COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

POSSIBLE CARCINOGENIC HAZARD TO CONSUMERS FROM INSULIN-LIKE GROWTH FACTOR-1 (IGF-I) IN THE DIET.

IGF-I and Prostate cancer

Introduction and background

1. As part of a horizon scanning paper considered in November 2008 (CC/2008/17), the Committee discussed the possible carcinogenic hazard from dietary insulin-like growth factor-1 (IGF-I). The discussion was prompted by the contents of a book which suggested that consumption of IGF-I in dairy produce could cause an increase in the risk of developing certain cancers. Since the use of bovine somatotropin (BST) was said to increase the amount of IGF-I in milk, concerns were expressed that increased dietary exposure to IGF-I from this source might increase the risk of consumers developing cancer.

2. Following this discussion, the COC then considered paper CC/09/08 in July 2009, which summarised the claims about the health effects of IGF-I that were presented in the book “Your Life in Your Hands” (Plant, 2007). The Committee drew a number of conclusions but requested additional data on a number of areas, most notably a systematic review of the risk of cancer from dietary IGF-I. Resources were not available to perform a systematic review. Instead the secretariat performed a narrative review that incorporated elements of a systematic review: recording details of literature searches and of the selection of articles used. The narrative review covers a wider selection of issues than would have been practical had a systematic review been performed.

3. As a result of the large database available, particularly of epidemiology studies, the review was split into several sections. In March 2012, the committee considered paper (CC/2012/06) which presented information on identity, physiological control of IGF-I, human physiological levels of IGF-I, IGF-I in food and tissues, the use of IGF-I as a human medicine, toxicology and other safety studies and information on the association between blood levels of IGF-I and breast cancer.

4. The COC made a number of comments and drew a number of conclusions from this data. The minutes have been attached at Annex A. For the purposes of this paper it has been presumed that comments made on issues such as analytical techniques would apply to the studies on prostate cancer as well as those on breast cancer and this discussion has not been repeated.

5. The current paper considers data on the potential association between blood levels of IGF-I and prostate cancer (Annex B). It is hoped that the IGF-I topic will be completed in a final paper in spring/summer 2013 when the potential association between IGF-I and other cancers and mechanistic data will be considered.

Questions for the Committee

6. Members are asked to consider the data in Annex B and :

a) To make any general comments they may have on the data.

b) Consider whether there is an association between circulating IGF-I levels and the risk of prostate cancer. If so, is it possible to draw any further conclusions on the level of IGF-I and the stage or severity of prostate cancer.

Secretariat
October 2012

References

Plant J, 2007, “Your Life In Your Hands”, updated edition, Virgin Books Ltd, London. ISBN 978 0 7535 1204 3.

Annex A to CC/2012/16

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

POSSIBLE CARCINOGENIC HAZARD TO CONSUMERS FROM INSULIN-LIKE GROWTH FACTOR-1 (IGF-I) IN THE DIET

IGF-I AND PROSTATE CANCER

Minutes of the March 2012 meeting

Secretariat
October 2012

ITEM 5: Possible Carcinogenic Hazard to Consumers from Insulin-like Growth Factor-I (IGF-I) in the Diet (CC/2012/06)

15. Dr N Wallis declared a personal specific interest as she is involved in research on IGF-I. Dr Wallis was excluded from participating in the discussion on this item. Professor A Boobis declared a lapsed personal specific interest having been member of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) during the assessment of bovine somatotropin which, when used in cows, is said to increase the amount of IGF-I in milk. This was noted but not considered to preclude full participation in the discussion.

16. This topic had been considered previously as part of the November 2008 horizon scanning discussion (CC/2008/17) and further in paper CC/2009/08 which summarised the claims about the health effects of IGF-I presented in Dr Plant's book "Your Life in Your Hands"[1]. The paper prepared for the current meeting presented information on identity, physiological control of IGF-I, human physiological levels of IGF-I, IGF-I in food and tissues, use of IGF-I as a human medicine, toxicology and other safety studies and the association between blood levels of IGF-I and breast cancer.

17. Measurement of IGF-I was discussed and it was noted that differences were found between results from studies using plasma measurements compared to those using serum measurements. It was also highlighted that the use of different anti-coagulants for plasma sample collection affected results. There was little information on differences arising from the techniques used for sample measurement as both in house and commercial methods had been used, and the possibility of a lack of specificity in commercial approaches was noted. Finally, it was not clear from some studies whether total IGF-I (i.e. bound and unbound IGF-I) or free IGF-I was being measured in the samples.

18. With respect to physiological levels of IGF-I, there were some suggestions of discrepancy between the plasma levels in animals and those in humans, as far higher plasma levels were reported in a study in Wistar rats than in humans. However, it was not clear what the plasma level had been in the Sprague Dawley rats used for the two year bioassay, and therefore how this would compare with humans. For humans it was agreed that the IGF-I would reach a maximum during puberty and then decline with age.

19. In considering the levels found in food, it was queried whether there were numerous or only one truncated form of IGF-I found in milk. Though there was little information, it was considered that there was only one form. Members were informed that human and bovine IGF-I were indistinguishable. The effect of dietary exposure to IGF-I was discussed. It was apparent that dietary IGF-I increased serum concentrations of IGF-I. However it was not

[1] Plant J, 2007 "Your Life in Your Hands", updated edition, Virgin Books Ltd, London. ISBN 978 0 7535 1204 3

clear that this was necessarily a direct effect or may have been mediated by increased protein intake. Members noted that IGF-I would probably be broken down in the stomach and need to diffuse or be taken up from the gut against a concentration gradient and that it was possible that the effect of dietary IGF-I on serum IGF-I was due to protein load or an effect of intake of dairy foods.

20. The findings of the two-year carcinogenicity study were considered and it was noted that the dose at which mammary tumours occurred was higher than that associated with increased mortality and effects such as hypoglycaemia. It was also noted that IGF-I had been administered subcutaneously and there would have been 100% bioavailability, while bioavailability from dietary IGF-I would be much lower. It was suggested that, while route to route extrapolation would be difficult, a worst case screen could be used assuming 100% oral bioavailability and using a margin-of-exposure approach between rat and human plasma levels.

21. It was queried whether there had been any follow up to the clinical studies or from medicinal use. While nothing had been identified at the last literature search, given that IGF-I had been used as a medicine in the US since 1995 it was considered likely that there would be data available.

22. The physiological importance of early life exposure to high dietary IGF-I was highlighted and the need to bear this in mind when interpreting studies where neonates receive high doses.

23. In considering Annex 2 to this paper, the Committee agreed with the conclusions drawn in paragraphs 104 to 109, with some minor changes suggested for paragraph 109 to clarify that high parenteral doses cause a slight increase in malignant mammary tumours in mice, the effect of maturation of the gut in neonatal animals and the assumptions regarding absorption from the gut.

24. The epidemiological database on the association between IGF-I and breast cancer included studies of different designs and with conflicting findings. A number of aspects were discussed. Differences were noted between results for pre- and post-menopausal women and it was highlighted that only one study had excluded peri-menopausal women. A difficulty in assessing and comparing the studies was that it was not always clear what adjustments had been made for confounding variables; it was agreed that this information should be included in the summary tables produced by the Secretariat where possible. Other points to take account of were which studies had measured IGF-I before diagnosis of cancer and how long the time period between measurement and diagnosis of cancer had been, and what associations other risks or confounders had with breast cancer in the studies.

25. It was noted that the three meta-analyses differed in their aims and findings. Only one had looked at the dose-response relationship and, while this meant there was less power, it was considered indicative of the quality of the individual studies as this meta-analysis excluded papers where there was

not enough information to determine a dose-response relationship between serum IGF-I and breast cancer.

26. In conclusion, the epidemiology papers indicated a tendency for association between dairy protein and circulating IGF-I levels and also between IGF-I and breast cancer in premenopausal women. It was considered that it should be possible to assess the association between dietary protein and breast cancer through IGF-I in appropriate studies. Overall, the database was deemed insufficient to link dietary IGF-I directly with breast cancer

27. A further paper on other cancers would be prepared for a future meeting and a statement prepared in due course.

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

POSSIBLE CARCINOGENIC HAZARD TO CONSUMERS FROM INSULIN-LIKE GROWTH FACTOR-1 (IGF-I) IN THE DIET –Part 2

IGF-I AND PROSTATE CANCER

Introduction

1. Prostate cancer is the most common cancer in men in the UK. A number of epidemiological studies have identified risk factors that influence the incidence of prostate cancer such as age, race, family history, genetic susceptibility and androgen metabolism as well as lifestyle factors such as smoking, exercise and body size.

2. Studies have also shown that dietary factors such as fat, protein and fibre intake could affect the aetiology of prostate cancer. Dietary fat for instance has been associated with increased prostate cancer risk. Consumption of plant-based foods like tomatoes, soy, cruciferous vegetables such as broccoli, cauliflower and Brussels sprouts have shown an inverse association with risk of developing prostate cancer. Epidemiological studies have also indicated that vitamins and other nutrients may have roles in preventing and inhibiting growth of prostate cancer. In their 2007 “Diet and Cancer Report” the World Cancer Research Fund (WCRF, 2007) concluded that diets high in calcium were a probable cause of prostate cancer and that there was limited evidence suggesting that high consumption of milk and dairy products was a cause of prostate cancer.

The IGF-I axis in prostate cancer

3. The mechanism of IGF-I action and regulation was considered in detail in CC/2009/08 and CC/2012/06. In brief, IGF-I (somatomedin C) is a peptide growth factor with a structure similar to insulin. It is largely produced in the liver in response to growth hormone. In circulation, IGF-I is largely bound to six binding proteins, most usually (>90%) IGFBP3. IGFBP-3 is cleaved by proteases which increase the availability of IGF-I. IGF-I acts via the IGF-I receptor. Levels of IGF-I are controlled via a feedback loop with free IGF-I inhibiting the secretion of growth hormone, in turn reducing the levels of IGF-I production. Free IGF-I binds to IGFBP-2 and IGFBP-5 with a greater affinity than it binds to the IGF-I receptor so increases in the levels of these binding proteins will reduce IGF-I activity.

4. IGFBP-2 is the most abundant IGFBP in seminal plasma and is one of the major IGFBPs in human prostate epithelial cells (Ismail *et al*., 2001).

Prostate Specific Antigen (PSA) is a glycoprotein of the kallikrein- related peptidase family which is present in seminal fluid; although it also occurs in other tissues and in both men and women. In healthy men, blood PSA should be less than 4 ng/ml. PSA is elevated in men with prostate cancer, though its positive predictive value is limited. PSA levels in the range 4-10 ng/ml are considered to be of uncertain predictive value and the measurement of other parameters such as IGF-I and IGFBP-3 have been considered as a means of improving screening procedures. PSA has a role in cleaving IGFBP-3 (Cohen *et al*., 1992).

Clinical Observations

Genetic variation

5. Nutrition is a key determinant of circulating IGF-I levels, but heritability studies have estimated that the proportion of variance explained by inherited genetic variation ranges from 38 to >80% for IGF-I and IGFBP-3 respectively (reviewed Schumacher *et al*., 2010). The specific genetic variants that contribute to heritable risk are not well defined.

6. African-Americans are more likely to be diagnosed with and die from prostate cancer and are reported to have lower IGF-I and IGFBP-3 serum concentrations than European Americans. The relationship between three common IGF polymorphisms [C/T single-nucleotide polymorphism (SNP) (rs 7965399) and a dinucleotide repeat $(Ca)_n$ within the 5' regulatory region of the IGF-I gene and the -202 A/C SNP in the IGFBP-3 gene], serum levels of IGF-I and IGFBP3, and prostate cancer risk was investigated in 767 African-Americans (401 cases and 366 age and ethnicity matched controls) enrolled in a clinic based study (Hernandez *et al*., 2007). The presence of at least one copy of the IGFBP3 -202 C allele was strongly associated with lower serum IGFBP-3 levels (3532 vs 3106 ng/ml); $p = 0.008$). A 2 fold increase in risk for prostate cancer was observed in individuals homozygous for this allele (OR;95%CI, 2.4;1.2-4.8, $p= 0.01$); these individuals were also more likely to have aggressive disease. IGF-I $(CA)_{19}$ genotypes were significantly associated with lower serum IGFBP3 levels ($p= 0.003$). The authors concluded that variation in the 5' un-translated region of the IGF-I and IGFBP3 genes may be influencing IGF serum levels in African-Americans. When considered as cases and controls, IGF-I and IGFBP3 levels were not significantly different. However, the aggressiveness of the disease was reduced among individuals in the second quartile of both IGF-I and IGFBP-3 compared to those in the first quartile. It was noted that the results differed from those of other authors but it was suggested that this could be due to different blood vitamin D concentrations since this had been reported to affect IGFBP-3 levels.

7. Johansson *et al*., (2007) analysed haplotypes and three haplotype tagging SNPs in the 3' region of the IGF-I gene in relation to circulating levels of IGF-I in 698 controls from the Cancer Prostate in Sweden (CAPS) study and 575 cases and controls from the prospective Northern Sweden Health

and Disease cohort (NSHDC) study. The IGF-I haplotype known as “TCC” which was previously associated with prostate cancer risk was also associated with increased IGF-I levels in the CAPS study but not in the NSHDC study (*p*= 0.02). The TCC haplotype, a rare allele carried on all loci, was associated with a 46% increased risk of prostate cancer. In contrast, three of the IGF-I htSNPs tagging this haplotype, rs 6220 and rs 7136446 were associated with increased IGF-I levels in the NSHDC study but not in the CAPS study (*p*= 0.03 and 0.04 respectively). A meta-analysis of these 2 studies and other association studies (Canzian *et al*., 2006; Al-Zahrani *et al*., 2005; plus unpublished data from the Dutch Prospect-EPIC study) on genetic variation on the 3’ region of the IGF-I gene in relation to circulating IGF-I levels was conducted. In the meta-analysis, the TCC haplotype and the rs6220 SNP were associated with elevated levels of IGF-I (*p* = 0.001 and 0.0001 respectively). There was no increased risk of prostate cancer or increased level of IGF-I associated with homozygote carriers of TCC in the meta-analysis possibly because the association with heterozygotes was due to chance or because the TCC haplotype had to be inherited with another genetic variation to produce IGF-I levels.

8. A study was conducted of the polymorphisms in the Cardiovascular Health Study cohort by Chen *et al.,* (2005) with the distribution of the genotypes *IGF-I* $(CA)_n$, *IGFBP-3* A-202C, and of the 2-bp deletion and $(AGG)_n$ in *IGF-I* receptor (*IGF-IR*) being compared. Among controls, the number of CA repeats in *IGF-I* was not associated with plasma IGF-I concentration but the *IGFBP-3* CC genotype was associated with a relatively low level of plasma IGFBP-3. No association with prostate cancer risk was detected, with the exception that men who did not carry two copies of the *IGF-IR* $(AGG)_7$ were at increased risk of prostate cancer.

9. The IGF-I $(CA)_n$ repeat sequence is 1 kb upstream of the IGF-I transcription start site and contains specific regulatory elements (Li *et al., 2004).* In a study of brothers (440 cases and 480 controls from 414 discordant families), no noteworthy differences were found in the frequency of IGF-I and IGFBP-3 polymorphisms between the cases and controls and neither of these was associated with prostate cancer. The population investigated was 91% Caucasian, 8% African-American and 1% Hispanic and Asian American.

10. Using a re-sequencing and tagging single-nucleotide approach, Schumacher *et al*., (2010) conducted a comprehensive analysis of the common genetic variation between *IGF1*, *IGFBP1* and *IGFBP3* genes with IGF-I and IGFBP-3 blood levels, and prostate cancer risk among Caucasians in the NCI Breast and Prostate Cohort Consortium, a pooled nested case-control study from 7 cohorts (CPS-II, ATBC, EPIC, HPFS, MEC, PHS and PLCO cited as Calle *et al*., 2002; ATBC, 1994; Riboli *et al*., 2002; Giovanucci *et al*., 2003; Kolonel *et al*., 2004; Hayes *et al*., 2000; Chan *et al*., 2002). Fourteen *IGF1* SNPs and sixteen *IGFBP/IGFBP3* SNPs were genotyped to capture common minor allele frequency ≥ 5% variation in this group. For each SNP, the geometric mean difference in IGF-I blood levels (n= 5684) and the association with prostate cancer risk was assessed in 6012 cases and 6641

controls. A non-synonymous *IGFBP3* SNP in exon1, rs2854746 (Gly32Ala) was associated with IGFBP-3 blood levels after adjusting for the previously established *IGFBP3* promoter polymorphism A-202c (rs2854744); IGFBP-3 blood levels were 6.3% higher for each minor allele. IGF-I levels were significantly associated with increased prostate cancer risk. For *IGF-I* SNP rs4764695, the risk estimates among heterozygotes were 1.01 (99%CI: 0.90-1.14) and 1.20 (99%CI: 1.06-1.37) for variant homozygotes with overall prostate cancer risk. It was concluded that SNPs were identified which were significantly associated with IGFBP-3 levels but none of them altered prostate cancer risk. However, a novel *IGF1* SNP, not associated with IGF-I blood levels, showed preliminary evidence for association with prostate cancer risk.

11. In another analysis of samples from the same cohort, common variation was systematically examined in 18 genes in the IGF-I signalling pathway for associations with circulating IGF-I and IGFBP-3 levels (Gu *et al*., 2010). In this study, 302 SNPs were genotyped in >5,500 Caucasian men and 5,500 Caucasian women. After adjusting for multiple testing, SNPs in the *IGF-I* and *SSTR5* genes were significantly associated with circulating IGF-I levels ($p < 0.002$). SNPs in the *IGFBP3* and *IGFALS* genes were significantly associated with circulating IGFBP-3 levels. Multi-SNP models explained R^2 = 0.62% of the variation in circulating IGF-I and 3.9% of the IGFBP3. No significant association between these multi-SNP predictors of circulating IGF-I and IGFBP3 levels and the risk of prostate cancer.

12. Safarinejad *et al*., (2011) investigated the effects of *IGFBP3* gene polymorphism on serum levels of IGF-I and IGFBP-3 and the incidence of prostate cancer and Benign Prostate Hyperplasia (BPH). The IGFBP3-202A/C polymorphism genotype frequencies showed a significant difference between both prostate cancer patients and controls ($\chi^2 = 6.27$, df= 2.0, p = 0.026) and BPH patients and controls ($\chi^2 = 11.57$, df= 4.0, p = 0.014). The AA genotype frequency was significantly decreased in prostate cancer and BPH patients compared to controls and the risk of prostate cancer and BPH occurrence was decreased accordingly. Age-adjusted mean serum IGFBP-3 concentrations were highest in the individuals with the AA genotype and diminished significantly in a stepwise manner in the presence of 1 or 2 copies of the C allele (4577, 3929 and 3349 ng/ml respectively). Patients with prostate cancer and BPH had lower serum IGF-I ($p = 0.001$ and $p = 0.01$ respectively) and IGFBP3 levels ($p = 0.001$ and $p = 0.01$ respectively) compared with controls. It was concluded that the AA genotype at IGFBP-3 gene polymorphism is associated with reduced risks of prostate cancer and BPH and IGF-I and IGFBP3 concentrations were associated with modified risks of prostate cancer and BPH. No further details are available at present.

Human studies of IGF-I and prostate cancer risk

13. The available studies are tabulated in Table 1 below and described in the text following the table.

Table 1: Summary of results of epidemiology studies of prostate cancer risk associated with IGF- and related substances

Subjects	Number of subjects	Was blood taken prospectively?	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
Retrospective studies							
American men (age not known)	32 cases; 8 controls	No	Radioimmuno assay	None	Age	IGF-I not elevated in prostate cancer patients, but IGFBP-2 was elevated	Cohen, *et al.,* 1993
Israeli men, aged 68.5±3.4 y	14 cases; 10 controls	No	Radioimmuno assay after acid extraction	None	-	IGF-I not elevated in prostate cancer patients, but IGFBP-2 was elevated	Kanety, *et al*., 1993
Australian men , aged 60-83 y	16 cases; 15 controls	No	Radioimmuno assay	None	-	IGF-I not elevated in prostate cancer patients, but IGFBP-2 & IGF-II were elevated	Ho and Baxter, 1997
Greek men, 38.5% aged <69 y, 34.6% aged 70-74 y & 26.9% aged >75 y	52 cases; 52 controls	No	Commercial radioimmuno-assay after ethanol extraction	Positive	Age	Unadjusted OR=1.71, comparing IGF-I in prostate cancer cases with controls	Mantzoros, *et al*., 1997
Swedish men, aged <80 y	210 cases; 224 controls	No	Commercial Immuno-radiometric assay. No interference detected	Positive	Age, height, BMI, total energy intake	OR=1.51 for men aged <80 y; OR= 2.93 for men aged <70 y.	Wolk, *et al*., 1998
Austrian white male patients, aged 56-79 y, with elevated	Cohort of 245, with 74 developing prostate cancer	No	Commercial immuno-radiometric assay	Positive	-	IGF-I level was greater in prostate cancer patients (176±26 ng/mL) than in those having no prostate cancer (136±23 ng/mL).	Djavan, *et al*., 1999

Subjects	Number of subjects	Was blood taken prospectively?	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
PSA							
Swedish men aged 69.9±6.3 y	208 cases; 70 controls	No	Commercial immuno-radiometric assay	None	Age, height, BMI.	No associations between IGF-I or IGFBP-3 and prostate cancer, but there was a positive association with IGFBP-1 levels	Signorello, *et al.,* 1999
UK men aged 69.9±6.3 y	37 cases; 57 controls	No	Commercial (?) Immuno-radiometric assay	None	Age	No associations between IGF-I levels and prostate cancer.	Cutting, *et al.,* 1999
US (mainly) white middle class men, aged 64.8±8.9 y	72 cases; 127 controls	No	Commercial radio-immunoassay	Positive	Age, length of sample storage, IGF-II, IGFBP-3, PSA	High IGF-I and low IGF-II were associated with high risk of prostate cancer. Adjusted OR for IGF-I = 3.1.	Harman, *et al.,* 2000
Greek men, mean age 67 and 69 y	34 cases; 131 BPH controls	No	Commercial immune radiometric assay	None	Total PSA, free PSA, PSA/IGF-I ratio	No difference between IGF-I in BPH and cancer, but PSA/IGF-I differed,	Koliakos, *et al.,* 2000
German men (mean age 66 or 64)	171 cases; 67 controls	No	Radioimmuno assay and chemi luminescence	None	Age, testosterone, anti-androgen treatment	No difference between IGF-I levels in prostate cancer patients (158.6 ng/mL) and controls (159.1 ng/mL).	Kurek, *et al*., 2000
US men (age not reported)	57 cases; 39 controls	No	Commercial active IGF-I ELISA	None	Age	IGF-I levels were lower in prostate cancer patients (125±58 ng/mL) than in controls (158±71 ng/mL).	Baffa, *et al*., 2000
US men aged 62 and 63y controls	38 cases; 40controls	No	Commercial ELISA or radioimmunoa ssay.	None	“Patient and specimen variations”	IGFBP2 levels were lower in recurring prostate cancer patients than in controls in remission. No differences in	Yu, *et al*., 2001

Subjects	Number of subjects	Was blood taken prospectively?	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
						IGF-I or IGFBP3	
Canadian men, aged 52-75 y	84 cases; 75 controls (BHP patients)	No	Commercial active IGF-I ELISA	Positive	Age, IGFBP-3 (intact, fragment, total), free & total PSA	Prostate cancer patients had higher levels of IGF-I (126.6±4.9 ng/mL *vs.* 101.2±5.5 ng/mL) and intact IGFBP-3 (1480±680 ng/mL *vs*. 1120±720 ng/mL)	Khosravi, *et al*., 2001
Canadian men, mean aged 65y cases-63 y controls	244 cases; 408 controls	No	ELISA	None until corrected for age and PSA	Age	IGF-I adjusted for age and PSA lower in cases. No difference in IGFBP3.	Ismail *et al*., 2002
Chinese men aged 71.9±7.5 y	112 cases; 306 controls	No	Commercial ELISA after acid-ethanol extraction	Positive	IGFBP-I, IGFBP-3, 5α-androstane-3α, 17β-diol glucuronide, sex hormone binding globulin, weight, height, BMI, waist-to-hip ratio	OR=2.64 comparing upper and lower quartiles of IGF-I levels. Prostate cancer risk was inversely related to levels of IGFBP-1 and IGFBP-3.	Chokkalingam, *et al.,* 2001
Japanese men, mean age 69.8y localised cases-and controls and 71.3y advanced cases	112 cases (84 advanced, 28 localised); 28 controls	No	Commercial immune-radiometric assay	None	PSA, IGFBP-3, IGF-I/PSA ratio, IGFBP-3/PSA ratio, age , BMI, smoking	IGF-I higher (171.8) in advanced prostate cancer than BPH controls (140.6 ng/ml) (p = 0.01). IGFBP3 lower (1790 ng/ml) in advanced cases compared to localised cases (2090 ng/ml) or BPH controls (2110 ng/ml).	Miyata *et al*., 2003
Italian men median age	171 cases: 174	No	Commercial ELISA	Positive	Human glandular Kallikrein (hK2),	IGF-I higher in prostate cancer (142 ng/ml) compared	Scorilas *et al*., 2003

Subjects	Number of subjects	Was blood taken prospectively?	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
68 and 65	controls				PSA, free/total PSA, hK2/PSA	to controls with BPH (143 ng/ml)	
Malaysian men mean age 70 68 (cases, BPH) and 57 (controls)	25 cases: 45 BPH, 69 controls	No	Commercial ELISA	None	-	No differences between the 3 groups.	Lopez *et al*., 2004
Turkish men	24 localised cases, 19 metastasised cases: 45 BPH controls	No	Immuno-radiometric assay	None	-	IGF-I levels similar in all groups.	Aksoy *et al*., 2004
British men, mean age 62	176 cases; 324 controls	No	Commercial ELISA	Positive, stronger for advanced-stage prostate cancer	Age, GP practice, recruitment date, IGFBP-3, smoking. Other variables BMI, class, exercise, alchol use, did not affect the model and were not used.	OR 3.00 (1.50-6.01) comparing upper and lower quartiles adjusted for IGFBP-3 and smoking.	Oliver *et al*., 2004
Austrian men. 67 and 69 y	156 cases; 271 controls	No	Immuno-radiometric assay	None	-	IGF-I levels similar in both groups.	Marszalek *et al*., 2005
Arab men.	30 cases; matched controls	No	Immuno-radiometric assay	Positive	Age	IGF-I levels higher in cases	Kehinde *et al*., 2005
Canadian men, aged	103 cases; 205	No	Commercial ELISA	None	Age, PSA, ethnic background, digital	IGF-I levels higher in cases of HGPIN (pre-neoplastic)	Nam *et al*., 2005

Subjects	Number of subjects	Was blood taken prospectively?	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
64 and 65 y	controls				rectal examination.	but not for prostate cancer.	
Chinese men (mean age 65y) with tPSA of 4/-10 ng/ml.	281 cases 503 controls	no	ELISA following acid ethanol precipitation	Positive	-	IGF-I and IGFBP3/fPSA higher in cases. No difference in IGFBP3 alone.	Zhigang *et al*., 2007
Men in Belarus	?	?		None	-	No significant differences between levels of IGF-I & IGFBP-3 in patients and those in controls.	Povelitsa & Nazarov. 2008
Prospective studies							
US male physicians aged 40 to 84 y	152 cases; 152 controls	Yes	Commercial ELISA	Positive	Age, smoking, duration of follow up.	Adjusted RR=4.3	Chan*, et al*., 1998a
US male physicians aged aged 40-84 y	530 cases; 534 controls	Yes	Commercial ELISA	None for all prostate cancer; Positive for advanced-stage prostate cancer	Age, smoking, IGFBP-3, BMI considered but not used.	For advanced stage prostate cancer there was a positive association with IGF-I and a negative association with IGFBP-3, with ORs of 5.1 & 0.2 comparing upper and lower quartiles	Chan *et al*., 2002
US health plan members, aged 40-80 y	Cohort of 765. 45 cases; 179 controls	Yes	Radioimmuno assay	None	Age, interval between serum collection and diagnosis	No association between IGF-I and prostate cancer I	Schaefer, *et al*., 1998
Swedish men. Median age = 59.7 y.	149 cases; 298 controls	Yes	Commercial immuno-radiometric assay after	Positive	Age, date of survey, residency, IGFBP-3, BMI, smoking	IGF-I and IGFBP-3 were positively associated with prostate cancer with respective ORs of 1.72 and	Stattin, *et al*., 2000

Subjects	Number of subjects	Was blood taken prospectively?	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
			acid extraction			1.82	
Swedish men. Median age = 59.9 y.	281 cases; 560 controls	Yes	Commercial immune-radiometric assay after acid extraction	Positive	Age, IGFBP-3, BMI, smoking	IGF-I associated with prostate cancer, OR= 1.67 (reduced by adjustment of IGFBP-3)	Stattin, *et al*., 2004
Finnish men aged 55-67	174 cases in a cohort of 665 men	Yes	Commercial ELISA after acid extraction	None	Age, IGFBP-3, PSA, prostate volume	No association between IGF-I and prostate cancer after adjustment for prostate volume	Finne, *et al*., 2000
US men, aged 58-86 y	30 cases; 60 controls	Yes	Commercial, ELISA	None	Age. No other confounders (smoking, marital status, education) "mattered".	No difference in IGF-I or IGFBP-3 levels between prostate cancer patients had and controls.	Lacey, *et al*., 2001
Meta-analysis	**-**	**-**		***Positive***		***OR for prostate cancer was 1.47 (95% CI = 1.23-1.77) among men with high IGF-I as compared with those with low IGF-I. The OR was 1.26 (95% CI = 1.03-1.54) for IGFBP-3.***	***Shi, et al., 2001***
Finnish male smokers (ATBC cohort)	100 cases: 400 controls	Yes	Commercial ELISA	None	Age, Intervention group, time between blood draws, IGFBP-3	No association between IGF-I and IGFBP3 levels and risk (OR 0.52 for fourth vs first quartile).	Woodson *et al*., 2003
Meta-analysis	**-**	**-**		***Positive***		***High concentrations of IGF-1 were associated with an increased risk of***	***Renehan, et al. 2004***

Subjects	Number of subjects	Was blood taken prospectively?	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
						prostate cancer (comparing 75th with 25th percentile, OR=1.49).	
Dutch men, aged 65-≥80 y	201 cases; 201 controls	Yes	Immuno-radiometric assay	None	Log total IGF-I, log free IGF-I, IGFBP-3, PSA density, PSA density of transition zone, age at baseline, log PSA at each visit.	No difference between total and free IGF-I or IGFBP-3 between cases and controls.	Janssen *et al*., 2004
American men, aged 65-≥80 y	174 cases; 174 controls	Yes	Immuno-radiometric assay after acid ethanol precipitation	None	Ethnicity, year of entry, age at entry, year of blood draw. (Marital status, education, aspirin use, NSAID use, waist-hip-ratio assessed but not used) IGFBP-3, PSA.	No Association (RR=0.67) lowest vs highest. Small decrease in risk with increasing IGFBP-3 levels.	Chen *et al*., 2005
French men, aged 65-≥80 y	100 cases; 100 controls	Yes	Chemi luminescent assay (no interference from IGFBPs	None	Age, intervention group, IGF variables, smoking, BMI, alcohol intake. Stratified by PSA level.	No Association (OR=0.67) lowest vs highest 1.83 (95%CI 0.85-3.95).	Meyer *et al*., 2005
US men	462 cases 462 controls	Yes	Commercial ELISA, no further details	Positive	Age, IGFBP-3, PSA, time, year & season of blood draw. Other prostate	Small association between IGF-I, and prostate cancer risk (OR top vs bottom quartile 1.37, 95% CI 0.76-2.49).	Platz *et al*., 2005

Subjects	Number of subjects	Was blood taken prospectively?	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
					cancer risk factors assessed but not presented.		
US men	1331 cases 1331 controls	Yes	Commercial ELISA, no further details	Positive	Age, IGFBP-3. Other prostate cancer risk factors assessed but not presented.	Association between IGF-I, and prostate cancer risk (OR top vs bottom quartile 1.41, 95% CI 1.12- 1.78). Stronger association for low than high grade tumours.	Nimptsch *et al*., 2010 Extension of above study.
British men	141 cases 423 controls	Yes	Commercial ELISA, no further details	None	Age, duration of sample storage. BMI, smoking, alcohol consumption	No association between IGF-I, and prostate cancer risk (OR top vs bottom quartile 1.37, 95% CI 0.92- 2.03). Association reduced by adjustment for IGBP-3.	Morris *et al*., 2006
Men resident in Australia	524 cases 1826 controls	Yes	Commercial ELISA, no further details	None	Country of birth, alcohol consumption. Other variables assessed (BMI, smoking, energy intake) but not used).	No association between IGF-I, and prostate cancer risk (OR top vs bottom quartile 1.07, 95% CI 0.79- 1.46).	Severi *et al*., 2006
Meta-analysis	**-**	**-**	**-**	***Positive***		***High concentrations of IGF-1 were associated with an increased risk of prostate cancer (OR, highest vs lowest quintile 1.38, 95% CI 1.19-1.60). Association more positive with low grade disease.***	**Morris *et al*., 2006**

Subjects	Number of subjects	Was blood taken prospectively?	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
European men from 10 countries	630 cases 630 controls	Yes	ELISA following acid ethanol precipitation	Positive	IGFBP-3 Other variables assessed (BMI, smoking, alcohol, exercise, marital status) but not used).	Small association between IGF-I and risk (OR1.35)	Allen *et al*., 2007
Men from PLCO cohort (US)	727 cases 887 controls	Yes	ELISA following acid ethanol precipitation	None	Times since initial screen, year of blood draw. IGFBP-3, IGF-I/IGFBP-3. Other variables assessed (BMI, height, diabetes, family history, smoking, activity, nutrients, study centre) but not used).	Small association between IGF-IGBP3 molar ratio in obese men (OR 2.34,1.10-5.01 highest vs lowest) risk higher for aggressive disease (2.80; 1.11-7.08)	Weiss *et al*., 2007
Meta-analysis	**-**	**-**		***Positive***		***High concentrations of IGF-1 were associated with an increased risk of prostate cancer (OR, highest vs lowest quintile 1.38, 95% CI 1.19-1.60). Association more positive with low grade disease.***	***Roddam, et al. 2008***
US and Canadian men	96 cases and 412 controls	Yes	Commercial ELISA, no further details	None	Age, religion, ethnicity.	No association between IGF-I, IGFBP-3 and prostate cancer risk overall (OR 1.26,	Borugian *et al*., 2008

Subjects	Number of subjects	Was blood taken prospectively?	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
						95% CI 0.66- 2.41) or by ethnic group.	
Meta-analysis	**-**	**-**		***Positive***		***Increased concentrations of IGF-1 were associated with an increased risk of prostate cancer (OR, 1.21, 95% CI 1.07-1.36) per standard deviation increase in peptide. Association more positive with more aggressive disease.***	***Rowlands, et al. 2010***

Retrospective studies

14. Cohen, *et al.* (1993) measured IGF-I, IGF-II, IGFBP-2 and IGFBP-3 (measured in arbitrary units) in serum taken from 32 prostate cancer patients in the USA. Comparisons were made with levels in pooled serum samples taken from 6 male volunteers and 6 pregnant women. No differences were found for levels of IGF-I, IGF-II or IGFBP3. Levels of IGFBP-2 were elevated in the prostate cancer patients, with particularly high levels being noted in those with high serum levels of prostate-specific antigen (PSA).

15. Kanety, *et al*. (1993) collected blood from 14 Israeli patients (aged 68.5 ± 3.4 years) with prostate cancer, including 12 with bone metastases, 4 patients with elevated PSA but without cancer and 6 healthy control subjects. Serum levels of IGF-I, IGF-II and IGFBPs were measured. Levels of IGFBP-2 were elevated in patients with metastatic prostate cancer compared to healthy controls (23.83 ± 6.93% *vs*. 2.95 ± 0.52% of total serum IGFBPs; $p<0.02$) and IGFBP-3 was decreased in the same patients (68.2±9.1% *vs*. 95.4 ± 0.9% of total serum IGFBPs; $p<0.02$). A more moderate increase in IGFBP-2 was seen in patients with raised PSA without malignancy. No group differences in the levels of IGF-I, IGF-II, IGFBP-1, IGFBP-4 and IGFBP-5 were reported.

16. Ho and Baxter (1997) examined blood from 16 Australian patients with inoperable prostate cancer, including 8 with abnormally high levels of PSA. The patients were aged 60.9 to 83.4 years (72.2 ±1.7 years). Most of the blood samples were taken during 13 months of treatment. For comparison, blood was also taken from 8 patients with BPH and 7 male control subjects with no known prostate abnormality. Serum from the blood samples was analysed for IGF-I, IGF-II, IGFBP-2 and IGFBP-3. Mean serum levels of IGFBP-2 were significantly elevated in men with prostate cancer and abnormal levels of PSA (560 ± 66 ng/ml) as compared with those with prostate cancer and normal PSA (297 ± 65 ng/ml; $p=0.02$), benign prostatic hyperplasia (364 ± 61 ng/lL; $p=0.03$) and controls (367±44 ng/m; $p=0.04$). Levels of IGF-II were significantly higher in controls than in men with prostate cancer ($p=0.03$) or benign prostate hyperplasia ($p=0.02$). There were no significant differences between the groups with regards to levels of IGF-I and IGFBP-3.

17. In a small case-control study, Mantzoros, *et al*. (1997) took blood from 52 incident cases of histologically confirmed prostate cancer and from 52 patients with BPH. The spread of ages of the patients was 38.5% ≤69 years, 34.6% 70-74 years and 26.9% ≥75 years. The authors compared IGF-I levels with blood from 52 age-matched healthy controls. The three groups were matched for age and town of residence (the Greater Athens area). The serum samples were analysed for IGF-I, steroid hormones and sex hormone-binding globulin (SHBG). There was a statistically significant trend ($p=0.01$) for a positive association between IGF-I levels and incidence of prostate cancer. Mean concentrations of IGF-I were higher in both sets of patients than in controls but the increase was greater and was statistically significant ($p=0.05$) only in the prostate cancer patients. The odds ratio for a 60 ng/ml increment of serum IGF-I (prostate cancer cases vs. controls) was 1.71 (unadjusted) and 1.91 when adjusted for age, height, body mass index, years of schooling, sex-

hormone binding globulin and steroid hormones (testosterone, dihydrotestosterone, oestradiol and dehydroepiandrosterone sulfate).

18. Wolk, *et al*. (1998) performed analyses of IGF-I and IGFBP-3 levels in blood from newly diagnosed prostate cancer patients, aged less than 80 years, as part of a Swedish case-control study. Cases (n = 210) were patients with cytologically or histologically confirmed prostate cancer who had been resident in Őrebro County at any time between January 1989 and September 1991. Control subjects (n = 224) were age-matched individuals from the same area who did not have prostate cancer. Mean serum IGF-I was statistically significantly higher (p=0.02) in prostate cancer patients (158.4 ng/ml) than in control subjects (147.4 ng/ml). Mean serum IGFBP-3 levels in prostate cancer patients (2668 ng/ml) were not significantly different (p>0.05) from the levels in controls (147.4 ng/ml). There was a significant (p=0.04) association between serum IGF-I levels and risk of prostate cancer (OR; 95% CI = 1.51; 1.0-2.26). The association was particularly strong in those younger than 70-years-of-age (2.93; 1.43-5.97). No association was found between serum IGF-I levels and disease stage.

19. Djavan, *et al*. (1999) took blood samples from 245 consecutive white male patients, aged 56 to 79 years, with serum levels of PSA of 2.5 to 15 ng/ml in a prostate cancer detection programme (n = 201) or attending a clinic at the University of Vienna for evaluation of lower urinary tract symptoms (n = 44) between May 1998 and February 1999. Prostate cancer was detected by biopsy in 74 of the 245 patients. The mean level of serum IGF-I was statistically significantly greater (p=0.03) in prostate cancer patients (176 ± 26 ng/ml) than in those having no prostate cancer (136 ± 23 ng/ml).

20. There was no significant difference in serum IGF-I levels between 37 biopsy patients who were found to have prostate cancer and 57 patients who had no evidence of malignancy (Cutting *et al*., 1999). The levels were 26.4 and 23.7 nmol/L (202 and 181.3 ng/ml) in the cases and controls respectively. In the patients with PSA levels of 4-20 µg/L, the IGF-I levels were 27.0 and 22.5 nmol/L (206.6 and 172.1 ng/ml) in the cases and controls respectively.

21. Signorello, *et al.* (1999) measured serum concentrations of IGF-I, IGFBP-1 and IGFBP-3 in 208 Swedish prostate cancer patients (mean age = 69.9 ± 6.3 years) and 70 healthy male control subjects (mean age = 70.9 ± 5.5 years). The findings are summarised in Table 2 below. IGFBP-1 levels were significantly elevated in prostate cancer patients compared with controls (Student's t-test, two-tailed: p<0.0001), whereas levels of IGF-I and IGFBP-3 were similar in the cancer patients and controls. Logistic regression analysis was used on the IGFBP-1 data to estimate odds ratios (ORs) for risk of prostate cancer. Data were categorised according to approximate quartiles of the control distribution, using the lowest quartile (≤7.8 ng/ml) as the referent group. The prostate cancer risk for the second quartile (7.9-10 ng/ml) did not differ from that of the lowest quartile, so the two lowest quartiles were combined and used as the referent group for the other two quartiles (see Table 3). A significantly increased risk of prostate cancer was seen in men in the upper quartile as compared with the combined first and second quartiles of IGFBP-1 levels (OR;95% CI, 5.1;2.4 – 10.7).

Table 2: Mean (± SD) serum concentrations of IGF-I, IGFBP-1 and IGFBP-3 in prostate cancer patients and controls (Signorello, *et al*., 1999)

Serum analyte	Prostate cancer (ng/mL)	Controls (ng/mL)
IGF-I	158 ± 54	152 ± 53
IGFBP-1	23.7 ±18.3	14.4 ± 11.6
IGFBP-3	2664 ± 1041	2556 ± 783

Table 3: Prostate cancer risk in relation to serum levels of IGFBP-1 (Signorello, *et al*., 1999)

Serum IGFBP-1 level (ng/ml)	Prostate cancer Patients No. (%)	Control subjects No. (%)	Odds ratio	95% CI
≤ 10.0	52 (25%)	33 (47%)	1.0	Referent
10.1 – 17	44 (21%)	20 (29%)	1.5	0.7 – 3.2
≥ 17	112 (54%)	17 (24%)	5.1	2.4– 10.7

22. IGF-I, total and free PSA were measured in the serum of 34 patients with prostate cancer and 131 patients with BPH in a study designed to improve screening (Koliakos *et al*., 2000). IGF-I concentrations did not significantly differ between the two groups being 116.3 and 104.8 ng/ml respectively, but it was considered that the PSA/IGF-I ratio could clearly distinguish the two groups of patients. IGF-I levels correlated with PSA levels in patients with cancer but not in patients with BPH. Receivers Operating Curve (ROC) analysis indicated a better sensitivity to specificity ratio for PSA/IGF-I than for PSA or free/total PSA.

23. Baffa, *et al*. (2000) collected blood samples from 57 patients in Philadelphia, USA, prior to their undergoing radical prostatectomy for adenocarcinomas and from 39 age-matched control subjects. Significantly lower *(p*=0.019) mean serum IGF-I levels were detected in prostate cancer patients (125 ± 58 ng/ml) than in controls (158 ± 71 ng/ml). Six months after prostatectomy, the levels of IGF-I (148 ± 57 ng/ml) were still lower in the patients than in the controls.

24. Kurek *et al*., (2000) compared IGF-I levels in 171 patients with prostate cancer and 67 controls matched for age. No significant differences were apparent in the mean levels (158.6 and 159.2 ng/ml in cases and controls respectively) or in levels before and after androgen therapy. There was also no association between IGF-I levels and testosterone concentrations. Freeze-thaw cycles were applied to the samples but did not affect the IGF-I levels measured. The IGF-I was measured using both a radioimmunoassay and a chemiluminescence method (both following acid extraction); the values obtained from the different methods were comparable, but slightly higher when measured by RIA (150.5 and 168.1 ng/ml respectively).

25. Oestradiol, epitestosterone, IGF-I and IGFBP-3 levels were measured in the serum of 71 patients suffering from various prostate conditions; 56 with BPH and 15 with prostate cancer (Hill *et al*., 2000). After age adjustment, IGF-I was found to correlate negatively with epitestosterone levels.

26. Finne, *et al*. (2000) identified subjects from the Finnish prostate screening trial of 15,036 men, aged 55-67 years. Blood samples were collected from each participant upon recruitment (up to 1997). Serum samples were analysed for PSA and those men with PSA levels > 4.0 ng/ml underwent trans-rectal ultrasound guided sextant biopsies of the prostate. By March 1998, 665 men had undergone biopsies and of those men 179 cases of prostate cancer were identified, along with 174 men with prostate hyperplasia and 268 with normal prostate histology. The serum samples from the 665 men who had had biopsies were analysed for IGF-I and IGFBP-3. Men with the highest quartile level of IGF-I had an OR:95%CI for prostate cancer of 0.50; 0.26-0.97 when adjusted for serum IGFBP-3, but after adjustment for prostate volume, the negative association was no longer statistically significant (OR; 95% CI = 0.57;0.28-1.16). There was no significant association between IGFBP-3 levels and prostate cancer risk (OR; 95% CI = 1.24; 0.68-2.24). The authors concluded that, in screen positive men with elevated serum PSA, serum IGF-I was not a useful diagnostic test for prostate cancer.

27. Khosravi, *et al*. (2001) investigated serum levels of IGF-I and levels of intact, fragment and total IGFBP-3 in patients with prostate cancer compared to levels in age-matched patients with BPH. Blood was collected from 75 men (aged 55-75 years) with BPH and 84 men (aged 52-75 years) with prostate cancer. Patients had PSA levels in the range 1.75 to 13.5 ng/ml (with concentrations being slightly higher in the cancer patients than in the patients with BPH) and had their diseases confirmed histologically. The prostate cancer patients had significantly higher levels of IGF-I (126.6 ±4 .9 ng/ml *vs.* 101.2 ± 5.5 ng/ml; $p<0.001$) and intact IGFBP-3 (1480 ± 680 ng/ml *vs*. 1120 ± 720 ng/mL; $p<0.001$) as compared with BPH patients. Levels of total IGFBP-3 were slightly, but not significantly, higher ($p=0.091$) and levels of fragments of IGFBP-3 were slightly lower (p=0.257) in prostate cancer patients than in those with BPH respectively.

28. Chokkalingam, *et al* (2001) performed a case-control study in a Chinese population in urban Shanghai considered to have a low risk of prostate cancer. 112 cases of primary prostate cancer newly diagnosed between 1993 and 1995 were identified from the Shanghai Cancer Registry. Age-matched controls were selected from adult male permanent residents of Shanghai. Blood samples were taken from cases after diagnosis but prior to treatment and from controls at the time of recruitment. Blood plasma was analysed for IGF-I, IGF-II, IGFBP-1, IGFBP-3, 5α-androstane-3α,17β-diol glucuronide (3α-diol G) and SHBG. Men in the highest quartile of IGF-I levels had a higher risk of prostate cancer than those in the lowest quartile (OR; 95% CI = 2.63; 1.19-5.79) with a significant positive trend ($p=0.01$). In contrast, men in the highest quartile for IGFBP-3 levels had a 45% lower risk than those in the lowest quartile (OR; 95% CI = 0.54; 0.26-1.15) but the trend was not significant ($p=0.08$). A similar result was obtained for IGFBP-1 (0.60; 0.31-1.17; $p=0.25$). Men in the highest quartile for the IGF-I:IGFBP-3 molar ratio (an indirect measure of free IGF-I) had a higher risk compared with those in the lowest quartile

(2.51; 1.32-4.75). These results were more pronounced when adjusted for serum levels of 3α-diol G and SHBG. There was no significant association between prostate cancer and IGF-II levels. The data were also analysed in relation to the severity of the prostate cancer. The cases were classified as having either localised (American Urological Association Stages A or B) or advanced (Stages C or D) disease. For localised disease, significant trends were obtained for IGF-I (p=0.001), and IGFI:IGFBP-3 (p<0.001) with OR; 95%CIs for comparison of lowest with highest quartile of 15.73; 3.04-81.94 and 6.30; 1.96-20.24, respectively. For advanced disease, significant trends were obtained for IGFBP-I (p=0.03), and IGFI:IGFBP-3 (p=0.003) with OR; 95%CIs for comparison of lowest with highest quartile of 0.32 ; 0.13-0.81 and 2.53;1.11-5.78, respectively.

29. In a pilot study carried out among the CLUE I population, 30 cases of prostate cancer were identified from samples in a serum bank and were matched with 60 controls by age and date of blood draw (Lacey *et al*., 2001). IGF-I levels were 119.8 ng/ml in the cases and 118.4 ng/ml in the controls (OR; 95%CI, 0.7; 0.2-2.3) with IGFBP-3 levels being 1042.5 and 1022.6 ng/ml respectively (OR; 95%CI, 1.1; 0.3-3.8). IGF-I ORs were only slightly modified by adjustment for IGFBP-3 levels (0.6; 0.1-2.9). The levels of IGF-II and IGFBP-I were also analysed but were not different between cases and controls.

30. The levels of IGF-I, IGFBP2 and IGFBP3 were measured in prostate cancer patients who had either developed recurring disease or were in remission following radical prostatectomy (Yu *et al*., 2001). Lower levels of IGFBP-2 and IGFBP-3 were measured in the case patients compared with the controls, but there were no differences in IGF-I levels between the two groups. Where serial samples were available (taken at median interludes of 1.6, 2.6, 3.5 and 4.5 years post-operatively) IGFBP-2 increased over time in the controls but did not change in the cases; there were no trends observed for IGFBP-3 or IGF-I concentrations in either group.

31. A study by Shariat *et al*., (2002) was designed to determine whether pre-operative levels of IGFBP-2 or IGFBP-3 would predict cancer stage and prognosis in patients undergoing radical prostatectomy. IGF-I, IGFBP-2 and IGFBP-3 were measured in 120 patients undergoing surgery (and post-operatively in 51 of these patients), in 44 healthy men and in 10 patients with bone metastases. IGF-I and IGFBP-3 levels were not associated with any of the clinical or pathological features of prostate cancer. IGFBP-3 levels were lowest in patients with bone metastases. IGFBP-2 levels were elevated in prostate cancer patients compared to controls, but within the patient group were lower in patients with advanced disease and declined on prostate removal. Median IGF-I levels were 151.1, 171.3, 156.4 and 153.4 ng/ml in pre-operative prostatectomy patients, healthy controls, patients with metastases to the lymph and metastases to the bone respectively.

32. Peng *et al*., (2002) measured serum IGF-I levels in Chinese patients with prostate cancer (n=81), BPH (n=55), uroepithelial tumour (n = 32) or healthy controls (n=84). IGF-I levels were higher in prostate cancer cases than in the controls or the other groups (OR;95%CI=2.86 ;1.38-5.3, p <0.05). No further details are available.

33. In a study designed to investigate the usefulness of IGF-I or IGFBP-3 in predicting the pathology results of Canadian men undergoing prostate biopsy, Ismail *et al.,* (2002) measured IGF-I and IGFBP-3 in 652 consecutive patients who had elevated PSA levels or abnormal physical examination results. Following biopsy, 244 men were diagnosed as having prostate cancer with the remaining 408 men having benign conditions. Mean IGF-I levels (± SD) were 176.1 ± 58.3 and 178.7 ± 54.7 ng/ml and IGFBP3 2724.1 ± 647 and 2673.7 ± 589 ng/ml in the cases and controls respectively. IGF-I:PSA and IGFBP3:PSA ratios were significantly lower in the cases compared to the controls. Adjustment for age showed significantly lower IGF-I levels in the cancer cases compared with the controls whereas there were no differences in IGFBP3 levels. Analysis by quartile showed an inverse relationship between cancer risk and age-adjusted IGF-I and IGFBP3 levels. However, ROC analysis indicated that free to total PSA had higher scores than the adjusted IGF-I. The authors concluded that while IGF-I might be a risk factor, it would not be a useful tumour marker.

34. Serum IGF-I, IGFBP-3 and PSA levels were measured in 112 patients with prostate cancer and compared to 32 patients with BPH (Miyata *et al*., 2003); of the patients with prostate cancer, 84 had advanced cancer and 38 had localised tumours. Serum IGF-I levels were higher in patients with advanced prostate cancer (171.8 ± 40.4 ng/ml) compared to the BPH controls (140.6 ± 42.5) (p = 0.01) but were not significantly different from the levels in patients with localised tumours. IGFBP-3 levels were significantly lower in patients with advanced prostate cancer (1790 ± 50 ng/ml) compared to the BPH controls (2111 ± 58 ng/ml) (p = 0.01) or the patients with localised tumours (2090 ± 58 ng/ml). Univariate analysis showed that serum PSA, IGF-I/PSA ratio and IGFBP-3 were correlated significantly with relapse-free survival of advanced prostate cancer patients treated with hormonal therapy. Multivariate analysis identified IGFBP-3/PSA as the only significant variable for relapse-free survival (OR; 95%CI = 5.81; 1.57-21.51). IGF-I and IGFBP-3 levels were significantly correlated. The authors concluded that IGFBP-3 could be a useful prognostic indicator.

35. IGF-I levels were significantly higher in 171 patients with prostate cancer (142 ng/ml) compared to 174 controls with BPH (143 ng/ml) (Scorilas *et al*., 2003). Multivariate logistic regression analysis identified IGF-I/free PSA as an independent predictor of prostate cancer. The study was designed to investigate the possible use of human glandular kallikrein, IGF-I and PSA in screening.

36. IGF-I levels were significantly higher (178 ng/ml) in 38 prostate cancer patients compared to 80 patients with BPH (136 ng/ml) p <0.05 (Trapeznikova *et al*., 2004). No further details are available.

37. IGF-I, IGFBP-3 and PSA were measured in the serum of 25 prostate cancer patients, 45 BPH patients and 69 healthy controls attending a hospital in Kuala Lumpur (Lopez *et al*., 2004). The mean (±SD) level of IGF-I was lower in the prostate cancer patients (98.3 ± 39.3 ng/ml) than in the BPH patients (119 ± 31.1) and the controls (119 ± 36.1); but the differences were not statistically significant. The mean IGFBP-3 concentrations in prostate cancer patients (2691 ± 1105 ng/ml, p = 0.029) and BPH patients (2618 ± 816, p= 0.006) were significantly lower than that of the controls (3119 ± 618 ng/ml) but the difference between the two groups of patients

was not significant. It was concluded that IGF-I and IGFBP-3 were inferior markers to PSA.

38. Oliver *et al.,* (2004a) reported on a case control study nested in a population based, multi-centre cross-sectional, randomised controlled trial of treatment for localised prostate cancer (ProtecT). 7,383 men aged 50-70 were recruited between 1999 and 2002. By April 2002, 176 cases (mean age 62.2) were identified for inclusion in the study and these were matched with 324 controls. Assays for IGF-I, IGF-II, IGFBP-2 and IGBP-3 were conducted by commercial ELISA or radioimmunoassay. The risk of prostate cancer increased across quartiles of IGF-I (highest vs lowest, OR;95%CI =2.34;1.26-4.34, *p* trend = 0.02) and IGF-II (1.78; 0.94-3.15, *p* trend = 0.09). Controlling for smoking and IGFBP-3 strengthened the association for both IGF-I (3.00;1.50-6.001, *p* trend = 0.005) and IGF-II (2.02; 1.07-3.84, *p* trend = 0.04. Associations between the IGFs and cancer risk were stronger for advanced cases. IGFBP-3 was not associated with increased prostate cancer risk. The authors noted that the study was limited by being of cross-sectional design, so that IGF-I levels could be influenced by the presence of the cancer, however as IGF-I production was largely hepatic it was unlikely that this would explain the findings, which had also been reported in prospective studies. It was later reported (Oliver *et al.,* (2004b) that IGF-1 was associated with PSA in 367 men without prostate cancer, since serum PSA was also associated with prostate size it was suggested that IGF-I could induce prostatic epithelial proliferation.

39. Serum IGF-I and IGFBP-3 levels were measured in 24 localised prostate cancer cases and 19 metastasised cases using radioimmunoassay and compared with levels in 45 cases of benign prostate hyperplasia (Aksoy *et al*., 2004). Few demographic details of the participants were provided but the authors were based at a hospital in Turkey. Serum IGF-I levels in both localised and metastasised prostate cancer cases were similar to those in the cases of benign prostate hyperplasia, being 138.3 ± 58.2, 137.7 ± 39.0 and 147.7 ± 4+4.2 ng/ml respectively. Serum IGFBP-3 levels were lower in the metastasised group compared to the BPH group (1,795.6 ± 305.6 compared to 2,196.0 ± 505.7 ng/ml, *p* = 0.005). In localised prostate cancer cases the serum IGFBP-3 levels (1,911.00 ± 349.58 ng/ml) were similar to those in the metastasised prostate cancer cases. There were significant correlations between serum IGFBP-3 levels and serum PSA levels.

40. Serum IGF-I levels were measured 156 Austrian men (median age 67y) with newly diagnosed, but untreated, prostate cancer and compared to 271 controls (median age 69y) (Marszalek *et al*., 2005). Serum IGF-I levels were similar in the cases (166 ± 6.1 ng/ml) compared to the controls (159 ± 4.5 ng/ml) and did not correlate with PSA levels. IGF-I levels were unaffected by age and did not correlate with the Gleason score of the tumours. The IGF-I was measured by the DSL-5600 immunoradiometric assay.

41. The incidence of prostate cancer is considered to be very low among Arab men. In a study by Kehinde *et al*., (2005), three groups of men were recruited, 383 indigenous healthy Arab men aged 15-90y, 30 men with newly diagnosed prostate cancer and 40 men with benign prostate hyperplasia. Serum IGF-I and IGFBP-3

levels declined in age in the healthy men and were lower than those reported for Caucasian men of the same age. It was noted that the IGF-I levels did not show a normal distribution. Arab men with newly diagnosed prostate cancer had significantly higher serum IGF-I ($p < 0.01$) and lower IGFBP3 ($p < 0.01$) levels than age-matched men without the disease. Elderly men with BPH had higher IGF-I levels than controls or those with prostate cancer. IGF-I levels were 127.60 ± 85.19 ng/ml compared with 71.09 ± 63.56 ng/ml in men aged 60-69 with IGFBP3 levels being 783.4 ± 37.18 ng/ml and 897.2 ± 44.72 ng/ml respectively.

42. A case control study to investigate whether pre-cancerous lesions were associated with altered IGF-I and IGFBP-3 levels, was conducted among 1031 Canadian men scheduled for prostate biopsy due to elevated PSA or abnormal rectal examination (Nam *et al*., 2005). Serum IGF-I and IGFBP-3 levels were measured prior to biopsy and then compared in 103 men with high grade prostatic interstitial neoplasia (HGPIN) and 205 men with normal prostate histology. The mean IGF-I level in patients with HGPIN was higher compared with controls (130.2 vs 118.8 ng/ml, $p = 0.01$). Mean IGFBP-3 levels were higher in the patients with HGPIN than in the controls but this was not significant (2393.9 vs 2276.0 ng/ml, $p = 0.06$). After adjusting for age, PSA, digital rectal examination and ethnic background, the crude OR;95%CI for having HGPIN for men in the highest relative to the lowest quartile of IGF-I levels was 1.94;1.0-3.7 $p = 0.04$. The crude OR for men in the highest relative to the lowest quartile of IGFBP3 levels was 2.04; 1.1-3.9 $p = 0.03$. In multi-variate analysis the ORs for age, digital rectal examination, PSA and ethnicity remained similar but the ORs for IGF-I levels were not predictive for HGPIN. IGF-I and IGFBP-3 were highly correlated and the latter was dropped from the analysis. When IGF-I alone was examined the ORs remained significant (1.95; 1.0-3.7, $p = 0.04$); similarly when IGFBP-3 was analysed alone the ORs for HGPIN were also significant (2.04; 1.1-3.9, $p = 0.03$). In a secondary analysis, the mean IGF-I level was 119.4 ng/ml in patients with cancer and was not significantly different from the controls 118.8 ng/ml. IGFBP3 levels were also not significantly different from the controls. It was concluded that there could be a relationship between high serum IGF-I and IGFBP-3 levels and the presence of early prostate neoplasia, but that this was distinct to previous reports that high levels of IGF-I were associated with an increased risk of future invasive prostate cancer.

43. In a study designed to improve screening, Zhigang *et al*., (2007) measured IGF-I and IGFBP-3 by ELISA in 586 men with total PSA (tPSA) between 4 and 10 ng/ml. Of these, 281 were diagnosed with prostate cancer and 305 were not. IGF-I, IGF-I density per unit prostate volume (IGFD), IGF-I/free PSA (fPSA) and IGFBP-3/fPSA were significantly higher in the prostate cancer cases than in the benign controls, whereas there were no differences between IGFBP-3 and IGFBP-3 per unit prostate volume (IGFBPD) levels. Mean IGF-I levels were 219 and 178 ng/ml (p= 0.001) and IGFBP-3, 2715 and 2694 ng/ml ($p = 0.32$) in cases and controls respectively. When corrected for free PSA, mean IGF-I/fPSA was 289.6 and 197.3 ng/ml (p 0.001) and IGFBP-3/fPSA 3691 and 3386 ng/ml (p 0.02) in the cases and controls respectively. The authors concluded that IGF-I/fPSA was a promising marker for ambiguous cases where tPSA levels were between 4 and 10 ng/ml.

44. Povelitsa and Nazarov (2008) measured IGF-I, IGFBP-3, total PSA and free PSA in plasma from patients with prostate cancer, BPHP or prostatic intraepithelial neoplasia at the Republican Centre for Research in radiation and Human Ecology at Gomel, Belarus. IGF-I levels were higher in all groups of patients than in control subjects (see Table 4). Levels of IGFBP-3 were slightly higher than controls in all groups of patient but the differences were not statistically significant.

Table 4: Plasma levels of IGF-I and IGFBP-3 in prostate patients (Povelitsa and Nazarov, 2008)

Group	**IGF-I (ng/mL)**	**IGFBP-3 (ng/mL)**
Controls	99.2 ± 34.4	5589 ± 260
Prostate cancer	119.2 ± 32.2	5553 ± 514
BHP	111.2 ±32.2	5421 ± 449
BHP + neoplasia	152.0 ± 51.4	5236 ± 827

Prospective studies and meta-analyses

45. A case-control study nested within the Physicians' Health Study cohort was conducted on prospectively collected plasma from 152 prostate cancer cases and 152 control subjects (Chan*, et al*., 1998a). The Physicians' Health Study was a randomised placebo-controlled trial of aspirin and β-carotene conducted amongst 22,071 US male physicians aged 40 to 84 years in 1982. Blood was collected in 1982 and subjects who had been diagnosed with prostate cancer by March 1992 were selected as cases. On average, 7 years elapsed between blood collection and diagnosis. Controls were selected at random from those in the Physicians cohort who had provided blood and had not been diagnosed with prostate cancer. There was a significant trend for increased relative risk with increased IGF-1 levels (p= 0.006 for unadjusted risk; p=0.001 when adjusted for IGF-II and IGFBP-3 levels). Men in the highest quartile of plasma IGF-I levels (293.76 ng/mL or more) had a relative risk (RR); 95% Confidence Intervals (CI) of 2.41;1.23-4.74 compared to men in the lowest quartile (184.8 ng/mL or less). The RR; 95% CI was 4.3;1.8-10.6 when adjusted for IGF-II and IGFBP-3.

46. In an update to the Physicians' Health Study, Chan, *et al*. (2002) conducted a further nested case-control study. Blood samples were originally provided in 1982, when the subjects were aged 40–84 years. By 31st December 1995, 786 incident cases of prostate cancer were diagnosed within the cohort of 14,916 men who had provided blood samples, and of these 530 had sufficient remaining plasma for analysis of IGF-I and IGFBP-3. One control subject was matched to each case patient on the basis of age and smoking status. Four people initially assigned as controls later became prostate cancer case patients, and an additional control subject was selected. Thus there was a total of 534 control subjects in the study. In the 379 new cases reported since the earlier study (see above), there was no association between IGF-I or IGFBP-3 and total prostate cancer risk, but with advanced-stage (Stages C and D) prostate cancer (n=93) there was a significantly

positive association for IGF-I (*p*=0.01) and a negative association with IGFBP-3 (*p*=0.02). There was no association between either IGF-I or IGFBP-3 for early-stage prostate cancer (Stages A and B). When both old and new cases were taken into account, comparison of the numbers of cases of advanced-stage prostate cancer (total number of cases = 142) in the first and fourth quartiles of IGF-I and IGFBP-3 levels gave RRs; 95%CI of 5.1; 2.0-13.3 and 0.2; 0.1-0.6, respectively, and the trends were statistically significant (*p*=0.002 for IGF-I and 0.01 for IGFBP-3) as shown in Table 5.

Table 5: RR (and 95% CI) of advanced-stage prostate cancer (n=142) associated with quartiles of IGF-I and IGFBP-3 in the Physician's Health Study (Chan, *et al*., 2002)

	Quartiles				P_{trend}
	1	**2**	**3**	**4**	
IGF-I	1.0 (referent)	3.2 (1.4-7.4)	3.5 (1.5-8.0)	5.1 (2.0-13.2)	0.002
IGFBP-3	1.0 (referent)	0.5 (0.2-1.0)	0.5 (0.2-1.2)	0.2 (0.1-0.6)	0.01

47. In the IGF-I system, the acid labile sub-unit (ALS) acts by binding circulating IGF-I in a ternary complex with IGFBP-3 to prevent IGF-I from crossing the endothelial cell barrier. In an update to Chan, *et al*. (2002), the relationship between ALS and IGF components was examined in 545 incident cases and 545 controls (Mucci *et al*., 2010). However, due to insufficient sample size, data on free IGF-I were obtained from only 538 matched pairs. Circulating ALS and free IGF-I were measured in the laboratory of one of the authors using an ELISA. Data on IGF-I and IGFBP-3 were included in the previous paper by Chan *et al*., 2002. Relative risks and 95% confidence intervals were calculated, adjusted for life-style factors and total IGF-I and IGFBP-3. ALS was positively associated with total IGF-I, IGFBP-3 and free IGF-I. Comparing highest vs lowest quartiles, there was no association between free IGF-I and prostate cancer risk (RR;95%CI, 0.9; 0.6-1.3). In contrast, ALS was positively associated with risk as below (RR; 94%CI), though this was not statistically significant:

	Quartiles				P_{trend}
	1	**2**	**3**	**4**	
ALS	1.0 (referent)	1.5 (1.0-2.3)	1.6 (1.1-2.5)	1.4 (0.9-2.1)	0.28

The association was stronger for advanced stage tumours (RR 2.0; 94%CI, 0.86-4.6); again this was not statistically significant. The authors considered that the lack of increase in the RRs for the quartiles suggested a threshold effect. Although there was no effect associated with IGF-I overall, men with low ALS had a 3.3 fold (95% CI 0.7-15.4) increased risk of advanced disease associated with higher free IGF-I.

48. A prospective study of IGF-I and several aging-related disorders, including prostate cancer, was performed in a sample of 765 men aged 60-91 at the start of the study (Schaefer, *et al*., 1998). The sample was randomly selected from 113,000 US health plan members (all ages; both sexes) who had undergone a health examination and had given blood in 1965 to 1970. Tumour registry data showed 45 cases of prostate cancer within the sample of 765 men diagnosed during 1971 to 1996. Mantel-Haenszel age-adjusted estimates of relative risk (RR)for the second to fourth quartiles of IGF-I concentrations as compared with the first quartile were, respectively, 0.62, 0.70 and 0.81, indicating that there was no association between serum concentrations of IGF-I and later onset of prostate cancer. The RR was recalculated using the upper quartile (≥ 293.76 ng/mL IGF-I) used in the Chan *et al*. (1998a) study, and the RR was slightly above 1. A second, separate analysis of the data compared the 45 cases with 179 age-matched controls selected from the sample of 765 men. Conditional logistic regression analysis confirmed the lack of association of IGF-I levels with prostate cancer rates.

49. In a letter, Chan, *et al*. (1998b) discussed the possible reasons for the difference between the findings of Chan, *et al*., (1998a) who found a positive association between serum IGF-I levels and prevalence of prostate cancer and those of Schaefer, *et al*. (1998) above, who found no association. The possible reasons suggested included lack of adjustment of the data for IGFBP-3 levels in the Schaefer study (Chan found a stronger association when the data were adjusted for IGFBP-3) and differences in the sample storage conditions and length of time the serum was stored before being analysed.

50. Harman, *et al.* (2000) reported the findings of a prospective cohort, case-control study, nested within the Baltimore Longitudinal Study on Aging (BLSA) population (a largely middle-class, 87% Caucasian, group who had been studied for over 40 years, with regular blood samples being taken). Participants of the BLSA who were diagnosed with prostate cancer between 1960 and 1997 were included in the study. The results for 72 prostate cancer cases (aged 64.8 ± 8.9 y) were compared with results from 137 controls (aged 65.7 ± 9.7y). Blood samples collected as near as possible to 10 years prior to diagnosis (approximately 9 years on average) were analysed for IGF-I, IGF-II, IGFBP-3 and PSA. The results showed high plasma IGF-I and low IGF-II to be independently associated with increased prostate cancer risk, but the association with high PSA was stronger. Adjusted (for age, date, date squared and co-variates {IGF-I, IGF-II, IGFBP-3 & PSA}) odds ratios; 95%CI for the high *vs* low tertile were 3.1;1.1-8.7 for IGF-I, 0.2; 0.07-0.6 for IGF-II, 0.71; 0.3-1.7 for IGFBP-3 and 12.5; 3.8-40.9 for PSA. For significant ORs, the estimated RR;95%CI for high vs low tertile was 2.03;1.08-2.95 for IGF-I, 0.31; 0.12-0.73 for IGF-II and 5.54; 2.92-7.62 for PSA.

51. Stattin, *et al*. (2000) reported the results of a prospective nested case-control study within the Northern Sweden Health and Disease Cohort Study. Blood had been collected from all people in the cohort on entry (from 1985 onwards – between 1 month and 10 years prior to diagnosis of prostate cancer). Between 1992 and March 1997, 166 men in the cohort were diagnosed with prostate cancer, and 149 of these (those with sufficient plasma remaining from their blood sample) were entered into the nested study. Plasma samples were analysed for IGF-I, IGFBP-1, IGFBP-2, IGFBP-3 and insulin. A control group of 298 men were randomly selected from the

cohort, with control men being matched to each subject on the basis of age, year of recruitment, and place of residence. The mean level of IGF-I was significantly (*p*=0.02) higher in men who later developed prostate cancer (229 ng/ml) than in controls (214 ng/ml). IGFBP-3 was also significantly higher (*p*=0.04) (2611 ng/ml) than in controls (2498 ng/ml). Men with elevated plasma levels of IGF-I or IGFBP-3 had an increased risk of prostate cancer (see Table 6). The association with IGF-I levels remained strong when the data for men under 59 years of age were analysed separately (n=30; *p*-value for trend = 0.01 for unadjusted and adjusted data), but the association with IGFBP-3 was not significant for this age group. Prostate cancer risk was not associated with levels of IGFBP-1, IGFBP-2 or insulin.

Table 6: Odds ratios (OR) of prostate cancer for quartiles of mean plasma concentrations of IGF-I and IGFBP-3 – unadjusted data and data adjusted for BMI and smoking (Stattin, *et al*., 2000)

	Quartiles				**p-value for trend**
	1	**2**	**3**	**4**	
IGF-I:					
Mean amount (ng/ml)	143.0	200.6	235.7	297.3	
OR (95% CI)	1.00 (referent)	0.89 (0.50-1.57)	1.48 (0.85-2.59)	1.57 (0.88-2.81)	0.02
Adjusted mean amount (ng/ml)	143.0	200.7	234.5	297.1	
Adjusted OR (95% CI)	1.00 (referent)	1.00 (0.56-1.78)	1.21 (0.66-2.20)	1.72 (0.93-3.19)	0.006
IGFBP-3:					
Mean amount (ng/ml)	1856	2365	2667	3250	
OR (95% CI)	1.00 (referent)	1.31 (0.74-2.31)	1.42 (0.80-2.52)	1.56 (0.86-2.83)	0.03
Adjusted mean amount (ng/ml)	1861	2363	2655	3233	
Adjusted OR (95% CI)	1.00 (referent)	1.49 (0.82-2.71)	1.70 (0.93-3.11)	1.83 (0.98-3.24)	0.007

52. Further analyses of these samples by Kaaks *et al*., (2003) explored the relationships between androgenicity (testosterone and SHGB) and IGF-I, IGFBP-3, insulin and leptin. Testosterone correlated with SHGB, whereas testosterone and SHGB correlated inversely with IGF-I, IGFBP-3, insulin, leptin and BMI. It was concluded that the lack of an association between plasma androgens and prostate risk (despite evidence suggesting a tumour stimulating effect) could reflect the more complex, mainly inverse, association between androgens and IGF-I, insulin and leptin, also implicated as risk factors for prostate cancer.

53. The Northern Sweden Health and Disease study was extended by Stattin *et al*., (2004). In this, IGF-I and IGFBP-3 were measured in pre-diagnostic blood samples from 281 men who were subsequently diagnosed with prostate cancer a median of 5 years after sampling and 560 matched controls. Logistic regression analysis showed an increase in prostate cancer risk with increasing plasma IGF-I levels (OR; 95%CI; highest vs lowest quartile (1.67; 1.02-2.71) P_{trend} 0.05). This was reduced by adjustment for IGFBP-3 to an OR of 1.47; 0.81-2.64. For men aged >59 years at recruitment the OR; 95%CI (highest vs lowest quartile) was 4.12; 1.01-16.70) P_{trend} 0.002 which was significantly stronger than for men older than 59 years $P_{interaction}$ = 0.006. For men with advanced cancer, the OR; 95%CI (highest vs lowest quartile) was 2.87; 1.01-8.12, P_{trend} 0.10). Plasma levels of IGF-I were significantly higher in cases than controls (218 and 208 ng/ml respectively) as were IGFBP-3 levels (2,442 and 2,360 ng/ml). When discussing the differences in the results for IGFBP-3 between studies it was noted that the commercial ELISA (made by DSL and used in a number of studies) mostly measured specific intact forms of IGFBP-3 whereas the DSL radioimmunometric assay, used by the authors, might detect more or different forms combined.

54. A meta-analysis was performed by Shi, *et al*. (2001). The 14 studies included in the meta-analysis were those reported in: Baffa, *et al*., 2000; Chan, *et al*., 1998a, Cohen, *et al*., 1993; Djavan, *et al*., 1999; Finne, *et al*., 2000; Harman, *et al*., 2000; Ho and Baxter, 1997; Kanety, *et al*., 1993; Khosravi, *et al*., 2001; Kurek, *et al*., 2000; Mantzoros, *et al*., 1997; Signorello, *et al*., 1999; Statin, *et al*., 2000; Wolk, *et al*., 1998. The mean and standard deviation of the levels of IGF-I were reported in only 12 of the reports, but data on IGF-I and IGFBP-3 were obtained directly from the authors of the other two studies (Chan, *et al*., 1998a; Harman, *et al*., 2000). Hedges' standardised mean difference (HSMD) and odds ratio (OR) were used to estimate the effect of circulating levels IGF-I and IGFBP-3 on prostate cancer risk. The combined data showed that IGF-I levels were significantly higher in prostate cancer patients than in controls (HSMD = 0.194). The OR;95% CI for prostate cancer was 1.47;1.23-1.77 among men with high IGF-I compared to those with low IGF-I. The OR was 1.26;1.03-1.54 for IGFBP-3. The authors concluded that circulating levels of IGF-I and IGFBP-3 were likely to be elevated in prostate cancer patients.

55. The association between IGF-I and IGFBP-3 levels and increased risk of prostate cancer was investigated in a case control study nested in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study (ATBC) in which smokers were given alpha tocopherol and/or beta-carotene or placebo as a chemopreventative measure (Woodson *et al*., 2003). The study included 100 incident prostate cancer cases, diagnosed at least 5y after baseline blood draw (range 5-12, median 9 years) and 400 matched controls. The association was assessed by conditional logistic regression analysis but no association was found between IGF-I and IGFBP-3 and prostate cancer risk. In a multi-variate analysis an OR; 95%CI of 0.52;0.23-1.16 for the fourth vs first quartile of serum IGF-I was determined. The model was adjusted for age, BMI, intervention group, and serum IGF or IGFBP-3 level. Within the same cohort, a sequential study was conducted among different cases and controls (21 of each) who had serial blood samples available (2-5y before diagnosis and within 1y of diagnosis for the cases). Serum IGF-I but not IGFBP-3 increased significantly over

time in cases but not in controls. The authors suggested that IGF-I was possibly serving as a tumour marker rather than an etiological factor.

56. Renehan, *et al*. (2004) performed a meta-analysis as part of a systematic review of the associations of circulating concentrations of IGF-I and of IGFBP-3 with the risks of cancers of the prostate, colorectum, pre-menopausal breast, post-menopausal breast and lung. Databases were searched for epidemiological studies published between January 1996 and December 2002. Six studies were evaluated (Chan, *et al*., 1998; Wolk, *et al*., 1998; Harman, *et al*., 2000; Stattin, *et al*., 2000; Finne, *et al*., 2000; Chokkalingam, *et al*., 2001). High concentrations of IGF-1 were associated with an increased risk of prostate cancer (comparing 75th with 25th percentile, OR; 95% CI =1.49; 1.14-1.95). On considering the association of IGFBP-3 with prostate cancer risk in three of the studies (Wolk, *et al*., 1998; Stattin, *et al*., 2000; Chokkalingam, *et al*., 2001), there was an overall odds ratio of 0.95; 0.70-1.28, comparing the highest and lowest categories of IGF-I exposure (eg quartiles or quintiles) used in each study. Dose-response analysis of the results from the three appropriate studies (Wolk, *et al*., 1998; Stattin, *et al*., 2000; Chokkalingam, *et al*., 2001) showed a positive trend (p = 0.003) for increased prostate cancer risk with increasing levels of IGF-I with an odds ratio comparing 75th with 25th percentile of 1.49; 1.14-1.95). The authors concluded that high circulating levels of IGF-I were associated with an increased risk of prostate cancer.

57. A nested case control study was conducted as part of a cohort involved in a study on the impact of screening (Janssen *et al*., 2004). A total of 4,133 men underwent a first round of screening, with 2,385 of the participants undertaking a second round of screening a mean of 4 years later. At this second screening, 201 prostate cancer cases were detected in men aged 55-70 and were then matched with 201 non-cancer controls by age, PSA level at first round screening and residence area. There were no differences in the baseline levels of total IGF-I, free IGF-I or IGFBP-3, whereas PSA velocity was significantly different. Total IGF-I was 17.5 and 17.72 nmol/L (133.9 and 135.6 ng/ml) in the cases and controls respectively, with free IGF-I being 92.9 and 93.1 pmol/L (710.7 and 712.2 pg/ml) and IGFBP-3 being 125.5 and 128.4 nmol/L respectively (equivalent to 3488.9 and 3556.7 ng/ml)[2]. In addition, when stratified by prostate volume, the levels of total IGF-I, free IGF-I and IGFBP-3 were not significantly different between cases and controls.

58. A nested case control study was conducted amongst the Cardiovascular Health Study cohort by Chen *et al.,* (2005). A total of 5,888 US men were enrolled in the study, which was designed primarily to investigate coronary heart disease and stroke between 1989 and 1993. Participants completed up to 10 annual clinic examinations until 1998-1999. Blood samples, medical history and demographic data were collected during these examinations; the men were aged 65- ≥80 y at the time of blood sampling. IGF-I, IGFBP-3 and insulin levels were measured in 174 men who were diagnosed with prostate cancer between 1990 and 1998, 1-9 years (mean 3.4) after the blood samples were taken and in 174 controls, free of prostate cancer who were matched for age, ethnicity, year of entry into the study and year of blood

[2] The molecular weight of IGFBP-3 depends on glycosylation so this conversion should b treated as approximate.

sampling. IGF-I levels were not associated with an increased risk of prostate cancer (RR;95%CI, 0.67 ;0.37-1.25 for the lowest vs highest quartile). The results were not altered by adjustment for IGBP-3 levels or by assessing IGF-I/IGFBP-3 ratios. A sub-group analysis among men with a PSA level of less than 4 ng/ml did not reveal any association. For IGFBP-3, the relative risks were 0.65; 0.35-1.20 suggesting a modest decease in risk with increasing IGFBP-3 level. Mean (± SD) IGF-I levels were 157.7 ± 94.5 ng/ml in the cases and 163.2 ± 77.7 ng/ml in the controls, with mean IGFBP-3 levels being 3101± 924 ng/ml in the cases and 3210 ± 843 ng/ml in the controls.

59. Meyer *et al*., (2005) reported a nested case control study conducted amongst the SU. VI. MAX cohort. The *S*U. VI. MAX study is a population based, double blind placebo controlled study design to assess whether supplementation with anti-oxidant vitamins and minerals could reduce the incidence of cancer and ischaemic heart disease in middle aged men and women. 100 prostate cancer cases were identified from the cohort (n= 4855 at baseline) during the 9 year follow up period and were matched by age with 4 controls; the volunteers were aged 45-60 at recruitment (Hercberg *et al*., 2004). After controlling for the intervention group in the trial and the other IGF-I axis variables, the OR;95%CIs for the upper vs lower quartile were 1.83; 0.85-3.95, 1.05; 0.35-3.18, 0.79;0.39-1.58 and 0.42; 0.12-1.52 for IGF-I, IGF-II, IGFBP-2 and IGFBP-3 respectively and were not significant. More suggestive associations were observed with advanced and aggressive cancers.

60. Platz *et al*., (2005) reported a case control study nested in the Health Professionals Follow-up Study. At enrolment, the study consisted of 51,529 US men aged 40-75, at baseline and biennially thereafter the participants responded to a questionnaire on demographics, medical history and lifestyle. Every 4 years a semi-quantitative food frequency questionnaire was completed. Between 1993 and 1995, 18, 018 of the men provided a blood sample. 462 prostate cancer cases were diagnosed between blood sampling in 1993 but before 1998. The controls were 462 age-matched men who had had a PSA test after providing a blood sample. Plasma IGF-I and IGBFP-3 were measured by ELISA. Conditional logistic regression was used to estimate odds ratios and 95% confidence intervals. Men with higher levels of IGF-I (lowest vs highest quartile OR; 95% = 1.37; 0.92-2.03, *p* trend = 0.05) and IGFBP-3 (1.62; CI 1.07-2.46, *p* trend = 0.08) had an increased risk of prostate cancer. After mutual statistical adjustment, the associations were reduced for both IGF-I (1.17; 0.69-1.99, *p* trend = 0.29) and IGFBP-3 (1.40; CI 0.80-2.44, *p* trend = 0.56). The levels of IGF-I measured were 181 and 173 ng/ml and IGFBP-3, 3003 and 2905 ng/ml in cases and controls respectively. No significant association was found between IGF-I and regionally invasive or metastatic cancer, although the number of cases was small. The authors concluded that the IGF-I and IGFBP-3 were not strongly linked to the risk of prostate cancer in the PSA era (ie when diagnosis occurred through elevated PSA levels rather than other ways) but this did not preclude the possibility that the IGF-I axis influences the early to late stage transition.

61. In an extension to the study by Platz *et al*., (2005), Nimptsch *et al*., (2010) reported the results of a nested case control study of 1,331 matched pairs identified during an additional follow up period from 1998-2004. The number of identified pairs also allowed the investigation of high and low grade cancer separately. Matched ORs and 95% confidence intervals were estimated using conditional logistic

regression. For total prostate cancer (top vs bottom quartile) the OR; 95%CIs were 1.41;1.12-1.78, *p* trend = 0.001for IGF-I and 1.58; 1.24-2.01, *p* trend = 0.003 for IGFBP-3. IGF-I was more strongly associated with low grade (top vs bottom quartile, OR; 95%CI, 1.61;1.16-2.25 *p* trend = 0.01) than with high grade 1.29; 0.89-1.88 *p* trend = 0.12) prostate cancer (*p* heterogeneity = 0.08). The authors suggested that high grade cancers were more autonomous, and, thus less sensitive to the action of IGF-I than low grade cancers. Mean plasma levels of both IGF-I and IGFBP-3 were statistically significantly higher in the cases than in the controls: 205 and 197 ng/ml for IGF-I (*p* = 0.0001) and 3632.6 ng/ml and 3536.9 (*p* = 0.001) for IGFPB-3 respectively. After mutual adjustment, the levels remained higher in the cases than the controls but a statistically significant difference persisted only for IGF-I. Compared with the matched controls, mean IGF-I was significantly higher in low grade but not high grade prostate cancer cases. IGFBP-3 after adjustment for IGF-I was not significantly different in either grade. A stronger association between IGF-I and prostate cancer was observed in men who had a family history of the disease, thought it was noted that there was not yet a biologically plausible explanation for this finding.

62. Morris *et al*., 2006 conducted a nested case control study amongst the BUPA cohort. The study was based on 21,520 professional men who attended the BUPA medical centre between 1975 and 1982 for routine screening when serum samples were taken. 141 cases or prostate cancer were identified during 15 years of follow up and matched with 423 controls. IGF-I, IGF-2 and IGFBP-3 were measured but were not associated with an increased risk of prostate cancer. The adjusted OR; 95%CIs for top vs bottom quartiles were 1.37; 0.76-2.49 *p* = 0.62, 1.47; 0.77-2.81 *p* = 0.19 and 1.40; 0.77-2.55, *p* = 0.42 for IGF-I, IGF-2 and IGFBP-3 respectively. Median concentrations of IGF-I were 122 and 124 ng/ml in the cases and controls, median IGF-2 levels were 639 and 636 ng/ml and median IGFBP-3 3200 and 3200 ng/ml respectively.

63. The results of the study by Morris *et al*., 2006 were included in a meta-analysis which also included data from the studies by Platz *et al*., 2005; Chen *et al*., 2005; Stattin *et al*., 2004; Meyer *et al*., 2005; Chan *et al*., 1998; Harman *et al*., 2000; Woodson *et al*., 2003 and Lacey *et al*., 2001. The OR; 95%CI of developing prostate cancer for highest vs lowest quartile of IGF-I was 1.31;1.03-1.67, a modest but statistically significant association. There was no significant heterogeneity between studies. There was no association between risk of prostate cancer and IGF-2 (0.72; 0.36-1.44) or IGFBP-3 levels (1.05; 0.82-1.35).

64. A nested case-control study was conducted among the Melbourne Collaborative Cohort study (Severi *et al*., 2006); a cohort of 41,528 individuals (17,049 men) aged 27-75 at recruitment. 524 cases of prostate cancer were diagnosed during a mean of 8.7 years follow up and these were matched with a randomly sampled sub-cohort of 1826 men. The random sub-cohort had a smaller proportion of older men compared to the cases, but other potential confounders (BMI, smoking, alcohol intake) were comparable. The association between the level of each peptide and prostate cancer risk was tested using Cox models adjusted for country of birth and alcohol consumption. The risk of prostate cancer was not associated with IGF-I or the molar ratio IGF-I/IGFBP-3 l (all ORs between 0.82 and

1.08; $p_{trend} \geq 0.2$). However, the risk increased with baseline levels of IGFBP-3 ($p_{trend} \geq 0.008$), the hazard ratio; 95%CI associated with a doubling of the IGFBP-3 concentration being 1.70;1.15-2.52. The HR for highest vs lowest quartile was 1.49;1.11-2.00. The hazard ratios did not differ by tumour aggressiveness or age at onset.

65. In a nested case control study conducted amongst the EPIC cohort, 630 incident prostate cancer cases were matched with 630 controls (Allen *et al*., 2007). The EPIC cohort includes 150,000 men across Europe with samples and information being collected between 1991 and 2001; cases were selected from men who had developed prostate cancer after recruitment into the study but before the end date, with the median time between blood collection and diagnosis being 3.4 years. The risk; 95%CI of total prostate cancer in the highest versus the lowest third of serum peptide concentration was 1.35; 0.99-1.28; $P_{trend} = 0.08$ for IGF-I and 1.39;1.02-1.89); $P_{trend} = 0.12$ for IGF-I adjusted for IGFBP-3. The risks for IGFBP-3 (top vs bottom third) were 1.22; 0.92-1.64; $P_{trend} = 0.38$ and 1.35; 0.74-1.37; $P_{trend} = 0.75$ for IGFBP-3 adjusted for IGF-I. There was no significant association between the levels of peptide hormones and stage of disease, although the association of IGF-I concentration was slightly higher for advanced-stage disease (1.65; 0.88-3.08; $P_{trend} = 0.21$ for IGF-I and 1.76; 0.92-3.40; $P_{trend} = 0.11$ for IGF-I adjusted for IGFBP-3). The authors concluded that IGF-I was not strongly associated with prostate cancer risk although the results were compatible with a small increase in risk, particularly for advanced –stage disease. No association between IGFBP-3 and prostate cancer risk was observed.

66. A nested case control study was conducted as part of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, a two-armed randomized trial designed to investigate the efficacy of screening and to investigate etiologic factors and early markers of cancer (Weiss *et al*., 2007). In this study 28,243 men were randomised to the screening arm of the study and included in the analytical cohort. A total of 727 incident cancer cases and 887 matched controls were identified; these men were described as non-Hispanic black or non-Hispanic white with other ethnic backgrounds being excluded. There was no clear overall association between IGF-I, IGFBP-3 or IGF-I:IGFBP-3 molar ratio and prostate cancer risk. However, when stratified by BMI, the molar ratio was associated with risk in obese men (BMI>30, *p* trend = 0.04) with a greater than 2-fold increased risk in the highest molar ratio quartile compared to the lowest (OR;95%CI, 2.34; 1.1-5.01). Risk was specifically increased for aggressive disease in obese men (2.80; 1.11-7.08). A number of factors were evaluated for inclusion in the conditional logistic analysis model, including BMI, family history, height , diabetes, physical activity, smoking and nutrient intake, but were not included in the final model as they did not affect risk estimates by 10% or more. When analysed by date of diagnosis, there was no difference between men diagnosed 1-2y after blood draw and those diagnosed 3-7y later. The authors suggested that the results could be due to increased levels of oestradiol and cytokines produced in peripheral adipose tissue by men with a high IGF-I:IGFBP3 molar ratio. The mitogenic and anti-apoptotic effect of IGF-I then interacting with the proliferative effects of excess oestradiol and cytokines resulting in tumour growth.

67. Borugian *et al*., 2008 conducted an extension to a case control study (Kolonel *et al*., 1995) which had been conducted amongst a multi-ethnic (Black, Asian or White) group of US and Canadian men. The men were recruited and blood samples taken in 1990-1992, cases were matched to controls by age, region and ethnicity. In the extended study, IGF-I and IGFBP-3 were measured in the serum of 96 cases (where prostate cancer occurred 1 year or more after blood sampling) and were matched with 4 controls. There was no association between pre-diagnostic IGF-I levels and prostate cancer risk (OR;95%CI,1.26 ; 0.66-2.41) for highest vs lowest quartile for all men. There were also no statistically significant case-control differences between IGF-I levels or IGFBP-3 levels for any ethnic group or between ethnic groups. Pre-diagnostic IGFBP-3 levels were positively associated with risk among Black men; however although levels were elevated in the second and third quartiles compared to the lowest quartile, they were not elevated in the highest quartile. The interaction between IGFBP-3 levels and ethnicity was not statistically significant. No association was observed for IGF-I or IGFBP-3 levels or the IGF to IGFBP-3 ratio and prostate cancer risk and mutual adjustment did not alter the results. It was noted that although there was no association with ethnicity, the numbers involved were small. The mean levels of IGF-I were 236 and 228 ng/ ml in Black cases and controls, 240 and 228 ng/ml in White cases and controls and 231 and 226 ng/ml in Asian cases and controls. The concentrations of IGFBP-3 were 3725 and 3688, 4027 and 3911, and 3670 and 3772 ng/ml in Black, White and Asian cases and controls respectively.

68. Roddam *et al*., (2008) performed a re-analysis of data on 3700 cases and 5200 controls from 12 studies. The studies were Harman et al., 2000; Lacey *et al*., 2001; Allen *et al*., 2007; Janssen *et al*., 2004; Platz *et al*., 2005; Schaefer *et al*.,1998; Severi *et al*., 2006; Stattin *et al*., 2000; Stattin *et al*., 2004; Chan *et al*., 1998; Chan *et al*., 2002; Oliver *et al*., 2004 and Meyer *et al*., 2005. On average, the 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 level, the greater the subsequent risk of prostate cancer (odds ratio; 95% CI in the highest vs lowest quintile 1.38;1.19-1.60, *P* for trend <0.001). Neither IGF-II nor IGFBP-2 concentrations were associated with risk, but statistical power was limited. IGF-I and IGFBP-3 were correlated (r = 0.58) and although IGFBP-3 seemed to be correlated with prostate cancer risk, this was secondary to its association with IGF-I levels. IGF-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, PSA level at recruitment, BMI, smoking or alcohol intake. It was noted that the concentrations of the growth factors were measured in only 1 sample for each participant and that the methods used to measure IGFs differed in each study.

69. A separate meta-analysis was conducted by Rowlands *et al*., (2009) on IGF-I, IGF-II, IGFBP-1, IGFBP-2, IGFBP-3 and IGF-I: IGFBP-3 ratio. For IGF-I the meta-analysis included 7481 cases and data from 14 prospective studies (Chan *et al*.,1998; Schaefer *et al*.,1998; Harman *et al*.,2000: Lacey *et al*.,200; Woodson *et al*.,2003; Janssen *et al*.,2004; Stattin *et al*.,2004; Chen *et al*.,2005; Meyer *et al*.,2005; Platz *et al*.,2005; Morris *et al*.,2006; Severi *et al*.,2006; Allen *et al*.,2007; Weiss *et al*.,2007) and 20 retrospective studies (Cohen *et al*., 1993;Kanety *et al*.,

1993; Mantzoros *et al*., 1997; Wolk *et al*., 1998; Cutting *et al*., 1999; Djavan *et al*., 1999; Baffa *et al*., 2000; Finne *et al*., 2000; Hill *et al*., 2000; Koliakos *et al*., 2000; Kurek *et al*., 2000; Chokkalingam *et al*., 2001; Khosravi *et al*., 2001; Ismail *et al*., 2002; Peng *et al*., 2000; Shariat *et al*., 2002; LI *et al*., 2003; Miyata *et al*., 2003; Scorilas *et al*., 2003; Aksoy *et al*., 2004; Lopez *et al*., 2004; Oliver *et al*., 2004; Trapeznikova *et al*., 2004; Kehinde *et al*., 2005; Marszalek *et al*., 2005; Nam *et al*., 2005; Hernandez *et al*., 2007; Zhigang *et al*., 2007). Overall (prospective and retrospective studies combined), the pooled random effects OR; 95 %CI per standard deviation increase in exposure were IGF-I OR; 95%CI = 1.21; 1.07-1.36, *p* =0.003; IGF-II, 1.17;0.93-1.47)*p* =0.18; IGFBP-I 1.21; 0.62-2.33 *p* =0.58; IGFBP-2 1.18; 0.90-1.54 *p* =0.24; IGFBP-3 0.88; 0.79-0.98 *p* =0.02; IGF-I:IGFBP-3 ratio, 1.10; 0.97-1.24 *p* =0.12. In the studies that presented both unadjusted and fully adjusted effect estimates, pooled analysis indicated that adjustment for potential confounding factors, including mutual adjustment for IGF-I and IGFBP-3 did not affect the overall OR for IGF-I with the unadjusted OR for IGF-I being 1.14; 1.05-1.25 and the adjusted OR = 1.17;1.04-1.31. Adjustment for IGF-I did shift the overall summary for IGFBP-3 from the unadjusted model being associated with increased risk OR = 1.04; 0.95-1.13 to the adjusted model being associated with a slight decreased risk, OR = 0.95; 0.85-1.06 however confidence intervals for both of these estimates include an OR of 1. Retrospective studies provided consistently stronger associations than prospective studies for all peptides investigated. IGF-I showed generally stronger associations with more aggressive and advanced cancers compared to non-aggressive and localised ones, but the statistical evidence was weak, a similar but opposite pattern was seen for IGFBP-3. Considerable heterogeneity was apparent even when considering only prospective studies. The reason for the heterogeneity was uncertain. In summary, it was concluded that the body of literature was consistent with an average 21% increased risk of prostate cancer per standard deviation increase in IGF-I and an average 12% reduced risk of prostate cancer per standard deviation increase in IGFBP-3. It was pointed out that although modest, the association was likely to be aetiologically important as it was of a similar magnitude to those for the risk factors for ischaemic heart disease risk factors such as diastolic blood pressure and total cholesterol. When discussing possible mechanisms, it was suggested that men with a higher concentration of IGF-I and/or lower levels of IGFBP-3 might have higher IGF-I bioactivity which could contribute to carcinogenesis and neoplastic progression via mechanism such as enhancing the survival of partially transformed cells, increasing the pool of cells available for subsequent hits and full transformation. It was also suggested that the association between IGF-I and IGFBP-3 and more advanced disease suggested that the IGF system played more of a role in cancer progression than induction. When discussing the reasons for the heterogeneity, it was pointed out that IGFBP-3 existed as both intact and fragmented forms in the blood, each of which may be present with multiple additional post-translational modifications. These differential forms could have complex and differential actions both dependent and independent of IGF-I with both positive and negative effects on cancer cells. Which of the form was measured in any particular assay was not well defined, and it is possible that different assays were measuring different peptides, increasing heterogeneity. IGF-I assays required a separation step to avoid the interference of IGFBPs and the efficiency of such steps varied considerably between assays and could be operator-dependent. Long term storage of IGF-I peptides in serum samples could be stable, but has also been observed to result in 3-4 fold variations in measured IGF-I levels in some assays - this was likely

to be more of an issue for the large prospective studies, particularly where there were multiple sites involved.

70. In a case-control study nested in the EPIC cohort, 1,542 incident prostate cases were matched to 1,542 controls by study centre, age at recruitment, duration of follow-up, time of day and duration of fasting at blood collection (Price *et al*., 2012). Conditional logistic regression models were used to calculate risk for prostate cancer association with IGF-I concentrations. Circulating IGF-I concentration was associated with a significantly increased risk for prostate cancer (OR;95%CI highest vs lowest quartile, 1.69; 1.35-2.13, $p_{\text{trend}} = 0.0002$). The positive association did not differ according to duration of follow up with ORs for highest vs lowest quartiles being 2.01; 1.35-2.99, 1.37; 0.94-2.00 and 1.80; 1.17-2.22 for cancers diagnosed <4, 4-7 and >7 years after blood collection respectively ($p_{\text{heterogeneity}} = 0.77$) or by stage, grade and age at diagnosis or age at blood collection (all sub-groups $p_{\text{heterogeneity}} = > 0.05$). No further details are available at present.

Summary and Discussion

71. Prostate cancer is the most common cancer in UK men. There are a number of risk factors associated with the condition including lifestyle and dietary factors as well as factors such as age, race, family history and genetic susceptibility. However, the specific genetic variants that might increase or decrease susceptibility are currently unknown.

72. A number of retrospective case control studies have been conducted, many with a view to improving prostate screening since the IGF-I can be produced by tumours. The results are inconsistent, with many studies reporting no difference in IGF-I levels between prostate cancer cases and controls but a similar number reporting elevated IGF-I levels in prostate cancer cases compared to controls. The results for IGFBP-3 are similarly varied with increases, decreases but most usually no differences being reported. The reasons for the differing results are uncertain and may be due to confounding by a number of factors. Many of the studies involve small numbers of participants with disease of varying degrees of severity (however, some authors (Oliver *et al*., 2004a) noted that the majority of IGF-I is produced hepatically so any contribution from tumours would be modest). There is generally little information on ethnicity or lifestyle factors and the controls were sometime patients with BPH rather than participants with normal prostate histology. It is unclear whether adjusting IGF-I for IGFBP-3 would have affected the results or not. In general it has been concluded that IGF-I has limited use as a diagnostic tool, but could be more useful in conjunction with PSA.

73. Where prospective studies have been conducted, the results are similarly variable, with around half of the studies reporting no association and the other half a positive association. It has been noted by several authors that the size of the positive associations tends to be smaller than in the retrospective studies. This could be due to the effects of adjusting for confounding variables. In the two largest studies (Nimptsch *et al*., 2010; Price *et al.,* 2012) higher levels of IGF-I are associated with a modest increase in risk of prostate cancer, though in the former study this was only

for low grade prostate cancer. The results of studies analysing the association between IGF-I levels and cancer stage and/or severity also appear to be inconsistent.

74. A total of five meta-analyses have been performed on the available data and all have reported a positive association between IGF-I levels and the risk of prostate cancer. In the analysis by Renehan *et al*., (2004) it was reported that dose response analysis of the three studies where this was possible indicated a positive trend. Significant heterogeneity has been noted among the studies and one of the reasons for this may be variations in assay methods between different studies both for sample storage and preparation and for analysis. Limited information on ethnicity is generally available and as it is known that certain ethnic groups have higher rates of prostate cancer this may also explain both the differences between individual studies and the heterogeneity in meta-analyses where this information was not adjusted for.

75. The results for the other peptides such as IGFBP-3 are more variable, but with the majority of studies, including the meta-analyses not reporting any significant associations.

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