

## Chronic rhinosinusitis in Asia



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Chronic rhinosinusitis (CRS), although possibly overdiagnosed, is associated with a high burden of disease and is often difficult to treat in those truly affected. Recent research has demonstrated that inflammatory signatures of CRS vary around the world, with less eosinophilic and more neutrophilic inflammation found in Asia compared with Europe and North America. Although in the Western world about 80% of nasal polyps carry a type 2 signature, this might be between 20% and 60% in China and Korea or Thailand, respectively. These differences are associated with a lower asthma comorbidity and risk of disease recurrence after surgery in the Asian population. As a hallmark of severe type 2 inflammation, eosinophils attacking *Staphylococcus aureus* at the epithelial barrier have been described recently; they also can be found in a subgroup of Asian patients with nasal polyps. Furthermore, the percentage of type 2 signature disease in patients with CRS is dramatically increasing (“eosinophilic shift”) in several Asian countries over the last 20 years. Establishing an accurate diagnosis along with considering the current and shifting patterns of inflammation seen in Asia will enable more effective selection of appropriate pharmacotherapy, surgical therapy, and eventually biotherapy. Determining the causes and pathophysiology for this eosinophilic shift will require additional research. (J Allergy Clin Immunol 2017;140:1230-9.)

**Key words:** Chronic rhinosinusitis, nasal polyps, phenotype, endo-type, asthma comorbidity, type 2 inflammation, eosinophilic extracellular traps

## Abbreviations used

CRS: Chronic rhinosinusitis  
CRSsNP: Chronic rhinosinusitis without nasal polyps  
CRSwNP: Chronic rhinosinusitis with nasal polyps  
EET: Eosinophilic extracellular trap  
GWAS: Genome-wide association study  
SE-IgE: *Staphylococcus aureus* enterotoxin-specific IgE

Chronic rhinosinusitis (CRS), an inflammatory condition of the nose and sinuses, is a common medical condition that affects about 11% of adults in Europe<sup>1</sup> and about 12% of adults in the United States.<sup>2</sup> CRS has a significant effect on health-related quality of life<sup>3,4</sup> and is associated with substantial health care<sup>5-7</sup> and productivity<sup>8</sup> costs. The prevalence of chronic rhinosinusitis with nasal polyps (CRSwNP) in Europe is estimated to be between 2.1% (France)<sup>9</sup> to 4.4% (Finland)<sup>10</sup> and is 4.2% in the United States.<sup>11</sup>

CRS is one of the most commonly diagnosed diseases of the upper airways not only in western countries but also increasingly in Asia. Overall, studies have indicated wide variations in the prevalence of chronic rhinosinusitis without nasal polyps (CRSsNP) and CRSwNP between Asian and European countries (Table I).<sup>1,9,10,12-17</sup> By using telephone<sup>12</sup> or face-to-face<sup>13</sup> interviews, multicenter studies from China reported that the prevalence of CRS using European Position Paper on Rhinosinusitis and nasal Polyps diagnostic criteria was 2.2%<sup>12</sup> or 8%,<sup>13</sup> respectively. The patients perceived themselves as having impaired quality of life.<sup>18</sup> Because the CRS definitions of those population-based surveys were based solely on symptomatic criteria, the self-reported prevalence of CRS might be overestimated.<sup>19</sup> Specifically, headache or migraine not related to sinusitis might be taken wrongly for sinusitis symptoms in epidemiologic studies or misdiagnosed in clinical settings.

Therefore the diagnostic accuracy of CRS needs to be increased by the addition of objective findings, either direct visualization or sinus imaging. Accurately identifying patients with CRS requires direct visualization of polyps or purulent secretions coming from paranasal sinus ostia by means of nasal endoscopy and/or polyps, air/fluid levels, and osteomeatal complex obstruction on sinus computed tomography. In 2 Korean nationwide surveys the prevalence of CRS, as defined by symptoms plus positive endoscopic findings, were 6.95%<sup>14</sup> and 8.4%.<sup>15</sup> The prevalence of CRSwNP diagnosed based on endoscopic results in the general population was 2.5%<sup>16</sup> or 2.6%<sup>15</sup> in Korea, which was very similar to the 2.7% reported in Sweden.<sup>17</sup> In China a prevalence of 1.1% was reported.<sup>13</sup>

CRS is often associated with lower airway disease, and comorbid diseases have also been recognized in Asia.<sup>20-24</sup>

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**TABLE I.** Studies documenting variation in prevalence of CRSsNP and CRSwNP between Asian and European countries

Asia/Europe	Publication year	Region/country	Population characteristics	Study design/method for assessing prevalence	Prevalence of CRS or CRSwNP (%)	Reference
Asia	2016	Eighteen major cities in mainland China	36,577 respondents	Telephone interview	2.1% CRS	12
	2015	Seven Chinese cities	10,636 respondents	Face-to-face interview	8% CRS; 1.1% CRSwNP	13
	2011	KNHANES	4,098 participants	Interview regarding nasal symptoms and endoscopic examination	6.95% CRS	14
	2016	KNHANES (2008-2012)	28,912 adults (aged ≥20 y)	Interview regarding nasal symptoms and endoscopic examination	8.4% CRS; 2.6% CRSwNP	15
	2015	KNHANES (2009-2011)	19,152 participants (aged ≥ 20 y)	Interview regarding physical examinations and endoscopic examination	2.5% CRSwNP	16
Europe	2011	Nineteen centers in 12 countries in Europe	57,128 adults aged 15-75 y	Postal questionnaire	10.9% CRS	1
	2005	France	10,033 subjects (aged ≥18 y)	A kind of validated questionnaire/algorithm (90% specificity and sensitivity)	2.1% CRSwNP	9
	1999	Southern Finland	4,300 adults aged 18-65 y	Postal questionnaire	4.4% CRSwNP	10
	2003	Skövde, Sweden	1,387 subjects (aged >20 y)	Interview regarding questions and endoscopic examination	2.7% CRSwNP	17

KNHANES, Korean National Health and Nutrition Examination Survey.

However, the incidences of concomitant asthma and aspirin-exacerbated respiratory disease in Chinese patients with CRS were low compared with those in white patients<sup>25,26</sup> and were associated with differences in the inflammatory cytokine profile.<sup>27</sup> Over a period of 12 years, the prevalence of comorbid asthma increased from 8% to 18% in a population with CRSwNP in Bangkok together with an increase in the incidence of eosinophilic polyps and *Staphylococcus aureus* colonization.<sup>28</sup>

There are limited data evaluating the disease burden of CRS in Asia.<sup>29</sup> A multicountry, cross-sectional, observational study that examined the economic burden of respiratory diseases in the Asia-Pacific region, including allergic rhinitis, CRS, asthma, and chronic obstructive pulmonary disease, demonstrated that, on average, patients were impaired for one third of their time at work and 5% of their work time was missed, which resulted in a 36% reduction in productivity. Patients with CRS most frequently visited a specialist.<sup>29</sup> Also, patients with CRS reported higher work productivity loss than other respiratory diseases in Korea, Taiwan,<sup>30</sup> and Thailand.<sup>31</sup>

## GENETIC AND EPIGENETIC CONSIDERATIONS

CRS is a complex disease; both genetic and environmental components are likely to contribute to its pathogenesis.<sup>32</sup> The presence of nasal polyposis in patients with cystic fibrosis, a common genetic disorder characterized by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, provides an important example of how genetically determined alterations can lead to the development of CRS.<sup>33</sup>

As with other common diseases, candidate gene studies or genome-wide association studies (GWASs) have been applied in the genetic exploration of CRS. A variety of cytokines, cytokine receptors, and immunity- and mucosal airway remodeling-related molecules have been associated with CRS in multiethnic populations. Among them, only 2 polymorphisms in the *IL1A* (rs17561) and *TNFA* (rs1800629) genes have been replicated.<sup>34</sup> Representative genetic and epigenetic studies conducted in patients with CRS in the Asian population are summarized in Table II.<sup>35-48</sup> Relatively few single-gene association studies in patients with CRS were performed in Asia, and no susceptibility genes and loci reported to be associated in the Asian population (*HLA*, *TGFB1*, thymic stromal lymphopoietin [*TSLP*], IL-1 receptor antagonist [*IL1RN*], *IL4*, Toll-like receptor 2 [*TLR2*], *EBI3*, matrix metalloproteinase 9 [*MMP9*], and *MMP2*)<sup>35-43,49</sup> could be replicated in another cohort. Concerning GWASs, to date, there is only one DNA pool-based GWAS performed in white patients with CRS and control subjects.<sup>50</sup> Zhang et al<sup>44</sup> tried to replicate 17 CRS susceptibility genes obtained from this study in a Han Chinese population and could only confirm 1 corresponding single nucleotide polymorphism locus (rs4504543) in the acylglyoxylase (*AOAH*) gene. This revealed the potential of a common and different genetic basis in the development of CRS in Chinese and white populations.

Other than genetics, epigenetic mechanisms offer yet another possibly more plausible explanation, focusing particularly on the ability of environmental factors to shape health and disease.<sup>51,52</sup> A recent Korean study examined genome-wide DNA methylation levels in tissue from patients with CRSwNP and peripheral blood

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