Background: Inflammatory bowel diseases (IBDs) are a result of interactions between luminal pathogens and the intestinal immune response. Cyclooxygenase-2 (COX-2) plays a key role in the regulation of the inflammatory response upon stimulation by luminal pathogens via Toll-like receptors. Methods: Genotypes of the COX-2/PTGS2/PGHS2 A-1195G (rs689466), G-765C (rs20417), and T8473C (rs5275) polymorphisms were assessed in a Scottish and Danish case–control study including 732 Crohn’s disease (CD) cases, 973 ulcerative colitis (UC) cases, and 1157 healthy controls using logistic regression. Results: Carriers of the COX-2 A-1195G variant allele had increased risk of UC (odds ratio [OR], 95% confidence interval [CI] = 1.25 [1.02–1.54], P = 0.03) and of both UC and IBD among never smokers (OR [95% CI] = 1.47 [1.11–1.96], P = 0.01 and OR [95% CI] = 1.37 [1.06–1.77], P = 0.02, respectively). Furthermore, this variant genotype was associated with increased risk of diagnosis of UC before age 40 years and with extensive UC (OR [95% CI] = 1.34 [1.11–1.62], P = 0.002 and OR [95% CI] = 1.32 [1.03–1.69], P = 0.03, respectively). Conclusions: COX-2 A-1195G polymorphism was associated with the risk of UC, especially among never-smokers, suggesting that low activity of COX-2 may predispose to UC. Our results suggest that inclusion of smoking status may be essential for the evaluation of the role of genetic predisposition to IBD.