Published in final edited form as:

Eur J Epidemiol. 2017 June ; 32(6): 477–479. doi:10.1007/s10654-017-0265-8.

Prostate cancer incidence as an iceberg

Lorelei A. Mucci, ScD, MPH^{1,2,3}, Claire H. Parnar, MPH¹, Sam Peisch, BA¹, Travis Gerke, ScD, MPH⁴, and Kathryn M. Wilson, ScD, MPH^{1,2}

¹Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA USA

²Channing Division of Network Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, MA USA ³Division of Public Health Sciences, University of Iceland, Reykjavik, Iceland ⁴Department of Epidemiology, Moffitt Cancer Center, Moffitt, FL USA

The epidemiology of prostate cancer is enigmatic. Globally, 1.6 million men were diagnosed with prostate cancer in 2015(1), a notable 66% rise in its incidence from the prior 10 years. It is the most commonly diagnosed cancer in men in 103 countries, yet there is marked variation in age-adjusted incidence rates across countries and populations. A panel of epidemiologists are likely to agree only on the following risk factors as “established”: older age, African ancestry, and positive family history of prostate cancer.(2) It is the cancer with the second-highest estimated heritability(3), and genome wide association studies have now confirmed more than 180 inherited genetic risk loci in ethnically diverse populations(4, 5). Taller height is also a probable risk factor for total prostate cancer.(6) Given the global burden of this cancer, it is alarming that there are no confirmed modifiable risk factors for prostate cancer incidence overall, which complicates our etiological understanding of the disease.

The study by Valberg *et al* in the *Journal* tackles part of prostate cancer's enigma by illuminating the dramatic effect prostate-specific antigen (PSA) screening on the descriptive epidemiology of prostate cancer.(7) The authors focus nicely on the “natural experiment” of PSA screening, first introduced in the United States (US) in the late 1980s and in other countries (including Norway) in the 1990s, and how its uptake has altered the diagnosis of this disease. The authors show that PSA screening has led to the characteristic patterns of prostate cancer incidence rates in Norway and the US; with rates increasing soon after screening was introduced in these countries followed by recent decreases in the US as the pool of susceptible men has been depleted.

Such time trend patterns were previously shown by Kvale *et al.*, who documented the mirrored age-specific prostate cancer incidence rates in the Nordic countries with the uptake of PSA screening.(8) In the US, it is striking to observe the dramatic and immediate effect of the 2012 US Preventive Services Task Force (USPSTF) recommendation against PSA screening on decreasing prevalence of PSA testing and the concomitant decrease in prostate cancer incidence.(9) The Valberg study is quite timely given the April 2017 release of the

updated USPSTF recommendation, which is likely to again shift screening prevalence and prostate cancer incidence.

A surprising result of the frailty modeling and authors' conclusion is that "the plots of the cumulative incidence rates (Fig. 6) indicate that there are not more (prostate cancer) cases being diagnosed in total even though the timing of diagnoses are moved to younger ages. This is a strong indication that there is a limited group of men with a detectable prostate cancer." The latter sentence should be considered in light of data from a meta-analysis estimating prostate cancer prevalence from autopsy studies, including 6,000 men who died of causes other than prostate cancer.(10) The autopsy data showed a linear increase by age group in the prevalence of latent prostate cancer among white, black and Asian men to age 70–79 years. This discrepancy between the Valberg et al. and the autopsy data may reflect in part not a "true limited group of men with detectable prostate cancer" but rather the extent of diagnostic intensity in the population. Surprisingly, some of the latent, prevalent cancers identified at autopsy were high-grade prostate cancers which hold a higher metastatic potential. Incidence rates have also increased in Japan and some other Asian and Eastern European countries where PSA testing has to date not been widely used.(11) Perhaps the discrepancy lies in the focus on the Valberg study on modeling heterogeneous "cancer risk" which is quite different from heterogeneous "detection risk", as PSA's sensitivity and specificity varies across demographic groups.(12)

Although not highlighted in the Valberg study, PSA has had other important effects over time on the descriptive epidemiology of prostate cancer. In addition to diagnosing prostate cancer cases at an earlier age, a consequence of the lead time of 3 to 10 years associated with screening(13), it has influenced the clinical presentation and staging of this disease. Prior to screening being introduced, many prostate cancer patients would present to their physician with bone pain, indicative of bone metastatic disease which was incurable. PSA screening has shifted the detection of prostate cancers to an earlier, more treatable stage, as well as increased the proportion of cancers considered "pseudodisease,"(14) i.e. cancers that would never have come to light clinically nor harmed a man during his lifetime.(13, 15) It is estimated that more than one-third of PSA-detected prostate cancer cases are over-diagnosed and subsequently over-treated(13), a statistic that has fueled an ongoing debate about the benefits and harms of prostate cancer screening.

Another consequence of PSA screening has likely been changes in the observed associations between specific lifestyle factors and risk of total prostate cancer in epidemiological studies. First, modifiable risk factors may affect prostate cancer across its pathogenesis from initiation to progression to metastases. As such, risk factor associations may differ according to clinical disease characteristics, such as those defined by cancer stage or tumor grade.(16) Indeed, it seems unlikely that the factors associated with development of indolent cancers would be similar to those associated with cancers demonstrating malignant potential. Second, PSA screening is one of the most powerful confounding factors in such studies, since men who engage in regular screening tend to engage in other healthy behaviors and screening is also strongly associated with prostate cancer incidence. Thus, an assessment of the quality of epidemiological studies in prostate cancer should include an evaluation of the ability of the study to integrate information on PSA screening. The effect of PSA screening

on epidemiological studies of prostate cancer risk factors is detailed nicely in a study by Zu et al., which examined the association between lycopene and prostate cancer risk in the pre-PSA and PSA eras.(17)

Prostate cancer is analogous to an iceberg. Its cumulative incidence across populations is the exposed tip of the iceberg. How much of that tip is visible above the ocean's surface is a function of the prevalence of etiologic factors as well as screening and diagnostic intensity in those populations. Meanwhile, below the surface lies a potentially larger pool of undiagnosed, latent prostate cancers. The density of an iceberg varies from its surface to its depth, which represents the heterogeneity in prostate cancer biology and metastatic potential. An iceberg's density, through Archimedes' principle, determines how much of the ice remains submerged. Similarly, prostate cancer's biological heterogeneity influences how much PSA screening will reach into the pool of latent cancers and raise them to the surface.

References

1. Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol.* 2017; 3(4):524–48. DOI: 10.1001/jamaoncol.2016.5688 [PubMed: 27918777]
2. Massimo Loda, LAM.Mittelstadt, Megan L.Van Hemelrijck, Mieke, Brid Cotter, Maura, editors. *Pathology and Epidemiology of Prostate Cancer.* 2016.
3. Mucci LA, Hjelmborg JB, Harris JR, et al. Familial Risk and Heritability of Cancer Among Twins in Nordic Countries. *JAMA.* 2016; 315(1):68–76. DOI: 10.1001/jama.2015.17703 [PubMed: 26746459]
4. Eeles RA, Olama AA, Benlloch S, et al. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. *Nat Genet.* 2013; 45(4):385–91. 91e1–2. DOI: 10.1038/ng.2560 [PubMed: 23535732]
5. Al Olama AA, Kote-Jarai Z, Berndt SI, et al. A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. *Nat Genet.* 2014; 46(10):1103–9. DOI: 10.1038/ng.3094 [PubMed: 25217961]
6. MacInnis RJ, English DR. Body size and composition and prostate cancer risk: systematic review and meta-regression analysis. *Cancer Causes Control.* 2006; 17(8):989–1003. DOI: 10.1007/s10552-006-0049-z [PubMed: 16933050]
7. Valberg M, Grotmol T, Tretli S, et al. Prostate-specific antigen testing for prostate cancer: Depleting a limited pool of susceptible individuals? *Eur J Epidemiol.* 2016; doi: 10.1007/s10654-016-0185-z
8. Kvale R, Auvinen A, Adami HO, et al. Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. *J Natl Cancer Inst.* 2007; 99(24):1881–7. DOI: 10.1093/jnci/djm249 [PubMed: 18073376]
9. Jemal A, Fedewa SA, Ma J, et al. Prostate Cancer Incidence and PSA Testing Patterns in Relation to USPSTF Screening Recommendations. *JAMA.* 2015; 314(19):2054–61. DOI: 10.1001/jama.2015.14905 [PubMed: 26575061]
10. Jahn JL, Giovannucci EL, Stampfer MJ. The high prevalence of undiagnosed prostate cancer at autopsy: implications for epidemiology and treatment of prostate cancer in the Prostate-specific Antigen-era. *Int J Cancer.* 2015; 137(12):2795–802. DOI: 10.1002/ijc.29408 [PubMed: 25557753]
11. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev.* 2010; 19(8):1893–907. DOI: 10.1158/1055-9965.EPI-10-0437 [PubMed: 20647400]
12. Preston MA, Batista JL, Wilson KM, et al. Baseline Prostate-Specific Antigen Levels in Midlife Predict Lethal Prostate Cancer. *J Clin Oncol.* 2016; 34(23):2705–11. DOI: 10.1200/JCO.2016.66.7527 [PubMed: 27298404]

13. Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. *J Natl Cancer Inst.* 2002; 94(13):981–90. [PubMed: 12096083]
14. Schwartz LM, Woloshin S, Fowler FJ Jr, Welch HG. Enthusiasm for cancer screening in the United States. *JAMA.* 2004; 291(1):71–8. DOI: 10.1001/jama.291.1.71 [PubMed: 14709578]
15. Ciatto S, Gervasi G, Bonardi R, et al. Determining overdiagnosis by screening with DRE/TRUS or PSA (Florence pilot studies, 1991–1994). *Eur J Cancer.* 2005; 41(3):411–5. doi:S0959-8049(04)00918-9 [pii] 10.1016/j.ejca.2004.09.030. [PubMed: 15691641]
16. Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. *Int J Cancer.* 2007; 121(7): 1571–8. DOI: 10.1002/ijc.22788 [PubMed: 17450530]
17. Zu K, Mucci L, Rosner BA, et al. Dietary lycopene, angiogenesis, and prostate cancer: a prospective study in the prostate-specific antigen era. *J Natl Cancer Inst.* 2014; 106(2):djt430.doi: 10.1093/jnci/djt430 [PubMed: 24463248]