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Patient Early-Risk Assignment: A Rational Approach to Personalized Medical Cancer Prevention

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Short Communication

The cancer burden is projected to increase in Europe from 3.6 million cases in 2015 to 4.3 million cases in 2035; an annual increase of approximately 20% or roughly 716,000 new cases. This anticipated trend is due partly to population aging and growth, and partly to lifestyle changes with increasing prevalence of risk factors, such as tobacco, obesity and physical inactivity. Colorectal cancer (CRC) is a life-threatening disease with high-incidence, -morbidity, and -mortality. What is worse, because of demographic and life-style changes, incidence of CRC is forecasted to grow dramatically. In Europe alone, the number of new cases is expected to rise by 30% from 447136 patients in 2012, to 582545patients by year 2035 [1].

Overall, the economic, societal and personal burden of CRC is staggering, and it is only set to worsen in the future. In spite of the latest improvements in diagnostic techniques and the introduction of molecular targeted treatments, approximately 40% of CRC patients will still eventually die from their disease, essentially due to development of drug resistance. The way this problem has been addressed so far has been to develop novel therapies that are based on our ever-increasing knowledge of tumor biology. Unfortunately, this approach has proven itself very challenging, costly and with limited success [2]. The growing burden of CRC will eventually threaten the sustainability of our health care systems, and the only realistic way to manage it, is by complementary efforts on treatment and prevention, in particular through the introduction of preventive medical intervention in patientsthat had pre-malignant colorectal lesions (high-risk adenomas) removed, but is still at high risk of future CRC development.

The Case for Early Detection of CRC

Adenomatous colonic polyps (adenomas) are the earliest recognized pre-malignant lesions of CRC. Screening and a surveillance colonoscopy program can largely avoid the morbidity and mortality associated with CRC by colonoscopic removal of pre-malignant adenomas or by early detection of CRC at a curable stage. At present, there is a severe lack of evidence-based knowledge about the risk of adenoma patients to develop CRC with time. We know that patients who have low-risk adenomas removed have a moderately lower risk of CRC related mortality as compared to the general population. Conversely, patients who had had high-risk adenomas removed show moderately higher risk of CRC related mortality as compared to the general population. These data support the notion that patients who have had a high-risk adenoma removed, remain at increased risk of later CRC development [3].

Current international guideline recommendations assign patient risk to low- or high-risk of later CRC development- based on size of the adenomas, number of adenomas and histological type (villous or tubular growth pattern with the serrated lesions now being added), and grade of dysplasia. However, several studies have shown a dangerously low inter-observer agreement between pathologists when risk-classifying adenoma samples [4]. In addition, the majority of high-risk adenoma patients will never present with CRC. Consequently, because the number of adenomas currently detected is very high (40%of all referrals to endoscopic examinations in areas with FIT testing whereof approximately one-fourth are classified as intermediate or high risk according to current guidelines) it is very important to identify those few (5-10 %) that are at true high risk of developing CRC. Thus, new and more precise molecular stratification methods for CRC risk in adenoma patients are greatly needed. But identifying those patients with high risk adenomas that will develop CRC is just the first step. We also need to be able to offer these patients a plausible and practical course of action, such as preventive cancer medicine. One example of preventive cancer medicine that works in CRC are non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin.

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Recent analyses of published data from 51 randomized controlled clinical trials concluded that aspirin use significantly reduced colorectal cancer incidence (25% reduction), as well as in-trial cancer deaths by nearly 40% from five years and onwards of aspirin intake [5]. Moreover, several randomized controlled trials (RCT) have also proven the effectiveness of NSAIDs such as cyclooxygenase-2 (COX-2) selective inhibitors (celecoxib or rofecoxib) or aspirin in preventing colorectal adenomas [6-8]. Unfortunately, all of these drugs are associated with important cardiovascular events and gastrointestinal harms. Given the patient setting, the use of any agent as chemo preventive for CRC will necessitate a favorable balance of benefits and risks. One way to shift the balance is with the use of predictive biomarkers. Should one be able to pinpoint those patients who will have most to gain from treatment, then the benefit could exceed the harms.

Future Perspectives

The path to take is now clear. We have the possibility to make major inroads in the management of CRC, but we lack some pieces of the puzzle. To address some of the issues we pointed out previously, we took an experimental approach implementing five independent but interconnected investigational lines:

1. We will establish a novel molecular classification of adenomas, which will allow for an objective and more precise risk stratification of the individual adenoma patient. Moreover, this classification will allow us to identify those individuals that should receive medical preventive treatment.DNA sequencing and proteomic analysis of high-risk adenomas are currently ongoing, and we expect to derive a molecular signature for risk of later cancer development. In this manner we can define true high-risk early lesions, amenable to medical intervention, such that we can block progression from benign to malignant lesions.

2. We are also in the process of validating predictive biomarkers for identification of patients bearing high-risk early lesions that will respond to aspirin. In this way we will not only identify a target group of patients that have a real need for preventive treatment, but we will also be able to select those patients that will respond, in a true personalized medical prevention setting.

3. Pharmacoepidemiological studies (using the Scandinavian Prescription Registries and Cancer Registries) are ongoing to identify additional current drugs that can be used in a preventive setting to prevent the re-occurrence of new lesions in those citizens bearing high-risk adenomas.

4. We are currently establishing a pre-clinical model that mimics the human adenoma to carcinoma progression process. The goal is to find an animal model that closely resembles the human CRC disease and molecular profile, which we can derive from comparative analysis from genomic and proteomic data of mouse and human adenoma and carcinoma tissue.

5. In collaboration with other research groups we will establish chemical libraries based around drugs identified in investigational line 2 that we can test in our model system for efficacy and toxicity.

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