Lung cancer screening in people who have never smoked: lessons from East Asia

Wayne Gao and colleagues argue that high detection rates and high survival rates in never smokers are less likely to be evidence of screening benefit and more likely to be evidence of its harm—overdiagnosis

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Lung cancer screening using computed tomography (CT) is typically restricted to people with a history of heavy cigarette smoking—the high risk group for which it was examined in randomised controlled trials. However, enthusiasm is growing for screening people who have never smoked,[1-3] partly because of the rising proportion of lung cancer diagnoses in this group.[4 5] The enthusiasm is also fuelled by compelling observations from East Asia, where opportunistic screening has become commonplace in some countries, including Taiwan and South Korea, where hospitals have promoted CT screening, regardless of smoking history.[6-8] Studies report CT screening detects numerous early stage lung cancers in people who have never smoked[9] and remarkably high survival rates for these screen detected cancers.[10] Screening proponents argue that these data are sufficient to presume that the 20% reduction in lung cancer mortality reported in randomised trials among people who smoke heavily[11 12] can be extrapolated to those who have never smoked.

However, a more plausible explanation for the rising proportion of lung cancers occurring among never smokers is that it reflects the success of tobacco control—namely, there are fewer people who smoke.[13] The problem is easily understood in the extreme case: if no one smokes, eventually 100% of lung cancers will be in people who have never smoked (nevertheless, most lung cancer deaths would be prevented). Furthermore, a presumption of benefit from screening in this population is based on misleading statistics—detection rates and survival rates—that represent deceptive feedback from screening itself. Closer examination of data from East Asia reveals four reasons why screening for people who have never smoked should not be implemented without further evidence from randomised trials.

CT screening detects non-lethal cancer in never smoking populations

Regular cigarette smoking is among the most potent risk factors for cancer. One of the first observations in chronic disease epidemiology was the strong relation between smoking and lung cancer death (fig 1 (top)).[14] Yet a 2001 study of CT population screening in Japan found little relation between smoking and lung cancer detection (fig 1 (bottom)).[15]

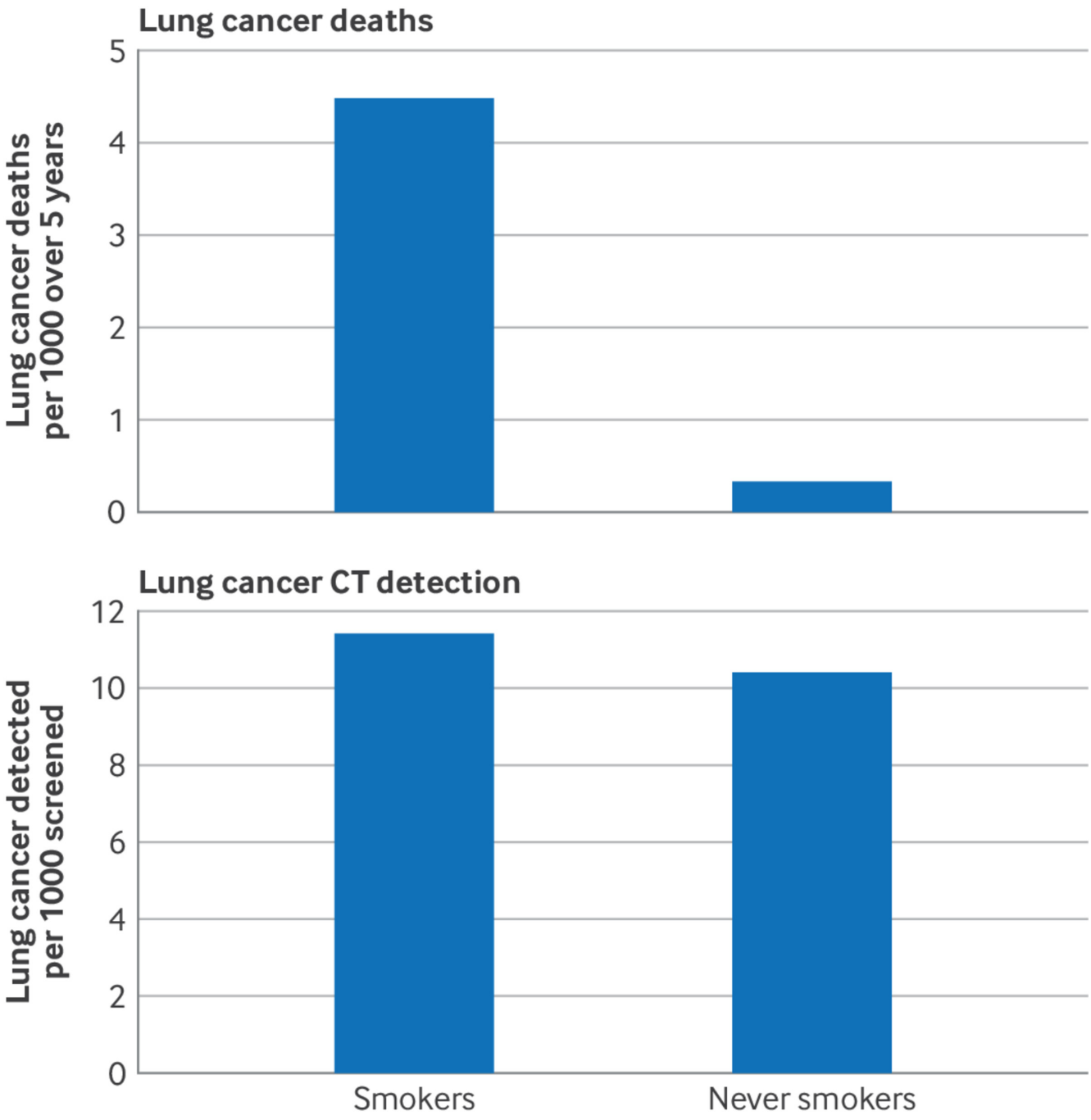

Fig 1 | Association between cigarette smoking and lung cancer death (top)[14] and lung cancer detection using CT (bottom)[15]

Why would smoking be so strongly associated with lung cancer death, yet so weakly related to lung cancer detection using CT? Proponents of screening might argue that the explanation is genetics—namely, that Asian people who have never smoked have an exceptionally high risk of lung cancer. However, lung cancer mortality is similar in Europe, Asia, and North America (21.4, 17.9, and 17.2 per 100 000, respectively),[16] making it unlikely that there are substantial genetic differences in the risk of clinically meaningful lung cancer.

Instead, the difference is more likely to be related to CT screening itself. Reported lung cancer detection rates in people who have never smoked have been extremely high in East Asia—nearly double that observed in randomised trials of people who smoked heavily (around 2% *v* 1%).[17 18] CT screening has obscured the association between smoking and lung cancer death with the addition of previously undetected, non-lethal lung cancers. Most cancers detected by CT in people who have never smoked cannot be seen on chest radiography; virtually all are adenocarcinomas (not large cell, small cell, or squamous cell carcinomas). Many are categorised as "minimally invasive" or even "in situ adenocarcinoma"—a term analogous to ductal carcinoma in situ detected in breast cancer screening.

Reported five year survival among people with adenocarcinoma presenting as ground glass opacities in East Asia now exceeds 95%.[19-21] Similar detection and survival rates might be expected among never smokers in other populations given equally aggressive screening practices.

Population screening does not reduce late stage presentation

Cancer overdiagnosis—the diagnosis of cancers that would otherwise not become clinically evident—is inferred from either long term follow-up of randomised trials of screening or patterns in population based cancer statistics.[22] Lung cancer overdiagnosis was first documented in the extended follow-up of a randomised trial of chest radiography screening in people who smoke heavily.[23 24] In the US National Lung Screening Trial (NLST), which recruited over 50 000 participants, CT screening was found to cause more overdiagnosis than chest radiography.[25]

Although no randomised trials have been conducted of lung cancer screening in never smokers, the effect of screening can be inferred from patterns in incidence of stage specific lung cancer. Effective screening should not only increase the incidence of early stage cancer but also decrease incidence of late stage cancer—demonstrating that early cancers detected by screening were otherwise destined to present as advanced cancers (ie, not overdiagnosed).

Stage specific incidence data are available for three East Asian countries (fig 2). The figure is restricted to women as the true occurrence of clinically meaningful lung cancer in Asian women would be expected to be stable given that their smoking prevalence has been stable at a low rate (<10%) for decades.[27 28] In contrast, the sharp decline in smoking prevalence among men has led to a fall in clinically meaningful lung cancer. The most prominent effect of screening of women who have never smoked has been increased lung cancer incidence: more early stage diagnoses, without a concomitant decline in late stage diagnoses. This suggests that CT screening of never smoking individuals leads to substantial overdiagnosis.

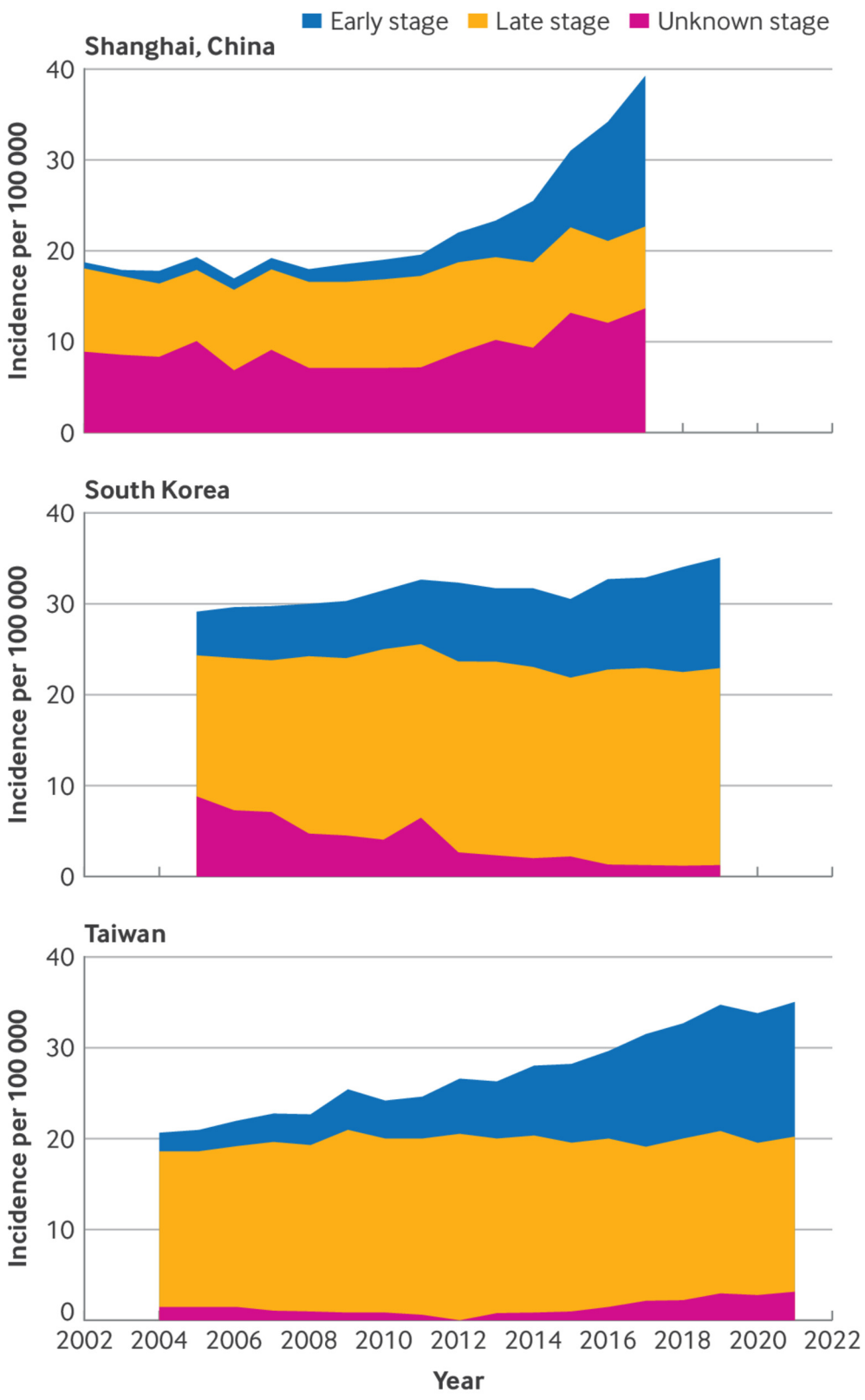

Fig 2 | Early and late stage lung cancer incidence among women in three countries in which CT screening has been promoted for people who have never smoked. Early stage comprises in situ and localised cancers; late stage comprises regional and metastatic cancers. Data are from Cancer Surveillance of Shanghai,[26] the Korea National Cancer Incidence Database, and the Taiwan National Cancer Registry

Proponents of screening might argue that long lead times make it too early to see the decline in late stage cancer. Indeed, assuming all cancers progress, the estimated average lead times in East Asia are long: 10 to 20 years compared with ≤ 2 years reported in

randomised trials.[29] However, long lead times themselves are a source of overdiagnosis—providing plenty of time for a patient to die from other causes before developing a symptomatic cancer. Furthermore, some cancers may regress.[30-32]

Screening induces more surgical procedures

Widespread screening in East Asian women has been associated with escalating lung resection surgeries, outpacing the rise in early stage lung cancer diagnoses (fig 3). Surgery is being used for diagnostic purposes, forgoing either less invasive biopsy procedures or serial imaging to assess nodule growth over time (reserving biopsy for those that grow). A Taiwanese study highlighted this phenomenon: among patients receiving pathological evaluation after CT screening, only 8% had a non-surgical biopsy (eg, needle biopsy, bronchoscopy), the remaining 92% went directly to surgery.[18] The median time from screening to diagnosis was roughly 3 months, suggesting most surgery was done soon after detection and that nodule assessment protocols were rarely used.

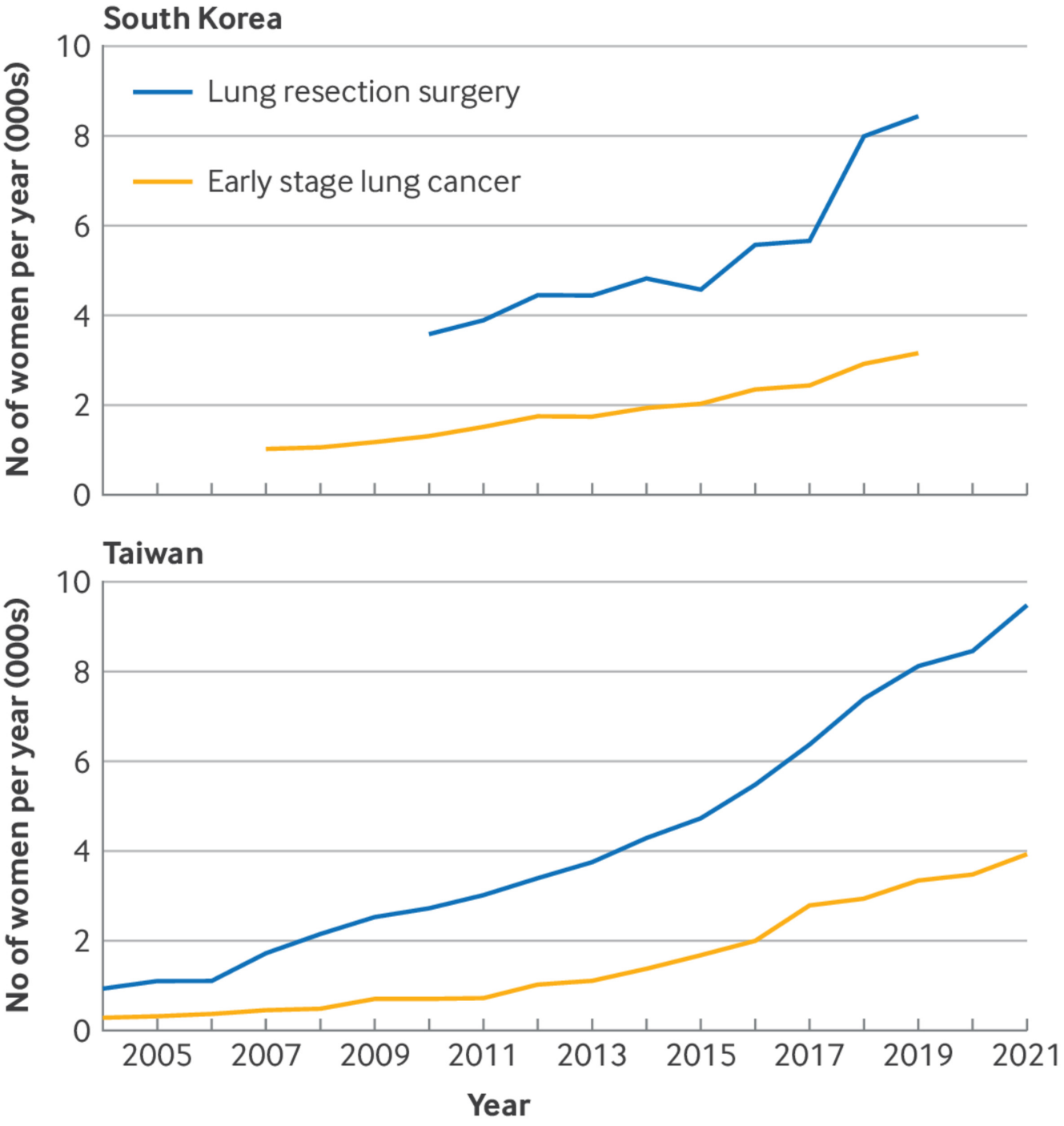

Fig 3 | Annual count of lung resection surgery and early stage lung cancer among South Korean and Taiwanese women. Lung resection surgery includes wedge resection, segmentectomy, lobectomy, and (rarely) pneumonectomy; early stage lung cancer includes in situ and localised lung cancers. Surgery data are from national health insurance claims in South Korea and Taiwan and incidence from national respective cancer registries

East Asian countries are not unique in using surgery without preoperative histological confirmation: early stage lung cancer is diagnosed surgically in a third of patients in the United States[33] and the Netherlands.[34] The "surgery first" approach has been fostered by the advent of minimally invasive alternatives to conventional thoracotomy (eg, video assisted thoracoscopic, robotic surgery) and evidence supporting limited resection.[35] Surgery is also encouraged, ironically, by the small size of CT detected lesions, which are easily missed by non-surgical biopsy.[36]

In the US, major complications are more common after surgery (25%) than bronchoscopy (16%) or needle biopsy (17%).[37] Any method of lung biopsy, however, poses a substantial risk of complications. The overall risk of complications in the US is roughly double that reported by the National Lung Screening Trial,[38] showing that complications in carefully managed trials are an underestimate of those in real world practice. These risks might be acceptable if CT screening reduced lung cancer mortality in people who had never smoked, but they are unacceptable when the benefit is unknown.

Screening produces deceptive feedback supporting more screening

Screening invariably produces feedback that seems to support more expansive screening. Efforts to look harder for cancer are immediately rewarded with higher cancer detection rates. The newly detected cancers are typically early stage, thus producing an apparently more favourable stage distribution. The proportion of diagnoses at a late stage will decrease simply because of the diluting effect of more early stage diagnoses, even if late stage incidence is unchanged.[39] Among Taiwanese women diagnosed with lung cancer, for example, the proportion diagnosed with late stage cancer fell from 90% in 2004 to 58% in 2018, even though the incidence of late stage cancer did not change.

By far and away the most deceptive feedback comes in the measurement of survival. In 2000, women diagnosed with lung cancer in East Asia had similar five year survival rates to those in other high income countries; now they far exceed them (over 50% in South Korea[40] and Taiwan[41] *v* 25% in England[42] and 30% in the US[43]). Because survival time is measured from the time of diagnosis, screening will always "start the clock earlier"—thus it will always lengthen survival times. Overdiagnosis magnifies the problem. Higher survival is taken as evidence that screening is effective at extending life. But lead time and overdiagnosis bias means screening always increases survival, even if no lives are extended.

Trial options

It is tempting to believe that efforts to detect cancer early can only help people. Yet only the very few never smokers destined to die from lung cancer could possibly benefit from screening, while all who are screened can be harmed. The East Asian experience has made those harms obvious: more surgery, more complications, and more overdiagnosis and overtreatment. What is not obvious is whether any lung cancer deaths have been avoided. Answering this question requires the highest standard of evidence from a randomised controlled trial.

Some might argue that modelling could show that a trial would be futile given the relatively low risk of lung cancer death in people who have never smoked. Modelling might show—even assuming the 20% relative risk reduction observed in trials among people who smoke could be extrapolated to those who never smoked—that the absolute mortality reduction is so small that screening could not be cost effective.[44] The model could also incorporate evidence suggesting that low risk groups do not benefit from screening: in the National Lung Screening Trial, for example, only one of the 88 lung cancer deaths prevented occurred among participants in the lowest quintile of lung cancer risk.[45] However, although a model might inform a trial, modelling is unlikely to deter proponents of screening for people who have never smoked.

Others might argue that risk prediction models could be used as trial eligibility criteria—to produce a higher risk, never smoking group (eg, Asian women with a family history and radon exposure) and increase the opportunity for screening to be effective. Although a higher risk group can be identified, it is hard to imagine that any combination of risk factors will approach the risks associated with cigarette smoking. In previous modelling of risk for 65 000 people who had never smoked, none exceeded the risk threshold proposed for screening (a 6 year risk of clinically detected lung cancer >1.5%).[46] Use of blood based biomarkers might help identify people at higher risk, but there is currently no evidence for this.

A better approach to a trial would be a pragmatic design using age criteria alone. Although risk based screening is conceptually appealing, it is problematic in practice. Discriminating among those who never smoked would be difficult for already overburdened primary care practitioners (imagine guidelines detailing how to handle mixed ethnicity or determine radon exposure). Adding further testing to determine eligibility would only add to that burden. The pragmatic policy question remains: should lung cancer screening be extended to those who have never smoked?

Whether eligibility is based on predicted risk or age alone, trials must also incorporate nodule assessment protocols to minimise overdiagnosis and overtreatment.[47] Although any trial would be expensive and take a long time, it would be far less expensive than putting population-wide screening into practice. Randomised trials have been the standard for other population-wide screening in breast, colorectal, ovarian, and prostate cancer. And there is no rush: lung cancer treatment is getting better and mortality is falling.

Public health policy makers must insist that the possible benefit of screening people who have never smoked is tested—not presumed or extrapolated. Modelling cannot produce evidence: all models require some assumption about a mortality reduction from screening or must infer benefit from a surrogate observation (eg, stage shift).[48] Non-randomised evidence should be ignored as such comparisons are vulnerable to prevention bias[49]: people who choose to be screened are systematically healthier than those who are not screened.[50]

Finally, policy makers have an ethical imperative to hold screening to the highest evidence standard. Whereas symptomatic patients actively seek medical care, preventive interventions are aimed at healthy people, who we persuade to consume medical care—and be exposed to its harms—on the implied promise of future benefit. Before exposing people who have never smoked to screening, we must be sure the promise is correct.

Key messages

- Enthusiasm is growing for lung cancer screening in people who have never smoked, despite their low risk of lung cancer death
- CT screening of never smokers has become common in parts of East Asia and has made the harms obvious
- Screening has resulted in more overdiagnosis and more lung resection (often without histological confirmation of cancer)

- The East Asian experience also highlights the deceptive feedback from screening, including high early stage detection rates and high survival rates
- Decisions about screening should be based on evidence from randomised trials in people who have never smoked not extrapolated from evidence in people who smoke heavily

Contributors and sources: HGW is a primary care practitioner and cancer epidemiologist who has investigated the effects of screening for 30 years. He wrote the initial draft and is the guarantor. WG is a professor of public health in Taiwan who served as the primary motivator for this article and contributed equally to HGW. He alerted HGW to the widespread opportunistic screening in East Asia, obtained the Taiwanese data, and made important revisions to the draft. FGW is a thoracic surgeon who helped interpret the surgical findings and ensured that the article's content was accessible to surgeons. SYK is a pulmonologist who obtained the Korean data and made important revisions to the draft. GAS is director of a lung cancer screening programme and was a site principal investigator for the National Lung Screening Trial (NLST). He was responsible for analysis and revisions of the article.

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