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Editorials

Case-control studies of the efficacy of screening for cancer: can we earn them some respect?

Selby *et al*[1] obtained about as convincing a result as possible from a case-control study of cancer screening. They found that 8.8% of persons who had died of cancer of the rectum or distal colon in the 10 years before diagnosis had undergone screening sigmoidoscopy, whereas the corresponding figure for controls matched for age and sex was 24.2% (matched odds ratio = 0.3, odds ratio further adjusted for the prior number of periodic health exams = 0.4). Several features of that study made the results particularly persuasive. Firstly, the study took place within a pre-paid health care plan. This allowed for the selection of comparable controls—members of the plan who did not die of colorectal cancer—and for medical records to be readily accessed to obtain objective information on the occurrence of and reasons for sigmoidoscopy. The latter is essential,[2] as sigmoidoscopy can be performed both for screening and in response to symptoms or signs of colorectal cancer. Secondly, the authors reported the results of an identical analysis for persons who died of more proximal colon tumours—those originating beyond the reach of the sigmoidoscope—which found almost no difference from controls with respect to a history of prior sigmoidoscopy. A subsequent case-control study,[3] based on a much smaller number of subjects, also observed a decreased risk of death from cancer of the rectum or distal colon in persons who had undergone screening sigmoidoscopy.

The results of Selby *et al* have figured prominently in the considerations of the various societies and organisations that make recommendations about the advisability of screening for cancer. Although they differ in the particulars of their recommendation, the American Cancer Society, American College of Obstetrics and Gynecology, American Gastroenterological Society, American College of Physicians, and a multidisciplinary panel on colorectal cancer screening[4] each advises that screening sigmoidoscopy be done. The US Preventive Services Task Force, in their *Guide to Clinical Preventive Services* (2nd ed), joins in this recommendation, but has the following reservations about the study of Selby *et al*: "This study was limited by a small number of cases, potential selection biases, and inability to provide prospective evidence of benefit". The Division of Cancer Prevention and Control (DCPC) of the US National Cancer Institute, on its Internet home page (http://www.nci.nih.gov/PLCO/) describing its ongoing, large randomised trial of screening that includes flexible sigmoidoscopy as one intervention, goes even further, claiming that the efficacy of screening sigmoidoscopy is "not well documented".

It is true that the study of Selby *et al* did contain some selection bias. The investigators included in their analyses persons whose diagnosis of colon or rectal cancer took place between 1971 and 1987, but only included deaths until the end of 1988. Thus study subjects eligible according to their date of diagnosis, but who would have gone on to die of colorectal cancer after 1988, could not be included as fatal cases. To the extent that sigmoidoscopy identifies tumours relatively early in their natural history, such deaths would be expected to be more common among screened than unscreened individuals. This bias would lead to a spuriously low frequency of screening among the fatal cases that were included, and thus a spuriously low estimate of the odds ratio associated with screening.[5,6] However, when Selby *et al* reanalysed their data to exclude cases diagnosed from 1984 onward (that is, those most likely to have been the source of this bias), the new odds ratios were only slightly higher than the original ones.[7]

The other concerns of the US Preventive Services Task Force seem less well founded. The number of cases in the study by Selby *et al*—261 who died of cancer of the rectum or distal colon—is hardly small. It is true that only 23 of these cases had undergone screening sigmoidoscopy, but if the test had been 100% effective in reducing mortality that number would have been zero! And, of course, the goal of including a large number of deaths in a study is to a great extent incompatible with the other expressed concern—that is, the lack of "prospective evidence of benefit". Prospective studies (that is, cohort studies or randomised trials) of the efficacy of sigmoidoscopy have provided

essentially no useful information to date, largely owing to the already low mortality rate from rectal and distal colon cancers in non-screened individuals. (The results of the randomised trial of sigmoidoscopy organised by the DCPC will probably not be available for at least another 10 years.)

If the study of Selby *et al* gets this sort of lukewarm reception, is it possible for the results of other, less definitive case-control studies of screening to have any credibility? Unfortunately, many persons do not have an appreciation of the contributions of non-randomised studies in general, and of case-control studies in particular, to our understanding of the cause of disease and of the efficacy and safety of therapeutic interventions. Undoubtedly, these persons will continue to view with skepticism even the most striking results of well done case-control studies that assess the efficacy of screening for cancer. But for the remainder of our audience—the size of which we can only hope grows with time!—we need to do what we can to enable our case-control studies of screening to provide as valid a result as possible. Although there is by no means unanimity about what should comprise the ingredients of a valid case-control study of screening efficacy, a consensus is beginning to form about some of these ingredients.[2 5 8] Certainly there will be instances in which the study group or data available for our case-control study of screening are suboptimal, and can lead only to an ambiguous interpretation no matter what the numerical results. In these instances, it is our responsibility as authors of such a study to issue a strong warning of caution to the reader.

By adhering to the principles underlying proper design and analysis when we conduct a case-control study of screening, and by recognising when circumstances prevent us from adhering to them, perhaps we can increase the chances that (*a*) those case-control studies of screening that yield valid findings will be heeded by a general audience and (*b*) the ones whose design has led to less easily interpretable findings will receive lesser attention, and then, primarily, from the afficionados of this corner of science.

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Screening for Huntington disease and certain other dominantly inherited disorders: a case for preimplantation genetic testing

This invited article describes a new screening strategy with implications for families at increased risk for certain serious dominantly inherited, late onset genetic disorders. The approach has public health implications for disease prevention and the gradual elimination of the disease gene. It also shows the ability of preimplantation genetic testing (PGT) to do more than provide an earlier alternative to conventional methods of prenatal testing like amniocentesis and chorionic villus sampling. This summary is substantially derived from our recent article on this subject.[1] Huntington disease is used as the model disorder for purposes of this discussion.

In Huntington disease the natural desire of patients to avoid the transmission of a genetic disease to their children may conflict with the adverse effects of presymptomatic diagnosis in the parent at risk. This dilemma has led to the development of elaborate protocols to ensure that individuals at risk understand and are emotionally competent to accept all of the implications of presymptomatic diagnosis. In practice, only a minority of all adults who are at risk elect to have presymptomatic testing.[2 3] As a consequence, the potential of antenatal diagnosis to reduce the burden of genetic disease in the population, and the tragedy of recurrent cases within a family, is seldom realised. PGT now provides an approach in which antenatal diagnosis can be offered without incurring the adverse effects of the presymptomatic diagnosis. We believe this approach should be reviewed along with other relevant reproductive options when counselling patients at risk for Huntington disease and possibly other dominantly inherited traits as well.

We consider that PGT is far more desirable and ethical than an alternative approach involving prenatal testing, which is partially informative, and, while protecting parents from unwanted genetic information about themselves, results in pregnancy terminations in which 50% of the fetuses destroyed are genetically normal.

PGT refers to a group of related technologies in which in vitro fertilisation (IVF) is used to produce early embryos which are then biopsied, often as early as the four cell stage, to permit genetic testing of the embryos by polymerase chain reaction-based methods. Although the reliable amplification of target regions of the genome in single cells is still a technical challenge, prenatal diagnoses have been made accurately by this method without adverse effects on the fetus.[4] For patients who are at high risk (typically 50%) of carrying a gene for Huntington disease, PGT enables them to participate in antenatal genetic testing without incurring the emotional, social, and financial burdens that might result from the presymptomatic disclosure of their own carrier status. Such patients could be offered IVF with preimplantation biopsy and testing of their embryos without ever being informed of the specific test results. The couples would be told that embryos were formed and tested, and that only apparently disease free embryos were replaced in the uterus (and, if sufficient numbers were