Editorial

New frontiers in fecal immunochemical and other fecal tests in colorectal cancer screening

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Introduction: colorectal cancer (CRC) and fecal immunochemical test for hemoglobin

Since 1993, fecal immunochemical tests for hemoglobin (FIT-Hb) have been used as an initial test in CRC screening programs (1,2,3) and a large amount of data have supported the efficacy of this strategy to reduce CRC mortality (3,4). In addition, new evidence of a reduced CRC incidence in subjects enrolled in long term screening programs comes from about 2,000 reports (4,5). The 'cost-effectiveness' of CRC screening programs are related to cost, advantages and harms and overall compliance of the target population together to organizational and institutional considerations, therefore it is difficult to evaluate this cost in detail. Nevertheless, several factors indicate the FIT based strategies as the most effective non-invasive investigation for CRC screening (6,7). Importantly, after that the European Union Guidelines have suggested the adoption of FIT-Hb screening in the European Community in 2010 (8), a lot of countries have started population screening programs and a growing interest in both analytical and clinical aspects of FIT was observed worldwide. Today, there are two main fields of research regarding FIT–Hb based CRC population screening.

Gastrointestinal bleeding detectable by FIT-Hb

The first research topic is related to interesting biological aspects that consist in the transition from 'pre-neoplastic' to 'malignant' lesions and the detection of gastrointestinal bleeding during 'pre-neoplastic' and/or inflammatory process. Indeed, detectable Hb concentrations can be found in the gastrointestinal tract, not only in neoplastic lesions, but also in 'pre-neoplastic' adenoma, hyperplastic polyps, diverticular disease, hemorrhoids, intestinal inflammatory process and in a significant number of participants with normal bowel on colonoscopy. Recent evidence indicates an increased individual CRC risk when detectable Hb levels with current FIT-Hb analyses are detectable.

The biological significances of low amounts of bleeding are not fully understood and Hb values below the cut-off used in FIT-Hb based screening programs (most frequently 20 µg Hb/g feces) are rarely associated to lesions detected by colonoscopy (9). But, the consequences of such gastrointestinal bleeding detectable by FIT-Hb are clearly reported in literature (10). The study of Grobbee *et al*. (11) should be considered in this context because it confirms the importance of fully understand the meaning of low fecal Hb concentrations and it addresses the specific related risk in individuals screened population in order to 'customize', for the single participant, the fecal Hb results obtained over sequential rounds of the screening. The value of finding a Hb value between the detection and decisional limits (reliable concentrations under selected the applied cut-off) consists in the identification of a sub-group of participants with an increased risk of developing CRC in subsequent years.

Epidemiological data have confirmed the close

associations of gastrointestinal bleeding with neoplastic risk, supporting to the concept of stratifying the risk of single individual participating in screening program. In particular, the study of Carrera *et al.* (12) found an increased risk of developing CRC in the years subsequent a negative colonoscopy into a cohort of participants with fecal Hb concentrations over the 'cut-off', applied in the screening program, and without detectable lesions at colonoscopy. It is known that a significant number of CRC are not detected by screening programs and during colonoscopy, hence, the investigation of interval cancers between subsequent screening rounds can offer an estimate of undetected neoplasms in a specific screening program. However, the number of undetected CRC in this kind of cohort seems to be too high to support epidemiological results on the bases of incomplete or incorrect colonoscopies.

Interestingly, a large multicenter case-control study on fecal DNA reports an increased sensitivity for 'pre-cancerous' lesions in proportion to lesion size from 57% for lesions >1 cm to 83% for those >3 cm, confirming the data on fecal Hb concentrations and severity of colorectal disease (13). Therefore, the increased risk to develop CRC seems to be related to the gastrointestinal 'bleeding' and the pre-malignant lesions more than to the neoplasms being undetected during colonoscopy. This significant epidemiological evidence must be considered to better address the frequency of FIT sampling in individuals. Medium and high-risk cohorts could have different intervals of FIT sampling or different control strategy, set overall by the screening programs in order to reduce the interval cancer proportion and optimize outcomes (14). As affirmed in 'Gut': development of a screening algorithm that combines FIT concentrations with other risk indicators (age, sex, screening history, deprivation) may enable improved clinical outcomes within the same colonoscopy resource and sets this concept as one of the main current topics in CRC screening (15).

Pre-analytical and analytical aspects of FIT-Hb

The second significant topic on FIT-Hb methods is strictly related to the method performance and characteristics of fecal tests and directly involves the sampled materials. The effectiveness of FIT based screening arises from two main advantages: the high compliance (high rate of uptake in the population invited to CRC screening programs), a major issue in population screening, and the possibility of 'determining a cut-off appropriate for the available colonoscopy resources' (15). High compliance with FIT is directly related to the initial materials used for the investigation, including the requirement only to sample one fecal sample into a simple to use, hygienic specimen collection device. The possibility to select subjects at higher risk, starting with a non-invasive and self-sampled material is probably the main reason for the high uptake recorded as compared to other CRC screening strategies, such as flexible sigmoidoscopy, or other organized screening programs based on laboratory investigation operating in Italy (16). The use of postal delivery (17), under controlled conditions, can avoid the inconvenience of delivering materials to specific collecting sites and can assure an optimum uptake, together with a higher analytical quality of the estimation of the fecal Hb concentration. The positive effect of the use of a self-sampled biological material is 'unconventional' in the laboratory of medicine setting, but, can be somewhat negated by significant problems caused by lack of knowledge and consideration of the effects of the sampled material on the specimen collection, handling and the analytical technique.

The importance of the sampling phase and the effects of feces consistency were pointed out some years ago by Fraser *et al.* (18), generating the second important research topic for the FIT-Hb, mainly addressed to the laboratory and the analytical aspects. Pre-analytical effects on FIT-Hb measurements involve a number of different items. Indeed, the interaction of fecal materials with sample collection devices (design of the specimen collection probe) can affect the amounts of feces collected during self-sampling (19). The adoption of a correct metrological strategy (μg Hb/mL faces) (20) to indicate the amount of material collected by different sampling devices can also cause significant progress to be made in the understanding and addressing sampling variability and the overall pre-analytical sources of variation. Whereas, the stability of the Hb which in the specimen collection devices are strictly related to the buffer composition, presence of stabilizers and preservatives (21). In this context, it is relevant to remember that the compositions of buffers are covered by manufacturers' licenses. Finally, the ionic strength and the pH of the buffer in the device can change after addition of the sampled fecal materials. These changes can affect the final results because of factors related to the capability of buffers to reduce the changes and the overall amount of feces added to the device (22).

All these aspects of the pre-analytical and analytical phases of FIT-Hb should be fully addressed to control

the overall variability of results allowing comparison of the Hb concentrations across geography and methods elimination the necessity to perform complex and expensive epidemiological investigation to determine the appropriate cut-offs for the available colonoscopy resources (17,23). This topic, together with other analytical aspects, is the subject of work, since January 2017 (23), by a Working Group of the Scientific Division of the International Federation of Clinical Chemistry and Laboratory Medicine and it has been extensively studied by the Italian SIBioC-GISCoR Working Group (Italian Society of Clinical Biochemistry and Clinical Molecular Biology—Italian Colorectal Screening Group) since 2014 (24).

Newer fecal tests

Although related to malignancy, the presence of Hb in gut cannot be considered 'cancer specific' and other new analytical methods should be developed to improve the performance of CRC screening programs. In 2014, the Food and Drug Administration (FDA) has approved a fecal DNA method as a screening test for CRC; a composite test that includes an immunochemical assay, similar to the one used in FIT, plus methylated markers and molecular mutations markers associated with CRC. Previous multicenter studies comparing fecal DNA test to FIT using colonoscopy as the gold standard showed that the fecal DNA test had a higher sensitivity than FIT for detecting CRC (92% *vs.* 74%), adenomas with high-grade dysplasia (69% *vs.* 46%), and serrated sessile polyps (42% *vs.* 5%) (24). Nevertheless, the high cost and the low specificity of this fecal DNA test (87–90%, compared to 95–96% of FIT-HB) (25) make the introduction of the test expensive in population screening, whereas DNA analysis can represent a most interesting strategy to improve the performances of the CRC screening.

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