Int Surg 2015;**100:**783–789
DOI: 10.9738/INTSURG-D-14-00154.1

Characteristics and Prognosis of Colorectal Cancer Associated With Rheumatic Disease

Junko Kishikawa[1], Kazushige Kawai[1], Nelson H. Tsuno[1,2], Soichiro Ishihara[1], Hironori Yamaguchi[1], Eiji Sunami[1], Toshiaki Watanabe[1]

[1]Department of Surgical Oncology and [2]Department of Transfusion Medicine, Faculty of Medicine, the University of Tokyo, Tokyo, Japan

It is well known that host immunity plays an important role in the defense against colorectal cancer (CRC) progression. The effects of autoimmune diseases, such as rheumatic disease (RD) in which the immune system is deregulated, on this immunity have not been fully investigated. The medical records of 1299 consecutive patients diagnosed with primary colorectal cancer who underwent surgical resection were retrospectively reviewed. The clinicopathologic factors of 28 subjects with RD (RD group) were compared with those of 1271 patients without RD (non-RD group). Compared to the non-RD group, the RD group was typified by a predominance of females ($P < 0.01$), older age ($P < 0.01$), and a lower incidence of rectal cancer ($P = 0.02$). Although no difference was observed between the groups in terms of TNM classification, disease-free and overall survival were significantly poorer in the RD group in both univariate and multivariate analyses. Subjects who had RD for more than 10 years tended to have a higher frequency of lymph node metastasis ($P = 0.06$) and a significantly higher incidence of synchronous distant metastasis ($P = 0.035$) at the time of cancer diagnosis. RD was associated with a significantly poorer prognosis of colorectal cancer, suggesting that deregulation of the immune system by autoimmune diseases may adversely affect the host immune defense against colorectal cancer progression.

Key words: Colorectal cancer – Rheumatic disease – Host immunity – Prognosis

It is well known that host immunity plays an important role in defenses against the development and progression of cancer. The degree of lymphocyte infiltration into tumors has been reported to correlate with improvements of patient survival.[1] In carcinogen-induced mouse models of cancer, primary tumor susceptibility has been found to be enhanced in immunocompromised mice;

Corresponding author: Junko Kishikawa, MD, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
Tel.: +81 3 3815 5411 (ext. 33246); Fax: +81 3 3811 6822; E-mail: takei-tky@umin.ac.jp

conversely, the capacity for such tumors to grow after transplantation into wild-type mice is reduced.[2,3] Although cancer cells originate from autologous normal tissue, the immune system can recognize even minimal cellular alterations, distinguish cancerous from normal cells, and elicit an immune response.

In autoimmune diseases represented by rheumatic disease (RD), the immune system loses the ability to distinguish nonself from self, eliciting an immune response against self-antigens; in this process, there is a possibility that immune defenses against nonnormal cells are lost or impaired, facilitating the development and progression of cancer. In addition, the development of RD associated with cancer has been reported, and as its development is dependent on the production of substances such as hormones, peptides, autocrine and paracrine mediators, and antibodies or the stimulation of cytotoxic lymphocytes, the condition is known as paraneoplastic rheumatic syndrome. In such cases, RD tends to be less responsive to therapy than its nonparaneoplastic equivalents, and instead, treatment of the underlying cancer usually results in regression of RD.[4,5] Thus, it is postulated that RD and cancer are closely associated. However, only a few reports on the incidence and risk of cancer among patients with RD exist,[6,7] and the characteristics and prognosis of colorectal cancer (CRC) in these patients remain to be elucidated.

In the present study, we investigated the development of CRC in the background of an immunologic disorder caused by RD, with the hypothesis that patients with CRC and autoimmune diseases such as RD will have a poorer prognosis than those without RD, as a result of depressed antitumor immunity caused by immune system incompetence. Thus, we aimed to clarify the features and prognosis of CRC-associated RD, and for this purpose, we compared the clinicopathologic features of patients with CRC with or without underlying RD.

Methods

The medical records of 1299 consecutive patients with primary CRC diagnosed between April 2004 and December 2012 who underwent surgical resection at the Department of Surgical Oncology, The University of Tokyo Hospital, were reviewed retrospectively. Patients with familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, and inflammatory bowel diseases, such as ulcerative colitis or Crohn's disease, were excluded from the study. RD was defined as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome, polymyalgia rheumatic, systemic scleroderma, or dermatomyositis, and 28 of 1299 patients with CRC displayed RD. After surgical resection of the tumor, all specimens were analyzed histopathologically, and the pathologic TNM classification and stage were determined according to the classification established by the American Joint Committee on Cancer.

Univariate analyses of clinicopathologic variables were conducted as follows. Continuous variables, such as age and tumor size, were analyzed using an unpaired t test, and variables categorized into 2 or more groups, such as gender and the presence/absence of metastasis, were analyzed using the chi-square test. Concerning variables related to RD, we defined 4 variables: type of RD, presence of steroid therapy, C-reactive protein (CRP) elevation, and time since the onset of RD. Multivariate analysis also was performed using logistic regression analysis. The Kaplan-Meier estimator, log-rank test, and Cox proportional hazard model were used for survival analysis. All analyses were performed using JMP 9.0 software (SAS Institute Inc, Cary, North Carolina), and differences at $P < 0.05$ were considered statistically significant.

Results

A comparison of the patients' characteristics between the RD and non-RD groups is presented in Table 1. Among the 1299 patients with CRC, 28 had an associated RD, giving an association rate of 2.2%. All 28 patients received oral nonsteroidal anti-inflammatory drugs. No patient received molecular-targeted drugs, such as antitumor necrosis factor-α drugs. The most frequent type of RD was RA, which comprised approximately half of the cases of RD, followed by SLE. Regarding patient gender, almost 75% of the enrolled subjects were females, suggestive of a high female/male ratio for RD. Additionally, patients with RD-associated CRC were significantly older than patients with CRC without RD. The pathologic evaluation of patients with CRC revealed that the majority of RD-associated CRCs were located in the colon, with a markedly lower incidence of rectal cancer compared to the findings in patients without RD. These 3 variables, namely gender, age, and cancer location, were found to be independent RD-associated CRC-related factors in multivariate analysis (Table 2). No difference was observed for the other clinicopatho-

Table 1 Comparison of the clinicopathologic features between RD and non-RD CRC

	RD	Non-RD	*P* value
Total	28	1271	
Gender			
Male	7 (25.0%)	781 (61.5%)	
Female	21 (75.0%)	490 (38.6%)	<0.001
Age	72.1 ± 8.3 years*	66.0 ± 11.2 years*	0.004
Types of RD			
Rheumatoid arthritis	15		
Systemic lupus erythematosus	5		
Sjögren syndrome	4		
Polymyalgia rheumatica	2		
Systemic scleroderma	1		
Dermatomyositis	1		
Location of cancer			
Right-side colon	13 (46.4%)	348 (27.4%)	
Left-side colon	11 (39.3%)	445 (35.0%)	
Rectum	4 (14.3%)	477 (37.6%)	0.016
Tumor diameter	35.4 ± 18.5 mm*	40.5 ± 23.1 mm*	0.252
Depth of invasion			
Tis/1/2	12 (42.9%)	425 (33.8%)	
T3/4	16 (57.1%)	839 (66.2%)	0.323
Regional lymph node metastasis			
Absent	18 (64.3%)	773 (61.3%)	
Present	10 (35.7%)	489 (38.8%)	0.743
Distant metastasis			
Absent	22 (78.6%)	1097 (86.6%)	
Present	6 (21.4%)	170 (13.4%)	0.252
Histologic classification			
Well-differentiated adenocarcinoma	16 (57.1%)	678 (53.6%)	
Moderately-differentiated adenocarcinoma	9 (32.1%)	507 (40.1%)	
Poorly-differentiated adenocarcinoma	2 (7.1%)	29 (2.3%)	
Mucinous adenocarcinoma	1 (3.6%)	37 (2.9%)	
Others	0	13 (1.0%)	0.715
Lymphatic invasion			
Absent	22 (78.6%)	900 (71.5%)	
Present	6 (21.4%)	359 (28.5%)	0.398
Venous invasion			
Absent	10 (35.7%)	425 (33.8%)	
Present	18 (64.3%)	834 (66.2%)	0.829

RD, rheumatic disease; CRC, colorectal cancer.

*Data presented as mean ± SD.

Table 2 Multivariate analysis of RD association and clinicopathologic factors

	P value	Relative risk	95% CI
Gender			
Male vs. female	0.0004	4.28	1.88–11.00
Age	0.0232	1.04	0.92–0.99
Cancer location			
Colon vs. rectum	0.0342	2.85	1.07–9.84

logic features associated with cancer progression, such as tumor depth, lymph node metastasis, or distant metastasis, between the RD-associated and non-RD–associated CRC groups. However, patients with RD exhibited significantly shorter disease-free and overall survival after curative resection of the primary tumor (Fig. 1). In multivariate analysis, RD was found to be an independent predictive factor of poor prognosis for both disease-free and overall survival (Table 3). The risk of cancer recurrence was

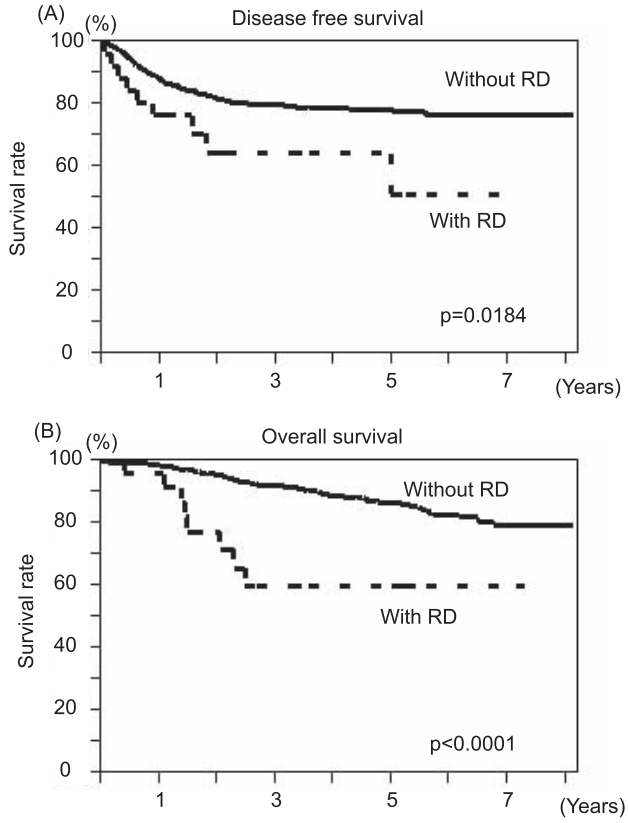

Fig. 1 Disease-free (A) and overall survival (B) after curative resection. The survival curves of patients with (dotted line) or without (solid line) rheumatic disease are presented using the Kaplan-Meier estimator, and the *P* values were calculated using the log-rank test.

more than 2-fold higher in RD-associated CRC group.

Next, we evaluated the association between RD-related characteristics and the TNM-related factors of colorectal cancer (Table 4). Gender, age, type of RD, use of corticosteroids, and elevation of CRP levels were not correlated with TNM-related factors. Comparing patients who had RD for 10 or more years (longer duration) with those who presented with RD less than 10 years previously (shorter duration), a trend toward a higher incidence of lymph node metastasis ($P = 0.06$) and a significantly higher rate of synchronous distant metastasis ($P = 0.035$) was observed for patients with a longer disease duration. However, there was no difference in depth of tumor invasion. Thus, we hypothesized that a longer RD duration ($\geq$10 years) was a prognostic factor for a poorer prognosis for RD-associated CRC, but the differences were not significant (Table 5; $P = 0.303$ for disease-free survival and $P = 0.591$ for overall survival). Instead, elevation of CRP levels (CRP $\geq$ 0.3, elevation above the normal limit of our institution), which is a marker suggestive of poor control of RD, tended to be correlated with a poorer prognosis for overall survival ($P = 0.069$). The mean CRP level among patients with RA 0.62 $\pm$ 1.53 mg/dL (mean $\pm$ SD), versus 0.71 $\pm$ 1.12 mg/dL for patients without RA ($P = 0.66$). Patients in the non-RD group who exhibited high CRP levels also displayed poorer overall survival than those with low CRP levels (5-year survival rate: 78.3% vs. 90.0%; $P = 0.044$; (data not shown).

Table 3 Univariate and multivariate analysis of prognostic valuables for disease-free survival and overall survival after curative resection

	Univariate analysis	Multivariate analysis		
	P value	*P* value	Relative risk	95% CI
Disease-free survival				
T (Tis-2 vs. T3–4)	<0.0001	<0.0001	2.48	1.63–3.92
N (N0 vs. N1–2)	<0.0001	0.0003	1.84	1.32–2.57
M (M0 vs. M1)	<0.0001	<0.0001	3.89	2.78–5.40
Lymphatic invasion (absent vs. present)	<0.0001	0.0109	1.5	1.10–2.05
Venous invasion (absent vs. present)	<0.0001	0.0058	1.66	1.15–2.45
Cancer location (colon vs. rectum)	0.0029	0.004	1.53	1.15–2.04
Rheumatic disease	0.0184	0.0237	2.44	1.14–4.59
Overall survival				
T (Tis-2 vs. T3–4)	<0.0001	0.0001	2.88	1.63–5.44
N (N0 vs. N1–2)	<0.0001	0.3962	1.22	0.77–1.92
M (M0 vs. M1)	<0.0001	<0.0001	2.86	1.76–4.55
Lymphatic invasion (absent vs. present)	<0.0001	0.0939	1.48	0.93–2.32
Venous invasion (absent vs. present)	0.0006	0.286	1.3	0.81–2.17
Cancer location (colon vs. rectum)	0.9287			
Rheumatic disease	<0.0001	0.0004	5.09	2.25–10.03

Table 4 Correlation between the RD-related characteristics and the TNM classification of CRC

RD-related characteristics	Tis-2	T3/4	*P* value	N0	N1/2	*P* value	M0	M1	*P* value
Gender									
Male	1 (14.3%)	6 (85.7%)		3 (42.9%)	4 (57.1%)		5 (71.4%)	2 (28.6%)	
Female	11 (52.4%)	10 (47.6%)	0.064	15 (71.4%)	6 (28.6%)	0.179	17 (81.0%)	4 (19.1%)	0.603
Age									
<75	6 (33.3%)	12 (66.7%)		12 (66.7%)	6 (33.3%)		14 (77.8%)	4 (22.2%)	
≥75	6 (60.0%)	4 (40.0%)	0.172	6 (60.0%)	4 (40.0%)	0.725	8 (80.0%)	2 (20.0%)	0.89
Type of RD									
Rheumatoid arthritis	6 (40.0%)	9 (60.0%)		11 (73.3%)	4 (26.7%)		11 (73.3%)	4 (26.7%)	
Others	6 (46.2%)	7 (53.9%)	0.743	7 (53.9%)	6 (46.2%)	0.282	11 (84.6%)	2 (15.4%)	0.464
Steroid									
Yes	8 (40.0%)	12 (60.0%)		13 (65.0%)	7 (35.0%)		17 (85.0%)	3 (15.0%)	
No	4 (50.0%)	4 (50.0%)	0.63	5 (62.5%)	3 (37.5%)	0.901	5 (62.5%)	3 (37.5%)	0.206
CRP									
<0.3	7 (41.2%)	10 (58.8%)		9 (52.9%)	8 (47.1%)		14 (82.4%)	3 (17.7%)	
≥0.3	5 (41.2%)	6 (54.6%)	0.823	9 (81.8%)	2 (18.2%)	0.11	8 (72.7%)	3 (27.3%)	0.548
Duration from onset of RD (years)									
<10	5 (33.3%)	10 (66.7%)		12 (80.0%)	3 (20.0%)		14 (93.3%)	1 (6.7%)	
≥10	7 (53.9%)	6 (46.2%)	0.273	6 (46.2%)	7 (53.9%)	0.06	8 (61.5%)	5 (38.5%)	0.035

RD, rheumatic disease; CRC, colorectal cancer.

Discussion

Although many reports have documented an increased risk of lymphoma in patients with RD,[8–11] it remains controversial whether RD is a risk factor for solid cancers. In a meta-analysis of 21 publications reported in 2008, RA was identified as a risk factor for lymphoma and lung cancer, but the incidence of colorectal and breast cancers was lower in patients with RA.[12] In a nationwide cohort analysis from Taiwan involving 11,763 patients with SLE, cancer developed during surveillance in 259 patients, including 14 cases of CRC, giving a standardized incidence ratio of 0.82.[8] Another nationwide Danish analysis that included 2040 patients with systemic scleroderma reported the development of 9 colon and 2 rectal cancers, giving standardized incidence ratios of 0.9 and 0.4, respectively.[6] Although some autoimmune diseases, such as ulcerative colitis and Crohn's disease, are known to increase the risk of CRC,[13,14] these precedent reports suggested that RD is not a risk factor for CRC. In our analysis, the incidence of RA among patients with CRC was 1.2%, and that of SLE among the same patients was 0.4%. The prevalence of RA in the general population is reported to be 0.1–0.5%[15]; thus, the incidence of RA among our CRC cohort was not high, considering that the average age of the patients was 66 years. Recently, it was demonstrated in a nationwide cohort study in Taiwan that RA patients did not have an increased risk of cancer, consistent with our results.[16]

The majority of patients with RD-associated CRC were female, and these patients were on average 6 years older than those with non-RD–associated CRC, reflecting the characteristics of RD. Interestingly, the proportion of patients with rectal cancer was significantly lower among patients with RD-associated CRC. Although the high incidence of colon cancer in patients with RD could be partly explained by the higher proportion of females and the older age of the patients,[17,18] females and older age were found to be an independent feature of RD-associated CRC in multivariate analysis. There are limited reports about the location of CRC in patients with RD, but 1 report identified a more than 4-fold higher incidence of colon cancer than rectal cancer in patients with systemic scleroderma, corroborating our finding.[6]

Presently, the correlation between underlying RD and the prognosis of solid cancer remains to be fully elucidated. Sihvonen *et al* reported that patients with RA were at increased risk of cancer-related death compared to the general population,[19] whereas Riise *et al* failed to demonstrate a statistically significant increase in cancer-related mortality.[20] Llorca *et al* also reported that age- and gender-standardized mortality ratios for cancer in patients with RA were not different from those of

Table 5 Univariate analysis of RD-related variables for disease-free and overall survivals

RD-related characteristics	n	Cumulative 5-year survival rate	*P* value
Disease-free survival			
Gender			
Male	7	0.0%	
Female	21	57.0%	0.032
Age			
<75	18	61.8%	
≥75	10	60.0%	0.675
Type of RD			
Rheumatoid arthritis	15	66.7%	
Others	13	54.4%	0.307
Steroid			
Yes	20	65.6%	
No	8	60.2%	0.558
CRP			
<0.3	17	56.6%	
≥0.3	11	72.7%	0.426
Duration from onset of RD (years)			
<10	15	69.1%	
≥10	13	53.7%	0.303
Overall survival			
Gender			
Male	7	50.0%	
Female	21	58.2%	0.979
Age			
<75	18	60.0%	
≥75	10	47.1%	0.822
Type of RD			
Rheumatoid arthritis	15	47.1%	
Others	13	68.6%	0.313
Steroid			
Yes	20	60.7%	
No	8	45.7%	0.646
CRP			
<0.3	17	40.9%	
≥0.3	11	69.2%	0.069
Duration from onset of RD (years)			
<10	15	62.9%	
≥10	13	52.1%	0.591

the general population; however, both high CRP levels and high erythrocyte sedimentation rates, which were indicative of a chronic inflammatory response and thus poor control of RA, were revealed as independent predictors of cancer-related mortality.[21] In their study, however, only a few patients (n = 17), including only 4 patients with colon cancer, were analyzed. Thus, the power of the study was insufficient to reach a conclusive scientific basis regarding the prognosis and characteristics of RD-associated solid cancer. In the present study, we speculated that patients with RD would have more advanced tumors than those without RD, but no difference was observed related to the tumor depth and incidence of regional lymph node and distant metastasis. Instead, patients with RD-associated CRC had significantly shorter recurrence-free and overall survival in both univariate and multivariate analyses. This suggests that the cancer-preventing immune response also might be suppressed in patients with RD, who have an immunologic disorder in distinguishing self from nonself.

We then evaluated the correlation of RD-related variables with the TNM classification and patient prognosis. Although no correlation with depth of invasion was found in patients with a longer RD duration (defined as 10 or more years), the incidence of distant metastasis was significantly higher. Incidence of lymph node metastasis also tended to be higher, compared to the findings in patients with a shorter RD duration (less than 10 years). These findings suggest that longstanding RD may be associated with reduced host immune defense, leading to a propensity for metastatic invasion. Because of the low incidence of RD in the general population, the number of patients RD among patients with CRC was also low, and only a limited patient sample could be evaluated. Possibly, the sample size was insufficient to demonstrate an evident correlation between any of the RD-related variables and cancer prognosis. Only CRP elevation displayed a trend of correlation with shorter overall survival. Several studies reported similar results including 1 study of 7072 patients with CRC, which demonstrated that an increased CRP level was an independent risk factor for poor prognosis.[22] Additionally, this result was consistent with a previous report identifying a correlation between CRP elevation and cancer-related mortality in patients with RA.[22] Because most of the drugs used in the treatment of RD exert anti-inflammatory and immunosuppressive effects, there is a possibility that the RD treatment itself promotes cancer metastasis and consequently shorter survival. However, in our series, no correlation of corticosteroid treatment with TNM classification and prognosis was observed, and many previous reports have identified no association of RA therapy, including gold, penicillamine, prednisone, and methotrexate, with increased cancer-related mortality,[23–25] corroborating our result.

The limitations of this study included the relatively small number of patients with RD investigated in the study because of the low

prevalence of RD, which may be the cause of the failure to elucidate a prognostic risk factor in RD patients. Multi-institutional studies with larger numbers of patients are needed.

Conclusion

RD was associated with a significantly worse prognosis of CRC, suggesting that deregulation of the immune system as a result of autoimmune diseases may adversely affect the host immune defense against cancer progression.

Acknowledgments

All authors have no conflicts of interest.

References

1. Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma VM. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. *J Pathol* 1997;**182**(3):318–324
2. Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ *et al*. IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. *Nature* 2001; **410**(6832):1107–1111
3. Swann JB, Vesely MD, Silva A, Sharkey J, Akira S, Schreiber RD *et al*. Demonstration of inflammation-induced cancer and cancer immunoediting during primary tumorigenesis. *Proc Natl Acad Sci U S A* 2008;**105**(2):652–656
4. Andras C, Csiki Z, Ponyi A, Illes A, Danko K. Paraneoplastic rheumatic syndromes. *Rheumatol Int* 2006;**26**(5):376–382
5. Thiers BH, Sahn RE, Callen JP. Cutaneous manifestations of internal malignancy. *CA Cancer J Clin* 2009;**59**(2):73–98
6. Olesen AB, Svaerke C, Farkas DK, Sorensen HT. Systemic sclerosis and the risk of cancer: a nationwide population-based cohort study. *Br J Dermatol* 2010;**163**(4):800–806
7. Shah AA, Rosen A. Cancer and systemic sclerosis: novel insights into pathogenesis and clinical implications. *Curr Opin Rheumatol* 2011;**23**(6):530–535
8. Chen YJ, Chang YT, Wang CB, Wu CY. Malignancy in systemic lupus erythematosus: a nationwide cohort study in Taiwan. *Am J Med* 2010;**123**(12):1150.e1–6
9. Ekstrom K, Hjalgrim H, Brandt L, Baecklund E, Klareskog L, Ekbom A *et al*. Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives. *Arthritis Rheum* 2003;**48**(4):963–970
10. Franks AL, Slansky JE. Multiple associations between a broad spectrum of autoimmune diseases, chronic inflammatory diseases and cancer. *Anticancer Res* 2012;**32**(4):1119–1136
11. Parikh-Patel A, White RH, Allen M, Cress R. Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. *Cancer Causes Control* 2008;**19**(8):887–894
12. Smitten AL, Simon TA, Hochberg MC, Suissa S. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. *Arthritis Res Ther* 2008;**10**(2):R45
13. Ahmadi A, Polyak S, Draganov PV. Colorectal cancer surveillance in inflammatory bowel disease: the search continues. *World J Gastroenterol* 2009;**15**(1):61–66
14. Dyson JK, Rutter MD. Colorectal cancer in inflammatory bowel disease: what is the real magnitude of the risk? *World J Gastroenterol* 2012;**18**(29):3839–3848
15. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum* 2006;**36**(3):182–188
16. Huang WK, Chiou MJ, Kuo CF, Lin YC, Yu KH, See LC. No overall increased risk of cancer in patients with rheumatoid arthritis: a nationwide dynamic cohort study in Taiwan. *Rheumatol Int* 2014;**34**(10):1379–1386
17. Benedix F, Kube R, Meyer F, Schmidt U, Gastinger I, Lippert H. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. *Dis Colon Rectum* 2010;**53**(1):57–64
18. Meguid RA, Slidell MB, Wolfgang CL, Chang DC, Ahuja N. Is there a difference in survival between right- versus left-sided colon cancers? *Ann Surg Oncol* 2008;**15**(9):2388–2394
19. Sihvonen S, Korpela M, Laippala P, Mustonen J, Pasternack A. Death rates and causes of death in patients with rheumatoid arthritis: a population-based study. *Scand J Rheumatol* 2004; **33**(4):221–227
20. Riise T, Jacobsen BK, Gran JT, Haga HJ, Arnesen E. Total mortality is increased in rheumatoid arthritis. A 17-year prospective study. *Clin Rheumatol* 2001;**20**(2):123–127
21. Swede H, Hajduk AM, Sharma J, Rawal S, Rasool H, Vella AT *et al*. Baseline serum C-reactive protein and death from colorectal cancer in the NHANES III cohort. *Int J Cancer* 2014;**134**(8):1862–1870
22. Llorca J, Lopez-Diaz MJ, Gonzalez-Juanatey C, Ollier WE, Martin J, Gonzalez-Gay MA. Persistent chronic inflammation contributes to the development of cancer in patients with rheumatoid arthritis from a defined population of northwestern Spain. *Semin Arthritis Rheum* 2007;**37**(1):31–38
23. Bologna C, Picot MC, Jorgensen C, Viu P, Verdier R, Sany J. Study of eight cases of cancer in 426 rheumatoid arthritis patients treated with methotrexate. *Ann Rheum Dis* 1997;**56**(2): 97–102
24. Fries JF, Bloch D, Spitz P, Mitchell DM. Cancer in rheumatoid arthritis: a prospective long-term study of mortality. *Am J Med* 1985;**78**(1a):56–59
25. Symmons DP, Ahern M, Bacon PA, Hawkins CF, Amlot PL, Jones EL *et al*. Lymphoproliferative malignancy in rheumatoid arthritis: a study of 20 cases. *Ann Rheum Dis* 1984;**43**(2):132–135