EGRP Research Highlights

Epidemiology and Genetics Research Program

Web Site: epi.grants.cancer.gov

The Epidemiology and Genetics Research Program (EGRP) supports approximately 400 grants and cooperative agreements annually. Investigators throughout the United States and internationally are funded to conduct population-based research to increase our understanding of cancer etiology and prevention. Some of their recent research findings are highlighted in the following pages. The names of the first authors and of the EGRP-supported Principal Investigators whose grants are credited in the published papers appear in boldface print. Please visit EGRP's Web site to view a special section with highlights from many other studies: *epi.grants.cancer.gov*.

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Bladder Cancer Risk Associated With Truncated Telomeres

Monica McGrath, Sc.D.

Telomeres maintain the structural integrity of chromosomes. Truncated telomeres are observed in a number of cancers, and cigarette smoking, a risk factor for bladder cancer, may cause oxidative stress that enhances telomere shortening.

Monica McGrath, Sc.D., of Harvard School of Public Health, and colleagues examined the association between relative telomere length, cigarette smoking, and bladder cancer. The researchers analyzed telomere length in peripheral blood leukocytes from 184 cases and 192 controls in case-control studies nested within the Health Professionals Follow-Up Study (HPFS) and the Nurses' Health Study (NHS).

They found that telomeres were significantly shorter in bladder cancer cases than controls; the adjusted odds ratio for bladder cancer was 1.88 (95% confidence interval (CI) = 1.05 to 3.36; $P_{trend} = 0.006$) for individuals in the quartile with the shortest telomeres compared to those in the quartile with the longest telomeres. A significant difference in telomere length also was associated with pack-years of smoking, with controls who had smoked for more than 30 pack-years having relatively shorter telomeres than never smokers. This was the largest population-based study to examine the contributions of telomere length to bladder cancer risk and the first large-scale study that used real-time PCR with peripheral blood leukocytes to determine relative telomere length.

EGRP funds numerous cancer epidemiology cohorts including HPFS, since 1991, and NHS, since 1973. Dr. McGrath's study was funded in part by an EGRP grant to **Hoda S. Anton-Culver, Ph.D., of the University of California, Irvine.**

McGrath M, Wong JY, Michaud D, Hunter DJ, De Vivo I. Telomere length, cigarette smoking, and bladder cancer risk in men and women. Cancer Epidemiol Biomarkers Prev. 2007 Apr;16(4):815-9.

Hormone Levels and Mammographic Density Independently Linked to Breast Cancer Risk in Postmenopausal Women

Rulla Tamimi, Sc.D.

Circulating sex hormone levels and mammographic density are strongly and independently related to breast cancer risk in postmenopausal women, according to a study by **Rulla M. Tamimi, Sc.D., of Brigham and Women's Hospital and Harvard Medical School**, and colleagues.

They examined plasma levels of estradiol, free estradiol, testosterone, and free testosterone as well as mammographic density in a cohort of 253 postmenopausal women with breast cancer and 520 healthy women from the Nurses' Health Study (NHS) who were not taking hormones.

Relative risk (RR) of breast cancer associated with mammographic density (RR for highest vs. lowest quartile = 3.8; 95% CI = 2.2 to 6.6; $P_{trend} < .001$) changed little after adjusting for circulating estradiol (RR = 3.9; 95% CI = 2.2 to 6.9; $P_{trend} < .001$) or circulating testosterone (RR = 4.1; 95% CI = 2.3 to 7.2; $P_{trend} < .001$). Circulating levels of estradiol (RR = 2.4; 95% CI = 1.4 to 4.0) and of testosterone (RR = 2.0; 95% CI = 1.2 to 3.1) both were associated with breast cancer risk before and after adjustment for mammographic density.

In a joint analysis of mammographic density and plasma testosterone, the risk of breast cancer was greatest in the highest tertiles of both factors relative to the lowest tertiles (RR = 6.0; 95% CI = 2.6 to 14.0). A joint analysis of mammographic density and plasma estradiol revealed a similar pattern (RR = 4.1; 95% CI = 1.7 to 9.8). This is the first study to indicate that the mechanism by which mammographic density increases breast cancer risk is independent of circulating sex hormone levels. On their own, circulating levels of sex hormones were associated with a twofold increased risk of breast cancer, and mammographic density was associated with an approximately fourfold increased risk of breast cancer.

This research was funded in part by an EGRP grant to **Susan E. Hankinson, Sc.D., of Brigham and Women's Hospital and Harvard Medical School.**

Tamimi RM, Byrne C, Colditz GA, Hankinson SE. Endogenous hormone levels, mammographic density, and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 2007 Aug 1;99(15):1178-87.

Increased Risk of Second Primary Cancers Found in Men With Breast Cancer


Sacha Satram-Hoang, Ph.D.

Men diagnosed with breast cancer may be at increased risk for second cancers. **Sacha Satram-Hoang, Ph.D., of the University of California, Irvine,** and colleagues performed a retrospective registry-based cohort study to analyze the risk of second primary cancers in men previously diagnosed with breast cancer.

The researchers identified 1,926 male breast cancer cases in the California Cancer Registry. Of the 1,926 cases, 211 developed a second primary cancer (standardized incidence ratio (SIR) = 1.16; 95% CI = 1.01 to 1.32); the men had a 16 percent increased risk of developing a new primary cancer compared with men in the general population. Most of the increased risk was attributable to the development of a second breast cancer (SIR = 52.12; 95% CI = 31.83 to 80.49), cutaneous melanoma (SIR = 2.98; 95% CI = 1.63 to 5.00), and stomach cancer (SIR = 2.11; 95% CI = 1.01 to 3.88). The risk of a second malignancy generally was higher among younger men (< 60 years of age) compared to older men.

This research was funded in part by an EGRP grant to **Hoda S. Anton-Culver, Ph.D., of the University of California, Irvine.**

Satram-Hoang S, Ziogas A, Anton-Culver H. Risk of second primary cancer in men with breast cancer. Breast Cancer Res. 2007;9(1):R10.

Cytochrome P450 Gene Variant Associated With Breast Cancer Risk in African Americans


Christopher Haiman, Sc.D.

Cytochrome P450 enzymes play a key role in the production of steroids, and genes that encode these enzymes could be predictors of breast and prostate cancer risk. P450 oxidoreductase (POR) is required for the activity of other P450 enzymes.

Christopher Haiman, Sc.D., of the University of Southern California Keck School of Medicine, and colleagues tested candidate polymorphisms at the POR locus for association with breast cancer risk in women in 1,615 cases and 1,962 controls from the Multiethnic Cohort (MEC) Study.

The SNP G5G was common only in African Americans and, when homozygous, was associated modestly with an increased risk of breast cancer (odds ratio = 1.64; 95% CI = 0.89 to 3.04; P = 0.12). The association was stronger in African Americans with advanced disease. These results suggest that this *POR* genotype increases breast cancer risk in African-American women.

EGRP has funded MEC since 1993. This research was funded in part by EGRP grants to **Dr. Haiman; Laurence N. Kolonel, M.D., Ph.D., of the Cancer Research Center of Hawaii; Brian E. Henderson, M.D., of the University of Southern California/Norris Comprehensive Cancer Center; and Leslie Bernstein, Ph.D., of the University of Southern California Keck School of Medicine.**

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Breast Cancer Risk Associated With Alleles in *FGFR2*

David Hunter, M.D., Sc.D.

Family history contributes to breast cancer risk, but the degree to which it contributes is uncertain. Fibroblast growth factor receptor-2 (*FGFR2*) is a tumor suppressor gene that has been observed to be amplified and over-expressed in breast cancer, and splice variants of the gene can transform mammary epithelial cells in culture.

David J. Hunter, M.D., Sc.D., of Harvard School of Public Health, and colleagues performed a genome-wide association study (GWAS) of breast cancer by genotyping more than 500,000 SNPs in 1,145 postmenopausal women with invasive breast cancer and 1,142 controls from the Nurses' Health Study I (NHS I).

The researchers identified four SNPs within intron 2 of *FGFR2* that were strongly associated with breast cancer. This association was confirmed in 1,776 affected individuals and 2,072 controls from the Nurses' Health Study II (NHS II); Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO); and the American Cancer Society Cancer Prevention Study-II (CPS-II). The association of the SNPs with breast cancer risk did not vary significantly by age of diagnosis. The *FGFR2* variants are hypothesized to be associated with risk of sporadic postmenopausal breast cancer.

NHS I and II are cancer epidemiology cohorts that EGRP has funded since 1973 and 1989, respectively. Dr. Hunter's study was conducted as part of the Cancer Genetic Markers of Susceptibility (CGEMS) Project, an NCI initiative to identify common genetic variations associated with risk for prostate and breast cancer. It is coordinated through the Division of Cancer Epidemiology and Genetics (DCEG), Core Genotyping Facility (CGF), and Office of Cancer Genomics (OCG).

The study was funded in part by EGRP grants to **Dr. Hunter and Susan E. Hankinson, Sc.D., of Harvard Medical School and Brigham and Women's Hospital; and Walter C. Willett, M.D., Dr.P.H., of Brigham and Women's Hospital and Harvard University.**

Hunter DJ, Kraft P, Jacobs KB, Cox DG, Yeager M, Hankinson SE, Wacholder S, Wang Z, Welch R, Hutchinson A, Wang J, Yu K, Chatterjee N, Orr N, Willett WC, Colditz GA, Ziegler RG, Berg CD, Buys SS, McCarty CA, Feigelson HS, Calle EE, Thun MJ, Hayes RB, Tucker M, Gerhard DS, Fraumeni JF Jr, Hoover RN, Thomas G, Chanock SJ. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet. 2007 Jul;39(7):870-4. Epub 2007 May 27.

Physical Activity May Protect Against Colorectal Cancer in Postmenopausal Women

Phuong Mai, M.D.

Cohort and case-control studies have determined that physical activity is inversely associated with colon cancer, particularly among men. This risk reduction has not been shown consistently for women, however. Hormone replacement therapy is associated with reduced colon cancer risk among postmenopausal women, studies have shown, and may mask any beneficial effects of physical activity for women who take these medications.

Phuong L. Mai, M.D., of the University of Southern California, and colleagues analyzed physical activity and colon cancer incidence among the 120,147 female participants in the California Teachers Study (CTS). When comparing women who did more than 4 hours per week per year of recreational physical activity with women who did less than 0.5 hours per week per year, the researchers found that lifetime moderate and strenuous physical activity were associated only modestly with a reduction in colon cancer risk (relative risk (RR) = 0.75; 95% CI = 0.57 to 1.00; $P_{trend} = 0.23$). Among women who had never used hormone therapy, lifetime physical activity was associated with reduced colon cancer risk (RR = 0.51; 95% CI = 0.31 to 0.85; $P_{trend} = 0.02$).

Postmenopausal women who had used hormone therapy had a lower risk of colon cancer, but their risk was not associated with physical activity. With hormone use declining, physical activity may offer a means to reduce women's colon cancer risk, the researchers suggest.

This research was funded in part by an EGRP grant to **Leslie Bernstein, Ph.D., University of Southern California Keck School of Medicine.**

Mai PL, Sullivan-Halley J, Ursin G, Stram DO, Deapen D, Villaluna D, Horn-Ross PL, Clarke CA, Reynolds P, Ross RK, West DW, Anton-Culver H, Ziogas A, Bernstein L. Physical activity and colon cancer risk among women in the California Teachers Study. Cancer Epidemiol Biomarkers Prev. 2007 Mar;16(3):517-25.

Colorectal and Prostate Cancer Share a Common Genetic Risk Factor

Brian Henderson, M.D.

Variants within three unlinked regions of chromosome 8q24 have been shown to contribute to prostate cancer risk. Although the region contains no known genes, it is frequently amplified in both prostate and colorectal cancer.

Christopher Haiman, Sc.D., of the University of Southern California Keck School of Medicine, and colleagues tested whether previously identified variants in 8q24 also affect colorectal cancer risk. They genotyped the variants in a total of 1,807 affected individuals and 5,511 controls in samples from the Multiethnic Cohort (MEC) Study (African Americans, Japanese Americans, Native Hawaiians, Latinos, and European Americans) and from two other studies of Japanese Americans and European Americans.

One variant within the region, rs6983267, was associated significantly with colorectal cancer risk (odds ratio = 1.22, 95% CI = 1.12 to 1.32). Other variants slightly affected risk, but the contributions of these variants to colorectal cancer risk differed from that for prostate cancer risk, indicating differences in the etiologic contributions of these variants to the two cancers.

EGRP has funded MEC since 1993. This study was funded in part by EGRP grants to **Dr. Haiman; Laurence N. Kolonel, M.D., Ph.D., of the Cancer Research Center of Hawaii; Löic Le Marchand, M.D., Ph.D., of the University of Hawaii, Honolulu; and Brian E. Henderson, M.D., of the University of Southern California/Norris Comprehensive Cancer Center and senior author of the paper (pictured).**

Haiman CA, Le Marchand L, Yamamato J, Stram DO, Sheng X, Kolonel LN, Wu AH, Reich D, Henderson BE. A common genetic risk factor for colorectal and prostate cancer. Nat Genet. 2007 Aug;39(8):954-6. Epub 2007 Jul 8.

Tobacco and Alcohol Independently Increase Risk of Head and Neck Cancer

Paolo Boffetta, M.D., M.P.H.

A combination of cigarette smoking and alcohol consumption is implicated in at least 75 percent of head and neck cancers. To understand the mechanism of head and neck carcinogenesis and assess the efficacy of interventions to control these risk factors, an understanding of the independent association of each risk factor with cancer risk is needed.

Mia Hashibe, Ph.D., of the International Agency for Research on Cancer (IARC), and colleagues performed a pooled analysis of data from 15 case-control studies of head and neck cancer risk and cigarette smoking or alcohol consumption in the absence of the other risk factor. This analysis included a total of 10,244 head and neck cancer cases and 15,227 controls obtained from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. INHANCE is an international collaboration of research groups conducting large ongoing or recently completed molecular epidemiology studies on head and neck cancer.

The researchers found that cigarette smoking in never drinkers was associated with an increased risk of head and neck cancer (OR = 2.13 compared to never smokers, 95% CI = 1.52 to 2.98). Alcohol consumption in the absence of tobacco use was associated with increased risk only at high frequencies of consumption (OR = 2.04 for three or more drinks per day versus never drinking, 95% CI = 1.29 to 3.21). Approximately one-quarter of head and neck cancers in never drinkers were attributable to smoking, and 7 percent of cancers in never users of tobacco were attributable to alcohol consumption.

The major strength of the pooled analyses, say the authors, was assembly of a very large series of never users of tobacco and never drinkers among head and neck cancer patients and control subjects, which allowed detailed examination of head and neck cancer risks and exploration of differences in risks by cancer subsite, geographic region, and sex. **Paolo Boffeta, M.D., M.P.H., of IARC (pictured),** directed this pooled analysis. Establishment of the INHANCE Consortium has allowed generation of large sample sizes for analysis of rare subgroups, such as head and neck cancer patients who are never smokers and/or never drinkers. EGRP is a major facilitator of the INHANCE Consortium and provided funding for this pooled analysis. It also provided grant support for some of the individual epidemiologic studies that contributed to the analysis.

EGRP supports cancer epidemiology consortia in numerous ways, such as through grant support, assistance in identifying partners with similar research interests, advice on policies and processes that have proven successful with other consor-

tia, participation on steering committees, and in evaluating established consortia.

Access EGRP's Consortia Web site to learn about the many ways in which the Program supports cancer epidemiology consortia (*epi.grants.cancer.gov/Consortia*).

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Newly Published Research on Non-Hodgkin Lymphoma Shows the Power of Consortia

InterLymph
International Lymphoma Epidemiology Consortium

Ten papers on non-Hodgkin lymphoma (NHL) were published in the March 2007 issue of *Cancer Epidemiology, Biomarkers & Prevention*. These papers stem from a symposium focusing on the role of the environment in NHL risk that was held at the April 2006 annual meeting of the InterLymph Consortium. The information presented at the symposium and published in the journal contributes to our understanding of how behavioral and environmental factors, such as infectious agents, sunlight exposure, obesity, and chemical exposure, affect the risk of developing NHL.

InterLymph is an EGRP-sponsored consortium for epidemiologic research on lymphoma. Members have completed or have ongoing case-control studies of lymphoma and participate in collaborative research by undertaking projects that pool data across studies. Consortia like InterLymph facilitate large-scale collaborations that are needed to address complex questions that cannot be answered through the efforts of investigators at a single institution or from a single discipline.

Access EGRP's Web site to learn more about InterLymph (*epi.grants.cancer.gov/InterLymph*) and about the many ways in which EGRP supports consortia (*epi.grants.cancer.gov/Consortia*).

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Prostate Cancer-Associated SNP Identified


Frederick Schumacher, Ph.D., M.P.H.

Recent studies have found chromosomal region 8q24 amplified in several tumor types, including prostate and breast. In addition, a region of 8q24 has been identified as being associated with prostate cancer in a linkage analysis of Icelandic families, and the findings have been replicated in three case-control studies of men with European ancestry in Iceland, Sweden, and the United States, and in a case-control study of African Americans.

Frederick R. Schumacher, Ph.D., M.P.H., of Harvard School of Public Health, and colleagues validated the association between a SNP in 8q24 (rs1447295) and prostate cancer in a large nested case-control study from the EGRP-funded Breast and Prostate Cancer Cohort Consortium (BPC3). This study included 6,637 prostate cancer cases and 7,361 controls. The researchers also examined whether this polymorphism was associated with breast cancer in 2,604 Caucasian breast cancer cases and 3,118 controls.

They found a strong association of this SNP and prostate cancer in Caucasians ($P = 1.23 \times 10^{-13}$) and a significant asso-

ciation in African-American men diagnosed with prostate cancer at an early age. The authors found no significant difference in risk when tumors were classified by Gleason score, stage, or mortality. They also found no association between this SNP and the risk of breast cancer.

"Although the gene responsible has yet to be identified, the validation of this marker in this large sample of prostate cancer cases leaves little room for the possibility of a false-positive result," the authors report.

This research was funded in part by EGRP grants to **David J. Hunter, M.D., Sc.D., Michael J. Thun, M.D., of the American Cancer Society; Elio Riboli, M.D., M.Sc., then with the International Agency for Research on Cancer (IARC); and Brian E. Henderson, M.D., of the University of Southern California/Norris Comprehensive Cancer Center.**

With support from EGRP, the BPC3 pools data and biospecimens from 10 large prospective cohorts to conduct research on gene-environment interactions in the etiology of breast and prostate cancer. Access EGRP's Web site to learn more about BPC3 (*epi.grants.cancer.gov/BPC3)*.

Schumacher FR, Feigelson HS, Cox DG, Haiman CA, Albanes D, Buring J, Calle EE, Chanock SJ, Colditz GA, Diver WR, Dunning AM, Freedman ML, Gaziano JM, Giovannucci E, Hankinson SE, Hayes RB, Henderson BE, Hoover RN, Kaaks R, Key T, Kolonel LN, Kraft P, Le Marchand L, Ma J, Pike MC, Riboli E, Stampfer MJ, Stram DO, Thomas G, Thun MJ, Travis R, Virtamo J, Andriole G, Gelmann E, Willett WC, Hunter DJ. A common 8q24 variant in prostate and breast cancer from a large nested case-control study. Cancer Res. 2007 Apr 1;67(7):2951-6.

Prostate Cancer Risk Affected by Multiple Regions Within 8q24

David Reich, Ph.D.

This study's authors previously conducted an admixture scan in African Americans with prostate cancer and identified a 3.8-Mb region of chromosome 8q24 that contained risk alleles that differed in frequency between West Africans and European Americans. A second group of researchers identified additional specific variants within this region that also were associated with increased risk of prostate cancer.

Christopher A. Haiman, Sc.D., of the University of Southern California Keck School of Medicine, and colleagues searched for additional variants in 8q24 that might contribute to prostate cancer risk. The group genotyped 1,521 variants in 1,175 African Americans diagnosed with prostate cancer who were under age 72 at diagnosis and 837 African-American controls, as well as 465 European-American cases and 446 European-American controls.

The researchers identified seven risk variants that independently predicted risk for prostate cancer. The variants spanned a more than fivefold range of cancer susceptibility in some populations. Several of the SNPs associated most strongly with prostate cancer also were genotyped in cases and controls from African-American, Japanese-American, Native-Hawaiian, Latino, and European-American (4,266 cases and 3,252 controls) populations.

This analysis strengthened the evidence for an association between these SNPs, with the strongest association with one in particular, rs16901979 ($P = 1.5 \times 10^{-18}$), and risk for prostate cancer. It also demonstrated that the risk allele at this SNP is more common in West Africans (54%) than European Americans (3%).

Although none of the risk variants aligned with known genes or altered the coding sequence of a known protein, this work suggests that there may be multiple unknown prostate cancer susceptibility genes located in 8q24. Additionally, the somatic amplification at 8q commonly observed in prostate tumors implies that the risk alleles make this entire region, including oncogenes such as *MYC*, prone to amplification.

The senior author of this study, David Reich, Ph.D., of Harvard Medical School and Broad Institute of Harvard and MIT, is pictured. This research was funded in part by EGRP grants to **Sue Ingles, Dr.P.H., of the University of Southern California/Norris Comprehensive Cancer Center; Kathleen S. Cooney, M.D., of the University of Michigan; and Alice S. Whittemore, Ph.D., of Stanford University.**

Haiman CA, Patterson N, Freedman ML, Myers SR, Pike MC, Waliszewska A, Neubauer J, Tandon A, Schirmer C, McDonald GJ, Greenway SC, Stram DO, Le Marchand L, Kolonel LN, Frasco M, Wong D, Pooler LC, Ardlie K, Oakley-Girvan I, Whittemore AS, Cooney KA, John EM, Ingles SA, Altshuler D, Henderson BE, Reich D. Multiple regions within 8q24 independently affect risk for prostate cancer. Nat Genet. 2007 May;39(5):638-44. Epub 2007 Apr 1.

Second Risk Locus for Prostate Cancer Identified at 8q24

Meredith Yeager, Ph.D.

A family history of prostate cancer and ethnic background are the only established risk factors for this cancer. Previous studies have identified SNPs in chromosome 8q24 that are associated with increased risk of prostate cancer, particularly among African-American men.

Focusing on men of Eastern European origin, **Meredith Yaeger, Ph.D., of the SAIC-NCI Frederick Cancer Research and Development Center (FCRDC) and the Division of Cancer Epidemiology and Genetics (DCEG)**, and colleagues conducted a genome-wide association study (GWAS) of 550,000 SNPs in a nested case-control study of 1,172 affected men (484 with nonaggressive prostate cancer; 688 with aggressive prostate cancer) and 1,157 controls.

The researchers confirmed in men of Eastern European descent an association between risk for prostate cancer and the SNP rs1447295, which has been associated with increased risk for the cancer in African-American men and with aggressive prostate cancer. In addition, they identified a new association with SNP rs6983267 and confirmed this finding in a combined analysis with four additional replication studies including 3,123 affected men and 3,142 controls. These findings indicate the presence of at least two independent loci within 8q24 that contribute to prostate cancer in men of European descent, the researchers report.

The research was performed as part of the Cancer Genetic Markers of Susceptibility (CGEMS) Project, an NCI initiative to identify common genetic variations associated with risk for prostate and breast cancer. It is coordinated through the Division of Cancer Epidemiology and Genetics (DCEG), Core Genotyping Facility (CGF), and Office of Cancer Genomics (OCG).

This study was funded in part by EGRP grants to **Walter C. Willett, M.D., Dr.P.H., of Harvard University and Brigham and Women's Hospital; David J. Hunter, M.D., Sc.D., of the Harvard School of Public Health; and Michael J. Thun, M.D., of the American Cancer Society.**

Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, Minichiello MJ, Fearnhead P, Yu K, Chatterjee N, Wang Z, Welch R, Staats BJ, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cancel-Tassin G, Cussenot O, Valeri A, Andriole GL, Gelmann EP, Tucker M, Gerhard DS, Fraumeni JF Jr, Hoover R, Hunter DJ, Chanock SJ, Thomas G. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet. 2007 May;39(5):645-9. Epub 2007 Apr 1.

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