Should we use total mortality rather than cancer specific mortality to judge cancer screening programmes?

James Penston believes all cause mortality is a more reliable measure of the effectiveness of screening, but Robert Steele and David Brewster think it is too stringent.

YES

Cancer screening is a source of much dispute—in the case of breast cancer, arguments have raged for more than a decade.¹ One major concern is how the effects are to be measured. Disease specific mortality is used extensively in trials of cancer screening,² ³ and as the aim of screening is to reduce deaths from the target disease,² ³ this might seem to be a suitable end point. But the arguments against using disease specific mortality weigh heavily, and all cause mortality is a better measure.

Uncertainties relating to cause of death

Clearly, the accuracy of disease specific mortality depends on correctly identifying the cause of death. However, this is often unreliable,² and it entails decisions that can introduce biases, either for or against screening.² ³ Claims that bias favouring screening predominates have been disputed.² ³ Nevertheless, one thing is sure: the accuracy of all cause mortality depends solely on the number of deaths identified and is not subject to bias. It is therefore a more reliable end point.

Disease specific mortality also ignores the fact that screening for cancer causes harm. Invasive procedures may have fatal complications, while overdiagnosis—that is, the identification and treatment of tumours that otherwise would have caused no disease—may also result in death.¹ ³ A review of 12 trials of screening for breast, lung, and bowel cancer raised doubts about both the identification of screening related deaths and their inclusion in disease specific mortality.² If screening related deaths are not included in the mortality figures, the results will be skewed in favour of screening. In contrast, all cause mortality balances the benefits and harms of screening in a single measure.

Shifting definition

Although disease specific mortality is unproblematic when used descriptively, difficulties arise when it is used as an end point in randomised controlled trials. Should the figure include death occurring in a case of overdiagnosis? And what about someone who does not have colorectal cancer but who dies from a perforation due to screening colonoscopy? Although such deaths are not...
strictly linked with disease specific mortality, they are obviously relevant.

We can accommodate all screening related deaths in a randomised trial only by changing disease specific mortality into a vague and arbitrary end point. Alternatively, we could use all cause mortality which is untouched by these problems.

The unfeasibility argument
Advocates of disease specific mortality have a fall-back position. The target cancer, they argue, contributes little to total mortality; trials would have to recruit millions of people to show a statistically significant reduction in all cause mortality; such trials are not feasible; hence, we have to rely on disease specific mortality.

This argument does not show that disease specific mortality is better than all cause mortality; indeed, it seems to concede the opposite point. It also assumes that huge trials would show a reduction in all cause mortality, whereas this is precisely what is in question. And it ignores the existing data that strongly support an absence of any effect of screening on all cause mortality, as, for example, in the case of bowel cancer screening.

Screening may cause harm in several ways. If the screening test is not highly sensitive, false negative results may induce reassurance

Too stringent
Demonstrating a reduction in all cause or total mortality, however, is a different matter. As even common cancers account for only a small proportion of total deaths (for example, in the United Kingdom, colorectal cancer accounts for 3% of all deaths), to show a reduction in disease specific mortality being translated into a reduction in total mortality would require trials that are too large to be feasible. Furthermore, it is inappropriate to use disease specific mortality as a surrogate for all cause mortality; cancer screening is not designed to reduce all cause mortality but the number of people dying prematurely, in a particularly unpleasant manner.

Proponents of using all cause mortality as an outcome indicator argue that it avoids the bias inherent in the determination of causes of death. In a frequently quoted paper that examined all cause mortality in randomised trials of cancer screening, the point was made that the effect on all cause mortality was often in the opposite direction from the effect on disease specific mortality. However, close examination of the data shows that the confidence intervals around the differences in all cause mortality figures were much wider than those around the disease specific figures and did not reach anywhere near statistical significance, with the exception of a beneficial effect on all cause mortality in the Edinburgh mammography trial. In the correspondence that followed this article, even the original authors concede that a significant reduction in all cause mortality is too stringent a requirement for the determination of the efficacy of screening.

Thus, if a trial shows a reduction in disease specific mortality, even though it has no demonstrable effect on total mortality, it has provided sufficient evidence to offer such screening to the population that has been studied in the trial. To insist that a trial should show a reduction in all cause mortality would deny society the opportunity to engage in screening that, on balance, is more likely to prevent cancer death than cause harm. On the other hand, it is reasonable to single out screening, which is an intervention with a specific aim, as having to prove a reduction in all cause mortality at a population level. If all medical interventions were similarly constrained, then much of what health professionals do would be deemed inappropriate.

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“Should we use total mortality rather than cancer specific mortality to judge cancer screening programmes?”

53% voted yes, out of a total 232 votes cast