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Risk of cancer in patients with recurrent aphthous stomatitis in Korea

A nationwide population-based study

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Abstract

The relationship between recurrent aphthous stomatitis (RAS), a common mucosal lesion, and cancer has not been demonstrated. This study investigated the risk for developing cancer in patients with RAS, based on data from Korea's National Health Insurance Sharing Service (NHISS). Nationwide population-based cohort data from 2005 to 2009 provided by the NHISS was used. The group diagnosed with RAS for 5 years and an undiagnosed control group were constructed through 1:1 propensity score matching (PSM). The experimental design compared the incidence rate of a cancer diagnosis from 2010 to 2015 between these 2 groups. After identifying 13,808 people that met our inclusion criterion from a 1 million cohort group, 13,808 controls were included in the study through PSM. Among all cancers, pancreatic cancer had an adjusted hazard ratio of 1.26 (95% confidence interval: 1.01–1.57, $P < .041$). For the rest of the cancers, there was no significant incidence rate. RAS was associated with an increased risk of pancreatic cancer in the analysis using large population-based cohort data. Further long-term follow-up studies are needed.

Abbreviations: aHR = adjusted hazard ratio, KCD-6 = Korean Standard Cause Classification of Diseases, NHISS = National Health Insurance Sharing Service, PSM = propensity score matching, RAS = recurrent aphthous stomatitis.

Keywords: case-control, pancreatic cancer, population-based study, recurrent aphthous stomatitis

1. Introduction

Recurrent aphthous stomatitis (RAS) is a disease that affects 10% to 20% of the entire population.[1] It is known to occur mainly in women in their teens and twenties.[1,2] Epithelial necrosis and neutrophilic infiltration are observed in the lesion center and C3, and immunoglobulin M can be deposited in blood vessels.[3] It is assumed that various factors such as viral or bacterial infections, eating habits, allergens, stress, and malnutrition are likely to affect RAS development.[1–4] In addition, genetic factors are considered to affect the incidence of RAS by ethnicity, and autoimmunity has been confirmed to be related to the prevalence of this disease.[3] In a group with RAS family history, the relationship between TNF-α activity and physical stress was analyzed through a family tree, and the association with autoimmune diseases suggested that RAS was associated with cancer.[5] Several studies have been conducted on the relationship between oral ulcers and cancer, but only 1 study on the relationship between RAS and cancer has been reported.[2–4,6] This study analyzed the link between RAS and cancer in a group of 1 million Korean citizens based on data from the National Health Insurance Sharing Service (NHISS), which is a large enough sample to predict the risk of cancer.

2. Methods

2.1. Ethical considerations

This analysis used nationwide population-based data and was approved by the NHISS's Ethics Committee. The study was performed after obtaining ethical approval by the Institutional Review Board (IRB approved No. 2018-08-022) of Kyung Hee University Hospital's Ethics Committee. Written consent was waived.

2.2. Database

The data were used for a nationwide population-based study, 2.0DB, provided by the NHISS. Since Korea's health insurance system is mandatory for all citizens by law, all data related to the use of medical institutions and pharmacies by all people are

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The datasets generated during and/or analyzed during the current study are publicly available.

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stored and managed in the NHISS. As of 2006, 48,222,537 Korean nationals retained the status of health insurance subscribers or medical benefit recipients for 1 year. Social demographic data such as patient residence, income quartile, and family relations are included in the National Health Insurance Corporation data. Inpatient medical records and pharmacy billing materials also are included. This analysis was based on the nationwide population-based study of 1 million people who met the representative criteria of the NHISS data.

2.3. Selection of study participants

From January 2005 to December 2009, a nationwide population-based study was performed, and diagnosis was based on the Korean Standard Cause Classification of Diseases (KCD-6), which is a revision of the International Classification of Diseases. A case-control study was conducted using 2 groups that consisted of RAS and non-RAS cohorts. The inclusion criterion for the RAS cohort group was individuals who were diagnosed with RAS (K12.0) twice or more during the study period. The inclusion criteria for the control group were individuals who had at least one classification code corresponding to appendectomy (Q2850, Q2861, Q2862, Q2863) or hemorrhoidectomy (Q3011-Q3017). Exclusion criteria for both groups were individuals with a history of cancer diagnosis or who were diagnosed with cancer during the wash out period. The target selection process is identified in Figure 1.

2.4. Exposure assessment

The primary outcome was cancer (Table 1). The corresponding disease codes were excluded from the wash out period from 2005 to 2009. Based on the final selected subjects, the period from 2010 to 2015 was set as the follow-up period.

2.5. Statistical analysis

Cases and controls were matched 1:1 through propensity score matching (PSM): age (under 10 years, 10s, 20s, 30s, 40s, 50s, 60s, 70s, 80s, or older), sex (male, female), location (city, other), income (0, 1–2 quartile, 3–4 quartile, 5–6 quartile, 7–8 quartile, 9–10 quartile), and disabled status (nondisabled, disabled). The difference in frequency of outcome variables in the case and control groups was confirmed through a Chi-Squared test. Hazard ratios were confirmed through a Cox proportional

Table 1

KCD-6 disease cancer codes.

Code	Cancer
C01-C14, C30-C33	head and neck cancer
C37-C39, C45	thorax
C15	esophagus
C16	stomach
C18-C20	colon and rectum
C21	anus and anal canal
C22	liver
C23-C24	gallbladder and biliary tract
C25	pancreas
C34	lung
C40-C41	bone
C50	breast
C51-C53	cervix
C54-C55	uterus
C56	ovary
C61	prostate
C62	testis
C64-C65	kidney
C66-C67	bladder
C70-C72	brain and spinal cord
C73	thyroid
C81	Hodgkin lymphoma
C82–C86	non-Hodgkin lymphoma
C91-C95	leukemia
C88, C90	multiple myeloma
C17, C26, C47, C57-C58, C60, C63, C68, C74-C76, C96	other

KCD = Korean Standard Cause Classification of Diseases.

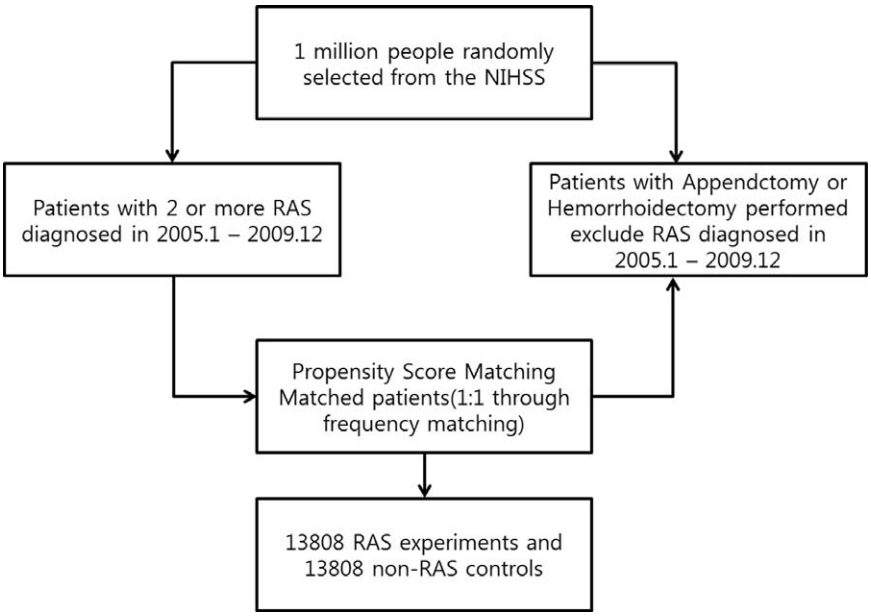

Figure 1. Flow diagram of patient enrollment.

Table 2

Demographic characteristics of recurrent aphthous stomatitis and control patients.

Factor	Number of cases (%)	Number of controls (%)	*P* value
Overall	13,808	13,808	
Age (y)			
<10	1139	1146	1.000
10–19	1431	1422	
20–29	1425	1430	
30–39	2287	2287	
40–49	2402	2402	
50–59	1968	1965	
60–69	1798	1806	
70–79	1187	1181	
>80	171	169	
Sex			
Male	5979	5655	.769
Female	8129	8153	
Income			
0th quartile	508	502	.995
1–2 quartile	1756	1749	
3–4 quartile	1812	1799	
5–6 quartile	2380	2418	
7–8 quartile	3173	3175	
9–10 quartile	4179	4165	
Location			
City (Seoul, Gyeonggi, Incheon)	7060	7095	.673
Other	6748	6713	
Disabled			
Non-disabled	13,157	13,151	.865
Disabled	651	657	

hazard model. In addition, through sub-group analysis, the risk of the cases on outcomes was further analyzed compared to controls according to sex (male, female) and age group (under 39, 40–59, over 60). The significance level for all statistical analyses was 0.05, and data were analyzed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC) (Table 2).

3. Results

In the RAS and non-RAS patient groups, sex ($P=1.000$), age ($P=.769$), income quartile ($P=.995$), location ($P=.673$), and disabled status ($P=.865$), which had no significant differences, were selected through PSM. According to the KCD-6 classification system, the adjusted hazard ratio (aHR) for overall cancer was 1.09, and no significant difference was found between the RAS and non-RAS groups (95% CI: 0.99–1.20, $P<.073$). The aHR for pancreatic cancer among all cancers was 1.26 (95% CI: 1.01–1.57, $P<.041$), which confirmed this was a significant result (Fig. 2). There were no significant differences between the 2 groups on the remaining 19 types of cancer (Table 3). In the subgroup analysis comparing all cancers according to sex and age, no significant difference was found between the 2 groups (Table 4).

4. Discussion

The main causes of oral ulcers are trauma, RAS, recurrent intraoral herpes simplex virus stomatitis, and cyclic neutropenia. The most common acute oral ulcer disease in the USA is RAS.[1] The general form of RAS shows a yellow and white fibrous membrane slough surrounded by erythema.[1] The simplest form of RAS usually lasts 1 to 2 weeks, sometimes longer if the lesion is large.[1,2] The triggering factor is not clearly known, but several

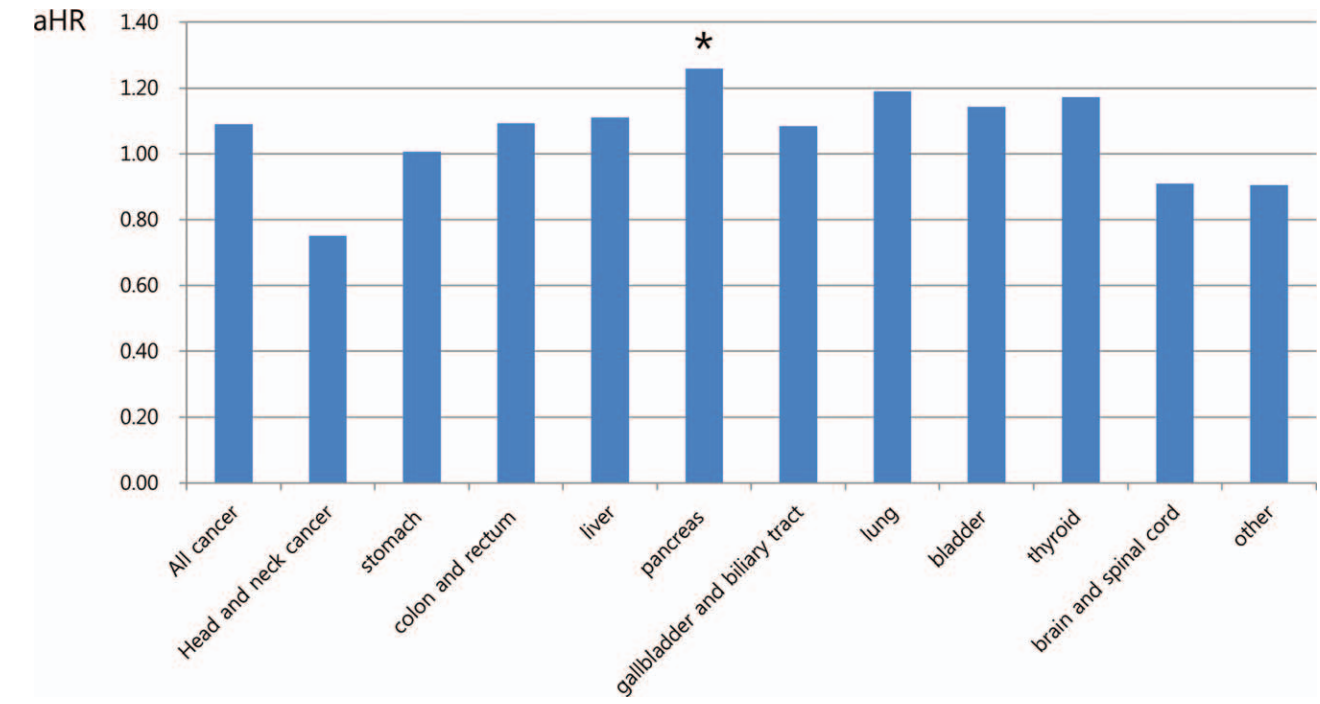

Figure 2. The aHR of each cancer over a 5-year follow-up in recurrent aphthous stomatitis patients. Asterix means that the *P* value was under .05. Thorax, esophagus, anus, and anal canal, bone, kidney, Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, multiple myeloma, retroperitoneum and peritoneum were not indicated due to insufficient statistics. aHR, adjusted hazard ratio.

Table 3

Prevalence of specific cancers over a 5-year follow-up in recurrent aphthous stomatitis patients and controls.

	Patients with RAS, n (%)	Controls, n (%)	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
Overall	882 (6.6)	820 (6.09)	1.09 (0.99, 1.19)	.090	1.09 (0.99, 1.20)	.073
Head and neck	23 (0.17)	31 (0.22)	0.74 (0.43, 1.27)	.281	0.75 (0.44, 1.29)	.301
Thorax	6 (0.04)	6 (0.04)	1.00 (0.32, 3.10)	1.000	1.02 (0.33, 3.15)	.979
Esophagus	7 (0.05)	6 (0.04)	1.17 (0.39, 3.47)	.782	1.18 (0.40, 3.51)	.767
Stomach	102 (0.74)	102 (0.74)	1.00 (0.76, 1.32)	1.000	1.01 (0.77, 1.33)	.958
Colon and rectum	228 (1.66)	209 (1.52)	1.09 (0.90, 1.32)	.365	1.09 (0.91, 1.32)	.355
Anus and anal canal	3 (0.02)	2 (0.01)	1.50 (0.25, 8.98)	.657	1.51 (0.25, 9.04)	.651
Liver	260 (1.89)	235 (1.71)	1.11 (0.93, 1.32)	.254	1.11 (0.93, 1.33)	.239
Pancreas	177 (1.28)	141 (1.02)	1.26 (1.01, 1.57)	.043	1.26 (1.01, 1.57)	.041
Gallbladder and biliary tract	40 (0.29)	37 (0.27)	1.08 (0.69, 1.69)	.731	1.08 (0.69, 1.69)	.723
Lung	164 (1.19)	140 (1.02)	1.17 (0.94, 1.47)	.165	1.19 (0.95, 1.49)	.129
Bone	4 (0.03)	10 (0.07)	0.40 (0.13, 1.28)	.121	0.40 (0.13, 1.28)	.121
Kidney	35 (0.25)	29 (0.21)	1.21 (0.74, 1.97)	.455	1.21 (0.74, 1.99)	.440
Bladder	60 (0.43)	53 (0.38)	1.13 (0.78, 1.64)	.511	1.14 (0.79, 1.65)	.480
Thyroid	129 (0.94)	110 (0.8)	1.18 (0.91, 1.52)	.213	1.17 (0.91, 1.51)	.222
Brain and spinal cord	20 (0.14)	22 (0.16)	0.91 (0.50, 1.67)	.757	0.91 (0.50, 1.67)	.761
Hodgkin lymphoma	1 (0.01)	4 (0.03)	0.25 (0.03, 2.24)	.215	0.25 (0.03, 2.24)	.216
Non-Hodgkin lymphoma	17 (0.12)	14 (0.10)	1.21 (0.60, 2.46)	.590	1.23 (0.61, 2.50)	.563
Leukemia	15 (0.11)	11 (0.08)	1.37 (0.63, 2.97)	.433	1.38 (0.63, 3.00)	.418
Multiple myeloma	11 (0.08)	8 (0.06)	1.38 (0.55, 3.42)	.493	1.39 (0.56, 3.45)	.481
Other	39 (0.28)	43 (0.31)	0.91 (0.59, 1.40)	.659	0.91 (0.59, 1.40)	.657

CI = confidence interval, HR = hazard ratio, aHR = adjusted hazard ratio, KCD-6 = Korean Standard Cause Classification of Diseases, 6th revision, RAS = recurrent aphthous stomatitis.

factors such as genetic, environmental, and immunological factors are known to be related.[1,2]

It is known that RAS causes ulceration by circulating humoral antibodies that cause destruction of the oral mucosa through increases in TNF-α, IL-2, and IFN-γ, and decreases in L-4, IL-5, and IL-10.[7] This in vivo response triggers a change in autoimmunity and was found to be related to Hashimoto's thyroiditis through an increase in autoimmune thyroiditis, especially Th/Tc1 cytokines.[7] When oxidative stress appears due to repeated inflammation, it causes deoxyribonucleic acid damage. When analyzing the family tree of RAS, HLA Haplotype A * 038B * 07DRB1 * 13 was associated with RAS, and other genetic factors were also confirmed.[8,9] Repeated mucosal ulcers have been reported to be associated with various systemic diseases such as Benin and Crohn disease.[8,9]

The epidemiologic link between RAS and cancer has been continuously studied, but the relationship between the 2 diseases has not been clearly identified.[2] No large-scale studies have been conducted to determine the RAS association with cancer. However, in 2018, Qin L reported a study examining cancer association with RAS through the National Health Insurance Research Database, where head and neck, colon, liver, pancreas, skin, breast, prostate, and hematologic cancers have been linked to RAS.[2] There have been cases where a lesion was initially diagnosed as RAS due to similar characteristics but was subsequently confirmed as gingival squamous cell carcinoma.[10] Unexpectedly in this study, RAS exhibited higher aHR than non-RAS only for pancreatic cancer.

Pancreatic cancer is the 11th most common cancer in the world and the seventh highest cause of death from cancer.[11] Pancreatic cancer and RAS have been commonly reported to be associated with overexpression of cytokines and *p53*.[12,13] In addition, it was confirmed that the serum level of vitamin D in patients with RAS or pancreatic cancer tended to be low.[14–16]

In RAS, when mucosal keratinocytes induce stimulation of T lymphocytes, they secrete cytokines such as TNF-a and IL.[17] TNF-a is known to induce activation of *NF-κB*, a transcription factor, to convert tumor suppressors to tumor promotors and substances such as IL-6 to induce pancreatic intraepithelial neoplasia.[18] In a previous nationwide population-based cohort study of the association between candidiasis and cancer, there was a significant association between candidiasis groups and pancreatic cancer. The association in this study was attributed as surveillance bias, but the association has been reported in various studies.[19]

Mutation of P53 is known to be related to the occurrence of several cancers, including pancreatic cancer.[13] In RAS, reactive

Table 4

Subgroup analysis of cancer hazard ratios in recurrent aphthous stomatitis and controls.

	Patients with RAS, n (%)	Controls, n (%)	HR (95% CI)	*P* value
Sex				
Male	363 (6.77)	345 (6.26)	1.08 (0.94, 1.26)	.279
Female	514 (6.48)	475 (5.97)	0.96 (0.96, 1.23)	.193
Age				
<=39	150 (2.40)	129 (2.06)	1.17 (0.92, 1.48)	.197
40–59	343 (8.15)	317 (7.44)	1.10 (0.94, 1.28)	.225
>=60	389 (13.35)	374 (12.71)	1.05 (0.91, 1.21)	.494

CI = confidence interval, HR = hazard ratio, RAS = recurrent aphthous stomatitis.

oxygenation and reactive nitrogen affect P53 as a repetitive inflammatory reaction, causing germ mutation and deletion.[20]

1,25 $(OH)_2D_3$, the biologically active form of vitamin D, affects vitamin D response elements that are known to cause inflammatory reactions in macrophages, dendritic cells, active B lymphocytes, and active T lymphocytes, playing a role in regulation of the immune response.[21–24] Cyclin dependent kinase gene *p21* and *p27* have vitamin D response elements in the promotor region and are known to induce arrest and withdrawal of the G1 cell-cycle, thereby inhibiting angiogenesis in tumor cells and inducing apoptosis.[25] Although the association of vitamin D level with pancreatic cancer is controversial, studies have been reported linking vitamin D level to pancreatic cancer after comparing differences in vitamin D level between ethnic groups, with evidence that it has an overall effect on incidence and mortality rate.[24,26–29]

It has been reported that chronic inflammation damages normal tissue through reactive oxygen and causes oxidative deoxyribonucleic acid damage.[30] However, the association between head and neck cancer and RAS causing repeated intraoral inflammation has not been confirmed.

The first limitation of this study is that the study period was short. The longest follow-up observation period after diagnosis was 10 years, potentially being somewhat insufficient. In particular, RAS is a disease with a high incidence in the 20s to 30s age range. Due to the characteristics of any cancer that develops at a relatively old age, this study is meaningful in the early stages of cancer but is less applicable to long-term cancers. Secondly, it is difficult to meaningfully compare samples with low incidence, such as Hodgkin lymphoma, because the study period is short and the number of cancer samples is insufficient. Third, RAS does not have a high hospital visit rate if the symptoms are mild. In contrast, cancer is diagnosed when most of the symptoms are present due to the high hospital access rate in Korea. Therefore, in the population-based study through NHISS, there are limitations in the measurement of cancer with respect to the correct number of RAS patients.

Although the limitations of the study are clear, patients with RAS showed a significantly increased risk of pancreatic cancer. More long-term cohort observational studies and mechanism studies on the connection between these 2 diseases will be needed to validate our findings.

Author contributions

Conceptualization: Ki Jin Kwon, Su Jin Jeong, Young-Gyu Eun, In Hwan Oh, Young Chan Lee.
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Investigation: Young Chan Lee.
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Writing – review and editing: Ki Jin Kwon, In Hwan Oh, Young Chan Lee.

References

[1] Cui RZ, Bruce AJ, Rogers RS. Recurrent aphthous stomatitis. Clin Dermatol 2016;34:475–81.
[2] Qin L, Kao YW, Lin YL, et al. Recurrent aphthous stomatitis may be a precursor or risk factor for specific cancers: a case-control frequency-matched study. Cancer Med 2018;7:4104–14.
[3] Stenman G, Heyden G. Premonitory stages of recurrent aphthous stomatitis. I. Histological and enzyme histochemical investigations. J Oral Pathol 1980;9:155–62.
[4] Li S, Lee YC, Li Q, et al. Oral lesions, chronic diseases and the risk of head and neck cancer. Oral Oncol 2015;51:1082–174.
[5] Norton E. Could recurrent aphthous stomatitis be linked to cancer development? Dentistry 3000 2017;5:2167–8677.
[6] Rotundo LD, Toporcov TN, Biazevic GH, et al. Are recurrent denture-related sores associated with the risk of oral cancer? A case control study. Rev Bras Epidemiol 2013;16:705–15.
[7] Ozdemir IY, Calka O, Karadag AS, et al. Thyroid autoimmunity associated with recurrent aphthous stomatitis. J Eur Acad Dermatol Venereol 2012;26:226–30.
[8] Chavan M, Jain H, Diwan N, et al. Recurrent aphthous stomatitis: a review. J Oral Pathol Med 2012;41:577–83.
[9] Najafi S, Yousefi H, Mohammadzadeh M, et al. Association study of interleukin-1 family and interleukin-6 gene single nucleotide polymorphisms in recurrent aphthous stomatitis. Int J Immunogenet 2015;42:428–31.
[10] Kumari PS, Kumar GP, Bai YD, et al. Gingival squamous cell carcinoma masquerading as an aphthous ulcer. J Indian Soc Periodontol 2013;17:523–6.
[11] Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol 2016;22:9694–705.
[12] Rodrigues P, Oshima F, Paiotti R, et al. Expression of apoptosis regulatory proteins p53, bcl-2 and bax in recurrent aphthous ulceration. J Eur Acad Dermatol Venereol 2012;26:1247–51.
[13] Kim H, An S, Lee K, et al. Pancreatic high-grade neuroendocrine neoplasms in the Korean population: a multicenter study. Cancer Res Treat 2020;52:263–76.
[14] Cho M, Peddi PF, Ding K, et al. Vitamin D deficiency and prognostics among patients with pancreatic adenocarcinoma. J Transl Med 2013;11:206.
[15] Öztekin A, Öztekin C. Vitamin D levels in patients with recurrent aphthous stomatitis. BMC Oral Health 2018;18:186.
[16] Khabbazi A, Ghorbanihaghjo A, Fanood F, et al. A comparative study of vitamin D serum levels in patients with recurrent aphthous stomatitis. Egypt Rheumatol 2014;37:133–7.
[17] Chaudhuri K, Nair KK, Ashok L. Salivary levels of TNF-α in patients with recurrent aphthous stomatitis: a cross-sectional study. J Dent Res Dent Clin Dent Prospects 2018;12:45–8.
[18] Shadhu K, Xi C. Inflammation and pancreatic cancer: an updated review. Saudi J Gastroenterol 2019;25:3–13.
[19] Chung LM, Liang JA, Lin CL, et al. Cancer risk in patients with candidiasis: a nationwide population-based cohort study. Oncotarget 2017;8:63562–73.
[20] Yamanishi Y, Boyle DL, Rosengren S, et al. Regional analysis of p53 mutations in rheumatoid arthritis synovium. Proc Natl Acad Sci USA 2002;99:10025–30.
[21] Agmon-Levin N, Theodor E, Segal RM, et al. Vitamin D in systemic and organ-specific autoimmune diseases. Clin Rev Allergy Immunol 2013;45:256–66.
[22] Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. Ann Rheum Dis 2007;66:1137–42.
[23] Antico A, Tozzoli R, Giavarina D, et al. Hypovitaminosis D as predisposing factor for atrophic type A gastritis: a case-control study and review of the literature on the interaction of vitamin D with the immune system. Clin Rev Allergy Immunol 2012;42:355–64.
[24] Mohamed AA, Aref AM, Talima SM, et al. Association of serum level of vitamin D and VDR polymorphism Fok1 with the risk or survival of pancreatic cancer in Egyptian population. Indian J Cancer 2019;56:130–4.
[25] Chiang KC, Chen TC. Vitamin D for the prevention and treatment of pancreatic cancer. World J Gastroenterol 2009;15:3349–54.
[26] Grant WB. Vitamin D status may help explain racial disparities in pancreatic cancer incidence and mortality in the United States. Clin Gastroenterol Hepatol 2020;18:1896.
[27] Krishnan AV, et al. Annu Rev Pharmacol Toxicol 2011;311–36.
[28] Liu SL, Zhao YP, Dai MH, et al. Vitamin D status and the risk of pancreatic cancer: a meta-analysis. Chin Med J 2013;126:3356–9.
[29] Ong JS, Gharahkhani P, An JY, et al. Vitamin D and overall cancer risk and cancer mortality: a Mendelian randomization study. Hum Mol Genet 2018;27:4315–22.
[30] Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; 420:860–7.