EDITORIAL

Screening for oesophageal cancer: is it timely or premature?

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Oesophageal cancer is currently the sixth leading cause of cancer death worldwide.[1] More than half of cases are diagnosed at an advanced stage when surgical removal is no longer a viable treatment strategy. As a result the overall five-year survival rate is low, but stage-specific survival rates vary substantially; after surgical removal of the tumour, the five-year survival rate has been reported to be greater than 95% for stage 0 disease, 50–80% for stage I disease, 30–40% for stage IIA disease, and 10–30% for stage IIB disease.[2] This raises the possibility that oesophageal cancer may be an attractive candidate for a screening test, to detect disease at an early stage when treatment would be more effective. However, before we endorse screening we should step back and consider the issue from a critical perspective to determine whether established criteria related to the condition, the test, and the treatment are satisfied.[3]

Because oesophageal cancer is rare, population screening is only done in a few areas of the world with very high incidence, such as some parts of northern China where annual rates among those aged over 55 may approach 200 cases per 100,000 individuals.[4,5] Squamous cell carcinoma accounts for most cases in these countries, and the major risk factors are exposures that cause chronic irritation of the oesophagus, including smoking, heavy alcohol use and consumption of poorly preserved foods. The incidence of oesophageal cancer is substantially lower in Western countries, with annual rates of less than 10 cases per 100,000.[6] These marked geographic differences in incidence rates necessitate separate evaluation of screening strategies for high- and low-risk areas; we focus on the latter for the remainder of this commentary, as they are far more common than the high-risk pockets. Although still low in absolute terms, the incidence of adenocarcinoma of the oesophagus has increased rapidly over the last several decades in Western populations and now accounts for over half of cases.[7] Gastro-oesophageal reflux disease and Barrett's oesophagus are both associated with increased risk of oesophageal adenocarcinoma.[8,9] Obesity is also an important risk factor,[10,11] and a recent report estimated that it may account for nearly 40% of this malignancy in Western society.[12] Patients with chronic reflux symptoms are considered for periodic endoscopic screening, and surveillance endoscopy is typically recommended for those who are found to have Barrett's oesophagus.[13,14]

There is also growing interest in identifying clinical biomarkers that would facilitate earlier detection of oesophageal cancer or its precursors. For example, a recent study in the *British Journal of Cancer* examined the performance of an assay for minichromosome maintenance (MCM5) protein as a diagnostic and screening tool.[15] Building on previous work showing overexpression of MCM proteins in dysplastic squamous epithelium and Barrett's oesophagus,[16,17] the investigators measured levels of MCM5 protein in gastric luminal samples from 40 symptomatic patients; 20 of these 40 had tumour present on biopsy, and they were compared with patients who were tumour negative. The investigators reported fairly high sensitivity and specificity of the MCM5 test, with a false-positive rate of about 4% (96% specificity) at a sensitivity of 75%.

In addition, the investigators used their data to compute the predictive values of the test, reporting a positive predictive value (PPV) of 94% and a negative predictive value (NPV) of 84%. Based on these findings, they concluded that this new protein-based approach would be a potentially useful screening and diagnostic tool for the detection of oesophageal cancer. This seems premature, however, given certain limitations of the study and what is known about the epidemiology and natural history of oesophageal cancer.

In this study, all of the patients were undergoing gastroscopy for known or suspected oesophageal cancer or for symptoms of dyspepsia. The sensitivity of the test will be higher in these patients than in asymptomatic individuals because a greater proportion will be in later stages of disease, and it will be reduced in a screening setting where the distribution will be weighted more towards those with no or early-stage disease.[18] This same issue related to the spectrum of disease manifestation has arisen in evaluations of the accuracy of other screening tests, such as the Papanicolaou test for cervical cancer.[19] The sensitivity of a given test will also depend on the timing and frequency of screening. The yield will be highest when a screening programme is first introduced into a population, because it will detect some prevalent cases in later stages of disease, close to the point where they would be diagnosed symptomatically. It will tend to decline in subsequent years, when a greater proportion of screen-detected incident cases will be earlier in the preclinical phase.[20] If a test is meant to be used as a diagnostic rather than a screening tool, evaluating its performance in a population with symptomatic disease may be appropriate. However, this is an important distinction that should be made explicit, as it relates directly to the performance of the test.

Furthermore, although a screening test must have fairly high sensitivity, this is not the only property that determines its overall effectiveness. The PPV – or the probability of having disease given a positive test result – also depends on the prevalence of the disease in the population and the false-positive rate. In the study described above, the investigators estimated the predictive values based on the prevalence of oesophageal cancer in their sample (over 40%), which is artificially high due to the selection of patients undergoing gastroscopy; hence, this overestimates the PPV in the general population. Assuming that the prevalence of oesophageal cancer in Western populations is approximately 1 in 10,000, the PPV at a specificity of 96% (4% false-positive rate) would be less than 1%, which is unacceptably low for a screening test. A high false-positive rate can also lead to a low PPV, because the number of true positives will be small relative to the total number who test

positive. A low PPV may be acceptable to the target population if the follow-up procedures for a positive test result are non-invasive and carry minimal risk (e.g. repetition of the test). In the case of oesophageal cancer, however, a low PPV would result in many unnecessary endoscopies and biopsies with associated costs and complications.

One way to increase the PPV would be to only screen individuals who have been classified as high risk, such as those with chronic reflux symptoms and/or Barrett's oesophagus, because the prevalence of disease would be higher in these groups. However, although these conditions are associated with high relative risks of developing oesophageal cancer, the absolute risk for an individual is still very low (only about 0.5% per year), which would yield a PPV of less than 10%. Other risk factors could be used in conjunction with reflux severity to create a risk profile that would help identify those most likely to benefit from screening. For example, age is often an initial criteria for cancer screening,[21] and gender and body mass index are other factors that could potentially be used to identify those at highest risk for developing oesophageal adenocarcinoma. A re-analysis of data collected from a Swedish nationwide case–control study, however, suggests that this type of approach to endoscopic screening would still result in a very low yield.[22] Even risk factors that are strongly associated with disease, with relative risks as high as 200, tend to perform poorly as screening tests, leading to low detection rates.[23]

Importantly, another problem with the high-risk strategy that has been described by Rose is that a large proportion of cases would be missed if only high-risk individuals were screened.[24] This is particularly relevant to our discussion of oesophageal cancer because less than 5% of patients with oesophageal cancer are known to have Barrett's oesophagus prior to diagnosis of their cancer,[25] suggesting that this condition is a marker of increased risk rather than an obligate precursor lesion. In addition, approximately 40% of patients have no history or symptoms of reflux.[8] These issues raise concerns about taking the high-risk approach to screening for oesophageal cancer, whether through endoscopic methods, assays for MCM proteins, or other techniques.

An alternative strategy for increasing the PPV would be to reduce the false-positive rate (i.e. increase the specificity). For quantitative tests, this can be done by modifying the cut-off point for what constitutes a positive test result; the investigators who conducted the study of the MCM5 protein test used several different cut-off points, such as $\geqslant$1500, $\geqslant$5000, and $\geqslant$7500 cells/well. However, increasing the specificity will lead to corresponding decreases in sensitivity. A balance between sensitivity and specificity must be achieved to maximize the area under the receiver–operating characteristic (ROC) curve and the predictive value of the test.

Does screening/surveillance and treatment of early-stage oesophageal cancer lead to reduced mortality? This is a crucial question for evaluating any potential screening test, but the evidence here is inconclusive. Oesophagectomy is currently the standard of care for localized disease, and other treatments such as radiotherapy and chemotherapy have not been clearly shown to offer substantial survival benefits over surgery alone.[2] Although patients with oesophageal cancer detected in endoscopic surveillance programmes are diagnosed at earlier stages and have longer life expectancies than patients whose cancers were detected when they presented with symptoms, these results could be affected by lead time and length bias and do not provide direct evidence of decreased mortality.[26] A 10-year cohort study of endoscopic surveillance among over 400 patients with Barrett's oesophagus cancer failed to show a mortality reduction,[27] and there is general controversy about whether this is an effective strategy.[28,29] Further studies are needed to examine the issue of whether earlier treatment leads to reduced mortality. Because individuals who choose to be screened may differ in important ways from those who do not, a randomized controlled trial of screening/surveillance for oesophageal cancer would be the most persuasive form of evidence, but no such study has been conducted at this point.

Given the low incidence of oesophageal cancer in Western populations and the lack of direct evidence showing that screening and surveillance can reduce mortality, it is premature to recommend population screening at this point in time, using assays for MCM5 protein or other methods; primary prevention through reduction of obesity, smoking, and alcohol consumption is currently the best available strategy. Established guidelines for evaluating the performance of screening tests should be considered and met before screening for any disease is recommended.[3] In particular, more information about the natural history of oesophageal cancer is needed to determine whether there is a detectable preclinical phase during which treatment is more effective than at a later stage. Furthermore, although sensitivity and specificity are important test characteristics, they may vary substantially depending on the spectrum of disease in the population. If a test is being considered for screening as well as diagnostic purposes, its performance must be examined in asymptomatic individuals (screening) as well as in those who present with clinical symptoms (diagnostic). Moreover, estimated predictive values of screening tests should be based on the prevalence of disease in the relevant population, rather than in a highly selected sample. Failure to abide by these principles and to minimize other potential sources of bias that can affect these types of studies may lead to non-reproducible results and subsequent disappointment about the actual performance of the test, which has occurred in the past with other proposed molecular markers for cancer diagnosis.[30–32] We must exercise caution, therefore, when interpreting results to avoid making recommendations before the time is right.

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REFERENCES

1 Paulson TG, Reid BJ. Focus on Barrett's esophagus and esophageal adenocarcinoma. *Cancer Cell* 2004;**6**:11–16
2 Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003;**349**: 2241–52
3 UKNSC. *NSC Criteria for Appraising the Viability, Effectiveness, and Appropriateness of a Screening Programme* March 24, 2003. Available at:http://www.nsc.nhs.uk/uk_nsc/uk_nsc_ind.htm (accessed 24 February 2005)
4 Riddell RH. Early detection of neoplasia of the esophagus and gastroesophageal junction. *Am J Gastroenterol* 1996;**91**:853–63
5 Yang L, Parkin DM, Ferlay J, Li L, Chen Y. Estimates of cancer incidence in China for 2000 and projections for 2005. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:243–50
6 International Agency for Research on Cancer. *Cancer Incidence in Five Continents* Vol VIII. Lyon, France: International Agency for Research on Cancer, 2002
7 Devesa SS, Blot WJ, Fraumeni Jr JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;**83**:2049–53

8 Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;**340**:825–31
9 Chang JT, Katzka DA. Gastroesophageal reflux disease, Barrett esophagus, and esophageal adenocarcinoma. *Arch Intern Med* 2004;**164**: 1482–8
10 Chow WH, Blot WJ, Vaughan TL, *et al.* Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst* 1998;**90**:150–5
11 Wu AH, Wan P, Bernstein L. A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus (United States). *Cancer Causes Control* 2001;**12**:721–32
12 International Agency for Research on Cancer. *Weight Control and Physical Activity* Vol VI. Lyon, France: International Agency for Research on Cancer, 2002
13 Mandal A, Playford RJ, Wicks AC. Current practice in surveillance strategy for patients with Barrett's oesophagus in the UK. *Aliment Pharmacol Ther* 2003;**17**:1319–24
14 Sampliner RE. Updated guidelines for the diagnosis, surveillance, and therapy of Barrett's esophagus. *Am J Gastroenterol* 2002;**97**: 1888–95
15 Williams GH, Swinn R, Prevost AT, *et al.* Diagnosis of oesophageal cancer by detection of minichromosome maintenance 5 protein in gastric aspirates. *Br J Cancer* 2004;**91**:714–19
16 Going JJ, Keith WN, Neilson L, Stoeber K, Stuart RC, Williams GH. Aberrant expression of minichromosome maintenance proteins 2 and 5, and Ki-67 in dysplastic squamous oesophageal epithelium and Barrett's mucosa. *Gut* 2002;**50**:373–7
17 Sirieix PS, O'Donovan M, Brown J, Save V, Coleman N, Fitzgerald RC. Surface expression of minichromosome maintenance proteins provides a novel method for detecting patients at risk for developing adenocarcinoma in Barrett's esophagus. *Clin Cancer Res* 2003;**9**: 2560–6
18 Irwig L, Bossuyt P, Glasziou P, Gatsonis C, Lijmer J. Designing studies to ensure that estimates of test accuracy are transferable. *BMJ* 2002; **324**:669–71
19 Fahey MT, Irwig L, Macaskill P. Meta-analysis of Pap test accuracy. *Am J Epidemiol* 1995;**141**:680–9
20 Morrison AS. *Screening in Chronic Disease*. 2nd edn. New York: Oxford University Press, 1992
21 Law MR, Morris JK, Wald NJ. The importance of age in screening for cancer. *J Med Screen* 1999;**6**:16–20
22 Lagergren J, Ye W, Bergstrom R, Nyren O. Utility of endoscopic screening for upper gastrointestinal adenocarcinoma. *JAMA* 2000;**284**:961–2
23 Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? *BMJ* 1999;**319**:1562–5
24 Rose G. *The Strategy of Preventive Medicine*. London: Oxford University Press, 1994
25 Koshy M, Esiashvilli N, Landry JC, Thomas Jr CR, Matthews RH. Multiple management modalities in esophageal cancer: epidemiology, presentation and progression, work-up, and surgical approaches. *Oncologist* 2004;**9**:137–46
26 Shaheen N, Ransohoff DF. Gastroesophageal reflux, Barrett esophagus, and esophageal cancer: scientific review. *JAMA* 2002;**287**:1972–81
27 Macdonald CE, Wicks AC, Playford RJ. Final results from 10 year cohort of patients undergoing surveillance for Barrett's oesophagus: observational study. *BMJ* 2000;**321**:1252–5
28 Sontag SJ. Preventing death of Barrett's cancer: does frequent surveillance endoscopy do it? *Am J Med* 2001;**111**:137S–41S
29 Spechler SJ. Screening and surveillance for complications related to gastroesophageal reflux disease. *Am J Med* 2001;**111**:130S–6S
30 Ransohoff DF. Rules of evidence for cancer molecular-marker discovery and validation. *Nat Rev Cancer* 2004;**4**:309–14
31 Ransohoff DF. Bias as a threat to the validity of cancer molecular-marker research. *Nat Rev Cancer* 2005;**5**:142–9
32 Ransohoff DF. Lessons from controversy: ovarian cancer screening and serum proteomics. *J Natl Cancer Inst* 2005;**97**:315–19