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Estimation of Absolute Risk for Prostate Cancer using Genetic Markers and Family History

Jianfeng Xu[1,2,†], **Jielin Sun**[1,2], **A. Karim Kader**[1,3], **Sara Lindström**[4], **Fredrik Wiklund**[5], **Fang-Chi Hsu**[1,2,6], **Jan-Erik Johansson**[7], **S. Lilly Zheng**[1,2], **Gilles Thomas**[8], **Richard B. Hayes**[8], **Peter Kraft**[8,9], **David J Hunter**[8,9], **Stephen J Chanock**[8], **William Isaacs**[10,†], and **Henrik Grönberg**[5]

[1]Center for Cancer Genomics, Wake Forest University School of Medicine, Winston-Salem, NC

[2]Center for Human Genomics, Wake Forest University School of Medicine, Winston-Salem, NC

[3]Department of Urology, Wake Forest University School of Medicine, Winston-Salem, NC

[4]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts

[5]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[6]Department of Biostatistical Sciences, Wake Forest University School of Medicine, Winston-Salem, NC

[7]Department of Urology, Örebro University Hospital, Örebro, Sweden

[8]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institute of Health, Bethesda, MD

[9]Program in Molecular and Genetic Epidemiology, Department of Epidemiology, Harvard School of Public Health, Boston, MA

[10]The Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, MD

Abstract

Background—Multiple DNA sequence variants in the form of single nucleotide polymorphisms (SNPs) have been found to be reproducibly associated with prostate cancer (PCa) risk.

Methods—Absolute risk for PCa among men with various numbers of inherited risk alleles and family history of PCa was estimated in a population-based case-control study in Sweden (2,893 cases and 1,781 controls), and a nested case-control study from the Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening Trial in the U.S (1,172 cases and 1,157 controls).

†Address for correspondence: Dr. Jianfeng Xu, Center for Cancer Genomics, Medical Center Blvd, Winston-Salem, NC 27157, Phone: (336) 713-7500, Fax: (336) 713-7566, jxu@wfubmc.edu, or Dr. William B. Isaacs, Marburg 115, Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, MD 21287, Phone: (410) 955-2518, Fax: (410) 955-0833, wisaacs@jhmi.edu.

Author Contributions:
JX, HG, WBI, AKK, SJC, RBH, DJH, PK, and GT contributed to the study concept and design. GH and JEJ were responsible for CAPS study subject recruitment. SLZ, SJC, GT, DD, and JC were responsible for genotyping. JX, JS, FCH, SL, FW, STK, YZ, ZZ, EAP, and PK were responsible for data analysis. JX, AKK, WBI, and HG wrote the report. All authors helped in the interpretation and discussion of the findings and approved the report. The study is partially supported by National Cancer Institute CA105055, CA106523 and CA95052 to Dr. Xu., Department of Defense grant PC051264 to Dr. Xu, Swedish Cancer Society (Cancerfonden) to Dr. Gronberg and Swedish Academy of Sciences (Vetenskapsrådet) to Dr. Gronberg. The support of William T Gerrard, Mario A Duhon, John and Jennifer Chalsty, and David Koch to Dr. Isaacs is gratefully acknowledged.

Conflict of interest statement
There is no potential conflict of interest relevant to this article.

Results—Increased number of risk alleles and positive family history were independently associated with PCa risk. Considering men with 11 risk alleles (mode) and negative family history as having baseline risk, men who had ≥ 14 risk alleles and positive family history had an Odds Ratio (OR) of 4.92 [95% confidence interval (CI): 3.64-6.64] in the Swedish study. These associations were confirmed in the U.S. population. Once a man's SNP genotypes and family history are known, his absolute risk for PCa can be readily calculated and easily interpreted. For example, 55 year old men with a family history and ≥ 14 risk alleles have a 52% and 41% risk of being diagnosed with PCa in the next 20 years in the Swedish and U.S. populations, respectively. In comparison, without knowledge of genotype and family history, these men had an average population absolute risk of 13%.

Conclusion—This risk prediction model may be used to identify men at considerably elevated PCa risk who may be selected for chemoprevention.

Keywords

SNPs; association; early detection; chemoprevention

Introduction

Genetic susceptibility to prostate cancer is well documented.[1] Recent genome-wide association studies (GWASs) have identified more than a dozen genetic variants that are associated with prostate cancer risk,[2-9] supporting the hypothesis of a polygenic inheritance for the disease. Although each of these variants is only moderately associated with prostate cancer risk, collectively, they have a stronger, dose-dependent association with prostate cancer risk as demonstrated in a 5-SNP model. [10-11] However, the associations, measured by odds ratio (OR) only, are of limited clinical utility due in part to the need for a comparison group for interpretation.[12-13] Absolute risk, a measurement of probability to develop a disease at a specific age, can be calculated based on an individual's own information and is easier to interpret. Herein, we report a prediction model of absolute risk for prostate cancer using 14 SNPs and family history.

Methods

Study population

A large population-based prostate cancer case-control study in Sweden named CAncer of the Prostate in Sweden (CAPS) was used to develop a risk prediction model. CAPS has been described in detail elsewhere and includes 2,899 prostate cancer patients and 1,722control subjects.[10] Positive family history was defined as any first- or second-degree relatives with a diagnosis of prostate cancer. Prostate cancer patients who met any of the following criteria were classified as aggressive disease: T3/4, N+, M+, Gleason score sum ≥ 8, or PSA > 50 ng/ml; otherwise, they were classified as non-aggressive disease. An independent study population in the U.S., which includes 1,172 prostate cancer patients and 1,157 control subjects nested in the Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening Trial, was used for confirmation.[8] The study was approved by the research ethics committees of each involved institute.

Selection of SNPs

We selected 14 SNPs discovered in four prostate cancer GWASs and follow-up fine mapping studies.[2-9,14-15] These included three SNPs at 8q24, two at 17q12, and one each at 3p12, 7p15, 7q21, 9q33, 10q11, 11q13, 17q24, 22q13, and Xp11. The SNP rs2735839 in the *KLK3* gene at 19q13 was not included because of a concern with possible PSA detection bias.[16] These 14 SNPs were genotyped in CAPS using a MassARRAY QGE iPLEX system (Sequenom, Inc.

San Diego, CA). Two duplicate test samples and two blinded water samples were included in each 96-well plate. The genotype call rate was 98.3% and the concordance rate was 99.8%. For PLCO, 13 SNPs were genotyped and one SNP was imputed (rs16901979 at 8q24, call rate = 100%),[17] from the GWAS described elsewhere.[8]

Statistical analyses

Tests for Hardy-Weinberg equilibrium were performed for each SNP among control subjects in each study using Fisher's exact test. The number of risk alleles of the 14 SNPs, determined from published studies, was counted for each subject. Men were classified into eight approximately equal sized groups based on number of risk alleles (≤ 7, 8, 9, 10, 11, 12, 13, and ≥ 14). Association of number of risk alleles and family history (yes or no) with prostate cancer risk was tested using a logistic regression model and adjusted for age and geographic region (for CAPS only). Number of risk alleles was modeled as a categorical variable with men who had 11 risk alleles (mode) serving as the baseline group. Multiplicative interaction of number of risk alleles and family history on prostate cancer risk was tested by including additional interaction terms (product of family history and number of risk alleles). ORs for prostate cancer for men with various combinations of number of risk alleles and family history were estimated from regression coefficients of these variables in the logistic regression model. Absolute risk was then estimated based on the OR, calibrated incidence rate of prostate cancer for men with the most common number of risk alleles and negative family history, and mortality rate for all causes excluding prostate cancer in Sweden and the U.S., respectively.[18] The calibrated incidence rates were calculated based on joint attributable risk of number of risk alleles and family history estimated from the data and population incidence rates in Sweden and the U.S. (2006 data),[19-20] as described by Chen et al.[21]

Role of the Sponsor

The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation or approval of the manuscript. Drs. Grönberg and Xu had full access to the CAPS study and take responsibility for the integrity of the data and the accuracy of data analysis. Drs. Chanock, Hayes, Hunter, Kraft, and Thomas provided PLCO data.

Results

The possible number of inherited risk alleles of these 14 SNPs range between 0 and 27 because one of the risk SNPs is on the X chromosome. The observed range was between 0 and 21, with the most common number of risk alleles (mode) being 11 among control subjects of CAPS in Sweden. An increased number of risk alleles of these 14 SNPs and positive family history were independently associated with increased prostate cancer risk in CAPS ($P = 5.9 \times 10^{-19}$ and 1.1×10^{-15}, respectively). Considering men with 11 risk alleles and negative family history as having baseline risk (OR = 1), men with < 11 risk alleles and negative family history had OR < 1, while men who had 11 or more and positive family history had OR > 1 (Table 1, top section). Men who had ≥ 14 risk alleles and positive family history, found in 4% of cases and 1% of controls, had the highest risk for prostate cancer, with an OR of 4.92 (95% CI: 3.64-6.64). No evidence of a multiplicative interaction effect on prostate cancer risk between number of risk alleles and family history was found ($P = 0.89$, degrees-of-freedom = 7). The OR of each increasing number of risk alleles on aggressive and non-aggressive was 1.11 (95% CI: 1.09-1.15) and 1.16 (95% CI: 1.13-1.20), respectively. The difference was not statistically significant between these two types of prostate cancer, $P = 0.8\times$. Men with higher numbers of inherited risk alleles of these 14 SNPs and positive family history had similar OR estimates for aggressive and non-aggressive prostate cancer. For example, men who had ≥ 14 risk alleles and positive family history were found in 3.52% and 4.62% of aggressive and non-aggressive

prostate cancer. Compared with men who had 11 risk alleles and negative family history, men who had ≥ 14 risk alleles and positive family history had an OR of 4.77 (95% CI: 3.41-6.69), and 5.05 (95% CI: 3.66-6.96) for aggressive and non-aggressive prostate cancer, respectively.

We performed a confirmation study of these 14 SNPs and family history on prostate cancer risk in the U.S. PLCO population. The most common number of risk alleles of these 14 SNPs was also 11 in control subjects of PLCO. We confirmed that the increased number of risk alleles of these 14 SNPs and positive family history were independently associated with increased prostate cancer risk in PLCO ($P = 1.3 \times 10^{-18}$ and 4.2×10^{-5}, respectively). Considering men with 11 risk alleles and negative family history as having baseline risk (OR = 1), men with < 11 risk alleles and negative family history had OR < 1, while men who had 11 or more and positive family history had OR > 1 (Table 1, bottom section). For example, men who had ≥ 14 risk alleles and positive family history also had the highest risk for prostate cancer; OR = 3.88 (95% CI: 2.83-5.33).

Absolute risk for prostate cancer at a specific age conditional on survival to that age can be estimated based on the OR estimates described above (Table 2). Assuming men with 11 risk alleles and negative family history to be at a baseline risk, men who have a higher number of risk alleles and/or positive family history had an elevated absolute risk. For example, 55 year old men with a family history and ≥ 14 risk alleles have a 52% and 41% risk of being diagnosed with prostate cancer in the next 20 years in Sweden and the U.S., respectively. In contrast, their risk is 8% and 6% risk, respectively in Sweden and in the U.S. if they have 0-7 risk alleles and do not have family history. Without knowledge of these SNPs and family history, these men would have an absolute risk of 13% due to their general population risk.

Discussion

We found that the number of risk alleles of the 14 SNPs and family history were independently associated with prostate cancer risk in a Swedish population and confirmed these findings in a U.S. population. We further developed a risk prediction model, measured by absolute risk, based on genotypes at 14 SNPs and family history. This risk prediction model is simple to use and easy to interpret. The number of risk alleles of these SNPs can be accurately measured from blood or saliva specimens in a single assay. The absolute risk for prostate cancer measures the likelihood of an individual's risk to develop prostate cancer at a specific age and can be easily estimated once his number of risk alleles and family history are known. The result of absolute risk is specific for men who have the same characteristics in terms of number of risk alleles and family history, and can be easily interpreted by physicians and patients without a need for a reference group. Another major feature of this risk prediction model is the fact that it is informative across a range of risk strata. It can distinguish the absolute risk of an individual from as low as 6-8% to as high as 41-52% in the next 20 years for 55 year old men in these two populations.

There are several major limitations of this risk prediction model. First, it is recognized that the vast majority of men will fall into risk categories that are at or close to average. This limitation reflects the underlying complexity of this disease where multiple genes and environmental exposures may contribute to its development. A risk prediction model that considerably separates risk to prostate cancer for all men in the population require predictors that have extraordinarily high OR for the disease (greater than 350), and is unlikely to be found for prostate cancer.[22] However, it is important to note that the primary utility of this risk prediction model is not to assess prostate cancer risk for all men but to identify a small subset of men at highest risk for prostate cancer. For this reason, we did not provide an estimate of area under curve (AUC) of the receiver operating characteristic of this prediction model which is an indication of its usefulness for the former purpose. It is striking to note that this model identifies

about 0.5-1% of men (those having ≥ 14 risk alleles and a positive family history) at greatest risk (41% and 52% risk) for developing prostate cancer between ages 55 to 74 years in the U.S. and Sweden, respectively. This frequency and magnitude of risk are comparable to breast cancer among women who have *BRCA1* and *BRCA2* mutations in the general popualtion.[23]

Information on prostate cancer risk has clinical and public health relevance. Men with a higher likelihood of prostate cancer may choose to begin PSA based prostate cancer screening at an earlier age. Men with greater risk may also pursue preventative measures, including diet/lifestyle intervention and chemoprevention. It is particularly important to note its potential utility in identifying a subset of men who are at greatest risk for prostate cancer for targeted chemoprevention. For example, finasteride is a chemopreventive agent for prostate cancer which has been shown to reduce prostate cancer risk by 25%.[24] However, targeting all men of age 55 and older is not cost-effective for society, and is estimated to yield a gain of 6 life-years per 1000 men treated at a cost of ~1,660,000 per life-year gained.[25] An alternative strategy is to target those men who are at elevated risk for prostate cancer for chemoprevention. The preventive effect of chemoprevention might be stronger among men at higher risk under a polygenic model.[26] Even if the chemoprevention effect is the same for men with higher or lower absolute risk for prostate cancer, the net gain would be larger for men at higher risk. For example, assuming a 25% reduction of prostate cancer using finasteride, men at 13% absolute risk (average risk to develop prostate cancer at age 55 to 74 years in the U.S. and Sweden) would decrease risk by 3% while men at 41-52% risk would decrease risk by 10-13%. Furthermore, men at elevated risk may be more likely to choose and adhere to a chemoprevention regimen. The potential clinical utility of this approach remains to be tested in a clinical trial.

The second major limitation is that this risk prediction model does not distinguish risk of aggressive from non-aggressive prostate cancer, and therefore may exacerbate the potential problem of over-diagnosis and over-treatment of prostate cancer. This limitation is primarily due to the drawback that these prostate cancer risk-associated SNPs were identified by comparing both types of prostate cancer with unaffected controls using GWAS. A recent large study comparing these risk associated SNPs among 1,253 aggressive and 4,233 non-aggressive prostate cancer cases using a case-case study design found that none of these 14 SNPs had significant differences in allele and genotype frequencies between the two types of prostate cancer.[27] While this concern needs to be addressed by including yet to be discovered genetic markers that distinguish aggressive from non-aggressive prostate cancer, this risk prediction model, when combined with its utility in promoting chemoprevention among men at elevated risk, may reduce prostate cancer incidence. Despite the inability of this approach to discern aggressive or non-aggressive prostate cancer, if chemoprevention could decrease the number of men developing any prostate cancer, such men would be spared the decisions which burden men diagnosed with prostate cancer. Again, the benefits and risks of this type of risk prediction modeling needs to be further evaluated.

There are three additional methodological considerations related to this study. Rather than give each of these SNPs the same weight in assessing their cumulative effect on prostate cancer risk by counting number of risk alleles, an alternative approach is to give different weights for these SNPs based on their OR. Although we believe this alternative method may provide a slightly better prediction model within any single study where the model is developed, it may be difficult to generalize the results to other studies because an accurate OR estimate of each SNP requires large sample sizes and the point estimate of each SNP may vary by study populations. Furthermore, our approach, by counting number of risk alleles, is less cumbersome for clinicians and patients alike.

The absolute risk in CAPS may be overestimated because ORs from the case-control study were used to approximate relative risk (RR) in CAPS. It is known that ORs tend to overestimate RRs when a disease incidence is high, especially when the ORs are farther away from the null (OR = 1). Estimates of absolute risk in PLCO are more reliable because the ORs are equivalent to RR due to the use of an incidence density sampling method for case/control selection. Differences in designs between the two studies may account for the slightly lower estimates of absolute risk in the U.S. population.

Finally, although we did not include the SNP rs2735839 in *KLK3* gene at 19q13 because of a concern with possible PSA detection bias,[16] several of the 14 SNPs we did include may also be susceptible to this bias because they are associated with PSA levels among men without prostate cancer.[28] If men inherit alleles that are associated with higher PSA levels, they will be more likely to have higher PSA levels, thus increasing the frequency of biopsy for prostate cancer, which in turn increases the chance of being diagnosed with prostate cancer. The potential bias of these SNPs in prostate cancer risk prediction models should be tested in studies, such as Prostate Cancer Prevention Trial,[24] where all men are biopsied for prostate cancer regardless of PSA levels.

The current risk prediction model was based on 14 risk SNPs that were discovered in the past two years.[2-9,14-15] More risk SNPs will most likely be discovered from ongoing and combined GWASs because these 14 risk SNPs account for less than 6% of genetic variation in prostate cancer risk in this Swedish population.[14] The ability to differentiate men's risk to prostate cancer may be further improved using additional risk SNPs for this polygenic disease,[29] although diminishing returns in prediction may be encountered.[13] However, it is important to stress that the potential benefit of using risk SNPs in predicting disease risk may be stronger in prostate cancer than other diseases because only three risk factors (age, race, and family history) have been consistently shown to be associated with prostate cancer.[1]

In conclusion, genetic markers have the potential to identify men at greater risk for prostate cancer. Larger cohort studies are warranted to obtain more accurate estimates of absolute risk. Geneticists, epidemiologists, clinicians, and genetic counselors need to work together to continue to improve the performance and implementation of these markers, and assess the risks and benefits of this information, to further improve the care of men at risk for prostate cancer.

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Table 1

Association of prostate cancer risk with number of risk alleles of 14 risk SNPs and family history in CAPS and PLCO

# of risk alleles	Family history	Number (%) of risk alleles		OR (95% CI)†
		Controls	Cases	
CAPS‡				
0-7	No	171 (9.94)	164 (5.66)	0.71 (0.55-0.91)
8	No	167 (9.70)	174 (6.00)	0.78 (0.61-1.01)
9	No	191 (11.10)	250 (8.63)	0.95 (0.76-1.21)
10	No	251 (14.58)	334 (11.53)	0.99 (0.80-1.24)
11	No	259 (15.05)	346 (11.94)	1.00 (Baseline)
12	No	223 (12.96)	353 (12.18)	1.13 (0.91-1.41)
13	No	147 (8.54)	281 (9.70)	1.41 (1.10-1.79)
≥ 14	No	149 (8.66)	446 (15.39)	2.26 (1.79-2.86)
0-7	Yes	17 (0.99)	30 (1.04)	1.54 (1.12-2.12)
8	Yes	16 (0.93)	37 (1.28)	1.70 (1.24-2.33)
9	Yes	23 (1.34)	57 (1.97)	2.07 (1.54-2.80)
10	Yes	19 (1.10)	65 (2.24)	2.16 (1.61-2.89)
11	Yes	26 (1.51)	71 (2.45)	2.17 (1.80-2.63)
12	Yes	31 (1.80)	88 (3.04)	2.45 (1.84-3.27)
13	Yes	16 (0.93)	82 (2.83)	3.06 (2.25-4.15)
≥ 14	Yes	15 (0.87)	120 (4.14)	4.92 (3.64-6.64)
PLCO¥				
0-7	No	111 (10.08)	53 (4.51)	0.56 (0.38-0.81)
8	No	111 (10.08)	78 (6.63)	0.76 (0.54-1.07)
9	No	146 (13.26)	94 (7.99)	0.73 (0.53-1.00)
10	No	181 (16.44)	155 (13.18)	0.93 (0.69-1.24)
11	No	185 (16.80)	163 (13.86)	1.00 (Baseline)
12	No	121 (10.99)	180 (15.31)	1.63 (1.21-2.20)
13	No	82 (7.45)	150 (12.76)	1.98 (1.42-2.74)
≥ 14	No	97 (8.81)	167 (14.2)	2.02 (1.48-2.78)
0-7	Yes	5 (0.45)	8 (0.68)	1.07 (0.74-1.55)
8	Yes	9 (0.82)	9 (0.77)	1.46 (1.03-2.06)
9	Yes	7 (0.64)	10 (0.85)	1.39 (1.01-1.92)
10	Yes	14 (1.27)	16 (1.36)	1.78 (1.33-2.37)
11	Yes	8 (0.73)	18 (1.53)	1.92 (1.41-2.62)
12	Yes	12 (1.09)	28 (2.38)	3.13 (2.32-4.22)
13	Yes	8 (0.73)	20 (1.70)	3.79 (2.73-5.26)
≥ 14	Yes	4 (0.36)	27 (2.30)	3.88 (2.83-5.33)

†OR (Odds ratio) was adjusted for age and geographic region (CAPS only)

‡CAPS: CAncer of the Prostate in Sweden

¥PLCO: Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening Trial

Table 2

Estimates of absolute risk for prostate cancer based on number of risk alleles and family history in CAPS and PLCO

# of risk alleles	Family history		Absolute Risk at specific age (year)†				
			55-59	60-64	65-69	70-74	55-74
CAPS‡							
0-7	No		0.01	0.02	0.02	0.03	0.08
8	No		0.01	0.02	0.03	0.03	0.08
9	No		0.01	0.02	0.03	0.04	0.10
10	No		0.01	0.02	0.03	0.04	0.11
11	No	Baseline£	0.01	0.02	0.03	0.04	0.11
12	No		0.01	0.03	0.04	0.04	0.12
13	No		0.02	0.03	0.05	0.05	0.15
≥ 14	No		0.03	0.05	0.07	0.09	0.24
0-7	Yes		0.02	0.04	0.05	0.06	0.17
8	Yes		0.02	0.04	0.06	0.07	0.18
9	Yes		0.02	0.05	0.07	0.08	0.22
10	Yes		0.03	0.05	0.07	0.08	0.23
11	Yes		0.03	0.05	0.07	0.08	0.23
12	Yes		0.03	0.06	0.08	0.09	0.26
13	Yes		0.04	0.07	0.10	0.12	0.32
≥ 14	Yes		0.06	0.11	0.16	0.18	0.52
PLCO¥							
0-7	No		0.01	0.01	0.02	0.02	0.06
8	No		0.01	0.02	0.03	0.03	0.08
9	No		0.01	0.02	0.02	0.03	0.08
10	No		0.01	0.02	0.03	0.04	0.10
11	No	Baseline£	0.01	0.02	0.03	0.04	0.11
12	No		0.02	0.04	0.06	0.06	0.18
13	No		0.03	0.04	0.07	0.08	0.21
≥ 14	No		0.03	0.05	0.07	0.08	0.22
0-7	Yes		0.01	0.02	0.04	0.04	0.12
8	Yes		0.02	0.03	0.05	0.06	0.16
9	Yes		0.02	0.03	0.05	0.05	0.15
10	Yes		0.02	0.04	0.06	0.07	0.19
11	Yes		0.02	0.04	0.07	0.07	0.21
12	Yes		0.04	0.07	0.11	0.12	0.34
13	Yes		0.05	0.09	0.13	0.14	0.40
≥ 14	Yes		0.05	0.09	0.13	0.15	0.41

†Absolute risk was estimated based on OR, calibrated incidence of prostate cancer for men without family history, and mortality rate for all causes excluding prostate cancer in Sweden and the U.S., respectively (19-20). Calibrated incidence rates were calculated based on joint attributable risk of number of risk alleles and family history and incidence rates in general populations of Sweden and the U.S., as described by Chen (21).

‡CAPS: CAncer of the Prostate in Sweden

¥PLCO: Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening Trial