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Case-control studies of screening for colorectal cancer: Tailoring the design and analysis to the specific research question

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Many cancers of the colon and rectum develop over a number of years, and (unlike most other forms of malignancy, such as prostate and lung cancers) have an identifiable non-malignant precursor lesion - an adenomatous polyp. For this reason, screening tests that can visualize the colon or detect bleeding produced by a polyp or by localized cancer can identify premalignant and malignant lesions that may be relatively amenable to treatment.

Randomized trials of screening sigmoidoscopy conducted in Great Britain, Italy, and the United States[1–3] have shown an approximately 50 percent decrease in mortality from distal colorectal cancer. Nonetheless, randomized trials cannot be relied on to answer all questions regarding the efficacy of screening for colorectal cancer. Such studies are often limited in duration, and rarely consider more than one approach to screening method and frequency. Randomized trials of screening generally need to be very large, and the cost associated with a large trial limits their number.

If screening histories can be ascertained in retrospect, a case-control study can complement the results from trials. For example, a case-control study that compared members of the Kaiser Permanente health plan who died of distal colorectal cancer during the 1970s and 1980s with other, demographically-similar, Kaiser Permanente enrollees identified a large difference in receipt of screening sigmoidoscopy prior to the onset of symptoms or signs of the cases' malignancies.[4] The relative mortality reduction that was estimated from these data was compatible with results of the randomized trials of screening sigmoidoscopy that did not become available until some 20 years later.

Depending on the ways in which case-control studies are designed (and, to some extent, analyzed), a variety of questions related to screening efficacy and frequency can be addressed. The purpose here is to describe these various designs, what they can accomplish, and potential problems that can arise in the analysis and interpretation of the results they generate.

Options in Case Definition

Persons with newly diagnosed invasive colorectal cancer

Screening endoscopy can identify polyps that can potentially degenerate into invasive cancer, and polyps can be excised during the procedure itself. Thus, the performance of

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screening endoscopy plausibly can reduce the incidence of colorectal cancer. The extent to which it does so can be assessed in a case-control study in which:

A. The screening history of each person with colorectal cancer is ascertained for the interval during which it is presumed that the premalignant lesion was present prior to its progression to malignancy; and

B. Comparable histories are obtained for a sample of members of the population from which the cases were derived who had not themselves been diagnosed with colorectal cancer as of the date of their respective case's diagnosis.[5]

While the onset of the development of a premalignant lesion can never be known in a given individual, nor the time of its transition to a malignant lesion, these can be estimated from knowledge of the prevalence of polyps and colorectal cancer, together with estimates of the incidence of polyps and cancer.[6] In practice, several analyses can be performed, each based on a different plausible estimate of the duration of the detectable premalignant lesion.

It must be kept in mind that the reduction in incidence associated with a given form of screening for colorectal cancer may not closely correspond to the reduction in mortality. Those cancers that arise from premalignant lesions with a lengthy natural history - the very cancers most amenable to prevention by means of precursor detection and removal - may also be the slowest to progress after becoming malignant, and thus be the most curable. For this reason, the screening-associated relative risk for mortality may be higher (suggesting less protection) than that for incidence. On the other hand, some tests (eg those seeking to identify fecal occult blood) may have a greater sensitivity for the presence of early cancer than they do for the presence of polyps, and so the impact of such screening on the incidence of colorectal cancer may be substantially less than on mortality from this disease. .

Persons with newly diagnosed late-stage colorectal cancer

When screening histories must be ascertained from interviews with cases and controls -- such as the practice of breast self-exam, which generally could not be ascertained in any other way -- case-control studies of efficacy against cancer mortality have defined cases as persons still alive but highly likely to die of their cancer. Such persons are those who had developed late-stage disease, whether at the time of diagnosis or later on. However, because the receipt and timing of screening tests for colorectal cancer tend to be more accurately ascertained from medical records than from interviews, this approach generally would not be used in case-control studies of screening for colorectal cancer.

Some studies have defined cases as persons with late-stage colorectal cancer at the time of diagnosis. Such studies ask whether screening can recognize colorectal cancer in asymptomatic persons before the disease has progressed to an advanced stage (i.e. regional or metastasic spread). Operationally, cases and controls (persons without a history of colorectal cancer at the time of their case's diagnosis) are compared for receipt of screening while the cancer (or the precursor lesion) would have been present but prior to the presumed transition from local to more advanced disease. (Because this interval cannot be known in a given individual, analyses can be done that consider various intervals, such as 3 months to 10 years prior to diagnosis, 6 months to 10 years prior to diagnosis, etc.). Defining cases as those with late-stage colorectal cancer at the time of diagnosis is feasible, and the focus on screening prior to the development of late-stage disease reduces the problem of distinguishing between the relatively small proportion of screening tests from the much larger proportion of diagnostic tests that are performed in cases around the time of diagnosis. Nonetheless, even if there is no effective treatment for colon polyps or early-stage cancer, there will be a smaller proportion of cases than controls with a history of screening as long as the test itself is sensitive. Therefore, this approach tends to be useful when there are

already strong reasons to believe that early treatment is likely to be beneficial. For example, because randomized trials of screening sigmoidoscopy have documented a reduction in mortality from distal colorectal cancer, there must be at least some efficacy of early treatment of distal colorectal cancer. This suggests that early treatment of proximal colorectal cancer probably is beneficial as well. Therefore, results of a case-control study of late-stage proximal colorectal at the time of diagnosis that suggest a reduced risk associated with receipt of screening colonoscopy during the 3 months to 10 years prior to diagnosis support the hypothesis that such screening can reduce mortality from proximal colorectal cancer (7).

Persons who have died as a result of colorectal cancer

Screening has the potential to prevent death from colorectal cancer either by preventing the disease - via the identification and removal of premalignant lesions - or by the identification of the malignancy at a stage at which it can be cured. Therefore, a case-control study of screening efficacy against colorectal cancer mortality must compare the screening histories of fatal cases and controls for an extended period of time prior to the case's first symptoms or diagnosis (whichever came first) - the "index date." Bias can result from an inability to obtain valid information on screening history for the whole of this interval.

In many case-control studies of screening, problems arise in dealing with tests done close to the time of diagnosis. The most common screening tests for colorectal cancer - endoscopy and fecal occult blood testing - can also be used to evaluate a patient with symptoms of this disease. However, the source of information about these tests - typically the medical record - may not have accurate information on the presence of an indication for testing. Tests done in response to symptoms will be far more numerous among cases than controls, and so a strategy of ignoring test indications[8] will generate a falsely high odds ratio (and thus a falsely low estimate of screening efficacy).

Faced with this limitation of the data source, some investigators [9,10] have excluded from consideration those tests most likely to have been ordered in response to symptoms of colorectal cancer, i.e. those performed close to the time of diagnosis. However, this analytic approach will yield a result that is biased toward overestimating efficacy. The problem lies in the asymmetrical distribution of screening histories in cases and controls (see Figure 1 in Weiss et al).[11] In controls, screening will have been distributed relatively uniformly during the years prior to the index date, perhaps increasing or decreasing over time to reflect trends in the use of the test in the underlying population. For the cases, in contrast, the majority of screens done during the time the tumor was present will have been at or very shortly before the date of diagnosis. Especially for a sensitive test such as colonoscopy or sigmoidoscopy, a test done earlier in time would have been positive and the date of diagnosis would have been correspondingly earlier in time. Given this case-control asymmetry, the impact of excluding true screening exams in the weeks or months prior to diagnosis will be much greater in cases than controls. Therefore, even if a sensitive screening test did not lead to effective treatment - in which circumstance there should be no true difference in a proportion of cases and controls who had been screened during the relevant period of time, and the true odds ratio would be 1.0 - an odds ratio less than 1.0 would be obtained.

Most tests for colorectal cancer performed well before the index date would have been negative for the presence of cancer (though not necessarily negative for the presence of polyps). Therefore, case-control studies of fatal colorectal cancer with information on testing, but without the ability to distinguish screening from diagnostic tests, can be used to address a different question: for what period of time (and to what degree) can a negative test predict a decreased risk of fatal colorectal cancer.[12] The data from such a study of

endoscopic screening, in which the large majority of tests were in truth performed for purposes of screening, might look as shown in the Table.

Whether or not early treatment is beneficial, the receipt of a test 1–2 years earlier that did not result in a cancer diagnosis was strongly predictive of a low risk. The magnitude of the reduction in risk waned with increasing time since the test was done. Had many of the endoscopic exams in fact been performed in response to symptoms or signs, however, the presence of false-negative exams likely would have caused the odds ratio for the 1–2 year period to have been considerably larger than 0.07. Therefore, without knowledge of the proportions of screening versus diagnostic tests in the population under study, the applicability of these results to persons who are negative on a screening test will be unclear.[13]

Analysis

Whether a study is assessing the influence of screening on the incidence of or the mortality from colorectal cancer, the analysis compares cases and controls for the receipt of one or more screens during the period of time in question. The impact of a series of repeated screens cannot be addressed in a case-control study. Even if there were no effective therapy, cases would have received but one round of a sensitive test if it had been administered during the detectable preclinical phase of the malignancy. Controls could have received multiple screens, and so the odds ratio associated with receipt of more than one screening exam would be falsely low, falsely suggesting efficacy.[14]

If the efficacy of more than one screening modality is to be considered, the odds ratio associated with the receipt of each modality with incidence (or mortality) should use subjects with no screening as the referent category. Despite the current emphasis on the study of “comparative effectiveness”, a head-to-head comparison (eg between screening colonoscopy vs. screening for fecal occult blood) should not be done, given the difference in the time period during which receipt of screening would be examined for the two modalities (relatively long and relatively short, respectively). This difference in time period renders a case-control study of screening efficacy unable to address the same question as the corresponding randomized trial. A trial might compare mortality for colorectal cancer between persons randomized to be screened by means of colonoscopy every 10 years or by means of fecal occult blood testing every two years, but a case-control study cannot. The best a case-control study could do is determine whether, compared with no screening, fecal occult-blood screening during the past 2 years (and, separately, colonoscopy during the prior 10 years) was associated with a decrease in risk, and by how much.

Dealing with Confounding

Having multiple close relatives with a history of colorectal cancer is related both to the risk of colorectal cancer death and the likelihood of receipt of screening. In studies in which there is access to medical records (and the records generally contain information on family history for controls as well as for cases), cases and controls with this sort of family background should be identified and excluded from the analysis, producing a study of the efficacy of screening in “average-risk” persons. Using those records, information on cigarette smoking should be ascertained as well, given that smoking may be associated with an increased probability of colorectal cancer death and a decreased probability of having been screened. Lack of information on other potential risk factors - such as diet and physical activity - would not be expected to give rise to any appreciable degree of confounding, given the at-most modest associations of these characteristics with both colorectal cancer incidence (and case fatality) and screening history.

On the other hand, it is desirable to identify those cases and controls with a history of colon polyps that were diagnosed prior to the interval during which screening histories are to be ascertained. Such persons are more likely to be screened subsequently, and also are at an increased risk of developing additional colorectal polyps and cancer. The analysis of screening efficacy can stratify persons on the basis of such a history, or restrict attention to (the majority of) persons without a remote diagnosis of polyps.

Probably the greatest source of potential confounding in case-control studies of the efficacy of screening for colorectal cancer is the receipt of other screening modalities. For example, screening endoscopy is almost certainly associated with a substantial reduction in colorectal cancer incidence and mortality. Persons who had previously undergone such screening may also have a relatively higher likelihood of subsequently being screened for the presence of fecal occult blood. Therefore, when trying to isolate the influence of just one of the screening modalities, it is necessary to deal with the potential confounding influence of the other during the relevant time period. This can be accomplished by statistical adjustment, or by restriction of the analysis to persons who had not been screened by the other modality in that time period.

The period of time that is “relevant” will differ for each test, depending on how early the given test can detect a cancer or precancerous lesion. For fecal occult-blood screening, the relevant period might be just the last year or two prior to diagnosis, given the limited sensitivity for early cancer and polyps of this type of testing. For screening endoscopy, the relevant period is likely to be a decade or more.

In sum, case-control studies of the efficacy of screening for colorectal cancer have the potential to address several specific questions. However, the design and analysis of these studies - and the interpretation of the results obtained - need to align with the question under consideration.

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Table

A hypothetical distribution of negative tests for colorectal cancer during the previous 10 years among controls and persons who later died from colorectal cancer. (Indication for the test could not be documented from information available to the study.)

Time of test prior to the case's diagnosis	Fatal case	Control	Odds ratio
1–2 years	2	18	0.07
3–5 years	18	22	0.49
6–9 years	30	30	0.60
No test	50	30	1.00
	100	100	

[a]Reference category