Gastric Cancer in Patients with Inflammatory Bowel Disease: More than just a Random Association?

Christian P. Selinger

Inflammatory Bowel Disease (IBD) can have a profound impact on patients' lives through direct results of intestinal inflammation and through indirect effects, which may affect other aspects of physical health and aspects of psychological well being and mental health [1, 2]. Due to the chronicity of IBD, the study of long term outcomes is paramount to understand the health care needs of patients with IBD. Naturally, it is important to understand which cancers may be associated with IBD as this helps patients understand their individual cancer risk. This may in turn influence decision making regarding immunosuppressive therapy, which may alter the risk of developing cancer due to reduced immune surveillance.

Furthermore, a good understanding of IBD related cancer epidemiology may help decisions on cancer screening or potential prophylaxis. While a statistical association between IBD and certain cancer is an important finding, we must remember that an association does not necessarily imply causation. Further detailed study is therefore needed to attempt to unravel any potential causative links. Potential causes for IBD related cancers include firstly direct effects of IBD on cancer risk. This is certainly true for IBD associated colorectal cancer where ongoing inflammation of the colonic mucosa poses the highest risk of dysplasia and/or cancer development [3, 4]. Secondly, IBD related cancers may arise as a consequence of medical conditions associated with IBD. The most common example of this type of causal relation is primary sclerosing cholangitis, which may lead to the development of cholangiocarcinomas [5, 6]. Thirdly, an association between a type of cancer and IBD may stem from a shared risk factor, for example cigarette smoking is both a risk factor in Crohn's disease and for the development of lung cancer [6, 7]. Fourthly, an associated cancer risk may stem from therapeutic interventions for IBD. Thiopurines, for example, have been associated with a significant increase in the risk of developing lymphoma [8].

Nissen et al. have examined large Dutch population-based registries to examine risk factors associated with the development of gastric cancers in patients with IBD [9]. In addition, they have investigated the clinical characteristics and disease course in comparison to gastric cancer patients from the general population [9]. By using cases from the nationwide PALGA registry of cyto- and histopathology results they identified 59 patients with IBD and gastric cancer. Using the cases identified by this robust methodological approach they performed two case control studies. The first study compared these cases to controls from the well-described and researched IBD South Limburg Cohort. The main findings were that cases were more likely to suffer from ulcerative colitis rather than Crohn's disease. Furthermore, cases were significantly older at IBD diagnosis than controls [9].

These findings are of great interest as they go some way in helping us understand direct causality. A direct link through IBD-related inflammation seems unlikely to contribute to gastric cancer development in IBD as ulcerative colitis in contrast to Crohn's disease can by definition not affect the stomach. The shorter exposure time to IBD also hints that there may not be a direct causal link between IBD and gastric cancer as controls were exposed to IBD risk factors for a much longer time period than cases. The main risk factor for gastric cancer in the general population is infection with Helicobacter pylori [10]. The incidence of Helicobacter pylori infection is however, significantly lower in IBD patients in general and in the South Limburg cohort [9, 11]. The second case control study compared the 59 IBD gastric cancer cases to controls with gastric cancer from the general population from the
Eindhoven Cancer registry. Gastric Epstein-Barr virus (EBV) infection has also been proposed as a mechanism involved in the development of gastric cancers in the general population [12]. In theory, this risk factor might be more relevant for IBD, as immunosuppressive therapy with thiopurines can impair the response to EBV. In his study, however, Nissen et al. found no increase in infection with EBV compared to general population controls [9]. As such, the study has reassured us that a number of common causes for gastric cancer in the general population are not key risk factors for the development of gastric cancer in patients with IBD.

In contrast to a previous study showing no difference in survival after gastric cancer diagnosis between IBD cases and controls [13], Nissen et al. found that IBD cases had significantly impaired survival [9]. Cases matched with controls for TNM stage and confounders had a hazard ratio of 1.35 (95% confidence interval 1.023-1.875). A major concern for clinicians when tasked with achieving or maintaining IBD symptom control is the role of IBD therapy after a cancer diagnosis. For both thiopurine and anti-TNF therapy, caution is usually advised as they interfere with the immune surveillance of established cancers. Nissen et al. addressed this issue with a subgroup analysis. While they found no difference in survival between IBD patients on immunosuppressive therapy after gastric cancer diagnosis compared to those without, the numbers are too small to draw any firm conclusions from this [9]. The main reason for the impaired survival of gastric cancer patients with IBD compared to those without, remains unclear.

While the overall incidence of gastric cancer does not significantly contribute to mortality from IBD [6], the relationship between gastric cancer and IBD remains incompletely understood. Further studies on the incidence are required to understand the magnitude of the problem and studies on risk factors may shine light into any possible causative links. It remains to be established whether the association between gastric cancer and IBD is random or potentially causal through direct IBD effects, associated co-morbidities, shared risk factors or IBD therapies.

Conflicts of interest: C.P.S. has received unrestricted research grants from Warner Chilcott and Abbvie, has provided consultancy to Warner Chilcott, Dr Falk, Abbvie, Takeda and Janssen, and had speaker arrangements with Warner Chilcott, Dr Falk, Abbvie, MSD and Takeda.

REFERENCES