

Expression of IGF/insulin receptor in prostate cancer tissue and progression to lethal disease

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Abstract

Circulating insulin-like growth factor-1 (IGF-1) is consistently associated with prostate cancer risk. IGF-1 binds to IGF-1 (IGF1R) and insulin (IR) receptors, activating cancer hallmark pathways. Experimental evidence suggests that *TMPRSS2:ERG* may interact with IGF/insulin signaling to influence progression. We investigated IGF1R and IR expression and its association with lethal prostate cancer among 769 men. Protein expression of IGF1R, IR, and ERG (i.e., a surrogate of *ERG* fusion genes) were assayed by immunohistochemistry. Cox models estimated hazard ratios (HR) and 95% confidence intervals (CI) adjusted for clinical characteristics. Among patients, 29% had strong tumor IGF1R expression and 10% had strong IR expression. During a mean follow-up of 13.2 years through 2012, 80 men (11%) developed lethal disease. Tumors with strong IGF1R or IR expression showed increased cell proliferation, decreased apoptosis, and a higher prevalence of ERG. In multivariable models, strong IGF1R was associated with a borderline increased risk of lethal prostate cancer (HR 1.7; 95% CI 0.9-3.1). The association appeared greater in ERG positive (HR 2.8; 95% CI 0.9-8.4) than ERG negative tumors (HR 1.3; 95% CI 0.6-3.0, p-heterogeneity 0.08). There was no association between IR and lethal prostate cancer (HR 0.8; 95% CI 0.4-1.9). These results suggest that tumor IGF1R expression may play a role in prostate cancer progression to a lethal phenotype, and that ERG positive tumors may be more sensitive to IGF signaling. These data may improve our understanding of IGF signaling in prostate cancer and suggest therapeutic options for disease subtypes.

Summary

Our study suggests that IGF signaling plays a key role with respect to the progression of ERG-positive tumors. These findings provide additional evidence for developing therapeutic agents to target the IGF/insulin signaling pathway for specific prostate cancer subtypes.

Introduction

There is ample evidence implicating the insulin-like growth factor (IGF) and insulin signaling pathways in prostate cancer initiation and progression[1, 2]. Molecular epidemiology studies consistently find that high pre-diagnostic circulating levels of the ligand IGF-1 are associated with an increased risk of prostate cancer, particularly advanced disease[3-6]. Experimentally, IGF-1 binds to both the IGF-1 (IGF1R) and insulin (IR) receptors to subsequently promote mitogenic signaling events, increase cell proliferation, and inhibit apoptosis[1]. Both IGF1R and IR are overexpressed in prostate tumor tissue[7], and therapeutic agents targeting the IGF1R/IR pathway are under development [8, 9].

Emerging evidence suggests the IGF/insulin signaling pathway may be relevant to the *TMPRSS2:ERG* gene fusion, the most common somatic event in primary prostate cancer[10, 11]. We previously reported that men with positive ERG protein expression (an established marker of the *TMPRSS2:ERG* fusion) have significantly higher protein expression of IGF1R and IR compared with men with ERG negative disease[12]. *In vitro* studies support this epidemiological finding by showing direct regulation of IGF1R by *TMPRSS2:ERG*. [13] Taken together, these data suggest that ERG positive tumors may be more sensitive to IGF/insulin signaling which could promote prostate cancer progression.

There is limited evidence to date on IGF1R and IR expression in tumor tissue and prostate cancer progression in patient cohorts, and none have used lethal disease as an endpoint[14]. We hypothesized that higher tumor expression of IGF1R and IR would be associated with an increased risk of lethal prostate cancer, with a stronger effect in men whose tumors were positive for ERG. Lethal prostate cancer was defined as prostate cancer death or distant metastases to bone or other organs. We undertook a prospective study of 769 men who were diagnosed with prostate cancer with long-term follow-up for metastasis and cancer death to investigate associations of tumor protein expression of IGF1R and IR with lethal prostate cancer.

Materials and methods

Study population

This study was nested within the Physicians' Health Study (PHS) and Health Professionals Follow-up Study (HPFS). The PHS I and II were randomized trials of aspirin and vitamin supplements in the prevention of cardiovascular disease and cancer among 29,071 U.S. male physicians[15, 16]. The HPFS is an ongoing cohort of 51,529 male health professionals followed with biennial questionnaires since 1986[17]. In both cohorts, men were cancer-free at baseline. Incident prostate cancers (ICD-9: 185) were initially identified through self-report and confirmed through medical record and pathology report review.

Archival prostate tumor tissue specimens have been collected from participants diagnosed prostate cancer when available. For this analysis, we focused on men diagnosed with prostate cancer between 1983 and 2004 who available had archival radical prostatectomy or transurethral resection of the prostate (TURP) tissue on constructed tumor tissue microarrays. Tumor tissue microarrays were constructed from the archival materials by taking at least three 0.6-mm cores of tumor tissue per case from the primary tumor nodule or the nodule with the highest Gleason grade. Our success rate in collecting tumor tissue materials from pathology departments has been 69%. The clinical and demographic characteristics of men with and without available tissue materials are similar.

Clinical and follow-up data.

Data on tumor stage, prostate specific antigen (PSA) levels at diagnosis, and primary treatments were abstracted from medical records and pathology reports. Standardized histopathologic review of H&E slides was performed by study pathologists to provide uniform Gleason grading (International Society of Urologic Pathology, 2014) and denote areas for construction of tissue microarrays (MF, SF)[18]. Prostate cancer patients have been followed prospectively with biennial questionnaires to collect detailed information regarding additional cancer treatments and development of metastases. For this analysis, lethal prostate cancer was defined as prostate cancer death or distant metastases to bone or other organs. Causes of death are determined by an endpoints review committee using all available data including medical records, death certificates and a search of the National Death Index (NDI). The completeness of follow-up for mortality in the cohorts is greater than 98%.

Tumor biomarkers.

We assessed protein expression of IGF1R and IR by immunohistochemistry on 5- μ m sections of tumor tissue microarrays constructed from prostatectomy (n=710) and TURP (n=59) specimens. Details of the immunohistochemical methods previously reported [7, 12, 19-22]. Briefly, IGF1R expression was assessed using an IGF1R β polyclonal rabbit antibody (Santa Cruz Biotechnology Inc, Santa Cruz, CA, sc-713) and for IR using an IR β rabbit immunoaffinity purified IgG antibody (Upstate Cell Signaling Solutions, Lake Placid, NY, #07-724). For both IGF1R and IR, tumor staining intensity expression was semi-quantitatively scored by study pathologists (LF, TAB) ranging from 0 to 3 as follows: no staining in tumor cells=0, faint=1, moderate=2, and intense staining=3. In a subset of samples, IR (n=328) and IGF1R (n=336) expression was also scored in tumor-adjacent 'normal' prostate tissue. We used the mean staining intensity across TMA cores as our primary exposures for both IGF1R and IR.

We characterized *TMPRSS2:ERG* status using a validated protocol for ERG protein expression (monoclonal antibody clone EPR3864, Epitomics, Inc.)[22]. We classified tumors as ERG positive if at least one core stained positive for ERG, and ERG negative if all cores stained negative for ERG, using ERG-positive nuclear staining of normal endothelial cells as internal controls. ERG tumor status was available among 739 of the 753 patients with IGF1R and among 707 of the 718 patients with IR.

IGF1R/IR pathway is a regulator of the phosphoinositide 3-kinase (PI3K) signaling pathway, and is involved in apoptosis and cell proliferation. As such, we leveraged data on additional tumor markers characterizing these features. Specifically, TUNEL was used to identify the percent of tumor cells undergoing apoptosis using the Apoptag Peroxidase In Situ Kit (Chemicon International), Ki67 for cell proliferation using the polyclonal anti-Ki67 antibody (Vector Labs), and endothelial cell marker CD34 for angiogenesis using a primary mouse monoclonal antibody anti-CD34 (QBEND10; Biogenex, San Ramon, CA)[19]. For the PI3K pathway, we evaluated three markers: PTEN using a rabbit monoclonal anti-PTEN antibody (Cell Signaling Technologies, #9188), pAKT expression using a rabbit polyclonal anti-pAKT (Cell Signaling Technologies,

#4060), and pS6 expression using a rabbit polyclonal anti-pS6 antibody (Cell Signaling Technologies, #2215S).

Statistical methods.

We compared demographic and clinical characteristics according to IGF1R and IR mean tumor intensity categorized as weak to none (0-1), moderate (>1-2), or strong (>2). We used the Kruskal-Wallis Test and the Cochran-Armitage trend test to assess associations across the biomarkers of IGF1R and IR with the tumor markers. Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (95% CI) of associations between IGF1R and IR with time to lethal prostate cancer, defined as prostate cancer death or distant metastases to bone or other organs. Person-time was calculated from the date of cancer diagnosis to the earliest of the following time points: development of lethal prostate cancer, censored at time of death from other causes, or end of follow-up at end of 2012.

Cox models were adjusted for age at diagnosis (years, continuous), and additionally adjusted for body mass index (BMI) (kg/m^2 , continuous), Gleason score (≤ 6 , 3+4, 4+3, 8-10), and clinical tumor stage (T1/T2 N0/Nx M0/Mx, T3 N0/Nx M0/Mx, and T4 or N1). To test for linear trends, we alternatively fitted continuous mean IGF1R and IR expression. We stratified Cox models according to tumor ERG status and tested the multiplicative interaction terms of ERG with IGF1R and IR in separate Cox models using Wald tests. Missing data on clinical (n=24) or pathologic tumor stage (n=18; only among prostatectomy cases) were replaced with the most common category of clinical (T1/T2 N0/Nx M0/Mx) or pathologic TNM stage (T2 N0/Nx M0/Mx). The proportional hazards assumption held when we tested the interaction between IGF1R and IR expression with follow-up time in Cox models.

Analyses were conducted using SAS version 9.2 (SAS institute Inc., Cary, NC), and all statistical tests were 2-sided with p-values below 0.05 considered statistically significant. The research project was approved by the Institutional Review Boards at Partners Healthcare and the Harvard T.H. Chan School of Public Health.

Results

Selected clinical and demographic characteristics of the patient cohorts are presented in **Table 1**. The cohorts are >95% white. There was strong tumor staining of IGF1R in 29% of patients, and of IR in 10% of patients. IGF1R and IR expression were significantly higher in tumor tissue compared with normal appearing tissue (data not shown). Tumor IGF1R and IR expression were not associated with age, BMI, PSA at diagnosis, Gleason score, or pathologic/clinical tumor stage at diagnosis. The prevalence of ERG-positive tumors was 30% in patients with absent to weak IGF1R expression, 48% in tumors with moderate IGF1R expression, and 66% in tumors with strong IGF1R expression. Similarly, the prevalence of ERG increased with higher IR protein expression.

Table 2 presents associations between tumor expression of IGF1R and IR with a range of tumor markers. Tumors with strong IGF1R and IR also exhibited increased tumor proliferation and lower apoptosis. In addition, IGF1R and IR protein expression were positively associated with expression of the PI3K markers pAKT and pS6. Strong IGF1R was suggestively associated with a more angiogenic profile ($p=0.06$), whereas no association for IR and angiogenesis was observed. There was no association between either IR or IGF1R and PTEN status.

During a mean follow-up of 13.2 years, 80 lethal events occurred among men with measured IGF1R expression ($n=753$) and 79 lethal events among men with measured IR ($n=718$). In the fully adjusted models, strong IGF1R expression was associated with a borderline significant increased risk of lethal prostate cancer (HR 1.7; 95% CI 0.9-3.1) (**Table 3**). In contrast, there was no association between IR expression and lethal prostate cancer. When we restricted to patients treated with radical prostatectomy alone and adjusted for pathologic tumor stage in place of clinical tumor stage, the results did not appreciably change (data not shown).

Table 4 shows associations of IGF1R and IR with risk of lethal prostate cancer according to ERG status. The positive association between IGF1R and lethal prostate cancer was restricted to men with ERG-positive tumors (HR 2.8; 95% CI 0.9-8.4), whereas there was no association between IGF1R and lethal cancer in ERG-negative diseases (HR 1.3; 95% CI 0.6-3.0) (**Table 4**). There was no association between IR expression in prostate cancer tissue and lethal prostate cancer risk regardless of ERG status.

Discussion

In this prostate cancer cohort with long-term follow-up, tumor expression of IGF1R was positively associated with risk of developing lethal prostate cancer after adjusting for clinical factors. Moreover, we found strong correlations between IGF1R expression and expression of other tissue markers including PI3K activation, cell proliferation, and reduced tumor apoptosis. While IR tumor expression was also correlated with a range of biomarkers, it was not associated with lethal disease.

The association between IGF1R and an increased risk of lethal prostate cancer is supported by experimental and epidemiological evidence that IGF signaling plays a role in prostate cancer progression. Circulating IGF-1 levels are mainly produced in the liver under the regulation of growth hormone, and normal prostatic stromal cells can produce IGF-I and IGF binding proteins locally in an autocrine/paracrine fashion. IGF-1 binds to IGF1R, IR, as well as to hybrid IR/IGF1R, activating the PI3K-AKT-TOR and RAF-MAPK pathways which promote cell survival and proliferation[1, 23]. Molecular epidemiology studies have found higher pre-diagnostic circulating IGF-1 levels to be consistently associated with a increased risk of incident prostate cancer[6, 24-27], in particular some reported an increased risk of advanced disease or disease-specific mortality[25][28-30]. Genetic variations in 26 IGF pathway-related genes were also reported to be significantly associated with prostate cancer mortality among 5887 prostate cancer cases in the Breast and Prostate Cancer Cohort Consortium (BPCCC).[31]

Data from experimental studies indicates that insulin signaling influences prostate carcinogenesis and tumor progression independently from IGF signaling pathways[32]. For example, *in vitro* studies reported that overexpression of IR was associated with increased proliferation, migration, angiogenesis, and decreased apoptosis[33, 34], whereas knockdown of IGF1R and IR resulted in reduced cell growth and proliferation and increased apoptosis.[35] However, epidemiology evidence for circulating insulin and prostate cancer risk is inconsistent. A study within the Health Professionals Follow-up Study used pre-diagnostic C-peptide levels as a marker of insulin and reported no association for risk total or aggressive prostate cancer.[36] However, other prospective studies showed that C-peptide was positively associated with the aggressive prostate cancer.[3, 4, 37, 38] Intratumoral correlations observed between IR expression and apoptosis, cell proliferation, and AKT expression imply the involvement of other pivotal markers in the complex signaling network.

The IGF1R and IR downstream signaling events are similar, but not identical. IGF1R signaling has been associated with increased mitogenesis while IR has been associated with metabolic events[1, 39], potentially explaining the lack of association between IR and lethal progression. The null association between IR and lethal prostate cancer may also be explained by the inability of our immunohistochemical assay to distinguish between IR isoform A (IR-A) and B (IR-B). Experimental evidence suggests that IR-B is predominantly responsible for the metabolic effects of insulin, while IR-A has a high affinity of IGF-1 and IGF-2 and has a mitogenic response when activated.[39] Activation of IR-A, but not IR-B, has been associated with proliferation, migration, and resistance to apoptosis.[33] In our cohort, any potential association between IR-A with lethal progression may have been obscured by IR-B.

Our results support the hypothesis that synergy between IGF1R expression and ERG status may be related to prostate cancer progression, as men with ERG positive tumors and upregulated expression of IGF1R had a 2.8-fold increased risk of lethal prostate cancer. Our previous study found higher IGF1R and IR tumor expression in ERG-positive tumors compared to ERG-negative.[12]. IGF1R interacts with androgen signaling potentially by activating androgen receptor (AR) co-factors that promote nuclear AR localization.[40, 41] A survey of ChIP-Seq data showed extensive ERG binding to the IGF1R promoter, thus regulating *IGF1R* expression.[42] In the *ERG* positive VCaP prostate cancer cell line, *IGF1R* is highly expressed compared with cell lines lacking ERG. Moreover, in cell lines exposed to IGF1R inhibitors, only VCaP cell lines showed strong growth inhibition.[42] IGF1 signaling may also be a mechanism for formation of Ewing's Sarcoma, that contains a high prevalence of ETS-associated fusion proteins, including ERG. [43, 44]. If replicated, these findings may help improve our understanding of different biological pathways associated with ERG prostate cancer. It may also highlight an opportunity to develop anti-IGF1R therapies that target ERG-positive tumors. These findings may also provide *in vivo* insights into the role of IGF1R in driving prostate cancer progression of ERG positive tumors.

The only other cohort study that has investigated cancer outcomes examined mRNA expression of *IGF1R* and *IR* in among 270 patients and used biochemical recurrence rather than lethal prostate cancer as the endpoint.[14] Although they found a positive correlation between *IGF1R*, *IR* and ERG, they found that *IR* and *IGF1R* expression were downregulated in tumor vs. benign tissue, which contrasts with our study findings.

Moreover, high *IGF1R* expression was inversely associated with biochemical recurrence, with a stronger association between *IGF1R* and ERG-negative cancer. Several possibilities may explain the divergent differences in the previous study and our results and the hypothesized association based on laboratory data. First, *IGF1R* and *IR* were measured at the mRNA level as opposed to protein expression in our study. Second, this cohort was smaller and had shorter follow-up than our study. Third, the risk of recurrence was surprisingly high in their cohort, with almost half of men experience recurrence during less than two years of follow-up, despite of the relatively low risk features of the cohort at baseline.

The validity of our study should be considered in the context of strengths and limitations. First, we had a large, well-annotated cohort with long and complete follow-up, which allowed us to investigate the most clinically relevant endpoint, lethal prostate cancer. Our study pathologists centrally reviewed and scored Gleason for all patients, minimizing measurement errors. We used an established immunohistochemical approach for assessing the tumor biomarkers of interest. However, our assay is unable to distinguish the two isoforms of IR, of which IR-A may be most relevant in prostate cancer [39]. Finally, white men (>95%) primarily comprise our cohort. Given the lower prevalence of *TMPRSS2:ERG* in black and Asian men[45], it will be important to investigate our results in large and diverse cohorts with lethal prostate cancer as the endpoint.

In conclusion, our epidemiological findings support the hypothesis that IGF signaling in prostate tumors plays a role in the progression of prostate cancer. Our findings align with previously published experimental studies and highlight both a potential mechanism of ERG formation and suggest that a subset of prostate cancers could be treated by therapeutic agents targeting the IGF/insulin signaling pathway.

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Conflict of Interest Statement: None declared.

Table I. Clinical characteristics among men diagnosed with prostate cancer between 1983 and 2004 in the Health Professionals Follow-up Study and the Physicians' Health Study, by insulin-like growth factor-1 receptor (IGF1R) or insulin receptor (IR)

Characteristic	IGF1R				IR			
	N	Weak to none (n=173)	Moderate (n=376)	Strong (n=204)	N	Weak to none (n=348)	Moderate (n=300)	Strong (n=70)
Age at diagnosis, years, mean (SD)	753	66.7 (6.3)	65.3 (6.4)	65.9 (6.4)	718	66.5 (6.3)	65.0 (6.4)	65.4 (5.9)
BMI at diagnosis, kg/m ² , mean (SD)	753	25.6 (3.4)	25.7 (3.8)	25.5 (3.0)	718	25.5 (3.1)	25.6 (4.0)	25.8 (3.2)
PSA at diagnosis, ng/ml, median (q1, q3)	640	7.4 (5.1, 12.0)	7.0 (5.0, 10.4)	7.0 (5.0, 11.7)	609	7.0 (5.0, 10.0)	6.9 (4.8, 10.8)	7.0 (5.1, 12.3)
ERG positive, n (%)	739	51 (30)	178 (48)	133 (66)	707	123 (36)	181 (61)	44 (64)
Gleason score, n (%)								
<7	160	43 (25)	87 (23)	30 (15)	148	79 (23)	54 (18)	15 (21)
3+4	266	50 (29)	131 (35)	85 (42)	257	116 (33)	115 (38)	26 (37)
4+3	182	40 (23)	91 (24)	51 (25)	174	85 (24)	75 (25)	14 (20)
≥8	145	40 (23)	67 (18)	38 (19)	139	68 (20)	56 (19)	15 (21)
Pathologic TNM, n (%)								
T2 N0/Nx	482	98 (65)	251 (73)	133 (73)	455	204 (70)	201 (71)	50 (74)
T3 N0/Nx	173	49 (32)	81 (24)	43 (24)	168	85 (29)	67 (24)	16 (24)
T4/N1	22	4 (3)	11 (3)	7 (4)	21	3 (1)	16 (6)	2 (3)
Clinical TNM, n (%)								
T1/T2 N0/Nx	686	155 (90)	347 (95)	184 (93)	650	313 (93)	270 (92)	67 (97)
T3 N0/Nx	34	13 (8)	10 (3)	11 (6)	33	15 (4)	17 (6)	1 (2)
T4/N1	15	3 (2)	9 (2)	3 (1)	15	9 (3)	5 (2)	1 (1)

Table II. Association^a between tumor expression of insulin-like growth factor-1 receptor (IGF1R) and insulin receptor (IR) with additional tissue markers among men diagnosed with prostate cancer in the Health Professionals Follow-up Study and the Physicians' Health Study

	IGF1R expression					IR expression				
	N	Weak to none	Moderate	Strong	P ^b	N	Weak to none	Moderate	Strong	P ^b
IR	702	0.3 (0, 1.0)	1.3 (1.0, 2.0)	2.0 (1.3, 2.0)	<0.0001	-	-	-	-	-
IGF1R	-	-	-	-	-	702	1.7 (1.0, 2.0)	2.0 (2.0, 2.7)	2.3 (2.0, 3.0)	<0.0001
Ki67 ^c	726	0.04 (0, 0.3)	0.1 (0, 0.4)	0.2 (0, 0.8)	<0.0001	692	0 (0, 0.3)	0.1 (0, 0.6)	0.1 (0, 0.5)	0.01
TUNEL ^d	638	1.0 (0.5, 3.0)	0.5 (0, 2.0)	0.5 (0, 2.0)	0.03	607	1.0 (0.5, 3.0)	0.5 (0, 2.0)	0.5 (0, 0.5)	<0.0001
PTEN loss, % ^e	570	17%	22%	16%	0.72	537	18%	22%	20%	0.32
pAKT ^f	682	0.02 (0, 0.07)	0.04 (0.01, 0.09)	0.08 (0.03, 0.17)	<0.0001	656	0.02 (0.01, 0.07)	0.06 (0.02, 0.14)	0.09 (0.04, 0.18)	<0.0001
pS6 ^f	717	0.09 (0.04, 0.19)	0.14 (0.05, 0.30)	0.16 (0.07, 0.35)	<0.0001	684	0.10 (0.04, 0.21)	0.16 (0.07, 0.34)	0.21 (0.09, 0.59)	<0.0001
Vessel area ^g	300	482 (324, 662)	491 (387, 672)	428 (302, 597)	0.06	280	459 (358, 620)	457 (341, 684)	470 (310, 600)	0.85

^a Values are presented as median (quartile 1, quartile 3) unless otherwise indicated

^b P-values calculated by Kruskal-Wallis Test except for PTEN which is calculated by the Cochran-Armitage Trend test

^c Ki67 percent positive nuclear staining

^d TUNEL percent positive nuclear staining

^e A tissue core was considered to have PTEN protein loss if the intensity of cytoplasmic and nuclear staining was markedly decreased or entirely negative across >10% of tumor cells compared to surrounding benign glands and/or stroma

^f Expressed as mean area values are median (quartile 1, quartile 3) unless otherwise indicated

^g Vessel area = area comprised by microvessels (in square micrometers); smaller vessels are more angiogenic

Table III. Hazard ratios (HR) and 95% confidence intervals (CI) of the association between insulin-like growth factor-1 receptor (IGF1R) and insulin receptor (IR) and risk of lethal prostate cancer among men in the Health Professionals Follow-up Study and the Physicians' Health Study

	N^a	Lethal events	Person-years	Model 1^b	Model 2^c
IGF1R expression					
Weak to none	173	18	2176	Reference	Reference
Moderate	376	34	4973	0.9 (0.5-1.6)	1.1 (0.6-2.0)
Strong	204	28	2763	1.3 (0.7-2.4)	1.7 (0.9-3.1)
Trend <i>p-value</i>				0.30	0.07
	N^a	Lethal events	Person-years	Model 1^b	Model 2^c
IR expression					
Weak to none	348	40	4343	Reference	Reference
Moderate	300	32	4091	1.0 (0.6-1.5)	0.9 (0.5-1.4)
Strong	70	7	974	0.8 (0.4-1.9)	0.8 (0.4-1.9)
Trend <i>p-value</i>				0.71	0.51

^a Total number of cases

^b Adjusted for age at diagnosis

^c Adjusted for age at diagnosis, BMI at diagnosis, Gleason score, and clinical TNM stage

Table IV. Hazard ratios (HR) and 95% confidence intervals (CI) of the association between insulin-like growth factor-1 receptor (IGF1R) and insulin receptor (IR) with lethal prostate cancer stratified by ERG tumor status among men in the Health Professionals Follow-up Study and the Physicians' Health Study

Lethal Prostate Cancer									
	ERG-negative				ERG-positive				
IGF1R	Lethal events	Person years	Model 1 ^a	Model 2 ^b	Lethal events	Person years	Model 1 ^a	Model 2 ^b	P int ^e
Weak to none	13	1411	Reference	Reference	4	712	Reference	Reference	0.08
Moderate	17	2474	0.8 (0.4-1.6)	1.2 (0.6-2.6)	16	2407	1.3 (0.4-3.8)	1.3 (0.4-3.9)	
Strong	10	872	1.3 (0.6-2.9)	1.3 (0.6-3.0)	18	1843	1.9 (0.6-5.5)	2.8 (0.9-8.4)	
Trend <i>p</i> -value			0.65	0.52			0.18	0.02	
IR									
Weak to none	24	2676	Reference	Reference	14	1596	Reference	Reference	0.45
Moderate	14	1540	1.1 (0.6-2.1)	0.9 (0.4-1.7)	18	2496	0.9 (0.5-1.9)	1.0 (0.5-2.0)	
Strong	3	342	1.0 (0.3-3.4)	0.6 (0.2-1.9)	4	614	0.8 (0.3-2.4)	1.4 (0.4-4.3)	
Trend <i>p</i> -value			0.86	0.36			0.68	0.72	

^a Adjusted for age at diagnosis

^b Adjusted for age at diagnosis, BMI at diagnosis, Gleason score, and clinical TNM

^c *p*-value based on Wald test of multiplicative interaction term between continuous IGF1R or IR and ERG status; adjusted for age at diagnosis, BMI at diagnosis, Gleason score, and clinical TNM

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