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Commentary

Less Invasive Screening for Colorectal Cancer by Microbiota Analysis: Is it a Reality or an Illusion?

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Colorectal cancer (CRC) is the second leading cause of cancer death, and accounts for approximately 9% of cancer deaths. Approximately one in three people diagnosed with CRC die of this disease in the five years after diagnosis. The most effective way to reduce mortality is to detect precancerous adenoma in an early stage. Removal of premalignant adenomas can prevent the cancer and removal of localized cancer may prevent CRC-related death.

Most colorectal cancers arise from adenomatous polyps that progress from small to large polyps and then to cancer. The progress from adenoma to carcinoma is believed to take at least 10 years on average, although is imprecise because polyps are ordinarily removed when found. Older tests, including guaiac-based fecal occult blood tests, flexible sigmoidoscopy, double-contrast barium enema, and colonoscopy with direct visualization have been recommended as screening options for many years. (Winawer et al., 1997) However a substantial proportion of the population has not undergone CRC screening, due to health seeking behaviors, public resources, healthcare accessibility and limitations of the screening tests. Conventional colonoscopy carries a small procedural risk, whereas flexible sigmoidoscopy is not effective in reducing proximal cancers (Schoen et al., 2012). Stool-based occult blood tests have a moderate sensitivity to detect CRC as a population-based screening test, with a sensitivity of 69–86% for the fecal immunochemical test (FIT). Nevertheless, it has a low sensitivity for advanced adenoma (Haug et al., 2010). An accurate, non-invasive test with high sensitivities for both CRC and advanced adenoma is highly desirable.

The advent of 16S rRNA-based analyses has allowed investigation of the human colonic microbiota at the level of phylotypes and bacterial species (Shen et al., 2010). It has become well established that host-associated microbial communities, termed microbiota, play integrated roles in modulating various aspects of host physiology (Nakatsu et al., 2015). This includes host process such as cellular metabolism and immune function that become highly dysregulated during carcinogenesis. However sequencing-based methods are more resource-consuming and affectable by many factors in library construction, sequencing platform. Therefore, mining the crucial factors/microbes in fecal microbiota and developing cost-effective, easy-to-apply methods are essential. This includes *Fusobacterium nucleatum* which is able to promote colorectal carcinogenesis (Kostic et al., 2013), whereas over-representation of other species from the *Peptostreptococcus* and *Parvimonas* genera have also been observed (Feng et al., 2015). Nevertheless, the potential utility of these microbial biomarkers in detecting colorectal neoplasia remains underexplored.

In *EBioMedicine*, Xie et al. have done a very interesting research using a novel biomarker based on fecal *Clostrisium symbiosum* to improve the detection of early and advanced colorectal cancer (Xie et al., n.d.). They measured *Clostrisium symbiosum* by qPCR in 781 cases including 242 healthy controls, 212 patients with colorectal adenoma (CRA), 109 patients with early CRC, 218 patients with advanced CRC. Significant stepwise increase of *Clostrisium symbiosum* was found in CRA, early CRC and advanced CRC ($p < 0.01$). The combination of *Clostrisium symbiosum* and FIT achieved the highest performance (AUC = 0.83 for development cohort and 0.707 for validation cohort). They concluded that fecal *Clostrisium symbiosum* is a novel biomarker for early and non-invasive detection of colorectal neoplasia, being more effective than reported markers such as *Fusobacterium nucleatum*, FIT and CEA. Combining the abundance of *Clostrisium symbiosum* and FIT may further improve the noninvasive diagnosis of early CRC.

In addition, the cost of the screening test is an important factor to consider when it is used as a screening modality for population-based programmes. A FIT kit costs an average of US$26 (Wong et al., 2015). While the commercial multitarget stool DNA costs over US$600 and may not be cost-effective for a screening setting (Ladabaum & Mannalithara, 2016), the addition of a single marker *Clostrisium symbiosum* may substantially reduce the cost. Hence, an incremental cost-utility analysis, taking into account the higher cost yet enhanced performance should be performed, so as to inform clinicians and policy makers. Besides, the affordability and acceptability of patients and physicians will need to be explored in future studies. Nevertheless, such relatively simple approach to add a single microbial marker will enhance the clinical applicability. Such studies take one step further towards a non-invasive, potentially more accurate and affordable diagnosis of advanced colorectal neoplasia.

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Disclosure

The author declared no conflicts of interest.

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