Cancer Screening, Surrogates of Survival and the Soma

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Summary

Screening leads to meaningful reductions in deaths from the respective cancers. However, reductions in all-cause mortality (ACM) are harder to demonstrate. Failure to demonstrate ACM benefit should not diminish advances in cancer screening. We consider how co-morbidities related to an aging and damaged soma can hinder achievement of ACM benefit.

Reducing deaths from a specific cause is the gold-standard primary endpoint for cancer screening trials. Reducing deaths from a particular cancer type should translate to an improvement in all-cause mortality (ACM), unless investigation of positive screen results leads to deaths from other causes. However, few studies are powered to detect the relatively small impact on ACM that one would anticipate from cancer screening.

Enthusiasm for the important reduction in lung cancer mortality demonstrated in the recently published NELSON lung CT screening trial (de Koning et al., 2020) has been offset by concerns from some on lack of ACM benefit. In the screened group, there were 160 lung cancer deaths out of 868 total deaths in 6583 patients, compared with 210 lung cancer deaths and 860 total deaths in 6612 patients in the control arm (de Koning et al., 2020). Whereas the reduction in lung cancer mortality was highly significant, there was no difference in ACM between the arms (13.93 versus 13.76 deaths per 1000 patient-years in the screening and control arms, respectively). In contrast, in the National Lung Screening Trial (NLST) with 53,000 participants, there was a 6.7% reduction in overall mortality (95% CI, 1.2 to 13.6; P=0.02) in the low-dose CT group relative to the chest radiography group (NLST, 2011).

Whereas there have been many trials of various forms of cancer screening showing a significant reduction in cause-specific mortality, NLST is unique in showing a significant effect on ACM. What transpires is that implementation decisions need to be made based on

imperfect evidence. Should a small hypothetical relative increased risk of all-other causes of mortality be allowed to counter-balance a clearly demonstrated reduction in cause-specific mortality (Saquib et al., 2015)?

Here we present the challenges in ACM endpoints and propose statistical solutions to address concerns regarding potential harm. We consider the challenges to improving ACM in the context of cancer evolution within an aging soma where the presence of a malignancy could reflect physiological decline, contributing to non-cancer deaths and permitting malignant clonal expansions. We argue for redoubled efforts to understand the biological links between aging and cancer and consider more holistic approaches to screening and preventive medicine.

The Problem of Power

The main reason for screening trials failing to demonstrate a reduction in ACM is that they are underpowered for an ACM endpoint. Screening studies would require hundreds of thousands, if not millions of patients to demonstrate a statistically significant reduction in overall mortality (Sasieni and Wald, 2017). Competing risks of death (colorectal cancer accounts for 3% of all deaths in the UK) mean ACM could only ever be lowered by 1-3% by a population screening procedure focussed on one cancer type (Penston, 2011). Studies powered to demonstrate ACM benefit are beyond the realms of all major funders, necessitating cancer-specific mortality endpoints.

Insisting on ACM endpoints for healthcare implementation would have a detrimental impact on the population. For instance, trials of HPV vaccination have not shown that vaccination leads to a reduction in invasive cervical cancer, let alone cervical cancer mortality and there is no evidence regarding ACM. Yet, HPV immunization, introduced from 2008, has led to dramatic reductions in type-specific HPV infections in targeted cohorts (Drolet et al., 2019) and this is the basis for the WHO's global strategy for elimination of cervical cancer. Had we required a reduction of ACM to be demonstrated before vaccines could be used outside of trials, we would still be far from licensing a vaccine. Not only would a whole generation of women have lost out due to lack of vaccine use, but no pharmaceutical company would have invested in vaccine development knowing that it would take so long (and so many billions of dollars) to conduct such a trial. Requiring demonstration of ACM in clinical trials before implementation would prevent virtually all public health advances.

First do no Harm

It is possible that a positive screen result (including a false positive) may have a detrimental impact on health, or "off-target deaths", due to further medical interventions or cardiac events and suicides. We know of no evidence demonstrating a sizeable number of such off-target deaths (there are very rare reports of individuals dying within 60 days of surgery investigating a positive screen). False-positive screens are not uncommon and if the harm of subsequent investigations was a moderate and long-term increase in mortality rates (as opposed to a massive but transitory increase) it would be difficult to detect.

Demonstrating a statistically significant reduction in ACM is, perhaps, too stringent. A more reasonable requirement might be a probability of say two-thirds that there is a relative reduction (RR) in ACM of at least 0.5% (i.e. RR < 0.995). A Bayesian approach requires a prior or distribution for the true effect. A reasonable prior for ACM relative risk might be a log normal distribution with mean 1 and standard deviation 0.025. Based on a fixed-effects meta-analysis of the ACM relative risk for the eight trials investigating mammographic breast screening (4), the estimated ACM relative risk is 0.981 (95% CI 0.961 – 1.002) with a posterior probability of 87% that it is less than 0.995. A similar meta-analysis of ACM relative risk for the lung CT trials including NLST and NELSON would be 0.970 (0.919 – 1.023) with a posterior probability of 68% that relative risk is less than 0.995. Indeed, for major cancers, there is a strong correlation between the observed (from meta-analysis of randomized controlled trials) relative hazard for ACM and the relative hazard that would be expected if screening affects the risk of cause-specific mortality without an effect on other causes (**Fig. 1 and Table S1**).

There is understandable urgency to act with respect to lung cancer screening. If results from the NELSON trial can be extrapolated to the global population, tens of thousands of deaths from lung cancer could be prevented. Whilst calls for suspending implementation until further lung cancer screening trials are completed are hard to justify, current ongoing studies could consider using statistical approaches to refute an increase in deaths associated with a positive screen. Bayesian utility analysis could be used to address whether lung cancer screening should be adopted nationally. One would combine the strong evidence from randomized controlled trials regarding a reduction in lung cancer-specific mortality with observational evidence on other causes of death from implementation cohorts, to analyze the expected utility of national roll-out.

Cancer and the Aging Soma

There is a third non-mutually exclusive reason for why the observed effect on ACM might be less than anticipated from the effect on lung cancer mortality, emerging from recent insights from studies of normal tissue. Perhaps a diagnosis of cancer is a marker of biological aging tissue which might lower the threshold for clonal expansions of pre-malignant cells and impact other organs such as the cardiovascular system. The risks of death from cancers, cerebrovascular disease, and ischaemic heart disease all rise concomitantly in the elderly **(Fig. 2A)**.

One example of this is clonal hematopoiesis of indeterminate potential (CHIP), which refers to the expansion of blood cell clones in patients without evidence of other hematological abnormalities (Cook et al., 2020). CHIP is commonly driven by oncogenic mutations, increases in prevalence with age, and is associated with smoking and inflammation. CHIP is a strong risk factor for leukemia, cancers in general, and ACM. Surprisingly, patients with CHIP exhibit a two-fold increased risk of coronary heart disease and a four-fold increased risk of myocardial infarction. Studies in mice show that hematopoietic clonal expansions involving TET2, frequently mutated in CHIP, can accelerate atheroma in mice prone to hypercholesterolemia, dependent on increased inflammation elicited by TET2 mutant myeloid cells (Cook et al.,

2020), suggesting that clonal hematopoiesis may directly promote cardiovascular disease (CVD). Another non-mutually exclusive explanation is that CHIP, cancer, and CVD are correlated because they share common underlying risk factors, such as aging, inflammation, and smoking.

Similarly, chronic damage to a tissue, such as from cigarettes, may permit clonal expansions and impair the function of multiple organ/tissue systems simultaneously (Laconi et al., 2020). Like aging, smoking increases the risk for many other diseases. Chronic obstructive pulmonary disease is associated with a several-fold increased risk of lung cancer independent from smoking (Takiguchi et al., 2014). Additionally, alpha-1-antitrypsin deficiency, a disorder that alters the lung microenvironment, results in premature emphysema in smokers, and a 4-7 fold increased risk of lung cancer in never smokers (Torres-Duran et al., 2015). Notably, CHIP is associated with chronic pulmonary disease and higher ECOG performance status scores (poorer functioning) (Cook et al., 2020), suggesting that multi-tissue/organ decline could contribute to increased risk of multiple diseases. Finally, the immune system declines in old age, and it has recently been suggested that thymic involution and declining T cell output with age explains relationships between infectious disease susceptibility, cancer and aging (Palmer et al., 2018).

Cancers of the lung and other sites are highly associated with comorbidities, even at diagnosis (Gould et al., 2017). Notably, the association of higher comorbidity classification and worse survival is strongest for localized disease (stage 0-II lung cancers) (Gould et al., 2017). The authors surmise that "*This finding has implications for lung cancer screening programs in that multimorbidity may be a marker of frailty or severity that would be a contraindication to screening.*" These associations are logical, as lung cancer is strongly associated with old age and cigarette smoking, which both increase the risks of many diseases such as CVD. Indeed, even without lung cancer-specific deaths, 35-40% of people diagnosed with lung cancer would die prematurely (from causes other than lung cancer), whereas the corresponding figures for breast and colorectal cancers were 2.5% and 10-15%, respectively (Sasieni et al., 2002).

Those with screen-detected (but eradicated) malignancies may not survive as long as those without cancer, due either to 1) complications resulting from surgery, radiation, or other intervention for the malignancy, or 2) other diseases associated with an aged or damaged soma that favored the growth of the tumor in the first place. Deeper analysis of individual patient data from screening trials could help unravel answers to these questions. Patient level data from screening trials may help address whether those with a positive screening result are at greater risk of co-morbidity that might pose a risk to future longevity that could be mitigated by further intervention.

Optimizing screening and addressing co-morbidities

Aging, smoking and other assaults on tissue health could concomitantly raise the risks of multiple diseases favored by aged and/or damaged tissues. Such diseases are manifestations of a declining or damaged soma. Understood from this perspective, an individual for whom screening detects an early stage malignancy, and thus decreases the odds of death from that

cancer, may still be at increased risk of other diseases (such as CVD and other cancers) relative to those with negative results from the screening (**Fig. 2B**).

Therefore, when a malignancy is identified through screening, perhaps more attention could be paid to the impact of systemic decline on other tissues. Arguably, a more holistic approach to the patient could be considered, monitoring and mitigating other high-risk events such as cardiovascular and cerebrovascular disease as well as second cancers.

Next steps

The challenges inherent to proving ACM benefit should not mean that early detection and screening approaches should be abandoned. Indeed, chasing ACM endpoints may not only be unobtainable in most cancer types, but would slow progress in early detection and prevent timely adoption of beneficial screening technologies. Nonetheless, statistical and modelling approaches can be taken to provide reassurance that off-target deaths are not a real concern and that ACM is almost certainly decreased as a result of screening that reduces cancer-specific mortality and to justify population-level implementation. We can also ask whether screening (and lung cancer screening, in particular) can be improved by assessing and responding to overall somatic decline and linked comorbidities associated with a cancer diagnosis.

We need approaches to determine when someone is truly at risk for cancer progression as opposed to those bearing a benign lesion or an indolent tumor that may never result in death, or when death from some other cause is likely to outpace cancer progression to a life-disruptive stage. The promise of ctDNA technologies to detect multiple distinct cancer types at an early stage may improve the sensitivity and specificity of early detection and screening approaches and hold promise to improve ACM outcomes (Srivastava and Hanash, 2020). For instance, in the Nelson trial (de Koning et al., 2020), there were 307 deaths from lung cancer and 607 from “other neoplasm” so a screening test that successfully targets multiple cancers (including lung) would likely have increased impact on ACM. Comprehensive screening tests that can detect multiple cancer types at an early stage are urgently needed.

Biological age based on CpG DNA methylation profiles has been shown to predict the risk of cancer, heart disease, and Alzheimer’s disease, as well as frailty and time to death (Horvath and Raj, 2018). CHIP may also serve as an indicator of overall physiological fitness, as clonal evolution is promoted by degraded tissue microenvironments (Laconi et al., 2020). Understanding the relationships between an aging adaptive immune system and how to reverse immune dysfunction may hold promise to reduce the risk of dying from both cancer and infectious disease with age. Leveraging indicators of biological age, with further study, could inform decisions on who to screen and, for those with positive results, whether interventions would be beneficial.

Finally, screening methods could be integrated with other measures of fitness decline like frailty. Risk stratification oriented to biological age rather than chronological age and focusing clinical care and screening approaches towards a systems level, rather than cancer-specific,

view may increase the impact of screening on ACM. CpG methylation profiling, CHIP and inflammatory markers could help hone the predictive value of early screening tests.

More radically, can we change how we respond to a positive test result, even if it leads to a diagnosis of cancer? In addition to eliminating the early malignant lesion, if we also recognize the cancer as a surrogate of declining soma, we might be able to develop interventions to simultaneously lower the risk of other diseases associated with aging tissues. Such interventions could include anti-inflammatory or CVD-risk lowering drugs, as well as dietary and exercise recommendations and support. Viewing a cancer diagnosis through the lens of an aging soma and understanding the biological basis of cancer and aging may encourage a broader, more holistic approach to screening and preventive medicine.

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Competing Interests

C.S. receives grant support from Pfizer, AstraZeneca, BMS, Roche-Ventana, Boehringer-Ingelheim, Ono Pharmaceutical and *Archer DX Inc (*Archer Dx Inc. collaboration in minimal residual disease sequencing technologies.) C.S. has consulted for Pfizer, Novartis, GlaxoSmithKline, MSD, BMS, Celgene, AstraZeneca, Illumina, Genentech, Roche-Ventana, GRAIL, Medicxi, and the Sarah Cannon Research Institute. C.S. is Chief Investigator for the AstraZeneca MeRmaiD1 clinical Trial). C.S. has stock options in Apogen Biotechnologies, Epic Biosciences and GRAIL, and has stock options in and is co-founder of Achilles Therapeutics. C.S. holds patents relating to assay technology to detect tumour recurrence (PCT/GB2017/053289); to targeting neoantigens (PCT/EP2016/059401); identifying patent response to immune checkpoint blockade (PCT/EP2016/071471); determining HLA LOH

(PCT/GB2018/052004); predicting survival rates of cancer patients (PCT/GB2020/050221); to treating cancer by targeting Insertion/deletion mutations (PCT/GB2018/051893); identifying insertion/deletion mutation targets (PCT/GB2018/051892); detecting tumor mutations (PCT/US2017/28013); and identifying responders to cancer treatment (PCT/GB2018/051912). P.S. has acted as a scientific advisor for GRAIL, which paid for his travel to the GRAIL meeting and for his time. J.D. and P.P. declare no competing interests.

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Figure Legends

Figure 1. Predicting all-cause mortality (ACM) under the assumption of no off-target effects.
The logarithm of the observed relative hazard for ACM is plotted against its predicted value. There is one point per screening modality. Each point is the pooled effect from a meta-analysis using all the data from Table 2 in Saquib et al. (Saquib et al., 2015), plus more recent results for ERSPC, UKCTOCS and NELSON (**Supplemental Table 1**). The predicted value is the logarithm of the ACM relative hazard assuming that screening reduced cause-specific mortality and had no effect on mortality from other causes. First a predicted value was calculated for each trial using the observed cause-specific relative hazard and the proportion of all deaths due to that cause in the control arm of the trial. Then an average value was calculated for each screening modality using inverse-variance weighted meta-analysis. The size of the points is proportionate to the inverse variance of the pooled effect estimates.

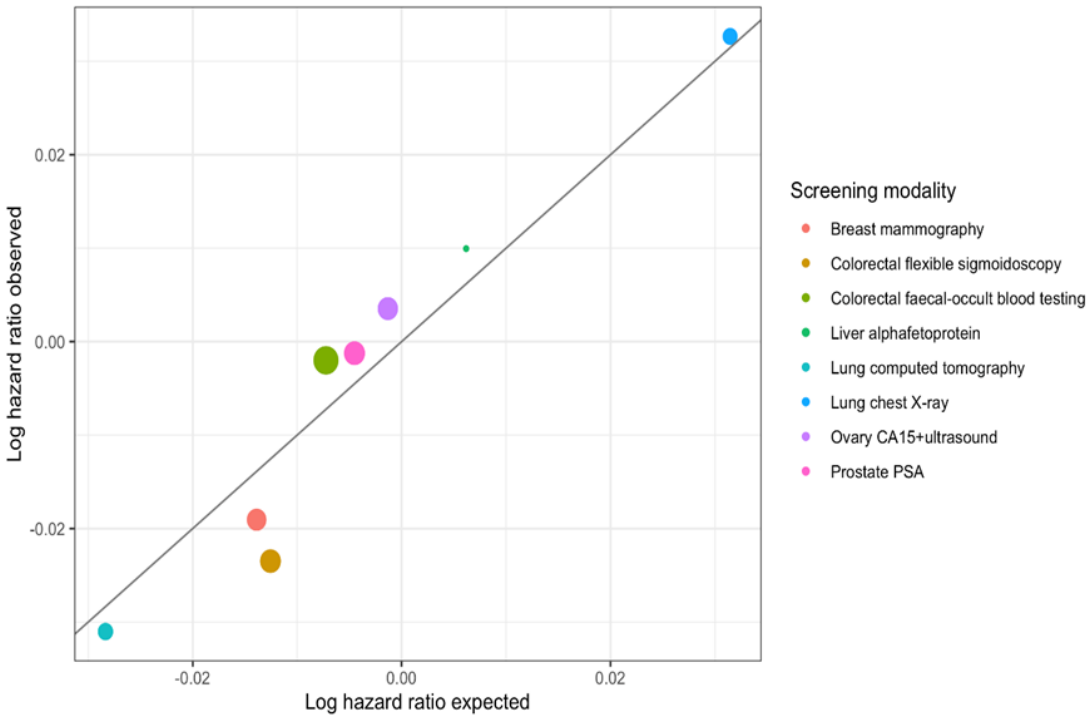

Figure 2. **Physiological decline with aging engenders risk for multiple diseases.**
A. Mortality in England in 2018 from the indicated cancers, cerebrovascular disease, ischaemic heart disease, and other causes. Data are from Office for National Statistics, Death Registrations, England and Wales 2018. (https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset). **B.** Aging and other factors (like smoking) lead to a multi-system physiological decline and increased risk of multiple diseases, which can be inferred from assays for CHIP, frailty and epigenetic age. We suggest that the detection of a cancer should also indicate increased risks from other diseases, which should stimulate enhanced monitoring and/or preventative interventions (CT screening for lung cancer shown as an example).