Research Article
Risk of Colorectal Cancer in Ulcerative Colitis Patients: A Systematic Review and Meta-Analysis

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Background. Ulcerative colitis (UC) patients have an increased risk for the development of colorectal cancer (CRC). Our aim was to assess the risk of CRC in UC patients compared with disease extent, disease duration, and geographic variation. Methods. In this systematic review and meta-analysis, we searched PubMed, scientific meetings, and the bibliographies of identified articles, with English language restrictions for studies published from 1988 to 2018, and assessed the risk of CRC in UC patients. Patients with Crohn’s disease, family history of CRC, and colorectal adenomatous polyp (CAP) were excluded from this research. The study was registered with PROSPERO, number CRD42018102213. Findings. We included 58 studies that included 267,566 UC patients. Extensive UC and left-sided UC had a higher risk of CRC than proctitis UC. Geography also played a role in UC-associated CRC development. The time of malignant transformation in Asian UC patients started after 10-20 years of this disease duration. North American UC-associated CRC patients significantly increased in more than 30 years of this disease duration. Conclusion. In a systematic review of the literature, we found that disease extent, disease duration, and geography were strong, independent risk factors in UC-associated CRC development.

1. Introduction

Ulcerative colitis (UC) is an idiopathic, chronic inflammatory disorder of the colonic mucosa, which started in the rectum and generally extended proximally in a continuous manner through part of, or the entire, colon [1]. The clinical course was unpredictable, marked by alternating periods of exacerbation and remission [2]. UC-associated colorectal cancer (CRC) represented a fraction of CRC cases, accounted for up to 5% of all CRC [3]. In contrast to sporadic CRC, UC-associated CRC did not follow the typical “adenoma-carcinoma” sequences [1]. Due to limited understanding of the natural history of UC-associated CRC, the knowledge concerning the CRC risk in UC patients was still inadequate.

The first retrospective analysis on the risk of CRC in UC was published in 1988. In this publication, the overall incidence of CRC in UC was reported as 4.25% [4]. Recent mounting evidences from numerous countries suggested that the CRC standardised incidence ratio (SIR) in
UC may differ based on disease duration and geographic variation. For example, the 10-year cumulative probability of cancer after the diagnosis of UC was 4.9%, not having a higher risk of cancer than an age-and sex-matched general population [5]. However, there was no synthesis of risk factors associated with disease extent, disease duration, and geographic variation. Therefore, we did a systematic review and meta-analysis to investigate the risk of CRC in UC patients compared with disease extent, disease duration, and geographic variation.

2. Methods

2.1. Search Strategy and Selection Criteria. We did a comprehensive literature research according to the Cochrane Handbook for Systematic Reviews of Interventions and followed the PRISMA and MOOSE guidelines for the reporting of meta-analyses. We searched PubMed, scientific meetings, and the bibliographies of identified articles, with English language restrictions for studies published from 1988 to Dec. 2018. All relevant articles included UC-associated CRC patients. Medical subject heading or keywords used in the search included the following: “Ulcerative Colitis” or “Inflammatory Bowel Disease (IBD)” or “Colorectal Cancer” or “Colorectal Neoplasia”. The full search strategies used for each database were described in Figure 1.

Articles were eligible for inclusion if they reported the UC patients were associated with CRC in terms of the sample size. We included incidence rates in our analyses as an indirect method of adjustment for disease extent, disease duration, and geography.

Two authors (Qing Zhou and Zhao-Feng Shen) independently screened the title and abstract according to these eligibility criteria, screened data extraction, and did quality evaluation. When the evaluation result was not consistent, they consulted other researchers to further resolve differences through consultation according to the literature on the raw data. When the title and abstract met the requirements of the literature, the full text was retrieved for data extraction. NoteExpress 2.0 was adopted to manage the literature, and the repeated literature was removed. The inclusion of the literature was checked according to the abovementioned inclusion criteria, and the related references were traced.

2.2. Exclusion Criteria. We excluded the studies in this meta-analysis that met the following inclusion criteria:

1. The literature type did not belong to the category of UC-associated CRC
2. The literature type was a meta-analysis or summarization
3. The literature type data was incomplete (UC and Crohn’s disease could not be distinguished effectively) and the additional data could not be further obtained
4. The literature type outcome evaluation index was not CRC
5. The literature type was Crohn’s disease, CAP, family history of CRC, or colectomy for UC
6. The literature type was repeated or republished

2.3. Data Extraction. Two researchers (Qing Zhou and Zhao-Feng Shen) independently extracted relevant information from all eligible studies using a predefined data extraction form: author, publication year, sample size, age, country, gender, disease extent, and disease duration. Diagnosis and confirmation of UC and CRC were according to the criteria [6]. For missing data, the researchers tried to contact the original literature author by e-mail to obtain
Table 1: Population and study characteristics.

| Author                        | Sample size (UC) | Study period | Mean age at diagnosis (UC) | Country | Sample size (CRC) | Mean age at diagnosis (CRC) | Gender | Disease extent | Time of duration (year) |
|-------------------------------|------------------|--------------|---------------------------|---------|------------------|----------------------------|--------|----------------|------------------------|
| Hata et al. [7]               | 217              | 1979-2001    | 31.4                      | Japan   | 5                | 46.6                       | 0      | 4              | 1                      | 0                      | 15.2                  |
| Kim et al. [8]                | 7061             | 1970-2005    | 37.9                      | Korea   | 26               | 49.6                       | 8      | 18             | 0                      | 0                      | 12.7                  |
| Gong et al. [9]               | 3922             | 1998-2009    | 40                        | China   | 34               | 57.5                       | 14     | 20             | 10                     | 12                     | 12.8                  |
| Matsuoka et al. [10]          | 1274             | 1984-2010    | 30                        | Japan   | 83               | 52                         | 43     | 40             | 66                     | 17                     | 10 22                 |
| Zhang et al. [11]             | 624              | 2000-2012    | 39                        | China   | 4                | 54.5                       | 2      | 2              | 4                      | 0                      | 15.5                  |
| Lee et al. [12]               | 2798             | 1989-2013    | 33                        | Korea   | 18               | 48                         | 7      | 11             | 16                     | 2                      | 0 15                  |
| Choi et al. [13]              | 522              | 2013-2013    | 0                         | Korea   | 12               | 0                          | 0      | 0              | 0                      | 0                      | 0                     |
| Shi et al. [14]               | 1225             | 1981-2013    | 41                        | China   | 15               | 0                          | 0      | 0              | 0                      | 0                      | 0                     |
| Yoshino et al. [15]           | 2137             | 2003-2013    | 0                         | Japan   | 43               | 53                         | 28     | 15             | 34                     | 8                      | 1 13                  |
| Wang et al. [16]              | 2663             | 1998-2013    | 43.1                      | China   | 18               | 0                          | 0      | 0              | 0                      | 0                      | 0 19.27               |
| Jung et al. [17]              | 9785             | 2011-2014    | 0                         | Korea   | 31               | 0                          | 20     | 11             | 0                      | 0                      | 0                     |
| Kishikawa et al. [18]         | 289              | 1979-2014    | 33                        | Japan   | 9                | 49                         | 5      | 4              | 28                     | 5                      | 0 16                  |
| Bopanna et al. [19]           | 1012             | 2004-2015    | 32.1                      | India   | 20               | 53.25                      | 14     | 6              | 16                     | 4                      | 0 18.7                |
| Selinger et al. [20]          | 504              | 1977-1992    | 0                         | Australia | 24              | 0                          | 0      | 0              | 12                     | 8                      | 4 0                   |
| Gupta et al. [21]             | 418              | 1996-1997    | 26.8                      | USA     | 1                | 0                          | 0      | 0              | 0                      | 0                      | 0                     |
| Jess et al. [22]              | 378              | 1940-2001    | 34                        | USA     | 6                | 50.67                      | 4      | 2              | 4                      | 2                      | 0 13.67               |
| Bitton et al. [23]            | 15346            | 1999-2008    | 0                         | Canada  | 53               | 0                          | 37     | 16             | 0                      | 0                      | 0                     |
| Hou et al. [24]               | 20949            | 1998-2009    | 0                         | USA     | 168              | 67                         | 97     | 71             | 0                      | 0                      | 0 3.6                 |
| Ananthakrishnan et al. [25]   | 5569             | 1998-2010    | 0                         | USA     | 126              | 0                          | 0      | 0              | 0                      | 0                      | 0                     |
| Navaneethan et al. [26]       | 997              | 1998-2011    | 0                         | USA     | 2                | 0                          | 0      | 0              | 0                      | 0                      | 0                     |
| Yadav et al. [5]              | 462              | 1940-2011    | 35                        | USA     | 13               | 66                         | 6      | 7              | 0                      | 0                      | 0 31                  |
| Ananthakrishnan et al. [27]   | 3546             | 2010-2013    | 0                         | USA     | 83               | 0                          | 0      | 0              | 0                      | 0                      | 0                     |
| Sonnenberg and Genta [28]     | 37043            | 2008-2014    | 49.6                      | USA     | 54               | 0                          | 0      | 0              | 0                      | 0                      | 0                     |
| Hou et al. [29]               | 881              | 1999-2014    | 0                         | USA     | 21               | 0                          | 0      | 0              | 0                      | 0                      | 0                     |
| Bettner et al. [30]           | 75               | 1990-2015    | 29                        | USA     | 1                | 59                         | 0      | 0              | 0                      | 0                      | 0 11.1                |
| Gyde et al. [4]               | 823              | 1944-1976    | 33.66                      | UK/Sweden | 35              | 56.69                      | 13     | 22             | 28                     | 7                      | 0 23.03               |
| Moody et al. [31]             | 175              | 1972-1981    | 58.4                      | UK      | 10               | 67                         | 6      | 4              | 7                      | 3                      | 0 9.6                 |
| Ekborn et al. [32]            | 3117             | 1922-1983    | 0                         | Sweden  | 91               | 0                          | 52     | 39             | 35                     | 17                     | 9 0                   |
| Lennard-Jones et al. [33]     | 401              | 1966-1987    | 29.73                      | UK      | 22               | 50.05                      | 13     | 9              | 0                      | 0                      | 0 20.31               |
| Löfberg et al. [34]           | 72               | 1973-1988    | 0                         | Sweden  | 1                | 42.25                      | 0      | 0              | 0                      | 0                      | 0                     |
| Author                  | Sample size (UC) | Study period | Mean age at diagnosis (UC) | Country          | Sample size (CRC) | Mean age at diagnosis (CRC) | Gender       | Disease extent | Time of duration (year) |
|-------------------------|------------------|--------------|-----------------------------|------------------|------------------|-----------------------------|--------------|----------------|------------------------|
| Stewtnius et al. [35]   | 471              | 1958-1990    | 38.3                        | Sweden           | 9                | 49.88                       | 3            | 6             | 7                      | 1                       | 1                       | 12.22                   |
| Biasco et al. [36]      | 65               | 1980-1992    | 32.9                        | Italy            | 4                | 59.5                        | 0            | 0             | 0                      | 0                       | 0                       | 13                      |
| Wandall et al. [37]     | 801              | 1973-1993    | 41                          | Denmark          | 6                | 57.33                       | 4            | 2             | 4                      | 1                       | 1                       | 10.83                   |
| Palli et al. [38]       | 689              | 1978-1996    | 0                           | Italy            | 4                | 0                          | 0            | 0             | 0                      | 0                       | 0                       | 0                      |
| Winther et al. [39]     | 1160             | 1962-1997    | 0                           | Denmark          | 8                | 6                          | 6            | 2             | 0                      | 0                       | 0                       | 0                      |
| Viscido et al. [40]     | 2006             | 1964-1997    | 38.5                        | Italy            | 28               | 0                          | 0            | 0             | 0                      | 0                       | 0                       | 0                      |
| Goldacre et al. [41]    | 6990             | 1963-1999    | 0                           | UK               | 103              | 0                          | 0            | 0             | 0                      | 0                       | 0                       | 0                      |
| Lindberg et al. [42]    | 90               | 1977-2002    | 0                           | Sweden           | 8                | 0                          | 0            | 0             | 0                      | 0                       | 0                       | 0                      |
| Jess et al. [43]        | 1437             | 1978-2002    | 0                           | Denmark          | 15               | 0                          | 0            | 0             | 0                      | 0                       | 0                       | 0                      |
| Hemminki et al. [44]    | 27606            | 1964-2004    | 0                           | Germany/Sweden   | 482              | 0                          | 0            | 0             | 0                      | 0                       | 0                       | 0                      |
| Katsanos et al. [45]    | 182              | 1983-2004    | 51.2                        | Greece           | 3                | 0                          | 2            | 1             | 0                      | 0                       | 0                       | 0                      |
| Katsanos et al. [46]    | 776              | 1991-2004    | 0                           | Netherlands      | 7                | 61.3                       | 0            | 0             | 0                      | 0                       | 0                       | 5.4                     |
| Jess et al. [47]        | 1575             | 1962-2005    | 0                           | Denmark          | 14               | 0                          | 8            | 6             | 0                      | 0                       | 0                       | 0                      |
| Stolwijk et al. [48]    | 293              | 1980-2005    | 33.8                        | Netherlands      | 23               | 49.2                       | 14           | 9             | 22                     | 1                       | 0                       | 10.2                    |
| Lakatos et al. [49]     | 723              | 2002-2005    | 36                          | Hungary          | 13               | 51                         | 0            | 0             | 8                      | 5                       | 0                       | 19                     |
| Cheddani et al. [50]    | 474              | 1998-2006    | 69                          | France           | 8                | 75                         | 0            | 0             | 0                      | 0                       | 0                       | 7.4                     |
| Manninen et al. [51]    | 1254             | 1986-2007    | 34                          | Finland          | 16               | 47.69                      | 14           | 2             | 10                     | 6                       | 0                       | 16.1875                 |
| Jess et al. [52]        | 32911            | 1979-2008    | 44.9                        | Denmark          | 268              | 64                         | 132          | 136           | 0                      | 0                       | 0                       | 19.1                    |
| Gordillo et al. [53]    | 403              | 2006-2009    | 42.91                       | Spain            | 3                | 58.9                       | 3            | 0             | 2                      | 1                       | 0                       | 12.5                    |
| Kappelman et al. [54]   | 35152            | 1978-2010    | 46.5                        | Denmark          | 437              | 0                          | 0            | 0             | 0                      | 0                       | 0                       | 7.8                     |
| Choi et al. [55]        | 1375             | 2003-2012    | 30                          | UK               | 88               | 55.5                       | 54           | 34            | 0                      | 0                       | 0                       | 25.5                    |
| Choi et al. [56]        | 987              | 2003-2012    | 30                          | UK               | 14               | 0                          | 0            | 0             | 0                      | 0                       | 0                       | 0                      |
| Hovde et al. [57]       | 519              | 1990-2013    | 0                           | Norway           | 14               | 0                          | 10           | 4             | 0                      | 0                       | 0                       | 0                      |
| Van den Heuvel et al. [58] | 1644           | 1991-2013    | 45                          | Netherlands      | 12               | 62.75                      | 6            | 6             | 4                      | 7                       | 1                       | 3.42                    |
| Nowacki et al. [59]     | 434              | 2013-2013    | 45.7                        | Germany          | 10               | 54.7                       | 5            | 5             | 6                      | 4                       | 0                       | 12                     |
| Rutegård et al. [60]    | 323              | 1977-2014    | 0                           | Sweden           | 10               | 0                          | 0            | 0             | 0                      | 0                       | 0                       | 0                      |
| Biancone et al. [61]    | 22666            | 2012-2014    | 0                           | Italy            | 24               | 64                         | 0            | 0             | 0                      | 0                       | 0                       | 12                     |
| Kekilli et al. [62]     | 275              | 1994-2008    | 35.9                        | Turkey           | 3                | 0                          | 0            | 0             | 0                      | 0                       | 0                       | 0                      |
relevant data. Data that cannot be obtained was converted according to the relevant requirements of the Cochrane evaluation manual (such as the calculation of standard deviation in continuous data).

2.4. Outcomes. The primary outcome measure was the incidence of CRC in UC patients, reported as SIR. We included SIR in our analyses as a direct method of adjustment. No restrictions about publication year, sample size,
age, country, gender, disease extent, and disease duration were applied.

The secondary outcomes were measuring the incidence of CRC in UC patients from disease extent, disease duration, geographic variation, and literature reporting time.

2.5. Analysis. We used random-effects meta-analysis to assess the incidence of CRC in UC patients. To calculate the pooled SIR of CRC, we combined the extracted study-specific estimates and 95% CIs using the DerSimonian-Laird random-effects model.

Publication bias (small-study effects) was examined with visual assessment of the symmetry of a funnel plot, the asymmetry of which will be assessed through Begg-Mazumdar’s rank test. Forest plots were made for the prevalence of the outcomes in overall and within groups.

Data manipulation and statistical analyses were undertaken using the R Software (version 3.4.4). All statistical tests, with the exception of the Q statistic, used a two-sided a value of 0.05 for significance.

The study was registered with PROSPERO, number CRD42018102213.

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3. Results

From 285 articles of potential relevance, 71 full-text articles were examined in detail and 58 studies were included in the final analysis; studies which identified 267566 UC patients, published from Nov. 1988 to Dec. 2018, with 2663 patients that reported UC-associated CRC were included in the meta-analysis. The population characteristics and outcomes of the included studies were summarized in Table 1.

3.1. Overall Risk of CRC in UC Patients. The overall risk of CRC in UC patients among the 58 studies was 1.4% (95% CI: 1.2-1.6; Figure 2). Gender-specific risk estimate for CRC in UC was reported in 30 of the 58 studies and varied from 0.89 (95% CI: 0.56-1.43) to 1.05 (95% CI: 0.68-1.63) in women and men, which has no difference (P = 0.62). Disease extent-specific risk estimates for CRC in UC were reported in 21 of the 58 studies, which show that extensive UC and left-sided UC had a higher risk of CRC (SIR: 1.42, 95% CI: 0.83-2.42; SIR: 0.56, 95% CI: 0.38-0.83) than proctitis UC (SIR: 0.18, 95% CI: 0.01-0.03) (P < 0.01) (Tables 2 and 3).

3.2. Disease Duration Risk of CRC in UC Patients. In the subgroup analysis by disease duration, the incidence of CRC in UC patients rose after 20 years of this disease duration (Table 4).

3.3. Geographic Variation Risk of CRC in UC Patients. In the subgroup analysis by geographic variation, Oceania has a higher incidence than other continents; however, it has only one article (Tables 1 and 5). In Europe, the risk of CRC in UC patients has no statistical difference in disease duration for 1-9 years, 10-20 years, 21-30 years, or more than 30 years. In Asia, the risk of CRC in UC increased after 10-20 years of this disease duration. In North America, the risk of CRC in UC increased significantly in more than 30 years of this disease duration (Tables 5 and 6).

Furthermore, we analyzed the CRC incidence in UC patients in each country; we found that Japan, UK, and Austria have the highest incidence, while Canada and Korea have the lowest incidence (Table 7).

3.4. The Literature Reporting Time of CRC Risk in UC Patients. In the subgroup analysis by literature reporting
time, we found that the risk of CRC in UC patients was higher in 1988-1995. As the research progresses, the CRC risk in UC was stable and maintained between 1.1% and 1.6% (Table 8).

### Table 6: Geographic variation in UC patients in different disease durations.

| Area      | 1-9 years     | 10-20 years    | 21-30 years    | More than 30 years |
|-----------|---------------|----------------|----------------|-------------------|
| Asia      | 0.0032        | 0.0128         | 0.0188         | 0.0106            |
| [0.0022; 0.0045] n = 1 | [0.0081; 0.0201] ▲ n = 6 | [0.0051; 0.0671] ▲ n = 4 | [0.0013; 0.0819] ▲ n = 2 |
| North America | 0.0043     | 0.0120         | —              | 0.0228            |
| [0.0009; 0.0196] n = 4 | [0.0058; 0.0245] n = 5 | —              | [0.0132; 0.0390] ▲ n = 2 |
| Europe    | 0.0097        | 0.0141         | 0.0222         | 0.193             |
| [0.0020; 0.0461] n = 6 | [0.0089; 0.0221] n = 10 | [0.0104; 0.0465] n = 7 | [0.0144; 0.0257] n = 10 |
| Oceania   | —             | 0.048          | —              | —                 |
| [0.029; 0.066] n = 1 | —              | —              | —                 |

▲P < 0.05 vs. 1-9 years; ▲▲P < 0.01 vs. 1-9 years.

### Table 7: CRC incidence in UC patients by country.

| Nation      | Article (n) | Proportion | 95% CI          | Weight (random) |
|-------------|-------------|------------|-----------------|-----------------|
| Canada      | 1           | 0.003      | 0.003-0.004     | 2.80%           |
| Korea       | 4           | 0.005      | 0.002-0.007     | 9.30%           |
| Spain       | 11          | 0.007      | 0.000-0.016     | 1.70%           |
| China       | 4           | 0.008      | 0.006-0.010     | 9.40%           |
| Italy       | 4           | 0.008      | 0.000-0.016     | 7.40%           |
| Denmark     | 6           | 0.009      | 0.007-0.012     | 14.70%          |
| Turkey      | 1           | 0.011      | 0.000-0.023     | 1.20%           |
| Finland     | 1           | 0.013      | 0.007-0.019     | 2.10%           |
| USA         | 10          | 0.013      | 0.008-0.017     | 19.40%          |
| Greece      | 1           | 0.016      | 0.000-0.035     | 0.70%           |
| France      | 1           | 0.017      | 0.005-0.028     | 1.30%           |
| Germany     | 2           | 0.018      | 0.016-0.019     | 3.80%           |
| Hungary     | 1           | 0.018      | 0.008-0.028     | 1.50%           |
| Netherlands | 3           | 0.019      | 0.004-0.035     | 4.80%           |
| India       | 1           | 0.02       | 0.011-0.028     | 1.70%           |
| Norway      | 1           | 0.027      | 0.013-0.041     | 1%              |
| Sweden      | 5           | 0.027      | 0.017-0.036     | 4.50%           |
| Japan       | 4           | 0.035      | 0.012-0.058     | 4.50%           |
| UK          | 6           | 0.039      | 0.022-0.055     | 7.50%           |
| Austria     | 1           | 0.048      | 0.029-0.066     | 0.70%           |

4. Discussion

UC, an uncontrolled colorectal inflammation, associated with systemic immune dysregulation, which impaired tumor surveillance, might play a role in colorectal carcinogenesis. Unlike the "adenoma-carcinoma sequence" classically described in sporadic CRC, UC-associated CRC arose from a larger field of colorectal mucosa that was "preconditioned" with a mutational burden that conferred an increased propensity for further dysplasia progression, a phenomenon known as "field cancerization" [55], which followed a sequence of genetic alterations "inflammation-dysplasia-carcinoma" [63]. Chronic colorectal inflammation generated extensive damage to epithelial cells that led to increased cell replication and/or direct DNA damage [1], which was known as one risk factor for the occurrence of CRC in UC patients [28].

This study first provided a picture of the incidence rate of UC-associated CRC from disease extent, disease duration, and geographic variation. Results showed that the overall risk of UC-associated CRC was 1.4%, which increased with disease duration. Extensive UC and left-sided UC had a greater risk of CRC than proctitis UC. There was no obvious gender specificity in CRC risk in UC patients. The strength of this study lies in the fact that we chose to focus on the CRC risk in UC patients from geographic variation. Results showed that the Asian and North American UC patients seemed to have a higher CRC risk. The time of malignant transformation in Asian UC patients started after 10-20 years of this disease duration. North American UC-associated CRC patients significantly increased in more than 30 years of this disease duration.

In this study, we can find that UC patient-relevant endpoint, the risk of CRC, has not decreased over the past decade, and the overall CRC incidence was stable from 1996 until today, which stayed around 1.1% to 1.6%. So the management of UC is still complex, and significant gaps in the literature remained regarding how clinicians could identify the risk associated with CRC and enhance the prevention of UC-associated CRC. 5-Aminosalicylate medications (mesalamine or sulfasalazine), the foundational first-line therapy for the induction and maintenance of mild-to-moderate UC, seemed not to protect against the likelihood of carcinogenesis at doses greater than 2.4 grams daily and still needed to be proven [64]. Other medicines, such as
thiopurines, reduced the immunosurveillance of malignant cells and impaired control of oncogenic viruses [65]. Prolonged treatment with thiopurines has been shown to determine an increased risk of a broad range of cancers in UC patients [66]. The impact of UC-related drug therapy on CRC development remained a matter of debate, and the potential benefit of surgery should need to be placed in the context of the risks associated with undertaking complex abdominopelvic reconstructive surgery. Therefore, UC-associated CRC rates still remained a challenging problem for UC patients.

At present, the majority of CRC cases (70%) could be explained by an inadequate surveillance procedure before the CRC diagnosis, and CRC is responsible for approximately 15% of deaths due to UC [67]. Therefore, it is not surprising that researchers have focused efforts on surveillance screening as an adjunct therapy to UC patients for CRC occurrence. UC patients need to be accurately evaluated for the risk of CRC according to the disease extent, disease duration, and geography and need to adhere to a surveillance schedule, such as screening colonoscopy, which should be performed every 1 to 3 years, because the malignant changes and the surrounding inflammation often grow flat and multifocal [68].

5. Conclusion
In a systematic review of the literature, we found that the incidence of CRC in UC patients increased with the disease duration. Asian and North American UC patients were more prone to concomitant CRC.

6. Limitations
Our study has limitations. Patients with Crohn’s disease, CAP, and a family history of CRC and who have undergone colectomy for UC were not included in this study. Patients with UC associated with extracolorectal malignancies (small intestine, blood systems, lung, thyroid, hepatobiliary, skin, melanoma, urinary bladder, breast, genital tract, and so on) were not included, which greatly reduced the risk of cancer in UC. Moreover, our search had English language restrictions. Articles in languages other than English were not included.

Abbreviations
UC: Ulcerative colitis
CRC: Colorectal cancer
IBD: Inflammatory bowel disease
SIR: Standardised incidence ratio
CAP: Colorectal adenomatous polyp.

Data Availability
The clinical data supporting this systematic review and meta-analysis are from previously reported studies and datasets, which have been cited. The processed data are available in Table 1 of our manuscript.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Authors’ Contributions
Qing Zhou and Zhao-Feng Shen independently screened the literature, extracted the data, performed the statistical analysis, cowrote the manuscript, and interpreted the statistical results. Ben-sheng Wu, Cheng-biao Xu, Zhong-qi He, Tao Chen, Hong-tao Shang, Chao-fan Xie, and Si-yi Huang checked this work again and critically revised the paper. Yu-gen Chen was the project leader for this research and participated in the critical revision of the manuscript. Corresponding authors (Yu-gen Chen, Hai-bo Chen, and Shu-tang Han) had the final responsibility to submit for publication. All authors have read and approved the final manuscript. Qing Zhou and Zhao-Feng Shen are the first two authors who contributed equally to this paper.

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