

Too Much Medicine: Time to Stop Indiscriminate Cancer Screening

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Like most industrialised countries in the world, cancer has now become the leading cause of mortality in Singapore. Approximately 1 in 3 deaths in Singapore today is as a result of cancer.¹ It is therefore unsurprising that cancer screening has become an integral part of health screening in primary health care today. The current Singapore's Ministry of Health as well as Academy of Medicine's guidelines are in keeping with most screening guidelines in the world in their recommendations of routine screening for breast, cervical and colorectal cancers in those with average risks based on appropriate age cutoff,^{2,3} as well as screening for additional cancers based on elevated risks such as family history. Nowhere in the guidelines are serum tumour markers recommended as a method of routine screening. Despite this, every day in primary health care setting in Singapore, serum tumour markers such as carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), CA153, alpha-fetoprotein (AFP), Epstein-Barr virus (EBV) serology are commonly included in packages of health screening. Indeed, an entire industry surrounding this concept of healthy living and early disease detection has sprung up locally in which one can spend a day in a spa-like "health screening centre" where health screening packages can be selected from a menu by a consumer. These packages are often dressed up in attractive sounding hyperboles such as "Premium", "Executive", "Deluxe", "Luxury" as well as the rather bland and less persuasive sounding "Basic" package. The last of which, ironically, is often the only one that is usually driven by guidelines. To compound this further, many of these health screening endeavours are not truly individualised according to personal risk factors despite their claims as such. In fact, the only personalised aspect of the screening appears to be based primarily on consumer request and how much he or she is willing to spend. Indeed, a healthy 30-year-old with no risk factors or symptoms can request and undergo a package that will include among them, a colonoscopy, an oesophago-gastroduodenoscopy and all the various serum tumour markers despite the fact that the likelihood of him being harmed far outweighs any potential miniscule benefit that may arise.

Just as troubling, is that these practices appeared to have also filtered across to many primary health practitioners as well as government hospitals in Singapore. Furthermore, third party health screening industries now also frequently contact business and educational institutions to sell health screening packages to their staff personnel.

In this issue of *Annals*, Tan et al⁴ described in a letter to the editor, 5 cases of medullary thyroid carcinoma detected through raised CEA from general health screening. They naturally concluded that the presence of a raised CEA should therefore prompt one to search for an underlying medullary thyroid carcinoma, with the inference that subsequent treatment will ultimately benefit the patient. However, a careful appraisal of the report and available data suggests that perhaps a very different conclusion should be made. In the 5 cases reported, the time it took from the detection of a raised CEA to the diagnosis of medullary thyroid carcinoma ranged from almost 2 to as long as 9 years. And despite this protracted interval, all of the cancers were still confined to the thyroid and none had metastasised to the lymph nodes. This suggests that there is a high probability that in fact, some of these tumours are incidental indolent cancers that would probably have never been detected or indeed become clinically relevant if it was not for the raised CEA. That is to say, that some, if not all, of the patients presented in the report would probably have died from other causes unrelated to thyroid cancer without ever having been diagnosed with the condition.

This seeming paradox is a well recognised phenomenon in screening known as overdiagnosis. Overdiagnosis occurs when a condition is diagnosed that would otherwise not go on to cause symptoms or death. Cancer overdiagnosis may have of 1 of 2 explanations: 1) The cancer never progresses or in fact, regresses, or 2) the cancer progresses so slowly that the patient dies of other causes before the cancer becomes symptomatic.⁵ Although the notion of an indolent cancer may be alien to many, the best example can be illustrated in prostate cancer. Autopsy series in men who have died from conditions unrelated to prostate cancer have demonstrated the presence of prostate cancer in as high as

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80% of 70-year-olds whom were not known to have this diagnosis previously.⁶ Yet for many, the probability of dying from prostate cancer remains significantly lower. This means that many men in their old age will develop prostate cancer but few will ever be aware of it or be clinically affected by it. But by screening for the disease in an asymptomatic elderly man, there is a high chance that the condition will be diagnosed. This phenomenon of overdiagnosis is now also well documented in multiple other malignancies including breast, lung, thyroid, neuroblastoma and kidney cancers.⁵

It is timely to revisit and understand the objectives of cancer screening. Screening aims to find a cancer earlier and therefore provide timely treatment with the ultimate goal of reducing long-term relapse and prolonging survival. However, if screening does not achieve the latter goals but merely finds the cancer earlier (known as lead time bias) or worse, just finds more cancers (overdiagnosis bias); then that screening itself is clearly undesirable. Overdiagnosis can be estimated through studies such as ecological, cohort and randomised control trials.⁷ Many randomised trials in cancer screening have been instrumental in allowing us to measure the benefits and harms of screening.

Take for example, ovarian cancer screening. CA125 is a serum tumour marker associated with ovarian cancer and a common test included in many of the health screening packages available in Singapore today. However, a recent trial of ovarian cancer screening provided some sobering results. In this study, close to 80,000 women aged 55 to 74 were randomised to receive annual CA125 blood test as well as transvaginal ultrasound compared to no screening,⁸ with the primary goal of demonstrating a reduction in mortality. Unfortunately the results showed no difference in the 2 groups in terms of number of ovarian cancers detected, the stages of cancer detected nor any differences in deaths from ovarian cancers or otherwise. Moreover, in women that were screened, 10% of them had a false positive result i.e. being told that they had cancer when they did not. Of these, one-third had to undergo major surgery and 15% suffered a major complication. These highly disappointing results underscore the importance of the necessity to base rational screening decisions on available evidence. Recent results from a separate randomised trial that interpreted serial CA125 change through a risk algorithm have shown more promising outcome in detecting ovarian cancers. However, final results on mortality outcome are still pending and eagerly awaited.⁹ Till then, it remains difficult for one to justify the utility of ovarian cancer screening. Indeed, based on the aforementioned study, not only is ovarian cancer screening with serum CA125 and ultrasound useless, it is actually potentially detrimental. To put this in another manner, if one were to submit to the reader for consideration, a new antihypertensive that does not actually reduce blood

pressure but has potential side effects that mimic cancer which may result in unnecessary surgery with resultant major complications; it is clear that no sane-minded readers, let alone the health funding authorities, will ever allow this medication to be included in the prescription list. Yet every day in Singapore right now, serum CA125 blood tests are being offered and performed in women as part of cancer screening despite clear evidence confirming these very detrimental harms.

Finally, it is perhaps pertinent in this editorial prompted by thyroid cancer to heed a cautionary tale from a neighbouring country, South Korea. The leading cancer diagnosed in South Korea today is thyroid cancer. The age-adjusted incidence rate of thyroid cancer per 100,000 persons soared astronomically from 7.2 in 1999 to 61.9 in 2010.¹⁰ There is no clear environmental reason for this rapid surge in thyroid cancer cases. Disturbingly, the root for this disconcerting epidemic appears to be iatrogenic. Many hospitals in South Korea market “health check-up” programmes that include thyroid cancer screening with ultrasonography and many general practitioners also have ultrasonography machines in their offices and routinely perform thyroid scanning.¹¹ With such a large increase in number of cases, one would naturally expect the death rate from thyroid cancer to fall correspondingly since one is detecting these cancers at an earlier stage and hence, treating and curing it. Yet despite this surge in diagnosis, the actual mortality from thyroid cancer has remained virtually unchanged in the country over the same time period. This suggests very strongly that all these excess cases are in fact, overdiagnosed, indolent and clinically irrelevant cancers. This disconcerting data rightfully led to concerns expressed by physicians in South Korea with calls for the screening to be banned in the country. Unfortunately, these pleas have been largely ignored¹² and with thyroid cancer now being the leading cancer in the country, this vicious cycle looks unlikely to abate with consumers and health providers seeing the cancer’s position on the league table alone as justification to continue this approach.

As much as 1.5 trillion won (S\$1.8 billion) is estimated to be spent annually on thyroid ultrasounds in Korea¹³ and the Korean National Health Insurance Service spent 260 billion won (S\$315,000,000) on treating thyroid cancer alone in 2012.¹⁴ It is not difficult to see who the eventual true beneficiaries from all these indiscriminate screenings are.

In conclusion, it is imperative for us to recognise that all screening endeavours cause harm. Some also generate good as well and it is only those that create more good than harm that should be considered for adoption in clinical practice. Although the aim of health providers in providing screening may have been well intended, failure to adhere to guidelines may inadvertently result in unfortunate

harms. Our supposedly noble profession is founded on the principle of *Primum non nocere*: First do no harm. We owe it to ourselves and the larger community to reconsider this current practice of potentially harmful, indiscriminate and non-evidence based cancer screening.

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