ELSEVIER

Journal of Clinical Epidemiology 66 (2013) 1144−1150

Journal of Clinical Epidemiology

In the era of widespread endoscopy use, randomized trials may strongly underestimate the effects of colorectal cancer screening

Hermann Brenner*, Christian Stock, Michael Hoffmeister

Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany

Accepted 14 May 2013; Published online 11 July 2013

Abstract

Objectives: Although randomized controlled trials (RCTs) are considered the most valid approach to evaluate screening effects, they also face a number of methodological challenges, including nonadherence and contamination. We aimed to quantify their potential impact in RCTs evaluating endoscopic screening for colorectal cancer (CRC).

Study Design and Setting: We carried out model calculations using plausible levels of nonadherence and contamination.

Results: Assuming medium values of adherence (70%) and contamination, that is, use of lower gastrointestinal endoscopy other than the one offered for screening (30%), true reductions in CRC incidence or mortality of 70%, 50%, or 30% would be expected to be attenuated to reductions of 43%, 29%, and 16%, respectively, in intention-to-screen analyses. In case of low levels of adherence (50%) and high but realistic levels of contamination (50%), even more severe attenuation of screening effects to estimated reductions of 27%, 17%, and 9% would be expected. The estimates are only slightly modified in sensitivity analyses, additionally allowing for differential adherence and contamination according to CRC risk.

Conclusion: In the era of widespread endoscopy use even outside the screening programs, RCTs may strongly underestimate the effects of CRC screening. Additional analyses accounting for nonadherence and contamination are crucial for disclosing the true screening effects.

Keywords: Colonoscopy; Colorectal cancer; Incidence; Mortality; Screening; Sigmoidoscopy

1. Introduction

Four recent randomized controlled trials (RCTs) have demonstrated a significant reduction in colorectal cancer (CRC) incidence and mortality by screening with flexible sigmoidoscopy. These trials were initiated in the 1990s in Norway [1], the United Kingdom [2], Italy [3], and the United States [4] and published between 2009 and 2012. RCTs on the impact of screening colonoscopy have been initiated more recently, and main results regarding the reduction of CRC incidence and mortality are expected in the 2020s [5,6]. RCTs are the gold standard for evaluating the effects of screening offers, but they also face a number of methodological challenges, including nonadherence in the screening group and contamination in the control group. The latter denotes the use of screening-equivalent procedures outside the screening offered in the RCT. In the context of RCTs on endoscopic screening for CRC, such procedures include sigmoidoscopies and colonoscopies conducted for other reasons, in particular the workup of symptoms or other screening tests, such as a positive fecal occult blood test.

Both nonadherence and contamination are substantial in RCTs on endoscopic screening for CRC and complicate the estimation of its true potential. For example, nonadherence in the four RCTs on screening sigmoidoscopy ranged from 13.4% in the US trial [4] to 41.7% in the Italian trial [2]. The extent of contamination was reported only in the US trial in which it was found to be substantial: 46.5% of participants in the control group had either sigmoidoscopy or colonoscopy during the screening phase (years 0−5). Although the results of intention-to-screen analyses were reported for all trials, only three trials also reported the per-protocol analyses in which only participants actually adhering to screening in the intervention group were compared with participants in the control group, thereby accounting for nonadherence [1−3]. Contamination was not adjusted for in any of the analyses included in the RCT reports. In this article, we provide model calculations to quantify the potential impact of nonadherence and contamination in RCTs evaluating endoscopic screening for CRC.

There was no extramural funding for this work.

Conflict of interest: None.

* Corresponding author. Tel.: +49-6221-421301; fax: +49-6221-421302.

E-mail address: h.brenner@dkfz.de (H. Brenner).

0895-4356/$ - see front matter
http://dx.doi.org/10.1016/j.jclinepi.2013.05.008

What is new?

- In the era of widespread endoscopy use, randomized controlled trials (RCTs) may strongly underestimate the effects of colorectal cancer (CRC) screening.
- We provide, for the first time, a systematic quantitative assessment of the impact of nonadherence and contamination on intention-to-screen estimates of the effects of endoscopic screening for CRC in RCTs.
- Given their expected strong impact, levels of nonadherence and contamination should be reported along with analyses, adjusting for them in such RCTs. Results of commonly reported standard intention-to-screen analyses need to be interpreted with due caution.

2. Methods

We carried out model calculations to derive expected estimates of relative CRC incidence or mortality in the intervention group compared with the control group in standard intention-to-screen analyses of RCTs. Both CRC incidence and mortality are relevant end points in RCTs of endoscopic screening (i.e., by sigmoidoscopy or colonoscopy), and our model calculations are equally applicable to both end points. In our model calculations, expected estimates of relative CRC incidence or mortality in intention-to-screen analyses, denoted RR′, were derived as a function of true relative incidence or mortality enabled by screening, denoted RR; the adherence proportion, denoted P_A, that is, the proportion of people in the intervention group adhering with the screening offer; and the contamination proportion, denoted P_C, that is, the proportion of people in the control group undergoing lower gastrointestinal (GI) endoscopy outside the screening program (e.g., because of symptoms or workup of other screening tests). In our model calculations, we also assumed the same contamination proportion among people in the intervention group who did not adhere with the screening offer. An overview of the model parameters, their definitions, and notation is given in Table 1.

Using this notation, CRC incidence or mortality in the screening and control groups, denoted R_I and R_C, would be $R_I = R_0 \times \mathrm{RR}$ and $R_C = R_0$, respectively, in the absence of nonadherence and contamination, and the ratio of both rates would yield RR, the "true screening effect." However, the relations become more complicated in the presence of nonadherence and contamination. In base-case analyses, we assumed that both adherence and contamination were unrelated to "baseline" CRC incidence or mortality, that is, CRC incidence or mortality expected in the absence of screening endoscopies or other lower GI endoscopies. Under this assumption, the expected CRC incidence or mortality in the intervention group, denoted R_I, equals

$$R_I = R_0 \times [P_A \times \mathrm{RR} + (1 - P_A) \times P_C \times RR + (1 - P_A) \times (1 - P_C)],$$

the expected CRC incidence or mortality in the control group, denoted R_C, equals

$$R_C = R_0 \times [P_C \times RR + (1 - P_C)],$$

and the expected apparent relative CRC incidence or mortality in the intention-to-screen analyses equals

$$\begin{aligned} \mathrm{RR}' &= [P_A \times \mathrm{RR} + (1 - P_A) \times P_C \times \mathrm{RR} + (1 - P_A) \times (1 - P_C)]/[P_C \times \mathrm{RR} + (1 - P_C)] \\ &= [P_A \times \mathrm{RR} + (1 - P_A) \times (P_C \times \mathrm{RR} + 1 - P_C)]/[P_C \times \mathrm{RR} + (1 - P_C)] \end{aligned} \quad (1)$$

Base-case analyses were carried out with individual and joint variations of RR, the true relative CRC incidence or mortality because of screening (0.3, 0.5, and 0.7, reflecting strong, moderate, and weak true screening effects, respectively), P_A (0.5, 0.7, and 0.9, reflecting moderate, fair, and high levels of screening adherence, respectively), and P_C (0.1, 0.3, and 0.5, reflecting low, moderate, and high levels of contamination, respectively).

In sensitivity analyses, we additionally allowed for variation of CRC incidence or mortality between attenders and nonattenders of screening in the intervention group and between contaminated and noncontaminated people in the control group as well as nonattenders in the intervention group. For this purpose, the relative CRC incidence or mortality expected even in the absence of any endoscopy between attenders and nonattenders and between contaminated and noncontaminated people was individually and jointly varied between 0.5, 1.0, and 1.5. The more complex derivation of RR′, the expected apparent relative CRC incidence or mortality, for these analyses is given in the Appendix at www.jclinepi.com. For the sake of space, presentation of the sensitivity analyses is restricted to the base-case scenarios with medium levels of adherence (70%) and contamination (30%).

3. Results

Results of the base-case analyses are shown in Table 2. Assuming medium values of the adherence proportion ($P_A = 0.7$) and contamination proportion ($P_C = 0.3$), true screening effects of RR = 0.30, 0.50, or 0.70 would be strongly underestimated (RR′ = 0.57, 0.71, and 0.84, respectively), that is, true reductions in CRC incidence or mortality of 70%, 50%, or 30% would be expected to be