Original-Titel

CRC Incidence versus Prevalence: How should incidence be defined?

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Brenner et al, When gold standards are not so golder: prevalence bias in randomized trials on endoscopic colorectal cancer screening. European J Epidemiology; https//doi.org/10.1007/s106654-023-01031-2

Kommentar

Prof. David Lieberman MD, Portland, 12.12.23

Colorectal cancer (CRC) screening of average-risk individuals can reduce both CRC incidence and mortality. Worldwide, the most commonly used screening tests are fecal immunochemical test (FIT) and colonoscopy. Mortality is reduced due to early CRC detection as well as prevention, by detection and removal of precancerous polyps. Incidence reduction may be due to many other factors aside from screening. Such factors include reduction in smoking, increased use of aspirin and non-steroidal anti-inflammatory drugs which may be chemopreventive, and the use of hormone replacement therapy in women over 30-year period, until use was discouraged due to adverse events. A dramatic decline in CRC incidence has been noted since the 1980's, albeit more dramatic since 2000, with increased use of screening.

Based on cohort studies, invasive screening with colonoscopy should be associated with significant incidence reduction due to polyp removal and cancer prevention. **The NordICC study** (1) is the first published randomized trial of colonoscopy. Individuals who were screen-eligible by age, were randomly assigned to be offered a colonoscopy or have no intervention except for usual care. Key outcomes included CRC incidence and mortality. Notably, only 42% of patients who were offered colonoscopy, completed the exam. The incidence reduction of 18% (0.70-0.93), and a mortality reduction of 28% (NS) were lower than expected from prior cohort studies, whereas the per-protocol analysis found significant incidence reduction of 31% (0.55-0.83) and mortality reduction of 50% (0.27-0.77). These results raised important doubts about the benefit of screening with colonoscopy.

Brenner et al (2) maintain that the analysis is flawed with regard to incidence, arguing that screening cannot prevent a prevalent CRC discovered at a screening exam. Therefore, when we analyze the impact of screening on incidence, prevalent cancers should be excluded from the analysis. In doing so, Brenner et al find that the NordICC study underestimated the impact of colonoscopy on CRC incidence, which increases from 18% to 32% reduction in the intention to treat analysis and from 31 to 54% in the per protocol analysis.

Brenner et al limit their discussion to invasive screening, but this issue may be relevant to incidence reduction with non-invasive screening tests. Several ongoing trials of colonoscopy versus FIT screening are in progress and nearing completion (3-5). Brenner et al would argue that prevalent CRCs should be excluded in the colonoscopy arms of these studies when calculating incidence.

What about the FIT arms of these studies? In the FIT arm, patients with abnormal FIT who receive colonoscopy, will also have prevalent CRCs detected. Arguably, these subjects might also be excluded from the incidence analysis, since these CRCs cannot be prevented.

Digging deeper into the implications of the analysis by Brenner et al, we might also consider patients in the FIT arm who have negative FIT, but may have an undetected prevalent CRC, which is discovered one or two years later. Arguably, since the CRC is not detected during initial screening, it meets criteria for being defined as an incident CRC, even though it may have been present during the initial colonoscopy. This approach might unfairly bias the incidence analyses in favor of colonoscopy, which would be more likely to detect CRC on the first exam.

These issues are highly relevant to the ongoing trials, and comes down to the definition of prevalence and incidence. The most straightforward approach would define prevalence as detection of CRC at the baseline screening, whether it is colonoscopy or FIT. Incidence should be defined as CRC detected after an initial screening, which does not detect CRC. Future studies could analyze incidence data in two ways. Traditional analysis (used in the flexible sigmoidoscopy studies and NordICC) would count any CRC discovered during the screening continuum as an incident CRC. A second analysis might define incidence to include only CRCs discovered after an initial negative screening test.

There are several important lessons from this analysis. First, screening will be less effective if it is not completed. Poor adherence to the invitation for colonoscopy in the NordICC study clearly reduced the potential benefit of colonoscopy, as shown in the per-protocol analysis. Second, CRC mortality reduction is an important aim of screening. CRC mortality can be reduced by both early cancer detection of prevalent lesions as well as cancer prevention by polyp removal. It makes sense to include both prevalent and incident CRCs in this part of the analysis. Third, incidence reduction is distinctly different than mortality reduction, and investigators should indicate how they define prevalent versus incident CRCs in future studies.

References:

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