Title

Associations between Etiologic or Prognostic Tumor Tissue Markers and Neighborhood Contextual Factors in Male Health Professionals Diagnosed with Prostate Cancer.

Journal

Cancer Epidemiology, Biomarkers and Prevention, 32(8)

Authors

Iyer, Hari

Kensler, Kevin

Vaselkiv, Jane

et al.

Publication Date

2023-08-01

DOI

10.1158/1055-9965.EPI-23-0217

Peer reviewed

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2023 August 01; 32(8): 1120–1123.

doi:10.1158/1055-9965.EPI-23-0217.

Associations between etiologic or prognostic tumor tissue markers and neighborhood contextual factors in male health professionals diagnosed with prostate cancer

Hari S. Iyer[1,§], **Kevin H. Kensler**[2], **Jane B. Vaselkiv**[3], **Konrad H. Stopsack**[3], **Charlotte Roscoe**[3,4], **Elisa V. Bandera**[1], **Bo Qin**[1], **Thomas L. Jang**[5], **Tamara L. Lotan**[6], **Peter James**[7,8], **Jaime E. Hart**[8,9], **Lorelei A. Mucci**[3,9], **Francine Laden**[3,8,9], **Timothy R. Rebbeck**[3,4]

[1]Section of Cancer Epidemiology and Health Outcomes, Rutgers Cancer Institute of New Jersey, New Brunswick, USA

[2]Division of Epidemiology, Population Health Sciences, Weill Cornell Medicine, New York, USA

[3]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, USA

[4]Division of Population Sciences, Dana-Farber Cancer Institute, Boston, USA

[5]Urologic Oncology Program, Rutgers Cancer Institute of New Jersey, New Brunswick, USA

[6]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, USA

[7]Division of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, USA

[8]Department of Environmental Health, Harvard T. H. Chan School of Public Health, Boston, USA

[9]Channing Division of Network Medicine, Department of Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, USA

Abstract

Background—There is growing evidence that unfavorable neighborhood contexts may influence prostate cancer (CaP) progression. Whether these associations may be explained in part by differences in tumor-level somatic alterations remain unclear.

Methods—Data on tumor markers (*PTEN*, *p53*, *ERG*, and *SPINK1*) were obtained from 1,157 participants with CaP in the Health Professionals Follow-up Study. Neighborhood greenness,

§ Corresponding author: Hari S. Iyer, ScD MPH, Section of Cancer Epidemiology and Health Outcomes, Rutgers Cancer Institute of New Jersey, 120 Albany St, Tower 2, 8th Floor, New Brunswick, NJ 08901, hi97@cinj.rutgers.edu.

Author's contributions:

Hari S. Iyer: Conceptualization, formal analysis, writing-original draft, writing-review and editing., **Kevin H. Kensler**: Conceptualization, writing-review and editing., **Jane B. Vaselkiv**: Formal analysis, writing-review and editing., **Konrad H. Stopsack**: Writing-review and editing., **Charlotte J. Roscoe**: Writing-review and editing.; **Elisa V. Bandera**: Writing-review and editing., **Bo Qin**: Writing-review and editing., **Thomas L. Jang**: Writing-review and editing., **Tamara L. Lotan**: Data curation, writing-review and editing., **Peter James**: Resources, writing-review and editing., **Jaime E. Hart**: Methodology, resources, writing-review and editing, **Lorelei A. Mucci**: Resources, funding acquisition, writing-review and editing, **Francine Laden**: Resources, funding acquisition, writing-review and editing, **Timothy R. Rebbeck**: Conceptualization, funding acquisition, resources, formal analysis, writing-review and editing.

Conflicts of Interest: None declared

Target: CEBP Null Results in Brief

socioeconomic status, and the income Index of Concentration at Extremes were obtained from satellite and Census data and linked to participants' address at diagnosis and at study enrollment. Exposures were scaled to an interquartile range and modeled as tertiles. Bivariate associations between tertiles of neighborhood factors and tumor markers were assessed in covariate adjusted logistic regression models to estimate odds ratios and 95% confidence intervals.

Results—There was no association between any of the neighborhood contextual factors and *PTEN*, *p53*, *ERG*, or *SPINK1* in bivariate or multivariable adjusted models. Results were generally consistent when modeling exposure using exposure at diagnosis or at study enrollment.

Discussion—In this multilevel study of men with CaP, we found no evidence of associations between neighborhood context and tumor tissue markers.

Impact—Our results provide some of the first empirical data in support of the hypothesis that CaP risk conferred by tumor tissue markers may arise independently of underlying neighborhood context. Prospective studies in more diverse populations are needed to confirm these findings.

Introduction

Research on neighborhood environments, including neighborhood socioeconomic status (nSES), segregation, and green spaces ("greenness"), has shown that men living in more favorable environments have lower rates of prostate cancer (CaP) incidence and mortality[1]. Neighborhood environments influence modifiable risk factors, including obesity and physical activity, that are associated with distinct molecular subtypes (*ERG* fusions) in men with CaP[2]. Therefore, somatic alterations in prostate tumors might explain the observed associations with neighborhood environments. We examined associations between neighborhood social environments, greenness, and tumor tissue markers in a sample of men with CaP.

Materials and Methods

Data were obtained from the US-based Health Professionals Follow-up Study (HPFS), an ongoing nation-wide prospective cohort of 51,529 male health professionals who were aged 40–75 at start of follow-up in 1986. Participants provided demographic, behavioral, and clinical information through biennial questionnaires and medical records. Of these, 1,686 men diagnosed with CaP between 1986 to 2009 had available archival tissue specimens from radical prostatectomy or transurethral resection of the prostate. A subset of men had tumor specimens with immunohistochemistry assays performed as part of ongoing research studies. Data were available for 1,157 men with ≥1 tissue marker obtained, and complete neighborhood and covariate information. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T. H. Chan School of Public Health, and those of participating registries as required.

Starting in 1988, participants provided either a home or work address which was updated every two years and geocoded. nSES was estimated by calculating an index using Census tract variables from the temporally closest Census capturing area-level educational attainment, income, wealth, occupation, and racial composition[3]. Income segregation was estimated using the Index of Concentration at Extremes (ICE)[4]. Neighborhood greenness

exposure was estimated using the Normalized Difference Vegetation Index (NDVI), available at 30m resolution since 1984. We calculated focal statistics, or spatial averages of the 30m NDVI data within 270m and 1230m areas around participants' addresses. To account for seasonal changes, we calculated average NDVI values from the least cloudy image obtained for each season during the two-year questionnaire cycle. All measures were linked to participant address at diagnosis, and during the first available year of follow-up (1988) as a sensitivity analysis. ICE Income was positively correlated with nSES and NDVI (Supplementary Figure S1).

Procedures for creating tumor tissue microarrays and performing immunohistochemistry have been previously described[5–8]. We selected *ERG*, *p53*, *PTEN*, and *SPINK1* markers, which reflect oncogene, PI3-Akt signaling, and AR-independent signaling pathway disruptions that are being considered for etiologic and prognostic subtyping. Moreover, there is growing evidence that modifiable risk factors, including obesity, physical activity, and statin use, may be associated with distinct alterations in *ERG* and *PTEN*[2].

We evaluated bivariate associations between tumor tissue markers using tertiles with chi-squared test of Fisher's exact test. We then fit logistic regression models to estimate odds ratios for the association between each neighborhood variable and each tumor marker (presence/absence), adjusting for age, screening for prostate specific antigen (PSA), PSA value, Body Mass Index, and population density. Exposures were modeled as continuous scaled to an interquartile range (IQR) and as tertiles with a test for ordinal trend.

We performed sensitivity analyses to account for possible selection bias using inverse probability of censoring weights (Supplementary Methods), and analyses without adjustment for Body Mass Index to evaluate potential mediation.

Data Availability

Because of participant confidentiality and privacy concerns, data are available upon reasonable written request. According to standard controlled access procedure, applications to use HPFS resources will be reviewed by our External Collaborators Committee for scientific aims, evaluation of the fit of the data for the proposed methodology, and verification that the proposed use meets the guidelines of the Ethics and Governance Framework and the consent that was provided by the participants. Investigators wishing to use HPFS data are asked to submit a brief description of the proposed project (go to https://www.nurseshealthstudy.org/researchers (contact: nhsaccess@channing.harvard.edu) and https://sites.sph.harvard.edu/hpfs/for-collaborators/ for details.

Results

Men had a mean age of 66.0 years at diagnosis (SD = 6.1) and were predominantly White (97%). Population characteristics were similar across *ERG*, *PTEN*, *p53*, and *SPINK1* status, except that somatic alterations were more prevalent in low population density settings (Table 1). There were no bivariate associations between any exposure and any tumor marker (Table S1), except between *ERG* and nSES, with higher prevalence of *ERG*+ tumors among lower tertiles of nSES (p=0.06). Results from covariate-adjusted models were similar to bivariate

results (Table 2). The strongest association observed was a 24% lower odds of *PTEN* loss associated with an IQR increase in nSES (aOR: 0.76, 95% CI: 0.58, 1.01). Associations with NDVI were weaker than for nSES and ICE Income. Results from sensitivity analyses using baseline exposure remained largely unchanged, except for an inverse association between NDVI within 1230m and *SPINK1* (Table S2). Incorporating inverse probability weights for censoring (Table S3), and excluding Body Mass Index as a covariate (Table S4) did not appreciably change results.

Discussion

We found no clear associations between neighborhood social environments and greenness in relation to somatic alterations in men with CaP. These findings are consistent with the hypothesis that prostate somatic markers are minimally influenced by neighborhood environments. Limitations include the case-only design, which precludes evaluation of causal relationships. Participants were indicated for surgery, and therefore selection bias may pose a threat to validity. This population of male health professionals is not representative of the US, though the nSES distributions are comparable[3]. While this reduces external validity, restricting demographic and socioeconomic variability limits confounding.

These findings from one of the first examinations of multilevel neighborhood and tissue-level alterations in men with CaP suggest that the somatic alterations investigated here are not associated with neighborhood social and natural environments. We encourage replication in more racially and socioeconomically diverse populations, and use of prospective designs to confirm these results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Dr. Massimo Loda for his contributions to the prostate tumor tissue biomarker data and analyses that supported this work. We gratefully acknowledge the participants and staff of the Health Professionals Follow-up Study for their valuable contributions. The authors would like to acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) and/or the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. Central registries may also be supported by state agencies, universities, and cancer centers. Participating central cancer registries include the following: Alabama, Alaska, Arizona, Arkansas, California, Delaware, Colorado, Connecticut, Florida, Georgia, Hawaii, Idaho, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Mississippi, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Puerto Rico, Rhode Island, Seattle SEER Registry, South Carolina, Tennessee, Texas, Utah, Virginia, West Virginia, Wyoming. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Funding:

The HPFS is supported by NCI grants (U01 CA167552 and P50 CA090381), and in part by funding from NCI Cancer Center Support Grants (P30 CA006516 and P30 CA006973). Tumor tissue microarrays used in this study were constructed at the Dana-Farber/Harvard Cancer Center Tissue Microarray Core and supported by NCI (P30 CA006516). H.S. Iyer was supported by the Program for Training in Cancer Epidemiology (T32 CA009001). K.H. Kensler was supported by NCI grant R00 CA245900. T.R. Rebbeck was supported by NCI Grant P20 CA233255. C.J. Roscoe was supported by the Department of Defense (Early-Investigator Research Award W81XWH2210030). J.E. Hart and F. Laden were supported by the NIEHS grant P30 ES000002. F. Laden was supported by the NIEHS

grant R01 ES028033. J.E. Hart was supported by NIEHS grant R01 ES028712. P. James was supported by NHLBI grant R01 HL150119.

References

1. DeRouen MC, Yang J, Jain J, Weden MM, Gomez SL, Shariff-Marco S. Disparities in Prostate Cancer Survival According to Neighborhood Archetypes, A Population-Based Study. Urology. 2022 May 1;163:138–47. [PubMed: 34303761]
2. Graff RE, Ahearn TU, Pettersson A, Ebot EM, Gerke T, Penney KL, et al. Height, Obesity, and the Risk of TMPRSS2:ERG-Defined Prostate Cancer. Cancer Epidemiol Biomarkers Prev. 2018 Feb 4;27(2):193–200. [PubMed: 29167279]
3. DeVille NV, Iyer HS, Holland I, Bhupathiraju SN, Chai B, James P, et al. Neighborhood socioeconomic status and mortality in the nurses' health study (NHS) and the nurses' health study II (NHSII). Environ Epidemiol. 2023 Feb;7(1):e235. [PubMed: 36777531]
4. Krieger N, Waterman PD, Spasojevic J, Li W, Maduro G, Van Wye G. Public Health Monitoring of Privilege and Deprivation With the Index of Concentration at the Extremes. Am J Public Health. 2016 Feb;106(2):256–63. [PubMed: 26691119]
5. Pettersson A, Graff RE, Bauer SR, Pitt MJ, Lis RT, Stack EC, et al. The TMPRSS2:ERG rearrangement, ERG expression, and prostate cancer outcomes: a cohort study and meta-analysis. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2012 Sep;21(9):1497–509.
6. Flavin R, Pettersson A, Hendrickson WK, Fiorentino M, Finn S, Kunz L, et al. SPINK 1 Protein Expression and Prostate Cancer Progression. Clin Cancer Res Off J Am Assoc Cancer Res. 2014 Sep 15;20(18):4904–11.
7. Ahearn TU, Pettersson A, Ebot EM, Gerke T, Graff RE, Morais CL, et al. A Prospective Investigation of PTEN Loss and ERG Expression in Lethal Prostate Cancer. JNCI J Natl Cancer Inst. 2016 Feb 1;108(2):djv346. [PubMed: 26615022]
8. Stopsack KH, Salles DC, Vaselkiv JB, Grob ST, Mucci LA, Lotan TL. p53 Immunohistochemistry to Identify Very High-risk Primary Prostate Cancer: A Prospective Cohort Study with Three Decades of Follow-up. Eur Urol Oncol [Internet]. 2021 Dec 27 [cited 2022 Aug 25]; Available from: https://www.sciencedirect.com/science/article/pii/S2588931121002194

Table 1.

Characteristics of 1,157 US Male Health Professionals with Prostate Cancer in the Health Professionals Follow-up Study Diagnosed Between 1986 and 2009 with at least One Tumor Marker Alteration[a]

	ERG+	ERG−	PTEN−	PTEN+	p53+	p53−	SPINK1+	SPINK1−
N	**459**	**516**	**109**	**675**	**24**	**697**	**55**	**481**
Demographics and Lifestyle								
Age at diagnosis (mean, SD)	65 (6.04)	66 (5.8)	66.2 (6.2)	66 (5.9)	65 (7.3)	66 (5.9)	65.1 (6.05)	65.6 (56.4)
Body Mass Index (mean, SD)	25.8 (3.5)	26.1 (3.2)	25.7 (3.1)	26.1 (3.4)	26 (4.3)	26 (3.3)	25.4 (3.0)	25.7 (3.4)
Height (mean, SD)	70.5 (2.7)	70.2 (2.7)	69.9 (2.4)	70.4 (2.7)	71.3 (3.1)	70.3 (2.7)	70.7 (2.9)	70.3 (2.8)
Vigorous MET-hours/week (median, [IQR])	0.8 [0.01, 10]	0.8 [0.01, 10]	0.3 [0.01, 10]	0.2 [0.01, 9.5]	2.4 [0.01, 12.2]	0.3 [0.01, 10]	3 [0.01, 10]	0.01 [0.01, 10]
Non-vigorous MET-hours/week (median, [IQR])	14 [4.5, 28]	15 [4.2, 27.5]	14.8 [4.5, 29.2]	15 [4.5, 29]	21.4 [7, 43]	15 [4.2, 27.5]	8.5 [4, 16]	13.3 [4.5, 27.5]
Clinical factors								
Diagnosis year, %								
≤1994	171 (37)	165 (32)	43 (39)	197 (29)	8 (33)	210 (30)	28 (51)	242 (50)
1995–1999	158 (34)	162 (31)	40 (37)	188 (28)	8 (33)	218 (31)	27 (49)	228 (47)
2000–2004	77 (17)	123 (24)	15 (14)	179 (27)	7 (29)	185 (27)	0 (0)	11 (2)
2005–2009	53 (12)	66 (13)	11 (10)	111 (16)	1 (4)	84 (12)	0 (0)	0 (0)
Family History of Prostate Cancer (Father or Brother), %	98 (21)	120 (23)	28 (26)	142 (21)	6 (25)	148 (21)	13 (24)	109 (23)
Ever PSA screened, %	160 (35)	232 (45)	32 (29)	319 (47)	8 (33)	314 (45)	13 (24)	106 (22)
PSA intensity, %	130 (28)	184 (36)	27 (25)	264 (39)	4 (17)	260 (37)	10 (18)	45 (9)
Diagnostic PSA, %								
<10 ng/ml	312 (68)	326 (63)	65 (60)	456 (68)	12 (50)	462 (66)	33 (60)	274 (57)
10-<20 ng/ml	70 (15)	91 (18)	19 (17)	105 (16)	2 (8)	124 (18)	6 (11)	90 (19)
≥20 ng/ml	37 (8)	43 (8)	10 (9)	55 (8)	5 (21)	63 (9)	10 (18)	49 (10)
Missing	40 (9)	56 (11)	15 (14)	59 (9)	5 (21)	48 (7)	6 (11)	68 (14)
Clinical Stage, %								
T1/N0/M0	242 (54)	308 (61)	41 (40)	415 (63)	11 (55)	400 (59)	24 (45)	239 (52)
T2/N0/M0	190 (43)	180 (36)	58 (57)	230 (35)	8 (40)	258 (38)	28 (53)	196 (43)
T3a/N0/M0	15 (3)	14 (3)	3 (3)	19 (3)	1 (5)	23 (3)	1 (2)	26 (6)

	ERG+	ERG−	PTEN−	PTEN+	p53+	p53−	SPINK1+	SPINK1−
N	**459**	**516**	**109**	**675**	**24**	**697**	**55**	**481**
Gleason score, %								
<7	267 (58)	290 (56)	39 (36)	398 (59)	8 (33)	395 (57)	31 (56)	277 (58)
7	148 (32)	164 (32)	46 (42)	208 (31)	10 (42)	226 (32)	17 (31)	151 (31)
>7	44 (10)	62 (12)	24 (22)	69 (10)	6 (25)	76 (11)	7 (13)	53 (11)
Neighborhood/Geographic								
Census Region, %								
Northeast	60 (13)	82 (16)	16 (15)	106 (16)	5 (21)	106 (15)	7 (13)	77 (16)
Midwest	128 (28)	149 (29)	30 (28)	185 (27)	9 (38)	201 (29)	13 (24)	130 (27)
South	148 (32)	139 (27)	37 (34)	193 (29)	6 (25)	202 (29)	15 (27)	135 (28)
West	123 (27)	146 (28)	26 (24)	191 (28)	4 (17)	188 (27)	20 (36)	139 (29)
Population density (median, [IQR])	2038 [586, 3895]	2535 [732, 4690]	1950 [453, 3983]	2409 [671, 4491]	1891 [322, 4400]	2300 [622, 4504]	2543 [816, 4737]	2295 [658, 4465]
nSES (mean, SD)	−0.37 (3.56)	−0.11 (3.71)	−0.88 (3.45)	−0.06 (3.71)	−0.97 (2.78)	−0.26 (3.61)	0.47 (3.41)	−0.31 (3.77)
ICE Income (mean, SD)	0.27 (0.48)	0.3 (0.45)	0.23 (0.47)	0.29 (0.44)	0.27 (0.49)	0.27 (0.44)	0.44 (0.49)	0.32 (0.51)
NDVI (270m) (mean, SD)	0.29 (0.12)	0.30 (0.12)	0.30 (0.12)	0.30 (0.12)	0.28 (0.13)	0.30 (0.12)	0.29 (0.12)	0.28 (0.12)
NDVI (1230m) (mean, SD)	0.30 (0.11)	0.30 (0.11)	0.30 (0.11)	0.31 (0.11)	0.31 (0.12)	0.31 (0.11)	0.29 (0.10)	0.29 (0.11)

Abbreviations: ICE=Index of Concentration at Extremes, IQR=Interquartile Range, MET=Metabolic Equivalent Task units, NDVI=Normalized Difference Vegetation Index, nSES=Neighborhood Socioeconomic Status, PSA=Prostate Specific Antigen

[a] All covariates assessed at time of prostate cancer diagnosis unless otherwise specified.

Table 2.

Odds Ratios and 95% Confidence Intervals for Association Between Neighborhood Contextual Factors at Diagnosis and Somatic Alterations in Tumor Tissue Among US Male Health Professionals with Prostate Cancer

	Continuous (IQR)	Tertile 1	Tertile 2	Tertile 3	P_{trend}
ERG+[a]					
nSES	0.91 (0.77, 1.07)	Ref	1.23 (0.90, 1.69)	0.85 (0.61, 1.17)	0.23
ICE Income	0.88 (0.73, 1.06)	Ref	0.71 (0.52, 0.98)	0.80 (0.59, 1.10)	0.13
NDVI 270m	0.92 (0.74, 1.14)	Ref	0.85 (0.62, 1.17)	0.88 (0.63, 1.22)	0.40
NDVI 1230m	0.93 (0.77, 1.12)	Ref	1.00 (0.73, 1.38)	0.85 (0.61, 1.18)	0.36
PTEN- [a]					
nSES	0.76 (0.58, 1.01)	Ref	0.72 (0.43, 1.19)	0.70 (0.41, 1.17)	0.19
Income ICE	0.81 (0.60, 1.09)	Ref	0.68 (0.41, 1.13)	0.68 (0.41, 1.12)	0.10
NDVI 270m	0.93 (0.65, 1.31)	Ref	0.74 (0.45, 1.23)	0.77 (0.45, 1.30)	0.29
NDVI 1230m	0.95 (0.69, 1.29)	Ref	0.80 (0.48, 1.33)	0.87 (0.51, 1.46)	0.55
p53+ [a]					
nSES	0.92 (0.52, 1.63)	Ref	1.32 (0.49, 3.58)	1.05 (0.34, 3.24)	0.93
ICE Income	1.12 (0.60, 2.11)	Ref	2.42 (0.81, 7.26)	1.63 (0.53, 5.00)	0.37
NDVI 270m	0.71 (0.36, 1.38)	Ref	0.84 (0.31, 2.26)	0.51 (0.17, 1.56)	0.25
NDVI 1230m	1.04 (0.57, 1.92)	Ref	0.52 (0.16, 1.65)	1.16 (0.42, 3.16)	0.85
SPINK1+ [a]					
nSES	1.30 (0.91, 1.83)	Ref	2.08 (0.97, 4.48)	1.99 (0.92, 4.34)	0.12
ICE Income	1.30 (0.86, 1.97)	Ref	1.03 (0.44, 2.39)	1.54 (0.78, 3.05)	0.20
NDVI 270m	1.10 (0.69, 1.78)	Ref	0.57 (0.27, 1.18)	1.05 (0.53, 2.08)	0.87
NDVI 1230m	1.07 (0.70, 1.64)	Ref	0.70 (0.35, 1.41)	0.94 (0.47, 1.90)	0.73

Abbreviations: ICE=Index of Concentration at Extremes, IQR=Interquartile Range, NDVI=Normalized Difference Vegetation Index, nSES=Neighborhood Socioeconomic Status, PSA=Prostate Specific Antigen

[a]Models adjusted for age (<65, 65–69, 70–74, ≥75 years), ever screened for PSA, family history of prostate cancer in father or brother, continuous BMI, population density (<1000, ≥1000 people/mi^2), PSA at diagnosis (≤6, 6–10, >10–20, >20 ng/mL)