Insulin-Like Growth Factor and Prostate Cancer Risk

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Abstract— Insulin-like growth factors (IGF-I, IGF-II) and their binding proteins (IGFBP-1–6) important role in cell proliferation, differentiation and apoptosis, suggesting possible involvement in carcinogenesis. Several epidemiological studies show the associations of IGFs with prostate cancer .We searched the published literature for all studies related with the levels of IGFs with prostate cancer. We performed random effects meta-analysis to calculate the summary odd ratios. The number of studies (prostate cancer cases) included in each meta-analysis were 42 (7,481) IGF-I; 10 (923) IGF-II; 3 (485) IGFBP-1; 5 (577) IGFBP-2; 29 (6,541) IGFBP-3 and 11 (3,545) IGF-1: IGFBP-3 ratio. The pooled odds ratios (95%confidence intervals) per standard deviation increase in peptide were: IGF-I, OR 5 1.21 (1.07, 1.36); IGF-II, OR 5 1.17(0.93,1.47) IGFBP-1, OR 5 1.21 (0.62, 2.33); IGFBP-2, OR 5 1.18 (0.90, 1.54); IGFBP-3, OR 5 0.88 (0.79, 0.98); IGFI:IGFBP-3 ratio, OR 5 1.10 (0.97, 1.24).There was weak evidence that associations of the IGF-I and IGFBP-3 with prostate cancer were stronger for the advanced disease. Our meta-analysis confirms that the raised circulating lGF-I is positively associated with prostate cancer risk.

Index Terms— prostate cancer,insulin-like growth factor; insulin-like growth factor binding protein, meta-analysis.

I. INTRODUCTION

Insulin-like growth factors (IGF-I and IGF-II) and their binding proteins (IGFBP-1–6) play a key role in cell proliferation, differentiation and apoptosis, in many tissues including the prostate. These processes are all involved in malignant transformation, and components of the IGF system may therefore be involved in the etiology and/or progression of prostate cancer.1Several epidemiological studies show positive associations of IGF levels with prostate cancer risk, but the results are inconsistent (1). A recently published analysis based on individual patient data from 12 prospective studies (n 5 3,700 prostate cancer cases)found an increased risk in the highest compared to the lowest quintiles of both IGF-I and IGFBP-3 (IGF-I odds ratio 5 1.38,96% confidence interval: 1.19,1.60; IGFBP-3 OR 1.23, 95% CI:1.06,1.43), although the risk associated with IGFBP-3 was abolished in models controlling for IGF-I.2 The authors found no association with IGF-II or IGFBP-2. Another meta-analysis of 9 prospective studies,3 which included 1,512 men with prostate cancer, found an increased risk associated with the highest compared to the lowest quartile of IGF-I (OR 5 1.31, 95% CI: 1.03,1.71), but no association of IGF-II or IGFBP-3. This association with IGF-Was weaker than that reported in an earlier meta-analysis published in 2004, 4 and based on 904 cases (OR 5 1.83, 95% CI:1.03,3.26) (2) .We performed a systematic review of studies reporting for sonication of IGFs and IGFBPs with the risk of prostate cancer. Unlike previous meta-analyses, we included retrospective and prospective studies. We have investigated several potential sources of heterogeneity, including separate analyses of prostate cancer by stage, grade and aggressiveness, and studied additional exposures not previously examined in meta-analyses of retrospective and prospective studies, including IGFBP-1. This review is the largest to date to assemble the published literature on the role of the IGF system in the etiology of prostate cancer (3).

Insulin-like growth factors (IGF) I and I1 are two peptides which have been isolated originally from a

Cohn fraction of human serum. The designation IGF has been proposed to stress the fact that they showed myogenic effects at concentrations in the Nano molar range in vitro, that they also exhibited insulin-like effects in adipose and muscle tissue and that their structure was homologous to that of (pro)insulin IGF I and I1 are also known as somatomedins.

The original observation was made by Salmon and Dough a day that pituitary growth hormone (GH) in vitro did not correct the defect in the synthesis of matrix proteins of hypophysec-tomized rats, whereas the serum of GH-treated hypophysec-tomized rats did. This has led to the so-called somatomedin hypothesis which states that GH acts on skeletal tissues by inducing the formation of a growth factor (= somatomedin) circulating in the blood and acting on the peripheral tissue. The subsequent isolation and amino acid sequence determination of somatomedin C and A has shown their identity with IGF I. The use of the two designations somatomedin and IGF I as synonyms is now generally accepted .However to equate IGF I1 with somatomedin is, at least at the present time, not justified because the formation of IGF I1 is under less stringent control of GH than that of IGF I, and because the physiological role of IGF I1 is far from clear. The literature on IGF has in recent years become so vast that the attempt to cover the entire field risks exceeding the competence of a single author and the length constraints of review papers in this journal. By necessity, therefore, this review cannot be comprehensive (4).

Certain topics will be treated in more detail than others, reflecting the partiality of the author.

Particularly, a certain bias towards the significance of IGF in man and against the application of IGF in animal husbandry could not be overcome. Some excellent reviews with emphasis on particular topics have been published recently.

II. MATERIAL &METHOD

Data Source

Clozapine is antipsychotic mediation which is mostly used in patients with treatment resistant schizophrenia and against the negative symptoms .In it the clinical response of 84 schizophrenic patients were examined, previous antipsychotic medication had been withdrawn, and patient were treated with clozapine according to standardization titration, we also observe the adverse effects, extrapyramidal symptoms , baseline pathology and literature of reviews. After all, these variables may have important for the use if clozapine and our understanding of the pathophysiology if treatment resistant – schizophrenias.

We conducted a systematic search of all published papers, letters, abstracts and review articles on the association of insulin-like growth factors and measures of insulin resistance with prostate cancer. We searched the Medline (1966–2007), Embassy (1980–2007) and Web of Science (1900–2007) bibliographic databases up to April 2007, using a combined text word and MESH heading search strategy (see Supp. Info.). The search was repeated on weekly basis to identify any newly published studies up to December 2007. We also searched the reference lists from relevant articles and review articles and previously published meta-analyses on the subject.2–5 Titles and abstracts were assessed using prespecified inclusion criteria (see below). When abstracts were not available, the full papers were obtained and assessed. Full papers of all studies that were not clearly ineligible were obtained, and two assessors (M-AR, RMM) independently reviewed all of these papers for inclusion. We identified duplicate publications by reviewing study name, authors, location, study population, dates and study designed. Where studies appeared to be published more than once, we took the most recent publication or the publication that contained the most cases. If results were updated but did not include all previous exposures, we took the most recent publication that included that exposure (5).

Inclusion and Exclusion Criteria

Clozapine is antipsychotic mediation which is mostly used in patients with treatment resistant schizophrenia and against the negative symptoms .In it the clinical response of 84 schizophrenic patients were examined, previous antipsychotic medication had been withdrawn, and patient were treated with clozapine according to standardization titration, we also observe the adverse effects, extrapyramidal symptoms , baseline pathology and literature of reviews. After all, these variables may have important for the use if clozapine and our understanding of the pathophysiology if treatment resistant – schizophrenia's

In this, we included all studies reporting blood levels of at least one of the following peptides: IGF-I, IGF-II, IGFBP-I, IGFBP-2, IGFBP-3, IGF-I: IGFBP-3 ratio (an indicator of biologically available IGF-I6)—and reporting prostate cancer incidence or prevalence. To be included, studies had to present categories of peptide concentrations or the mean or median and standard deviation of the peptide in prostate cancer case and control groups. We did not apply any language restrictions (6).We included population based studies, whether retrospective or prospective. We excluded case reports, animal or in vitro studies and research published as a Additional Supporting Information may be found in the online version of this article. Inference abstract only. We excluded one paper where the age ranges of cases and controls did not overlap, because of the strong association of age with both IGF levels and prostate cancer (7).

Data Extraction

Two investigators (M-AR, RMM or DG) extracted data from each paper independently using a standardized data extraction form. Data were extracted on study design, laboratory procedures, potential sources of heterogeneity (age of participants, date study conducted, inclusion of screen-detected cases, control group used (men with benign prostatic hyperplasia, healthy men, or a mixture of the two, and whether controls were selected from the general population or a hospital)), confounding factors controlled for and results from unadjusted, adjusted but excluding adjustment for one of the other peptides, and fully adjusted (including adjustment for one of the other peptides) models. Where studies included separate healthy and benign prostatic hyperplasia (BPH) control groups, we extracted data on the healthy control group only(8)Authors were contacted where data were missing or not clear or where it was stated that subgroup analyses had been carried out but no results were presented in the publication. The two sets of extracted data were entered into an electronic database and checked for consistency using an automated procedure. Any disagreements were resolved by discussion between M-AR, RMM and DG (9).

Statistical Analysis

To compare across studies, we calculated the log odds ratio (OR) or risk ratio (RR) per standard deviation (SD) increase in growth factor, with and without controlling for potentially confounding factors. For studies presenting results as a difference in means in healthy and diseased groups, we calculated the log odds ratio or risk ratio per unit increase in exposure using the method of Cheˆne and Thompson.8 For studies presenting their results within categories of exposure (e.g. quantiles), we used the mean or median exposure in each category when they were reported, and calculated the log OR / RR per unit increase in exposure using the method of Greenland and Longnecker.9 When the mean or median in each group was not reported, and a range of exposure in each group was given, we estimated the mean exposure in each group using the method of Cheˆne and Thompson, which assumes a normal distribution of the exposure in the population.8 Where no information was presented on the exposure levels in each group, a normal distribution was assumed based on the number of subjects in each group, and the log OR or RR per SD increase calculated based on this assumption. Log OR RR per unit increase and their standard errors were converted to a per SD increase by multiplying by the SD of the exposure. When this was not reported, the estimated SD from the Chine and Thompson method was used.8 where studies only presented subgroup analyses and not an overall cancer group, we combined the subgroups statistically where possible, by calculating pooled means (10).

For papers presenting data in several ways, the order of preference for choosing the data to be pooled was: (i) reported coefficients (log odds ratio or risk ratio (per unit increase)—of fully adjusted then unadjusted;

(ii) fully adjusted categorical data; (iii) unadjusted categorical data; and (iv)continuous data (presented as mean or median). To assess the effect of controlling for potential confounding factors on the results, we compared adjusted and unadjusted models from those prospective studies that presented both models. Two studies presented their results in a way that was not possible to combine with other studies: one stated that there was ‘‘no difference’’ between cases and controls but did not provide raw data for the IGF-II and IGFBP-1 associations10 and another presented IGFBP-2 as a percentage of total serum IGFBPs.11

We performed random and fixed effects meta-analysis to calculate summary OR estimates, using the metan command.12 ThebDerSimonian and Laird model relaxes the assumption of a common treatment effect. Effect sizes are assumed to have a Normal distribution with variance s2which is based on Cochran’s Q statistic for heterogeneity. This additional source of variation has the effect of making study weightings in the meta-analysis more similar in the presence of heterogeneity; the greater the heterogeneity, the more weight is given to smaller studies.13 We calculated the I2statistic as a quantitative measure of the degree of inconsistency across studies (heterogeneity).14 Small study effects were assessed by inspection of funnel plots and computation of Egger et al.15and Beg and Mazumdar16 tests. Because there was evidence of substantial heterogeneity, we report random effects models throughout this article, but for the main analyses, we also present fixed effect models for comparison (11).

Subgroup Analyse

The Stage and grade. To investigate whether the IGFs or IGFBPs were associated more strongly with more advanced or clinically significant prostate cancers, we conducted separate meta-analyses of the association of these peptides with localized and advanced cancers, and with low and high Gleason grade cancers. Because definitions of ‘‘advanced,’’ ‘‘localized,’’ ‘‘low grade’’ and ‘‘high-grade’’ differed between studies, and some studies grouped cancers as ‘‘aggressive’’ (a combination of high grade/advanced stage) or ‘‘nonaggressive’’ (a combination of low grade/localisedstage), we analyzed them in these groups and then created com-binned groups. Our combined groups were defined as: (1) ‘nonaggressive,’’ consisting of low Gleason grade and/or localized stagehand/or ‘‘nonaggressive’’ cancer; and (ii) ‘‘aggressive,’’ defined as high Gleason grade and/or advanced stage and/or ‘‘aggressive’ ’cancers. Where studies presented both stage and grade analyses, we included the stage analysis only in the pooled group, because it’s an indicator of cancer that has or has not progressed, though we also repeated the grouping using the grade analysis and found similar results (12).Where authors stated that they carried out stratified analyses but did not present their results, we contacted authors for the original data, and received one response.17 We used metered egression to investigate whether associations of prostate cancer with IGFs/IGFBPs differed between nonaggressive compared with aggressive cancers (heterogeneity) after excluding papers where both subgroups of prostate cancer were compared to one single control group (13).We repeated the analysis including such studies to check that the results were similar, although we recognize that including studies with nondependent control groups will give standard errors that are too small . One study18 (n 5 120 cases) provided results for localized and advanced cancers separately, but not an overall prostate cancer group. We could not easily combine these results to get an overall cancer group because medians were presented. In this case, we included the results for localized prostate cancer in our overall meta-analysis because the other included studies contained a majority of localized cancers, and then included them in the localized subgroup analysis in addition(14). Another study only included advanced cancers; so, we excluded it from the overall meta-analyses but used the results in the advanced cancer subgroup analysis.

Study design characteristics and quality. We did not formally assess the quality of the included studies as there is no validated set of quality criteria for observational studies.20 Instead, we first compared results from retrospective and prospective study designs using met regression (15-19)

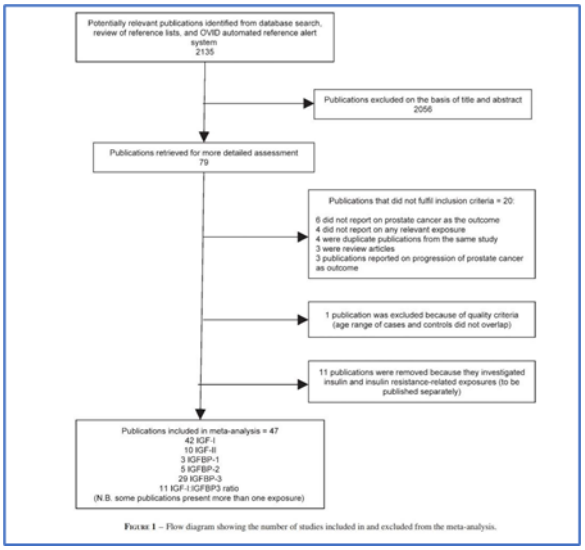

FIGURE 1 – Flow diagram showing the number of studies included in and excluded from the meta-analysis.

Retrospective studies to be influenced by reverse causality (changes in IGF or IGFBP levels in response to cancer) and selection bias. We therefore conducted subgroup met regression analyses to investigate the influence of the following, a priori defined study factors on effect estimates in prospective studies only: (i) mid-year the study was c(20-22) as this was considered an indicator of whether the study was conducted in the pre-PSA or post PSA screening era (our cutpoint for the pre-PSA era was 1993, as before this time period PSA screening was not widespread),21 (ii)whether the study was population- or hospital-based, an indicator of potential selection bias; (iii) number of cases (split into two groups by the median of 128) to investigate small study effects;15 (iv) sample type (serum or plasma), because other studies have found that this influences the overall estimate;4 (v) assay type (ELISA or other), because the assay method has been reported as a source of variability22 (vi) study location (North America, UK and Europe, or Other); (vii) whether cases were screen detected or clinically detected, or a combination of the two; (viii) whether the presence of prostate cancer was histologically confirmed or not; and (ix) whether models were mutually adjusted for IGF-I and IGFBP-3(23).

RESULT

These searches yielded 2,135 references. After title and abstract review, 79 papers were selected as potentially relevant and were retrieved for more detailed assessment. Forty-seven of these stud-ies provided an estimate of the association of at least one IGF peptide (IGF-I, IGF-II, IGFBP-I, IGFBP-2 or IGFBP-3) with prostate cancer occurrence, and were included in the metaanalysis (Fig.1). Sixteen were prospective and 31 were retrospective studies (Table I).The total number of prostate cancer cases per study ranged from 14 to 727, and the number of controls ranged from 6 to2, 167. All the identified studies were published from 1993onwards, but covered recruitment periods beginning in 1960. Ethnicity was only reported in 34% of studies. All prospective studies and 18 of the retrospective studies used healthy controls; of the remaining retrospective studies, 9 used men with benign prostatic hyperplasia (BPH) as controls, and 4 used a mixture of both healthy and BPH controls. Prostate cancers were histologically confirmed in 33 studies. There was an indication of funnel plot asymmetry for IGFBP-2and IGFBP-3 (Fig. 2), and this was supported by results from the Egger (IGFBP-2 p 5 0.02, IGFBP-3 p 5 0.002) and Begg (IGFBP-2 p 5 0.09, IGFBP-3 p 5 0.004) tests. For IGFBP-3, the smaller studies were suggesting larger inverse associations with prostate cancer, whereas for IGFBP-2, the smaller studies provided larger positive associations. There was no indication of funnel plot asymmetry for IGF-I (Egger p 5 0.66, Begg p 5 0.66),IGF-II (Egger p 5 0.48, Begg p 5 0.11), or IGFI:IGFBP-3 ratio(Egger p 5 0.67, Begg p 5 1.0). There were too few studies to assess funnel plot asymmetry for IGFBP-1.

Subgroup Analyse

The all exposures, there was evidence of substantial heterogeneity (all I2 > 75%), and we investigated potential sources of between study variation in a number of subgroup analyses shown below.

Study Design Characteristic and – Investigating Heterogeneity

When considering prospective studies alone, we still observed considerable heterogeneity in three of the four exposures (IGF-I: I2 5 59%, IGF-II: I2 5 81%, IGFBP-2: I2 5 0%, IGFBP-3: I2 5 49%). There were insufficient numbers of studies to do subgroup analyses on IGF-II, IGFBP-1, IGFBP-2 and the ratio of IGFI:IGFBP-3; so, we restricted the subgroup analyses to the 14 prospective studies presenting IGF-I and the 13 prospective studies presenting IGFBP-

3.There was little evidence that any of the 9 factors investigated (e.g. date study conducted; study setting) explained the observed heterogeneity (all p values for heterogeneity between strata of each variable >0.09, all I2 values within strata >0.34). The lowest p value of 0.09 was for control source for IGF-I (hospital vs. population-based control)(24).In meta-regression analyses of retrospective studies, investigating control type, control source or number of prostate cancer cases, we found no difference between groups. Retrospective studies may be more likely to contain advanced cases, which could lead to an overestimation of associations as a result of reverse causality; however, the reporting of cancer stage did not allow us to adequately investigate this in a subgroup analysis (25).

DISCUSSION

Summary of Finding

The Our meta-analysis revealed that the body of the world-wide published literature is 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. For IGF-II, IGFBP-2 and the ratio of IGF-I: IGFBP-3, there were positive but weaker associations with prostate cancer risk. Only the associations of IGF-I andIGFBP-3 excluded an odds ratio of 1 (no difference), and this was only the case for the random effects model for IGFBP-3. Our sensitivity analysis excluding one extreme outlying retrospective study resulted in a shift of the pooled IGFBP-3 OR towards the null (and therefore more in line with the prospective pooled result), with the associated p value changing from <0.02 to 0.57.The overall heterogeneity changed from 81.2 to 52.9%. We observed that effect estimates were consistently stronger in retrospective than prospective studies, suggesting that the true effect of IGF-I may be weaker than indicated by the retrospective studies, and that there is no association in prospective studies (positive or negative) of levels of IGF-II, IGFBP-2, IGFBP-3 and the ratio of GFI:IGFBP3 with prostate cancer risk (26-27). This suggests that they may not be involved in the etiology of prostate cancer but may be useful tumor markers as shown by the positive association in retrospective studies. IGFBP-1 showed no association with prostate cancer in either retrospective or prospective studies (28).

We observed considerable heterogeneity within both study types, as indicated by the I2 values, which were generally greater than 50%. It is widely accepted that prospective studies are less likely than retrospective studies to be influenced by reverse causality (changes in IGF or IGFBP levels in response to cancer) and selection (29) .We therefore conducted subgroup analyses to investigate several potential sources of between-study variation in effect-estimates in prospective studies. There was no strong evidence that any single factor played an important role in explaining the heterogeneity observed.Eight prospective studies (totalling 3,428 cases) presented results stratified by subgroups of prostate cancer, either by stage,Gleason grade or aggressiveness and there was weak evidence that associations of IGF-I (p for difference 5 0.2) and IGFBP-3 (p for difference 5 0.02) were stronger with more advanced or aggressive disease (30,31).

CONCLUSION

The Even though we observed a modest increase in risk of prostate cancer associated with higher levels of IGF-I, and a slight reduced risk with higher levels of IGFBP-3, neither of these peptides are likely to be useful as additional measurements in prostate cancer PSA screening. The strength of the associations are too weak to have any value as a screening test because at these odds ratios, the detection rate (sensitivity) is less than 8% for a 95% specificity(5% false positive rate).3,74 This issue has been investigated by Oliver et al.75 who found no evidence that measures of IGFs or IGFBPs enhanced the specificity of prostate cancer detection beyond that achievable by the currently used free/total PSA index.Future research should be aimed at clarifying the associations of IGF-II, IGFBP-2 and IGFBP3 with prostate cancer, in large prospective studies.

The magnitude of the increased risk of prostate cancer per SD increase in IGF-I (21%), although modest, is likely to be etiologically important as demonstrated by the fact that it is of the same order of magnitude as that for well-known ischemic heart disease (IHD) risk factors in population-based cohorts. For example, a

one SD increase in diastolic blood pressure is associated with a 26% increased risk of IHD, and a one SD increase in total cholesterol is associated with a 44% increased risk of IHD.76 So although IGF-Measurements is unlikely to increase the discriminatory accuracyof current prostate cancer screening methods (serum prostate specific antigen or digital rectal examination), it does represent a potentially modifiable risk factor for prostate cancer, and this could be achieved through dietary or lifestyle interventions which may alter IGF-I levels.77 In addition, the IGF system is likely to become a potential therapeutic target either alone or in combination with other chemotherapeutic agents, and anticancer therapiesthat aim to target the IGF system are currently under investigaation.

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