Research Fellowship Scheme

F3 - Establishing a Best Panel of Stool-based Detection for Non-invasive Colorectal Neoplasm Screening

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Introduction and Project Objectives: Colorectal cancer (CRC) screening can facilitate successful treatment and reduce cancer incidence. We aimed to establish stool-based multitarget tests to improve colorectal neoplasm screening by involving our previously identified CRC-associated miRNAs (reflecting changes in host cells) and bacterial markers (reflecting environmental risk factors).

Methods: Multiplex TaqMan probe-based qPCR for bacterial markers (Fusobacterium nucleatum (Fn), Bacteroides clarus (Bc), Clostridium hathewayi (Ch), a Lachnoclostridium sp. 'm3' and an undefined species 'm7') and multiplex MGB probe-based RT-qPCR for miRNAs (miR92a, miR135b, miR21, miR145 and miR133a) were established. Stool samples from 698 subjects, consisting of 203 patients with CRC, 207 patients with adenoma (120 advanced adenoma (AA) and 87 non-advanced adenoma (NAA)) and 288 normal controls, were tested. Statistical modelling to employ these markers with/without fecal immunochemical test (FIT) was conducted using logistic regression (LR), multinomial logistic regression (mLR) and random forest classification, with best subsets regression and cross validation where appropriate. Diagnostic performance of the new models were assessed.

Results: With conventional cutoff at 100 ng Hb/mL, FIT detected 72.3%, 17.9% and 0% of CRC, AA and NAA respectively although at superior specificity of 99.5%. Without FIT, combining 4Bac (Fn, m3, Bc and Ch) and 3 miRNAs (miR92a, miR145 and miR135b) by mLR model showed sensitivities of 89.9%, 44.6% and 45.6% for CRC, AA and NAA respectively at 84.8% specificity. Bacterial markers (Fn, m3, Bc, Ch) combined with FIT by LR model showed sensitivities of 94.4%, 44.1% and 38.4% for CRC, AA and NAA respectively at 84.7% specificity. miRNAs (all five) combined with FIT by LR model showed sensitivities of 90.2% for CRC and 43.3% for AA at 80.3% specificity, although not satisfactory for NAA. Models involving all three types of markers showed further improved diagnostic performances. The mLR model involving 4Bac (Fn, m3, Bc, Ch), 3 miRNAs (miR92a, miR145, miR135b) and FIT detected 96.9%, 48.2% and 43.0% of CRC, AA and NAA respectively at 84.8% specificity. The random forest classifier involving 2Bac (Fn, m3), 4 miRNAs (miR92a, miR21, miR135b, miR133a) and FIT showed sensitivities of 94.3%, 46.4% and 46.8% for CRC, AA and NAA respectively at 84.8% specificity.

Conclusion: The combination of fecal bacterial and miRNA markers increases the sensitivity for colorectal neoplasm detection, and could be easily implemented with FIT. This study provides marker panels and corresponding modelling methods, involving fecal bacterial and miRNA markers with or without FIT, for clinical implementation to improve colorectal neoplasm screening.

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