Changing Epidemiology and Future Challenges of Inflammatory Bowel Disease in Asia

Siew C Ng, MBBS, MRCP, Ph.D.

Institute of Digestive Disease, Chinese University of Hong Kong, Hong Kong

In the past decade, many countries in Asia, in particularly in East Asia, are experiencing a progressive rise in the incidence and prevalence of inflammatory bowel disease (IBD). Improved physician awareness and diagnostic methods are unlikely to fully account for this rapid increase. This epidemiological shift is likely to relate to industrialization, westernization of lifestyles and changes in eating habits, as part of the socioeconomic development in Asia, although many of these putative environmental factors have not been formally investigated in Asian cohorts. Genetic factors for IBD differ between Asia and the West. NOD2/CARD15 mutation, repeatedly observed in the Caucasian populations, is not associated with Crohn's disease in Asian populations. Familial clustering is generally uncommon in Asia but it is expected to increase as the IBD prevalence in this region rises. Ethnic-racial differences of IBD have been described and Indians appear to be most affected in South-East Asia. Clinical manifestation of IBD in Asia resemble the Western population in general, but with some differences, including higher prevalence of males and ileocolonic disease, lower disease severity, surgical rates and extraintestinal manifestations. These differences may relate to time factor, genetic background and environmental factors. This review summarises recent epidemiological data of IBD including environmental factors associated with the development of IBD in Asia. Future research focusing on studying the epidemiology of IBD in an area of rapidly increasing prevalence such as Asia will allow the opportunity to identify potential risk factors and provide a better understanding of the aetiology of disease in the Asian population. (**Intest Res 2010;8:1-8**)

Key Words: Inflammatory Bowel Disease; Asia; Epidemiology; Genetics; Environmental Factors

BACKGROUND

Crohn's disease (CD) and Ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) of unknown aetiology. The pathophysiology of IBD relates to a dysregulated mucosal immune response to antigenic stimulation from gut microbiota on a background of genetic susceptibility.¹ IBD represents an important public health problem because it affects mostly young people at an age when they are most active in their private and professional lives,² and a management challenge because of its unpredictable relapsing nature. During the last few decades the incidence of IBD has

changed in many ways. Incidence rates of traditionally high incidence areas such as Western Europe is relatively stable or even decreasing,³ while diseases have become more prevalent in previously low incidence areas, such as Asia and Eastern Europe.⁴⁻⁷

The reason for these changes remains unknown. They are unlikely to be merely increased awareness of the disease and differences in diagnostic practices, but most likely reflect real differences secondary to environmental factors, lifestyle changes and genetic factors.⁸ Genetic susceptibility is different in Asian compared to Western patients.⁷ Apart from geographic differences, ethnic differences have been described in multi-racial countries including Malaysia and Singapore. Indians appeared to be more susceptible to IBD than Chinese and native Malays.⁹

Half the world's population reside in the Asia-Pacific region and the continuing rise in incidence of IBD will have important implications for health care providers in

Received April 20, 2010. Accepted May 29, 2010.

• Correspondence to : Siew C Ng, MBBS, MRCP, Ph.D., Institute of Digestive Disease, Department of Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong
Tel: +852-2637-3509, Fax: +852-2646-8915
E-mail: siewchiennng@cuhk.edu.hk

many Asian countries who will need to address both health needs of patients and the social burden of these chronic diseases.¹⁰⁻¹³ The epidemiology and clinical characteristics of IBD in Asia has been recently reviewed in two comprehensive reviews,^{7,14} and consensus for the management of IBD from several countries in Asia has been published.¹⁵⁻¹⁸ In this paper, I have provided an update on the incidence and prevalence of IBD, and susceptibility genes identified to date in studies from Asia. Environmental factors that may play a role in the rising incidence of IBD in this region were reviewed. Clinical features and complications of IBD in Asia were compared with the West, and clinical challenges and future research questions were discussed.

INCIDENCE AND PREVALENCE

The incidence rates of CD and UC vary worldwide between 0.1 to 16 per 100,000 inhabitants and 0.5 to 24.5 per 100,000 inhabitants, respectively.^{19,20} IBD is more common in the Northern than the Southern part of the world, and it is more common among Caucasian compared with non-caucasian populations. The highest incidence rates have been recorded in North America

and North and West Europe, while lower rates have been reported in South America, Africa and Asia.²¹ The incidence of IBD in Australia has recently been shown to equal to the highest in the world.²² Epidemiological studies in the West have shown that the increase in incidence of UC precedes the increase of incidence of CD by about 15 to 20 years.²³⁻²⁵

In Asia, several studies have indicated a rising trend of the incidence and prevalence of IBD although only few data are available on the true epidemiology of IBD in Asia.⁷ Studies reporting the incidence of IBD in Asia have been derived mostly from hospital based database in which confirmed cases of IBD were extrapolated to the area that the hospital serves with the population in that area used as a denominator. Japan is the only country in Asia that has a national IBD registry maintained by the Ministry of Health, Labour and Welfare. Data reporting time trend increase in the incidence of IBD in Asia are now available.²⁶⁻²⁹ In Japan, cumulative numbers of IBD patients has risen by three-fold. The estimated annual incidence of CD in Japan have increased from approximately 0.6 per 100,000 in 1986 to 1.2 per 100,000 population in 1998.³⁰ In Hong Kong, there is a three-fold increase in the incidence of CD in Chinese patients from 0.3 per 100,000 in 1986 to 1 per

Table 1. Incidence and Prevalence of IBD in Asia

Authors	Country	Years	Incidence		Prevalence	
			CD	UC	CD	UC
Higashi et al. 1988 ³⁶	Japan	1984-1985	—	—	1.86	7.85
Yoshida et al. 1990 ²⁶	Japan	1965	0.01	0.08	5.85	5.5
Morita et al. 1995 ³⁷	Japan	1991	0.51	1.95	5.85	18.12
Yao et al. 2000 ³⁰	Japan	1998	1.2	—	13.5	—
Yang et al. 2008 ^{27,38}	South Korea	1986-1990	0.05	0.34	—	—
		1991-1995	0.22	0.87	—	—
		1996-2000	0.52	1.74	—	7.57
		2001-2005	1.34	3.08	11.24	30.87
		—	—	—	—	—
Sung et al. 1994 ³⁹	Hong Kong	1994	—	—	1.3	—
Leong et al. 2004 ²⁸	Hong Kong	1999-2001	1.0	1.2	—	—
Lok et al. 2008 ⁴⁰	Hong Kong	1997	—	0.35	—	2.3
		2001	—	0.85	—	4.9
		2006	—	0.40	—	7.0
		—	—	—	—	—
Zheng et al. 2005 ⁴¹	China	1950-2000	0.28	—	1.38	—
Lee et al. 2000 ³³	Singapore	1999	—	—	3.6	6.0
Thia et al. 2006 ⁴²	Singapore	2004	—	—	7.2	—
Sood et al. 2003 ³²	North India	1999-2000	—	6.02	—	44.3
Niriella et al. 2010 ⁴³	Sri Lanka	2007-2008	0.09	0.69	1.2	5.3

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis.

100,000 in 1991-2001. In China, a four-fold increase in the prevalence of IBD since the 1990s have been observed.³¹

Only very few population-based IBD studies exist in the Asian population. One study in India performed a community based survey in random selected districts in Punjab and reported a crude incidence for UC of 6.02 cases per 100,000 inhabitants.³² This figure is likely to be an underestimation of the true prevalence of UC as not all patients had a sigmoidoscopy or biopsy to confirm disease. Another population-based study in Korea has shown a steady rise in the mean annual incidence of CD and UC in the Songpa-Kangdong district of Seoul from 0.05 and 0.34 per 100,000 inhabitants, respectively, in 1986-1990 to 1.34 and 3.08 per 100,000 inhabitants, respectively, in 2001-2005.²⁷ In countries of multi-ethnic population such as Singapore and Malaysia, Indians have a higher prevalence of UC and CD than Chinese and Malays.³³⁻³⁵ Overall, published studies in Asia have confirmed that the incidence and prevalence of both UC and CD are increasing in Asia although the reported rates are still lower than in North America and Europe. There is also a time lag phenomenon compared to time trends in the West. Table 1 shows the incidence and prevalence of CD and UC from studies derived mostly from East Asia and South-East Asia.

GENETICS

Variation is evident in the genetic susceptibility for IBD between Asian and the White population. For instance, nucleotide oligomerization domain-2 (NOD2/CARD 15) variants which account for approximately 20% of CD in white and Jewish populations^{44,45} have not been detected in studies of IBD subjects from Hong Kong,⁴⁶ China,⁴⁷ Japan⁴⁸ and Korea.^{49,50} In addition IL-23 receptor (IL-23R) and autophagy-related 16-like 1 (ATG16L1) genes which have been firmly associated with CD in the White population,^{51,52} were reported to have no associations with CD in Japanese⁵³ and Korean patients.⁵⁴ Susceptibility loci on IBD5 locus and *IRGM* genes are also not associated with CD in Japanese.^{55,56} For UC, several susceptibility genes have been identified in the Caucasian populations which have not been associated

with the Asian populations.⁵⁷⁻⁵⁹ In India, potential associations between UC and SNP5 in the North Indian populations suggest that there is allelic heterogeneity in UC susceptibility.⁶⁰ Racial variation is evident suggesting host genetic predisposition. Indians in South East Asia are more prone towards the development of IBD than Chinese and Malays.⁶¹ Table 2 shows the genetic susceptibility loci in Asian IBD patients.

Compared with Caucasians, familial clustering for both CD and UC is rare in Asian patients.^{7,9,62} A family history of IBD has been reported in up to 3% and 10% of UC and CD patients in Asian studies.^{27-29,33,40,63} This lower rates of familial aggregation in Asia is most likely related to the overall low disease prevalence, and as disease prevalence increases with time, the attributable risk of a positive family history is likely to be similar in Asian and Caucasian patients.⁶⁴

ENVIRONMENTAL FACTORS

Changes in lifestyle in Asia during the last two decades have resulted in a more “westernized” standard way of living, with increased consumption of refined sugar, fatty acids, fast food, cereals and bread and reduced consumption of fruit, vegetables and fibres.^{82,83} With all of these aspects of westernization previously being associated with IBD,^{84,85} westernization of lifestyle could potentially explain the observed increases

Table 2. IBD Susceptibility Genes Associated with the Asian Population

Ethnicity	Associated with CD	Associated with UC
Japanese	TNFSF15 ⁶⁵ DLG5 ⁶⁶	CTLA-4 ⁶⁷ HLA-DRB1*1502 ⁶⁸ HLA B5 DR2 ⁶⁹
South Koreans	TNFSF15 ⁷⁰ IL-23R ⁵⁴	HLA-DRB1*1502, DR2 alleles ⁷¹
Han Chinese	IL-23R ⁷²	CTLA-4 ⁷³⁻⁷⁵ MCP-1 ⁷⁶ IL-1Beta ⁷⁶ MICB0106 ⁷⁷ MICA*A5.1 allele ^{78,79} IL-17F 7488-A ⁸⁰ MDR1 gene ⁸¹
Indians	—	
Malaysians	NOD2/CARD15 ⁶¹	

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis.

of incidence of UC and CD.^{20,82,86} In Japan, the increased intake of dairy products and meat has paralleled the rising trend of UC,²⁹ and a higher consumption of sweets and high fat diet has been associated with UC and CD.⁸⁷

Other more controversial risk factors such as tonsillectomy, perinatal infections, oral contraceptives, breastfeeding and vaccinations have been proposed as being associated with IBD, but these factors have not been studied in the Asian cohorts. The only factors that have been proven to be important environmental factors in both UC and CD in studies from the West are smoking and appendectomy. Small studies in East Asia however have not shown an association between smoking and CD.^{28,88} Conversely the protective effect of smoking on UC had been confirmed in studies from Japan and China.^{37,89} Consistent with Western data, case-control studies in Asia has demonstrated the protective effect of appendectomy in UC.^{89,90} Overall, Asian populations probably has genetic susceptibility, that when exposed to putative environmental factors will develop IBD. This predisposition appears to be stronger in certain racial groups.

CLINICAL CHARACTERISTICS

Clinical manifestation of IBD in Asia is relatively similar to that of the West although disease severity may be less in Asia. A few studies have reported differences

in the clinical phenotypes and complications of IBD, including higher prevalence of ileocolonic involvement in CD, lower surgical rates, and a low frequency of primary sclerosing cholangitis among IBD patients in Asia.^{7,14} Differences in disease, severity and complications may relate to genetic background, environmental factors such as diet and intestinal flora, and the duration of disease.⁷ The peak age of disease onset in Asia is 20 to 50 years, and a second peak after 50 years old is less common in Asian patients.⁹¹ Combined small and large bowel involvement appears to be most common in East Asia. In South and West Asia, distribution of disease site is more variable.^{9,27,62} Extraintestinal manifestations are less common in Asian populations. Table 3 summarises the clinical features of IBD in Asian compared with the Western population.

CURRENT CHALLENGES AND FUTURE DIRECTIONS

Current major clinical challenge relates to the accurate diagnosis of IBD in countries with a high background prevalence of infections. The diagnosis of CD in geographical areas where tuberculosis is common poses a diagnostic challenge. Infections may mimic IBD, and can complicate the course of existing IBD. Limited availability of diagnostic tests in particularly radiological imaging may delay diagnosis. Screening for latent infections specifically for tuberculosis and

Table 3. Clinical Features of IBD in Asia and the West

Clinical features	Asian IBD populations compared with Western populations
Gender distribution	West: Female predominance for CD ⁸⁶ Asia: Slight male predominance for UC and CD ^{26-28,30,33,37,42,92}
Peak age of disease onset	West: 20–30 years old for CD and 30–40 years old for UC ⁹³ Asia: Similar to the West but smaller second peak for CD and UC ²⁷
UC distribution and severity	Asia: Proportion of extensive and pancolitis (18–46%) relatively similar to the West but milder disease course ^{40,94}
CD distribution & behaviour	Asia: Mostly resemble the West except ileocolonic predominant in East Asia ^{27,92,95}
Extraintestinal disease	West: 21 to 41% ⁹⁶ Asia: 6 to 14% ^{62,97} Geographical variations in Asia
Colorectal cancer in UC	Primary sclerosing cholangitis (<1%) rare in Asia ^{28,31,98} West: 3 to 5% ⁹⁹ Asia: 0 to 1.8% ^{7,9,97,100}
Colectomy rates	Variable in Asia ⁷

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis.

hepatitis B deserve special consideration in Asia given the high prevalence of these diseases in the Asian populations. Recently biological therapy has entered the armamentarium of IBD, and the efficacy and side effects of biologics in Asian cohorts warrant further investigations. There is also a diverse medical practice in South Asia and South East Asia which include alternative and complementary medicine, Ayurveda, Homeopathy, and some patients with IBD may prefer to present to traditional and alternative health practitioners.

With the exception of Japan, Asia currently lacks population based registries of IBD. Constraints in health care resources have made the conduct of an epidemiological study in developing countries a challenge. Larger epidemiological data over time are necessary to describe the true incidence of IBD and further characterize the clinical features and risk factors of IBD in different geographical areas in the Asia-Pacific region. The conduct of an epidemiology study in Asia requires good case ascertainment in a well defined area with known denominator. Such studies will better define the burden of illness, explore the mechanism of association with environmental factors as well as identify new risk factors. Future studies to determine whether smoking plays a lesser role in the development of CD in Asian populations are needed. Studying exposure and risk factors for IBD require prospectively collected data from questionnaires on diet and environmental exposure in order to minimise recall bias and incomplete data. A large scale web-based epidemiology study (EpiCOM) organised by the European Crohn's and Colitis Organisation (ECCO) is currently in progress in East and West Europe. A second project known as the Origin study, also conducted by ECCO, aims to prospectively recruit first degree relatives of probands with CD and follow them for at least ten years to assess the genotype, gut microbiota, immune function biomarkers and environmental exposures of subjects at risk of developing IBD.

Most genetic variants associated with IBD identified in Asia so far, through fine-mapping and candidate gene approach, vary according to ethnicity and nationalities. There is a lack of Genome wide association studies in Asia, and to identify novel Asian IBD-associated genes, such a study will require collaborative efforts between

various centres in Asia in order to collect large number of samples. If the genetic and clinical heterogeneity of IBD in Asia is different from Western populations, response to medical therapy may also be different in our patients.

IBD represents an important public health problem affecting both the patient's education, working abilities, social life and quality of life. Apart from direct medical costs associated with hospitalisations and surgery, IBD is associated with substantial indirect costs related to activity impairment, especially since the onset of IBD typically occurs during adulthood. Little is also currently known of the cost of management of IBD in Asia.⁹¹ More likely than not, the incidence of IBD will continue to surge in Asia in the next decade. Effective research and development of IBD therapies will require network and collaboration between multiple centres in Asia. Although yet incorporated into practice in Asia, optimal patient management will need to move towards multi-disciplinary approach, including the active involvement of specialist dietitians, radiologist, surgeons, and in some tertiary IBD centres, IBD nurse specialist and psychologists. New systems and opportunities for education in IBD should be incorporated into training of specialists.

CONCLUSION

The rising incidence of IBD in Asia in the last two decades is a real phenomenon, which is considered to be the result of environmental changes secondary to economic growth and affluence. There appears to be variation in the incidence, prevalence and disease characteristics between Asians of different nationalities and geography. Well conducted epidemiological studies of IBD will not only inform health care policy of the true scale of the disease in Asia but also offer the opportunity to help clinicians and researchers elucidate the role of environmental factors and identify new aetiological factors responsible for this "IBD epidemic" in Asia.

REFERENCES

1. Danese S, Fiocchi C. Etiopathogenesis of inflammatory bowel

- diseases. *World J Gastroenterol* 2006;12:4807-4812.
2. Riis L, Vind I, Politi P, et al. Does pregnancy change the disease course? A study in a European cohort of patients with inflammatory bowel disease. *Am J Gastroenterol* 2006;101:1539-1545.
3. Molinié F, Gower-Rousseau C, Yzet T, et al. Opposite evolution in incidence of Crohn's disease and ulcerative colitis in Northern France (1988-1999). *Gut* 2004;53:843-848.
4. Lakatos L, Mester G, Erdelyi Z, et al. Striking elevation in incidence and prevalence of inflammatory bowel disease in a province of western Hungary between 1977-2001. *World J Gastroenterol* 2004;10:404-409.
5. Sincić BM, Vucelić B, Persić M, et al. Incidence of inflammatory bowel disease in Primorsko-goranska County, Croatia, 2000-2004: a prospective population-based study. *Scand J Gastroenterol* 2006;41:437-444.
6. Lakatos PL, Fischer S, Lakatos L. Is the epidemiology of inflammatory bowel disease changing in Eastern Europe? *Scand J Gastroenterol* 2006;41:870-871.
7. Thia KT, Loftus EV Jr, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. *Am J Gastroenterol* 2008;103:3167-3182.
8. Lakatos PL. Recent trends in the epidemiology of inflammatory bowel diseases: up or down? *World J Gastroenterol* 2006;12:6102-6108.
9. Goh K, Xiao SD. Inflammatory bowel disease: a survey of the epidemiology in Asia. *J Dig Dis* 2009;10:1-6.
10. Longobardi T, Bernstein CN. Health care resource utilization in inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2006;4:731-743.
11. Longobardi T, Jacobs P, Wu L, Bernstein CN. Work losses related to inflammatory bowel disease in Canada: results from a National Population Health Survey. *Am J Gastroenterol* 2003;98:844-849.
12. Longobardi T, Jacobs P, Bernstein CN. Work losses related to inflammatory bowel disease in the United States: results from the National Health Interview Survey. *Am J Gastroenterol* 2003;98:1064-1072.
13. Feagan BG, Vreeland MG, Larson LR, Bala MV. Annual cost of care for Crohn's disease: a payor perspective. *Am J Gastroenterol* 2000;95:1955-1960.
14. Hou JK, El-Serag H, Thirumurthi S. Distribution and manifestations of inflammatory bowel disease in Asians, Hispanics, and African Americans: a systematic review. *Am J Gastroenterol* 2009;104:2100-2109.
15. Ouyang Q, Tandon R, Goh KL, Ooi CJ, Ogata H, Fiocchi C. The emergence of inflammatory bowel disease in the Asian Pacific region. *Curr Opin Gastroenterol* 2005;21:408-413.
16. Ooi CJ, Fock KM, Makharia GK, et al. The Asia-Pacific consensus on ulcerative colitis. *J Gastroenterol Hepatol* 2010;25:453-468.
17. Ye BD, Jang BI, Jeon YT, Lee KM, Kim JS, Yang SK. Diagnostic guideline of Crohn's disease. *Korean J Gastroenterol* 2009;53:161-176.
18. Choi CH, Jung SA, Lee BI, Lee KM, Kim JS, Han DS. Diagnostic guideline of ulcerative colitis. *Korean J Gastroenterol* 2009;53:145-160.
19. Russel MG. Changes in the incidence of inflammatory bowel disease: what does it mean? *Eur J Intern Med* 2000;11:191-196.
20. Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut* 1996;39:690-697.
21. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology* 2004;126:1504-1517.
22. Wilson J, Hair C, Knight R, Bell S. High incidence of inflammatory bowel disease in Australia: a prospective population-based Australian Incidence Study. *Inflamm Bowel Dis* 2010 (in press).
23. Ekblom A, Helmick C, Zack M, Adami HO. The epidemiology of inflammatory bowel disease: a large, population-based study in Sweden. *Gastroenterology* 1991;100:350-358.
24. Munkholm P, Langholz E, Nielsen OH, Kreiner S, Binder V. Incidence and prevalence of Crohn's disease in the county of Copenhagen, 1962-87: a sixfold increase in incidence. *Scand J Gastroenterol* 1992;27:609-614.
25. Binder V, Both H, Hansen PK, Hendriksen C, Kreiner S, Torp-Pedersen K. Incidence and prevalence of ulcerative colitis and Crohn's disease in the County of Copenhagen, 1962 to 1978. *Gastroenterology* 1982;83:563-568.
26. Yoshida Y, Murata Y. Inflammatory bowel disease in Japan: studies of epidemiology and etiopathogenesis. *Med Clin North Am* 1990;74:67-90.
27. Yang SK, Yun S, Kim JH, et al. Epidemiology of inflammatory bowel disease in the Songpa-Kangdong district, Seoul, Korea, 1986-2005: a KASID study. *Inflamm Bowel Dis* 2008;14:542-549.
28. Leong RW, Lau JY, Sung JJ. The epidemiology and phenotype of Crohn's disease in the Chinese population. *Inflamm Bowel Dis* 2004;10:646-651.
29. Kitahara T, Utsunomiya T, Yokota A. Epidemiological study of ulcerative colitis in Japan: incidence and familial occurrence. The Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan. *J Gastroenterol* 1995;30(Suppl 8):5S-8S.
30. Yao T, Matsui T, Hiwatashi N. Crohn's disease in Japan: diagnostic criteria and epidemiology. *Dis Colon Rectum* 2000;43(10 Suppl):85S-93S.
31. Jiang L, Xia B, Li J, et al. Retrospective survey of 452 patients with inflammatory bowel disease in Wuhan city, central China. *Inflamm Bowel Dis* 2006;12:212-217.
32. Sood A, Midha V, Sood N, Bhatia AS, Avasthi G. Incidence and prevalence of ulcerative colitis in Punjab, North India. *Gut* 2003;52:1587-1590.
33. Lee YM, Fock K, See SJ, Ng TM, Khor C, Teo EK. Racial differences in the prevalence of ulcerative colitis and Crohn's disease in Singapore. *J Gastroenterol Hepatol* 2000;15:622-625.
34. Tan YM, Goh KL. Ulcerative colitis in a multiracial Asian country: racial differences and clinical presentation among Malaysian patients. *World J Gastroenterol* 2005;11:5859-5862.
35. Hilmi I, Tan YM, Goh KL. Crohn's disease in adults: observations in a multiracial Asian population. *World J Gastroenterol* 2006;12:1435-1438.
36. Higashi A, Watanabe Y, Ozasa K, Hayashi K, Aoike A, Kawai

- K. Prevalence and mortality of ulcerative colitis and Crohn's disease in Japan. *Gastroenterol Jpn* 1988;23:521-526.
37. Morita N, Toki S, Hirohashi T, et al. Incidence and prevalence of inflammatory bowel disease in Japan: nationwide epidemiological survey during the year 1991. *J Gastroenterol* 1995;(30 Suppl 8):1S-4S.
38. Yang SK, Hong WS, Min YI, et al. Incidence and prevalence of ulcerative colitis in the Songpa-Kangdong District, Seoul, Korea, 1986-1997. *J Gastroenterol Hepatol* 2000;15:1037-1042.
39. Sung JJ, Hsu RK, Chan FK, Liew CT, Lau JW, Li AK. Crohn's disease in the Chinese population. An experience from Hong Kong. *Dis Colon Rectum* 1994;37:1307-1309.
40. Lok KH, Hung HG, Ng CH, et al. Epidemiology and clinical characteristics of ulcerative colitis in Chinese population: experience from a single center in Hong Kong. *J Gastroenterol Hepatol* 2008;23:406-410.
41. Zheng JJ, Zhu XS, Huangfu Z, Gao ZX, Guo ZR, Wang Z. Crohn's disease in mainland China: a systematic analysis of 50 years of research. *Chin J Dig Dis* 2005;6:175-181.
42. Thia KT, Luman W, Jin OC. Crohn's disease runs a more aggressive course in young Asian patients. *Inflamm Bowel Dis* 2006;12:57-61.
43. Niriella MA, De Silva AP, Dayaratne AH, et al. Prevalence of inflammatory bowel disease in two districts of Sri Lanka: a hospital based survey. *BMC Gastroenterol* 2010;10:32.
44. Hugot JP. CARD15/NOD2 mutations in Crohn's disease. *Ann N Y Acad Sci* 2006;1072:9-18.
45. Ogura Y, Bonen DK, Inohara N, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature* 2001;411:603-606.
46. Leong RW, Armuzzi A, Ahmad T, et al. NOD2/CARD15 gene polymorphisms and Crohn's disease in the Chinese population. *Aliment Pharmacol Ther* 2003;17:1465-1470.
47. Guo QS, Xia B, Jiang Y, Qu Y, Li J. NOD2 3020insC frameshift mutation is not associated with inflammatory bowel disease in Chinese patients of Han nationality. *World J Gastroenterol* 2004;10:1069-1071.
48. Inoue N, Tamura K, Kinouchi Y, et al. Lack of common NOD2 variants in Japanese patients with Crohn's disease. *Gastroenterology* 2002;123:86-91.
49. Croucher PJ, Mascheretti S, Hampe J, et al. Haplotype structure and association to Crohn's disease of CARD15 mutations in two ethnically divergent populations. *Eur J Hum Genet* 2003; 11:6-16.
50. Lee GH, Kim CG, Kim JS, Jung HC, Song IS. Frequency analysis of NOD2 gene mutations in Korean patients with Crohn's disease. *Korean J Gastroenterol* 2005;45:162-168.
51. Van Limbergen J, Russell RK, Nimmo ER, et al. IL23R Arg381Gln is associated with childhood onset inflammatory bowel disease in Scotland. *Gut* 2007;56:1173-1174.
52. Tremelling M, Cummings F, Fisher SA, et al. IL23R variation determines susceptibility but not disease phenotype in inflammatory bowel disease. *Gastroenterology* 2007;132:1657-1664.
53. Yamazaki K, Onouchi Y, Takazoe M, Kubo M, Nakamura Y, Hata A. Association analysis of genetic variants in *IL23R*, *ATG16L1* and 5p13.1 loci with Crohn's disease in Japanese patients. *J Hum Genet* 2007;52:575-583.
54. Yang SK, Park M, Lim J, et al. Contribution of *IL23R* but not *ATG16L1* to Crohn's disease susceptibility in Koreans. *Inflamm Bowel Dis* 2009;15:1385-1390.
55. Tosa M, Negoro K, Kinouchi Y, et al. Lack of association between IBD5 and Crohn's disease in Japanese patients demonstrates population-specific differences in inflammatory bowel disease. *Scand J Gastroenterol* 2006;41:48-53.
56. Aizawa H, Kinoichui Y, Negoro K, et al. Lack of association between IRGM and Crohn's disease in Japanese patients demonstrates population-specific differences in inflammatory bowel disease. *Gastroenterology* 2008;134(4 Suppl 1):A460.
57. Franke A, Balschun T, Sina C, et al. Genome-wide association study for ulcerative colitis identifies risk loci at 7q22 and 22q13 (IL17REL). *Nat Genet* 2010;42:292-294.
58. Franke A, Balschun T, Karlsen TH, et al. Sequence variants in IL10, ARPC2 and multiple other loci contribute to ulcerative colitis susceptibility. *Nat Genet* 2008;40:1319-1323.
59. Silverberg MS, Cho JH, Rioux JD, et al. Ulcerative colitis-risk loci on chromosomes 1p36 and 12q15 found by genome-wide association study. *Nat Genet* 2009;41:216-220.
60. Juyal G, Amre D, Midha V, Sood A, Seidman E, Thelma BK. Evidence of allelic heterogeneity for associations between the NOD2/CARD15 gene and ulcerative colitis among North Indians. *Aliment Pharmacol Ther* 2007;26:1325-1332.
61. Chua KH, Hilmi I, Ng CC, et al. Identification of NOD2/CARD15 mutations in Malaysian patients with Crohn's disease. *J Dig Dis* 2009;10:124-130.
62. Sood A, Midha V. Epidemiology of inflammatory bowel disease in Asia. *Indian J Gastroenterol* 2007;26:285-289.
63. Cao Q, Si JM, Gao M, Zhou G, Hu WL, Li JH. Clinical presentation of inflammatory bowel disease: a hospital based retrospective study of 379 patients in eastern China. *Chin Med J (Engl)* 2005;118:747-752.
64. Park JB, Yang SK, Byeon JS, et al. Familial occurrence of inflammatory bowel disease in Korea. *Inflamm Bowel Dis* 2006;12:1146-1151.
65. Yamazaki K, McGovern D, Ragoussis J, et al. Single nucleotide polymorphisms in TNFSF15 confer susceptibility to Crohn's disease. *Hum Mol Genet* 2005;14:3499-3506.
66. Yamazaki K, Takazoe M, Tanaka T, et al. Association analysis of SLC22A4, SLC22A5 and DLG5 in Japanese patients with Crohn disease. *J Hum Genet* 2004;49:664-668.
67. Machida H, Tsukamoto K, Wen CY, et al. Association of polymorphic alleles of CTLA4 with inflammatory bowel disease in the Japanese. *World J Gastroenterol* 2005;11:4188-4193.
68. Yoshitake S, Kimura A, Okada M, Yao T, Sasazuki T. HLA class II alleles in Japanese patients with inflammatory bowel disease. *Tissue Antigens* 1999;53:350-358.
69. Asakura H, Tsuchiya M, Aiso S, et al. Association of the human lymphocyte-DR2 antigen with Japanese ulcerative colitis. *Gastroenterology* 1982;82:413-418.
70. Yang SK, Lim J, Chang HS, et al. Association of TNFSF15 with Crohn's disease in Koreans. *Am J Gastroenterol* 2008;103: 1437-1442.
71. Myung SJ, Yang SK, Jung HY, et al. HLA-DRB1*1502 confers susceptibility to ulcerative colitis, but is negatively associated with its intractability: a Korean study. *Int J*

- Colorectal Dis 2002;17:233-237.
72. Bin C, Zhirong Z, Xiaoqin W, et al. Contribution of rs11465788 in IL23R gene to Crohn's disease susceptibility and phenotype in Chinese population. *J Genet* 2009;88:191-196.
73. Luo Y, Xia B, Li C, Chen ZT, Ge LQ, Jiang T. Association of cytotoxic T lymphocyte antigen-4 promoter C-658T polymorphism with ulcerative colitis in Chinese. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2009;26:431-434.
74. Jiang Y, Xia B, Jiang L, et al. Association of CTLA-4 gene microsatellite polymorphism with ulcerative colitis in Chinese patients. *Inflamm Bowel Dis* 2006;12:369-373.
75. Zhou F, Xia B, Guo QS, et al. Cytotoxic T lymphocyte antigen-4 promoter gene polymorphism is significantly associated with ulcerative colitis. *Zhonghua Nei Ke Za Zhi* 2006;45:478-481.
76. Li KS, Wang BY, Liu SY, Yao SP, Guo L, Mao DW. The combination of polymorphisms within MCP-1 and IL-1beta associated with ulcerative colitis. *Int J Immunogenet* 2009;36:135-139.
77. Li Y, Xia B, Lü M, et al. An association between MICB 0106 allele and ulcerative colitis in Chinese Han in Hubei province. *Zhonghua Nei Ke Za Zhi* 2008;47:213-216.
78. Lü M, Xia B, Ge L, et al. Role of major histocompatibility complex class I-related molecules A*A5.1 allele in ulcerative colitis in Chinese patients. *Immunology* 2009;128(1 Suppl):e230-e236.
79. Ding Y, Xia B, Lü M, et al. MHC class I chain-related gene A-A5.1 allele is associated with ulcerative colitis in Chinese population. *Clin Exp Immunol* 2005;142:193-198.
80. Chen B, Zeng Z, Hou J, Chen M, Gao X, Hu P. Association of interleukin-17F 7488 single nucleotide polymorphism and inflammatory bowel disease in the Chinese population. *Scand J Gastroenterol* 2009;44:720-726.
81. Juyal G, Midha V, Amre D, Sood A, Seidman E, Thelma BK. Associations between common variants in the MDR1 (ABCB1) gene and ulcerative colitis among North Indians. *Pharmacogenet Genomics* 2009;19:77-85.
82. Frangos CC, Frangos CC. Inflammatory bowel disease: reviewing an old study under a new perspective. *Gut* 2007;56:1638-1639.
83. Jowett SL, Seal CJ, Pearce MS, et al. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. *Gut* 2004;53:1479-1484.
84. Hanauer SB. Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities. *Inflamm Bowel Dis* 2006;12(Suppl 1):3S-9S.
85. Krishnan A, Korzenik JR. Inflammatory bowel disease and environmental influences. *Gastroenterol Clin North Am* 2002;31:21-39.
86. Vind I, Riis L, Jess T, et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003-2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol* 2006;101:1274-1282.
87. Sakamoto N, Kono S, Wakai K, et al. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. *Inflamm Bowel Dis* 2005;11:154-163.
88. Jang JY, Kim HJ, Jung JH, et al. The role of smoking as a risk factor in inflammatory bowel diseases: single center study in Korea. *Korean J Gastroenterol* 2006;47:198-204.
89. Jiang L, Xia B, Li J, et al. Risk factors for ulcerative colitis in a Chinese population: an age-matched and sex-matched case-control study. *J Clin Gastroenterol* 2007;41:280-284.
90. Naganuma M, Iizuka B, Torii A, et al. Appendectomy protects against the development of ulcerative colitis and reduces its recurrence: results of a multicenter case-controlled study in Japan. *Am J Gastroenterol* 2001;96:1123-1126.
91. Ouyang Q, Tandon R, Goh KL, et al. Management consensus of inflammatory bowel disease for the Asia-Pacific region. *J Gastroenterol Hepatol* 2006;21:1772-1782.
92. Chow DK, Leong RW, Lai LH, et al. Changes in Crohn's disease phenotype over time in the Chinese population: validation of the Montreal classification system. *Inflamm Bowel Dis* 2008;14:536-541.
93. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology* 2004;126:1504-1517.
94. Ling KL, Ooi CJ, Luman W, Cheong WK, Choen FS, Ng HS. Clinical characteristics of ulcerative colitis in Singapore, a multiracial city-state. *J Clin Gastroenterol* 2002;35:144-148.
95. Jiang L, Xia B, Li J, et al. Retrospective survey of 452 patients with inflammatory bowel disease in Wuhan city, central China. *Inflamm Bowel Dis* 2006;12:212-217.
96. Rankin GB, Watts HD, Melnyk CS, Kelley ML Jr. National Cooperative Crohn's Disease Study: extraintestinal manifestations and perianal complications. *Gastroenterology* 1979;77:914-920.
97. Wang YF, Zhang H, Ouyang Q. Clinical manifestations of inflammatory bowel disease: East and West differences. *J Dig Dis* 2007;8:121-127.
98. Park JB, Yang SK, Myung SJ, et al. Clinical characteristics at diagnosis and course of Korean patients with Crohn's disease. *Korean J Gastroenterol* 2004;43:8-17.
99. Dobbins WO 3rd. Dysplasia and malignancy in inflammatory bowel disease. *Annu Rev Med* 1984;35:33-48.
100. Bai AP, Ouyang Q, Hu RW. Basic research on inflammatory bowel disease in China. *J Dig Dis* 2007;8:194-197.