Targeting diagnostic interventions for oesophageal cancer

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Worldwide oesophageal cancer cases and deaths are increasing, largely because global population growth is outstripping moderate declines in age-specific incidence and mortality.[1] Around 500,000 new cases were reported in 2017, with the highest incidence in China, followed by several African countries. There are two main histological subtypes of oesophageal cancer, squamous cancer and adenocarcinoma, each with different risk factors. Up to half of cases of both subtypes are attributable to tobacco use, although adenocarcinoma is associated more with excess alcohol use and obesity.[2–5] As with most cancers, three main areas offer possible improvement: prevention, earlier detection, and better treatment. In oesophageal cancer, prevention is particularly attractive, because early detection by screening or symptomatic diagnosis has proved elusive: most cancers are diagnosed at a stage where curative treatment is impossible.[5] Prevention—and screening, if a successful modality can be identified—can be implemented at a population level, or may be targeted at those with most to benefit.

In *The Lancet Regional Health—Europe*, Hippesley-Cox and colleagues report the creation of the CanPredict algorithm that predicts the 10-year risk of oesophageal cancer irrespective of histological subtype.[6] The algorithm was derived using Cox proportional hazards analyses on anonymised data from UK electronic primary care records in practices hosting 12.9 million patients. It was then internally validated in a further 4.12 million patients in the same database, and finally validated externally in a separate UK primary care records database from practices with 2.53 million patients. The size, contemporaneity and representativeness of the two record systems suggest the validation was as good as realistically possible. The explanatory variables included predictors of future cancer development (risk factors) and those indicative of cancer already present (risk markers). The algorithm's 10-year timeframe and the selection of both risk factors and markers reduce its usefulness as an early diagnosis intervention in the symptomatic population.

Barrett's oesophagus, a precursor lesion for adenocarcinoma, unsurprisingly has the strongest association with oesophageal cancer. However, its inclusion is controversial, for two reasons. First, it is diagnosed using oesophagoscopy, a procedure normally expected to identify cancer as well. Secondly, patients with Barrett's oesophagus have a clearly defined surveillance follow-up, including periodic oesophagoscopy for most patients. The algorithm may be more usefully focused on the population without a diagnosis of Barrett's oesophagus, for whom no targeted screening or prevention intervention is in place. Additionally, removing Barrett's oesophagus from the model may restore the predictive power of the low-risk markers of oesophageal cancer risk that had to be omitted. This may have two benefits. First, it may increase the potential for identifying those with undiagnosed Barrett's oesophagus or oesophageal cancer. Secondly, it may rebalance the algorithm towards identifying squamous cell carcinomas. It would also open the possibility of using Cytosponge-trefoil factor 3 (a small brush swallowed in a dissolvable capsule, which samples cells from the lower oesophagus, and is retrieved by an attached string) or other diagnostic tests to triage the population with low-risk symptoms in the future, informed by selection using the CanPredict algorithm.

Could the algorithm allow targeting of screening? It could, either as a one-off, akin to aortic aneurysm screening offered to 65-year-old males in the UK, or at an appropriate frequency similar to existing UK screening programmes for colorectal, breast and cervical cancer. Reporting the cancer yield per year of follow-up would have helped inform possible screening intervals using the CanPredict algorithm, and justified the choice of a 10-year prediction risk. The algorithm could identify high-risk subpopulations who would receive a true survival benefit of screening over and above the known lead-time and length biases (overdiagnosis of oesophageal cancer is unlikely to be an issue).[7] All this remains hypothetical until a proven screening modality for oesophageal cancer is found, but the algorithm could underpin trials of any putative screening instrument. This is likely to be its main value, though if recurrent screening is to be considered, a new algorithm matching the proposed screening interval would be needed.

In theory, the algorithm could allow targeted prevention. This may not be realistic, however, because reductions in obesity, smoking and excess alcohol use have such large population benefits beyond cancer, let alone oesophageal cancer in isolation. The effort involved in the selection process would almost certainly outweigh benefits from targeting. Indeed, it is hard to see how any campaign for one of these three major public health scourges would gain much additional traction with the wider population simply from adding its postulated benefit of oesophageal cancer prevention.

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In summary, it is now possible to identify with more precision higher risk groups for future oesophageal cancer. This is helpful, but currently the missing jigsaw piece is a proven screening modality. Knowing whom to screen remains valuable, but currently more from a research aspect than for clinical implementation.

Contributors

After joint discussion, WH wrote the first draft, and SP revised critically. Both authors created the final version.

Declaration of interests

None to declare.

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