

Colorectal cancer screening and survival

It is difficult to resist the undeniable allure of screening as a means to diagnose common, potentially serious diseases before their natural history reaches an incurable stage. Colorectal cancer (CRC) is a classical example where the benefits seem to be within reach: we have technologies available that allow its diagnosis before symptoms or signs develop, at a reasonable cost, and using methods acceptable by a significant percentage of the population.

Interest in CRC screening is not recent. The first controlled clinical trials, which were performed in the United States and Europe (1-3) in the 1970s and 1980s, showed that guaiac-based fecal occult blood testing (FOBT) reduced CRC-related mortality by 15-33%. Bearing this evidence in mind, the Council of the European Union recommended in 2003 that member states should implement FOBT-based CRC screening programs for both men and women between 50 and 74 years of age (4).

While the importance of early diagnosis and treatment cannot be downplayed, screening inevitably involves exposure of asymptomatic people to the risks inherent in any medical procedure. Complex interactions between multiple variables, dependent both on the potential users and the health care system involved, condition results and must be acknowledged and evaluated before implementation. Amongst other factors, lack of population awareness, healthcare access inequalities, and deficient scientific-technical quality in the provision of services, aspects that are currently highly dependent on difficult-to-standardize human factors, may lessen or cancel out screening benefits.

Regardless of screening test, colonoscopy is the key procedure to confirm the diagnosis of, and to treat, most identified neoplasms. Multiple studies have shown that the endoscopist's skill in examining the mucosa, knowledge about neoplasm identification and characterization (5), and ability to make rational decisions on the best way to manage and follow up lesions are highly variable and relevant aspects that impact both clinical outcomes (6-8) and resource use efficiency (9). Obviously, while not a part of the screening process proper, quality in the performance of surgical procedures and suitability in the selection of cancer treatment and monitoring modality also have a key impact on outcome. Challenges to achieve excellence in each of these areas are formidable, and major controversies remain regarding the best screening approach.

Despite consideration of colonoscopy as the most sensitive procedure for the detection of colorectal neoplasms, evidence on its role in secondary prevention remains incomplete. Higher technical complexity, risks, and costs, together with limited acceptance when compared to other non-invasive tests, restrict its use in this setting. Controlled clinical trials have shown that sigmoidoscopy diminishes both the incidence of CRC and CRC-related mortality (10-13) and in our setting colonoscopy-screened subjects in the COLONPREV (14) clinical trial had a significantly higher proportion of advanced adenomas and neoplasms as compared to those who took part in the first round and underwent screening with immunological FOBT. However, the proportion of cancers per invited subject in the intent-to-screen analysis, a perspective particularly relevant from a population standpoint, was similar in both groups. Although resection of low-risk adenomas has been associated with a reduction in CRC risk (15), the relevance of colonoscopy's greater sensitivity in the identification of non-invasive neoplasms in the context of population screening programs remains to be established.

In the present issue of *The Spanish Journal of Gastroenterology (Revista Española de Enfermedades Digestivas)*, Cienfuegos et al. (16) retrospectively analyze the effect of opportunistic screening with colonoscopy on survival in a large series of patients with non-metastatic colorectal cancer who underwent surgery in a reference center. Their results show that patients diagnosed within the screening program had earlier-stage tumors and a lower proportion of lesions with adverse histopathologic markers. Along the same lines, the finding that the percentage of patients with relapsing lesions detected by follow-up also was significantly lower among screened subjects (7.2% vs 20.9%; OR: 0.294; 95% CI: 0.17-0.48, $p < 0.01$), thus confirming improved clinical outcomes in this group, is likewise positive.

The study's primary endpoint, disease-free survival at five and ten years, was also clearly superior in the screened group (HR 2.93, 95% CI: 1.82-4.72; $p < 0.01$), a favorable difference that persisted even following stage adjustment between both groups. Thus, patients diagnosed with stage III by the screening program had a 5-year disease-free survival of 79.1%, significantly higher than 61.7% as obtained for patients diagnosed with stage III disease after symptom onset (HR 2.14; 95% CI: 1.09-4.19; $p = 0.02$).

This improved stage-adjusted survival rate among screened patients, also identified in other studies (17-20), points however to the presence of additional underlying determinants, which in spite of being less obvious clearly play a prog-

nostic role. As the authors appropriately suggest, at least part of these differences may be accounted for both by potential differences in the previous health status of the two populations, and by the well-known biases inherent in screening itself. Survival measures time elapsed from diagnosis, hence the latter's shift to the presymptomatic period increases survival length. Because of this "lead-time bias," even in cases where ineffective therapy fails to modify the condition's natural outcome, screening will prolong disease awareness for both patients and doctors, thus faking increased survival. Furthermore, a neoplasm's own behavior may influence the odds of its being identified by the screening procedure, which is known as length-time bias. In this case, tumors with mutations that condition a poorer clinical outcome may have a greater impact on intestinal function or invade other organs, thus inducing signs or symptoms earlier in the course of disease. In contrast, neoplasms with a slower evolution, hence with a potentially better prognosis, may have a longer natural history with lengthier asymptomatic periods and a greater likelihood of detection by screening. In the latter scenario, overdiagnosis may become an undesirable screening result, since individuals with less clinically relevant neoplasms, which might not condition their vital prognosis or quality of life, become exposed to therapy-related risks.

However, a comparative analysis of mortality rates between screened and non-screened populations, which requires extremely complex, long-term studies, allows to assess screening results without the biases associated with a survival analysis. The annually screened population with guaiac-based FOBT in the Minnesota Colon Cancer Control Study showed a CRC-related mortality rate that was 32% lower than the control group's after 30 years of follow-up (21). Similarly, the population biennially screened with a similar test in the Nottingham study also had its CRC-related mortality rate reduced by 13% after 20 years of follow-up (22). While, admittedly, none of these studies showed a decrease in all-cause mortality, both confirm that screening benefits are real and persist long-term. Although not a screening study, hence its results must be cautiously interpreted, patients with endoscopically resected adenomas in the *National Polyp Study* (23) had a death rate that was 53% lower than the reference population's after a mean follow-up of over 15 years. The long-term follow-up of patients included in the COLONPREV and CONFIRM clinical trials (24), comparing the impact of screening with immune FOBT and with colonoscopy on CRC-related mortality, will provide new evidence on which of these options is more effective in the upcoming years.

CRC screening will no doubt remain a highly relevant subject over the next few years. The warranted optimism that results from the pervasiveness of population screening programs should detract interest neither from their assessment and a critical analysis of their benefits, risks, and actual costs, nor from the potential identification of areas in need of improvement and the development of technologies and processes to refine their results.

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