, no significant difference was observed in the prognosis of patients with different N stages, which is a novel and important finding of this study. Possible reasons include an insufficient number of lymph nodes examined to obtain an accurate N stage, and differences in disease status of distant metastatic organs, such as the size, number, and extent of metastases. More clinical research is needed to further investigate this finding.

The study by Yi et al. (11) found that among patients with single organ metastases of metastatic colorectal cancer, those with solitary pulmonary metastasis had the highest median OS. However, Siebenhüner et al. (22) reported that compared with patients undergoing resection of PM or liver and lung metastases, those with LM have better OS and CSS rates after metastatic tumors resected, which is consistent with our research results. These results show that the organ affected by distant metastasis also influences the long-term outcomes of patients after surgical resection.

In our study, race and primary tumor size were not significantly correlated with the prognosis of patients. A recent study by Feng et al. (23) using the SEER database to investigate the association between tumor size as a continuous variable and prognosis in nonmetastatic colon cancer suggested that there was a strong negative relationship between the primary tumor size and patient prognosis. However, this relationship was not found in this study. Yu et al. (15) reported that female sex was a positive prognostic factor for survival. However, our study found that male sex was a favorable factor for CSS. More clinical studies are still needed for further verification. Due to the limited patient information available in the SEER database, we were not able to study other factors that may affect prognosis. Some studies have reported that postoperative complication rates and mortality risk increased significantly when the primary tumor and synchronous liver metastases were resected simultaneously; therefore, staged operation should be recommended (24–26). However, a prospective study involving 84 patients found that when primary colorectal cancer and simultaneous liver metastases were resected at the same time, there appeared to be no difference in the complication rate. Delayed resection often compromises overall survival (27). Moreover, Zhang et al. (28) and Silberhumer et al. (29) also concluded that simultaneous surgical resection is a safe and effective treatment option for patients with CRC LM. Compared with staged surgery, there was no significant difference in the long-term prognosis of patients. At present, simultaneous surgical resection has become an optional treatment option for CRC patients with LM or PM. The lack of cytokeratin 20 expression in metastases is associated with poor overall survival for CRC PM patients (30). Isolated unilateral lung metastasis with normal CEA levels and no lymph node involvement is a positive prognostic factor for patients (31, 32). Another study reported that patients with hepatic regional lymph node involvement who underwent resection of CRC liver metastases had inferior survival compared to patients with negative nodes. Despite this poor prognostic factor, a small proportion of cases with involved nodes do achieve favorable long-term survival outcomes (33). For some CRC patients with LM and/or PM, surgical resection combined with chemotherapy or radiotherapy may also bring survival benefits (28, 34).

The study used the SEER database to explore the prognostic factors of patients with CRC LM and/or PM after surgical resection, and the results offer some very important insights and supporting evidence, providing a theoretical basis for clinical practice. Nevertheless, we must point out that this research still has some limitations. First, there was a lack of information about the patient's general physical condition in the database, such as body mass index and comorbidities. Some studies have reported that patients with serious concomitant diseases often have a poor prognosis (10, 25). Second, the different levels of experience among surgeons can influence patient outcomes and may bias the results. Third, some important potential prognostic variables were not tested in this analysis. The SEER database contains information on the surgical treatments and general outcomes of the patients, but information on preoperative tumor markers, the extent of disease at the distant metastatic site, biological features such as microsatellite status, RAS-RAF mutations, adjuvant systemic and/or local-regional therapies is lacking, limiting further analyses of the possible factors affecting the prognosis of patients. Thus, the effect of selection bias could not be controlled. Finally, control of the indication for surgery, subjective definition of resectability, and access to tertiary care may influence the results of the study to some extent. Hence, we hope that a more complete public electronic database system can be established and that further clinical studies can be designed to overcome some of these problems

to ensure that this evidence base is more comprehensive and reliable.

CONCLUSION

For CRC patients with LM and/or PM who underwent resection of metastatic tumors, age < 65 years is associated with better long-term outcomes. Nevertheless, a significant number of elderly patients (≥65 years) may still benefit from surgical resection and achieve good long-term survival outcomes. Primary tumors located on the left side are positive prognostic factors for CRC patients with LM and/or PM compared with primary tumors located on the right side. When the primary tumor stage is T3, patients often can achieve better long-term survival, which should be further verified by more clinical studies. In addition, the number of regional lymph nodes examined appears to be positively correlated with long-term outcomes and compared with CRC patients with PM only or both PM and LM, patients with only LM have a better long-term prognosis.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/).

AUTHOR CONTRIBUTIONS

PP and YC contributed to conception and design of the study. YL, PS, LW, XZ, YW, XC, PR, QL, YY, HC, HM, BS and XF contributed to the acquisition, analysis, or interpretation of data for the work. PP wrote the first draft of the manuscript. Then, YC critically revised this report. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin* (2021) 71(1):7–33. doi: 10.3322/caac.21654
2. Morris EJ, Forman D, Thomas JD, Quirke P, Taylor EF, Fairley L, et al. Surgical Management and Outcomes of Colorectal Cancer Liver Metastases. *Br J Surg* (2010) 97(7):1110–8. doi: 10.1002/bjs.7032
3. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of Long-Term Survival After Hepatic Resection for Metastatic Colorectal Cancer: A Multifactorial Model of 929 Patients. *Ann Surg* (2008) 247(1):125–35. doi: 10.1097/SLA.0b013e31815aa2c2
4. Cummings LC, Payes JD, Cooper GS. Survival After Hepatic Resection in Metastatic Colorectal Cancer: A Population-Based Study. *Cancer* (2007) 109 (4):718–26. doi: 10.1002/cncr.22448
5. Booth CM, Nanji S, Wei X, Mackillop WJ. Outcomes of Resected Colorectal Cancer Lung Metastases in Routine Clinical Practice: A Population-Based Study. *Ann Surg Oncol* (2016) 23(4):1057–63. doi: 10.1245/s10434-015-4979-0
6. Embun R, Rivas de Andrés JJ, Call S, de Olaiz Navarro B, Freixinet JL, Bolufer S, et al. Causal Model of Survival After Pulmonary Metastasectomy of Colorectal Cancer: A Nationwide Prospective Registry. *Ann Thorac Surg* (2016) 101(5):1883–90. doi: 10.1016/j.athoracsur.2015.12.017
7. Patel D, Townsend AR, Karapetis C, Beeke C, Padbury R, Roy A, et al. Is Survival for Patients With Resectable Lung Metastatic Colorectal Cancer Comparable to Those With Resectable Liver Disease? Results From the South Australian Metastatic Colorectal Registry. *Ann Surg Oncol* (2016) 23 (11):3616–22. doi: 10.1245/s10434-016-5290-4
8. Okumura T, Boku N, Hishida T, Ohde Y, Sakao Y, Yoshiya K, et al. Surgical Outcome and Prognostic Stratification for Pulmonary Metastasis From Colorectal Cancer. *Ann Thorac Surg* (2017) 104(3):979–87. doi: 10.1016/j.athoracsur.2017.03.021
9. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser Y, Al-Batran S-E, et al. FOLFIRI Plus Cetuximab Versus FOLFIRI Plus Bevacizumab as First-Line Treatment for Patients With Metastatic Colorectal Cancer (FIRE-3): A Randomised, Open-Label, Phase 3 Trial. *Lancet Oncol* (2014) 15(10):1065–75. doi: 10.1016/S1470-2045(14)70330-4
10. Booth CM, Nanji S, Wei X, Mackillop WJ. Management and Outcome of Colorectal Cancer Liver Metastases in Elderly Patients: A Population-Based Study. *JAMA Oncol* (2015) 1(8):1111–9. doi: 10.1001/jamaoncol.2015.2943
11. Yi C, Li J, Tang F, Ning Z, Tian H, Xiao L, et al. Is Primary Tumor Excision and Specific Metastases Sites Resection Associated With Improved Survival in Stage IV Colorectal Cancer? Results From SEER Database Analysis. *Am Surg* (2020) 86(5):499–507. doi: 10.1177/0003134820919729
12. Vallance AE, Young AL, Kuryba A, Braun M, Hill J, Jayne DG, et al. The Impact of Advancing Age on Incidence of Hepatectomy and Post-Operative Outcomes in Patients With Colorectal Cancer Liver Metastases: A Population-Based Cohort Study. *HPB (Oxford)* (2019) 21(2):167–74. doi: 10.1016/j.hpb.2018.06.1808
13. Nardo B, Serafini S, Ruggiero M, Grande R, Fugetto F, Zullo A, et al. Liver Resection for Metastases From Colorectal Cancer in Very Elderly Patients: New Surgical Horizons. *Int J Surg* (2016) 33(Suppl 1):S135–141. doi: 10.1016/j.ijsu.2016.06.014
14. Corsini EM, Mitchell KG, Correa A, Morris VK. Effect of Primary Colorectal Cancer Tumor Location on Survival After Pulmonary Metastasectomy. *J Thorac Cardiovasc Surg* (2021) 162(1):296–305. doi: 10.1016/j.jtcvs.2020.03.181
15. Yu WS, Bae MK, Choi JK, Hong YK, Park IK. Pulmonary Metastasectomy in Colorectal Cancer: A Population-Based Retrospective Cohort Study Using the Korean National Health Insurance Database. *Cancer Res Treat* (2021) 53 (4):1104–12. doi: 10.4143/crt.2020.1213
16. Engstrand J, Nilsson H, Strömberg C, Jonas E, Freedman J. Colorectal Cancer Liver Metastases - A Population-Based Study on Incidence, Management and Survival. *BMC Cancer* (2018) 18(1):78. doi: 10.1186/s12885-017-3925-x
17. Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, et al. Improved Survival in Metastatic Colorectal Cancer is Associated With Adoption of Hepatic Resection and Improved Chemotherapy. *J Clin Oncol* (2009) 27(22):3677–83. doi: 10.1200/JCO.2008.20.5278
18. Missiaglia E, Jacobs B, D'Ario G, Di Narzo AF, Soneson C, Budinska E, et al. Distal and Proximal Colon Cancers Differ in Terms of Molecular, Pathological, and Clinical Features. *Ann Oncol* (2014) 25(10):1995–2001. doi: 10.1093/annonc/mdu275
19. Mukund K, Syulyukina N, Ramamoorthy S, Subramaniam S. Right and Left-Sided Colon Cancers - Specificity of Molecular Mechanisms in Tumorigenesis and Progression. *BMC Cancer* (2020) 20(1):317. doi: 10.1186/s12885-020-06784-7
20. Zhao B, Lopez NE, Eisenstein S, Schnickel GT, Sicklick JK, Ramamoorthy SL, et al. Synchronous Metastatic Colon Cancer and the Importance of Primary Tumor Laterality - A National Cancer Database Analysis of Right- Versus Left-Sided Colon Cancer. *Am J Surg* (2020) 220(2):408–14. doi: 10.1016/j.amjsurg.2019.12.002
21. Guan X, Wang Y, Hu H, Zhao Z, Jiang Z, Liu Z, et al. Reconsideration of the Optimal Minimum Lymph Node Count for Young Colon Cancer Patients: A Population-Based Study. *BMC Cancer* (2018) 18(1):623. doi: 10.1186/s12885-018-4428-0

22. Siebenhüner AR, Güller U, Warschkow R. Population-Based SEER Analysis of Survival in Colorectal Cancer Patients With or Without Resection of Lung and Liver Metastases. *BMC Cancer* (2020) 20(1):246. doi: 10.1186/s12885-020-6710-1
23. Feng H, Lyu Z, Zheng J, Zheng C, Wu Q, Liang W, et al. Association of Tumor Size With Prognosis in Colon Cancer: A Surveillance, Epidemiology, and End Results (SEER) Database Analysis. *Surgery* (2021) 169(5):1116–23. doi: 10.1016/j.surg.2020.11.011
24. Driedger MR, Yamashita TS, Starlinger P, Mathis KL, Smoot RL, Cleary SP, et al. Synchronous Resection of Colorectal Cancer Primary and Liver Metastases: An Outcomes Analysis. *HPB (Oxford)* (2021) 23(8):1277–84. doi: 10.1016/j.hpb.2021.01.002
25. Robertson DJ, Stukel TA, Gottlieb DJ, Sutherland JM, Fisher ES. Survival After Hepatic Resection of Colorectal Cancer Metastases: A National Experience. *Cancer* (2009) 115(4):752–9. doi: 10.1002/cncr.24081
26. Tsilimigras DI, Sahara K, Hyer JM, Diaz A, Moris D, Bagante F, et al. Trends and Outcomes of Simultaneous Versus Staged Resection of Synchronous Colorectal Cancer and Colorectal Liver Metastases. *Surgery* (2021) 170 (1):160–6. doi: 10.1016/j.surg.2021.01.041
27. Boudjema K, Locher C, Sabbagh C, Ortega-Deballon P, Heyd B, Bachellier P, et al. Simultaneous Versus Delayed Resection for Initially Resectable Synchronous Colorectal Cancer Liver Metastases: A Prospective, Open-Label, Randomized, Controlled Trial. *Ann Surg* (2021) 273(1):49–56. doi: 10.1097/SLA.0000000000003848
28. Zhang YF, Mao R, Chen X, Zhao JJ, Bi XY, Li ZY, et al. Prognostic Analysis of 102 Patients With Synchronous Colorectal Cancer and Liver Metastases Treated With Simultaneous Resection. *Chin Med J (Engl)* (2017) 130 (11):1283–9. doi: 10.4103/0366-6999.206349
29. Silberhumer GR, Paty PB, Denton B, Guillem J, Gonen M, Araujo RLC, et al. Long-Term Oncologic Outcomes for Simultaneous Resection of Synchronous Metastatic Liver and Primary Colorectal Cancer. *Surgery* (2016) 160(1):67–73. doi: 10.1016/j.surg.2016.02.029
30. Gössling GCL, Chedid MF, Pereira FS, da Silva RK, Andrade LB, Peruzzo N, et al. Outcomes and Prognostic Factors of Patients With Metastatic Colorectal Cancer Who Underwent Pulmonary Metastasectomy With Curative Intent: A Brazilian Experience. *Oncologist* (2021) 26(9):e1581–8. doi: 10.1002/onco.13802
31. Zellweger M, Abdelnour-Berchtold E, Krueger T, Ris HB, Perentes JY, Gonzalez M, et al. Surgical Treatment of Pulmonary Metastasis in Colorectal Cancer Patients: Current Practice and Results. *Crit Rev Oncol Hematol* (2018) 127:105–16. doi: 10.1016/j.critrevonc.2018.05.001
32. Gonzalez M, Poncet A, Combescure C, Robert J, Ris HB, Gervaz P, et al. Risk Factors for Survival After Lung Metastasectomy in Colorectal Cancer Patients: A Systematic Review and Meta-Analysis. *Ann Surg Oncol* (2013) 20(2):572–9. doi: 10.1245/s10434-012-2726-3
33. Nanji S, Tsang ME, Wei X, Booth CM. Regional Lymph Node Involvement in Patients Undergoing Liver Resection for Colorectal Cancer Metastases. *Eur J Surg Oncol* (2017) 43(2):322–9. doi: 10.1016/j.ejso.2016.10.033
34. Li Y, Qin Y. Peri-Operative Chemotherapy for Resectable Colorectal Lung Metastasis: A Systematic Review and Meta-Analysis. *J Cancer Res Clin Oncol* (2020) 146(3):545–53. doi: 10.1007/s00432-020-03142-9

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Association of CT-Based Delta Radiomics Biomarker With Progression-Free Survival in Patients With Colorectal Liver Metastases Undergo Chemotherapy

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Predicting the prognosis of patients in advance is conducive to providing personalized treatment for patients. Our aim was to predict the therapeutic efficacy and progression free survival (PFS) of patients with liver metastasis of colorectal cancer according to the changes of computed tomography (CT) radiomics before and after chemotherapy.

Methods: This retrospective study included 139 patients (397 lesions) with colorectal liver metastases who underwent neoadjuvant chemotherapy from April 2015 to April 2020. We divided the lesions into training cohort and testing cohort with a ratio of 7:3. Two - dimensional region of interest (ROI) was obtained by manually delineating the largest layers of each metastasis lesion. The expanded ROI (3 mm and 5 mm) were also included in the study to characterize microenvironment around tumor. For each of the ROI, 1,316 radiomics features were extracted from delineated plain scan, arterial, and venous phase CT images before and after neoadjuvant chemotherapy. Delta radiomics features were constructed by subtracting the radiomics features after treatment from the radiomics features before treatment. Univariate Cox regression and the Least Absolute Shrinkage and Selection Operator (LASSO) Cox regression were applied in the training cohort to select the valuable features. Based on clinical characteristics and radiomics features, 7 Cox proportional-hazards model were constructed to predict the PFS of patients. C-index value and Kaplan Meier (KM) analysis were used to evaluate the efficacy of predicting PFS of these models. Moreover, the prediction performance of one-year PFS was also evaluated by area under the curve (AUC).

Results: Compared with the PreRad (Radiomics form pre-treatment CT images; C-index [95% confidence interval (CI)] in testing cohort: 0.614(0.552-0.675) and PostRad models (Radiomics form post-treatment CT images; 0.642(0.578-0.707), the delta model has better PFS prediction performance (Delta radiomics; 0.688(0.627-0.749). By incorporating clinical characteristics, CombDeltaRad obtains the best performance in both training cohort [C-index (95% CI): 0.802(0.772-0.832)] and the testing cohort (0.744 (0.686-0.803). For 1-year PFS prediction, CombDeltaRad model obtained the best

performance with AUC (95% CI) of 0.871(0.828-0.914) and 0.745 (0.651-0.838) in training cohort and testing cohort, respectively.

Conclusion: CT radiomics features have the potential to predict PFS in patients with colorectal cancer and liver metastasis who undergo neoadjuvant chemotherapy. By combining pre-treatment radiomics features, post-treatment radiomics features, and clinical characteristics better prediction results can be achieved.

Keywords: radiomics, computed tomography, progression-free survival, colorectal liver metastases, chemotherapy

INTRODUCTION

Globally, colorectal cancer ranks as the third most common type of cancer but ranks second in terms of mortality (1). Approximately 50% to 60% of patients diagnosed with colorectal cancer will develop colorectal metastases (2–4) and the liver is the most common location for of metastasis (5). Colorectal metastasis is usually metachronous (after local colorectal cancer treatment) (5). An estimated 20%–34% of patients with colorectal cancer present with synchronous liver metastases (6, 7). Synchronous colorectal liver metastases (CRLM) patients tend to have a poor prognosis with a reported 1-year survival less than 30% and a 5-year survival less than 5% if untreated. The 5-year survival rates for the selected group that can undergo curative surgical resection can be up to 60% (8). For patients with CRLM, complete surgical resection of all metastases is considered to be the only curative method (9, 10). However, 80%–90% of the patients with CRLM cannot receive curative surgical resection due to either the tumor being too large or medical conditions accompanying the disease (3, 6, 11–16). Patients with unresectable CRLM have indications for palliative systemic treatment and will undergo neoadjuvant chemotherapy (14, 17). Depending on the therapeutic effect of neoadjuvant chemotherapy, patients may receive surgical resection or local treatment (18). Predicting the prognosis of patients with neoadjuvant chemotherapy in advance will help doctors in making treatment decisions or adjustments.

Computerized tomography (CT) imaging plays a vital role in the diagnosis and efficacy prediction of CRLM. To date, the main content of imaging prediction includes the visual assessment of the lesion size and morphological changes in response to treatment. However, the information obtained from CT is limited because it mainly relies on visual assessment. Fortunately, recent studies have shown that texture analysis enhances the interpretation of CT images, which may reveal underlying tumor biology (19). It can directly extract biological data from radiographic images without invasive operations, thereby, saving cost, time, and avoiding most of all risk to the patient. Texture analysis of CT images involves a computational process, which can spatially quantify the voxel of CT images and effectively correlate the structural features of tumors with the voxel features of CT images (20). In patients with CRLM, texture analysis has been studied using CT data. To date, two main settings have been explored: one group of studies focused on the intralesional texture of the liver metastases itself, which was found to be significantly correlated with the response to chemotherapy, as well as with patient survival (21–24). Other studies focused not on the texture of the metastases but on that of the surrounding liver parenchyma and showed that diffuse parenchymal textural changes may hold promise as a prognostic marker to assess and even predict the occurrence of metastatic disease in the liver (23, 24). Although the texture of metastatic liver cancer and their surrounding parenchyma has been studied, to our knowledge, whether the differences in the focal image texture before and after treatment can predict the curative efficacy has not been reported. This will be an interesting study that will provide valuable insights into the relationship between novel imaging biomarkers and underlying tumor behavior.

The purpose of this study is to combine CT imaging and clinical characteristics to study the image texture changes of colorectal liver metastases before and after treatment, in the hope of helping to predict the efficacy of chemotherapy, and thus contributing to treatment decision-making.

METHODS

Patients

The retrospective study included patients with liver metastases from colorectal cancer diagnosed at the Sixth Affiliated Hospital of Sun Yat-sen University from April 2015 to April 2020. The TNM Classification of Malignant Tumors (TNM) stages, pathological types and differentiation, chemotherapy regimen, immunohistochemistry, gene detection and laboratory results (alanine transaminase, aspartate transaminase, glutamine transaminase, alkaline phosphatase, total bilirubin, direct bilirubin, total bile acid, alpha fetoprotein, carcinoembryonic antigen) of the patients were reviewed. All patients met the following inclusion criteria: (a) pathologically confirmed colorectal adenocarcinoma, (b) first-time and untreated patients, (c) CT plain scan and enhanced examination were performed, and (d) reexamined within 3 months after chemotherapy. The exclusion criteria for this study were: (a) patients who had received neoadjuvant chemotherapy or radiotherapy before surgery and (b) first-time patients without liver metastases. A total of 139 patients with an average age of 57 ± 10 years were included.

Treatments and Follow-Up

All patients underwent neoadjuvant chemotherapy and underwent imaging follow-up. The time of our study began with CT plain scan and contrast-enhanced CT examination at the first diagnosis. After chemotherapy, patients were followed up every 2-4 months until the progression of liver metastasis, other distant metastasis, the last follow-up date, or death occured. Progression free survival (PFS) was measured in months from the date of first diagnosis to the first date of local recurrence or progression, distant metastasis, last follow-up date, or death, whichever came first. Overall survival (OS) was measured in months from local recurrence or progression to the date of death or the last follow-up. The last follow-up date was February 5, 2021.

CT Image Acquisitions

A Toshiba 640-slice CT scanner (Toshiba Medical Systems, Tokyo, Japan) was used to perform contrast-enhanced CT examinations at a tube voltage of 120 kV, automatic tube current modulation, 0.814 pitch, and 0.5 mm reconstruction section thickness. All patients received intravenous injection of a contrast agent (Iopromide, Bayer Healthcare, 370 mg / ml, 1.3-1.5ml / kg, and a injection rate of 3 - 4 ml / s). After the injection of the contrast agent, double helix scan in the arterial phase and portal venous phase were acquired. In order to avoid the possibility of image information loss, we obtained DICOM images directly from the picture archiving and communication system (PACS) system without compression and down sampling.

Radiomic Analysis

The four steps of radiomic analysis workflow are presented in **Figure 1**, including lesion segmentation, image preprocessing, radiomic feature extraction, radiomic feature selection, model building, and model evaluation and application.

Lesion Segmentation

Two-dimensional manual segmentation of lesion in axial image of plain scanning, arterial, and venous phases was performed by an open-source ITK-SNAP software (www.itksnap.org). The largest section of the lesion was selected. Regions-of-interest (ROI) were manually delineated by a radiologist who had 5 years of experience in abdomen CT imaging interpretation and checked by a senior radiologist with 5 years of experience in liver CT imaging interpretation. Because of the presence of patients with multiple metastases, only the largest five lesions were selected for analysis in each patient. When the number of metastases was greater than 5, we chose to include all of them.

Image Preprocessing and Radiomic Feature Extraction

Image preprocessing and radiomic feature extraction were carried out with in-house software (Artificial Intelligence Kit, v. 3.3.0, GE Healthcare). The steps are as follows: firstly, every image and the corresponding ROI were resampled to a uniform pixel dimension size of 1×1 mm^2; and secondly, each delineated ROI (ROI_delineated) was expanded the edge by 3mm and 5mm in AK software, automatically. In this way, we acquired 2 circular ROIs (ROI_circle3 and ROI_circle5) and two enlarged ROIs (ROI_expand3 and ROI expand5). The diagram of ROI expansion is shown in **Figure 1**. Each circular ROI and enlarged ROI were checked. The ROI was manually corrected for regions outside of liver parenchyma. Finally, we performed radiomics feature extraction on ROI_delineated, ROI_circle3, ROI_circle5, ROI_ expand3 and ROI_expand5. For each phase (non-enhanced, arteria,l and venous images phase) in pre-treatment and post-treatment CT images, we extract 6,580 radiomic features (1,316 radiomic features for one ROI, with 5

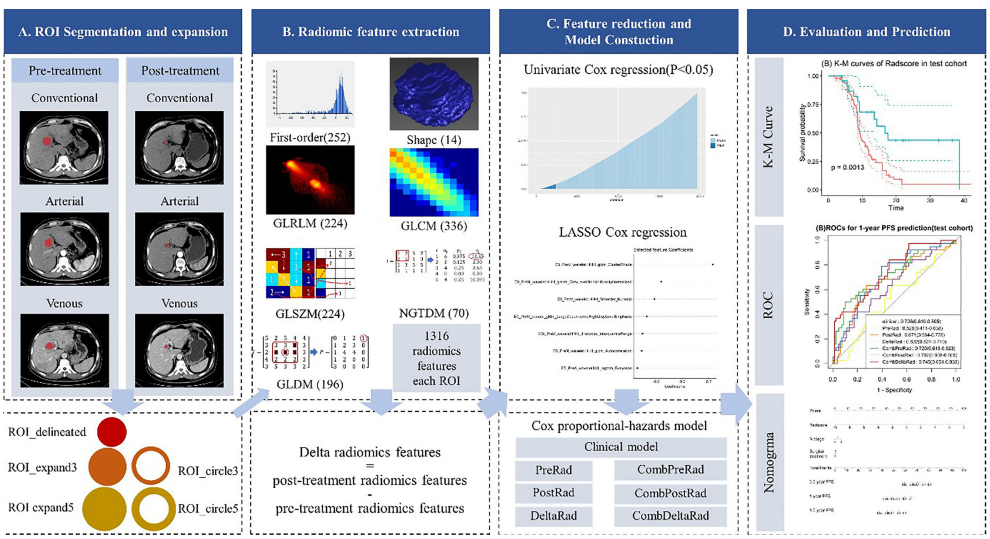

FIGURE 1 | Radiomics framework of predicting the PFS of patients with colorectal liver metastases undergo neoadjuvant chemotherapy. PFS, progress-free survival.

ROI in total). Finally, we obtained 19,740 features on the pre-treatment and post-treatment CT images, respectively. In order to explore the changes in the feature values before and after the treatment, we obtained the delta feature by subtracting the features after the treatment from the features before the treatment.

Among these 1,316 features, 7 categories of features were extracted: shape features (n = 14), first order features (n = 252), Gray Level Co-occurrence Matrix (GLCM, n = 336), Gray Level Run Length Matrix (GLRLM, n = 224), Gray Level Size Zone Matrix (GLSZM, n = 224), Gray Level Dependence Matrix (GLDM, n = 196), Neighboring Gray Tone Difference Matrix (NGTDM, n = 70).

Radiomic Feature Selection

Patients were randomly assigned to training or testing groups and we ensured that the ratio of the number of lesions in the training and testing groups was 7:3. All cases in the training cohort were used to train the predictive model and cases in the testing cohorts were used to evaluate the model's performance. Features with zero variance were excluded and missing values and outliers were replaced by the median. Finally, the Z-score is used to standardize the data and the data of different magnitudes are uniformly converted into the same magnitude to ensure the comparability between the data (25, 26).

Although a large number of radiomics features were extracted in previous step, not all of them are relevant to the prognosis of patients with liver metastases from colorectal cancer. In this study, the univariate Cox regression and least absolute shrinkage and selection operator (LASSO) Cox regression were used to select valuable features from the training cohort. Univariate Cox proportional hazard regression model was first applied to each feature. If the p-value of a feature in the univariate Cox model was less than 0.05, the feature was selected, otherwise the feature was removed. LASSO Cox regression was then performed for multivariate feature selection by introducing a penalizing parameter (lambda). Tuning lambda can affect the weight coefficients of each feature and the performance of the Lasso cox model. The features with a weight coefficient of 0 in Lasso cox model were eliminated. In order to get an optimal feature number and avoid over-fitting, the parameter tuning was performed under ten-fold cross-validation. The parameters were finally determined by the performance of LASSO Cox model.

Model Building

Multivariate Cox proportional hazard model was used to build a prognostic prediction model for liver metastasis from colorectal cancer.

Clinical Model

Seven Candidate clinical variables for the prognosis of liver metastasis from colorectal cancer were selected, including age, sex, T stage, N stage, M stage, metastasis status, and surgical treatment. Univariate Cox regression was used to assess predictive power of the clinical candidates. Clinical variables with a P value less than 0.05 were selected to construct clinical models.

Radiomics Model

Three radiomic models were constructed using radiomic features extracted from pre-treatment, post-treatment images, and differences between the two, namely pre-treatment radiomics model (PreRad), post-treatment radiomics model (PostRad), and delta radiomics model (DeltaRad). The feature selection process is shown in section "Radiomic Feature selection". A radiomics score (Rad-Score) was calculated for each patient by linear combination of radiomic features with associated weights.

Combined Model

Radscores from pre- and post-treatment imaging features and their differences were separately combined with clinical features significant in the univariate analysis to form three combined prediction models: CombPreRad, CombPostRad, and CombDeltaRad.

Model Evaluation and Application

C-index was used to evaluate model performance. It reflects the consistency between the PFS predicted by the model and the actual PFS of all patients. The value range of C-index is 0.5-1 A C-index of 0.5 indicates that the predicted value is poor and a C-index greater than 0.7 indicates moderate to excellent performance.

Based on result of the three models in the training cohort, X-tile was performed to stratify patients into high-risk group and low-risk group in both training and testing cohorts. The Kaplan–Meier (KM) survival curve analyses of PFS was performed and log-tank test is used to compare the difference in survival curves between high- and low- risk groups.

In addition, we evaluated the effectiveness of the combined COX model in predicting the probability of PFS at a given time point (PFS of 1 years in this study). Receiver operating characteristic (ROC) analysis was performed to estimate the prognostic performance of the three combined models in predicting 1-year PFS. The calibration curves and Hosmer-Lemeshow test were utilized to assess the agreement between predicted and actual probabilities of various models. The net reclassification index (NRI) and total integrated discrimination index (IDI) were used to assess the clinical benefit of different models.

For model visualization and clinical application, we constructed a nomogram based on the model with the highest discriminative efficiency.

Statistical Analysis

All statistical analyses were performed using R 3.6.1. Where appropriate, the two-sample t-test, chi-square test, or Mann-Whitney U test was applied to the training and validation cohorts to assess clinical findings, image characteristics, and median PFS time. The Lasso-based feature selection, C-index calculation, and X-tile-based threshold acquisition were implemented using the "glmnet", "survcomp" and "survminer" package, respectively. The Cox proportional hazard model construction, Kaplan-Meier curve analysis, and Log-rank test used the "survival " package. The construction of nomogram and calibration curve were implemented with the "rms" package. A two-tailed P-value less than 0.05 was considered statistically significant.

RESULT

Patient Characteristics

In this study, 397 lesions from 139 patients were included. The patient characteristics are presented in **Table 1**. The clinical characteristics of different lesions in the same patient are assigned the same value as the patient. The average age of the patients was 56.96 ± 11.06 years. The number of male patients was 96 (69.06%). There were 43 (30.94%), 22 (15.83%), 22 (15.83%), 15 (10.79%) and 37 (26.62%) patients with 1, 2, 3, 4 and 5 metastases lesions, respectively. The mean PFS time was 11.80 ± 7.93 months.

Feature Selection and Radiomics Signature Construction

Ct-Stage and surgical treatment were significant clinical features in the univariate Cox regression analysis. The HR values and 95% confidence interval (CI) of Ct-stage and surgical treatment in multivariate cox regression are 2.033 (1.507~0.433) and 0.582 (1.507~0.433), respectively. These two clinical features were used to construct a clinical model.

Based on the dimensionality reduction methods of univariate cox regression and lasso cox regression analysis, the PreRad, PostRad and DeltaRad models are constructed by 7, 15, and 24 features, respectively.

A radscore was calculated based on radiomic features and their associated weight from lasso cox model. **Figure 2** shows the coefficients of each feature based on PreRad model.

TABLE 1 | Clinical characteristics of patients.

Characteristics	Patients (N = 139)
Age (years, mean ± SD)	56.96 ± 11.06
Gender (%)	
Male	96 (69.06%)
Female	43 (30.94%)
cT stage (%)	
3	85 (61.15%)
4	54 (38.85%)
cM.stage (%)	
1	139 (100.00%)
cN stage (%)	
0	6 (4.32%)
1	36 (25.90%)
2	97 (69.78%)
Metastasis to other sites	
No	93 (66.91%)
Yes	46 (33.09%)
Surgical treatment	
No	78 (56.12%)
Yes	61 (43.88%)
Number of metastatic lesions per patient	
1	43 (30.94%)
2	22 (15.83%)
3	22 (15.83%)
4	15 (10.79%)
5	37 (26.62%)
Mean PFS time (months, mean ± SD)	11.80 ± 7.93

PFS Prediction Performance of Various Models

Seven models were constructed by combining clinical variable with radscore calculated from CT images before and after treatment, namely clinical, namely PreRad, PostRad, DeltaRad, CombPreRad, CombPostRad, and CombDeltaRad, respectively. The C-index of these models in the training cohort and testing cohort are shown in **Table 2**.

The performance of the clinical model is moderate, with a C-index value and 95% CI of 0.661(0.600-0.721) and 0.673 (0.583-0.763) in the training and testing cohort. The combined model demonstrated an increased performance. For radiomics features, the performance is ranked as DeltaRad, PostRad, and PreRad in descending order, both in training and testing cohort. CombDeltaRad achieved the best performance in both training cohort (C-index (95% CI): 0.802(0.772-0.832)) and the testing cohort (0.744(0.686-0.803)).

1-Year PFS Probability Prediction of Various Models

For 1-year PFS probability prediction, the training and testing performance of different models are shown in **Table 3**. The result is consistent with PFS prediction performance. CombDeltaRad model obtained the best performance with area under the curve (AUC) and 95% CI of 0.871(0.828-0.914) and 0.745(0.651-0.838) in training cohort and testing cohort, respectively. The ROCs for 1-year PFS probability prediction of various models are presented in **Figure 3**. The calibration curves and Hosmer-Lemeshow test results of various models are presented in **Supplementary Material**. The p-value of both the training cohort and the testing cohort of the CombDeltaRad model is greater than 0.05. The reclassification measures of discrimination confirmed that DeltaRad, CombPreRad, CombPostRad and CombDeltaRad better than the clinical models with NRI of 0.042 [-0.205 - 0.289], 0.008 [-0.180 - 0.195], 0.049 [-0.135 - 0.232] and 0.033 [-0.188 - 0.254] Respectively; and IDI of 0.034 [-0.166 - 0.233], 0.006 [-0.146 - 0.158], 0.039 [-0.109 - 0.187] and 0.026 [-0.152 - 0.205], respectively (**Supplementary Material**, **Supplementary Tables 2, 3**).

Kaplan-Meier Analysis

The X-tile method was used to determine the cutoff value of the CombDeltaRad model in training cohort data. Then, the patients were divided into high-risk groups and low-risk groups based on this cutoff value. In this study, the cutoff value of the CombDeltaRad model was 0.183. **Figure 4** shows the Kaplan-Meier analysis of the CombDeltaRad model.

For the training cohort, the median PFS times were 8.67 months and 21.67 months in the high-risk and low-risk groups, respectively. For the testing cohort, the median PFS times were 9.17 months and 16.70 months in the high-risk and low-risk groups, respectively. There were significant differences between the low- and high-risk groups (log-rank test, $P < 0.0001$, $P = 0.0013$, respectively).

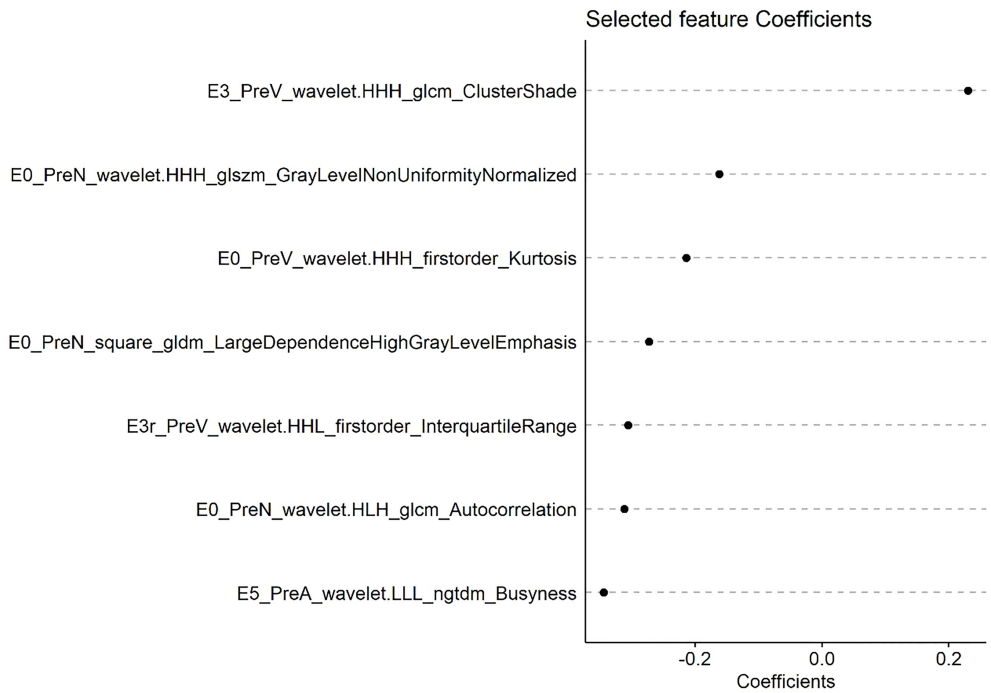

FIGURE 2 | The coefficients of each feature based on PreRad model.

Nomogram Construction

For clinical use, we built a nomogram based on the CombDeltaRad model (**Figure 5**). The nomogram consists of three factors: N-stage, surgical treatment, and radscore (delta). A total score was calculated by summing the scores of each factor for each patient. The higher the score, the lower the 1-, 3-, and 5- year survival probability.

DISCUSSION

Previous studies have used a large number of clinical, pathological, and molecular factors to predict the survival rate of patients with colorectal cancer after hepatectomy (27–33). This includes: the stage of primary tumor, preoperative serum CEA concentration, the size and number of metastases, whether there is extrahepatic metastasis, or the size of the retained edge during resection. Based on these data, people have established the survival scale, of which the most widely recognized is described by Fong et al. and Iwatsuki et al. (34, 35). However, these studies rarely extract useful texture features and clinical features through imaging images. At the same time, it is difficult to predict the curative effect for the lesions with no obvious imaging changes in a short time. In order to solve this problem, in our study, we predicted the efficacy and prognostic value of CT imaging features in patients with liver metastasis after neoadjuvant chemotherapy. The results show that this method has a good prediction effect on PFS. Our research will help to predict the efficacy and progress of patients after neoadjuvant chemotherapy through image texture features and changes, so as to assist in the clinical treatment decision-making process.

TABLE 2 | PFS prediction performance of various models.

Models	Training cohort C-index (95 CI %)	Testing cohort C-index (95 CI %)
Clinical	0.661 (0.600-0.721)	0.673 (0.583-0.763)
PreRad	0.669 (0.626-0.712)	0.614 (0.552-0.675)
PostRad	0.757 (0.721-0.793)	0.642 (0.578-0.707)
DeltaRad	0.800 (0.771-0.829)	0.688 (0.627-0.749)
CombPreRad	0.701 (0.662-0.740)	0.696 (0.638-0.754)
CombPostRad	0.763 (0.728-0.798)	0.694 (0.633-0.755)
CombDeltaRad	0.802 (0.772-0.832)	0.744 (0.686-0.803)

Image feature extraction includes conventional scanning, arterial scanning, and venous scanning, which helps to increase the number of extracted features adding diversity of feature extraction. We chose 2D ROI for sketching, because while previous studies have shown that both 3D and 2D segmentation are reliable, the 2D method is more practical, time-saving, and can reduce the contour change between readings (34).

When clinical features were combined with radiomics features, CombDeltaRad performed best in the training cohort (Cindex (95% CI): 0.802 (0.772-0.832)) and the testing cohort Cinde (95% CI): 0.744 (0.686-0.803)); The AUC (95% CI) of CombDeltaRad model obtained the best performance in the training queue 0.871 (0.828-0.914) and the test queue 0.745 (0.651-0.838). The one-year PFS prediction was consistent with the PFS prediction performance. This shows that when

TABLE 3 | 1-year PFS prediction performance of various models.

Models	cohort	AUC (95% CI)	ACC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Clinical	training	0.689 (0.626-0.753)	0.622 (0.621-0.624)	0.745 (0.657-0.833)	0.560 (0.488-0.632)
	testing	0.708 (0.610-0.805)	0.664 (0.660-0.668)	0.711 (0.566-0.855)	0.642 (0.538-0.746)
PreRad	training	0.725 (0.663-0.787)	0.673 (0.671-0.674)	0.638 (0.541-0.735)	0.690 (0.623-0.757)
	testing	0.526 (0.414-0.638)	0.395 (0.391-0.399)	0.974 (0.923-1.025)	0.123 (0.052-0.195)
PostRad	training	0.804 (0.751-0.856)	0.709 (0.707-0.710)	0.734 (0.645-0.823)	0.696 (0.629-0.762)
	testing	0.632 (0.524-0.740)	0.681 (0.677-0.684)	0.421 (0.264-0.578)	0.802 (0.716-0.889)
DeltaRad	training	0.852 (0.807-0.897)	0.759 (0.758-0.760)	0.840 (0.766-0.914)	0.717 (0.652-0.782)
	testing	0.707 (0.608-0.806)	0.664 (0.660-0.668)	0.789 (0.660-0.919)	0.605 (0.498-0.711)
CombPreRad	training	0.777 (0.721-0.832)	0.741 (0.740-0.742)	0.564 (0.464-0.664)	0.832 (0.777-0.886)
	testing	0.671 (0.564-0.778)	0.697 (0.694-0.701)	0.632 (0.478-0.785)	0.728 (0.632-0.825)
CombPostRad	training	0.840 (0.791-0.888)	0.773 (0.772-0.775)	0.745 (0.657-0.833)	0.788 (0.729-0.847)
	testing	0.720 (0.618-0.823)	0.773 (0.770-0.776)	0.500 (0.341-0.659)	0.901 (0.836-0.966)
CombDeltaRad	training	0.871 (0.828-0.914)	0.809 (0.808-0.810)	0.745 (0.657-0.833)	0.842 (0.790-0.895)
	testing	0.745 (0.651-0.838)	0.639 (0.635-0.642)	0.842 (0.726-0.958)	0.543 (0.435-0.652)

combining clinical features with radiological features, the radiological score can provide more prognostic information than a single clinical or radiological feature through clinical features and extracted image features. Therefore, it can be used as a reference to obtain prognosis, so as to provide the ability to improve or predict prognosis. At the same time, radscore can divide patients into high-risk group and low-risk groups, which is helpful to the stratification of patients. Patients with higher radscore have poorer PFS, suggesting that the risk of recurrence and metastasis is higher, and early treatment is more favorable. Our findings will open a key step to enable surgeons to tailor different treatment options for high-risk and low-risk colorectal cancer patients with liver metastasis according to specific clinical and radiological characteristics.

Among the 1,316 radiological features, 7 categories of image features were extracted and combined with clinical features to obtain 3 combined models, namely CombPreRad, CombPostRad, and CombDeltaRad. Finally, 24 were identified as predictive features of PFS, of which 16 were wavelet features, which may indicate that wavelet features contain more prognostic information. In addition, two logarithmic features are extracted from the image. Wavelet features reflect tumor information from eight spatial domains and logarithmic features reflect tumor information from three frequency domains. This result shows that much prediction information can be mined by wavelet and logarithmic transformation of the original image. This further reflects the advantages of the radiomics method, because it is good at mining high-dimensional information which is difficult to perceive manually. For example, selecting "SumEntropy" in wavelet subspace and "skewness" in logarithmic subspace shows that tumor heterogeneity described by entropy and tumor intensity has prognostic value in high-dimensional wavelet and logarithmic space.

Although the radiology score was good, our study had some limitations. Firstly, we mine seven features from CT images and combine their manifestations with clinical factors. However, the association between radioactive characteristics and biological level events has not been explained. Secondly, this study is a single center study and the sample size is small. In the future, we plan to cooperate with multiple centers for research and plan to

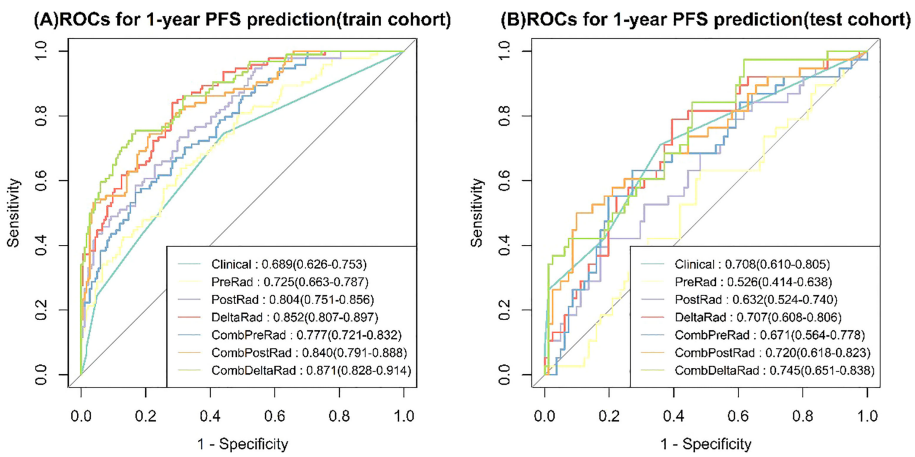

FIGURE 3 | ROCs for 1-year PFS probability prediction of various Models. **(A)** train cohort, **(B)** test cohort.

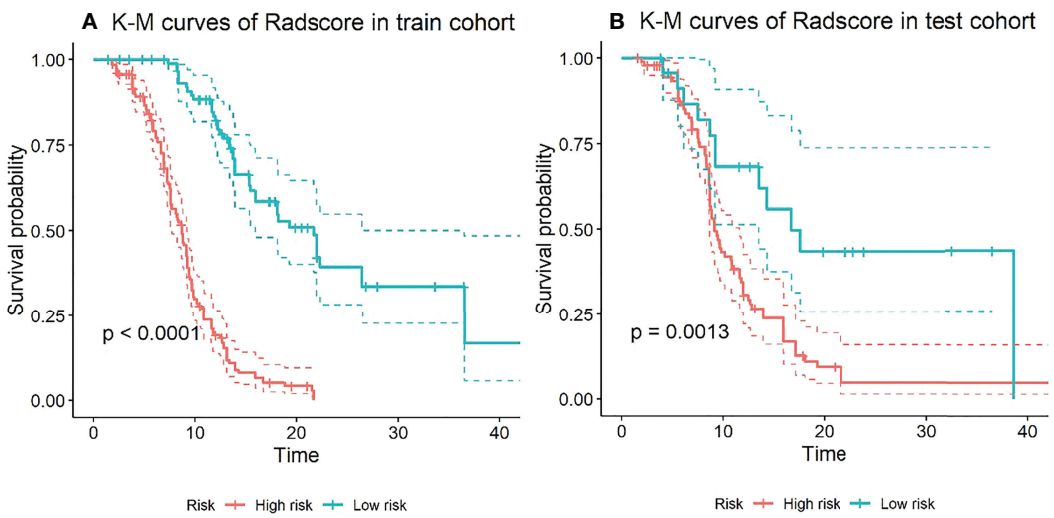

FIGURE 4 | Kaplan-Meier analysis of PFS based on CombDeltaRad model. **(A)** train cohort, **(B)** test cohort.

combine genotyping with radiation characteristics. Thirdly, the longest PFS of the data we included is only 43 months and the current model may not be able to predict long-term PFS. We will continue to follow up the data and verify the model's prediction of long-term PFS in the next step. In addition, as an emerging method in medical image analysis, deep learning can provide valuable features and supplement radiological features (35).

In conclusion, this study provides a noninvasive and preprocessing method for CT based PFS of colorectal cancer liver metastasis. In addition, for each patient with colorectal cancer liver metastasis, the radiation score can divide the patients into a high-risk group and a low-risk group. This study may provide some important insights for precise treatment and valuable guidance for clinicians.

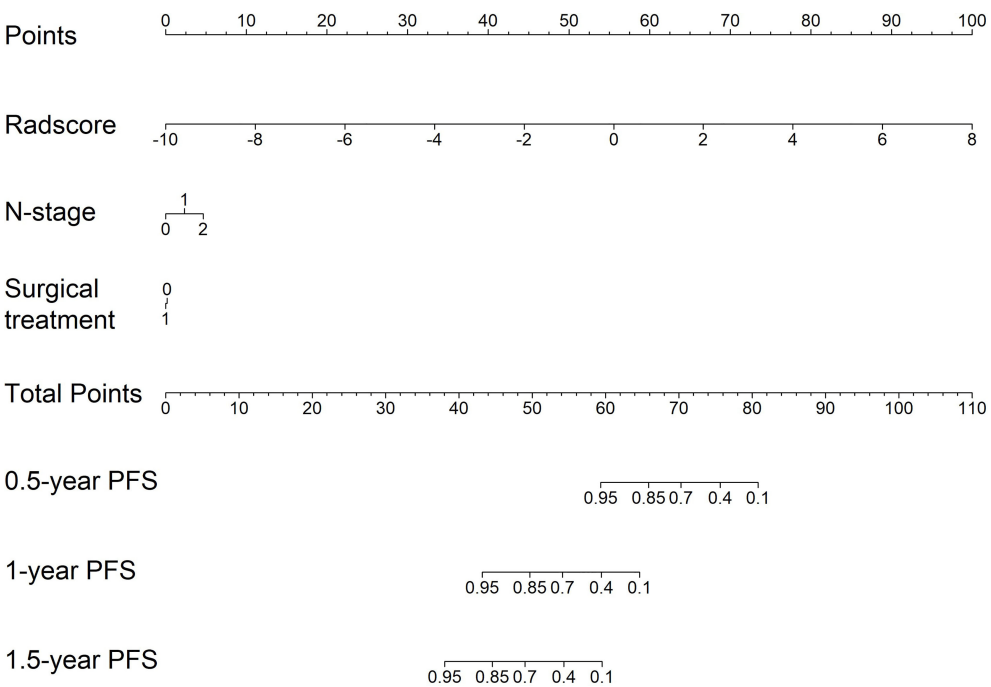

FIGURE 5 | The nomogram for PFS probability prediction based on CombDeltaRad model.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

SY: Formal analysis, Investigation, Writing - original draft. YH: Investigation KXN: Investigation YTL: Methodology, Software. XCT: Conceptualization, Supervision, Writing – review and editing. XMP participated in data collection, data analyses, software, and interpretation. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIALS

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.843991/full#supplementary-material

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660
2. Lee WS, Yun SH, Chun HK, Lee WY, Yun HR, Kim J, et al. Pulmonary Resection for Metastases From Colorectal Cancer: Prognostic Factors and Survival. *Int J Colorect Dis* (2007) 22:699–704. doi: 10.1007/s00384-006-0218-2
3. Van Cutsem E, Nordlinger B, Adam R, Köhne CH, Pozzo C, Poston G, et al. Towards a Paneuropean Consensus on the Treatment of Patients With Colorectal Liver Metastases. *Eur J Cancer* (2006) 42:2212–21. doi: 10.1016/j.ejca.2006.04.012
4. Yoo PS, Lopez-Soler RI, Longo WE, Cha CH. Liver Resection for Metastatic Colorectal Cancer in the Age of Neoadjuvant Chemotherapy and Bevacizumab. *Clin Colorectal Cancer* (2006) 6:202–7. doi: 10.3816/CCC.2006.n.036
5. Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, et al. Liver Resection for Colorectal Metastases. *J Clin Oncol* (1997) 15:938–46. doi: 10.1200/JCO.1997.15.3.938
6. Muratore A, Zorzi D, Bouzari H, Amisano M, Massucco P, Sperti E, et al. Asymptomatic Colorectal Cancer With Un-Resectable Liver Metastases: Immediate Colorectal Resection or Up-Front Systemic Chemotherapy? *Ann Surg Oncol* (2007) 14:766–70. doi: 10.1245/s10434-006-9146-1
7. Hayashi M, Inoue Y, Komeda K, Shimizu T, Asakuma M, Hirokawa F, et al. Clinicopathological Analysis of Recurrence Patterns and Prognostic Factors for Survival After Hepatectomy for Colorectal Liver Metastasis. *BMC Surg* (2010) 10:27. doi: 10.1186/1471-2482-10-27
8. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and Management of Liver Metastases From Colorectal Cancer. *Ann Surg* (2006) 244(2):254–9. doi: 10.1097/01.sla.0000217629.94941.cf
9. Noren A, Eriksson HG, Olsson LI. Selection for Surgery and Survival of Synchronous Colorectal Liver Metastases; a Nationwide Study. *Eur J Cancer* (2016) 53:105–14. doi: 10.1016/j.ejca.2015.10.055
10. Bipat S, Niekel MC, Comans EF, Nio CY, Bemelman WA, Verhoef C, et al. Imaging Modalities for the Staging of Patients With Colorectal Cancer. *Netherl J Med* (2012) 70(1):26–34. doi: 10.3402/ljm.v7i0.19086
11. Alberts SR, Horvath WL, Sternfeld WC, Goldberg RM, Mahoney MR, Dakhil SR, et al. Oxaliplatin, Fluorouracil, and Leucovorin for Patients With Unresectable Liver-Only Metastases From Colorectal Cancer: A North Central Cancer Treatment Group Phase II Study. *J Clin Oncol* (2005) 23:9243–9. doi: 10.1200/JCO.2005.07.740
12. Dawood O, Mahadevan A, Goodman KA. Stereotactic Body Radiation Therapy for Liver Metastases. *Eur J Cancer* (2009) 45:29472959. doi: 10.1016/j.ejca.2009.08.011
13. Kemeny N. Management of Liver Metastases From Colorectal Cancer. *Oncol (Williston Park)* (2006) 20(10):1161–76, 1179; discussion 1179–80, 1185–6.
14. Eisenhauer E, Therasse P, Bogaerts J, Schwartz L, Sargent D, Ford R, et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). *Eur J Cancer* (2009) 45(2):228–47. doi: 10.1016/j.ejca.2008.10.026
15. Robinson PJ. The Effects of Cancer Chemotherapy on Liver Imaging. *Eur Radiol* (2009) 19(7):1752–62. doi: 10.1007/s00330-009-1333-6
16. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* (2000) 92(3):205–16. doi: 10.1093/jnci/92.3.205
17. Castellano G, Bonilha L, Li LM, Cendes F. Texture Analysis of Medical Images. *Clin Radiol* (2004) 59(12):1061–9. doi: 10.1016/j.crad.2004.07.008
18. Niekel MC, Bipat S, Stoker J. Diagnostic Imaging of Colorectal Liver Metastases With CT, MR Imaging, FDG PET, and/or FDG PET/CT: A Meta-Analysis of Prospective Studies Including Patients Who Have Not Previously Undergone Treatment. *Radiology* (2010) 257(3):674–84. doi: 10.1148/radiol.10100729
19. Lubner MG, Stabo N, Lubner SJ, del Rio AM, Song C, Halberg RB, et al. CT Textural Analysis of Hepatic Metastatic Colorectal Cancer: Pre-Treatment Tumor Heterogeneity Correlates With Pathology and Clinical Outcomes. *Abdom Imaging* (2015) 40(7):2331–7. doi: 10.1007/s00261-015-0438-4
20. Miles KA, Ganeshan B, Griffiths MR, Young RC, Chatwin CR. Colorectal Cancer: Texture Analysis of Portal Phase Hepatic CT Images as a Potential Marker of Survival. *Radiology* (2009) 250(2):444–52. doi: 10.1148/radiol.2502071879
21. Rao SX, Lambregts DM, Schnerr RS, Beckers RC, Maas M, Albarello F, et al. CT Texture Analysis in Colorectal Liver Metastases: A Better Way Than Size and Volume Measurements to Assess Response to Chemotherapy? *United Eur Gastroenterol J* (2016) 4(2):257–63. doi: 10.1177/2050640615601603
22. Caruso D, Zerunian M, Ciolina M, de Santis D, Rengo M, Soomro MH, et al. Haralick's Texture Features for the Prediction of Response to Therapy in Colorectal Cancer: A Preliminary Study. *Radiol Med* (2017) 123(3):161–7. doi: 10.1007/s11547-017-0833-8
23. Beckers RCJ, Lambregts DMJ, Schnerr RS, Maas M, Rao S-X, Kessels AGH, et al. Whole Liver CT Texture Analysis to Predict the Development of Colorectal Liver Metastases—A Multicentre Study. *Eur J Radiol* (2017) 92:64–71. doi: 10.1016/j.ejrad.2017.04.019
24. Rao SX, Lambregts DM, Schnerr RS, van Ommen W, van Nijnatten TJ, Martens MH, et al. Whole-Liver CT Texture Analysis in Colorectal Cancer: Does the Presence of Liver Metastases Affect the Texture of the Remaining Liver? *United Eur Gastroenterol J* (2014) 2(6):530–8. doi: 10.1177/2050640614552463
25. Ko J, Park U, Kim D, Kang SW. Quantitative Electroencephalogram Standardization: A Sex- and Age-Differentiated Normative Database. *Front Neurosci* (2021) 15:766781. doi: 10.3389/fnins.2021.766781
26. Haga A, Takahashi W, Aoki S, Nawa K, Yamashita H, Abe O, et al. Standardization of Imaging Features for Radiomics Analysis. *J Med Invest* (2019) 66(1.2):35–7. doi: 10.2152/jmi.66.35

27. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical Score for Predicting Recurrence After Hepatic Resection for Metastatic Colorectal Cancer: Analysis of 1001 Consecutive Cases. *Ann Surg* (1999) 230:309–18. doi: 10.1097/00000658-199909000-00004
28. Iwatsuki S, Dvorchik I, Madariaga JR, Marsh JW, Dodson F, Bonham AC, et al. Hepatic Resection for Metastatic Colorectal Adenocarcinoma: A Proposal of a Prognostic Scoring System. *J Am Coll Surg* (1999) 189:291–99. doi: 10.1016/S1072-7515(99)00089-7
29. Mann CD, Metcalfe MS, Leopardi LN, Maddern GJ. The Clinical Risk Score: Emerging as a Reliable Preoperative Prognostic Index in Hepatectomy for Colorectal Metastases. *Arch Surg* (2004) 139:1168–72. doi: 10.1001/archsurg.139.11.1168
30. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of Long-Term Survival After Hepatic Resection for Metastatic Colorectal Cancer: A Multifactorial Model of 929 Patients. *Ann Surg* (2008) 247:125–35. doi: 10.1097/SLA.0b013e31815aa2c2
31. John SK, Robinson SM, Rehman S, Harrison B, Vallance A, French JJ, et al. Prognostic Factors and Survival After Resection of Colorectal Liver Metastasis in the Era of Preoperative Chemotherapy: An 11-Year Single-Centre Study. *Dig Surg* (2013) 30:293–301. doi: 10.1159/000354310
32. Nash GM, Gimbel M, Shia J, Nathanson DR, Ndubuisi MI, Zeng ZS, et al. KRAS Mutation Correlates With Accelerated Metastatic Progression in Patients With Colorectal Liver Metastases. *Ann Surg Oncol* (2010) 17:572–78. doi: 10.1245/s10434-009-0605-3
33. Smith DL, Soria JC, Morat L, Yang Q, Sabatier L, Liu DD, et al. Human Telomerase Reverse Transcriptase (hTERT) an Ki-67 Are Better Predictors of Survival Than Established Clinical Indicators in Patients Undergoing Curative Hepatic Resection for Colorectal Metastases. *Ann Surg Oncol* (2004) 11:45–51. doi: 10.1007/BF02524345
34. Rizzetto F, Calderoni F, De Mattia C, Defeudis A, Giannini V, Mazzetti S, et al. Impact of Inter-Reader Contouring Variability on Textural Radiomics of Colorectal Liver Metastases. *Eur Radiol Exp* (2020) 4(1):62. doi: 10.1186/s41747-020-00189-8
35. Li H, Xu C, Xin B, Zheng C, Zhao Y, Hao K, et al. 18f-FDG PET/CT Radiomic Analysis With Machine Learning for Identifying Bone Marrow Involvement in the Patients With Suspected Relapsed Acute Leukemia. *Theranostics* (2019) 9(16):4730–9. doi: 10.7150/thno.33841

Conflict of Interest: Author YTL was employed by GE Healthcare Pharmaceutical Diagnostics.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Combined Effect of Healthy Lifestyle Factors and Risks of Colorectal Adenoma, Colorectal Cancer, and Colorectal Cancer Mortality: Systematic Review and Meta-Analysis

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Background: In addition to adiposity, lifestyle factors such as poor diet, low physical activity, alcohol intake and smoking are noted to be associated with the development of colorectal cancer (CRC). This study aims to investigate the association and dose-response relationship between adherence to a healthy lifestyle and CRC risk.

Methods: A systematic literature search was conducted in MEDLINE and EMBASE for studies examining multiple lifestyle factors with risk of CRC, incident colorectal adenoma (CRA), and CRC-specific mortality through June 2021 without restrictions on language or study design. Meta-analysis was performed to pool hazard ratios using random-effects model. Subgroup analyses were performed based upon study and sample characteristics. Random-effects dose-response analysis was also conducted for CRC risk to assess the effect of each additional healthy lifestyle factor.

Results: A total of 28 studies (18 cohort studies, eight case-control studies, and two cross-sectional study) were included. When comparing subjects with the healthiest lifestyle to those with the least healthy lifestyle, the pooled HR was statistically significant for CRC (0.52, 95% CI 0.44-0.63), colon cancer (0.54, 95% CI 0.44-0.67), rectal cancer (0.51, 95% CI 0.37-0.70), CRA (0.39, 95% CI 0.29-0.53), and CRC-specific mortality (0.65, 95% CI 0.52-0.81). The pooled HR for CRC was 0.91 (95% CI: 0.88-0.94) for each increase in the number of healthy lifestyles. The inverse association between healthy lifestyle and CRC risk was consistently observed in all subgroups (HR ranging from 0.26 to 0.86).

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Conclusions: Adoption of a higher number of healthy lifestyles is associated with lower risk of CRC, CRA, and CRC-specific mortality. Promoting healthy lifestyle could reduce the burden of CRC.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=231398, identifier CRD42021231398.

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INTRODUCTION

Globally, colorectal cancer (CRC) ranks the third most commonly diagnosed malignancy and the second leading cause for cancer mortality (1). In 2020, CRC accounted for approximately 1.9 million new cases and more than 935,000 deaths worldwide (1). Its disease burden is projected to continue increasing globally, particularly in regions undergoing rapid industrialization (2). The increased risk of CRC and colorectal adenoma (CRA), one of its primary precancerous lesions (3), is closely linked to a variety of modifiable lifestyle risk factors, including excess adiposity (4–6), physical inactivity (7, 8), high intake of red meat and/or processed meat (9, 10), alcohol consumption (11, 12), and smoking (13); higher intake of dietary fiber, vegetables, and fruits are noted to be protective against CRC and CRA (14–17).

While the associations between CRC and single lifestyle factors have been extensively investigated in previous studies (18–21), far fewer studies have examined the effect of the adherence to a healthy lifestyle, defined as a combination of various modifiable factors. A latest meta-analysis that included 17 studies showed an overall inverse association between combined healthy lifestyle factors and CRC risk (22). However, it remains unclear whether the association differs by study settings or population characteristics and whether the association presents a dose-response relationship. In addition to CRC incidence, healthy lifestyle is also suggested to be related to CRC mortality in both CRC patients and general population (23–25). However, to the best of our knowledge, no systematic review and meta-analysis are available so far on the combined healthy lifestyle in relation to CRC-specific mortality.

Hence, this systematic review aims to investigate the association between adherence to a healthy lifestyle and the risk of CRC, CRA, and CRC-specific mortality, and to examine whether the association is dose-dependent and any potential effect modification by population characteristics.

METHODS

This systematic review was registered on PROSPERO (CRD42021231398) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (26).

Data Sources and Search

We searched MEDLINE and EMBASE for relevant studies from their inceptions through June 2021. The search strategy combined three groupings of keywords with their derivatives and synonyms related to the following concepts: 1) combined or integrated effect; 2) lifestyle factors or health behaviors; and 3) colorectal cancer and adenoma. The search terms of these three concepts were combined using the Boolean operator "AND". More details on search strategy is described in **Supplementary Tables 1** and **2**. The reference lists of eligible studies and relevant reviews were manually searched to identify additional publications. The search strategy did not impose any restriction on language, publication period, or publication status.

Eligible Criteria and Study Selection

We included epidemiological studies that investigated the association between combined lifestyle factors and colorectal outcomes. The exposure was combination of lifestyle factors, including but not limited to diet, smoking, alcohol consumption, physical activity, overweight/obesity, sleep duration, and others. The primary outcomes were risk of CRC, colon cancer, and rectal cancer. The secondary outcomes included risk of incident CRA, advanced colorectal neoplasia, and CRC-specific mortality. We included cross-sectional studies, case-control studies, and cohort studies. For CRC-specific mortality, we included studies of healthy population or CRC patients, while for the other outcome, the study population should be free of the outcomes at baseline if the study design was prospective cohort.

We excluded studies if they were (1) reviews, protocols, conference abstracts or not peer-reviewed publications, (2) focusing on a single lifestyle factor or a combination of less than three factors, (3) development or validation of prediction models, or (4) not reporting relevant data. For duplicate reports from the same cohort, we only included the report that had examined the largest number of lifestyle factors.

We used a two-step study selection procedure. The title and abstract of all electronically and manually identified records were screened first to identify potentially eligible studies. Second, full texts of the potentially eligible studies were examined for final eligibility. Two authors independently performed the selection process. All disagreements were resolved by discussion with a third reviewer until consensus was reached.

Data Extraction and Quality Assessment

Data were extracted by using an *a priori* designed form which collected the following information: (1) basic characteristics of study and subjects (e.g. first author, publication year, country, study period, sample size), (2) basic characteristics of participants (e.g. age, gender, ethnicity); (3) methodological characteristics, including study design, exposure definitions, outcome attainment,

and follow-up period (for cohort studies) (4) effect estimates for the associations of interest, and (5) other information for quality assessment.

The methodological quality of cohort studies, case-control studies, and cross-sectional studies were assessed by the Newcastle-Ottawa Scale, which covers three domains: selection of participants, comparability of study groups, the ascertainment of exposure (for case-control studies) or outcomes (for cohort studies and cross-sectional studies) (27, 28). A star system, with a maximum of nine stars for cohort studies and case-control studies and ten stars for cross-sectional studies, was used to present the result of quality assessment, with more stars representing higher quality and lower risk of bias. We consider cohort studies and case-control studies high quality if they received more than seven stars, moderate quality if they received five or six stars, otherwise low quality. Cross-sectional studies were considered of high quality if they received more than eight stars, moderate quality if they received six or seven stars, otherwise low quality. Data extraction and quality assessment were performed independently by two authors. Any discrepancy was resolved by discussion until consensus was reached.

Data Synthesis and Analysis

There has been no universal consensus on the quantification of combined lifestyle factors. Most studies constructed a simple unweighted lifestyle score, where one point was given to each of the present healthy lifestyles, although the exact lifestyle factors may vary across studies; for example, in Carr 2018 (29), Hang 2015 (30), and Kirkegaard 2010 (31). Some studies used weighted lifestyle score, in which the factors were weighted differently; for example, in Harnack 2002 (32) and Romaguera 2015 (33). However, some studies constructed risky lifestyle score that assign points to presence of unhealthy lifestyle habits; for example, in Cho 2019 (34) and Erdrich 2015 (35). In order to keep the directionality consistent with studies examining healthy lifestyle factors, we calculated a new score by deducting the original risky lifestyle score from the total number of the lifestyle factors for the studies that focus on unhealthy lifestyle habits (34, 35). The healthy lifestyle score was either used as a continuous variable (measuring the effect of per 1-unit increase in score) or transformed into a categorical variable (measuring the effect of adherence to healthiest lifestyle relative to the least healthy lifestyle) in original studies. In the originals studies, the five most commonly examined lifestyle factors were: diet, smoking status, alcohol consumption, physical activity level, and body measure. Most studies examined all five factors while others included some of them (see **Supplementary Table 3**).

Effect measures comparing the group with the healthiest lifestyle to the group with the least healthy lifestyle was pooled to present the associations of interest. Hazard Ratios (HR) with 95% confidence intervals (CIs) was the most commonly used as the measure of effect in original studies and was therefore used in this meta-analysis. Odds ratios, where applicable, were transformed into RR using the following formula: $RR=OR/[(1-P_0)+(P_0*OR)]$, where P_0 is the risk of an event in the non-exposed group (36). The transformed RRs and those extracted from some original studies were converted into HR using the formula: $RR=(1-e^{HR\ ln(1-r)})/r$, where r is the rate of outcome in reference group (37).

Studies reporting the effect size for each unit increase in lifestyle score were included in a separate meta-analysis. Given the heterogeneity across studies in study population characteristics and healthy lifestyle scoring (the number, component, and weights of different lifestyle factors), all meta-analyses were conducted using random-effects model.

Pre-specified subgroup analyses were performed to detect potential effect modification, according to study design (cohort, case-control), study setting (Europe, North America, Asia, Africa), ethnicity of the predominant study population (Caucasian, Asian, African, African American), mean age (<60, ≥60 years), follow-up time (<10 years, ≥10 years, unknown), gender (women, men, both), scoring system [simple lifestyle score, WCRF/AICR (World Cancer Research Fund and the American Institute for Cancer Research) recommendation adherence score, ACS (American Cancer Society) guideline adherence score], examined factors (five factors, smoking excluded, smoking and diet excluded, smoking, alcohol, and body measure excluded), and study quality (high, moderate, low). Cochran's Q test and I^2 were used to assess the heterogeneity across studies, with $p<0.05$ and/or $I^2>50\%$ indicating significant heterogeneity (38, 39). Potential publication bias was assessed by visual inspection of funnel plots as well as the Egger's test when the number of included studies is more than 10 (40). P-value <0.05 in Egger's test indicates presence of publication bias. Sensitivity analysis was performed to assess the robustness of the summary estimates by excluding studies of low quality and by including studies with relative comprehensive covariates only.

Random-effect dose-response analysis with one-stage method was used to generate the study slope lines (41). To minimize the impact of methodological heterogeneity on effect estimates in dose-response analysis, we only included studies using simple unweighted scoring. We further standardized the score scale so that each point represents adherence to one healthy lifestyle. For example, we modified the score scale in studies that assigned two points to each lifestyle factors by multiplying the original score by 0.5. We investigated potential non-linear relationship by using restricted cubic splines with three knots located at 10^{th}, 50^{th}, and 90^{th} percentiles of the exposure category (42). These three knots accordingly represented 0.5, 2.5, and 4.5 points in the 5-point healthy lifestyle score scale. The curve segments before the first knot and after the last knot was assumed to be linear. Akaike information criteria (AIC) was used to compare the fitness of models, with the lower AIC indicating the better-fitting model (43). All quantitative data analyses were conducted by using Stata 14.0 (Stata Corp LP, College Station, TX, USA).

RESULTS

Summary of Study Selection

A total of 10,555 unique records were identified from the literature search, 28 of which were considered eligible and were

included. Among the eligible studies, 18 reported the risk of CRC (29–32, 34, 35, 44–55), five reported the risk of incident CRA (56–60), two reported the risk of advanced colorectal neoplasia (57, 61), and five reported CRC-specific mortality (33, 50, 62–64). The details of study selection are outlined in **Figure 1**. Among the five studies on CRC-specific mortality, two were conducted on CRC patients (50, 62) while the other three were conducted among healthy populations (33, 63, 64).

Characteristics of Included Studies

The characteristics of included studies are shown in **Table 1** and **Supplementary Table 3**. Among the 28 studies included in the analyses, 18 were cohort studies, eight case-control studies, and two cross-sectional studies. The mean age at baseline ranged from 46.1 to 78.9 years. Eight studies were conducted among women (32, 35, 46, 47, 50, 54, 55, 62) while one was conducted among men (51); the other studies included both sexes, one of which (49) reported data separately for men and women. In terms of the study setting, 12 were conducted in the US, 10 in European countries, five in Asia, and one in Africa. The mean sample size was 51,735, with a range between 138 and 521,330. The median follow-up of cohort studies ranged from 3.1 years to >24 years.

Quality Assessment

Using the Newcastle-Ottawa Scale, the included cohort studies received ratings ranging from five to eight stars. Nine studies were rated as of high quality (31, 32, 35, 48, 49, 51, 54, 62, 63), nine studies of moderate quality (33, 44, 46, 47, 50, 52, 53, 55, 64). None of the studies got star for the ascertainment of exposure because the lifestyle habits were self-reported by participants. In some studies, the sample was not well representative of general population. The included case-control studies received three to seven stars. Two studies were rated as high quality (29, 60), two moderate quality (30, 59), and four low quality (34, 45, 56, 58). The common biases in low quality studies were introduced by poor selection of cases and controls and unclear outcome ascertainment. Of the two cross-sectional studies included, one was rated as high quality (61) while the other moderate quality (57). The assessment results of all the included studies are described in **Supplementary Table 4**.

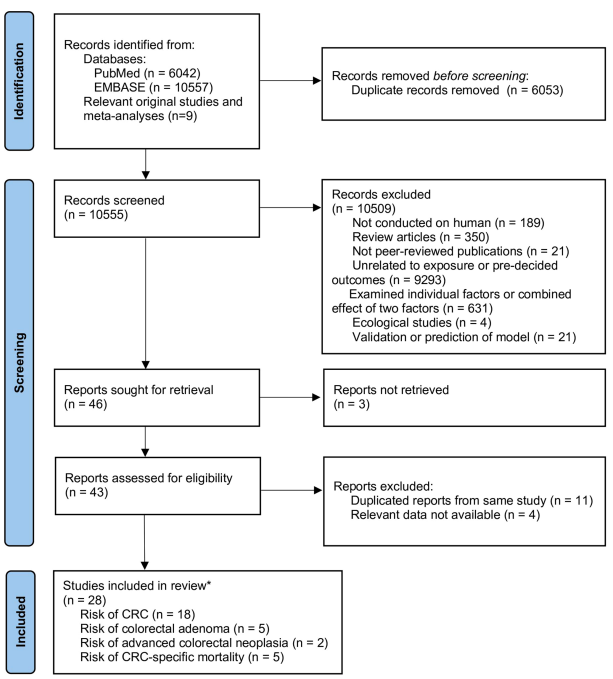

FIGURE 1 | Flow chart of study selection.

Meta-Analysis

Overall Risk for CRC

We included 15 studies (1,139,361 participants), 11 studies (953,541 participants) and 8 studies (788,038 participants) in the meta-analyses of CRC, colon cancer and rectal cancer, respectively (**Figure 2**). Compared with the least healthy lifestyle, the adherence of the healthiest lifestyle was associated with 48% (HR=0.52, 95% CI 0.44-0.63, I^2 = 86.2%), 46% (HR=0.54, 95% CI 0.44-0.67, I^2 = 80.2%), and 49% (HR=0.51, 95% CI 0.37-0.70, I^2 = 92.0%) lower risk of CRC, colon cancer and rectal cancer, respectively. After pooling the studies using continuous lifestyle scores, the results showed that the per 1-unit increase in healthy lifestyle score was associated with a pooled HR of 0.88 (95% CI 0.84-0.92) for CRC, 0.87 (95% CI 0.83-0.92) for colon cancer, and 0.86 (95% CI 0.79-0.90) for rectal cancer (**Supplementary Figure 1**).

Nine studies were included in the dose-response meta-analysis for risk of CRC (29, 30, 45, 49–52, 55, 65). The reported risk estimates for association between the number of present healthy lifestyles and risk of CRC from these studies generally showed an inverse linear relationship, as displayed in **Figure 3A**. The AIC was -54.7 for linear model (**Figure 3B**) and -44.1 for model using cubic splines (**Figure 3C**). Given the lower AIC, the linear model was considered better-fitting and was adopted for further analysis. Overall, the pooled HR for CRC was 0.91 (95% CI 0.88-0.94) per 1-unit increase in the number of healthy lifestyles, similar to the overall estimate in the meta-analysis of continuous lifestyle scores.

The result of subgroup analyses was presented in **Figure 4**. Overall, the inverse association between healthy lifestyle and risk for CRC was consistently observed within each subgroup (HR ranging from 0.26 to 0.86), and the association was statistically significant for all subgroups except among African Americans. Similarly, the inverse association for colon cancer was statistically significant in all subgroups, except among African Americans (**Supplementary Figure 2**). The associations for rectal cancer similarly remained directionally consistent with the primary analysis, although statistical significance was not reached in some subgroups (**Supplementary Figure 3**).

In sensitivity analysis, we conducted separate meta-analysis for risk of CRC of (1) all studies after excluding the two studies of low quality (34, 45); and (2) the three studies that adjusted for a

TABLE 1 | Basic characteristics of the included studies (n=28).

Study ID	Country	Study design	Sample size	Mean age (range)	Male %	Median follow-up year	Outcomes assessed (n)	Healthy lifestyle components					
								Diet	Smoking	Alcohol use	Physical activity	Body measure	Other
Aleksandrova (52)	10 European countries	Cohort	521330	51.8 (25-70)	35.0	12.0	CRC (3579) Colon cancer (2359) Rectal cancer (1390)	X	X	X	X	X	
Barrubes (53)	Spain	Cohort	7216	67.0 (62-72)	57.4	6.0	CRC (101)	X	X	X	X	X	
Byrd (56)	US	Case-control	2751	55.5 (NA)	47.5	NA	CRA (765)		X	X	X	X	
Carr (29)	Germany	Case-control	7124	68.2 (32-99)	60.8	NA	CRC (4092) Colon cancer (24579) Rectal cancer (1633)	X	X	X	X	X	
Cheng (54)	US	Cohort	35221	61.7 (55-69)	0	>10.0	CRC (1737)		X		X	X	
Cho (34)	South Korea	Case-control	1927	56.1 (NA)	68.3	NA	CRC (632) Colon cancer (318) Rectal cancer (304)	X	X	X	X	X	
Dartois (55)	France	Cohort	64732	NA (43-68)	0	15.0	CRC (481)	X	X	X	X	X	
Erdrich (35)	US	Cohort	81092	63.0 (40-89)	0	24.0	Colon cancer (1127)	X	X	X	X	X	
Erben (57)	Germany	Cross-sectional	13600	62.9 (NA)	50.3	NA	CRA (2839) Advanced colorectal neoplasia (1375)	X	X	X	X	X	
Fliss-Isakov (58)	Israel	Case-control	788	58.8 (NA)	52.7	NA	CRA (403)	X	X		X	X	
Fu (59)	US	Case-control	5208	57.4 (40-75)	63.0	NA	Advanced CRA (386) Non-advanced CRA (1220)	X	X			X	X [e]
Hang (30)	China	Case-control	61693	68.9 (23-98)	45.2	NA	CRC (1144)	X		X	X		X [a]
Harnack (32)	US	Cohort	34708	61.7 (55-69)	0	13.0	Colon cancer (619)	X		X	X	X	
Hastert (44)	US	Cohort	66920	61.1 (50-76)	49.0	7.6	CRC (546)	X		X	X	X	
Hatime (45)	Morocco	Case-control	2906	56.0 (NA)	49.3	NA	CRC (1453) Colon cancer (729) Rectal cancer (724)	X	X	X	X	X	
Inoue-Choi (62)	US	Cohort	2017	78.9 (72-88)	0	5.4	CRC-specific mortality (23)	X		X	X	X	
Jones (46)	UK	Cohort	30963	52.3 (NA)	0	18.7	CRC (444) Colon cancer (322) Rectal cancer (146)	X		X	X	X	X [b]
Kirkegaard (31)	Denmark	Cohort	55487	56.0 (50-64)	48.0	9.9	CRC (678) Colon cancer (420) Rectal cancer (258)	X	X	X	X	X	
Knudsen (61)	Norway	Cross-sectional	6315	62.0 (NA)	48.0	NA	Advanced colorectal neoplasia (311)	X	X	X	X	X	
Lohse (63)	Switzerland	Cohort	16722	46.1 (25-74)	48.8	21.7 [d]	CRC-specific mortality (79)	X		X	X	X	
Nomura (47)	US	Cohort	49103	38.2 (21-69)	0	15.1	CRC (328) Colon cancer (259)	X		X	X	X	
Odegaard (48)	Singapore	Cohort	50466	55.9 (45-74)	46.4	11.5	CRC (969) Colon cancer (590) Rectal cancer (379)	X	X	X	X	X	X [a]

(Continued)

TABLE 1 | Continued

Study ID	Country	Study design	Sample size	Mean age (range)	Male %	Median follow-up year	Outcomes assessed (n)	Healthy lifestyle components					
								Diet	Smoking	Alcohol use	Physical activity	Body measure	Other
Petimar (49) (m)[c]	US	Cohort	45442	52.8 (40-75)	100	>24.0	CRC (1151) Colon cancer (907) Rectal cancer (244)	X		X	X	X	
Petimar (49) (f)[c]	US	Cohort	68977	52.8 (30-55)	0	>24.0	CRC (1298) Colon cancer (1023) Rectal cancer (275)	X		X	X	X	
Romaguera (33)	10 European countries	Cohort	3292	64.6 (NA)	45.5	4.2	CRC-specific mortality (872)	X		X	X	X	X[b]
Sotos-Prieto (64)	US	Cohort	87113	51.7 (40-75)	66.9	NA	CRC-specific mortality (684)	X	X	X	X	X	
Tabung (60)	US	Case-control	138	NA (30-80)	49.3	NA	CRA (47)	X	X	X	X	X	
Thomson (50)	US	Cohort	65838	63.2 (50-79)	0	12.6	CRC (751) CRC-specific mortality (190)	X		X	X	X	
Zhang (51)	China	Cohort	59503	55.3 (40-74)	100	9.3	CRC (674) Colon cancer (400) Rectal cancer (274)	X		X	X	X	

[a]*Sleeping duration included as a component;*
[b]*Breastfeeding (applicable to women) included as a component;*
[c]*Petimar 2019 reported outcome on males and females separately and was therefore included as two separated studies in analysis;*
[d]*mean follow-up;*
[e]*Regular nonsteroidal anti-inflammatory drug use; CRC, colorectal cancer; CRA, colorectal adenoma; NA, not available.*

relative comprehensive list of covariates (socio-demographic factors, family history, and intake of nutritional supplement and nonsteroidal anti-inflammatory drugs at baseline) (45, 49, 50). The results of these analyses were consistent with main analysis (**Supplementary Figure 4**).

Overall Risk for Colorectal Adenoma and Advanced Colorectal Neoplasia

Four studies (21,697 participants) reporting risk for incident colorectal adenoma using categorical lifestyle variables were included in the analysis (**Figure 2**), and the pooled HR was 0.39 (95% CI 0.29-0.53, I^2 = 90.1%). Two studies reported the risk for advanced colorectal neoplasia and the pooled HR for the healthiest group was 0.43 (95% CI 0.33-0.57, I^2 = 0.0%).

Overall Risk for CRC-Specific Mortality

Five studies with 174,982 participants were included in the analysis of CRC-specific mortality. The group with the highest lifestyle score showed 35% lower risk (HR=0.65, 95% CI 0.52-0.81, I^2 = 37.5%) compared to the group with lowest score (**Figure 2**). Using continuous lifestyle score, 1-unit increase in healthy lifestyle score was associated with an HR of 0.84 (95% CI 0.77-0.91) (**Supplementary Figure 1**). Subgroup analyses showed largely consistent results of similar directions (**Supplementary Figure 5**).

Publication Bias

The result of Egger's test suggested no evidence of significant publication bias (p=0.23 for CRC risk, p=0.09 for colon cancer risk). The funnel plots for these two outcomes with more than 10 studies showed overall asymmetrical pattern (**Supplementary Figure 6**).

DISCUSSION

This systematic review and meta-analysis found that adopting multiple healthy lifestyles is associated with a considerably lower risk of multiple colorectal diseases. Compared with individuals with the least healthy lifestyle, those with the healthiest lifestyle had 48%, 46% and 49% lower risk of CRC, colon cancer, and rectal cancer, respectively. The associations were consistent across populations with different socio-demographic characteristics. A dose-response relationship between the number of healthy lifestyles and risk of CRC was identified, and adoption of each additional healthy lifestyle lowers the risk of CRC by 9% on average. We have also found that adherence to the healthiest lifestyle was associated with 61% lower risk of incident colorectal adenoma and 57% lower risk of advanced colorectal neoplasia. Among CRC survivors, those with the healthiest lifestyle had 31% lower risk of CRC-specific mortality.

The dose-response relationship between various individual lifestyle factors and CRC risk has been well established. It is reported that the relative risk for developing CRC is 0.90 for an increase of 10 g/day of dietary fibre (14), 1.24 for 120 g/day increase of red meat, 1.36 for 30 g/day increase of processed meat (66), 1.34 for one-point increase of Dietary Inflammatory Index (67), 1.38 for 50 g/day increase of alcohol intake (68), 1.07 for 2 kg/m^2 increase in BMI, 1.04 for 2-cm increase in

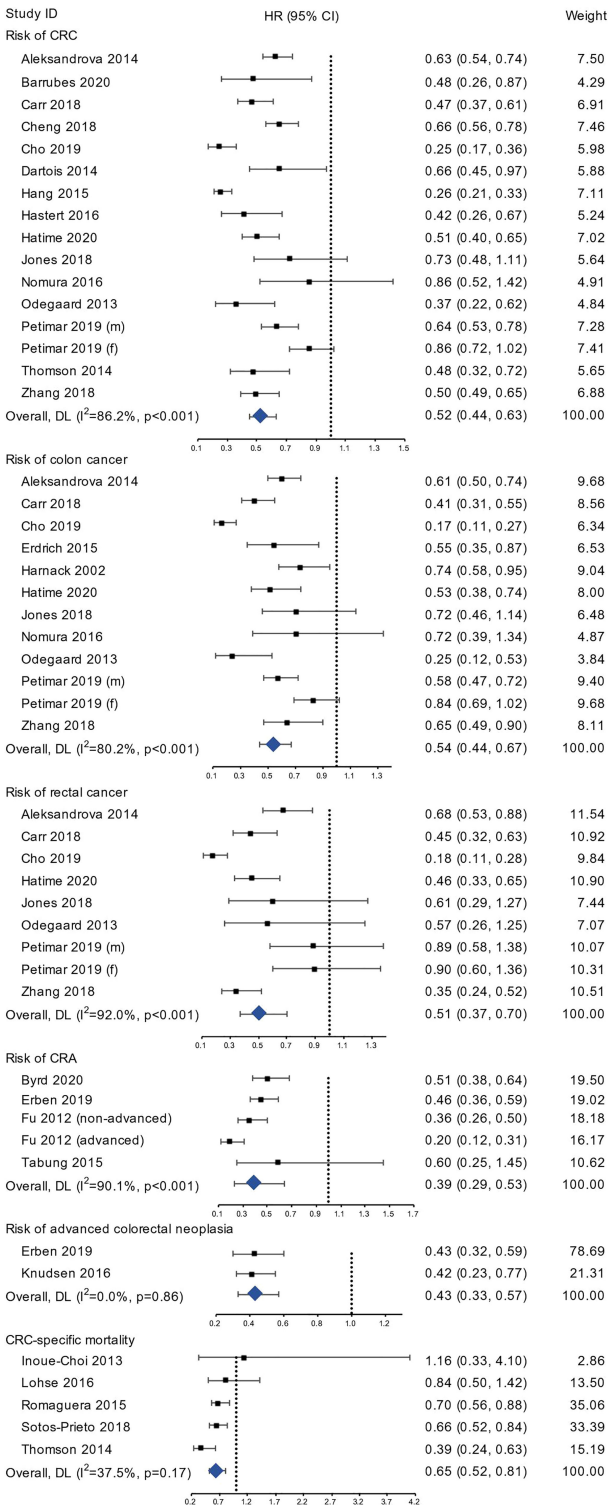

FIGURE 2 | The forest plots of risk of CRC, colon cancer, rectal cancer, CRA, advanced colorectal neoplasia, and CRC-specific mortality.

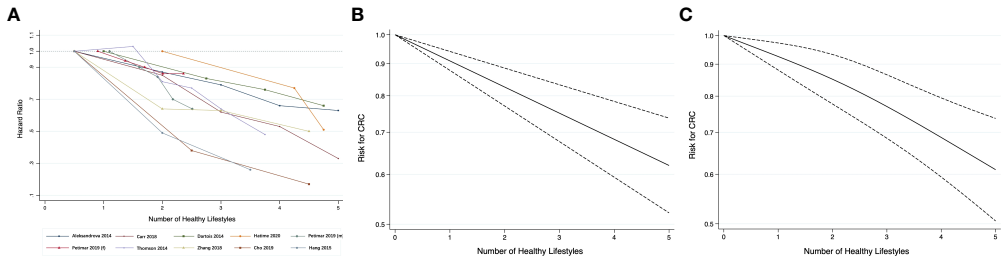

FIGURE 3 | **(A)** Line graph of association between healthy lifestyles and risk for CRC; dose-response relationship between the number of healthy lifestyles and the risk for CRC: **(B)** Linear trend; **(C)** Restricted cubic splines.

waist circumference (69), and 0.99 for 1 metabolic equivalent task (MET)-hour/week increase when the physical activity is over 10 MET-hour/week (70). In this study, we further revealed a dose-response association between the number of adopted healthy lifestyles and CRC risk, which further supports the significant difference in CRC risk between those with the healthiest lifestyle and those with the least. Previous studies have reported that healthy or unhealthy lifestyles tend to aggregate in individuals (71, 72), and the prevalence of adopting a healthiest lifestyle is generally low among general populations. For example, only 5.7% of the study population reported having all four healthy lifestyles (non-smoking, low alcohol consumption, sufficient fruit and vegetable consumption, regular physical activity) in England (73), while in Netherland, approximately 20% of the general population presented at least three of the five unhealthy lifestyles (smoking, low vegetable and fruit consumption, excessive alcohol intake, low physical activity) examined and all lifestyle factors showed significant clustering (72). It can, therefore, be expected that promotion of all healthy lifestyles among the populations could produce a synergistic effect on preventing CRC. A prospective study from the US estimated that 71% of colon cancer risk was attributable to a combination of unhealthy lifestyles, including being overweight, physical inactivity, alcohol consumption, smoking, and unhealthy diet (74). A prospective study in Denmark estimated that an overall 16% of the new CRC cases (22% for male and 11% for female) were attributable to lack of adherence to a combination of five healthy lifestyle factors (healthy weight, physical activity, non-smoking, limited alcohol consumption, healthy diet) (52).

The subgroup analyses showed that associations between multiple lifestyle factors and colorectal cancer risk were largely

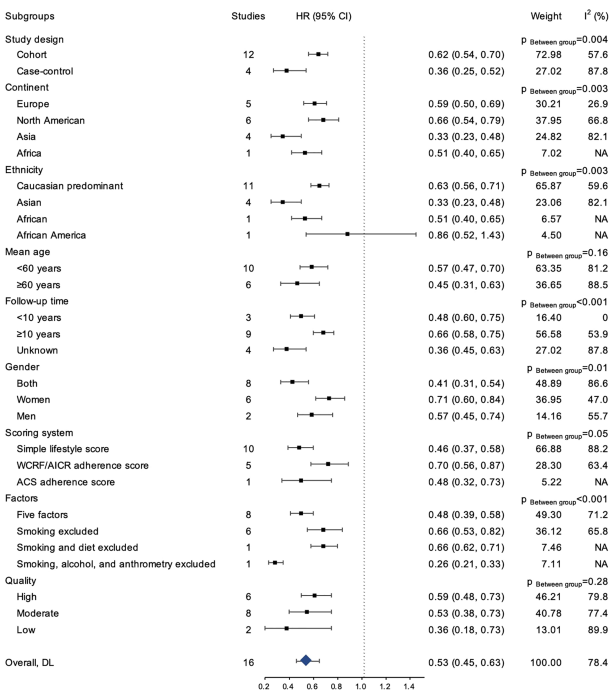

FIGURE 4 | The results of the subgroup analyses for risk of CRC.

consistent across different age groups, sexes, geographic settings, and ethnicities. This suggests that the promoting healthy lifestyles could benefit populations universally regardless of their demographic characteristics. However, it should be noted that the association was found not statistically significant in the group of African American, but given that only one study was included in this group, future studies with bigger sample size are warranted to further explore the association among this ethnicity.

A previous meta-analysis concluded that adherence to at least four of the five healthy lifestyles examined (non-smoking, normal weight, healthy diet, moderate or lower alcohol consumption, and regular physical activity) could reduce all-cause mortality by 66% compared to those with no more than one healthy lifestyle (75). Our result suggested that adopting the healthiest lifestyle lowers CRC-specific mortality by 35%, and this protective effect was found significant among both CRC patients and healthy populations. This indicates that improving lifestyles could significantly benefit CRC survivors. Previous evidence has demonstrated that a variety of interventions are effective in improving awareness of CRC risk factors and facilitating adoption of healthy lifestyles among CRC patients after diagnosis, including telephone-delivered coaching (76), combined exercise and dietary advice (77), and education and behavioral change techniques (78). Such strategies could be considered as an integral part of CRC management to improve survival outcomes.

This study is the first systematic review and meta-analysis to reveal the dose-response relationship between the number of healthy lifestyles and CRC risk. Given the lack of large randomized controlled trials to examine the effect of adopting multiple healthy lifestyles on the risk of CRC and CRA as well as the survival outcomes of CRC patients, our study has provided high quality evidence by including a pooled sample of more than one million participants and generating results that are unlikely to be affected by publication bias. Our findings support the recommendations by the World Health Organization (79), American Cancer Society (80), and WCRF/AICF (81) on prevention and management of cancer. Adopting healthy lifestyles could not only prevent colorectal adenoma and CRC among the general population, but also improve clinical outcomes among CRC survivors. Nonetheless, international evidence has shown that population at risk of CRC generally demonstrated low awareness of lifestyle risk factors of CRC, particularly the effect of weight and physical activity (78, 82, 83). It would be strategic to provide information to increase awareness of lifestyle risk factors and promote interventions targeting behavior change among both healthy populations and CRC patients. Similar to our findings, previous meta-analyses have revealed that adopting multiple healthy lifestyles is associated with lower risk for cardiovascular disease (84), all-cause mortality (85), and type 2 diabetes (86), and such associations are generally found to be consistent among different populations. Hence, promoting healthy lifestyles could produce health benefits not only for CRC, but also for a variety of other health outcomes.

A few limitations should be noted when interpreting the study results. First, composition of healthy lifestyle and definitions of lifestyle factors varied considerably across studies, which may introduce heterogeneity to meta-analysis. We used random-effects model to minimize the effect of heterogeneity on the overall estimates. To explore the potential heterogeneity caused by this variation, we conducted subgroup analysis based on scoring system and factor composition. Although heterogeneity remained substantial within subgroups, the protective effect was still consistent within each group. For dose-response relationship, we only included studies using unweighted score system to exclude this attrition. Second, most original studies are from high-income, Western settings whose populations are comprised predominantly of Caucasians. Hence, more evidence from other populations, particularly Asian and African populations is needed. Third, only five studies have reported on CRC-specific mortality, which may restrict the power of performing stratified analyses. Fourth, socio-economic status is a key determinant for individual lifestyles (87–89), but few included studies have fully adjusted for all socio-economic factors. Other factors related to CRC risk, such as the use of certain pharmacological agents and nutritional supplements at baseline, were not collected and therefore not adjusted for in some studies. Despite this heterogeneity of covariate adjustment, the consistent finding from sensitivity analysis supports the robustness of the pooled estimate from the main analysis. Lastly, immortal time bias may exist in the original cohort studies assessing mortality given the possible time gap between study initiation and exposure assessment.

In conclusion, the number of healthy lifestyle attributes is inversely correlated with the risk of colorectal adenoma, cancer, and CRC-specific mortality. Lifestyle interventions could effectively reduce incidence of CRC. Future research may explore the effect of complex interventions targeting multiple lifestyle factors on prevention and management of CRC; randomized controlled trial is needed to provide high-quality evidence on the combined effect of healthy lifestyles and CRC risk.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

JY, QF, and YZ designed the research. JY and QF conducted literature search and performed data extraction and meta-analysis. JHK and YZ reviewed studies for inclusion. JY, QF, JHK, and YZ contributed to the interpretation of data. JY drafted the paper. QF, JHK, and YZ made substantial contribution to the critical revision and editing of the manuscript. All authors contributed to the article and approved the submission version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.827019/full#supplementary-material

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2021) 71(3):209–249. doi: 10.3322/caac.21660
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660
3. Fearon ER, Vogelstein B. A Genetic Model for Colorectal Tumorigenesis. *Cell* (1990) 61(5):759–67. doi: 10.1016/0092-8674(90)90186-I
4. Song M, Hu FB, Spiegelman D, Chan AT, Wu K, Ogino S, et al. Long-Term Status and Change of Body Fat Distribution, and Risk of Colorectal Cancer: A Prospective Cohort Study. *Int J Epidemiol* (2016) 45(3):871. doi: 10.1093/ije/dyv177
5. Dong Y, Zhou J, Zhu Y, Luo L, He T, Hu H, et al. Abdominal Obesity and Colorectal Cancer Risk: Systematic Review and Meta-Analysis of Prospective Studies. *Biosci Rep* (2017) 37(6):20170945. doi: 10.1042/BSR20170945
6. Hong S, Cai Q, Chen D, Zhu W, Huang W, Li Z. Abdominal Obesity and the Risk of Colorectal Adenoma: A Meta-Analysis of Observational Studies. *Eur J Cancer Prev* (2012) 21(6):523–31. doi: 10.1097/CEJ.0b013e328351c775
7. Wolin KY, Yan Y, Colditz GA. Physical Activity and Risk of Colon Adenoma: A Meta-Analysis. *Br J Cancer* (2011) 104(5):882–5. doi: 10.1038/sj.bjc.6606045
8. Schmid D, Leitzmann MF. Television Viewing and Time Spent Sedentary in Relation to Cancer Risk: A Meta-Analysis. *JNCI J Natl Cancer Inst* (2014) 106 (7):dju098. doi: 10.1093/jnci/dju098
9. Vieira A, Abar L, Chan D, Vingeliene S, Polemiti E, Stevens C, et al. Foods and Beverages and Colorectal Cancer Risk: A Systematic Review and Meta-Analysis of Cohort Studies, an Update of the Evidence of the WCRF-AICR Continuous Update Project. *Ann Oncol Off J Eur Soc Med Oncol* (2017) 28 (8):1788–802. doi: 10.1093/annonc/mdx171
10. Xu X, Yu E, Gao X, Song N, Liu L, Wei X, et al. Red and Processed Meat Intake and Risk of Colorectal Adenomas: A Meta-Analysis of Observational Studies. *Int J Cancer* (2013) 132(2):437–48. doi: 10.1002/ijc.27625
11. International Agency for Research on Cancer. *Agents Classified by the IARC Monographs*, Vol. 1-123. (2018). Lyon: IARC
12. Zhu J-Z, Wang Y-M, Zhou Q-Y, Zhu K-F, Yu C-H, Li Y-M. Systematic Review With Meta-Analysis: Alcohol Consumption and the Risk of Colorectal Adenoma. *Aliment Pharmacol Ther* (2014) 40(4):325–37. doi: 10.1111/apt.12841
13. Giovannucci E, Marti ME. Tobacco, Colorectal Cancer, and Adenomas: A Review of the Evidence. *J Natl Cancer Institute J Natl Cancer Inst* (1996) 88:1717–30. doi: 10.1093/jnci/88.23.1717
14. Aune D, Chan DSM, Lau R, Vieira R, Greenwood DC, Kampman E, et al. Dietary Fibre, Whole Grains, and Risk of Colorectal Cancer: Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. *BMJ* (2011) 343(7833):1082. doi: 10.1136/bmj.d6617
15. Dahm C, Keogh R, Spencer E, Greenwood D, Key T, Fentiman I, et al. Dietary Fiber and Colorectal Cancer Risk: A Nested Case-Control Study Using Food Diaries. *J Natl Cancer Inst* (2010) 102(9):614–26. doi: 10.1093/jnci/djq092
16. Millen AE, Subar AF, Graubard BI, Peters U, Hayes RB, Weissfeld JL, et al. Fruit and Vegetable Intake and Prevalence of Colorectal Adenoma in a Cancer Screening Trial. *Am J Clin Nutr* (2007) 86(6):1754–64. doi: 10.1093/ajcn/86.5.1754
17. Nucci D, Fatigoni C, Salvatori T, Nardi M, Realdon S, Gianfredi V. Association Between Dietary Fibre Intake and Colorectal Adenoma: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* (2021) 18(8):4168. doi: 10.3390/ijerph18084168
18. Harriss DJ, Atkinson G, George K, Tim Cable N, Reilly T, Haboubi N, et al. Lifestyle Factors and Colorectal Cancer Risk (1): Systematic Review and Meta-Analysis of Associations With Body Mass Index. *Color Dis* (2009) 11(6):547–63. doi: 10.1111/j.1463-1318.2009.01766.x
19. Harriss DJ, Atkinson G, Batterham A, George K, Cable NT, Reilly T, et al. Lifestyle Factors and Colorectal Cancer Risk (2): A Systematic Review and Meta-Analysis of Associations With Leisure-Time Physical Activity. *Color Dis* (2009) 11(7):689–701. doi: 10.1111/j.1463-1318.2009.01767.x
20. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and Colorectal Cancer: A Meta-Analysis. *JAMA* (2008) 300 (23):2765–78. doi: 10.1001/jama.2008.839
21. Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M. The Impact of Dietary and Lifestyle Risk Factors on Risk of Colorectal Cancer: A Quantitative Overview of the Epidemiological Evidence. *Int J Cancer* (2009) 125(1):171–80. doi: 10.1002/ijc.24343
22. Zhang Y-B, Pan X-F, Chen J, Cao A, Zhang Y-G, Xia L, et al. Combined Lifestyle Factors, Incident Cancer, and Cancer Mortality: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *Br J Cancer* (2020) 122 (7):1085–93. doi: 10.1038/s41416-020-0741-x
23. Van Zutphen M, Kampman E, Giovannucci EL, Van Duijnhoven FJB. Lifestyle After Colorectal Cancer Diagnosis in Relation to Survival and Recurrence: A Review of the Literature. *Curr Colorectal Cancer Rep* (2017) 13(5):370–401. doi: 10.1007/s11888-017-0386-1
24. Jayasekara H, English DR, Haydon A, Hodge AM, Lynch BM, Rosty C, et al. Associations of Alcohol Intake, Smoking, Physical Activity and Obesity With Survival Following Colorectal Cancer Diagnosis by Stage, Anatomic Site and Tumor Molecular Subtype. *Int J Cancer* (2018) 142(2):238–50. doi: 10.1002/ijc.31049
25. Haydon AMM, MacInnis RJ, English DR, Giles GG. Effect of Physical Activity and Body Size on Survival After Diagnosis With Colorectal Cancer. *Gut* (2006) 55(1):62. doi: 10.1136/gut.2005.068189
26. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ* (2021) 372:n71. doi: 10.1136/bmj.n71
27. Stang A. Critical Evaluation of the Newcastle-Ottawa Scale for the Assessment of the Quality of Nonrandomized Studies in Meta-Analyses. *Eur J Epidemiol* (2010) 9):25. doi: 10.1007/s10654-010-9491-z
28. Amedeo Modesti P, Reboldi G, Cappuccio FP, Agyemang C, Remuzzi G, Rapi S, et al. Panethnic Differences in Blood Pressure in Europe: A Systematic Review and Meta-Analysis Working Group on CV Risk in Low Resource Settings. *PLoS ONE* (2016) 11(1): e0147601. doi: 10.1371/journal.pone.0147601
29. Carr PR, Weigl K, Jansen L, Walter V, Erben V, Chang-Claude J, et al. Healthy Lifestyle Factors Associated With Lower Risk of Colorectal Cancer Irrespective of Genetic Risk. *Gastroenterology* (2018) 155(6):1805-1815.e5.
30. Hang J, Cai B, Xue P, Wang L, Hu H, Zhou Y, et al. The Joint Effects of Lifestyle Factors and Comorbidities on the Risk of Colorectal Cancer: A Large Chinese Retrospective Case-Control Study. *PloS One* (2015) 10(12):e0143696. doi: 10.1371/journal.pone.0143696
31. Kirkegaard H, Johnsen NF, Christensen J, Frederiksen K, Overvad K, Tjønneland A. Association of Adherence to Lifestyle Recommendations and Risk of Colorectal Cancer: A Prospective Danish Cohort Study. *BMJ* (2010) 341(7780):978. doi: 10.1136/bmj.c5504
32. Harnack L, Nicodemus K, Jacobs DR, Folsom AR. An Evaluation of the Dietary Guidelines for Americans in Relation to Cancer Occurrence. *Am J Clin Nutr* (2002) 76(4):889–96. doi: 10.1093/ajcn/76.4.889
33. Romaguera D, Ward H, Wark PA, Vergnaud AC, Peeters PH, van Gils CH, et al. Pre-Diagnostic Concordance With the WCRF/AICR Guidelines and Survival in European Colorectal Cancer Patients: A Cohort Study. *BMC Med* (2015) 13(1):45. doi: 10.1186/s12916-015-0332-5
34. Cho YA, Lee J, Oh JH, Chang HJ, Sohn DK, Shin A, et al. Genetic Risk Score, Combined Lifestyle Factors and Risk of Colorectal Cancer. *Cancer Res Treat* (2019) 51(3):1033–40. doi: 10.4143/crt.2018.447
35. Erdrich J, Zhang X, Giovannucci E, Willett W. Proportion of Colon Cancer Attributable to Lifestyle in a Cohort of US Women. *Cancer Causes Control* (2015) 26(9):1271–9. doi: 10.1007/s10552-015-0619-z
36. Zhang J, Yu KF. What's the Relative Risk? A Method of Correcting the Odds Ratio in Cohort Studies of Common Outcomes. *J Am Med Assoc* (1998) 280 (19):1690–1. doi: 10.1001/jama.280.19.1690
37. Shor E, Roelfs D, Vang ZM. The "Hispanic Mortality Paradox" Revisited: Meta-Analysis and Meta-Regression of Life-Course Differentials in Latin American and Caribbean Immigrants' Mortality. *Soc Sci Med* (2017) 186:20–33. doi: 10.1016/j.socscimed.2017.05.049
38. Higgins JPT, Thompson SG. Quantifying Heterogeneity in a Meta-Analysis. *Stat Med* (2002) 21(11):1539–58. doi: 10.1002/sim.1186

39. Ju SY, Lee JY, Kim DH. Low 25-Hydroxyvitamin D Levels and the Risk of Frailty Syndrome: A Systematic Review and Dose-Response Meta-Analysis. *BMC Geriatr* (2018) 4;18(1):206. doi: 10.1186/s12877-018-0904-2
40. Egger M, Smith GD, Schneider M, Minder C. Bias in Meta-Analysis Detected by a Simple, Graphical Test. *Br Med J* (1997) 315(7109):629–34. doi: 10.1136/bmj.315.7109.629
41. Orsini N, Bellocco R, Greenland S. Generalized Least Squares for Trend Estimation of Summarized Dose-Response Data. *Stata J DPC Nederland* (2006) 6:40–57. doi: 10.1177/1536867X0600600103
42. Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*. SecondNew York: Springer (2015).
43. Akaike H. A New Look at the Statistical Model Identification. *IEEE Trans Automat Contr* (1974) 19(6):716–23. doi: 10.1109/TAC.1974.1100705
44. Hastert TA, White E. Association Between Meeting the WCRF/AICR Cancer Prevention Recommendations and Colorectal Cancer Incidence: Results From the VITAL Cohort. *Cancer Causes Control* (2016) 27(11):1347–59. doi: 10.1007/s10552-016-0814-6
45. Hatime Z, El Kinany K, Huybrechts I, Gunter MJ, Khalis M, Deoula M, et al. Extended Healthy Lifestyle Index and Colorectal Cancer Risk in the Moroccan Population. *Eur J Nutr* (2021) 60:1013–22. doi: 10.1007/s00394-020-02311-3
46. Jones P, Cade JE, Evans CEL, Hancock N, Greenwood DC. Does Adherence to the World Cancer Research Fund/American Institute of Cancer Research Cancer Prevention Guidelines Reduce Risk of Colorectal Cancer in the UK Women's Cohort Study? *Br J Nutr* (2018) 119(3):340–8. doi: 10.1017/S0007114517003622
47. Nomura SJO, Dash C, Rosenberg L, Yu J, Palmer JR, Adams-Campbell LL. Is Adherence to Diet, Physical Activity, and Body Weight Cancer Prevention Recommendations Associated With Colorectal Cancer Incidence in African American Women? *Cancer Causes Control* (2016) 27(7):869–79. doi: 10.1007/s10552-016-0760-3
48. Odegaard AO, Koh WP, Yuan JM. Combined Lifestyle Factors and Risk of Incident Colorectal Cancer in a Chinese Population. *Cancer Prev Res* (2013) 6 (4):360–7. doi: 10.1158/1940-6207
49. Petimar J, Smith-Warner SA, Rosner B, Chan AT, Giovannucci EL, Tabung FK. Adherence to the World Cancer Research Fund/American Institute for Cancer Research 2018 Recommendations for Cancer Prevention and Risk of Colorectal Cancer. *Cancer Epidemiol Biomarkers Prev* (2019) 28(9):1469–79. doi: 10.1158/1055-9965.EPI-19-0165
50. Thomson CA, McCullough ML, Wertheim BC, Chlebowski RT, Martinez ME, Stefanick ML, et al. Nutrition and Physical Activity Cancer Prevention Guidelines, Cancer Risk, and Mortality in the Women's Health Initiative. *Cancer Prev Res* (2014) 7(1):42–53. doi: 10.1158/1940-6207.CAPR-13-0258
51. Zhang QL, Zhao LG, Li HL, Gao J, Yang G, Wang J, et al. The Joint Effects of Major Lifestyle Factors on Colorectal Cancer Risk Among Chinese Men: A Prospective Cohort Study. *Int J Cancer* (2018) 142(6):1093–101. doi: 10.1002/ijc.31126
52. Aleksandrova K, Pischon T, Jenab M, Bueno-de-Mesquita HB, Fedirko V, Norat T, et al. Combined Impact of Healthy Lifestyle Factors on Colorectal Cancer: A Large European Cohort Study. *BMC Med* (2014) 12(1):1–15. doi: 10.1186/s12916-014-0168-4
53. Barrubés L, Babio N, Hernández-Alonso P, Toledo E, Ramírez Sabio JB, Estruch R, et al. Association Between the 2018 WCRF/AICR and the Low-Risk Lifestyle Scores With Colorectal Cancer Risk in the Predimed Study. *J Clin Med* (2020) 9(4):1215. doi: 10.3390/jcm9041215
54. Cheng E, Um CY, Prizment AE, Lazovich DA, Bostick RM. Evolutionary-Concordance Lifestyle and Diet and Mediterranean Diet Pattern Scores and Risk of Incident Colorectal Cancer in Iowa Women. *Cancer Epidemiol Biomarkers Prev* (2018) 27(10):1195–202. doi: 10.1158/1055-9965.EPI-17-1184
55. Dartois L, Fagherazzi G, Boutron-Ruault MC, Mesrine S, Clavel-Chapelon F. Association Between Five Lifestyle Habits and Cancer Risk: Results From the E3N Cohort. *Cancer Prev Res* (2014) 7(5):516–25. doi: 10.1158/1940-6207.CAPR-13-0325
56. Byrd DA, Judd S, Flanders WD, Hartman TJ, Fedirko V, Bostick RM. Associations of Novel Dietary and Lifestyle Inflammation Scores With Incident, Sporadic Colorectal Adenoma. *Cancer Epidemiol Biomarkers Prev* (2020) 29(11):2300–8. doi: 10.1158/1055-9965.EPI-20-0568
57. Erben V, Carr PR, Holleczek B, Stegmaier C, Hoffmeister M, Brenner H. Strong Associations of a Healthy Lifestyle With All Stages of Colorectal Carcinogenesis: Results From a Large Cohort of Participants of Screening Colonoscopy. *Int J Cancer* (2019) 144(9):2135–43. doi: 10.1002/ijc.32011
58. Fliss-Isakov N, Kariv R, Webb M, Ivancovsky-Wajcman D, Zaslavsky O, Margalit D, et al. A Healthy Lifestyle Pattern has a Protective Association With Colorectal Polyps. *Eur J Clin Nutr* (2020) 74(2):328–37. doi: 10.1038/s41430-019-0481-2
59. Fu Z, Shrubsole MJ, Smalley WE, Wu H, Chen Z, Shyr Y, et al. Lifestyle Factors and Their Combined Impact on the Risk of Colorectal Polyps. *Am J Epidemiol* (2012) 176(9):766–76. doi: 10.1093/aje/kws157
60. Tabung FK, Steck SE, Burch JB, Chen CF, Zhang H, Hurley TG, et al. A Healthy Lifestyle Index Is Associated With Reduced Risk of Colorectal Adenomatous Polyps Among Non-Users of Non-Steroidal Anti-Inflammatory Drugs. *J Prim Prev* (2015) 36(1):21–31. doi: 10.1007/s10935-014-0372-1
61. Knudsen MD, De Lange T, Botteri E, Nguyen DH, Evensen H, Steen CB, et al. Favorable Lifestyle Before Diagnosis Associated With Lower Risk of Screen-Detected Advanced Colorectal Neoplasia. *World J Gastroenterol* (2016) 22 (27):6276–86. doi: 10.3748/wjg.v22.i27.6276
62. Inoue-Choi M, Robien K, Lazovich D. Adherence to the WCRF/AICR Guidelines for Cancer Prevention is Associated With Lower Mortality Among Older Female Cancer Survivors. *Cancer Epidemiol Biomarkers Prev* (2013) 22(5):792–802. doi: 10.1158/1055-9965.EPI-13-0054
63. Lohse T, Faeh D, Bopp M, Rohrmann S. Adherence to the Cancer Prevention Recommendations of the World Cancer Research Fund/American Institute for Cancer Research and Mortality: A Census-Linked Cohort. *Am J Clin Nutr* (2016) 104(3):678–85. doi: 10.3945/ajcn.116.135020
64. Sotos-Prieto M, Mattei J, Cook NR, Hu FB, Willett WC, Chiuve SE, et al. Association Between a 20-Year Cardiovascular Disease Risk Score Based on Modifiable Lifestyles and Total and Cause-Specific Mortality Among US Men and Women. *J Am Heart Assoc* (2018) 7(21):e010052. doi: 10.1161/JAHA.118.010052
65. GBD 2016 Alcohol Collaborators MG, Fullman N, Hawley C, Arian N, Zimsen SRM, Tymeson HD, et al. Alcohol Use and Burden for 195 Countries and Territories, 1990-2016: A Systematic Analysis for the Global Burden of Disease Study 2016. *Lancet (London England)* (2018) 392 (10152):1015–35. doi: 10.1016/S0140-6736(18)31310-2
66. Norat T, Lukanova A, Ferrari P, Riboli E. Meat Consumption and Colorectal Cancer Risk: Dose-Response Meta-Analysis of Epidemiological Studies. *Int J Cancer* (2002) 98(2):241–56. doi: 10.1002/ijc.10126
67. Syed Soffian SS, Mohammed Nawi A, Hod R, Ja'afar MH, Isa ZM, Chan HK, et al. Meta-Analysis of the Association Between Dietary Inflammatory Index (DII) and Colorectal Cancer. *Nutr* (2022) 14(8):1555.
68. Fedirko V, Tramacere I, Bagnardi V, Rota M, Scotti L, Islami F, et al. Alcohol Drinking and Colorectal Cancer Risk: An Overall and Dose–Response Meta-Analysis of Published Studies. *Ann Oncol* (2011) 22(9):1958–72. doi: 10.1093/annonc/mdq653
69. Moghaddam AA, Woodward M, Huxley R. Obesity and Risk of Colorectal Cancer: A Meta-Analysis of 31 Studies With 70,000 Events. *Cancer Epidemiol Prev Biomarkers* (2007) 16(12):2533–47. doi: 10.1158/1055-9965.EPI-07-0708
70. Li T, Wei S, Shi Y, Pang S, Qin Q, Yin J, et al. The Dose-Response Effect of Physical Activity on Cancer Mortality: Findings From 71 Prospective Cohort Studies. *Br J Sports Med* (2016) 50(6):339–45. doi: 10.1136/bjsports-2015-094927
71. Morris LJ, D'Este C, Sargent-Cox K, Anstey KJ. Concurrent Lifestyle Risk Factors: Clusters and Determinants in an Australian Sample. *Prev Med (Baltim)* (2016) 84:1–5. doi: 10.1016/j.ypmed.2015.12.009
72. Schuit AJ, Van Loon AJM, Tijhuis M, Ocké MC. Clustering of Lifestyle Risk Factors in a General Adult Population. *Prev Med (Baltim)* (2002) 35(3):219–24. doi: 10.1006/pmed.2002.1064
73. Poortinga W. The Prevalence and Clustering of Four Major Lifestyle Risk Factors in an English Adult Population. *Prev Med (Baltim)* (2007) 44(2):124–8. doi: 10.1016/j.ypmed.2006.10.006
74. Platz EA, Willett WC, Colditz GA, Rimm EB, Spiegelman D, Giovannucci E. Proportion of Colon Cancer Risk That Might be Preventable in a Cohort of Middle-Aged US Men. *Cancer Causes Control* (2000) 11(7):579–88. doi: 10.1023/A:1008999232442

75. Loef M, Walach H. The Combined Effects of Healthy Lifestyle Behaviors on All Cause Mortality: A Systematic Review and Meta-Analysis. *Prev Med* (2012) 55p:163–70. doi: 10.1016/j.ypmed.2012.06.017
76. Hawkes AL, Chambers SK, Pakenham KI, Patrao TA, Baade PD, Lynch BM, et al. Effects of a Telephone-Delivered Multiple Health Behavior Change Intervention (CanChange) on Health and Behavioral Outcomes in Survivors of Colorectal Cancer: A Randomized Controlled Trial. *J Clin Oncol* (2013) 31 (18):2313–21. doi: 10.1200/JCO.2012.45.5873
77. Bourke L, Thompson G, Gibson DJ, Daley A, Crank H, Adam I, et al. Pragmatic Lifestyle Intervention in Patients Recovering From Colon Cancer: A Randomized Controlled Pilot Study. *Arch Phys Med Rehabil* (2011) 92 (5):749–55. doi: 10.1016/j.apmr.2010.12.020
78. Anderson AS, Caswell S, Macleod M, Craigie AM, Stead M, Steele RJC, et al. Awareness of Lifestyle and Colorectal Cancer Risk: Findings From the BeWEL Study. *BioMed Res Int* (2015) 2015:871613. doi: 10.1155/2015/871613
79. World Health Organization. *Tackling NCDs: 'best buys' and Other Recommended Interventions for the Prevention and Control of Noncommunicable Diseases*. Geneva: World Health Organization (2017).
80. Kushi L, Doyle C, McCullough M, CRock C, Demark-Wahnefried W, Bandera E, et al. American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention: Reducing the Risk of Cancer With Healthy Food Choices and Physical Activity. *CA Cancer J Clin* (2012) 62(1):30–67. doi: 10.3322/caac.20140
81. World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: A Global Perspective A Summary of the Third Expert Report*. Washington DC: AICR (2018).
82. Keighley MRB, O'Morain C, Giacosa A, Ashorn M, Burroughs A, Crespi M, et al. Public Awareness of Risk Factors and Screening for Colorectal Cancer in Europe. *Eur J Cancer Prev* (2004) 13(4):257–62. doi: 10.1097/01.cej.0000136575.01493.9b
83. Lynes K, Kazmi SA, Robery JD, Wong S, Gilbert D, Thaha MA. Public Appreciation of Lifestyle Risk Factors for Colorectal Cancer and Awareness of Bowel Cancer Screening: A Cross-Sectional Study. *Int J Surg* (2016) 36:312–8. doi: 10.1016/j.ijsu.2016.11.002
84. Tsai M-C, Lee C-C, Liu S-C, Tseng P-J, Chien K-L. Combined Healthy Lifestyle Factors are More Beneficial in Reducing Cardiovascular Disease in Younger Adults: A Meta-Analysis of Prospective Cohort Studies. *Sci Rep* (2020) 10:18165. doi: 10.1038/s41598-020-75314-z
85. Zhang Y-B, Pan X-F, Chen J, Cao A, Xia L, Zhang Y, et al. Combined Lifestyle Factors, All-Cause Mortality and Cardiovascular Disease: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *J Epidemiol Community Heal* (2021) 75(1):92–9. doi: 10.1136/jech-2020-214050
86. Zhang Y, Pan XF, Chen J, Xia L, Cao A, Zhang Y, et al. Combined Lifestyle Factors and Risk of Incident Type 2 Diabetes and Prognosis Among Individuals With Type 2 Diabetes: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *Diabetol Diabetol* (2020) 63:21–33. doi: 10.1007/s00125-019-04985-9
87. Roos E, Prättälä R, Lahelma E, Kleemola P, Pietinen P. Modern and Healthy?: Socioeconomic Differences in the Quality of Diet. *Eur J Clin Nutr* (1996) 50 (11):753–60.
88. Ball K, Crawford D. Socioeconomic Status and Weight Change in Adults: A Review. *Soc Sci Med* (2005) 60(9):1987–2010. doi: 10.1016/j.socscimed.2004.08.056
89. Hiscock R, Bauld L, Amos A, Fidler JA, Munafò M. Socioeconomic Status and Smoking: A Review. *Ann New Y Acad Sci* (2012) 1248p:107–23. doi: 10.1111/j.1749-6632.2011.06202.x

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Risk of adenoma recurrence after polypectomy in patients younger than 50 years vs. 50 years old and over with diminutive or small adenomas

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Background and aims: Current studies have shown that polyp recurrence occurs after colonic adenomas polypectomy (AP), but the difference in recurrence risk between patients in patients older than 50 years and younger than 50 years has not been clearly studied.

Methods: 490 patients after AP were enrolled in the study. The patients were classified according to age (<50 years old or ≥50 years old), and then further categorized according to the baseline adenoma characteristics: Group 1: 1–2 non-advanced adenomas (NAAs) 1–5 mm in size; Group 2: ≥3 NAAs, 1–5 mm; Group 3: 1–2 NAAs, 6–9 mm; Group 4: ≥3 NAAs, 6–9 mm; and Group 5: advanced adenomas.

Results: During a mean follow-up interval of 2.52 years (2.51 years for ≥50 years old and 2.55 years for patients <50 years old), NAA recurrence was detected in 147 patients (30.0%). Overall, the hazard ratio (HR) for NAA recurrence after AP was higher in patients ≥50 years old than that in patients <50 years old (HR, 1.774, P = 0.003). For patients <50 years old, HRs (Group 2-5 vs. G1, respectively) for NAA recurrence were 0.744 (P = 0.773), 3.885 (P = 0.007), 5.337 (P = 0.003), and 3.334 (P = 0.015). For patients ≥50 years old, HRs (Group 2-5 vs. G1, respectively) for NAA recurrence were 1.033 (P = 0.965), 1.250 (P = 0.405), 2.252 (P = 0.015), and 1.887 (P = 0.009). For G1, the risk of NAA recurrence was significantly higher in patients ≥50 years old (HR, 2.932, P = 0.011) than that in patients <50 years old; for G2–G5, the risk was similar in the two age groups (P > 0.05).

Conclusions: For patients <50 years old with less than 3 NAAs that are 1–5 mm in size, the recurrence rate of NAA is less than that of patients ≥50 years old with

the same index colonoscopy findings. When the adenomas are ≥5 mm, or their number exceeds 3, they have similar recurrence risk as that for patients ≥50 years old.

KEYWORDS

adenoma, colorectal cancer, polyp, age, risk factor, surveillance

1 Introduction

Colorectal cancer (CRC) was estimated to be the fifth most commonly diagnosed cancer and a leading cause of death related to cancer worldwide in 2020 (1). Colonoscopy and polypectomy are routine methods for CRC and precancerous lesion screening to prevent CRC. As evidenced by clinical practice, removal of adenomatous polyps reduces the incidence and mortality rate of CRC (2, 3). Adenoma is one important type of precancerous lesions, and it is thought that almost 90% of CRC develops from adenoma (4). Therefore, it is recommended that adenomatous polyp be removed immediately after identification during colonoscopy (5). Nevertheless, the recurrence rate of adenoma is very high, reaching nearly 50% during follow-up (6). This suggests that patients with adenomas should be followed up in accordance with the risk of adenoma recurrence and metachronous CRC development.

According to the current guideline (7), patients ≥50 years old should be stratified based on the polyp baseline number, size, and histology during post-polypectomy surveillance. Specifically, tubular adenomas smaller than 10 mm and without high-grade dysplasia are classed as non-advanced adenomas (NAAs), and one to two NAAs that are smaller than 10 mm are classed as low-risk adenomas (7). Timely intervention and follow-up are essential to improve the prognosis of patients with NAAs. Several studies have demonstrated a major protective effect of polypectomy in patients with NAAs (8, 9). According to these studies, after polypectomy, the risk of CRC in patients with NAAs is lower than that in the general population. But the difference in recurrence risk between patients older than 50 and those younger than 50 has not been clearly elucidated (10, 11). This makes choosing an appropriate surveillance interval for these patients very difficult. Further, analysis of subcategories of NAAs of different sizes (1–5 mm vs. 6–9 mm) in individuals >50 years old revealed different risks of developing metachronous advanced neoplasia associated with NAAs of different sizes (12–18). It is not known whether the same is true for individuals younger than 50 years.

Accordingly, in the current study, we compared the risk of adenoma recurrence after NAA polypectomy in patients <50 years old and those ≥50 years old, to determine whether the currently recommended surveillance intervals are also suitable for patients <50 years old.

2 Methods

2.1 Study population

Patients undergoing colonoscopy from January 2012 to January 2020 at the Endoscopic Center of Wuhan Union Hospital (Wuhan, China) were considered for the study. Only patients who had undergone polypectomy of at least one polyp and were followed up for more than 1 year were included. And all the patients involved in this study were with Boston bowel preparation score greater than 6.

The exclusion criteria were: all resected polyps pathologically confirmed to be non-adenomatous; a history of CRC, inflammation bowel disease, schistosomiasis, and previous resection of any part of the colon; diagnosed with CRC, irritable bowel disease, and schistosomiasis at an index colonoscopy; poor bowel preparation; and lack of clinical information or histologic information on the polyps.

The endoscopic findings and histologic results were based on well-established electronic medical records. Data, including an identifier, sex, age, and polyp number, size, and histology were collected. All endoscopic reports and pathologic reports were manually reviewed by experienced endoscopists and pathologists.

2.2 Colonoscopy and histologic examination

All colonoscopies were performed using Olympus (Tokyo, Japan) CF-Q260 or CF-Q290 by experienced endoscopists. Polyp number and size were determined during the colonoscopy (11, 19, 20). Polyp size was determined after resection or using standard clinical practices, such as open biopsy forceps method. Polypectomy was carried on through argon plasma coagulation (APC), cold or hot snare

polypectomy, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), where the polypectomy regimen was determined by endoscopist according to the actual condition of the patient. All collected specimens were carefully histologically investigated by pathologists.

2.3 Measurement and definition

Adenomas were stratified as follows: diminutive adenoma, 1–5 mm in diameter; small adenoma, 6–9 mm in diameter; advanced adenoma (AA), ≥10 mm in diameter, with tubulovillous or villous histology, or with high-grade dysplasia (7). Advanced neoplasia (AN) referred to the occurrence of either AAs or CRC. Serrated adenomas were excluded from consideration.

Patients were classified into two groups according to age, i.e., <50 years old (n = 163) and ≥50 years old (n = 327), and further sub-divided into five groups according to the number, size, and histology of polyps: Group 1 (G1), 1–2 diminutive NAAs; Group 2 (G2), 3 or more diminutive NAAs; Group 3 (G3), 1–2 small NAAs; Group 4 (G4), 3 or more small NAAs; and Group 5 (G5), AAs. The size of the adenoma was determined for the largest of the several present.

2.4 Statistical analysis

Baseline characteristics were compared using Chi-squared test, for categorical variables, and ANOVA, for continuous variables. Hazard ratios (HRs) for metachronous AN and adenoma recurrence were calculated using Cox proportional hazards regression model with 95% confidence interval (CI). Disease-free survival probabilities were determined using Kaplan–Meier method and survival curves were compared by log-rank test. All reported *P*-values are two-tailed, and $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed using R software version 4.0.3, packages "survival" and "survminer" (21, 22).

3 Results

3.1 Patient characteristics

The study workflow is shown in Figure 1. After initial patient screening using the inclusion and exclusion criteria, 490 patients were eligible for inclusion in the study. The patients were stratified per age, and then into predefined risk groups, according to the size, number, and histology of polyps. The demographic characteristics of patients included in the study at an index colonoscopy are shown in Table 1. The mean age was 54.1 ± 10.9 years; 29.8% (146/490) of the patients were female. The sex distribution did not differ significantly between all groups. The mean interval between the colonoscopy and surveillance was 2.52 ± 1.25 years (median: 2.18 years; range: 1.52–3.32 years), and the mean interval was 2.51 years for patients ≥50 years old and 2.55 years for patients <50 years old. The clinical findings of the surveillance are summarized in Table 2. During the follow-up, advanced neoplasia was rare, and found in only 18 patients (3.7%); NAA recurrence was more frequent, and detected in 147 patients (30.0%).

3.2 Risk of NAA recurrence after resection of diminutive vs. small adenomas in different age groups

The cumulative incidence of NAA was compared across different age groups and the polyp size–number groups (Table 3). The risk of NAA recurrence was significantly higher in patients aged ≥50 years than that in patients aged <50 years [HR, 1.77 (95% CI, 1.21–2.60), $P = 0.003$]. Further, the risk in the G3, G4, and G5 group was significantly lower than the individual risk in the G1 group [HR, 1.75 (95% CI, 1.11–2.78), $P = 0.017$, G3 vs. G1; 2.90 (95% CI, 1.66–5.06), $P < 0.001$, G4 vs. G1; and 2.32 (95% CI 1.52–3.54), $P < 0.001$, G5 vs. G1), but the risk in G2 group was similar to that in the G1 group [HR, 0.71 (95% CI, 0.22–2.31), $P = 0.570$]. This suggests that older age, large polyp size, and the presence of numerous polyps are potential risk factors for the recurrence of NAA after polypectomy.

In the two age groups, the trend of the recurrence risk was similar, with some specific differences (Table 3). For patients <50 years old, the risks in the G3, G4, and G5 groups were significantly higher than that in the G1 group [HR, 3.89 (95% CI, 1.45–10.45), G3 vs. G1; HR, 5.34 (95% CI, 1.78–15.98), G4 vs. G1; and HR, 3.33 (95% CI, 1.27–8.79), G5 vs. G1], but the risk in G2 was not significantly different from that in the G1 group [HR, 0.74 (95% CI, 0.09–6.08), $P = 0.773$]. For patients ≥50 years old, the risks of recurrence in G4 and G5 groups were significantly higher than that in G1 group [HR, 2.25 (95% CI, 1.17–4.33), G4 vs. G1; HR, 1.89 (95% CI, 1.18–3.02), G5 vs. G1], but the differences in the risks in the G2, G3, and G1 groups were not significant [HR, 1.03 (95% CI, 0.25–4.34), $P = 0.965$, G2 vs. G1; HR, 1.25 (95% CI, 0.74–2.11), $P = 0.405$, G3 vs. G1].

We next conducted subgroup analysis for age (≥50 years old vs. <50 years old) and the G1–G5 groups (Table 3 and Figure 2). The analysis revealed that in the G1 group, the risk in the ≥50 years old group was remarkably higher than that in the <50 years old group [HR, 2.93 (95% CI, 1.28–6.72), $P = 0.011$] (Figure 2A). However, in other groups, the analysis did not reveal any significant differences by age (Figures 2B–E).

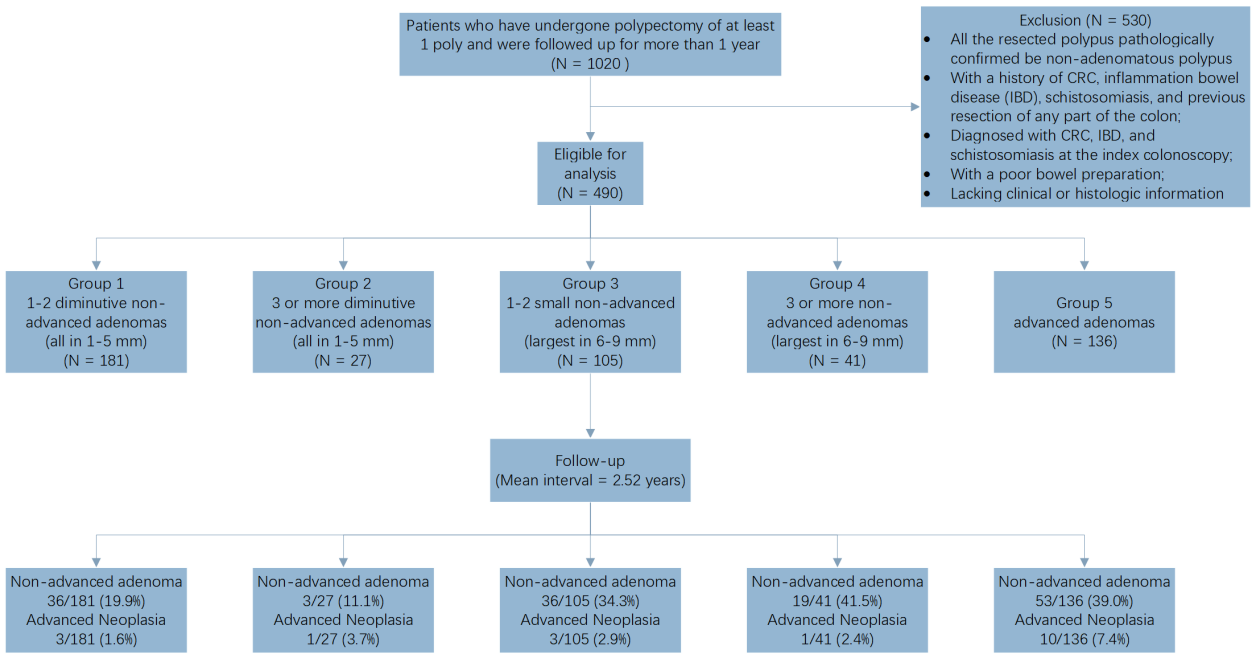

FIGURE 1
Study workflow.

3.3 Risk of metachronous AN after resection of adenomas in different age groups

Cumulative risks of metachronous AN in the different age groups are shown in Table 4 and Figure 3. After adenoma resection, no differences in recurrence rates of AN [3.1% (n = 5) for <50 years old patients and 4.0% (n = 13) for ≥50 years old patients] were apparent in the two age groups [HR, 1.20 (95% CI, 0.42–3.41), $P = 0.732$). The general recurrence rate was 3.7% in all patients.

3.4 Risk of metachronous AN with NAA recurrence vs. without NAA recurrence

Patients whom were found with polyp recurrence during surveillance would undergo polypectomy. To determine whether

TABLE 1 Demographic characteristics of patients.

		1-2 diminutive NAAs	1-2 small NAAs	≥3 diminutive NAAs	≥3 small NAAs	AAs	*P*
n	Overall	181	27	105	41	136	
	<50yr	67	16	26	14	40	
	≥50yr	114	11	79	27	96	
Age [mean (SD)]	Overall	53.77 (10.15)	47.26 (11.17)	64.67 (11.25)	54.10 (11.35)	55.46 (11.12)	0.010
	<50yr	43.33 (5.38)	40.44 (8.42)	39.23 (6.56)	41.93 (7.58)	42.40 (5.89)	0.063
	≥50yr	59.91 (6.64)	57.18 (5.95)	59.75 (7.04)	60.41 (6.95)	60.90 (7.73)	0.493
Gender [Female (%)]	Overall	61 (33.5)	10 (37.0)	25 (23.8)	10 (24.4)	40 (29.4)	0.357
	<50yr	23 (34.3)	5 (31.2)	6 (23.1)	2 (14.2)	11 (27.5)	0.570
	≥50yr	38 (33.3)	5 (45.5)	19 (24.1)	8 (29.6)	29 (30.2)	0.531
Surveillance interval [mean (SD)]	Overall	2.52 (1.25)	1.95 (0.84)	2.55 (1.27)	2.50 (1.19)	2.61 (1.31)	0.170

NAA, Non-advanced adenoma; AA, Advanced adenomas; SD, Standard deviation.

TABLE 2 Pathologic findings during the surveillance.

		N (%)
Advanced neoplasia		18 (3.7)
	Cancer	9 (1.8)
	Adenoma ≥10 mm in size	0 (0)
	Adenoma with tubulovillous histology	8 (1.6)
	Adenoma with villous histology	1 (0.2)
Non-advanced adenoma		147 (30.0)

TABLE 3 Risk of non-advanced adenoma recurrence according to the colonoscopy results.

		N	Adenoma	Hazard Ratio	*P*
Overall		490	147		
	<50yr	162	33	1 (Ref)	
	≥50yr	328	114	1.77 (1.21-2.60)	0.003**
Overall		490	147		
	G1	181	36	1 (Ref)	
	G2	27	3	0.71 (0.22-2.31)	0.570
	G3	105	36	1.75 (1.11-2.78)	0.017*
	G4	41	19	2.90 (1.66-5.06)	<0.001***
	G5	136	53	2.32 (1.52-3.54)	<0.001***
<50yr		162	33		
	G1	67	7	1 (Ref)	
	G2	16	1	0.74 (0.09-6.08)	0.773
	G3	26	9	3.89 (1.45-10.45)	0.007**
	G4	14	6	5.34 (1.78-15.98)	0.003**
	G5	39	10	3.33 (1.27-8.78)	0.015*
≥50yr		328	114		
	G1	114	29	1 (Ref)	
	G2	11	2	1.03 (0.25-4.34)	0.965
	G3	79	27	1.25 (0.74-2.11)	0.405
	G4	27	13	2.25 (1.17-4.33)	0.015*
	G5	97	43	1.89 (1.18-3.03)	0.009**
G1		181	36		
	<50yr	67	7	1 (Ref)	
	≥50yr	114	29	2.93 (1.28-6.72)	0.011*
G2		27	3		
	<50yr	16	1	1 (Ref)	
	≥50yr	11	2	1 (0-Inf)	1
G3		105	36		
	<50yr	26	9	1 (Ref)	
	≥50yr	79	27	0.86 (0.40-1.84)	0.697
G4		41	19		
	<50yr	14	6	1 (Ref)	
	≥50yr	27	13	1.11 (0.41-2.96)	0.838
G5		136	53		
	<50yr	39	10	1 (Ref)	
	≥50yr	97	43	1.71 (0.86-3.42)	0.128

*, **, and *** denotes P < 0.05, 0.01, and 0.001, respectively. G1 - G5, Group1 - Group5.

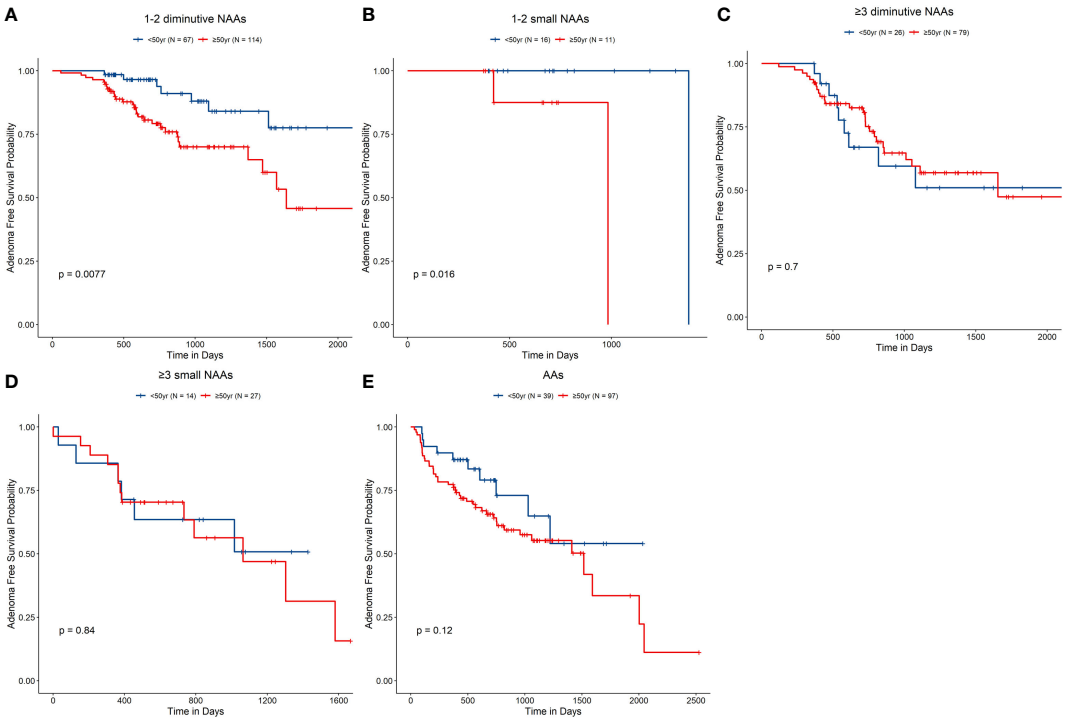

FIGURE 2
Non-advanced adenoma (NAA)–free survival rate according to the index colonoscopy results. **(A–E)**, G1–G5, accordingly. G1, Group 1, 1–2 diminutive NAAs; G2, Group 2, 3 or more diminutive NAAs; G3, Group 3, 1–2 small NAAs; G4, Group 4, 3 or more small NAAs; and G5, Group 5, advanced adenomas.

polyp recurrence, suggesting that these patients are more prone to metachronous AN, we compared the outcomes in patients with and without NAA recurrence in each age group. Cox regression analysis did not reveal significant differences in the risk of metachronous AN between patients with and without NAA recurrence [HR, 0.25 (95% CI 0.06–1.10), P = 0.066]. However, log-rank test of the survival curves of patients with and without NAA recurrence indicated significant differences between the groups (P = 0.047) (Table 4 and Figure 4A). The differences were more pronounced for patients who were over 50 years old than for younger patients (Figures 4B, C). Log-rank test showed in patients ≥50 years old, the risk of metachronous AN was higher in patients without NAA recurrence than that of patients with NAA recurrence (P = 0.005), while in patients <50 years old this difference was insignificant (P = 0.47).

4 Discussions

In the current study, we compared the risk of NAA recurrence in two age groups (<50 years old and ≥50 years old) of patients with different numbers of different-sized adenomas. The presented data support the hypothesis that the NAA recurrence risk in patients with adenomas who are <50 years old is lower than that in patients ≥50 years old. Therefore, for patients with adenomas who are <50 years old, one may consider a different follow-up strategy than that for older patients.

The main results of the current study can be summarized as follows. (1) For patients <50 years old with 1–2 diminutive adenomas, the NAA recurrence risk after polypectomy is significantly lower than that for patients ≥50 years old with 1–2 diminutive adenomas. Hence, for these patients, one could recommend a surveillance interval that is longer than that recommended for patients ≥50 years old. (2) For patients <50 years old with small adenomas, the NAA recurrence risk is similar to that for patients ≥50 years old with small adenomas. Consequently, for these patients, the recommended surveillance frequency may be similar to that recommended for patients ≥50 years old.

Adenomatous polyps are typically considered to be a type of precancerous lesion before CRC (4) and most CRCs are thought to originate from adenomas. Removal of adenomas, once found, and subsequent surveillance are a standardized procedure in the US (5, 7). The current US Multi-Society Task Force guideline recommends stratifying patients ≥50 years old into different risk groups according to the baseline colonoscopy findings. According to the guideline,

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TABLE 4 Risk of metachronous advanced neoplasia between different groups.

		N	Advanced neoplasia	Hazard Ratio	*P*
Overall		490	18		
	<50yr	162	5	1 (Ref)	
	≥50yr	328	13	1.20 (0.42-3.41)	0.732
Overall		490	18		
	Without non-advanced adenoma recurrence	343	16	1 (Ref)	
	With non-advanced adenoma recurrence	147	2	0.25 (0.06-1.10)	0.066
<50yr		162	5		
	Without non-advanced adenoma recurrence	129	3	1 (Ref)	
	With non-advanced adenoma recurrence	33	2	1.92 (0.32-11.56)	0.477
≥50yr		328	13		
	Without non-advanced adenoma recurrence	214	13	1 (Ref)	
	With non-advanced adenoma recurrence	114	0	0 (0-Inf)	0.998

1–2 NAAs that are <10 mm in size are considered low-risk adenoma, with a recommended 7–10-year surveillance interval for patients after polypectomy. Other adenomas are considered high-risk adenomas, with a recommended 3–5-year surveillance interval after polypectomy. However, the surveillance intervals recommended by the current guideline have some limitations and should be improved. Specifically, the guideline only provides recommendations for patients ≥50 years old, because of lack of research focusing on younger patients (<50 years old). Further, it does not discriminate between diminutive and small adenomas, even though some experts suggest that there are differences in the risk for these two types of adenomas to develop into malignant lesions (11, 14–17, 20). Similarly, the guidelines of European Society of Gastrointestinal Endoscopy (ESGE) and British Society of Gastroenterology (BSG) do not discriminate between diminutive and small adenomas and suggest a simpler follow-up protocol (23, 24). In ESGE and BSG guidelines, only adenomas ≥10mm, or with high grade dysplasia are regarded as high-risk adenomas, irrespective of villous components; others are all regarded as low-risk adenomas. ESGE guideline recommends that patients with 1-4 low-risk adenoma do not need any surveillance, while patients with ≥5 adenomas or with

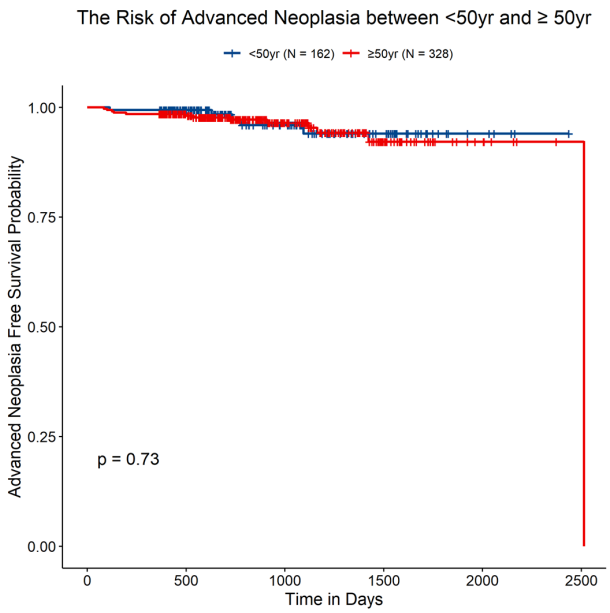

FIGURE 3
Advanced neoplasia-free survival rate in patients <50 years old and ≥50 years old.

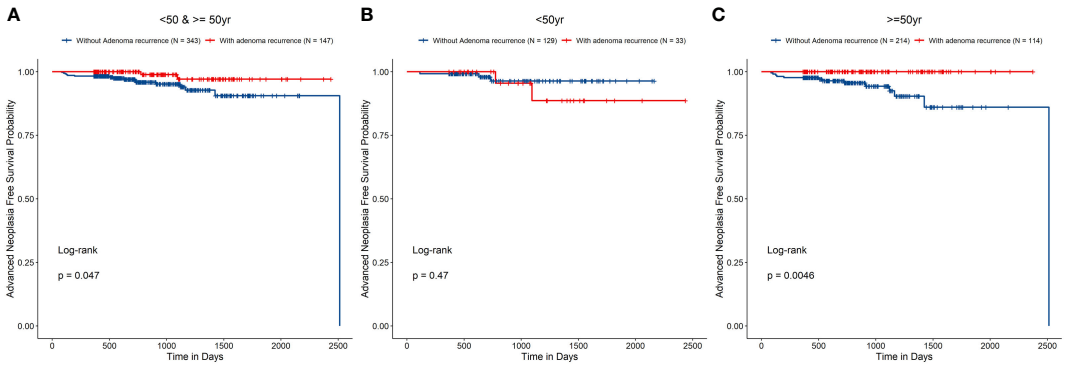

FIGURE 4
Risk of metachronous advanced neoplasia in groups (**A** All patients, **B** patients younger than 50 years old, and **C** patients 50 years old and over) with and without non-advanced adenoma recurrence.

high-risk adenoma require surveillance colonoscopy in 3 years after index colonoscopy (23). BSG guideline is very similar with ESGE guideline, which recommends only patients with ≥2 premalignant polyps including ≥1 high-risk adenoma, or patients with ≥5 adenomas require surveillance colonoscopy in 3 years (24).

The risks of metachronous AN in patients who had undergone polypectomy of diminutive or small adenoma have been compared in several other studies (11, 14–17, 20). Although the endpoint chosen in the current study was different from those of the other studies, the conclusions presented herein are still generally in line with those of previous studies. In all studies, patients with 1–2 diminutive NAAs were at a lower risk of either metachronous AN or NAA recurrence than patients with 1–2 small NAAs. Sneh Arbib et al. (14) were the first to report that patients with 1–2 diminutive NAAs were at a different risk of metachronous AN than patients with 1–2 small NAAs. However, no differences in the risk in patients with ≥3 polyps were reported in that study (14). These observations were further validated in subsequent investigations worldwide (11, 15, 17, 20). Kim et al. (11, 20) validated these conclusions in Asian populations. The authors reported that while patients with high-risk adenoma (including ≥3 diminutive adenomas, ≥3 small adenomas, and AAs) shared a similar risk of metachronous AN, the risk was reduced in patients with 1–2 diminutive NAAs. Further, the risk was different for patients <50 years old and patients ≥50 years old. In patients <50 years old with high-risk adenoma, the risk was no longer similar to that of patients ≥50 years old with high-risk adenoma (20). The risk of metachronous AN in patients with ≥3 diminutive adenomas was lower than that in patients with ≥3 small adenomas, but was not different from that in patients with low-risk adenoma. Kim et al. (11) did not conduct any further subgroup analysis according to age in each group. Nonetheless, they concluded that the surveillance strategy should probably be different for patients <50 years old and ≥50 years old. Our study supported this notion, but with some specific cases. For example, we did not find any differences between the risk of NAA recurrence in patients with ≥3 diminutive adenomas between patients <50 years old and ≥50 years old [HR, 0.86 (95% CI, 0.40–1.84), $P = 0.697$].

Considering the above, the follow-up strategy for the surveillance interval should be updated to guide long-term prognostic assessment and follow-up. Jung et al. (12) proposed a new classification that entails three groups (low, intermediate, and high-risk groups) instead of two groups (low and high-risk groups). They suggested that 1–2 NAAs sized 6–9 mm and 3–10 NAAs sized 1–5 mm should be regarded as an intermediate-risk group and require a different surveillance interval than other groups. However, the authors did not recommend any specific surveillance intervals for the risk groups in their study. Similar to the observations of Jung et al. (12) for patients ≥50 years old, we here observed that 1–2 small NAAs are more dangerous than 1–2 diminutive NAAs in that patient group. In addition to showing that the same holds for patients <50 years old, we also found that even with just 1–2 diminutive NAAs, patients ≥50 years old are at a much greater risk of adenoma recurrence than patients <50 years old [HR 2.93 (95%CI 1.28–6.72)]. Therefore, an individualized surveillance strategy should be established that considers various factors, especially age.

We also here analyzed the risk of metachronous AN in patients with and without NAA recurrence. A notion exists in clinical practice that polyp removal always reduces a patient's risk of colorectal cancer. However, there is little evidence on the degree of the associated risk reduction. The observations presented herein demonstrate that during surveillance, recurrent NAAs which were timely resected would not increase the chances of metachronous AN comparing to patients without NAA recurrence. This result provides indirect evidence for the protective effect of polypectomy.

Further, we did not observe a significant difference in the risk of metachronous AN in patients <50 years old and ≥50 years old. We suggest that the low incidence of AN and some confounding factors, such as subsequent polypectomy after an index colonoscopy, may have impacted this finding. Because of the low incidence of AN, the sample size in the current study was not sufficient for subgroup analysis with respect to the size and number of adenomas. Consequently, while we conclude that the general risk of metachronous AN in patients <50 years old and ≥50 years old is similar, the risk in each subgroup requires further consideration.

One potential confounding factor needed to be considered was that there might be a few polyps missed at the first index colonoscopy, then regarded as recurrent polyps at the subsequent colonoscopy. Missing adenoma could not be avoided, but since the colonoscopies were all done by experienced endoscopists in our center, and all the patients included in the study were with a fair bowel preparation quality, this influence could be minimized. Our study showed a similar polyp recurrence rate with previous researches (11, 14), which also proved this confounding factor had little effect on the finding of the study. In our study, we found that the overall non-advanced adenoma recurrence rate during a median follow-up of 2.18 years was 30%. And in similar researches, Sneh Arbib et al. reported that the overall non-advanced adenoma recurrence rate during a median follow-up of 2.67 years was 30.5% (14). Kim et al. reported that 3-year nonadvanced adenoma cumulative recurrence rates after polypectomy were 39.2% for high-risk population (high-risk referred to those having an advanced adenoma or >3 adenomas) in 50-54 age, and 38.8% for high-risk population in 20-49 age (11). And for advanced neoplasia, similar to our study, there are several studies have reported a similar advanced neoplasia recurrence rate. Kim et al. reported that the overall advanced adenoma recurrence rate during a median follow-up of 3.2 years was 5.6% (20). And in another study, Kim et al. reported that 3-year cumulative advanced adenoma recurrence rate was 0.9-4.0% varying from patients with different baseline adenoma numbers and sizes (13).

The current study has several limitations. First, the follow-up period was relatively shorter than that recommended by the current guideline but close to that used in similar studies. The average follow-up time is 2.52 years (median: 2.18 years), while the median follow-up time was 2.67 years for the study by Sneh Arbib et al. (14). Second, the sample size of some subgroups was inadequate to detect associations, such as the G2 group (n = 27) and G4 group (n = 41). However, the primary conclusions of the current study are not based on data for the G2 group and G4 group and, therefore, this limitation does not undermine the primary conclusions of the study. Since a small sample size may produce a false-negative error, the true correlations for the G2 group should be validated in a large-sample study. Third, the cohort in the current study was based on the medical records of Wuhan Union Hospital. The cohort was a hospital-based population, and we selected all patients and checkup populations who met the inclusion criteria in the study, which may have introduced selection bias. Further, the retrospective design of the study did not allow a constant follow-up duration. The time interval between the index colonoscopy and subsequent colonoscopy varied, which could also result in bias. Accordingly, we used the survival analysis method to minimize the effects of any such potential bias. Fourth, we found a slight difference on the mean ages of G1-G5 on the baseline. Thus, we conducted a subgroup analysis, divided the patients into the subgroups of <50 years old and ≥50 years old and found this heterogeneity was eliminated in each subgroup. So, this heterogeneity would not influence our major conclusions since our major conclusions were based on the subgroup analysis results. This also suggested the necessity to discriminate the patients <50 years old and ≥50 years old, which is the major topic of our research.

Several important aspects of the current study should be highlighted. To the best of our knowledge, the current study is the first to focus on the differences of adenoma recurrence risk in patients <50 years old and ≥50 years old. Some previous studies reported that the metachronous AN risk is different across age groups, but no further subgroup analysis for age was conducted (11, 20). Further, we chose NAA recurrence as the primary endpoint, which is a feasible endpoint in clinical practice. In conclusion, we showed that it is necessary to distinguish between patients ≥50 years old and <50 years old with 1–2 adenomas sized 1–5 mm because they are at a different risk of NAA recurrence, which may ultimately affect the risk of CRC development.

Data availability statement

The data generated and analyzed during this study is included in the article. Further inquiries can be directed to the corresponding author on reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (IORG number: IORG0003571). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SC and HS contributed equally to this work. RL designed and supervised the study and data analysis; SC and HS

performed most of data collection, analysis, and wrote the manuscript. MF provided help in data collection and analysis. QZ provided pathological assessment and analysis. The authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* (2021) 0:1–41. doi: 10.3322/caac.21660

2. Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* (2012) 366:687–96. doi: 10.1056/NEJMoa1100370

3. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. *New Engl J Med* (1993) 329:1977–81. doi: 10.1056/NEJM199312303292701

4. Cotton S, Sharp L, Little J. The adenoma-carcinoma sequence and prospects for the prevention of colorectal neoplasia. *Crit Rev Oncogenesis* (1996) 7:293–342. doi: 10.1615/critrevoncog.v7.i5-6.10

5. Kaltenbach T, Anderson JC, Burke CA, Dominitz JA, Gupta S, Lieberman D, et al. Endoscopic removal of colorectal lesions: Recommendations by the US multi-society task force on colorectal cancer. *Am J Gastroenterol* (2020) 115:435–64. doi: 10.14309/ajg.0000000000000555

6. Martínez ME, Baron JA, Lieberman DA, Schatzkin A, Lanza E, Winawer SJ, et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. *Gastroenterology* (2009) 136:832–41. doi: 10.1053/j.gastro.2008.12.007

7. Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, et al. Recommendations for follow-up after colonoscopy and polypectomy: A consensus update by the US multi-society task force on colorectal cancer. *Am J Gastroenterol* (2020) 115:415–34. doi: 10.14309/ajg.0000000000000544

8. Cottet V, Jooste V, Fournel I, Bouvier AM, Faivre J, Bonithon-Kopp C. Long-term risk of colorectal cancer after adenoma removal: A population-based cohort study. *Gut* (2012) 61:1180–6. doi: 10.1136/gutjnl-2011-300295

9. Click B, Pinsky PF, Hickey T, Doroudi M, Schoen RE. Association of colonoscopy adenoma findings with long-term colorectal cancer incidence. *JAMA* (2018) 319:2021. doi: 10.1001/jama.2018.5809

10. Nagpal SJS, Mukhija D, Sanaka M, Lopez R, Burke CA. Metachronous colon polyps in younger versus older adults: A case-control study. *Gastrointest Endosc* (2018) 87:657–65. doi: 10.1016/j.gie.2017.05.011

11. Kim HG, Cho YS, Cha JM, Shin JE, Kim KO, Yang HJ, et al. Risk of metachronous neoplasia on surveillance colonoscopy in young patients with colorectal neoplasia. *Gastrointest Endosc* (2018) 87:666–73. doi: 10.1016/j.gie.2017.05.053

12. Jung YS, Kim TJ, Nam E, Park CH. Comparative systematic review and meta-analysis of 1- to 5-mm versus 6- to 9-mm adenomas on the risk of metachronous advanced colorectal neoplasia. *Gastrointest Endosc* (2020) 92:692–701. doi: 10.1016/j.gie.2020.04.042

13. Kim NH, Jung YS, Lee MY, Park JH, Park D, Sohn C. Risk of developing metachronous advanced colorectal neoplasia after polypectomy in patients with multiple diminutive or small adenomas. *Am J Gastroenterol* (2019) 114:1657–64. doi: 10.14309/ajg.0000000000000296

14. Sneh Arbib O, Zemser V, Leibovici Weissman Y, Gingold-Belfer R, Vilkin A, Eizenstein S, et al. Risk of advanced lesions at the first follow-up colonoscopy after polypectomy of diminutive versus small adenomatous polyps of low-grade dysplasia. *Gastrointest Endosc* (2017) 86:713–21. doi: 10.1016/j.gie.2017.02.034

15. Anderson JC, Rex DK, Robinson C, Butterly LF. Association of small versus diminutive adenomas and the risk for metachronous advanced adenomas: data from the new Hampshire colonoscopy registry. *Gastrointest Endosc* (2019) 90:495–501. doi: 10.1016/j.gie.2019.05.029

16. Laish I, Sergeev I, Stein A, Naftali T, Konikoff FM. Risk of metachronous advanced lesions after resection of diminutive and small, non-advanced adenomas. *Clin Res Hepatol Gastroenterol* (2019) 43:201–7. doi: 10.1016/j.clinre.2018.03.001

17. Hartstein JD, Vemulapalli KC, Rex DK. The predictive value of small versus diminutive adenomas for subsequent advanced neoplasia. *Gastrointest Endosc* (2020) 91:614–21. doi: 10.1016/j.gie.2019.08.047

18. Gupta S, Jacobs ET, Baron JA, Lieberman DA, Murphy G, Ladabaum U, et al. Risk stratification of individuals with low-risk colorectal adenomas using clinical characteristics: A pooled analysis. *Gut* (2017) 66:446–53. doi: 10.1136/gutjnl-2015-310196

19. Hiraoka S, Kato J, Fujiki S, Kaji E, Morikawa T, Murakami T, et al. The presence of large serrated polyps increases risk for colorectal cancer. *Gastroenterology* (2010) 139:1503–10. doi: 10.1053/j.gastro.2010.07.011

20. Kim JY, Kim TJ, Baek SY, Ahn S, Kim ER, Hong SN, et al. Risk of metachronous advanced neoplasia in patients with multiple diminutive adenomas. *Am J Gastroenterol* (2018) 113:1855–1861. doi: 10.1038/s41395-018-0210-9

21. Therneau TM, Grambsch PM. *Modeling survival data: Extending the {C}ox model*. New York: Springer (2000).

22. Kassambara A, Kosinski M, Biecek P. Survminer: Drawing survival curves using "ggplot2." (2021). Available at: https://cran.r-project.org/package=survminer.

23. Hassan C, Antonelli G, Dumonceau J-M, Regula J, Bretthauer M, Chaussade S, et al. Post-polypectomy colonoscopy surveillance: European society of gastrointestinal endoscopy (ESGE) guideline - Update 2020. *Endoscopy* (2020) 52:687–700. doi: 10.1055/a-1185-3109

24. Rutter MD, East J, Rees CJ, Cripps N, Docherty J, Dolwani S, et al. British Society of Gastroenterology/Association of coloproctology of great Britain and Ireland/Public health England post-polypectomy and post-colorectal cancer resection surveillance guidelines. *Gut* (2020) 69:201–23. doi: 10.1136/gutjnl-2019-319858

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