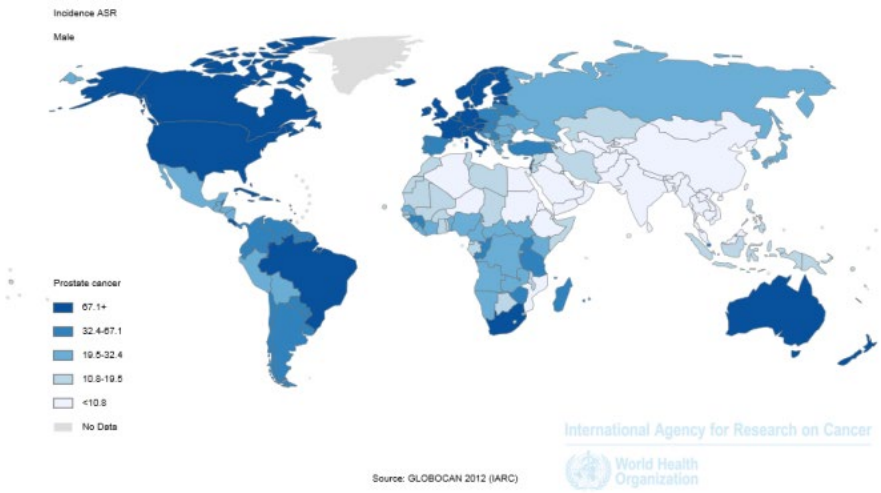
Ideas for the Prostate Cancer Study Committee

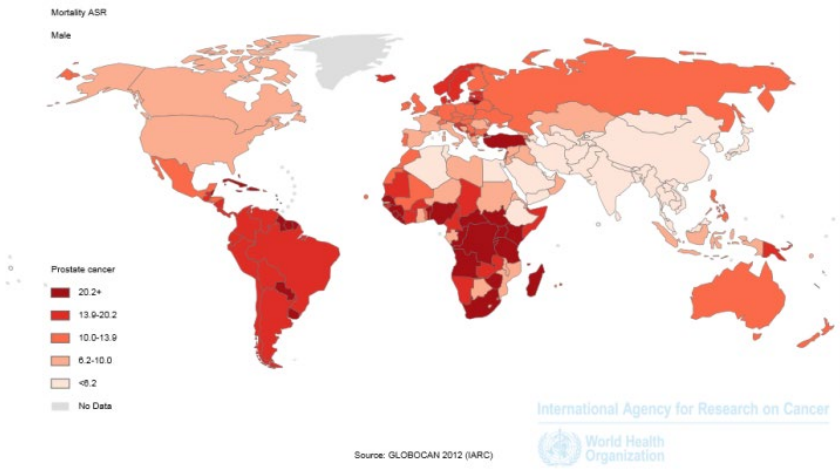
Submitted by Dr. James R. Hébert on 30 November 2023

The Problem: Prostate cancer (PrCA) is often an indolent disease (i.e., it is usually slow-growing and unlikely to lead to disability or death in most men). However, in a subset of men (i.e., especially African Americans and individuals with a family history of prostate cancer) the disease can be deadly. Therefore:

1. It is important to distinguish the primary non-behavioral risk factors according to their relative importance. Prostate cancer rates will increase by age. However, as with most hormone-sensitive cancer virulence (i.e., aggressiveness) decreases with age! The most important background factors are race and family history.
2. It is also important to keep in mind that broad, population-based screening fell into disfavor after the US Preventive Services Task Force recommendation was released in 2008. [1] The rationale behind this recommendation is nicely described in a 2011 article, also published in the Annals of Internal Medicine [2] and other commentaries published shortly after the report was released.[3,4]
3. Aware of the problems with overtreating indolent PrCA (e.g., harmful side effects of treatment including impotence and incontinence) I was initially supportive of the US Preventive Services Task Force recommendations. However, upon closer examination of the data, I became a skeptic.

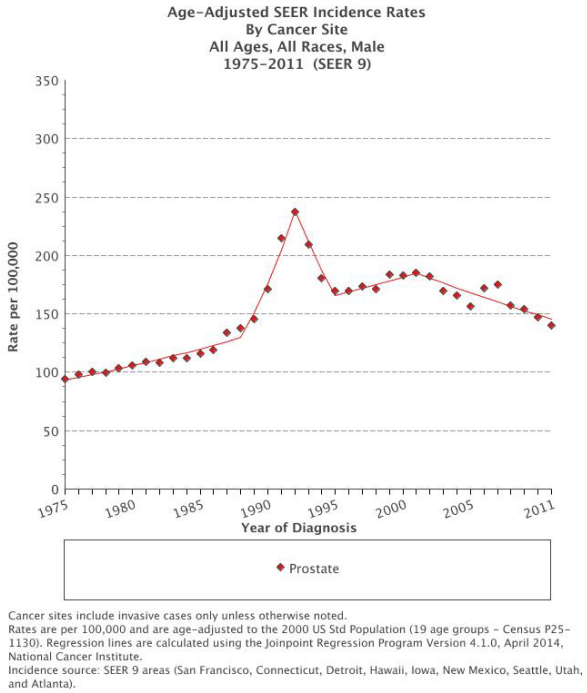


As these maps based on data from IARC (these are from 2015, well after the new US guidelines went into effect) show, there is an interesting inverse relationship between global prostate cancer (PrCA) incidence ↑ and ←mortality. Here we can see that countries with very high rates of PSA screening tend to have

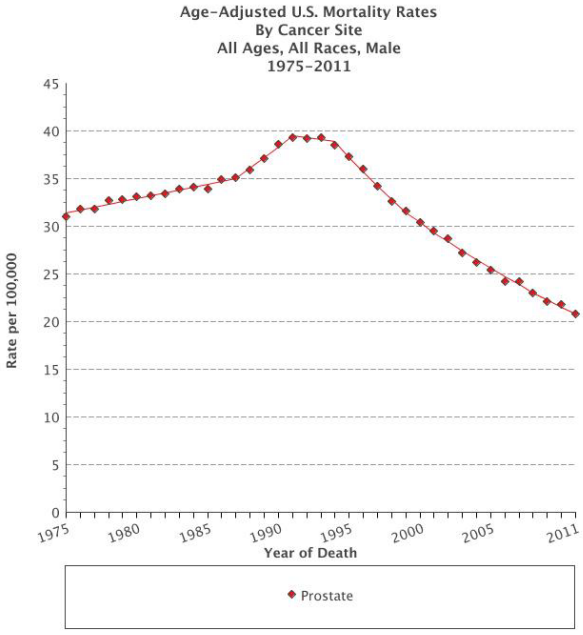


very high PrCA incidence. However, it's equally (maybe more!) interesting to note that many of these countries; e.g., the US, have a relatively low mortality rate (i.e., we are only in the second mortality quintile).

Even cursory examination of US PrCA incidence and mortality data reveals that the US has such high incidence because we have had a long (>quarter of a century – from 1989 to 2008)



Cancer sites include invasive cases only unless otherwise noted.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 4.1.0, April 2014, National Cancer Institute.
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).



Cancer sites include invasive cases only unless otherwise noted.
Mortality source: US Mortality Files, National Center for Health Statistics, CDC.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 4.1.0, April 2014, National Cancer Institute.

tradition of PSA screening . What is interesting in those data is a decrease in mortality, which is totally consistent with: a) the international view (seen in the maps shown above) and b) mortality reduction in at least some subset of the US population.

So, I would infer from this relatively simple, though stark, comparison that such heavy screening leads to a reduction in overall mortality (otherwise, we would be in the highest quintile for both incidence and mortality). The problem, of course, is that we identify many indolent cancers that are treated much too aggressively. Hence, the US Preventive Services Task Force recommendation against universal, population-based screening. To some extent, the failure to target how, and in whom, to screen has led to the current sad state of affairs. In a very practical sense, the largest disbeneficiary group has been African-American men.

4. Although the US Preventive Services Task Force was incorrect regarding their final conclusion, they were right about one thing: a single PSA measure is less than useless as a screening test for PrCA. With this in mind we set out to test the utility of multiple PSA tests. The ideal data set in which to examine the hypothesis that additional days of data improve prediction for high-risk PrCA is the National Cancer Institute's large Prostate, Lung, Colorectal, and Ovarian Cancer (PCLO) screening trial. In that trial, disease-free individuals

were screened on a yearly basis for these cancers. So, we had data on >20,000 individuals who submitted to annual PSA screens. We devised an algorithm to identify high-risk prostate cancer that dramatically increased sensitivity and specificity of the test (to about 97% for each overall – paper attached). [5] Although it is unusual to be granted a patent on an algorithm, we were granted US Patent 10,042,977 by the USPTO on 7 August 2018 for a "Method Utilizing Repeat PSA Screening for Diagnosis of Virulent Prostate Cancer."

Next Steps:

1. Given what I heard on the 29th of November, there seems to be enthusiasm for beginning a program to screen for virulent prostate cancer. PSA alone is an inexpensive test. Though a single PSA measure is close to useless (and this formed the basis for US Preventive Services Task Force recommendation), it there is evidence that multiple PSAs are useful in detecting virulent prostate cancer. Many committee members expressed that the focus should be on rural areas. I would be fine with including both rural and urban areas. However, I do think we should focus on areas that have high proportion of African-American residents. Salient points regarding the design of a screening program:
   a) We would want to establish a program through which we could conduct annual screening along the lines of what the PLCO did. While I do think this should have a research component, the main purpose would be to identify people who have a high likelihood of harboring and aggressive PrCA based on the screening algorithm.
   b) Because aggressive cancers are more likely to occur in African Americans and the most dangerous of these will develop at young ages, we should focus on younger men in whom we are more likely to find aggressive disease.
   c) In order to entice people to participate we need to have strong community support. We have had a lot of experience conducting community-based participatory research (CBPR) and many people in the room have excellent community relations. So, this could go well.
   d) We need to include an important educational component. There's no point in screening people do not know, specifically, what they will do with the information obtained from screening.
   e) There is also an important need, as mentioned in our meeting to educate providers. This should be an important part of the program.
   f) Besides conducting repeat PSA's, we also could randomize areas to provide digital rectal exams (DRE). This could provide a really interesting contrast between PSA + DRE and repeat PSA alone.
   g) If we are able to get this off the ground we could invite other centers from around the country to participate. I know there's a lot of interest in doing this in the VA and other places in the South, West Coast, Midwest, and Northeast. First, however, we need to "get our ducks in order."

   I have written an entire protocol on this. However, I believe it is premature to share this.

2. We could also use existing data from the South Carolina Central Cancer Registry (SCCCR) to deepen our understanding of the problem. For example, previously we examined the association between prostate cancer incidence and soil and groundwater zinc levels (zinc is

implicated in PrCA and African-Americans down regulate zinc absorption). [6] This enabled us to use environmental data from the Data Warehouse that was created by the Budget and Control Board under the leadership of Frank Fusco. This is a novel use of data that are uniquely available in South Carolina. Such analyses could be done fairly inexpensively and relatively quickly.

3. The South Carolina Cancer Alliance (SCCA) was created as an alliance of organizations. We have previously obtained funding from the SCCA to conduct prostate cancer research. Many of the organizations represented by people on this committee are SCCA members.

References:

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2. Chou R, Croswell JM, Dana T, Bougatsos C, Blazina I, Fu R, Gleitsmann K, Koenig HC, Lam C, Maltz A, Rugge JB, Lin K. Screening for prostate cancer: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2011;155(11):762-71.
3. Lewis CL, Couper MP, Levin CA, Pignone MP, Zikmund-Fisher BJ. Plans to stop cancer screening tests among adults who recently considered screening. J Gen Intern Med 2010;25(8):859-64.
4. Zeliadt SB, Hoffman RM, Etzioni R, Gore JL, Kessler LG, Lin DW. Influence of publication of US and European prostate cancer screening trials on PSA testing practices. J Natl Cancer Inst 2011;103(6):520-3.
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6. Wagner SE, Burch JB, Hussey J, Temples T, Bolick-Aldrich S, Mosley C, Liu Y, Hebert JR. Soil zinc content, groundwater usage, and prostate cancer incidence in South Carolina. Cancer Causes Control 2009;20(3):345-53.