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Commentary

Is SPINK1 gene mutation associated with development of pancreatic cancer? New insight from a large retrospective study

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Patients with hereditary pancreatitis due to a serine protease 1 (PRSS1) gene mutation are well known to develop pancreatic exocrine insufficiency and diabetes in later life, and represent a high-risk group for pancreatic cancer (PC) [1]. In contrast, the natural history of acute recurrent or chronic pancreatitis (CP) patients with serine protease inhibitor Kazal type 1 (SPINK1) mutations remains controversial. The c.101A>G (p.N34S) mutation is the most common, present even in 1–2% of otherwise healthy individuals. Although an underlying molecular mechanism has yet to be identified, this variant is thought to be a disease-modifying factor that lowers the activation threshold of trypsin. The next most frequent mutation is the c.194+2T>C mutation, which has often been reported in East-Asian populations [2]. In the c.194+2T>C variant, because exon 3 encoding the trypsin-binding site is skipped due to a slicing aberration, trypsin activation cannot be inhibited, and continuous inflammation leads to CP [3]. Several reports have shown that both variants are related to increased risk of CP [4,5], but a meta-analysis revealed a lower association between SPINK1 variants and development of PC [6].

In an article in EBioMedicine, Muller and colleagues retrospectively reviewed 209 patients with SPINK1 mutations and 302 patients with idiopathic pancreatitis as controls [7]. Importantly, the cancer risk was 12-times higher in patients with SPINK1 mutations than in controls. The cumulative rates of PC before 50, 60, 70, and 80 years old were 0.8%, 11.9%, 27.7%, and 51.8%, respectively. In the >50-years-old population, these rates are similar to that in hereditary pancreatitis (HP) patients with or without PRSS1 mutation [8,9]. Since the p.N34S mutation was observed in 176 of the 209 patients (154 heterozygous patients, 22 homozygous patients), involvement of other in the development of PC would be expected. In patients heterozygous for N34S mutation with co-mutation on the cystic fibrosis transmembrane conductance regulator (CFTR) and/or chymotrypsin C (CTRC) gene, which are well described as factors facilitating CP, a tendency toward links to early-onset symptoms was seen. Further, ductal abnormalities and pancreatic calcification were observed in over 70% of patients. These results support the notion that long-term inflammation and existing CP involving hyperplasia and metaplasia of the pancreatic duct epithelium, but not the mutations by themselves, increase the risk of PC. Although the number of PC patients was small in that study (5 with heterozygous p.N34S mutation, 2 with SPINK1 deletion), the authors concluded that only p.N34S may be associated with development of PC. However, c.194+2T>C mutation may also be involved in the increased incidence of PC. In fact, heterozygous Spink1c.194+2T>C mutant mice spontaneously develop CP accompanied by the presence of protein plugs [10]. Clinicians should be aware of the risk of PC, regardless of the types of gene mutation.

An understanding of the natural history of patients with SPINK1 mutations will lead to better management, including a step-up approach and improvement of quality of life. To date, no fundamental treatments for pancreatitis related to gene mutations have been identified. A step-up strategy has become increasingly standard and applied for the treatment of patients with HP. This strategy starts with endoscopic treatment and progresses to surgery if endoscopic therapy fails or proves technically impossible. As the risk of PC was decreased in patients who underwent surgery for the treatment of CP [11], this strategy would presumably contribute to resolving symptoms and pancreatic attacks, eventually decreasing the risk of PC even in patients with SPINK1 gene mutations.

In summary, the SPINK1c.194+2T>C and p.N34S mutations coupled with other pancreatitis-related germline mutations represent risk factors for CP. To prevent pancreatic attacks and continuous inflammation, an appropriate step-up strategy treatment that leads to a decreased risk of developing PC is required. Clinicians should carefully follow-up CP patients with SPINK1 mutations, particular

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in patients showing pancreatic calcifications indicating a potentially high risk of developing PC.

Declaration of Competing Interest

The authors declared no conflicts of interest.

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