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The Effect of Bias on Estimation of Improved Survival After Diagnosis of Barrett's Esophagus

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Abstract

Adjustments for lead and length time bias has been used when examining apparent survival advantages from screening procedures. However, these estimates depend on several assumptions and are modeled from malignancies that are fairly common and large cohorts are available. In smaller retrospective cohorts, adjustments themselves may be based on estimates that may not be biological nor statistically accurate, which can lead to divergent results as has been found in several recent studies of screening in Barrett's esophagus. Only a prospective randomized controlled trial can really determine the benefit though this may not be feasible.

To make an impact on the mortality for esophageal adenocarcinoma, several societies have recommended that selective screening be implemented (1). The primary motivation for this has been the unfortunate situation that over 90% of those that develop this malignancy never had a previous diagnosis of Barrett's esophagus and present with obstructive symptoms (2,3). The mortality rates for symptomatic esophageal adenocarcinoma are among the top five cancers in the United States despite the advancements in neo-adjuvant therapy and esophagectomy (4). The recommendation for screening is more born from frustration than evidence that screening will be successful in decreasing mortality.

It is a tenet of cancer screening and surveillance that earlier detection will lead to discovery of earlier stage disease that in turn can lead to successful treatment and improved survival. However, in several neoplastic processes, this has not been found to be the case and earlier diagnosis has not really changed the ultimate course of the disease. The best study design by which improved outcomes from screening can be shown is by a population-based prospective randomized trial comparing a screening procedure to no screening and examining overall and disease-specific mortality as the end points. Unfortunately, this study design is the least often performed, given the large number of patients who would have to be enrolled and the long time periods needed for observation to demonstrate a survival benefit. In this issue the study by Tramantano *et al.* (5), the investigators examined retrospective data

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and utilized outcomes from Medicare databases for follow-up that is a much more feasible study methodology. They examined 4,978 Medicare patients in the Surveillance, Epidemiology, End Results (SEER) database, to determine the benefit of detecting the pre-malignant condition Barrett's esophagus in those that were older than 65 years of age and determined if there was an effect on cancer stage and mortality. They found that there was a significant improvement in cancer stage if Barrett's esophagus was detected prior to the diagnosis of cancer. However, when the investigators adjusted their apparent survival benefits for both lead and length time bias, there was no longer a survival advantage. This is consistent with prior publications that have found that endoscopy prior to detection of esophageal adenocarcinoma did not seem to have an effect on outcomes (6). A Cochrane review on the benefits of screening for esophageal cancer highlighted the need for randomized controlled trials as existing retrospective cohort studies found benefits that could be explained by lead and length time bias (7). However, another recent large study of 29,536 veterans and 424 esophageal adenocarcinomas found a mean survival benefit of almost a year and significant improved overall survival rates even when adjusting for bias (8).

It is difficult to understand the differences in conclusions, given the large patient populations studied and the careful methods used by experienced investigators. First, it is important to realize that the populations selected are primarily of convenience since esophageal cancer is not common necessitating very large cohorts to be assembled with lengthy follow-up periods. However, the difficulty with using these large databases is the need to reduce confounding by imputing a mathematical model to account for bias from lead and length time. The two are related since those more indolent tumors that are detected more often by screening contribute to lead time bias by being more available for detection by periodic surveillance. These less aggressive tumors also contribute to length time bias by tending to have longer survival. The adjustment used by the investigators was first described by Duffy *et al.* (9) and was based on screening for breast cancer using mammography. These investigators created models to compensate lead time bias that is related to the apparent increase in survival that occurs when a disease is diagnosed earlier, but the clinical course is actually unchanged. This is carried out by estimating the size of tumors that are detected on surveillance and the size of tumors found in patients not in surveillance, and then comparing their subsequent survival. These calculations are based on estimations of sojourn time that is defined as being the period a tumor is detectable by screening but asymptomatic. The sojourn time is assumed to follow an exponential distribution. In the calculations used to develop lead time bias adjustment, the authors used data from other large breast cancer screening studies to estimate the sojourn time. To correct for length time bias, probabilities were estimated for a two tumor type model; one tumor type being a rapidly growing tumor and another being significantly slower with each having different probabilities to be screen-detected. The probabilities were then examined using plausible values that were varied using sensitivity analysis. Using these calculations, it was found that to assume length time bias totally accounted for differences in screening detected cancer survival, the group with the slower tumors would have to consist of at least 30% of total tumors and be five times more likely to be detected by surveillance.

There are several differences in the population and assumptions used in this study to explain the lack of benefit that is found. Since the authors of this Barrett's esophagus study confined

the sample to those over 65 years of age due to the need to use the Medicare database, it would appear that both length and lead time bias adjustments would need to be shortened since the initial age of detection could only begin at age 65. It needs to be kept in mind that screening, when suggested by most gastroenterology societies, would begin by age 50. This raises the possibility that the fast growing cancer type that is more aggressive may no longer be available for screening at this age as this may have already produced mortality.

In addition, these adjustments are statistically based and the larger the patient population used, the more accurately a probability can be calculated. Esophageal adenocarcinoma is much less common than breast cancer. The breast cancer example used to estimate lead and length time bias had 15,862 breast cancers, which is over three times the cohort in the SEER database of esophageal cancer used in this study. There is also a question of biological plausibility for the assumption of two populations of cancers used to adjust for bias. In the recent The Cancer Genome Atlas publication on the genetic composition of esophageal adenocarcinoma of the tubular esophagus assumed to be primarily related to Barrett's esophagus, no distinct subset could be found as distinguished by methylation profiles, expression profiles, copy-number abnormalities, or genetic mutations that raises the issue of the two different populations of cancer being too simplistic (10). There does not really seem to be two distinct populations with different sojourn times if esophageal cancers are so genetically diverse. In breast cancer, it has been found that those with estrogen receptor positivity do constitute a more indolent form of the cancer with prolonged survival times that makes the adjustment more plausible in this malignancy.

These issues are typically why it is necessary to perform the randomized control trial to really be able to be certain that screening can actually affect outcomes. In lieu of the definitive studies, it is necessary to estimate as best as we can the potential bias, but in diseases with relatively small number of events, it is not surprising that different groups arrive at different estimates of length and lead time bias that confirm the benefits in one study but completely eliminate them in another.

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