

# Insulin-like Growth Factors, Their Binding Proteins, and Prostate Cancer Risk: Analysis of Individual Patient Data from 12 Prospective Studies

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**Background:** Some, but not all, published results have shown an association between circulating blood levels of some insulin-like growth factors (IGFs) and their binding proteins (IGFBPs) and the subsequent risk for prostate cancer.

**Purpose:** To assess the association between levels of IGFs and IGFBPs and the subsequent risk for prostate cancer.

**Data Sources:** Studies identified in PubMed, Web of Science, and CancerLit.

**Study Selection:** The principal investigators of all studies that published data on circulating concentrations of sex steroids, IGFs, or IGFBPs and prostate cancer risk using prospectively collected blood samples were invited to collaborate.

**Data Extraction:** Investigators provided individual participant data on circulating concentrations of IGF-I, IGF-II, IGFBP-II, and IGFBP-III and participant characteristics to a central data set in Oxford, United Kingdom.

**Data Synthesis:** The study included data on 3700 men with prostate cancer and 5200 control participants. On average, case patients were 61.5 years of age at blood collection and received a diagnosis of prostate cancer 5 years after blood collection. The greater the serum IGF-I concentration, the greater the subsequent

risk for prostate cancer (odds ratio [OR] in the highest vs. lowest quintile, 1.38 [95% CI, 1.19 to 1.60];  $P < 0.001$  for trend). Neither IGF-II nor IGFBP-II concentrations were associated with prostate cancer risk, but statistical power was limited. Insulin-like growth factor I and IGFBP-III were correlated ( $r = 0.58$ ), and although IGFBP-III concentration seemed to be associated with prostate cancer risk, this was secondary to its association with IGF-I levels. Insulin-like growth factor I concentrations seemed to be more positively associated with low-grade than high-grade disease; otherwise, the association between IGFs and IGFBPs and prostate cancer risk had no statistically significant heterogeneity related to stage or grade of disease, time between blood collection and diagnosis, age and year of diagnosis, prostate-specific antigen level at recruitment, body mass index, smoking, or alcohol intake.

**Limitations:** Insulin-like growth factor concentrations were measured in only 1 sample for each participant, and the laboratory methods to measure IGFs differed in each study. Not all patients had disease stage or grade information, and the diagnosis of prostate cancer may differ among the studies.

**Conclusion:** High circulating IGF-I concentrations are associated with a moderately increased risk for prostate cancer.

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Prostate cancer is one of the most common types of cancer in men, yet few risk factors for the disease, other than age, race, and a family history, have been established (1, 2). Insulin-like growth factors (IGFs) and their associated binding proteins (IGFBPs) have been the subject of many epidemiologic investigations of prostate cancer because they are known to help regulate cell proliferation, differentiation, and apoptosis (3). Although results from some, but not all, studies suggest an association between IGFs and IGFBPs and prostate cancer risk, there has been much uncertainty about its consistency and magnitude. A previous meta-analysis that included only 3 prospective studies suggested that high levels could be associated with more than a 2-fold increase in risk (4), although recent studies have suggested the risk is lower. Furthermore, given that these peptides are correlated with each other, uncertainty remains about any observed relationships. The individual studies are rarely large enough to allow proper mutual adjustment for these correlated factors, and they are

insufficiently powered to investigate the consistency of their findings in key subgroups (for example, stage and grade of disease). Such analyses are important because studies have suggested that IGF-I might be more associated with advanced than with localized disease (5, 6).

The Endogenous Hormones and Prostate Cancer Collaborative Group was established to conduct collaborative reanalyses of individual data from prospective studies on

### Context

Insulin-like growth factors (IGFs) and IGF binding proteins may be associated with some cancers.

### Contribution

This reanalysis of individual patient data from 12 studies of the association between IGFs and IGF binding proteins and prostate cancer suggests that higher levels of serum IGF-I are associated with higher risk for prostate cancer.

### Caution

The 12 studies varied in the types of patients they studied and in how they measured IGFs.

### Implication

High IGF-I levels seem to be a risk factor for prostate cancer.

the relationships between circulating levels of sex hormones and IGFs and subsequent prostate cancer risk. Results for the sex hormones have been reported elsewhere and show no statistically significant relation between androgen or estrogen levels in men and the subsequent risk for prostate cancer (7). We report results for concentrations of IGFs and IGFBPs.

## METHODS

### Participants

The Endogenous Hormones and Prostate Cancer Collaborative Group is described in detail elsewhere (7). In brief, the group invited principal investigators of all studies, found by searching PubMed, Web of Science, and CancerLit, that provided data on circulating concentrations of sex steroids, IGFs or IGFBPs, and prostate cancer risk by using prospectively collected blood samples to join the collaboration. Thirteen studies collected data on circulating IGF concentrations and the subsequent risk for prostate cancer (5, 6, 8–20), of which 1 contributed only data on sex hormones (20). Eleven of the studies used a matched case–control design nested within a prospective cohort study (5, 6, 8–12, 16, 19) or a randomized trial (13–15, 17). One study used a case–cohort design (18) and was converted into a matched case–control design by randomly matching up to 3 control participants to each case patient by age at recruitment, time between blood collection and diagnosis, time of blood draw, and race. (Table 1 provides a full description of the studies and matching criteria used.) Most of the prospective studies were population-based, with the exception of 1 based on health plan members (9), 1 that recruited male health professionals (16), and 1 that was a combination of an intervention study and a monitoring study for cardiovascular disease (6, 10). Two of the randomized trials did not have

prostate cancer as a primary end point (5, 8, 15); the other 2 were based within a screening trial (13) or were about treatment of prostate-specific antigen (PSA)–detected prostate cancer (14).

Individual participant data were available for age; height; weight; smoking status; alcohol consumption; marital status; socioeconomic status (assessed by educational achievement); race; concentrations of IGFs, IGFBPs, and endogenous sex steroids; and PSA level. Information sought about prostate cancer included date of diagnosis, stage and grade of disease, and method of case patient ascertainment.

Some studies (5, 6, 8, 10, 16) published more than 1 article or performed assays at different times on the association between IGFs and prostate cancer risk, sometimes with different matched case–control sets, laboratory measurements, and durations of follow-up. For each study, we created a single data set in which each participant appeared only once. In our analysis, we treated any participant who appeared in a study as both a control participant and a case patient as a case patient only. We removed matched set identifiers, and we generated a series of strata (equivalent to matched sets) in which participants in each study were grouped according to age at recruitment (2-year age bands) and date of recruitment (by year), because these matching criteria were common to most studies (Table 1). The number of strata used in the collaborative analysis was slightly less than that of matched sets used in the original analyses. To ensure that this process did not introduce any bias, we checked that the results for each study, using the original matched sets, were the same as those using the strata described above.

Tumors were classified as advanced if the tumor was described as extending beyond the prostate capsule (T3/T4), and/or there was lymph node involvement (N1/N2/N3), and/or there were distant metastases (M1); tumors were classified as localized if they were T0/T1/T2 and N0/NX and M0. We classified tumors as high-grade if they had a Gleason score of 7 or more or were moderately poorly or poorly differentiated; otherwise, they were classified as low-grade.

### Statistical Analysis

We calculated partial correlation coefficients between log-transformed IGF and IGFBP concentrations among control participants, adjusted for age at blood collection (<50, 50 to 59, 60 to 69, or ≥70 years) and study. For each IGF and IGFBP, we categorized men into quintiles of IGF and IGFBP serum concentrations, with cut-points defined by the study-specific quintiles of the distribution within control participants. For studies with more than 1 publication or in which the serum assays were done at different times, resulting in different absolute levels of IGFs (5, 6, 8, 10, 16), we calculated cut-points separately for each substudy. We used a conditional logistic regression stratified by study, age at recruitment (2-year age bands),

**Table 1. Study Characteristics**

Study, Year (Reference)	Sample	Location	Study Recruitment Dates	Prostate Cancer Ascertainment Method	Nested Case–Control Study Characteristics	
					Ratio of Case Patients to Control Participants: <i>n:n</i>	Matching Criteria
BLSA, 2000 (11)	Population-based cohort study of the physiology of aging	United States	1958–onward	Self-report with medical record review	1:2	Age ( $\pm 2$ y); same age at first visit; follow-up time longer than time between recruitment and time case patients received diagnosis
CHS, 2005 (17)	Population-based cohort study	United States	1989–1993	Cancer registry linkage or self-report with hospital discharge confirmation	1:1	Age (within 3 y); year of entry; year of blood draw; control participants survived to same age as case patient; race
CLUE, 2001 (12)	Population-based cohort study	United States	1974–onward	Cancer registry linkage	1:1	Age ( $\pm 1$ y); date of recruitment ( $\pm 3$ wk)
EPIC, 2007 (19)	Population-based cohort study	7 European countries	1991–2001	Cancer registry linkage; health insurance record linkage; self-report (validated)	1:1	Age ( $\pm 6$ mo); follow-up time; time of blood draw ( $\pm 1$ h); recruitment center; time between blood draw and last food or drink consumption
ERSPC, 2004 (13)	Population-based randomized trial of PSA screening	The Netherlands	1991–2000	Diagnosis as part of trial protocol	1:1	Age (per 1-y group); PSA level at first visit ( $< 2$ , 2–3, 3–4 $\mu\text{g/L}$ ); postal code
HPFS, 2005 (16)	Cohort study of male dentists, optometrists, osteopathic physicians, podiatrists, pharmacists, and veterinarians	United States	1986	Self-report with medical record review	1:1	Year of birth ( $\pm 1$ y); date of recruitment (same year); time of blood collection (12 a.m.–9 a.m.; 9 a.m.–12 p.m.; 12 p.m.–4 p.m.; 4 p.m.–12 a.m.); PSA test before blood draw; season; control participants had $\geq 1$ screening PSA test after the date of blood draw
KPMCP, 1998 (9)	Health plan members	United States	1964–1970	Record linkage to tumor registry	1:3	Same age
MCCS, 2006 (18)	Population-based cohort study	Australia	1990–1994	Cancer registry linkage	Not matched: designed as a case-cohort study	Not matched: designed as a case-cohort study
NSHDC, 2000 (10) and 2004 (6)	Combination of a population-based intervention study to decrease cardiovascular disease and a population-based monitoring study of cardiovascular disease	Sweden	1985–onward	Cancer registry linkage	1:2	Age ( $\pm 6$ mo); date of recruitment ( $\pm 2$ mo); town or area of residency
PHS, 1998 (8) and 2002 (5)	Randomized trial of aspirin and $\beta$ -carotene among physicians	United States	1982	Self-report with medical record review	1:1	Age ( $\pm 1$ y); date of recruitment ( $\pm 3$ wk); never had total or partial prostatectomy; smoking status
ProtecT, 2004 (14)	Population-based PSA testing and randomized, controlled trial of treatments of localized prostate cancer	United Kingdom	1999–2002	Diagnosis as part of trial protocol	1:2	Age (2-y bands); closest calendar date; primary care practice
SU.VI.MAX, 2005 (15)	Randomized trial of antioxidant and mineral supplementation	France	1994	Medical record linkage	1:3	Same age

BLSA = Baltimore Longitudinal Study of Aging; CHS = Cardiovascular Health Study; CLUE = Campaign Against Cancer and Stroke (“Give Us a Clue to Cancer”) Study; EPIC = European Prospective Investigation into Cancer and Nutrition; ERSPC = European Randomized Study of Screening for Prostate Cancer; HPFS = Health Professionals Follow-up Study; KPMCP = Kaiser Permanente Medical Care Program; MCCS = Melbourne Collaborative Cohort Study; NSHDC = Northern Sweden Health & Disease Cohort; PHS = Physicians’ Health Study; ProtecT = Prostate Testing for Cancer and Treatment Study; PSA = prostate-specific antigen; SU.VI.MAX = Supplémentation en Vitamines et Minéraux Antioxydants.

**Table 2. Participant Characteristics\***

Study, Year (Reference)	Case Patients/Control Participants, n/n*	Mean Age at Recruitment, y	Mean Body Mass Index, kg/m <sup>2</sup>	Married, %	Current Smokers, %	Mean Alcohol Intake, g/d	Family History of Prostate Cancer, %
BLSA, 2000 (11)	176/220	58.9/60.5	25.3/26.1	92.6/88.2	6.9/14.5	NA/NA	NA/NA
CHS, 2005 (17)	174/174	72.5/72.4	26.8/26.7	87.4/83.3	8.6/13.8	NA/NA	NA/NA
CLUE, 2001 (12)	124/181	62.7/62.3	NA/NA	92.7/85.0	23.6/20.4	NA/NA	NA/NA
EPIC, 2007 (19)	643/636	61.0/60.9	26.7/27.0	87.7/89.1	23.0/27.9	22.1/21.7	NA/NA
ERSPC, 2004 (13)	201/201	61.8/61.8	NA/NA	NA/NA	NA/NA	NA/NA	18.1/15.7
HPFS, 2005 (16)	682/670	65.3/65.1	25.9/26.1	93.4/92.8	4.8/4.0	11.9/11.5	14.2/9.9
KPMCP, 1998 (9)	45/218	71.5/71.9	25.7/25.8	86.8/82.8	20.0/17.8	18.7/14.9	NA/NA
MCCS, 2006 (18)	524/932	61.8/59.1	27.2/27.2	NA/NA	9.7/12.0	19.7/20.9	NA/NA
NSHDC, 2000 (10) and 2004 (6)	280/555	58.0/58.0	26.1/26.6	NA/NA	18.9/20.4	NA/NA	NA/NA
PHS, 1998 (8) and 2002 (5)	546/701	59.8/60.0	24.8/24.7	NA/NA	8.1/8.0	NA/NA	NA/NA
ProtecT, 2004 (14)	176/324	61.8/61.7	27.3/27.0	88.3/88.8	12.5/10.8	NA/NA	7.4/3.8
SU.VI.MAX, 2005 (15)	100/400	55.1/55.0	25.7/25.4	NA/NA	13.3/13.2	25.2/28.1	NA/NA
Overall	3671/5212	62.0/61.2	26.2/26.3	90.6/88.7	12.4/14.0	18.0/19.3	13.6/8.8

See Table 1 for expansion of study names. IGF = insulin-like growth factor; IGFBP = insulin-like growth factor binding protein; NA = not available.

\* Data are expressed as values in case patients/control participants. The numbers of case patients and control participants are the maximum numbers for whom hormone measurements were available, and numbers varied by hormone.

and date of recruitment (single year) as our main method of analysis. To provide a summary measure of risk, we calculated a linear trend by scoring the quintiles of the serum IGF or IGFBP concentrations as 0, 0.25, 0.5, 0.75, and 1. Under the assumption of linearity, a unit change in this trend variable is equivalent to the odds ratio (OR) comparing the highest with the lowest quintile.

All results are unadjusted for participant characteristics, except for those controlled by the stratification variables. We examined the possible influence of 5 participant characteristics by adjusting the relevant conditional logistic regression models for body mass index (BMI) (<22.5, 22.5 to 24.9, 25.0 to 27.4, 27.5 to 29.9, or >30 kg/m<sup>2</sup>), marital status (married or cohabiting, or not married or cohabiting), educational status (did not attend college or university, or attended college or university), smoking (never, previous, or current), and alcohol consumption (<10 or ≥10 g/d). We excluded participants from the analysis if they had a missing value for the characteristic under examination.

We assessed heterogeneity in linear trends among studies by using a chi-square statistic to test whether the study-specific ORs were statistically different from the overall OR (21). Heterogeneity among studies was also quantified by calculating the *H* and *I*<sup>2</sup> statistics (22).

To test whether the linear trend OR estimates for each IGF and IGFBP varied according to case patient characteristics, we estimated a series of subsets for each characteristic: stage at diagnosis (localized or advanced), grade at diagnosis (low or high), year of diagnosis (before 1990, 1990 to 1994, or 1995 onward; these year cutoffs were chosen to attempt to reflect differences in the use of the PSA test for cancer detection), age at diagnosis (<60, 60 to 69, or ≥70

years), and time between blood collection and diagnosis (<3, 3 to 6, or ≥7 years). We excluded case patients from the analyses of stage and grade at diagnosis if the relevant information was not available. For each of these case patient characteristics, we calculated a heterogeneity chi-square statistic to assess whether the estimated ORs statistically differed from each other (21). To assess whether the OR estimate of the linear trend for each IGF or IGFBP varied according to PSA level at recruitment (<2 μg/L or ≥2 μg/L), we entered an interaction term into the conditional logistic regression model for each IGF or IGFBP, and we tested the statistical significance of the interaction term with a likelihood ratio test.

Statistical significance was set at the 5% level. All statistical tests were 2-sided. All statistical analyses were done with Stata, version 9.0 (StataCorp, College Station, Texas).

## RESULTS

Table 1 shows the characteristics of the studies. The 12 prospective studies included approximately 3700 case patients with prostate cancer and 5200 control participants. Insulin-like growth factor I and IGFBP-III measurements were available for all and 3600 case patients, respectively. However, IGF-II and IGFBP-II measurements were available for only 379 and 419 case patients, respectively (Table 2). Mean age at blood collection was 61.5 years (range, 55 to 73 years). Data on race were available for most studies; however, we did not explore associations by race because more than 95% of participants were white. The median concentration of IGF-I was higher in case patients than in control participants in 9 of 12 studies; the

Table 2—Continued

PSA at Recruitment, $\mu\text{g/L}$	Median Concentration			
	IGF-I, $\mu\text{g/L}$	IGF-II, $\text{mg/L}$	IGFBP-II, $\mu\text{g/L}$	IGFBP-III, $\mu\text{g/L}$
1.6/0.8	143/140	0.282/0.347	NA/NA	2800/2800
7.1/NA	141/147	NA/NA	NA/NA	2997/3267
4.1/1.0	117/118	0.509/0.519	NA/NA	1005/1045
NA/NA	173/165	NA/NA	NA/NA	3788/3743
2.5/2.4	130/127	NA/NA	NA/NA	3595/3658
NA/NA	183/173	NA/NA	NA/NA	3382/3263
NA/NA	160/161	NA/NA	NA/NA	NA/NA
3.6/0.9	170/168	NA/NA	NA/NA	3030/2971
4.7/1.1	219/207	NA/NA	606/590	2415/2384
3.0/1.3	178/175	NA/NA	NA/NA	3011/3052
5.5/1.2	127/124	0.431/0.425	508/531	3366/3326
3.0/1.0	149/143	1.066/1.082	217/237	4000/4100
3.6/1.1	169/162	0.475/0.608	443/384	3232/3174

picture is less clear for IGFBP-III, and 5 of 11 studies showed lower concentrations in case patients than in control participants (Table 2). Insulin-like growth factor II and IGFBP-II concentrations were similar between case patients and control participants. On average, case patients received a diagnosis 5 years after their blood was drawn, were age 67 years at diagnosis, and received the diagnosis after 1995 (Table 3). When data were available, most case patients had localized disease (range across studies, 70% to

80%) and most were low-grade lesions (range across studies, 60% to 80%).

Insulin-like growth factor I and IGF-II concentrations were correlated with each other ( $r = 0.39$ ), but both were more strongly correlated with IGFBP-III ( $r = 0.58$  and  $0.51$ , respectively); IGFBP-II was weakly correlated with other components of the IGF system. The IGF or IGFBP concentrations and PSA levels, however, had no statistically significant correlations. We found no correlations between IGFs or IGFBPs and endogenous sex hormone concentrations; however, sex hormone-binding globulin was correlated with IGF-I, IGF-II, IGFBP-II, and IGFBP-III ( $r = -0.12, -0.19, 0.39, \text{ and } -0.28$ , respectively).

Figure 1 shows that the higher the concentration of IGF-I, the greater the risk for prostate cancer: The OR in the highest versus lowest quintile was 1.38 (95% CI, 1.19 to 1.60), with a highly statistically significant trend ( $P < 0.001$  for trend). This result is based on 3299 case patients and 4436 control participants from 12 studies with no statistically significant heterogeneity in the findings among studies (Figure 2). Restricting the analysis to population-based cohort studies did not materially change the results (data not shown). Neither IGF-II nor IGFBP-II was associated with prostate cancer risk (Figure 1), and no statistically significant heterogeneity was seen among studies (Appendix Figures 1 and 2, available at [www.annals.org](http://www.annals.org)), although not all studies measured these factors and statistical power was limited. Insulin-like growth factor binding protein III concentration was associated with prostate cancer risk with the OR in the highest versus lowest quintile of 1.23 (CI, 1.06 to 1.43). The test for linear trend was sta-

Table 3. Characteristics of Case Patients with Prostate Cancer\*

Study, Year (Reference)	Time from Blood Collection to Diagnosis			Age at Diagnosis			Diagnosis Year			Disease Stage			Disease Grade		
	<3 y	3–6 y	$\geq 7$ y	<60 y	60–69 y	$\geq 70$ y	Before 1990	1990–1995	1995–Onward	Localized	Advanced	Unavailable	Low	High	Unavailable
BLSA, 2000 (11)	4.6	14.8	80.7	4.0	30.7	65.3	29.6	44.3	26.1	77.3	22.7	50.0	64.7	35.3	22.7
CHS, 2005 (17)	46.6	51.1	2.3	0.0	8.6	91.4	0.0	62.1	37.9	76.1	23.9	32.8	78.2	21.8	18.4
CLUE, 2001 (12)	16.1	25.0	58.9	8.9	39.5	51.6	100.0	0.0	0.0	75.3	24.7	34.7	71.4	28.6	21.0
EPIC, 2007 (19)	42.5	52.9	4.7	19.1	63.1	17.7	0.0	0.9	99.1	68.7	31.3	30.0	67.7	32.3	27.7
ERSPC, 2004 (13)	0.0	100.0	0.0	5.0	69.7	25.4	0.0	0.0	100.0	94.5	5.5	0.0	79.3	20.7	1.5
HPFS, 2005 (16)	45.3	54.4	0.3	13.6	38.3	48.1	0.0	11.3	88.7	82.9	17.1	43.3†	60.4	39.6	9.7
KPMCP, 1998 (9)	17.8	17.8	64.4	0.0	6.7	93.3	100.0	0.0	0.0	61.9	38.1	53.3	90.0	10.0	77.8
MCCS, 2006 (18)	29.8	41.0	29.2	11.3	55.9	32.8	0.0	17.4	82.6	91.3	8.7	20.6	62.6	37.4	1.9
NSHDC, 2000 (6) and 2004 (10)	27.1	49.6	23.2	17.1	77.5	5.4	0.0	10.4	89.6	80.9	19.1	0.7	84.9	15.1	0.7
PHS, 1998 (5) and 2002 (8)	9.2	21.4	69.4	11.7	48.4	39.9	31.5	64.8	3.7	69.1	30.9	11.7	65.7	34.3	2.7
ProtecT, 2004 (14)	100.0	0.0	0.0	29.6	69.9	0.6	0.0	0.0	100.0	73.9	26.1	0.0	70.5	29.5	0.0
SU.VI.MAX, 2005 (15)	14.0	38.0	48.0	34.0	66.0	0.0	0.0	0.0	100.0	NA	NA	100.0	57.4	42.6	6.0

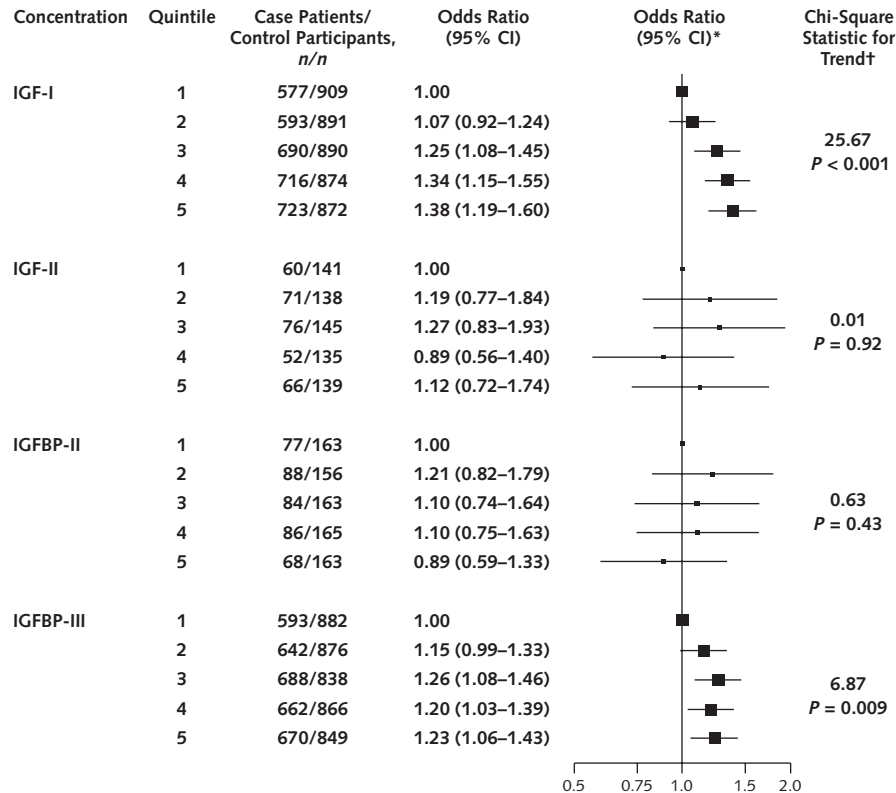
See Table 1 for expansion of study names. NA = not available.

\* Data are percentages of case patients among those with a known value for the characteristic. Percentages may not add to 100 because of rounding. Stage and grade of disease are unavailable for some case patients, and the percentages shown are among case patients with known information as well as those with unknown information.

† In the published results (16), stage information was unavailable for 15% of case patients; the higher proportion of case patients with no available stage information reported here is due to the inclusion of extra unpublished data for which stage information had not been obtained.



**Figure 1. Association of prostate cancer risk with increasing quintiles of insulin-like growth factors (IGFs) and their main binding protein concentrations.**



IGFBP = insulin-like growth factor binding protein.

\* All odds ratios (ORs) are unadjusted except for factors controlled for by stratification (study, age, and year of recruitment). The position of each square indicates the magnitude of the OR, and the area of the square is proportional to the amount of statistical information available (inverse of the variance of the logarithm of the OR). The horizontal line indicates the 95% CI.

† Chi-square statistic for linear trend, calculated by replacing the categorical variables with a variable that was scored as 0, 0.25, 0.5, 0.75, and 1.

tistically significant ( $P = 0.009$  for trend), but this was mainly because of the difference between the lowest and all other quintiles, because there seemed to be little difference between the second lowest and the other quintiles (Figure 1). Statistically significant heterogeneity was observed across studies for IGFBP-III ( $P = 0.044$  for heterogeneity) (Figure 3), with 47% of the variation due to heterogeneity.

Adjustment of the results for IGF-I by IGFBP-III and vice versa resulted in the findings for IGF-I remaining highly statistically significant. The OR for linear trend in IGF-I concentration was 1.42 (CI, 1.24 to 1.63;  $P < 0.001$  for trend) before and 1.42 (CI, 1.21 to 1.68;  $P < 0.001$  for trend) after adjustment for IGFBP-III. In contrast, the OR for linear trend in IGFBP-III concentration was 1.19 (CI, 1.04 to 1.37;  $P = 0.010$  for trend) before and 0.98 (CI, 0.83 to 1.15;  $P = 0.79$  for trend) after adjustment for IGF-I concentration.

To further explore the joint relationship among IGF-I, IGFBP-III, and prostate cancer risk, within each study we calculated the residuals from a linear regression of IGF-I on IGFBP-III—this new variable being an estimate of IGF-I

adjusted for IGFBP-III—and categorized it into quintiles. We calculated the residuals from linear regression of IGFBP-III on IGF-I in a similar way. By using this alternative method, the association between IGF-I adjusted for IGFBP-III was statistically significantly related to prostate cancer risk, with an OR of 1.25 (CI, 1.08 to 1.46;  $P = 0.002$  for trend) for the highest versus lowest quintile. However, IGFBP-III adjusted for IGF-I by this method was not related to risk, with an OR of 1.09 (CI, 0.93 to 1.26;  $P = 0.36$  for trend) for the highest versus lowest quintile. It would thus seem that the results for IGFBP-III are indirect because of its association with IGF-I.

Adjustment of the results for IGF-I by levels of testosterone, free testosterone, estradiol, free estradiol, and sex hormone-binding globulin (in the subset of 8 studies that measured them) made no material difference to the estimated ORs for IGF-I, nor did it change the statistical significance of the relationship between IGF-I and prostate cancer risk (data not shown). The unadjusted estimates of association between IGF and IGFBP and prostate cancer risk were similar to those adjusted for patient characteris-

tics (BMI, marital status, educational status, smoking, and usual alcohol consumption [data not shown]).

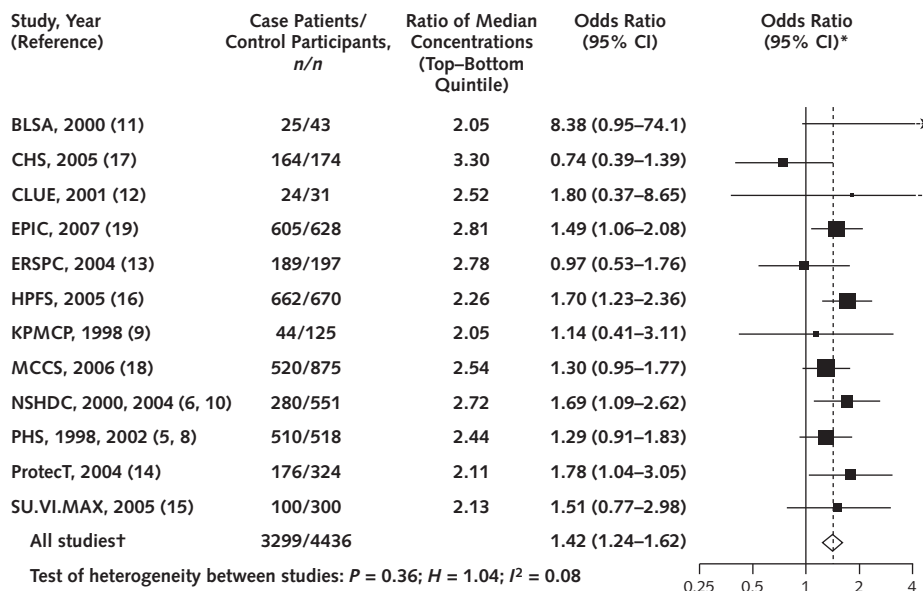
The association between IGF-I and prostate cancer risk had no statistically significant heterogeneity by patient characteristics (PSA level at blood collection, BMI, smoking habits, alcohol consumption, or family history of prostate cancer), age at diagnosis, year of diagnosis, time between blood collection and diagnosis, or tumor stage. The only statistically significant difference was for grade of disease ( $P = 0.027$  for heterogeneity) (Figure 4). The OR for the linear trend in IGF-I was 1.57 (CI, 1.32 to 1.87) for low-grade disease and 1.12 (CI, 0.87 to 1.43) for high-grade disease; however, given the number of statistical tests, this could be due to chance. Analyses jointly classifying tumors by both stage and grade did not provide evidence of additional heterogeneity in risk for any of the subgroups compared with the differences seen in analyses of stage and grade reported above (results not shown). The association of any other IGF components with prostate cancer risk had no statistically significant heterogeneity according to any of the subgroups considered (Appendix Figures 3, 4, and 5, available at [www.annals.org](http://www.annals.org)). Subgroup results remained unchanged after adjustment for potential confounding variables, including BMI (data not shown).

## DISCUSSION

This collaborative analysis of individual data from 12 studies found that increasing levels of circulating IGF-I were statistically significantly associated with a moderately increased risk for subsequent prostate cancer. Insulin-like growth factor binding protein III concentrations were also associated with an increased risk, but IGFBP-III is correlated with IGF-I, and the association was no longer evident after adjustment for IGF-I. Neither IGF-II nor IGFBP-II was associated with risk for prostate cancer, although these analyses were based on much less information than that for IGF-I and IGFBP-III. Further adjustment for potential confounding variables made little difference to any of the risk estimates. The association of serum IGF-I levels was somewhat stronger for low-grade than high-grade cancer, but this could be due to chance.

This collaborative analysis includes information from 12 of the 13 prospective studies that published information on IGFs, IGFBPs, and prostate cancer. The only study that we did not include had 100 case patients with prostate cancer (20) and reported no association between IGF-I or IGFBP-III levels and prostate cancer risk. We also include further unpublished data from the Health Professionals Follow-up Study. After the database was closed for analy-

Figure 2. Association of prostate cancer risk with insulin-like growth factor I concentration, by study.



For expansion of study names, see Table 1.

\* All odds ratios (ORs) are unadjusted except for factors controlled for by stratification (study, age, and year of recruitment). The OR is the estimate of the linear trend for insulin-like growth factor I obtained by replacing the categorical variable with a variable that was scored as 0, 0.25, 0.5, 0.75, and 1. The position of each square indicates the magnitude of the OR, and the area of the square is proportional to the amount of statistical information available (inverse of the variance of the logarithm of the OR). The horizontal line indicates the 95% CI. The dashed line represents the all-studies OR. † Heterogeneity between studies was assessed by using the chi-square statistic, which tested whether the study-specific results statistically significantly differed from the overall result. The  $P$  value for statistical significance of the chi-square statistic is 2-sided. Heterogeneity was also quantified by using the  $H$  and  $I^2$  statistics.

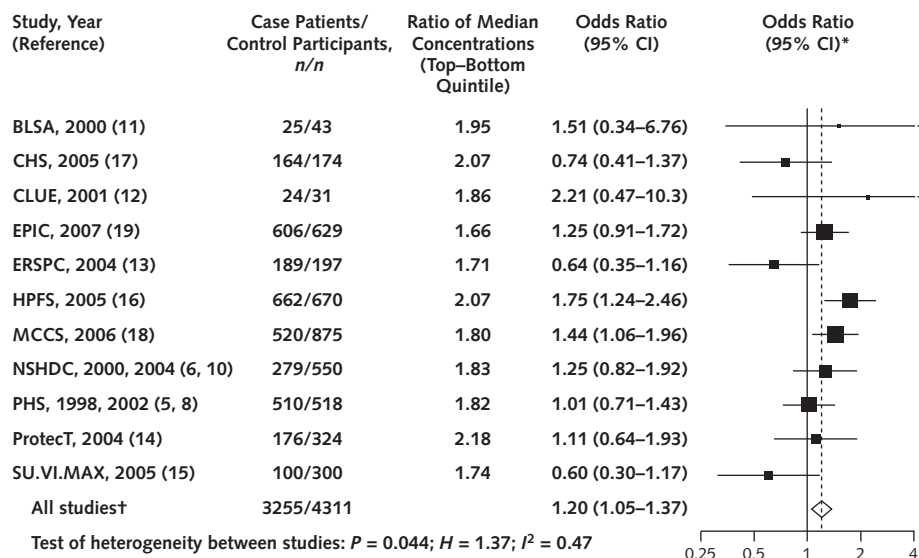
sis, 3 further studies with 141, 727, and 96 case patients of prostate cancer have been published (23–25). One reported a small association between IGF-I and prostate cancer risk (23), 1 reported no association (25), and 1 reported an association of a similar magnitude to our collaboration (24). Including these additional studies in the collaboration would not have materially changed our results, and our findings therefore provide a reliable summary of the totality of the evidence on the association between IGF and IGFBP levels and prostate cancer risk.

The increase in prostate cancer risk associated with serum IGF-I concentration is thought to be related to the mitogenic and antiapoptotic effects of IGF-I (3, 26–28). The overall bioactivity of IGF-I is the result of a series of complex interactions among IGF-I, its binding proteins, and their cellular receptors. More than 90% of circulating IGF-I is bound to IGFBP-III and an acid-labile subunit, which cannot transfer from the circulation to the target tissues. A decrease in circulating levels of IGFBP-III has been suggested to result in a relative increase in bioactive IGF-I. Thus, a decreased IGFBP-III concentration might perhaps be expected to be associated with an increased risk for prostate cancer. However, recent *in vitro* experiments have shown that IGFBP-III can modulate the effects of IGF-I and, under some conditions, enhance the proliferative effects of IGFs (28, 29).

Our study showed a modest correlation between IGF-I and IGFBP-III levels, reflecting the fact that growth hormone largely controls synthesis of both peptides and IGF-I is bound and stabilized by IGFBP-III. After mutual adjustment, the increased risk between IGF-I and prostate cancer remained, whereas the association with IGFBP-III was attenuated. This suggests that the association of IGFBP-III with prostate cancer risk is secondary to the association with IGF-I. In addition, the association of IGFBP-III and prostate cancer risk had statistically significant heterogeneity among studies, which may reflect differences in the assays used by different studies (Appendix Table 1, available at [www.annals.org](http://www.annals.org), shows detailed descriptions of laboratory methods). It has been suggested that different assays may have different specificities for the intact and the nonintact, proteolytically cleaved forms of IGFBP-III; furthermore, specificities may have changed over time owing to recalibration, making comparisons among methods (and hence studies) difficult to interpret (30).

No obvious biological mechanism can explain the apparent stronger association of IGF-I with low-grade than high-grade disease, and this may be a chance finding. The distinction between low- versus high-grade cancer is unlikely to represent 2 distinct types of disease, and prostate cancer grading has varied considerably over time, making interpretation of this finding difficult (31). Studies with

Figure 3. Association of prostate cancer risk with insulin-like growth factor binding protein III concentration, by study.



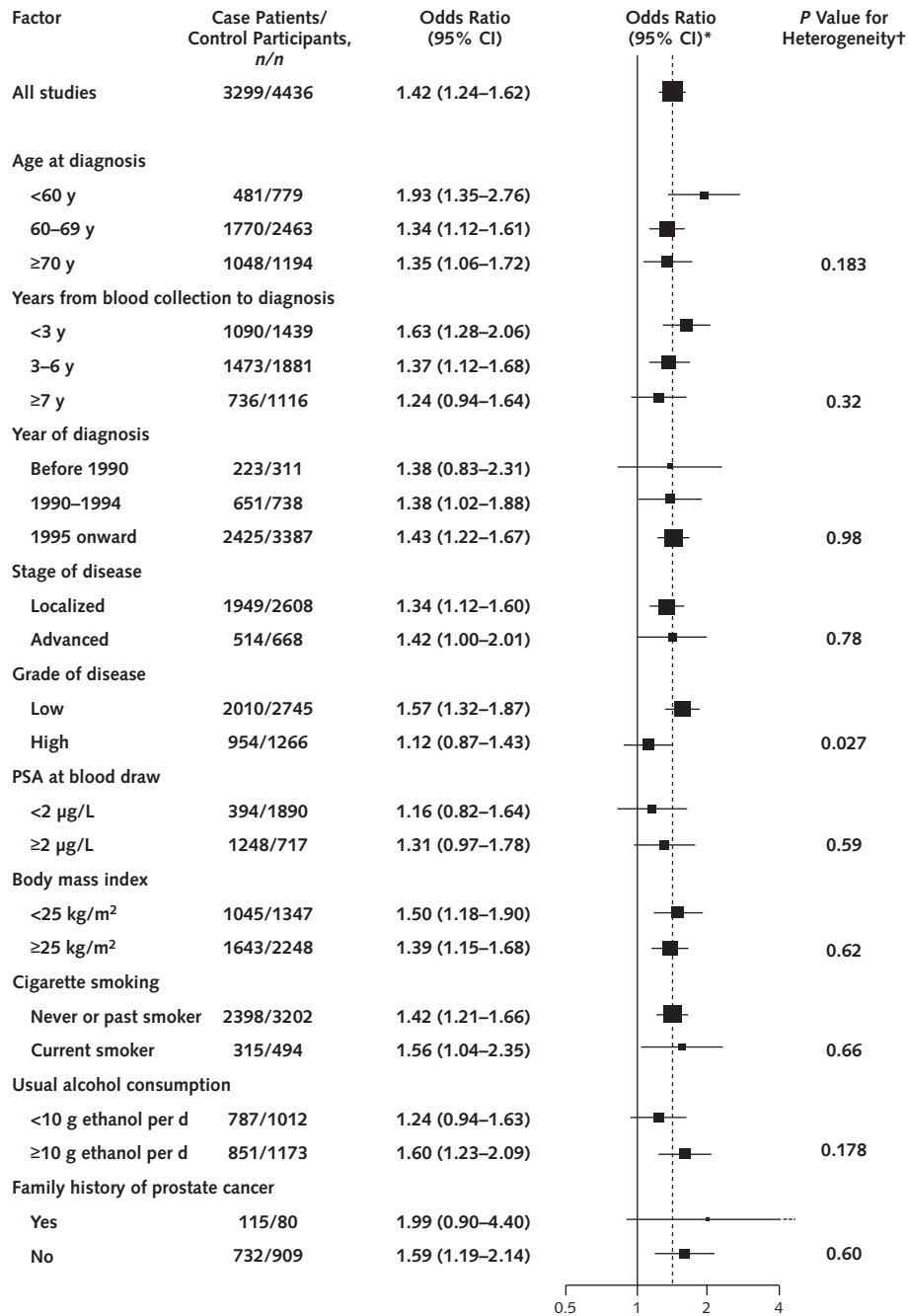
For expansion of study names, see Table 1.

\* All odds ratios (ORs) are unadjusted except for factors controlled for by stratification (study, age, and year of recruitment). The OR is the estimate of the linear trend for insulin-like growth factor binding protein III obtained by replacing the categorical variable with a variable that was scored as 0, 0.25, 0.5, 0.75, and 1. The position of each square indicates the magnitude of the OR, and the area of the square is proportional to the amount of statistical information available (inverse of the variance of the logarithm of the OR). The horizontal line indicates the 95% CI. The dashed line represents the all-studies OR.

† Heterogeneity between studies was assessed by using the chi-square statistic, which tested whether the study-specific results statistically significantly differed from the overall result. The  $P$  value for statistical significance of the chi-square statistic is 2-sided. Heterogeneity was also quantified by using the  $H$  and  $I^2$  statistics.



**Figure 4. Association of prostate cancer risk with insulin-like growth factor I concentration, by tumor and participant characteristics.**



\* All odds ratios (ORs) are unadjusted except for factors controlled for by stratification (study, age, and year of recruitment). The OR is the estimate of the linear trend for insulin-like growth factor I obtained by replacing the categorical variable with a variable that was scored as 0, 0.25, 0.5, 0.75, and 1. The position of each square indicates the magnitude of the OR, and the area of the square is proportional to the amount of statistical information available (inverse of the variance of the logarithm of the OR). The horizontal line indicates the 95% CI. The dashed line represents the all-studies OR. † *P* value from a chi-square test for heterogeneity to assess whether the OR estimates for each characteristic differ from each other.

uniform procedures for grading cancer are needed to investigate this finding further.

We found no evidence that high circulating levels of IGF-II or IGFBP-II are related to an increased risk for

prostate cancer, although with few case patients, statistical power was limited (we had approximately 80% power to detect an OR of 1.7).

Detection of localized prostate cancer has increased

substantially since the introduction of the PSA test in the late 1980s (32). The mix of a growing proportion of early, localized cancers with a decreasing number of advanced cancers can lead to difficulty in the interpretation of studies, particularly because some early-stage PSA-detected cancers never progress to clinical disease (33). The lead time associated with PSA testing (number of years earlier the tumor is detected by testing) has been estimated to be as high as 12 years in men age 55 years (34). We did not have detailed information on each participant's PSA screening history or on which of the tumors were PSA detected. However, the lack of any detectable heterogeneity in risk estimates, according to tumor characteristics, suggests that the introduction of PSA testing and differences in its use in various populations are unlikely to have unduly influenced the associations.

Our study has several limitations. The analysis relies on measurement of IGF in only 1 sample at 1 time point. These single measures provide an imperfect estimate of a man's usual hormonal status and are influenced both by within-person errors and analytic errors. However, because both types of error are likely to lead to attenuation of the relationship between IGF concentration and risk, this would imply that the true association between IGF-I and prostate cancer risk may be greater. Although a single IGF measurement has been shown to reliably reflect average exposure over a few years (16), whether it also adequately reflects lifetime exposure is unknown. Insulin-like growth factors play a major role in growth during childhood (35), and circulating IGF concentration during this period could also be an important exposure window for subsequent prostate cancer development.

A further limitation is that many of the studies did not record information on the clinical diagnosis of cancer, such as basis of diagnosis, biopsy protocol, or staging criteria, or on how these may have changed over time. However, with no evidence of heterogeneity among studies and stability in the estimates with year of diagnosis, such differences are unlikely to have had a major influence on the results. Furthermore, some of the studies were based within randomized trials, and the participants may therefore have benefited from closer investigation and clinical follow-up. However, after excluding these studies, we obtained essentially the same results. Finally, the IGF levels vary among studies, which may be mostly due to differences in assay methods (**Appendix Table 1**, available at [www.annals.org](http://www.annals.org)). Our method of analysis allows for this by defining study quintiles of hormone concentration and pooling study specific estimates of ORs. This method assumes that the quintiles are similar among studies, and if this assumption is not true, estimates of the OR may be biased. However, because heterogeneity was not evident among studies and the distributions of IGF-I concentration were not expected to differ greatly among the men in the different studies, this assumption seems reasonable.

In summary, this collaborative analysis of worldwide

data on IGFs and their main binding proteins and prostate cancer risk demonstrates that the higher the circulating level of IGF-I, the greater the subsequent risk for prostate cancer. Given the need to identify modifiable risk factors for prostate cancer (36), the current results suggest IGF-I as a possible candidate because it is both associated with the disease and is potentially modifiable through its association with many dietary and lifestyle factors (37–40).

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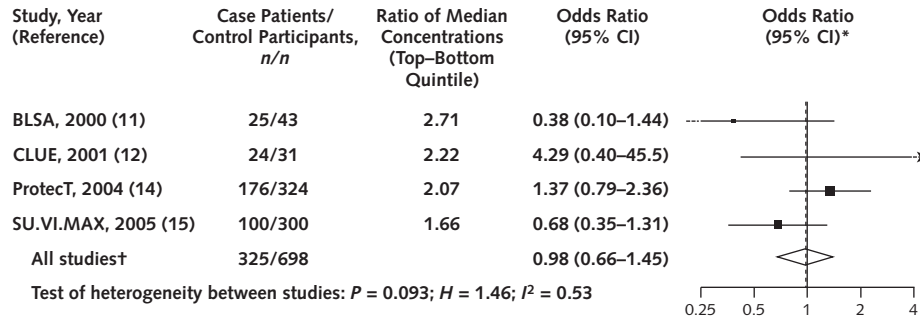
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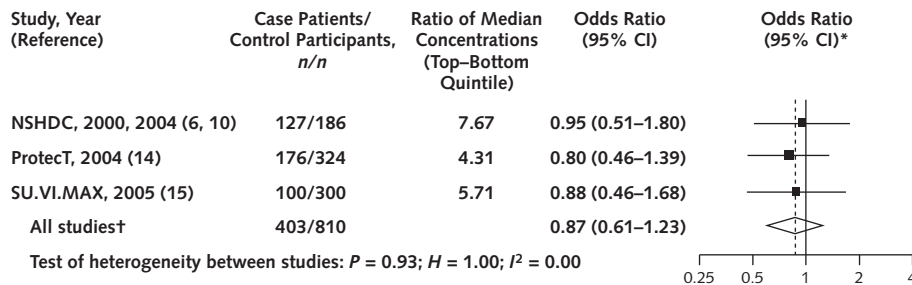
**Appendix Figure 1. Association of prostate cancer risk with insulin-like growth factor II concentration, by study.**



For expansion of study names, see Table 1.

\* All odds ratios (ORs) are unadjusted except for factors controlled for by stratification (study, age, and year of recruitment). The OR is the estimate of the linear trend for insulin-like growth factor II obtained by replacing the categorical variable with a variable that was scored as 0, 0.25, 0.5, 0.75, and 1. The position of each square indicates the magnitude of the OR, and the area of the square is proportional to the amount of statistical information available (inverse of the variance of the logarithm of the OR). The horizontal line indicates the 95% CI. The dashed line represents the all-studies OR. † Heterogeneity among studies was assessed by using a chi-square statistic that tested whether the study-specific results statistically significantly differed from the overall result. The  $P$  value for statistical significance of the chi-square statistic is 2-sided. Heterogeneity was also quantified by using the  $H$  and  $I^2$  statistics.

**Appendix Figure 2. Association of prostate cancer risk with insulin-like growth factor binding protein II concentration, by study.**



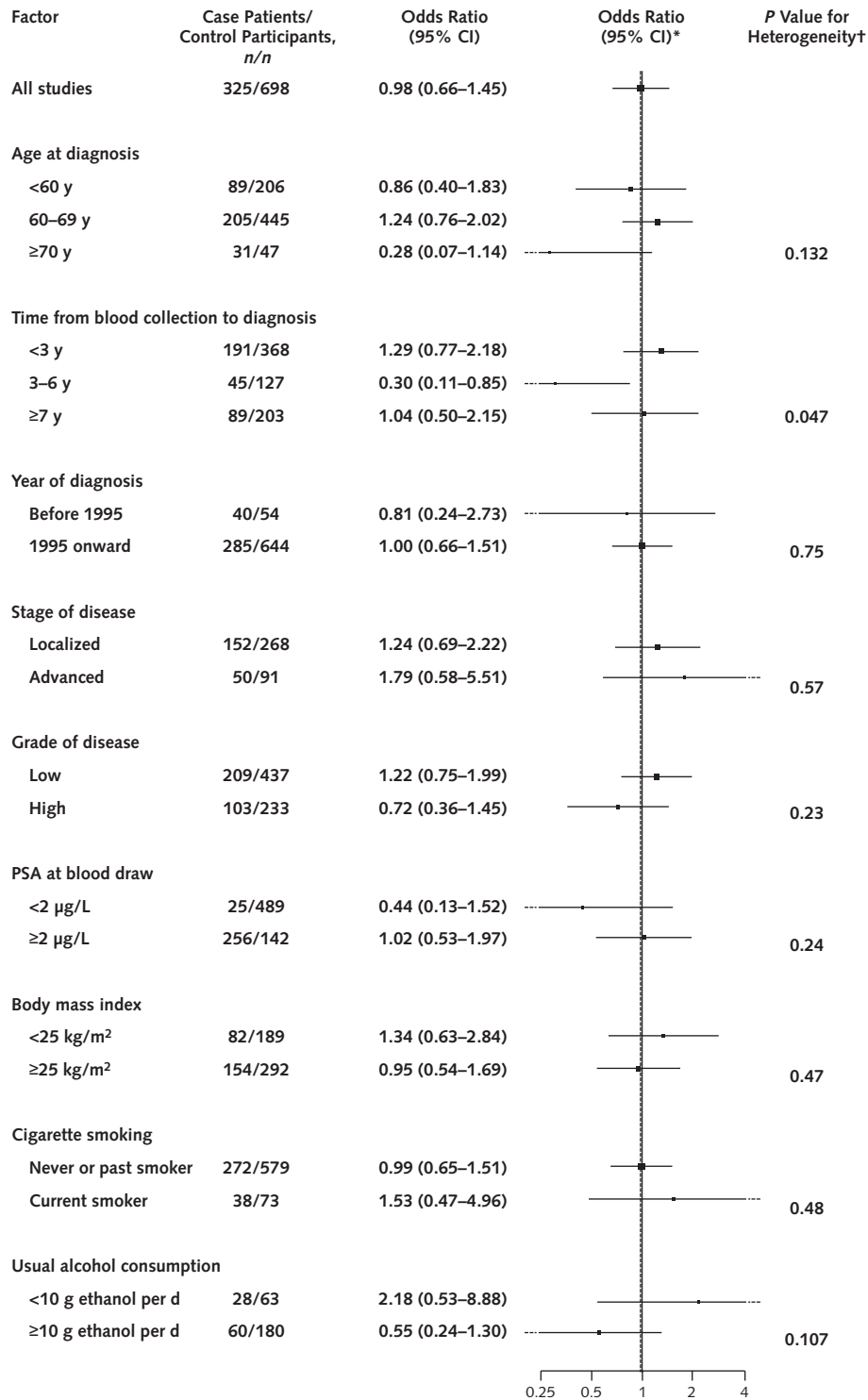
For expansion of study names, see Table 1.

\* All odds ratios (ORs) are unadjusted except for factors controlled for by stratification (study, age, and year of recruitment). The OR is the estimate of the linear trend for insulin-like growth factor binding protein II obtained by replacing the categorical variable with a variable that was scored as 0, 0.25, 0.5, 0.75, and 1. The position of each square indicates the magnitude of the OR, and the area of the square is proportional to the amount of statistical information available (inverse of the variance of the logarithm of the OR). The horizontal line indicates the 95% CI. The dashed line represents the all-studies OR.

† Heterogeneity among studies was assessed by using a chi-square statistic that tested whether the study-specific results statistically significantly differed from the overall result. The  $P$  value for statistical significance of the chi-square statistic is 2-sided. Heterogeneity was also quantified by using the  $H$  and  $I^2$  statistics.

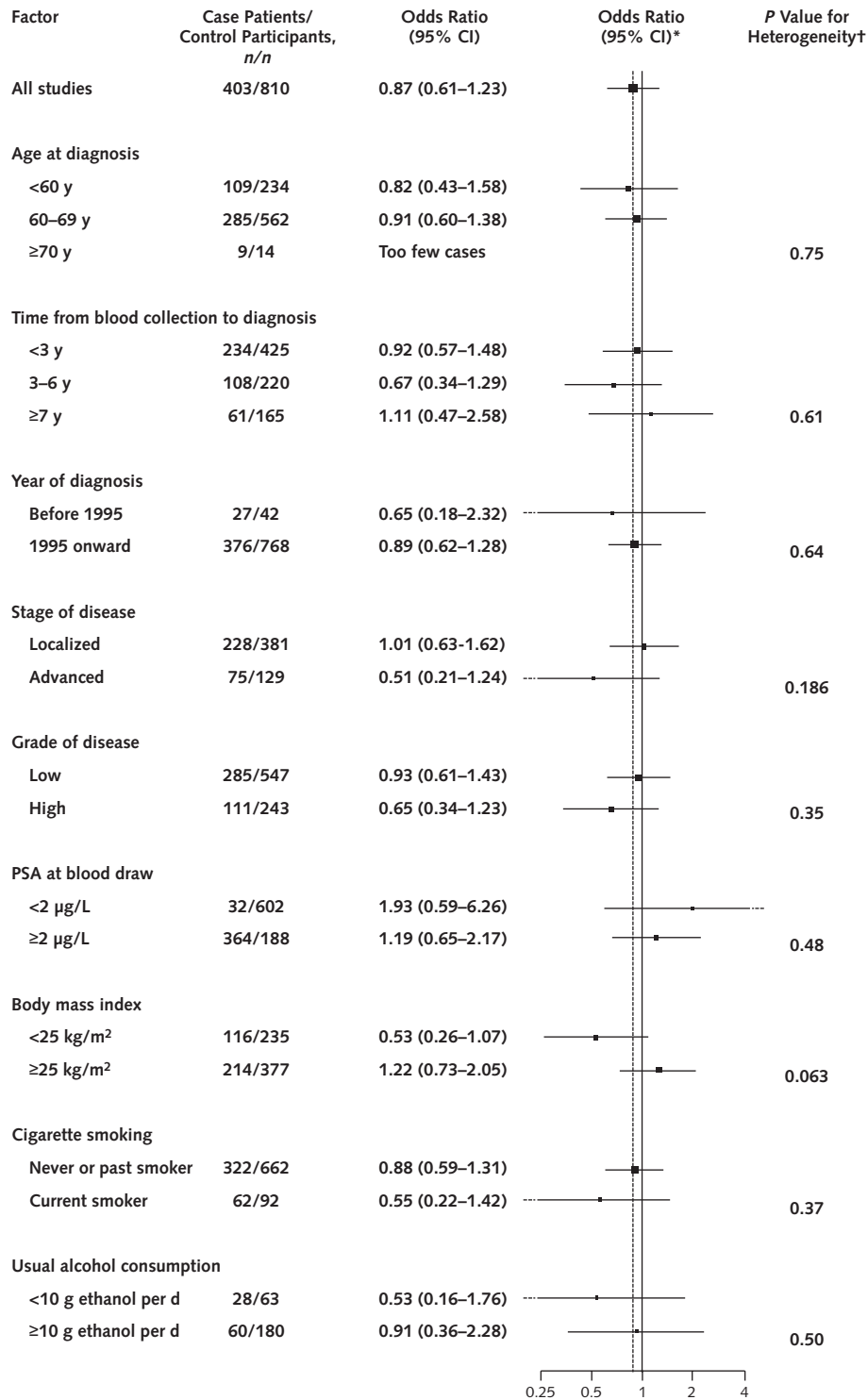


**Appendix Figure 3. Association of prostate cancer risk with insulin-like growth factor II concentration, by tumor and participant characteristics.**



\* All odds ratios (ORs) are unadjusted except for factors controlled for by stratification (study, age, and year of recruitment). The OR is the estimate of the linear trend for insulin-like growth factor II obtained by replacing the categorical variable with a variable that was scored as 0, 0.25, 0.5, 0.75, and 1. The position of each square indicates the magnitude of the OR, and the area of the square is proportional to the amount of statistical information available (inverse of the variance of the logarithm of the OR). The horizontal line indicates the 95% CI. The dashed line represents the all-studies OR. † P value from a chi-square test for heterogeneity to assess whether the OR estimates for each characteristic differed from each other.

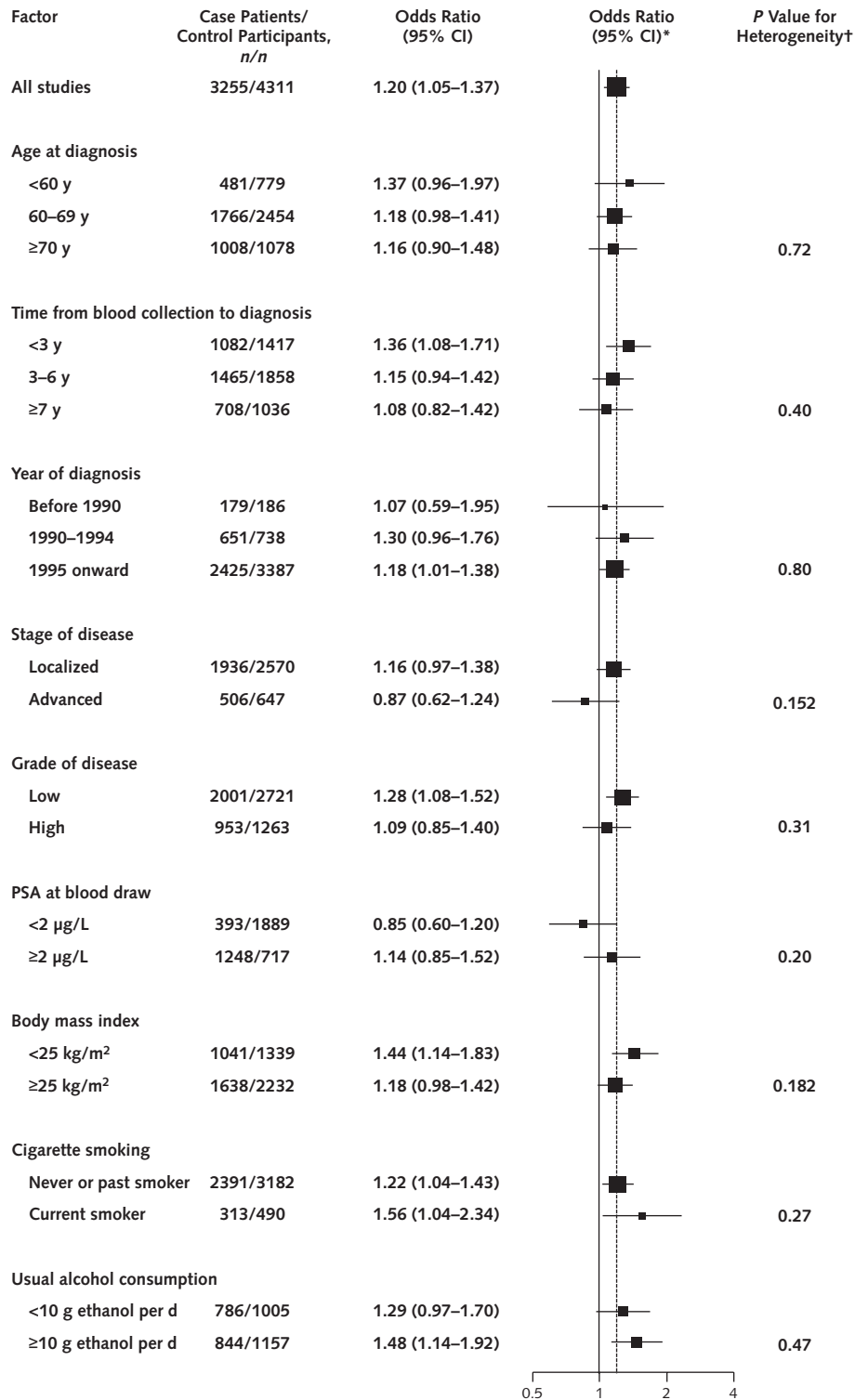
**Appendix Figure 4. Association of prostate cancer risk with insulin-like growth factor binding protein II concentration, by tumor and participant characteristics.**



\* All odds ratios (ORs) are unadjusted except for factors controlled for by stratification (study, age, and year of recruitment). The OR is the estimate of the linear trend for insulin-like growth factor binding protein II obtained by replacing the categorical variable with a variable that was scored as 0, 0.25, 0.5, 0.75, and 1. The position of each square indicates the magnitude of the OR, and the area of the square is proportional to the amount of statistical information available (inverse of the variance of the logarithm of the OR). The horizontal line indicates the 95% CI. The dashed line represents the all-studies OR.

† P value from a chi-square test for heterogeneity to assess whether the OR estimates for each characteristic differed from each other.

**Appendix Figure 5. Association of prostate cancer risk with insulin-like growth factor binding protein III concentration, by tumor and participant characteristics.**



\* All odds ratios (ORs) are unadjusted except for factors controlled for by stratification (study, age, and year of recruitment). The OR is the estimate of the linear trend for insulin-like growth factor binding protein III obtained by replacing the categorical variable with a variable that was scored as 0, 0.25, 0.5, 0.75, and 1. The position of each square indicates the magnitude of the OR, and the area of the square is proportional to the amount of statistical information available (inverse of the variance of the logarithm of the OR). The horizontal line indicates the 95% CI. The dashed line represents the all-studies OR.

† P value from a chi-square test for heterogeneity to assess whether the OR estimates for each characteristic differed from each other.

**Appendix Table. Assay Method, Manufacturer, and Reported Intra-assay Coefficients of Variation (CVs) for Each Study**

Study, Year (Reference)	IGF-I	IGF-II	IGFBP-II	IGFBP-III
BLSA, 2000 (11)	RIA (CV = 4.6%–20%)*†	RIA (CV = 4.9%–9.6%)*†	NA	RIA (CV = 5.1%–13%)*†
CHS, 2005 (17)	IRMA (CV = 3.0%–3.8%)*‡	NA	NA	IRMA (CV = 2.1%–5.8%)*‡
CLUE, 2001 (12)	ELISA (CV unknown)‡	Unknown (CV unknown)	NA	ELISA (CV unknown)‡
EPIC, 2007 (19)	ELISA (CV = 3.0%)*‡	NA	NA	ELISA (CV = 5.3%)*‡
ERSPC, 2004 (13)	IRMA (CV = 3.4%)*‡	NA	NA	IRMA (CV = 3.9%)*‡
HPFS, 2005 (16)	ELISA (CV = 2.6%)*‡	NA	NA	ELISA (CV = 3.5%)*‡
KPMCP, 1998 (9)	RIA (CV unknown)§	NA	NA	NA
MCCS, 2006 (18)	ELISA (CV = 11.1%)*‡	NA	NA	ELISA (CV = 9.5%)*‡
NSHDC, 2000, 2004 (6, 10)	IRMA (CV = 8.6%–11.0%)*	NA	RIA (CV = 2.5%)*‡	IRMA (CV = 3.6%–4.9%)*
PHS, 1998, 2002 (5, 8)	ELISA (CV = 4.9%–6.5%)*‡	NA	NA	ELISA (CV = 7.0%–9.0%)*‡
ProtecT, 2004 (14)	ELISA (CV = 3%)*‡	ELISA (CV = 5%)*‡	RIA (CV = 5%)*‡	RIA in-house (CV = 4%)*‡
SU.VI.MAX, 2005 (15)	Chemiluminescence (CV = 5.3%)*¶**	IRMA (CV = 6.8%)*¶	RIA (CV = 8.6%)*¶	Chemiluminescence (CV = 6.3%)*¶  **

For expansion of study names, see Table 1. ELISA = enzyme-linked immunosorbent assay; IGF = insulin-like growth factor; IGFBP = insulin-like growth factor binding protein; IRMA = immunoradiometric assay; NA = not applicable; RIA = radioimmunoassay.

\* After acid-ethanol extraction.

† Endocrine Sciences, Calabasas Hills, California.

‡ Diagnostic Systems Laboratories, Webster, Texas.

§ Nichols Institute Diagnostics, San Clemente, California.

|| Immunotech, Marseille, France.

¶ Type of CV not reported.

\*\* Diagnostic Products, Los Angeles, California.