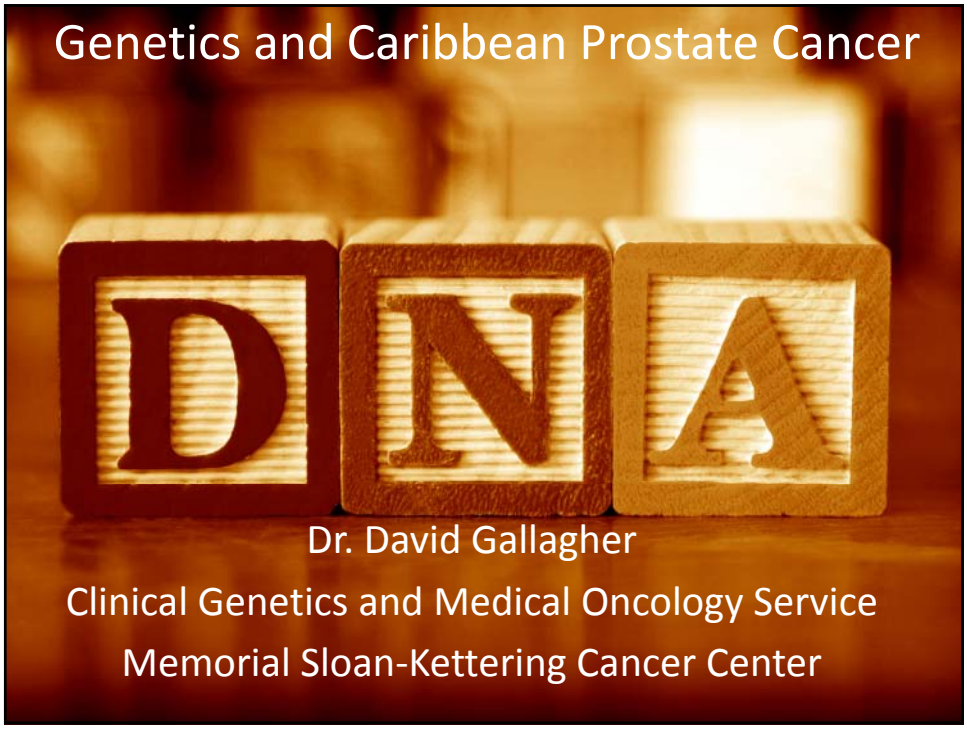
Genetics and Caribbean Prostate Cancer



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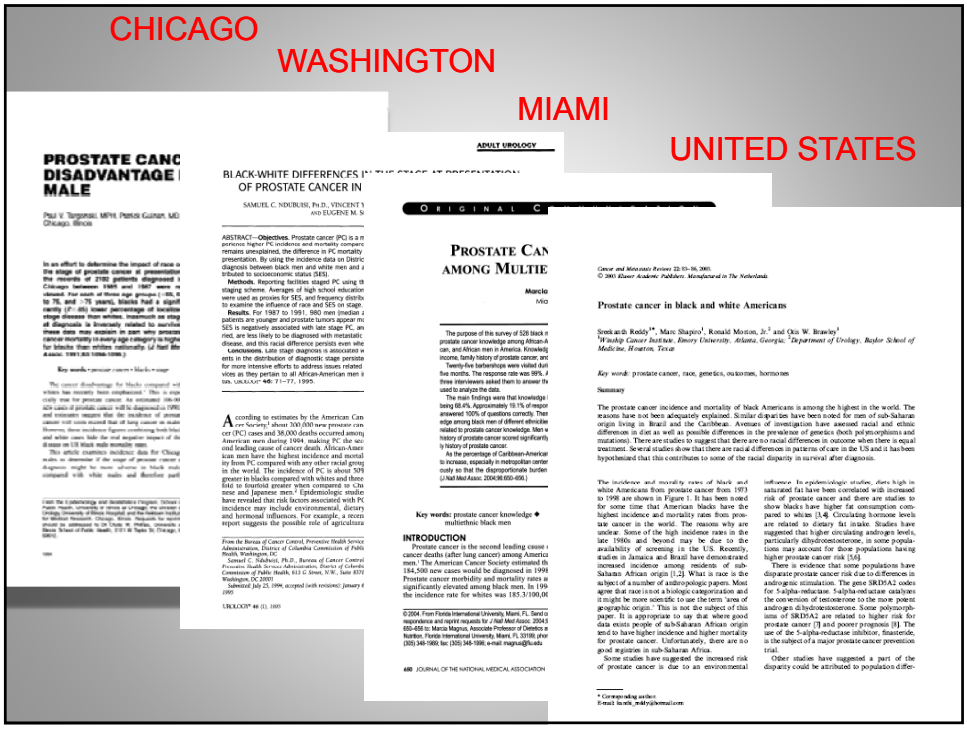
304 cases/100,000 men

Glover et al, J Urol, 1998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PROSTATE CANC
DISADVANTAGE
MALE
BLACK-WHITE DIFFERENCES
OF PROSTATE CANCER IN
ADULT UROLOGY
PROSTATE CAN
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Prostate cancer in black and white Americans
INTRODUCTION


FRANCE
SWEDEN
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Prostate Cancer Characteristics in a Multi
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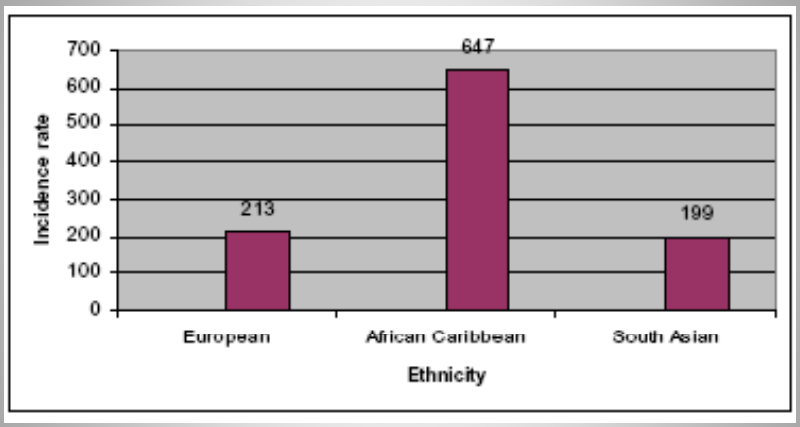
Sweden, 1961–2004
Prostate Cancer
The Risk of Prostate Cancer amongst Black Men in the
United Kingdom: The PROCESS Cohort Study

UK age-adjusted prostate cancer incidence



Chinegwundoh et al, BJU International 2006

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A BRIEF ORIGINAL CONTRIBUTION

Alcohol Use and Prostate Cancer Risk in US Blacks and Whites

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Prostate cancer is the most common malignancy in US men (more than 165,000 cases per annum) and occurs substantially more frequently in blacks than in whites. The causes of this disease are, however, poorly understood. Alcohol consumption, which has been clearly related to malignancies of the upper aerodigestive tract, may also increase risk of cancer at other sites, including the prostate. The authors investigated alcohol use as a risk factor for prostate cancer among US blacks and whites. A population-based, case-control study was carried out among 981 men (479 blacks and 502 whites) with pathologically confirmed prostate cancer diagnosed between August 1, 1986, and April 30, 1989, and 1,315 controls (594 blacks and 721 whites) who resided in Atlanta, Georgia; Detroit, Michigan; and 10 counties in New Jersey, geographic areas covered by three population-based cancer registries. In-person interviews elicited information on alcohol use and other factors possibly related to prostate cancer. Compared with never-users, risk for prostate cancer increased with amount of alcohol drunk (χ^2_{trend}, $p < 0.001$), with significantly elevated risks seen for those who had 22–56 drinks per week (odds ratio = 1.4; 95% confidence interval 1.0–1.8) and 57 or more drinks per week (odds ratio = 1.9; 95% confidence interval 1.3–2.7). The finding was consistent among blacks (χ^2_{trend}, $p < 0.01$) and whites (χ^2_{trend}, $p < 0.05$), and among young and old subjects; it was not restricted to a specific type of alcoholic beverage. In this first large study among US blacks and whites, increased risk for prostate cancer was associated with increased alcohol use. The risk was similar for whites and blacks and could not be attributed to tobacco use or to a number of other potential confounders. *Am J Epidemiol* 1996;143:692–7.

alcohol; case-control studies; prostatic neoplasms

Prostate cancer is the most frequently diagnosed cancer in US men, with more than 165,000 new cases annually. Incidence rates of this disease are 27 percent greater and mortality is more than twofold greater in US blacks compared with whites (1). The causes of this disease are poorly understood, as are the reasons for the ethnic difference in occurrence.

Alcoholic beverage consumption has been causally related to malignant tumors of the oral cavity, pharynx, larynx, esophagus, and liver (2), and there is growing, but as yet inconclusive, evidence that it is related to more moderate increases in risk for malignancies at other major organ sites (3, 4), including the prostate (5–7). The common occurrence of prostate cancer implies that even moderately increased risks may have substantial public health significance. Therefore, data from a large population-based, case-control study were used to investigate alcohol consumption as a potential risk factor for prostate cancer among US blacks and whites.

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Abbreviations: CI, confidence interval; OR, odds ratio.

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MATERIALS AND METHODS

Study design

This case-control study of prostate cancer is one component of a multicenter study of cancers of the esophagus, pancreas, and prostate and of multiple myeloma among US blacks and whites. Study subjects resided in geographic areas covered by the population-based cancer registry of the Georgia Center for Cancer Statistics (Fulton and DeKalb counties), the Metropol-

Increased risk but no racial variation

Differences in saturated fat intake may account for about 10% of the difference in incidence rate

Cancer Causes Control
DOI 10.1007/s10552-010-9520-y

ORIGINAL PAPER

Body size and risk of prostate cancer in Jamaican men

Maria D. Jackson · Susan P. Walker · Candace M. Simpson · Norma McFarlane-Anderson · Franklyn I. Bennett · Kathleen C. M. Coard · William D. Allen · Trevor Tulloch · Tomlin J. Paul · Robert L. Wan

Received: 12 June 2009 / Accepted: 4 February 2010

Abstract We investigated the associations between body size and risk of prostate cancer in a hospital-based case–control study in Jamaica. Height, weight, waist, and hip circumference were measured at enrollment, and data collected on medical and lifestyle factors for newly diagnosed cases (n = 243) and controls (n = 275). Compared with men in the normal range of waist-hip ratio (WHR), men with WHR ≥0.95 were at greater risk of total prostate cancer (OR, 1.72; CI, 1.01–3.00) and high-grade cancer (OR, 2.02; CI, 1.03–3.96). With additional control for BMI, the association with WHR remained significant for total prostate cancer (OR, 1.90; CI, 1.01–3.53) and high-grade disease (OR, 2.94; CI, 1.34–6.38). There was no association between waist circumference and cancer without control for BMI but after controlling for BMI, waist circumference >90 cm (OR, 2.45; CI, 1.01–5.94) and >102 cm (OR, 5.57; CI, 1.43–18.63) showed a dose–response relationship with high-grade disease. Height and BMI were not associated with risk of prostate cancer. Abdominal obesity may be associated with risk of high-grade prostate cancer. Risk may be greater in those with higher abdominal obesity relative to overall size. The results further highlight the importance of investigating relationships by characteristics of the tumor.

Keywords Prostate cancer · Tumor characteristics · Body size · Blacks

Introduction

Prostate cancer is the most commonly diagnosed solid malignancy in Jamaican men and ranks highest in cancer-related mortality. Reviews of age-specific incidence of cancer revealed that the age-standardized rate of prostate cancer increased from 36.6/100,000 to 56.4/100,000 from

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Published online: 16 February 2010

Prostate Cancer in Relation to Diet, Physical Activity, and Body Size in Blacks, Whites, and Asians in the United States and Canada

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Background: **International and interethnic differences in prostate cancer incidence suggest an environmental, potentially modifiable etiology for the disease.** ***Purpose:*** **We conducted a population-based case–control study of prostate cancer among blacks (very high risk), whites (high risk), and Asian-Americans (low risk) in Los Angeles, San Francisco, Hawaii, Vancouver, and Toronto. Our aim was to evaluate the roles of diet, physical activity patterns, body size, and migration characteristics on risk in these ethnic groups and to assess how much of the interethnic differences in risk might be attributed to interethnic differences in such lifestyle characteristics.** ***Methods:*** **We used a common protocol and questionnaire to administer personal interviews to 1655 black, white, Chinese-American, and Japanese-American case patients diagnosed during 1987–1991 with histologically confirmed prostate carcinoma and to 1645 population-based control subjects matched to case patients by age, ethnicity, and region of residence. Sera collected from 1127 control subjects were analyzed for levels of prostate-specific antigen (PSA) to permit comparison of case patients with control subjects lacking serological evidence of prostate disease. Odds ratios were estimated using conditional logistic regression. We estimated the proportion of prostate cancer attributable to certain risk factors and the proportion of interethnic risk differences attributable to interethnic differences in risk-factor prevalence.** ***Results:*** **A positive statistically significant association of prostate cancer risk and total fat intake was found for all ethnic groups combined. This association was attributable to energy from saturated fats; after adjusting for saturated fat, risk was associated only weakly with monounsaturated fat and was unrelated to protein, carbohydrate, polyunsaturated fat, and total food energy. Saturated fat intake was associated with higher risks for Asian-Americans than for blacks and whites. In all ethnic groups combined, the risk tended to be higher when only case patients with advanced disease were compared with control subjects with normal PSA levels. Among foreign-born Asian-Americans, risk increased independently with years of residence in North America and with saturated fat intake. Crude estimates suggest that differences in saturated fat intake account for about 10% of black–white differences and about 15% of white-Asian-American differences in prostate cancer incidence. Risk was not consistently associated with intake of any micronutrients, body mass, or physical activity patterns.** ***Conclusions:*** **These data support a causal role in prostate cancer for saturated fat intake but suggest that other factors are largely responsible for interethnic differences in risk. [J Natl Cancer Inst 87:652–661, 1995]**

Cancer of the prostate is the fourth most common cause of cancer among men throughout the world (*1*). In Canada and the United States in 1993, incidence rates of prostate cancer were higher than those of any other (non-skin) cancer, accounting for approximately 178 000 new cases of prostate cancer and approximately 39 000 deaths (*2,3*). This disease does not occur equally among men in different countries or of different ethnicities; incidence rates in China and Japan are less than one tenth of those of U.S. blacks (*1*). Chinese-Americans and Japanese-Americans have rates that, while lower than those of U.S. whites and blacks, nevertheless are higher than those of their counterparts in Asia. These differences suggest an environmental, potentially modifiable etiology for the disease.

We conducted a population-based case–control study of prostate cancer among blacks, whites, Chinese-Americans, and Japanese-Americans in the United States (Los Angeles, San Francisco, and Hawaii) and Canada (Vancouver and Toronto)

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*Correspondence to: Alice S. Whittemore, Ph.D., Department of Health Research and Policy, Redwood Building, Room T200, Stanford University School of Medicine, Stanford, CA 94305-5405.
See "Notes" section following "References."

Caribbean families in UK consume significantly less fats than Asian and White households (p=0.029)

Lip et al, Int J Cardiol 1995

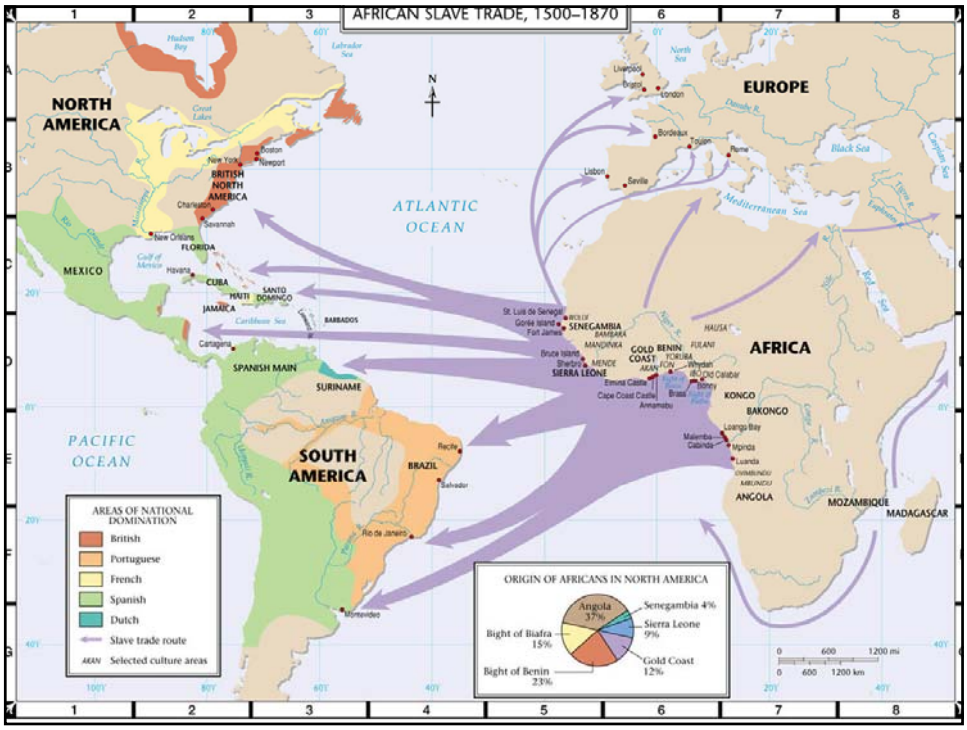


TABLE 3. EFFECTS OF HERITABLE AND ENVIRONMENTAL FACTORS IN CANCERS AT VARIOUS SITES, ACCORDING TO DATA FROM THE SWEDISH, DANISH, AND FINNISH TWIN REGISTRIES.

SITE OR TYPE	PROPORTION OF VARIANCE (95% CI)*			FIT OF MODEL	
	HERITABLE FACTORS	SHARED ENVIRONMENTAL FACTORS	NONSHARED ENVIRONMENTAL FACTORS	χ^2 (df)	P VALUE
Stomach	0.28 (0–0.51)	0.10 (0–0.34)	0.62 (0.49–0.76)	8.9 (38)	1.0
Colorectum	0.35 (0.10–0.48)	0.05 (0–0.23)	0.60 (0.52–0.70)	25.8 (38)	0.93
Pancreas†	0.36 (0–0.53)	0 (0–0.35)	0.64 (0.47–0.86)	0.5 (3)	0.92
Lung	0.26 (0–0.49)	0.12 (0–0.34)	0.62 (0.51–0.73)	28.1 (38)	0.88
Breast‡	0.27 (0.04–0.41)	0.06 (0–0.22)	0.67 (0.59–0.76)	10.1 (18)	0.93
Cervix uteri†‡	0 (0–0.42)	0.20 (0–0.35)	0.80 (0.57–0.97)	0.3 (3)	0.96
Corpus uteri‡	0 (0–0.35)	0.17 (0–0.31)	0.82 (0.64–0.98)	6.6 (18)	0.99
Ovary‡	0.22 (0–0.41)	0 (0–0.24)	0.78 (0.59–0.99)	6.0 (18)	1.0
Prostate§	0.42 (0.29–0.50)	0 (0–0.09)	0.58 (0.50–0.67)	26.5 (18)	0.09
Bladder†	0.31 (0–0.45)	0 (0–0.28)	0.69 (0.53–0.86)	1.7 (3)	0.64
Leukemia†	0.21 (0–0.54)	0.12 (0–0.41)	0.66 (0.45–0.88)	0.0 (3)	0.99

*CI denotes confidence interval.
†Data for all countries and both sexes are pooled because of small numbers.
‡Data are for women only.
§Data are for men only.

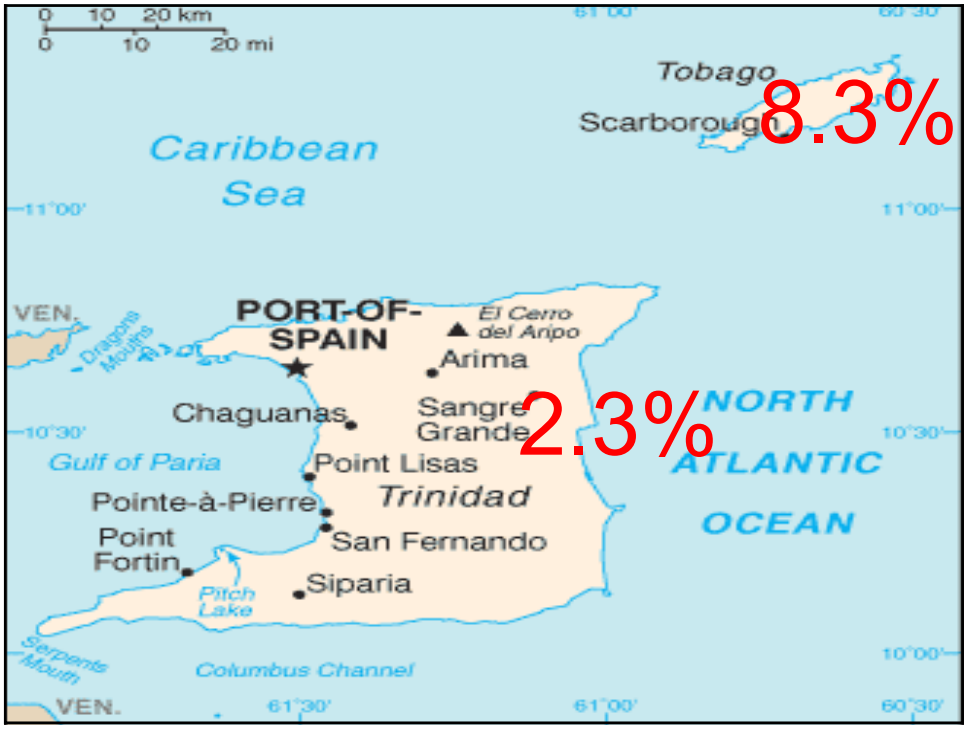
Lichenstein et al, NEJM 2000;343:78

TABLE I. *Odds ratio of developing prostate cancer as a function of family history among first and second degree relatives of 263 patients with prostate cancer and 263 control patients from Kingston, Jamaica*

Type of Relative Affected	No./Total (%)	Odds Ratio	Confidence Interval	*P* Value
First degree				
Controls	15/263 (5.7%)	2.1	1.1–4.4	0.014
Patients with prostate cancer	30/263 (11.4%)			

TABLE II. *Family history of various malignancies in 263 patients with prostate cancer and 263 control patients in Kingston, Jamaica*

Type of Cancer	Patients with Cancer	Control Patients
Colon	5 (1.9%)	3 (1.1%)
Lung	7 (2.7%)	8 (3.0%)
Uterine	10 (3.8%)	7 (2.7%)
Breast	16 (6.1%)	18 (6.8%)
Other	37 (14.1%)	35 (13.3%)
Prostate	30 (11.4%)	15 (5.7%)


0 10 20 km
0 10 20 mi
Tobago
Scarborough
8.3%
Caribbean Sea
11°00'
PORT-OF-SPAIN
El Cerro del Aripo
Arima
VEN.
Dragons Mouths
Chaguanas
Sangre Grande
2.3%
NORTH ATLANTIC OCEAN
10°30'
Gulf of Paria
Point Lisas
Trinidad
Pointe-à-Pierre
San Fernando
Point Fortin
Siparia
Pitch Lake
Serpents Mouth
Columbus Channel
10°00'
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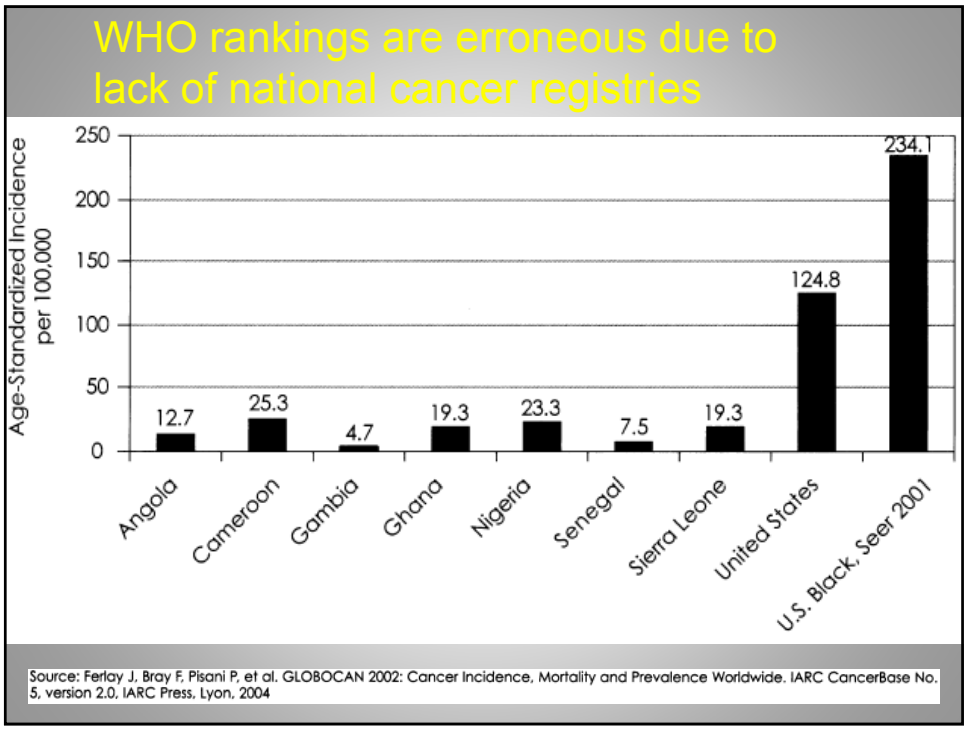

WHO rankings are erroneous due to lack of national cancer registries
Age-Standardized Incidence per 100,000
250
200
150
100
50
0
12.7
25.3
4.7
19.3
23.3
7.5
19.3
124.8
234.1
Angola
Cameroon
Gambia
Ghana
Nigeria
Senegal
Sierra Leone
United States
U.S. Black, Seer 2001
Source: Ferlay J, Bray F, Pisani P, et al. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase No. 5, version 2.0, IARC Press, Lyon, 2004

ORIGINAL COMMUNICATION

Roots of Prostate Cancer in African-American Men

Folakemi T. Odedina, PhD; J. Olufemi Ogunbiyi, MBBS, FWACP (Lab Med); and Flora A.M. Ukoli, MBBS, DPH, MPH

Tallahassee, Florida; Ibadan, Nigeria; and Nashville, Tennessee

To fully understand the role of genetics and environment (biotic, abiotic and sociocultural) in the prostate cancer disparity experienced by African-American men, this paper examined the rates of prostate cancer among African-American men and one of their ancestral populations in west Africa. Data sources were from the World Health Organization [WHO] and reported hospital records in the literature. Based on the WHO's worldwide cancer data, west African men have much lower prostate cancer incidence and mortality compared to African-American men. For example, compared to Nigerian men, African-American men are >10 times likely to develop prostate cancer and 3.5 times likely to die from the disease. However, contrary to the global ranking by WHO, there is documented evidence in the literature indicating that prostate cancer in at least one west African country is similar to rates found in the United States and in Caribbean Islands. To better address prostate cancer disparity, future studies should study populations and subgroups from central and west Africa, the original source population for African Americans.

Key words: prostate cancer ■ African Americans ■ men's health

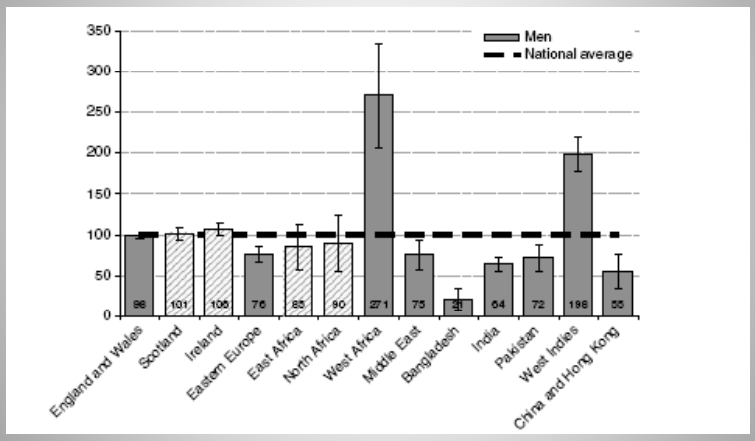
© 2006. From The Economic, Social & Administrative Pharmacy Division (Odedina, professor and division director) and Florida A&M University Center for Minority Prostate Cancer Training & Research, Florida A&M University College of Pharmacy & Pharmaceutical Sciences, Tallahassee, FL (Odedina, program director); Department of Pathology (anatomic pathology), University College Hospital, Ibadan, Nigeria (Ogunbiyi, professor); and Prostate Cancer Research Program, Department of Surgery, Meharry Medical College, Department of Surgery, Nashville, TN (Ukoli, associate professor). Send correspondence and reprint requests for J Natl Med Assoc. 2006;98:539–543 to: Dr. Folakemi T. Odedina, Suite 200, Dyson Pharmacy Building, Florida A&M University Economic, Social and Administrative Pharmacy Division, Tallahassee, FL 32307; e-mail: folakemi.odedina@famu.edu

The report of the Descriptive Epidemiology Group of the International Agency for Research on Cancer (IARC)[1] presents estimates of the incidence and prevalence of and mortality from 27 cancers for all countries in the world. The report estimated that in 2002, prostate cancer ranked first for the five-year prevalent cases of all cancers among men in the world. There were 2,368,669 reported cases. Prostate cancer ranked second among men for new cancer cases for all ages worldwide. In the United States, the 2005 cancer morbidity and mortality estimates by the American Cancer Society[2] indicate that prostate cancer will continue to lead the new cancer cases and will be the second leading cause of cancer deaths in men. Among men, it is estimated that 232,090 new prostate cancer cases and 30,350 prostate cancer deaths will be reported in 2005.[2] Although prostate cancer affects men regardless of their racial group, a disproportionate burden is experienced by African-American men. African-American men are 2.4 times more likely to die of prostate cancer compared with white men.[3] They also have the highest incidence of prostate cancer compared to other racial/ethnic groups in the United States.

The worldwide differences in the incidence of prostate cancer and the noticeable variations among ethnic groups are noted by Gronberg[4] to be caused by multiple factors, including genetic susceptibility, external risk factors, health differences and cancer registration. A comprehensive understanding of the reason(s) for the ethnic variations in prostate cancer morbidity and mortality within the United States remains elusive. This ethnic variation has even been found to persist when dietary and lifestyle factors were accounted for among men of similar educational level.[4] An important question that needs to be answered is: Does this prostate cancer disparity also exist among the original source population for African Americans? In this paper, we examined the prostate cancer burden experienced by one of the ancestral populations of African Americans in attempt to understand the prostate cancer disparity experienced by African-American men.

Case reports in Nigeria suggest incidence rates in region of 127/100,000

Standard mortality rates for prostate cancer by country of in England and Wales, 2001-2003



EUROPEAN JOURNAL OF CANCER 45 (2009) 2168–2179

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Trends in cancer mortality among migrants in England and Wales, 1979–2003

Seeromanie Harding[a,*], *Michael Rosato*[b], *Alison Teyhan*[a]

Table 1a – Men 30–69 years: All malignant neoplasms, and lung and colon cancers by country of birth and time period. Percentage change in the death rates and 95% confidence interval (CI).

	Percentage change in cancer mortality rates			
	Change between 1989–93 and 1979–83[a]		Change between 1999–2003 and 1989–93[b]	
	%	95% CI	%	95% CI
All cancers				
England and Wales	−9.3	(−10.0, −8.6)	−20.4	(−21.1, −19.8)
Jamaica	11.4	(−1.7, 26.3)	19.8	(7.6, 33.2)

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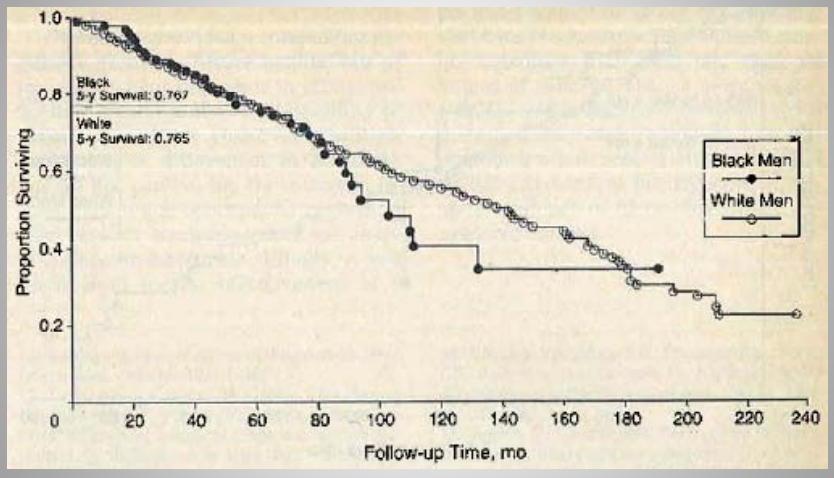

ARTICLE

Racial Disparities in Cancer Survival Among Randomized Clinical Trials Patients of the Southwest Oncology Group

Kathy S. Albain, Joseph M. Unger, John J. Crowley, Charles A. Coltman Jr, Dawn L. Hershman

Background Racial disparities in cancer outcomes have been observed in several malignancies. However, it is unclear if survival differences persist after adjusting for clinical, demographic, and treatment variables. Our objective was to determine whether racial disparities in survival exist among patients enrolled in consecutive trials conducted by the Southwest Oncology Group (SWOG).

Methods We identified 19457 adult cancer patients (6876 with breast, 2699 with lung, 1244 with colon, 1429 with ovarian, and 1843 with prostate cancers; 1291 with lymphoma; 2067 with leukemia; and 2208 with multiple myeloma) who were treated on 36 SWOG randomized phase III clinical trials from October 1, 1974, through November 20, 2001. Patients were grouped according to studies of diseases with similar histology and stage. Cox regression was used to evaluate the association between race and overall survival within each disease site grouping, controlling for available prognostic factors plus education and income, which are surrogates for socioeconomic status. Median and two-year overall survival estimates were derived by the Kaplan–Meier method. All statistical tests were two-sided.

Results Of 19457 patients registered, 2308 (11.9%, range = 3.9%–21.8%) were African American. After adjustment for prognostic factors, African American race was associated with increased mortality in patients with early-stage premenopausal breast cancer (hazard ratio [HR] for death = 1.41, 95% confidence interval [CI] = 1.10 to 1.82; $P = .007$), early-stage postmenopausal breast cancer (HR for death = 1.48, 95% CI = 1.28 to 1.73; $P < .001$), advanced-stage ovarian cancer (HR for death = 1.31, 95% CI = 1.16 to 2.16; $P = .002$), and advanced-stage prostate cancer (HR for death = 1.21, 95% CI = 1.08 to 1.37; $P = .001$). No statistically significant association between race and survival for lung cancer, colon cancer, lymphoma, leukemia, or myeloma was observed. Additional adjustments for socioeconomic status did not substantially change these observations. Ten-year (and median) overall survival rates for African American vs all other patients were 68% (not reached) vs 77% (not reached), respectively, for early-stage, premenopausal breast cancer; 52% (19.2 years) vs 62% (13.5 years) for early-stage, postmenopausal breast cancer; 13% (1.3 years) vs 17% (2.3 years) for advanced ovarian cancer; and 6% (2.2 years) vs 9% (2.7 years) for advanced prostate cancer.

Conclusions African American patients with sex-specific cancers had worse survival than white patients, despite enrollment on phase III SWOG trials with uniform stage, treatment, and follow-up.

J Natl Cancer Inst 2009;101:984–992

Measurable declines in overall cancer death rates for many major cancers along with improved survival rates have been reported recently (1). However, racial and ethnic disparities in cancer-specific death rates for most cancers indicate that not all segments of the US population have benefited equally from such advances (1,2). The disparity in population-based survival statistics is greatest for patients with cancers of the breast, prostate, colon, ovary, lung, and cervix. However, racial disparities in cancer outcomes can be attributed to many factors, including access to quality care resulting in more advanced stage at presentation (3–5), differences in tumor biology resulting in increased aggressiveness or resistance to treatment (6), differences in the quality of care after diagnosis (7,8), and socioeconomic factors influencing treatment options (9,10). There is controversy whether race affects outcome independently of these factors.

The randomized clinical trial setting of cancer cooperative groups presents several advantages in terms of assessing survival

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See "Funding" and "Notes" following "References."

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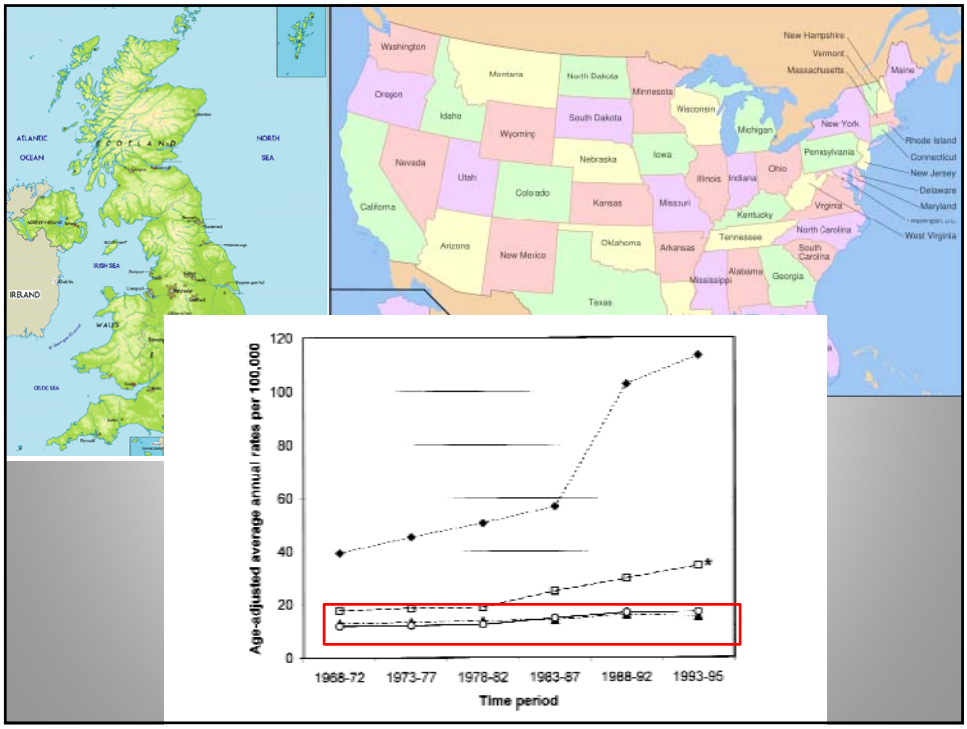
African-American prostate cancer patients have worse outcome on clinical trial.


Washington
Oregon
California
Idaho
Nevada
Montana
Wyoming
Utah
Arizona
Colorado
New Mexico
North Dakota
South Dakota
Nebraska
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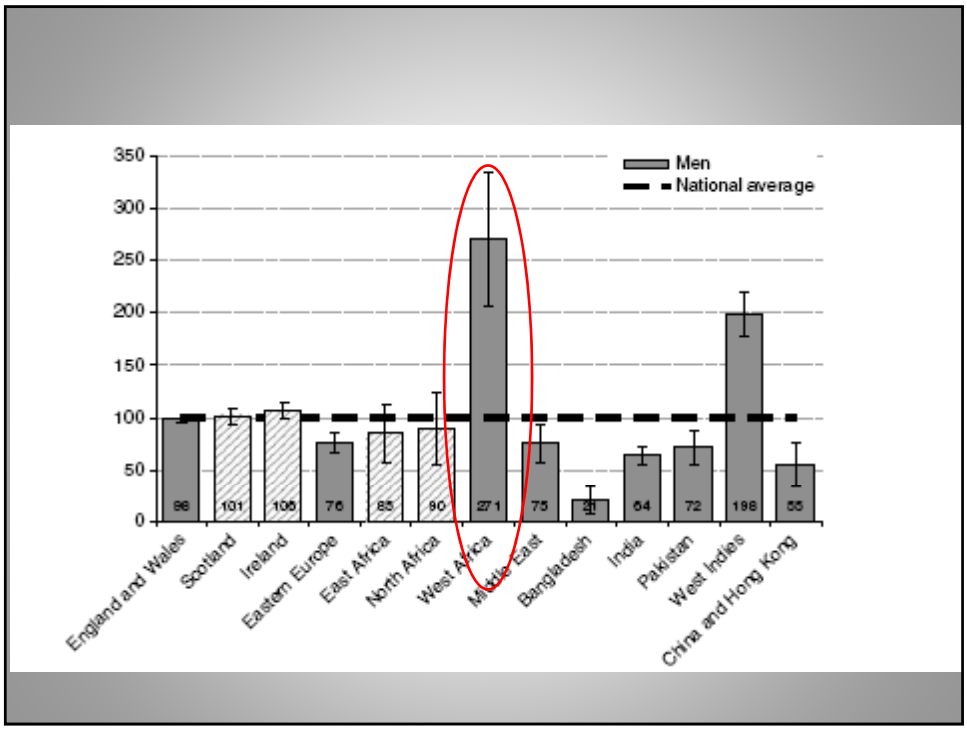
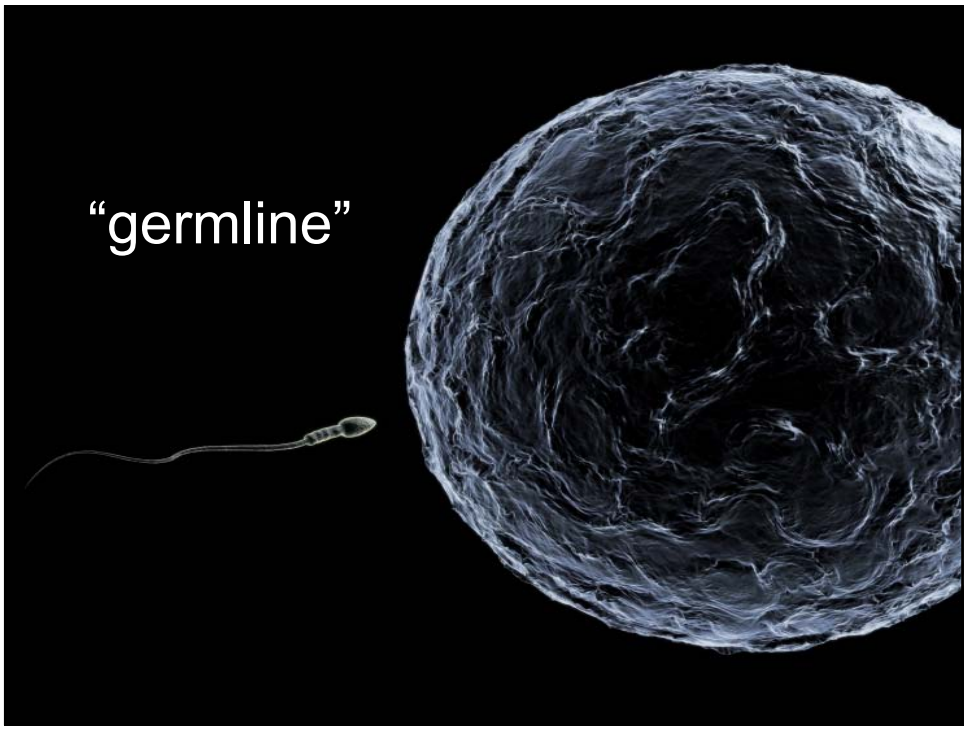
Oklahoma
Texas
Minnesota
Iowa
Missouri
Arkansas
Louisiana
Wisconsin
Illinois
Michigan
Indiana
Ohio
Kentucky
Tennessee
Mississippi
Alabama
Georgia
Florida
South Carolina
North Carolina
Virginia
West Virginia
Pennsylvania
New York
Maryland
Delaware
New Jersey
Connecticut
Rhode Island
Massachusetts
Vermont
New Hampshire
Maine
ATLANTIC OCEAN
SCOTLAND
NORTH SEA
IRISH SEA
IRELAND
WALES
Age-adjusted average annual rates per 100,000
120
100
80
60
40
20
0
1968-72
1973-77
1978-82
1983-87
1988-92
1993-95
Time period


Men
National average
350
300
250
200
150
100
50
0
86
101
105
76
85
90
271
75
31
64
72
198
55
England and Wales
Scotland
Ireland
Eastern Europe
East Africa
North Africa
West Africa
Middle East
Bangladesh
India
Pakistan
West Indies
China and Hong Kong

1. Are increased prostate cancer incidence and increased mortality in Jamaican men genetically linked?

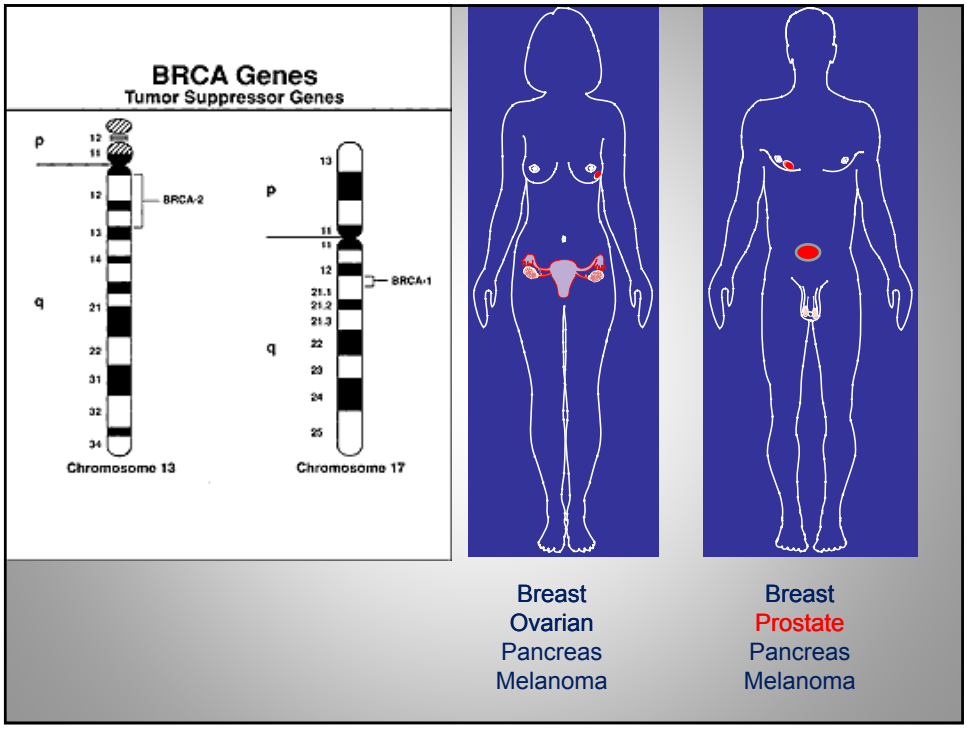


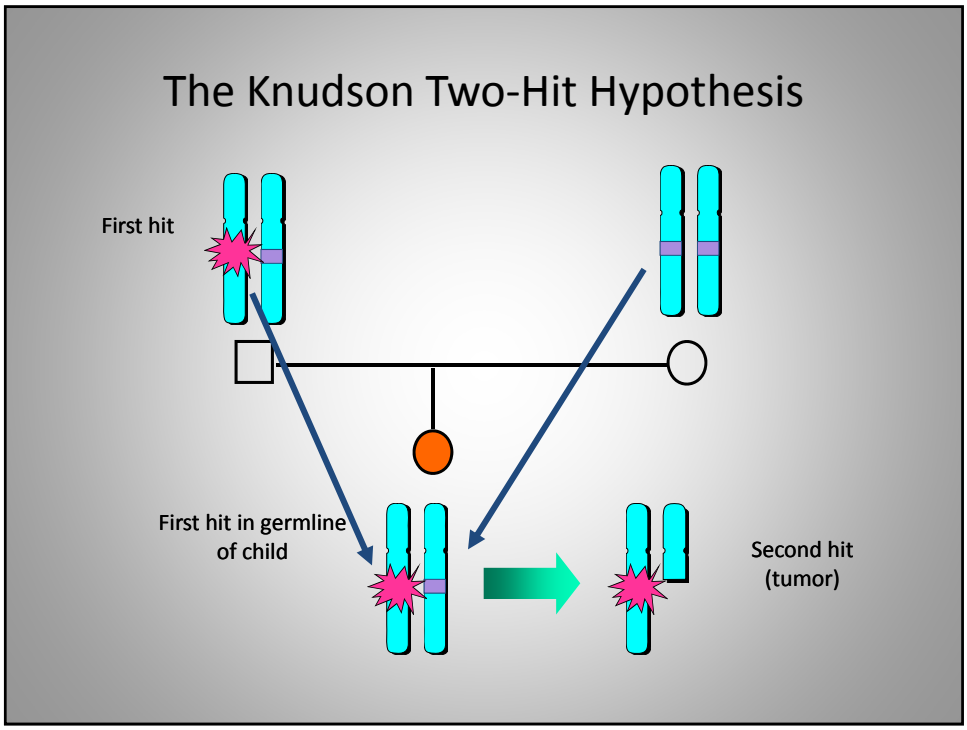
Prostate Cancer Candidate Genes
BRCA1
BRCA2
HPC1
AR
PCAP
HPCX
CAPB
HPC20
MRS1
HPC2/ELAC2
CHK2
RNASEL
NBS1

Androgen receptor CAG repeats are shorter in African American men

CAG Repeat Length	≤ 18 (n = 83)	18-21 (n = 122)	≥ 22 (n = 114)	P
Race				.001
% African-American	36.0	33.3	30.6	
% White	15.9	32.9	51.2	
Gleason score				.37
% < 8	24.9	35.4	39.6	
% ≥ 8	26.9	26.9	46.1	
PSA level				.36
% < 10 ng/mL	22.1	33.5	44.3	
% ≥ 10 ng/mL	28.6	33.1	38.2	
Stage				.09
% stage A-C	21.5	33.1	45.4	
% stage D	29.8	37.2	33.1	

Bennett et al, JCO, 2002
Sartor, Zheng, Eastham et al, Urology 1999


BRCA Genes
Tumor Suppressor Genes
p
q
BRCA-2
BRCA-1
Chromosome 13
Chromosome 17
Breast
Ovarian
Pancreas
Melanoma
Breast
Prostate
Pancreas
Melanoma


The Knudson Two-Hit Hypothesis
First hit
First hit in germline
of child
Second hit
(tumor)

Ashkenazi Jewish

Cases	Controls
894	454

Gallagher et al. Clin Cancer Res. 2010 Mar 9. [Epub ahead of print]

	Case N (%)	Control N (%)	Age-adjusted OR (95% CI)	p-value
Non-carrier	806 (96.9)	447 (98.5)	1.00	
BRCA1 carrier	6 (0.7)	4 (0.9)	0.38 (0.05, 2.75)	0.34
BRCA2 carrier	20 (2.4)	3 (0.7)	3.18 (1.52, 6.67)	0.002

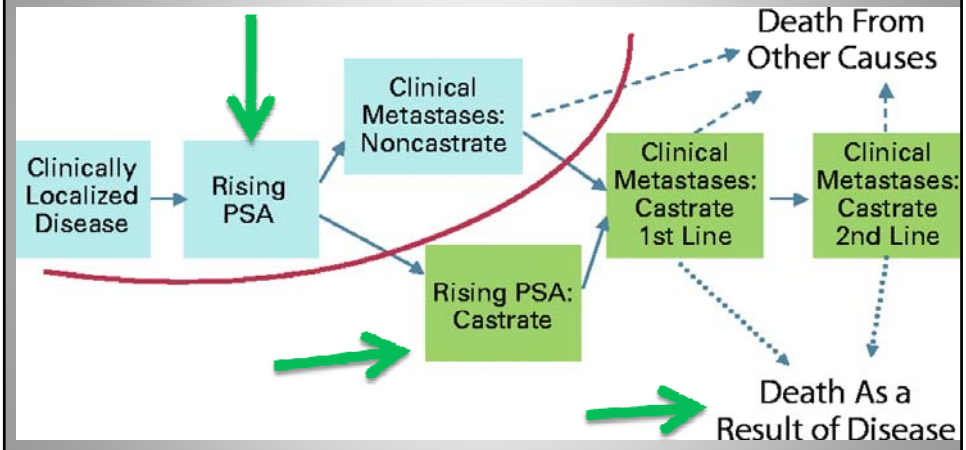
Features of prostate cancer cases

	BRCA wild-type	*BRCA1* mutant	*BRCA2* mutant	p-value
Total N (%)	806 (96.9)	6 (0.7)	20 (2.4)	
Median age (range)				0.057
Gleason score < 7 (%)				
Gleason score ≥ 7 (%)				0.009
Median PSA (range)				0.99
Treatment				
RP				
XRT	493	4	10	
Hormone therapy alone	35	2	0	
Chemotherapy alone	1	0	0	
Watchful waiting	34	0	0	

BRCA2: P = 0.0002

BRCA1: P = 0.71

Prostate Cancer Disease States Model

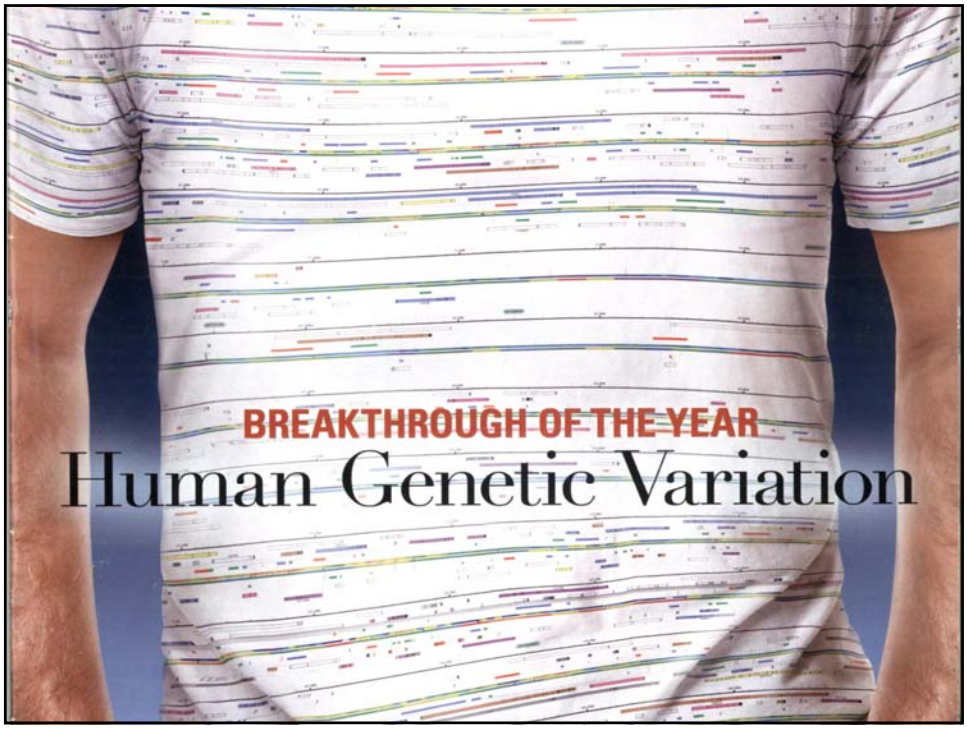


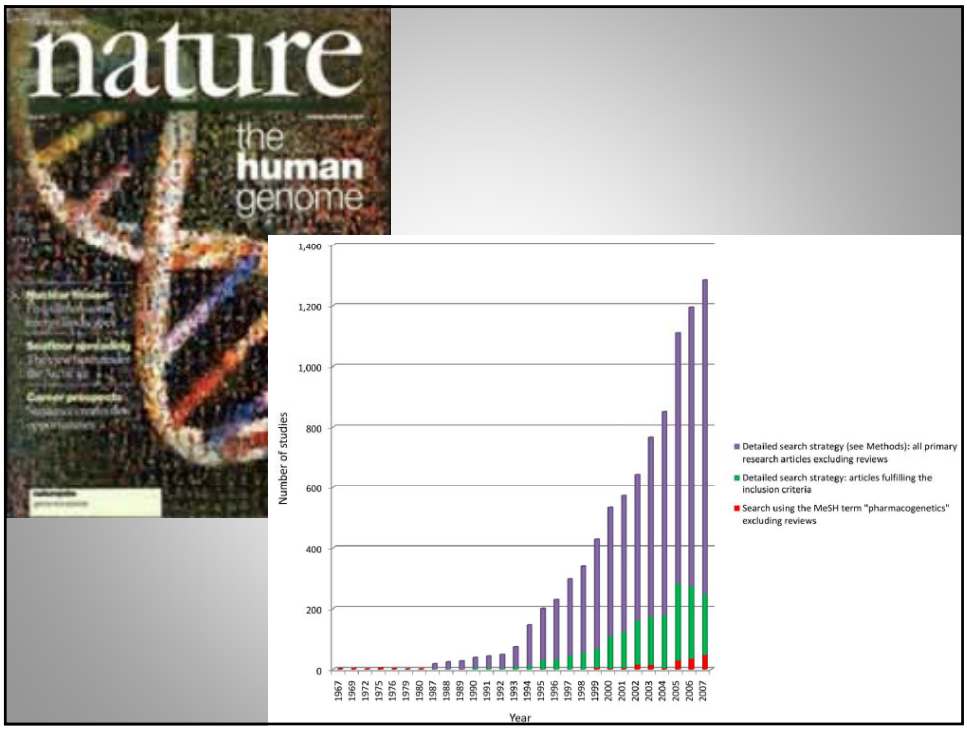
Scher HI et al. Urology. 2000

Outcomes	No. (%) of Events	Median Survival Time	Total Person-Years	HR	95% CI
Biochemical Recurrences					
No mutation	354 (43.9)	8.7	4560.3	1.00	
BRCA 1 mutation	4 (66.7)	2.3	19.6	3.08	(0.98, 9.69)
BRCA2 mutation	11 (55.0)	2.6	72.4	**2.62**	(1.34, 5.15)
Castration Metastasis					
No mutation	149 (21.2)	17.2	6669.0	1.00	
BRCA 1 mutation	2 (33.3)	10.5	49.9	2.01	(0.28, 14.52)
BRCA2 mutation	7 (35.0)	10.5	139.9	**3.25**	(1.39, 7.64)
Death due to Prostate Cancer					
No mutation	91 (11.3)	22.0	7036.2	1.00	
BRCA 1 mutation	3 (50.0)	13.0	54.0	**7.19**	(1.72, 30.16)
BRCA2 mutation	5 (25.0)	13.8	161.1	**6.00**	(2.26, 15.91)
Death due to Any Cancer					
No mutation	132	19.1	7036.2	1.00	
BRCA 1 mutation	3	13.0	54.0	**4.10**	(1.00, 16.87)
BRCA2 mutation	8	12.5	161.1	**5.74**	(2.53, 13.01)

[1]HR were adjusted for clinical stage, PSA levels, and Gleason score at biopsy

BRCA2, a germline mutation, predicted increased risk of prostate cancer and also the occurrence of aggressive disease.


BREAKTHROUGH OF THE YEAR
Human Genetic Variation


nature
the human genome
Number of studies
1,400
1,200
1,000
800
600
400
200
0
1967
1969
1972
1975
1976
1979
1980
1987
1988
1989
1990
1991
1992
1993
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1996
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1998
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2000
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2004
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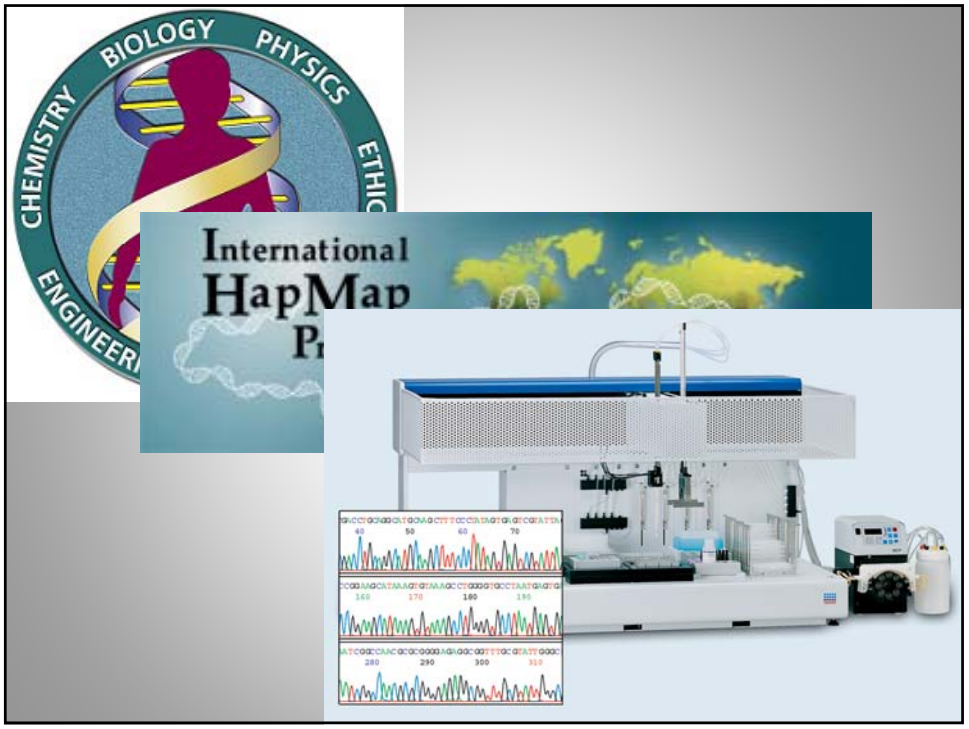
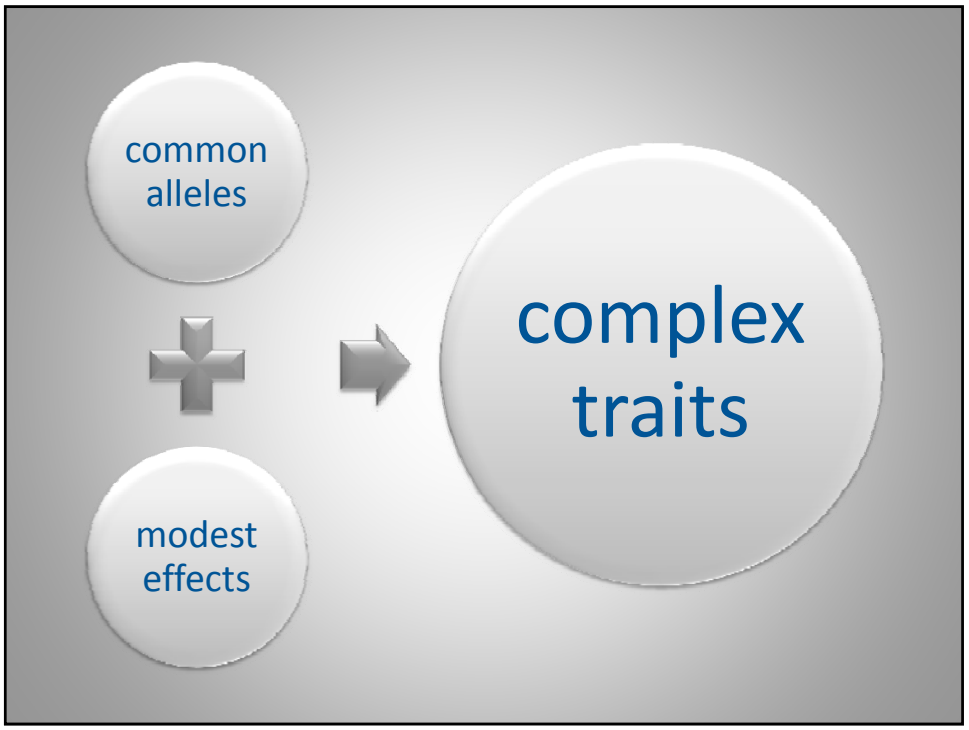
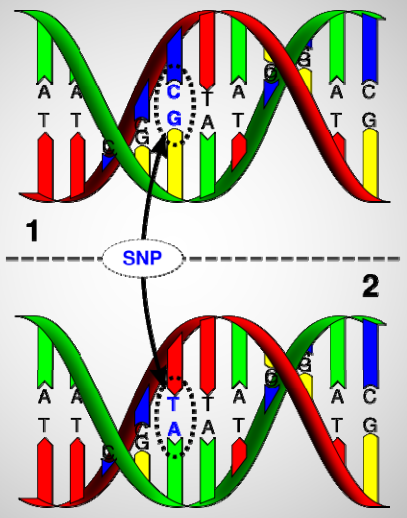
2006
2007
Year
Detailed search strategy (see Methods): all primary research articles excluding reviews
Detailed search strategy: articles fulfilling the inclusion criteria
Search using the MeSH term "pharmacogenetics" excluding reviews


BIOLOGY
PHYSICS
CHEMISTRY
International
HapMap


common alleles
modest effects
complex traits

What is a SNP?



Cancer	# GWAS	# Implicated Loci	# Candidate Genes
Breast	10	13	14
Prostate	8	21	27
Colon	7	10	7
Lung	5	3	9
Bladder	2	3	4
Neuroblastoma	2	2	3
Glioma	2	5	5
ALL	2	3	3
CLL	1	6	7
Thyroid	1	2	0
MPN	1	1	1
TGCT	2	4	3
Pancreas	1	1	1
Ovarian	1	1	1

SNPs Associated with Prostate Cancer Diagnosis in Genome Wide Association Studies to date

Locus Chromosomal Region	SNP	Association Odds ratio	p value	Reference
2p15	rs721048	1.15	7.7×10^{-9}	Gudmundsson et al. Nature Genet 2008
3p12	rs2660753	1.3	2.7×10^{-8}	Eeles et al. Nature Genet 2008
6p25	rs9364554	1.21	5.5×10^{-10}	Eeles et al. Nature Genet 2008
7q21	rs6465657	1.19	1.1×10^{-9}	Eeles et al. Nature Genet 2008 Gudmundsson et al. Nature Genet 2007 Haiman et al. Nature Genet 2007 Yeager et eal. Nature Genet 2007
8q24 (region 2)	rs16901979	1.52	1.1×10^{-9}	Eeles et al. Nature Genet 2008 Haiman et al. Nature Genet 2007 Yeager et eal. Nature Genet 2007
8q24 (region 3)	rs6983267	1.25	9.4×10^{-13}	Eeles et al. Nature Genet 2008 Gudmundsson et al. Nature Genet 2007 Haiman et al. Nature Genet 2007 Yeager et eal. Nature Genet 2007
8q24			[18]	Eeles et al. Nature Genet 2008
8q24			[29]	Thomas et al. Nature Genet 2008
8q24			[8]	Eeles et al. Nature Genet 2008
8q24				Thomas et al. Nature Genet 2008
8q24			[12]	Thomas et al. Nature Genet 2008
8q24				Eeles et al. Nature Genet 2008
8q24			[11]	Gudmundsson et al. Nature Genet 2007
8q24				Thomas et al. Nature Genet 2008
8q24				Eeles et al. Nature Genet 2008
17q24	rs1859962	1.2	2.5×10^{-10}	Gudmundsson et al. Nature Genet 2007 Eeles et al. Nature Genet 2008
19q13	rs2735839	1.37	1.5×10^{-18}	Yaeger et al. Nature Genet 2007 Eeles et al. Nature Genet 2008 Gudmundsson et al. Nature Genet 2008
Xp11	rs5945619	1.29	1.5×10^{-9}	Eeles et al. Nature Genet 2008
Xp11	rs5945572	1.23	3.9×10^{-13}	Gudmundsson et al. Nature Genet 2008
12	rs902774	1.34		Eeles et al. Nature Genet 2008
10	rs7920517	1.15		Eeles et al. Nature Genet 2008
8	rs13254738	1.18		Haiman et al. Nature Genet 2007 Gudmundsson et al. Nature Genet 2007
17q12	rs7501939	1.17	<0.001	Levin et al. Cancer Res 2008 Zheng et al. JNCI 2007
8q24	rs4242382	1.39	1.3×10^{-4}	Fitzgerald Clin Can Res 2009
8q24	rs10090154	1.64	1×10^{-3}	Cheng I et al. Eur J Clin Gen 2008 Salinas et al. Cancer Epi Bio Prev. 2008
8q24 (region 2)	rs1016343	1.32	5×10^{-5}	Eeles et al. Nature Genet 2008
7JAZF1	rs10486567	0.74	2.4×10^{-6}	Thomas et al. Nat Genetic 2008 Yaeger et al. Nature Genet 2007
8q24	rs4242384	1.86		Eeles et al. Nature Genet 2008
11q13	rs10896449	0.78	1.76×10^{-9}	Thomas et al. Nat Genetic 2008 Salinas et al. Cancer Epi Bio Prev. 2008
8q24 (region 3)	rs7000448	1.19	3.3×10^{-1}	Haiman et al. Nature Genet 2007
8q24 (region 2)	rs6983561	1.26	3×10^{-2}	Haiman et al. Nature Genet 2007
8q24	rs7008482		5×10^{-4}	Robbins et al. Genome Res 2007

8q24

Susceptibility Loci Associated with Prostate Cancer Progression and Mortality

David J. Gallagher MB BCh BAO, Vijai Joseph Ph.D., Angel M. Cronin MS., Tomas Kirchhoff, Ph.D., Andrew J Vickers Ph.D., James Eastham M.D., Howard Scher M.D., Peter Scardino M.D., Robert J. Klein, Ph.D., Hans Lilja M.D. Ph.D., Kenneth Offit M.D. MPH

ASCO GU, San Francisco, March 5th 2010

Inherited genetic variant predisposes to aggressive but not indolent prostate cancer

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Communicated by Rod Tabing, Johns Hopkins University School of Medicine, Baltimore, MD, December 9, 2009 (received for review October 21, 2009)

Autopsy studies suggest that most aging men will develop lesions that, if detected clinically, would be diagnosed as prostate cancer (PCa). Most of these cancers are indolent and remain localized; however, a subset of PCa is aggressive and accounts for more than 27,000 deaths in the United States annually. Identification of factors specifically associated with risk for more aggressive PCa is urgently needed to reduce overdiagnosis and overtreatment of this common disease. To search for such factors, we compared the frequencies of SNPs among PCa patients who were defined as having either more aggressive or less aggressive disease in four populations examined in the Genetic Markers of Susceptibility (GEMS) study performed by the National Cancer Institute. SNPs showing possible associations with disease severity were further evaluated in an additional three independent study populations from the United States and Sweden. In total, we studied 4,029 and 12,205 patients with more and less aggressive disease, respectively. We found that the frequency of the TT genotype of SNP rs4054823 at 17p12 was consistently higher among patients with more aggressive compared with less aggressive disease in each of the seven populations studied, with an overall P value of 2.1×10^{-6} under a recessive model, exceeding the conservative genome-wide significance level. The difference in frequency was largest between patients with high-grade, non-organ-confined disease compared with those with low-grade, organ-confined disease. This study demonstrates that inherited variants predisposing to aggressive but not indolent PCa exist in the genome, and suggests that the clinical potential of such variants as potential early markers for risk of aggressive PCa should be evaluated.

association | genetics | SNP | Gleason grade | stage

Prostate cancer accounts for one-fourth of all cancer diagnoses in men in the United States, with an estimated 192,280 new cases in 2009 (1). Although most men will have an indolent form of the disease, aggressive prostate cancers are currently the second leading cause of cancer deaths in men in this country. Most cases of prostate cancer are diagnosed as a result of having an elevated serum level of prostate-specific antigen (PSA), PSA-based disease screening leading to early detection and treatment of prostate cancer (PCa) has contributed to the reduction in mortality observed for this disease in the US over the past several years (1). However, results from two large randomized trials in Europe and the US provide strong evidence that PSA-based screening for PCa is associated with a high risk of overdiagnosis (2, 3). In the European trial, PSA screening was associated with decreased PCa related mortality but at a great cost; ~1,410 men needed to be screened, and 48 additional PCa cases would need to be treated to prevent one death from PCa (2). Although interpretation of these findings is still a subject of discussion, the current inability to accurately distinguish risk for life-threatening, aggressive PCa from the overwhelming majority of indolent cases contributes to the dilemma. Based upon existing evidence for a genetic predisposition to aggressive PCa (4) and PCa-specific death (5), we hypothesized that inherited genetic variants exist that could be used as markers to identify men at risk for more aggressive disease at an early, curable stage of the disease.

Recent breakthroughs in genome-wide association studies (GWAS) have led to the discovery of more than two dozen reported SNPs that are associated with PCa risk by comparing men with or without PCa using case-control study designs (6–25). Unfortunately, none of these PCa risk-associated SNPs consistently distinguish risk for more or less aggressive cancer (26–28), nor are they associated with prostate cancer-specific mortality (29). As a result, there has been much debate regarding the clinical utility of these SNPs as a risk stratification tool (30, 31). Clearly, an alternative approach is needed to search for genetic markers that distinguish those men who are at risk for developing more aggressive PCa. Herein, we report our findings from a systematic evaluation of ~27,000 SNPs in the genome by comparing 4,029 patients with more aggressive disease and 12,205 patients with less aggressive disease from seven study populations using a case-case study design.

Results

To identify inherited genetic markers that are associated with aggressiveness of PCa, we first analyzed publicly available genotype data for ~27,000 SNPs across the genome among 1,980 patients with more aggressive disease and 2,109 patients with less aggressive disease from four CGEMS study populations (PLCO, CPS-II, HPFS, and ATBC) using a case-case analysis (Fig. 1, Table 1). Based on the results of a combined allelic test, we selected a subset of SNPs ($n = 74$) for further evaluation, where $P < 0.05$ for the difference between more and less aggressive disease, and the direction of association was consistent among the four studies. These SNPs were subsequently evaluated in an independent cohort of 1,251 patients with more aggressive disease and 1,619 patients with less aggressive disease from the CAPS study (Table S1). Six of these 74 SNPs were confirmed; $P < 0.05$ for the allelic test, with the same direction of association (Dataset S1). We then evaluated these six SNPs in 1,403 patients with more aggressive disease and 4,218 patients with less aggressive disease from the Johns Hopkins Hospital (JHH) study

Author contributions: J.X., H.G., and W.B.I. designed research; J.X., S.L.Z., S.D.I., K.E.W., F.W., J.S., A.K.K., G.L., L.D.P., S.-T.K., F.-C.H., R.S., J.H., J.A., P.C.W., J.M.T., D.D., J.C., H.G., and W.B.I. performed research; J.X., F.W., J.S., A.K.K., S.-T.K., and F.-C.H. analyzed data; and J.X., H.G., and W.B.I. wrote the paper.

The authors declare no conflict of interest.

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This article contains supporting information online at www.pnas.org/cgi/content/full/0913039107/DCSupplemental.

www.pnas.org/cgi/doi/10.1073/pnas.0913039107 PNAS Early Edition | 1 of 5

"A SNP panel…may be used to target PSA-based prostate cancer screening, reducing overdiagnosis…and also reduce mortality by identifying those with aggressive disease, requiring aggressive treatment…"

Xu et al, PNAS, 2010

The effect and frequency of risk variants varies across populations

SNP	Chr./Nearest Gene	Allele tested	OR (95% CI)*/Risk Allele Frequency					Pooled (2,768 ca/2,359 co)	P
			African Americans (860 ca/575 co)	European Americans (468 ca/419 co)	Latinos (603 ca/572 co)	Japanese Americans (725 ca/684 co)	Native Hawaiians (112 ca/109 co)		
rs721048	2p15 *EHBP1*	A	0.86 (0.59-1.26) 0.05	0.87 (0.67-1.12) 0.19	1.49 (1.19-1.87) 0.14	1.05 (0.71-1.56) 0.04	0.52 (0.24-1.12) 0.09	1.08 (0.94-1.25) 0.09	0.26
rs2660753	3p12.1	T	0.97 (0.83-1.14) 0.46	1.06 (0.81-1.39) 0.13	1.15 (0.94-1.40) 0.20	1.30 (1.09-1.55) 0.24	0.94 (0.56-1.57) 0.18	1.11 (1.01-1.21) 0.26	0.034
rs9364554	6q25.3 *SLC22A3*	T	1.10 (0.82-1.48) 0.07	1.06 (0.86-1.30) 0.27	1.15 (0.95-1.39) 0.21	1.09 (0.93-1.29) 0.34	1.07 (0.69-1.68) 0.22	1.10 (1.00-1.21) 0.22	0.062
rs10486567	7p15.2 *JAZF1*	G	1.18 (1.00-1.40) 0.70	1.50 (1.19-1.89) 0.74	1.19 (1.00-1.40) 0.53	1.14 (0.88-1.48) 0.09	1.25 (0.83-1.89) 0.36	1.23 (1.12-1.35) 0.47	2.1×10^{-5}
rs6465657	7q21.3 *LMTK2*	C	0.91 (0.72-1.14) 0.85	1.08 (0.89-1.31) 0.45	0.94 (0.78-1.12) 0.70	1.04 (0.82-1.33) 0.90	0.98 (0.65-1.49) 0.67	0.99 (0.89-1.09) 0.75	0.80
rs10993994	10q11.23 *MSMB*	T	1.05 (0.90-1.24) 0.59	1.15 (0.96-1.39) 0.42	1.06 (0.90-1.25) 0.37	1.26 (1.08-1.46) 0.45	1.10 (0.75-1.61) 0.64	1.13 (1.04-1.23) 0.47	3.1×10^{-3}
rs12769019	10q26.13 *CTBP2*	G	1.20 (0.98-1.47) 0.16	1.12 (0.90-1.39) 0.26	1.00 (0.83-1.21) 0.24	1.43 (0.75-2.76) 0.01	1.42 (0.68-2.95) 0.07	1.11 (0.99-1.25) 0.15	0.062
rs7931342	11q13.2	G	1.12 (0.93-1.35) 0.76	1.28 (1.05-1.55) 0.51	1.27 (1.07-1.51) 0.37	0.87 (0.73-1.05) 0.23	1.19 (0.79-1.80) 0.48	1.13 (1.03-1.23) 0.45	8.4×10^{-3}
rs11649743	17q12 *HNF1B*	G	1.04 (0.79-1.38) 0.91	1.05 (0.82-1.35) 0.82	1.29 (1.04-1.61) 0.82	1.08 (0.91-1.27) 0.70	0.96 (0.65-1.41) 0.62	1.10 (0.99-1.22) 0.80	0.067
rs4430796	17q12 *HNF1B*	A	0.99 (0.84-1.16) 0.35	1.44 (1.18-1.74) 0.48	1.26 (1.07-1.50) 0.57	1.04 (0.89-1.22) 0.64	1.23 (0.79-1.90) 0.70	1.15 (1.06-1.25) 0.53	9.1×10^{-4}
rs1859962	17q24.3	G	1.01 (0.86-1.19) 0.32	1.00 (0.83-1.20) 0.51	1.10 (0.93-1.30) 0.60	1.06 (0.89-1.25) 0.26	1.03 (0.69-1.52) 0.56	1.04 (0.96-1.13) 0.42	0.35
rs2735839	19q13 *KLK2/3*	G	0.80 (0.67-0.95) 0.71	1.33 (1.02-1.75) 0.84	1.15 (0.94-1.40) 0.77	1.21 (1.03-1.41) 0.58	0.91 (0.61-1.35) 0.51	1.06 (0.97-1.16) 0.70	0.20
rs5945572	Xp11.22 *NUDT10/11*	A	1.34 (1.05-1.71) 0.26	1.25 (0.95-1.66) 0.35	1.32 (0.98-1.77) 0.17	1.25 (0.86-1.82) 0.08	1.65 (0.61-4.46) 0.06	1.31 (1.13-1.51) 0.19	2.6×10^{-4}

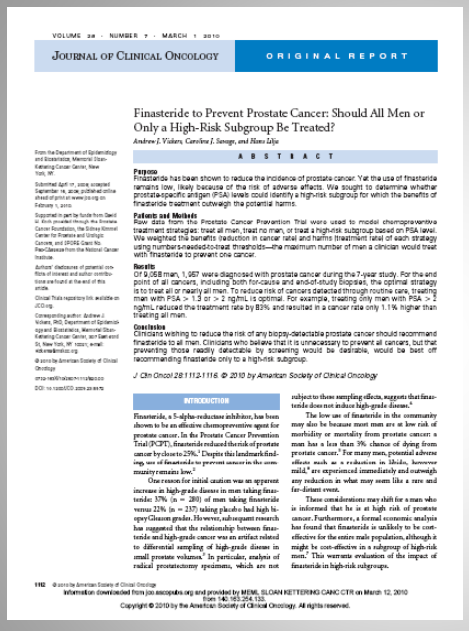
Waters et al, Cancer Epidemiol Biomarkers Review, 2009

1. Yoruba people of Ibadan, Nigeria
2. Japan
3. China
4. U.S. residents with northern and western European ancestry

Risk

Mortality

Treatment



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JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Finasteride to Prevent Prostate Cancer: Should All Men or Only a High-Risk Subgroup Be Treated?

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ABSTRACT

Purpose
Finasteride has been shown to reduce the incidence of prostate cancer. Yet the use of finasteride remains low, likely because of the risk of adverse effects. We sought to determine whether prostate-specific antigen (PSA) levels could identify a high-risk subgroup for which the benefits of finasteride treatment outweigh the potential harms.

Patients and Methods
Raw data from the Prostate Cancer Prevention Trial were used to model chemopreventive treatment strategies: treat all men, treat no men, or treat a high-risk subgroup based on PSA level. We weighted the benefits (reduction in cancer rate) and harms (treatment rate) of each strategy using numbers-needed-to-treat thresholds—the maximum number of men a clinician would treat with finasteride to prevent one cancer.

Results
Of 9,068 men, 1,057 were diagnosed with prostate cancer during the 7-year study. For the end point of all cancers, including both for-cause and end-of-study biopsies, the optimal strategy is to treat all or nearly all men. To reduce risk of cancers detected through routine care, treating men with PSA > 1.3 or > 2 ng/mL is optimal. For example, treating only men with PSA > 2 ng/mL reduced the treatment rate by 83% and resulted in a cancer rate only 1.1% higher than treating all men.

Conclusion
Clinicians wishing to reduce the risk of any biopsy-detectable prostate cancer should recommend finasteride to all men. Clinicians who believe that it is unnecessary to prevent all cancers, but that preventing those readily detectable by screening would be desirable, would be best off recommending finasteride only to a high-risk subgroup.

J Clin Oncol 28:1112-1116. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Finasteride, a 5-alpha-reductase inhibitor, has been shown to be an effective chemopreventive agent for prostate cancer. In the Prostate Cancer Prevention Trial (PCPT), finasteride reduced the risk of prostate cancer by close to 25%.[1] Despite this landmark finding, use of finasteride to prevent cancer in the community remains low.[2]

One reason for initial caution was an apparent increase in high-grade disease in men taking finasteride: 37% (n = 280) of men taking finasteride versus 22% (n = 237) taking placebo had high biopsy Gleason grades. However, subsequent research has suggested that the relationship between finasteride and high-grade cancer was an artifact related to differential sampling of high-grade disease in small prostate volumes.[3] In particular, analysis of radical prostatectomy specimens, which are not subject to those sampling effects, suggests that finasteride does not induce high-grade disease.[4]

The low use of finasteride in the community may also be because most men are at low risk of morbidity or mortality from prostate cancer: a man has a less than 3% chance of dying from prostate cancer.[5] For many men, potential adverse effects such as a reduction in libido, however mild,[6] are experienced immediately and outweigh any reduction in what may seem like a rare and far-distant event.

These considerations may shift for a man who is informed that he is at high risk of prostate cancer. Furthermore, a formal economic analysis has found that finasteride is unlikely to be cost-effective for the entire male population, although it might be cost-effective in a subgroup of high-risk men.[7] This warrants evaluation of the impact of finasteride in high-risk subgroups.

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Prevention in high risk men

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questions?