



**Karolinska  
Institutet**

**Institutionen för Molekylär Medicin och Kirurgi**

# **CYP2W1 in colorectal cancer – aspects of risk, prognosis and future treatment options**

**AKADEMISK AVHANDLING**

som för avläggande av medicine doktorsexamen vid Karolinska  
Institutet offentligen försvaras i Nanna Svartz Auditorium,  
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av

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## ABSTRACT

Colorectal cancer (CRC) is a common disease and a major cause of cancer related death globally. Prognosis is rather good in early stages but worse in cases with disseminated disease. There is a constant need of developing all treatment modalities, which also has been done over the last decades. There are needs to find predictive markers in order to assess who will and who will not benefit of chemotherapy, just as there are needs to develop drugs targeting novel pathways and proteins prevalent in primary tumors and metastases. CYP2W1 is a member of the cytochrome P450 superfamily of enzymes with unknown physiological functions but found to have the capacity to metabolize both carcinogens and various other xenobiotic substances. It is expressed in fetal rat colonic tissue and in human colorectal tumors, but not to our knowledge in any adult normal human tissue. CYP2W1 expression, both mRNA and protein, has previously been studied in a material consisting of about 50 colorectal tumor samples.

We wanted to investigate the extent of CYP2W1 expression in a larger tumor material using immunohistochemistry. We found it also interesting to see if CYP2W1 expression affects prognosis. Another aim of the thesis was to assess the association between polymorphism in the *CYP2W1* gene and risk to develop CRC. A last aim was to evaluate the CYP2W1 expression in metastases.

For the first aim, we used three different patient cohorts, two of which were derived from a randomized Nordic trial aiming to compare no adjuvant versus adjuvant treatment in patients with stage II and III CRC. These cohorts consisted of 162 and 235 patients respectively. The third patient cohort consisted of 96 patients being resected for liver metastases from CRC. All tumor manifestations in these patients were investigated with immunohistochemistry, addressing both the first and the last aim, and the findings indicate that CYP2W1 is expressed at high levels in between 26-36% of the primary tumors. It is expressed in about one third of lymph node metastases and almost half of the liver metastases.

We performed two investigations regarding CYP2W1 as a prognostic factor using the two cohorts from the Nordic study (n=162 and n=235). In the first study, high CYP2W1 expression was of independent prognostic value for poor survival together with stage. In the second study aiming to reproduce this, the result was not as clear-cut, CYP2W1 was of prognostic value only in multivariate analysis but not in univariate analysis. In the subgroup of patients with stage III CRC (n=132), CYP2W1 expression was of independent prognostic value.

The third aim was addressed using a material of DNA from individuals in a large case-control study aiming to investigate various polymorphisms and their relation to CRC risk. DNA from 1785 CRC patients and 1761 control subject was analyzed regarding three *CYP2W1* variants. We also experimentally assessed enzymatic activity of the gene products of the variants studied. No difference was seen, neither in CRC risk between cases and controls, nor in enzymatic activity between the three variant proteins.

In conclusion, CYP2W1 seems to be expressed in about one third of primary CRC and half of the liver metastases. The association with prognosis in CRC requires further studies to be elucidated. Genetic polymorphism in the *CYP2W1* gene does not seem to have any impact on CRC risk.

The tumor specific expression of a catalytic enzyme in CRC and metastases is interesting in the aspect of future targeted anti-cancer therapies.