ColoRectal cancer (CRC) is a major health concern ranking as the second leading malignancy with the highest incidence in Portugal in both genders. Nonsteroidal anti-inflammatory drugs (NSAID) where shown to exert their anti-inflammatory and anti-tumor activities through the suppression of cyclooxygenase (COX) enzymes. The inducible isoenzyme, COX-2, was found to be overexpressed in approximately 85% of colorectal adenocarcinomas, contributing to key steps in tumor development. The general aim of this thesis was to understand the influence of three COX-2 polymorphisms, previously associated with the development of colorectal tumors as systematically reviewed, on the genetic susceptibility for CRC in a Northern Portuguese population.

We conducted a hospital-based case-control study involving 373 participants: 117 consecutively enrolled CRC patients and 256 healthy individuals without any clinical evidence of cancer. The -1329A>G, -899G>C and *429T>C COX-2 polymorphisms were characterized through PCR-RFLP or Real-Time PCR allelic discrimination techniques.

Our findings revealed an interesting synergistic interaction between the -1329A>G polymorphism and smoke consumption in men that was translated in a 9-fold increased risk for CRC onset. Furthermore, these individuals, men ever-smokers carrying the -1329G allele had an earlier onset of disease, with CRC diagnosis anticipated by seven years compared with -1329AA genotype carriers.

The -1329A>G COX-2 polymorphism appears to modulate the genetic susceptibility for CRC onset, especially in men ever-smokers. This genetic profiling based higher-risk group definition may help shift the balance between risk and benefits for the use of COX-2 inhibitors in chemoprevention that is currently hampered by the adverse gastrointestinal and cardiovascular side effects.