Committee on CARCINOGENICITY

Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC)

COC Statement 2018/S01

Statement on possible carcinogenic hazard to consumers from insulin-like growth factor-1 (IGF-1) in the diet

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Background

1. The issue of carcinogenic hazard arising from dietary insulin-like growth factor-1 (IGF-1) was first considered in 2008. The Food Standards Agency (FSA) and the Veterinary Medicines Directorate (VMD) had been contacted regarding the import of cows which had been treated with bovine somatotropin (BST). The concern was prompted by the book "Your Life in your hands" by Professor Jane Plant (Plant, 2000). The book suggested that consumption of IGF-1 in dairy products could increase the risk of cancer, particularly breast and prostate cancer[1]. The concern was therefore expressed that if cattle treated with BST had increased levels of IGF-1 in their milk, then consumers of the milk could have an increased risk of cancer. Although BST is not permitted for use in the EU for reasons of animal welfare, imports of milk products derived from cattle legally treated with BST are not banned

2. The COC conducted a narrative review of this topic from 2012 to 2016; the search strategy is attached at Annex A to this statement. The issues considered were covered in a number of discussion papers:

- CC/2008/17- Horizon scanning 2008
- CC/2009/08- Possible carcinogenic hazard to consumers from insulin-like growth factor (IGF-1) in the diet.
- CC/2012/06 - Possible carcinogenic hazard to consumers from insulin-like growth factor (IGF-1) in the diet[2].
- CC/2012/16 - Possible carcinogenic hazard to consumers from insulin-like growth factor (IGF-1) in the diet. IGF-1 and prostate cancer.
- CC/2016/01 - Possible carcinogenic hazard to consumers from insulin-like growth factor (IGF-1) in the diet. Part 3- the potential association of IGF-1 with colorectal cancer risk and lung cancer risk.
- CC/2016/11 - Possible carcinogenic hazard to consumers from insulin-like growth factor (IGF-1) in the diet. Influence of diet on IGF-1 levels and cancer risk.

These can be accessed here: [*https://www.gov.uk/government/collections/coc-guidance-statements*]

3. The key points of these papers and the conclusions reached by the COC are set out in the following statement; this has been updated and amended from the discussion papers published between 2012 and 2016. Therefore, some data may have been included in the statement, which were not included in the original discussion papers. The epidemiology studies seen by the Committee are summarised in Tables 1-4 of Annex B.

[1] A detailed analysis of the arguments made in Dr Plant's book is set out in CC/2009/08.
[2] Includes the information on IGF-I and breast cancer.

Introduction

Previous considerations

4. The possibility that milk from BST treated cows could increase the risk of cancer in consumers was considered initially in 1999 by the Veterinary Products Committee (VPC) (VPC, 1999) and most recently at a meeting in 2008. Based on the normal blood concentration of endogenous IGF-1, the VPC considered it unlikely that sufficient additional IGF-1 could be absorbed from drinking milk to increase the circulating amount of endogenous IGF-1 enough to have any effects on tissues. However, the possibility that dietary IGF-1 could cause cell proliferation of the gut mucosae with the potential of increasing cancer could not be excluded.

IGF-1 and cancer

5. There are a number of reasons that IGF-1 may be linked to cancer. These are outlined below and were discussed in more detail in CC/2009/08.

6. Individuals with the condition acromegaly produce excess growth hormone and thus have high endogenous levels of IGF-1. These individuals also have a high prevalence of colorectal neoplasia. Tall individuals are at increased risk of certain cancers (WCRF, 2015) and although the mechanism is uncertain, this may be due in part to elevated levels of growth hormone and thus IGF-1.

7. IGF-1 has been reported to cause proliferation in a number of cell types and may also have a role in cell differentiation and inhibition of apoptosis. This was discussed in more detail in CC/2009/08.

8. The drug Tamoxifen, which is used against breast cancer, reduces serum concentration of IGF-1 (Pollak et al., 1992).

IGF-1: identity, structure and physiological control

9. IGF-1 is a 70 amino acid polypeptide growth factor mainly produced in the liver (Chan *et al*., 1998)[3]; it has a variety of autocrine, paracrine and endocrine functions. The amino acid sequence of IGF-1 is highly conserved in mammalian species and is identical in humans, cattle and pigs (European Commission, 1999).

10. In the circulation, IGF-1 is bound to one of six IGF-1 binding proteins (IGFBPs) with the majority (>90%) binding to IGFBP-3 (Sandhu *et al*., 2002). IGFBP-3 was considered by the COC as part of the assessment of IGF-1 since changes to IGFBP-3 concentrations could alter the IGF-1: IGFBP-3 ratio, changing the circulating concentration of free IGF-1, the active form of the peptide.

[3] The structure, metabolism and regulation of IGF-I are discussed in detail in CC/2012/06.

11. The rate of secretion of IGF-1 and the degree to which it is protein bound in the bloodstream is determined by a complex interaction of physical factors. These include energy intake, body mass index (BMI) and physical activity as well as levels of hormones including insulin, growth hormone (GH), oestrogen, testosterone and thyroid hormones (Yu and Rohan, 2002). IGF-1 production in humans was estimated to be 9.95 mg/day (Guler *et al*., 1989).

12. The levels of IGF-1 in the blood are controlled by a feedback mechanism involving IGF-binding proteins, insulin and GH.

13. In circulation, IGF-1 exists as a ternary complex with an IGF binding protein and a glycoprotein called the acid-labile sub-unit which does not cross the vascular barrier (Rajaram *et al*., 1997; Guidi *et al*., 2007). Free IGF-1 is prone to degradation in the bloodstream whereas the ternary complex is more stable (Wu *et al*, 2008). IGFBP-3 protease releases the IGF-1 so it can then leave the bloodstream and act on surrounding tissues; the free IGF-1 may then bind to smaller binding proteins such as IGFBP-4 which can cross the vascular barrier but protect the IGF-1 on the journey to the target tissues. The action of IGFBP-4 protease, which is released by the target tissue, makes the IGF-1 available to receptors. Tissue-specific regulation of IGFBP proteolysis may provide a mechanism for controlling the bioavailability of IGF-1 to receptors through the effects of local growth factors.

Analysis of IGF-1 and IGFBP-3

14. IGF-1 and its binding proteins can be analysed in a variety of ways, most commonly Enzyme Linked Immunosorbent Assay (ELISA) or Radioimmunoassay (RIA). Many analyses report total IGF-1 which might not necessarily reflect the availability of IGF-1 to receptors. In many literature reports it was noted that IGF-1 was removed from its binding proteins, usually by acid-alcohol extraction. However, it is not always clear if this was the case.

15. Renehan *et al.* (2003) reported that higher concentrations of IGF-1 were measured in EDTA plasma compared to heparin plasma or serum.

16. Stattin *et al*. (2004) noted that commercial ELISAs largely measured specific intact forms of IGFBP-3 whereas radioimmunological methods might measure more, or different, forms of IGFBP-3 combined.

17. Thus, caution should be exercised when comparing analytical results between studies, since many papers report only IGF-1 or IGFBP-3 levels without stating the analytical method used in adequate detail. Where known, the analytical method used has been included in the summary tables in Annex B.

Human physiological levels of IGF-1 and its binding proteins

18. Factors affecting the circulating levels of IGF-1 and its binding proteins were discussed in detail in CC/2012/06.

19. The circulating levels of IGF-1 and its binding proteins vary depending on factors such as age, sex, ethnicity, diet, exercise, smoking status and levels of hormones such as insulin, growth hormone and oestrogens (Kaklamani *et al*., 1999; Sandhu *et al*., 2002; Holmes *et al*., 2002; Chang *et al*., 2002). IGF-1 levels increase throughout childhood reaching a peak plasma concentration at about 12 and 14 years of age in girls and boys respectively (Perdue, 1984; Yu and Rohan, 2002). After puberty IGF-1 levels decline to around a third to a half of peak levels, gradually declining with age thereafter. IGF-1 levels are generally higher in men than women and change in different physiological states such as sleep, fasting and pregnancy (Perdue, 1984; Underwood *et al*., 1980; Yu and Rohan, 2002). Data on IGF-1 concentrations are summarised in Table 1 of CC/2012/16[4]. For the purposes of illustration, average IGF-1 concentrations were reported to be 80-200, 200-500, 290 and 160 ng/ml in pre-pubertal children, pubertal children, 20 year old adults and 70 year old adults respectively (Juul *et al*., 1994a; Juul *et al*., 1994b; Perdue, 1984).

20. There are fewer data available on the circulating levels of IGF-1 binding proteins. In healthy adults, IGFBP-3 remained fairly constant but as with IGF-1 tended to decrease with age (Juul *et al*., 1994 a and 1994b). IGFBP-3 was reported to be lower in men and may differ in smokers (Kaklamani *et al*., 1999; Diorio *et al*., 2008; Platz *et al*. 1999). IGFBP-3 may also be affected by reproductive history, BMI and physical activity, but this was not necessarily comparable in all groups (Holmes *et al*., 2002; Chang *et al*., 2002).

21. On a molar basis, human serum levels of IGFBP-3 are around 3-4 times greater than those of IGF-1 (Rajaram *et al*., 1997).

22. Serum levels of IGF-1 and IGFBP-3 are low in starvation (Pollak *et al*., 2000) and where protein is restricted (Sandhu *et al*., 2002). However, obese individuals appear to be resistant to the effects of dietary restriction of IGF-1 levels (Thissen *et al*., 1994).

23. IGF-1 has also been measured in saliva, gastric juice, jejunal chyme, pancreatic juice, bile, bone and human milk (Chaurasia *et al*, 1994; Costigan *et al., 1988;* Outwater *et al*., 1997; Seck *et al*., 1998). Different combinations of IGFBPs have been detected in various body fluids including blood, milk, urine, cerebrospinal fluid, follicular fluid, amniotic fluid, lymph and seminal fluid (Rajaram *et al*., 1997).

Truncated IGF-1

24. It has been noted (European Commission, 1999) that about 3% of the IGF-1 in milk is in N-terminally truncated forms which are missing a few amino acids. These truncated forms have a reduced affinity for IGF-binding proteins and have been reported to be approximately 10 times more potent as mitogens than intact IGF-1 in *in vitro* assays (Burrin, 1997; European Commission, 1999).

[4] The IGF-1 concentrations for individual epidemiology studies are given in the summary tables in Annex B.

Dietary exposure of humans to IGF-1

25. With the exception of milk, there are few data available on concentrations of IGF-1 in foods derived from animals. No data have been identified on levels in meat, offal or eggs from food-producing animals.

26. A wide range of IGF-1 concentrations (1 to 1850 ng/ml) has been found in cows' milk (Miller *et al*. 1989; Mepham *et al*., 1994; Outwater *et al*., 1997; Daxenberger *et al*., 1998; Ginjala and Pakkanen, 1998) with the majority of samples containing less than 100 mg/ml. The level in milk is affected by genetic factors, such as the breed of cow, and external factors, such as the diet fed to the cows. The highest level of IGF-1 was measured in the first post-partum milking, reflecting the high level of IGF-1 that is known to occur in colostrum (Ginjala and Pakkanen, 1998). The levels of IGF-1 in cows' milk decrease with time after parturition. The colostrum is normally fed to calves and is only rarely eaten by humans. The highest concentration of IGF-1 in milk commonly consumed by humans is unlikely to be greater than 100 ng/ml.

27. Neonates are likely to have more systemic exposure to dietary IGF-1, through consumption of maternal milk and to have a greater exposure of the luminal side of the gut to IGF-1 than is the case in older individuals. The higher concentration of IGF-1 found in colostrum provides neonates with a high dietary intake of IGF-1. It is feasible that this high exposure and bioavailability of IGF-1 in neonates is related to a normal physiological role of IGF-1 in the growth and development of the new-born.

28. Exposures in human neonates will vary depending on the feeding regimen, as only infants fed human milk would be exposed to IGF-1, since formula does not contain IGF-1. Since weaning does not occur until 4-6 months of age when the gut is more mature, some infants would not be exposed to exogenous IGF-1 until 4-6 months of age or later. Current recommendations are that cows' milk is not introduced until 12 months of age (NHS Choices, 2017).

29. There are more data available on the concentrations of IGF-1 in the tissues of experimental animals. For example, IGF-1 concentrations of 11 to 92 µg/kg in muscle, 84 to 89 µg/kg in liver and 180 to 816 µg/kg in kidney (up to 3469 µg/kg in kidneys of diabetic animals) and have been reported (this is set out in Table 4 of CC/2012/06).

30. Dietary exposure to IGF-1 per kg body weight (bw) has been estimated in Table 1 below:

Table 1: Chronic exposure assessment for IGF-1 in Milk and Meat (including poultry) and their products - UK Toddlers aged 1 to 3 years

Food Group	Number of consumers	Consumer mean exposure rate (µg/kg bw/d)	Consumer $P_{97.5}$ exposure rate (µg/kg bw/d)	Consumer max exposure rate (µg/kg bw/d)
Milk; including recipes	595	2.54	7.04	22.35
Milk and milk products (e.g. yogurt, butter, cream etc.); including recipes	597	2.70	7.15	22.35
Milk and milk products and cheese and cheese products; including recipes	597	2.77	7.19	22.37
Meat and meat products; including recipes	568	0.24	0.59	1.23
Milk and milk products and cheese and cheese products, meat and meat products; including recipes	601	2.98	7.33	22.92

Table 2: Chronic exposure assessment for IGF-1 in Milk and Meat (including poultry) and their products - UK Adults aged 19 years and older

Food Group	Number of consumers	Consumer mean exposure rate (µg/kg bw/d)	Consumer $P_{97.5}$ exposure rate (µg/kg bw/d)	Consumer max exposure rate (µg/kg bw/d)
Milk; including recipes	3335	0.28	0.82	2.75
Milk and milk products (e.g. yogurt, butter, cream etc.); including recipes	3356	0.32	0.91	2.76
Milk and milk products and cheese and cheese products; including recipes	3364	0.34	0.94	2.77
Meat and meat products; including recipes	3165	0.11	0.28	0.72
Milk and milk products and cheese and cheese products, meat and meat products; including recipes	3369	0.45	1.08	2.85

31. The estimates are very conservative, assuming an IGF-1 concentration of 101 µg/kg[5] in all relevant foods including meat and meat products, cheese and cheese products, and milk and milk products and using consumption data from the National Diet and Nutrition Survey (NDNS) (Bates *et al*., 2014; Bates *et al*., 2016). The highest mean and high level (97.5%) dietary exposure to IGF-1 in toddlers is

[5] The highest reported concentration in milk from the 5th post-partum milking of Ayrshire cows.

2.98 and 7.33 µg/kg bw (body weight)/day in toddlers and 0.45 and 1.08 µg/kg bw/day in adults.

32. Endogenous production of IGF-1 has been estimated to be 10,000 µg/day (VPC, 1999). This is equivalent 128 µg/kg bw/day in 78 kg adults; suggesting that, in adults, high level dietary exposure to IGF-1 would generally be less than 1% of endogenous production[6]. Toddlers are likely to have higher dietary exposure than adults, because of the higher proportion of milk in their diet as well as their smaller body size. However, as there are no data on endogenous IGF-1 production in toddlers, it has not been possible to compare this with dietary exposure.

The effect of dietary components on IGF-1 concentrations

33. A number of studies in both humans and animals have indicated that serum IGF-1 concentrations could be associated with diet. These are noted briefly below but considered in more detail in CC/2016/11.

Animal studies

34. The effect of dietary composition has been assessed in a number of species including rats, mice, pigs, horses and chickens. In general, increased protein intake was associated with a higher level of IGF-1 but not necessarily with increases in growth hormone levels. Although the increased permeability of the gut in new-borns may mean that IGF-1 is more likely to be absorbed intact, higher IGF-1 levels were not found in foals who had been fed colostrum from their dams rather than milk replacer (Palm et al., 2012).

Human epidemiology studies (largely cross sectional)

35. IGF-1 levels are generally reported to be lower in breast fed babies compared to formula fed babies (Madsen et al., 2011; Martin et al., 2005).

36. A number of studies have investigated the association between dietary patterns and IGF-1 levels; these are considered in detail in CC/2016/11. The results are not consistent but, in general, total energy, protein, fats, milk, fish, and calcium have been associated with increased IGF-1 levels. Conversely, malnutrition is associated with lower levels of IGF-1.

Human intervention studies

37. A variety of intervention studies have also been conducted, assessing the effects of supplementing the diet with protein, milk or other components; these are considered in detail in CC/2016/11.

[6] The reference for the estimate of 10,000 µg/day was not given, but it may have been taken from Guler *et al*., 1989.

Protein

38. Numerous studies (e.g. Schürch et al., 1998; Roughead et al., 2003; Ballard et al., 2005; Arjmandi et al., 2009) have shown that protein supplementation (meat, vegetable, milk, soy) increases serum IGF-1 levels.

Milk

39. In general, and as noted above, formula fed babies have higher levels of circulating IGF-1 than breast fed babies, and where the formula has a higher protein content, the levels of circulating IGF-1 are higher still (Socha et al., 2011). Supplementation of the diet with whole milk has been shown to increase IGF-1 in both children and adults; this was also observed in a small study where adult volunteers were supplemented with colostrum (Mero et al., 2002). In a small number of studies where milk protein has been compared to other proteins it has been reported that milk protein increased IGF-1 more than meat protein (Hoppe et al., 2004) but less than soy protein (Arjmandi et al., 2009). However, it should be noted that there are few studies available which do a direct comparison. In other studies, calcium, soy and low fat/high fibre diet interventions were not shown to significantly affect IGF-1 levels.

Absorption, distribution, metabolism and excretion of IGF-1

40. IGF-1 is normally rapidly digested in the stomach and small intestines. However some components of the diet such as casein (Xian et al., 1995) appear to confer some protection from digestion, so some IGF-1 might pass through the gut without being broken down. Concentrations of IGF-1 in the gut lumen are likely to be lower than the levels in the blood since IGF-1 levels are lower in jejunal chyme and plant-derived foods do not contain IGF-1, this would dilute the concentration of IGF-1 in the gut lumen so passive absorption of IGF-1 is not anticipated since any absorption of IGF-1 from the gut lumen would need to operate against a concentration gradient. This suggests that, even if the IGF-1 was not digested, it would be unlikely to be absorbed to any significant extent.

41. There are few data on oral dosing in human volunteers. In the single available study, Mero et al., (2002) gave 12 adult volunteers Iodine123 labelled recombinant IGF-1; serum samples were taken 60 minutes after dosing and were subjected to gel electrophoresis. It was concluded that the IGF-1 was fragmented during circulation since no radioactive IGF-1 was eluted at the positions of free IGF-1 or the IGF-1 binding proteins, only smaller molecules being detected.

42. In neonatal animals, IGF-1 is less readily broken down in the gut (Rao et al., 1998). There are limited and inconsistent data to suggest that absorption of IGF-1 might occur in young individuals (Philipps et al., 2000).

43. Parenterally administered IGF-1 was distributed to all parts of the body, with well-perfused organs (kidney, liver and lungs) having the highest levels (EMEA, 2007). Much of the IGF-1 remained in the bloodstream bound to IGFBPs.

44. It is expected that IGF-1 metabolism would proceed by breakdown to amino acids, which would then be either used to build body proteins or broken down further by normal body processes to produce energy and waste products such as carbon dioxide, urea and water (EMEA, 2007).

45. Excretion of the ultimate products of metabolism was expected to be via exhaled carbon dioxide and in the urine (EMEA, 2007). Excretion/secretion of intact IGF-1 in milk, saliva, digestive juices and bile also occurs. Free IGF-1 is rapidly removed from plasma (elimination half-life < 30 minutes), but protein-binding can considerably slow down the elimination (EMEA, 2007).

Direct effects of IGF-1 on the gut

46. Studies of the trophic effects of IGF-1 and related substances on gut tissues showed that oral or parenteral doses (by total parenteral nutrition catheter) could cause growth of the intestines, typically characterised by increases in intestinal weight, intestinal length, mucosal mass, protein synthesis and villus length. A concentration of 750 ng/ml IGF-1 in milk replacer was the lowest oral dose reported to cause intestinal growth in calves, but a level without effect was not detected (Baumrucker et al., 1996).

Toxicological studies of rhIGF-1

47. Toxicological studies of recombinant human (rh) IGF-1, which is used medicinally, involved parenteral (*intra venous* (i.v,) or *subcutaneous* (s.c.)) dosing; no oral toxicity studies were performed (EMEA, 2007). A carcinogenicity bioassay of subcutaneously administered rhIGF-1 showed that rats developed malignant mammary tumours (4 mg/kg bw/day), benign mammary tumours (NOEL = 1 mg/kg bw/day), benign proliferative lesions of the adrenal medulla (at all doses: NOEL<0.25 mg/kg bw/day) and benign skin tumours (NOEL = 1 mg/kg bw/day). A special study of implants of cancer cells into the caeca of mice showed lower numbers of caecal tumours and hepatic metastases in transgenic mice with impaired hepatic production of IGF-1 than in normal mice or transgenic mice that had injections of IGF-1. rhIGF-1 was not genotoxic in an *in vitro* cytogenetics assay in Chinese hamster lung fibroblasts nor in an *in vivo* mouse micronucleus test.

48. Several clinical studies of rhIGF-1 have been performed in humans as part of its development as a medicinal product. Single s.c. or i.v. doses of 0.01 mg/kg bw caused reduced serum glucose and increased serum IGFBP-3 concentrations. Twice-daily s.c. doses of 60 to 120 µg/kg bw given for several years caused decreased serum levels of glucose, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), reduced packed cell volume and haemoglobin, but had no effect on electrocardiogram measurements. In premature babies, formula

supplemented with 100 ng/ml of IGF-1 had no effect on serum levels of IGF-1, IGFBP-1, IGFBP-3 or GH, but there was decreased gut permeability compared with controls. There was no evidence from the clinical studies to suggest that treatment with rhIGF-1 caused any cancer in treated patients.

Epidemiology studies: cancer and IGF-1

49. A number of human studies have examined the relationship between blood IGF-1 concentrations and cancer. These studies cover several cancer sites and include case-control studies and prospective studies as well as meta-analyses. Different studies have measured varying combinations of parameters but only IGF-1 and IGFBP-3 have been considered in detail. The studies considered by the Committee have been tabulated in Annex B to this statement, with the key points being summarised below.

Breast cancer

50. Breast cancer is the most common cancer in the UK, affecting 1 in 8 women[7] (Cancer Research UK, 2017a). Most women develop breast cancer when post-menopausal but around 20% of cases occur in pre-menopausal women. Breast cancer risk is affected by family history and age as well as life style factors such as diet and smoking. The studies considered by the Committee have been summarised in Table 1 of Annex B and the relationship between circulating IGF-1 concentrations and breast cancer is discussed in detail in CC/2012/06.

51. The retrospective studies comparing circulating blood IGF-1 levels in women with breast cancer and controls have reported inconsistent results, with both increased or no difference in the levels of IGF-1 in cancer patients compared to controls being reported.

52. The results of the prospective studies investigating levels of IGF-1 and breast cancer risk are also inconsistent. Some studies report an association between IGF-1 and cancer risk and others report no association. Where women have been considered in terms of their menopausal status, the associations reported for post and pre-menopausal women have also differed.

53. Several meta-analyses have been performed. These have also produced conflicting results, although more generally reported positive associations. Renehan et al. (2004) reported a positive association between IGF-1 and risk in pre- but not post-menopausal women, Shi et al. (2004) in post-menopausal women only, Sugumar et al. 2004 reported a marginally positive association in pre-menopausal women and Key et al. (2010) found a weak positive association in pre-menopausal women and stronger ones in post-menopausal women, as well as an association between IGF-1 and oestrogen positivity in the cancer.

[7] Although breast cancer also affects men, the studies considered in this section are all on women.

54. It has been suggested that high levels of IGFBP-3 are protective by reducing the concentration of free IGF-1 in the circulation, but the results from the available studies on breast cancer are inconsistent.

Prostate cancer

55. 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 (Cancer Research UK, 2017b). The studies considered by the Committee have been summarised in Table 2 of Annex B and the relationship between circulating IGF-1 concentrations and prostate cancer is discussed in detail in CC/2012/16.

56. A number of retrospective case control studies have been conducted, many with a view to improving prostate screening since IGF-1 can be produced by tumours. The results are inconsistent, with many studies reporting no difference in IGF-1 levels between prostate cancer cases and controls but a similar number reporting elevated IGF-1 levels in prostate cancer cases compared to controls.

57. 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-1 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-1 levels and cancer stage and/or severity also appear to be inconsistent.

58. A total of five meta-analyses have been performed on the available data and all have reported a positive association between IGF-1 levels and the risk of prostate cancer (Shi et al., 2001; Renehan et al., 2004; Morris et al., 2006; Roddam et al., 2008; Rowlands et al., 2009). 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.

59. 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. The results for IGFBP-3 are similarly varied with increases, decreases but most usually no differences being reported.

Colorectal cancer

60. Colorectal cancer is the fourth most common cancer in the UK. Risk factors include family, history, diet, smoking, obesity, alcohol and ionising radiation (Cancer Research UK, 2017c). Some examples of genetic polymorphism have been reported. Unlike other cancer sites, IGF-1 may influence the occurrence of colorectal cancer through direct contact in the gut lumen (via ingestion) as well as by elevated blood levels. The studies considered by the Committee have been summarised in Table 3 of Annex B and the relationship between circulating IGF-1 concentrations and colorectal cancer is discussed in detail in CC/2016/01.

61. Patients with acromegaly and thus elevated growth hormone and IGF-1 levels are thought to have an increased risk of developing tumours of the gastrointestinal tract compared to normal subjects (Ron et al., 1991; Cats et al., 1996; Jenkins et al., 1997; Colao et al., 1997; Bolfi et al., 2013)

62. Studies comparing circulating serum or plasma IGF-1 levels in patients with colorectal cancer and controls have reported both increased levels of IGF-1 in the cancer patients compared to the controls and no difference between the two groups.

63. The results of the prospective studies investigating levels of IGF-1 and colorectal cancer risk are also inconsistent. Some studies report an association between IGF-1 and others report no association.

64. Five meta-analyses have also been performed (Renehan et al., 2004; Morris et al., 2006; Rinaldi et al., 2010; Chi et al., 2013; Yoon et al., 2015). These reported positive associations for IGF-1 and cancer risk.

65. Results for an association of colorectal cancer risk with IGFBP-3 are also inconsistent. It has been suggested that high IGFBP-3 is protective by taking free IGF-1 out of circulation, but the results from the studies are inconsistent.

Lung cancer

66. Lung cancer is the third most common cancer in the UK with very low survival rates. Lung cancer can be divided into two types: Non-Small Cell Lung Cancer, and Small Cell Lung Cancer. Lung cancer is considered to be 89% avoidable with risk factors including smoking, occupational exposure and exposure to ionising radiation being associated with an increased risk of the condition. The studies considered by the Committee have been summarised in Table 4 of Annex B and the relationship between circulating IGF-1 concentrations and breast cancer is discussed in detail in CC/2016/01.

67. Studies comparing circulating serum or plasma IGF-1 levels in patients with lung cancer and controls have reported increased, decreased and no difference in the levels of IGF-1 in the cancer patients. Since cancers may produce their own growth factors, the results are difficult to interpret.

68. The results of the prospective studies investigating levels of IGF-1 and lung cancer risk are also inconsistent. Some studies report an association between IGF-1 and others report no association.

69. Three meta-analyses have also been performed (Renehan et al., 2004; Morris et al., 2006; Chen et al., 2009). These produced results which generally did not show any association.

70. It has been suggested that high IGFBP-3 is protective by taking free IGF-1 out of circulation. However, results for an association between lung cancer IGFBP-3 are also inconsistent.

Time trends and tumour markers

71. The vast majority of prospective studies which consider the association between circulating IGF-1 and cancer risk only have baseline IGF-1 measurements. However, in a small case control study investigating prostate cancer, Yu et al. (2001) reported that there were no time trends in the levels of IGF-1 or IGFBP-3 in either cases or controls in the individuals where serum samples were available (up to 4.5 years post–operatively). Woodson et al. (2003) noted that serum IGF-1, but not IGFBP-3, increased over time in prostate cancer cases but not in controls (2-5 years before diagnosis and within one year of diagnosis) suggesting that IGF-1 could be a tumour marker. Soubry et al. (2012) reported an association between colorectal adenoma and increasing IGF-1 level or IGF-1:IGFBP-3 molar ratio.

72. The interpretation of results is complicated by the observation that tumours are able to produce their own growth factors. However, Oliver et al. (2004) noted that hepatic IGF-1 production dominated that from other tissues so that it was unlikely that IGF-1 production by a tumour would significantly increase circulating IGF-1 levels. Renehan et al. (2001) reported that IGF-1 and IGFBP-3 levels were unaffected by removal of colorectal adenomas.

Diet, IGF-1 and cancer risk

73. There are numerous epidemiology studies investigating the possible links between diet and cancer. It is not possible to review these, but an overview can be obtained from the World Cancer Research Fund (WCRF) Continuous Update Project (WCRF, 2017). The WCRF considered that there was limited, suggestive evidence that milk might be associated with prostate cancer and dairy products and cheese with colorectal cancer but also limited, suggestive evidence that milk could be protective against bladder and colorectal cancer (WCRF, 2007).

74. There are only a few studies in humans in which diet, blood IGF-1 and cancer risk were considered together. Two of these are discussed below in detail as they consider milk and/or dairy products.

75. Ma et al. (1999 & 2001) performed a nested case-control study within the Physicians' Health Study cohort (a total of 22,071 healthy men aged 40 to 84 years in 1982 with blood samples available from 14,916 of the men), using prospectively collected plasma from 193 men within the cohort who had developed colorectal cancer in the following 13 years and 318 age and smoking-matched controls. Intakes of skimmed milk, low fat milk, calcium from milk and calcium from dairy produce were associated with modest increases in plasma IGF-1, but intakes of red meat, poultry and fish were not associated with plasma IGF-1 levels, see Table 3 below. Non-drinkers of milk who had the highest tertile ratio[8] of IGF-1:IGFBP-3 (i.e. higher levels of free IGF-1) had an increased risk of colorectal cancer (relative risk = 3.05; 1.29-7.24), but the risk was not significantly increased in frequent drinkers of low fat milk with the highest tertile IGF-1:IGFBP-3 ratio (relative risk = 1.05; 0.41-2.69). The authors concluded that there was a protective effect of dietary calcium on colorectal cancer incidence among men with a high IGF-1:IGFBP-3 ratio, despite a moderate positive influence of milk or dairy food on circulating IGF-1 levels.

Table 3: Relative risks (RR) of colorectal cancer according to IGF-1:IGFBP-3 ratio in plasma and intakes of various foods (Ma et al., 1999 & 2001)

	IGF-1:IGFBP-3 molar ratio					
	Tertile 1		**Tertile 2**		**Tertile 3**	
	No Case subjects/No control subjects	**RR (95% CI)**	**No Case subjects/No control subjects**	**RR (95% CI)**	**No Case subjects/No control subjects**	**RR (95% CI)**
Skim/low-fat milk						
Tertile 1	15/37	1 (Referent)	27/35	1.96 (0.83-4.62)	31/25	3.05 (1.29-7.24)
Tertile 2	22/44	1.18 (0.48-2.93)	11/36	0.84 (0.33-2.16)	30/34	2.24 (0.97-5.18)
Tertile 3	13/17	1.59 (0.55-4.64)	16/29	1.43 (0.59-3.51) $P_{interaction}$ = 0.03 *	16/39	1.05 (0.41-2.69)
Calcium from total milk						
Tertile 1	18/38	1 (Referent)	23/36	1.48 (0.65-3.39)	28/28	2.24 (1.00-5.02)
Tertile 2	22/40	1.02 (0.44-2.40)	18/35	1.14 (0.48-2.69)	31/29	2.49 (1.09-5.68)
Tertile 3	14/25	1.04 (0.41-2.64)	15/34	0.99 (0.43-2.28) $P_{interaction}$ = 0.18 *	21/46	1.00 (0.43-2.36)

[8] A high molar ratio suggests higher circulating concentrations of free (i.e. active IGF-I).

	IGF-1:IGFBP-3 molar ratio					
	Tertile 1		Tertile 2		Tertile 3	
	No Case subjects/No control subjects	RR (95% CI)	No Case subjects/No control subjects	RR (95% CI)	No Case subjects/No control subjects	RR (95% CI)
Calcium from dairy food						
Tertile 1	21/37	1 (Referent)	18/40	0.80 (0.34-1.91)	27/29	2.05 (0.93-4.55)
Tertile 2	22/45	0.81 (0.36-1.84)	22/32	1.23 (0.54-2.77)	37/29	2.78 (1.23-6.27)
Tertile 3	12/24	0.75 (0.29-1.93)	16/34	0.89 (0.39-2.03)	18/48	0.72 (0.31-1.67)
				$P_{interaction}$ = 0.14 *		
Red meat						
Tertile 1	13/29	1 (Referent)	19/31	1.83 (0.72-4.61)	22/31	2.38 (0.93-6.07)
Tertile 2	21/26	2.12 (0.84-5.36)	21/35	1.61 (0.66-3.92)	24/43	1.91 (0.76-4.80)
Tertile 3	21/49	1.14 (0.48-2.71)	14/39	0.99 (0.38-2.61)	35/30	3.12 (1.30-7.49)
				$P_{interaction}$ = 0.38 *		
Poultry						
Tertile 1	10/18	1 (Referent)	11/13	1.86 (0.50-6.93)	8/9	1.71 (0.46-6.32)
Tertile 2	17/47	0.63 (0.23-1.73)	20/41	0.94 (0.35-2.55)	33/48	1.61 (0.62-4.16)
Tertile 3	28/38	1.45 (0.57-3.67)	22/52	0.93 (0.38-2.28)	41/47	2.06 (0.81-5.19)
				$P_{interaction}$ = 0.50 *		
Fish						
Tertile 1	16/34	1 (Referent)	13/32	1.04 (0.41-2.68)	25/28	2.63 (1.08-6.39)
Tertile 2	26/40	1.63 (0.70-3.78)	24/43	1.46 (0.63-3.37)	30/32	2.24 (0.98-5.12)
Tertile 3	13/30	0.86 (0.33-2.26)	17/31	1.34 (0.53-3.39)	27/44	1.90 (0.81-4.44)
				$P_{interaction}$ = 0.93 *		

RR -Adjusted for age, smoking, BMI, alcohol intake, multivitamin use, aspirin use and exercise.
* All P-values were two-sided.

76. The association between colorectal cancer risk with serum IGF-1, total IGFBP-3 and intact IGFBP-3 was investigated in a large case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (Rinaldi et al., 2010). Between 1992 and 1998, blood samples were taken prospectively from participants from eight European countries. Those who developed cancer by December 2002 were identified from national cancer registries. Investigators compared 1,121 cases of colorectal cancer with 1,121 matched

controls. Relative risks (RR) for colon and rectal cancers and 95% confidence intervals (CI) were calculated in relation to quintile categories of serum IGF-1 concentrations by conditional logistic regression. Possible confounders that were considered for to use for adjustment included BMI, ratio of waist to hip circumference, height, smoking status, education, physical activity, alcohol intake and dietary intakes of red meat, processed meat, dairy products, fruit, vegetables and fibre. The results showed no associations with risk of colorectal cancer overall. Sub-group analyses showed some moderate positive associations of IGF-1 levels with risk: in younger participants (less than 55 years old) for colon cancer only (RR per quintile increase = 1.18; 95% CI = 1.00-1.39) and among participants whose milk intake was in the lowest tertile of the population distribution (RR for an increase in serum IGF-1 of 100 ng/ml = 1.43; 95% CI = 1.13-1.93). There were no statistically significant ($p>0.05$) increases in colorectal cancer risk for an increase of 100 ng/ml of serum IGF-1 associated with dietary intakes of dairy calcium, non-dairy calcium, dairy proteins, non-dairy proteins, red and processed meat, red and processed meat plus poultry and fish, fruit and vegetables, and fibre. Neither total IGFBP-3 nor intact IGFBP-3 were associated with risk of colorectal cancer with colon or rectal cancers separately.

77. In a nested case control study of individuals from the Health Professionals Follow up Study and the Nurses' Health study (Wu et al., 1011) there were no differences in IGF-1 levels or in milk consumption between the 499 colorectal cancer cases and 992 matched controls.

Conclusions of the Committee

78. A sequence of papers examining the possible association between circulating IGF-1 and the risk of certain cancers has been considered. The topic originally arose as a result of concerns that cattle treated with the hormone BST might have increased levels of IGF-1 in their milk and since this was a known growth factor, this could increase the risk of cancers in consumers.

General conclusions

IGF-1 in food

79. IGF-1 is present in milk, notably colostrum, and in other animal tissues, though there are no data on levels in other animal-derived foods. Using very conservative assumptions, the highest mean and 97.5% ile dietary exposures to IGF-1 in humans has been estimated to be 2.98 and 7.33 µg/kg bw/day in toddlers and 0.45 and 1.08 µg/kg bw/day in adults. Since production of IGF-1 has been estimated to be 10,000 µg/day, dietary IGF-1 is likely to add less than 2% of endogenous production to overall exposure in adults, even if it was absorbed intact. The proportion in toddlers could be higher but data on endogenous IGF-1 are not available.

IGF-1 in the gut

80. As a peptide, it is likely that following ingestion, IGF-1 is rapidly broken down in the stomach and small intestine, although limited data suggests it is possible that some IGF-1 might pass through the gut without being completely broken down. Concentrations of IGF-1 in the gut lumen are likely to be lower than in the blood, so passive absorption of any intact IGF-1 is unlikely. In conclusion, it is IGF-1 is unlikely to be absorbed from the gut to any great extent. Metabolism of exogenous IGF-1 would be expected to be comparable to that of endogenously produced IGF-1.

81. It has been suggested that a truncated form of IGF-1 missing several amino acids might be more potent than IGF-1 itself, but no recent data have been identified and it is unclear whether a truncated form would be absorbed or, if active *in vivo*, could only act in the gut lumen.

82. It is highly unlikely that dietary IGF-1 could elicit an effect in the gastrointestinal tract of adults as it is unlikely that the cells of the intestinal epithelium would respond to luminal growth factors. However, the presence of IGF-1 in colostrum indicates that it may be involved in the maturation of the neonatal gut.

The effect of diet on circulating IGF-1 concentrations

83. A number of epidemiological and intervention studies have indicated that IGF-1 levels could be positively associated with milk intake. However, this could be due to the protein and/or calcium content of the milk as both of these components have been reported to have this effect when considered separately.

Toxicological studies on medicinal recombinant human IGF-1 (rhIGF)

84. The results of studies of the safety of rhIGF-1 indicate that parenteral doses can be carcinogenic, causing malignant mammary tumours in rats, although rhIGF-1 itself does not appear to be genotoxic. It remains unclear whether dietary doses of IGF-1 would be carcinogenic since it is unlikely that it is absorbed to any significant extent and is unlikely to act in the lumen.

85. Several clinical studies of rhIGF-1 have been performed in humans as part of its development as a medicinal product. There was no evidence from the clinical studies to suggest that treatment with rhIGF-1 caused any cancer in treated patients.

Circulating IGF-1 and cancer risk – comments on studies in general.

86. A variety of observational studies in humans have considered the association between circulating IGF-1 and the risk of cancers. Many of these are inconclusive with respect to the effects of dietary IGF-1 due to the absence of good exposure data. Since the majority of IGF-1 measurements were taken only at baseline, it is not possible to assess time trends. Where these data are available, the results are inconsistent.

87. The results of the available studies assessing the risk of cancer related to circulating IGF-1 are frequently inconsistent. There are a number of issues related to design and conduct which apply to all the cancer sites considered. For example:

i) There are a wide range of different study designs and a range of potentially confounding factors that may influence the results, which have not been considered consistently across the different studies.

ii) The number of participants is often small, particularly in retrospective studies. The cases themselves may have disease of varying degrees of severity, this may be important since tumours produce their own growth factors complicating the interpretation of retrospective studies, although the extent to which tumour derived IGF-1 contributes to circulating levels is uncertain.

iii) The control subjects for some studies were patients with other conditions such as benign prostate hyperplasia, gastrointestinal polyps or benign lung disease rather than being healthy participants with normal pathology and thus results may not have been comparable across studies.

iv) Data on lifestyle factors such as diet and demographic factors, notably ethnicity, is often absent or inconsistent across studies. This may be important if particular lifestyle factors or genetic polymorphisms are relevant to IGF-1 levels.

v) IGF-1 concentrations may be measured and reported as total or free IGF-1 or this may not be specified. Some studies adjust the IGF-1 results for IGFBP-3 and vice versa, and others present information on the IGF-1/IGFBP-3 molar ratio.

vi) The choice of assay used to measure IGF-1 may also be important since it is unclear to what extent active (free) IGF-1 is measured by the different procedures. The time from sample collection to diagnosis may also vary between studies.

IGF-1 and breast cancer

88. There are sixteen retrospective studies comparing circulating blood IGF-1 levels in women with breast cancer and matching controls, these have reported both increased levels of IGF-1 in cancer patients compared to controls, and no difference.

89. The results of the twenty one prospective studies investigating levels of IGF-1 and breast cancer risk are also inconsistent. Some studies report an association between IGF-1 and others report no association. Where women have been considered in terms of their menopausal status, the associations reported for post-

and pre-menopausal women have also differed. Only one study excluded peri-menopausal women from the analysis.

90. Four meta-analyses have been performed. These also produced conflicting results, although generally they were more likely than individual studies to report a positive in association.

91. Overall, the database was deemed insufficient to link dietary IGF-1 exposure directly with breast cancer risk.

92. Although high levels of IGFBP-3 may reduce the risk of cancer by reducing the amount of free IGF-1 in circulation, the results from studies on breast cancer are inconclusive.

IGF-1 and prostate cancer

93. Twenty six retrospective studies have been considered; the results are inconsistent, with many studies reporting no difference in IGF-1 levels between prostate cancer cases and controls, but with a similar number reporting elevated IGF-1 levels in prostate cancer cases compared to controls.

94. Of the twenty prospective studies considered, the results are similarly variable, with around half of the studies reporting no association and the other half a positive association. The results of studies analysing the association between IGF-1 levels and prostate cancer stage and/or severity also appear to be inconsistent.

95. A total of five meta-analyses have been performed on the available data and all have reported a positive association between IGF-1 levels and the risk of prostate cancer. Significant heterogeneity has been noted among the studies: some of the reasons for this have been considered above.

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

97. Overall, conclusions could not be drawn with regard to dietary IGF-1 exposure and prostate cancer risk.

IGF-1 and colorectal cancer

98. Unlike other cancer sites, the intestinal tissues may be directly exposed to dietary IGF-1 if it survives digestion in the stomach.

99. Of the eleven retrospective studies comparing circulating serum or plasma IGF-1 levels in patients with colorectal cancer and controls, both increased levels of IGF-1 and no difference between the cancer patients and controls have been reported.

100. The results of the nineteen prospective studies investigating levels of IGF-1 and colorectal cancer risk are also inconsistent. Some studies report an association between IGF-1 and colorectal cancer risk, while other studies report no association.

101. Five meta-analyses have also been performed. These generally indicated a positive association between circulating IGF-1 and the risk of colorectal cancer.

102. Results for an association of colorectal cancer risk with IGFBP-3 are also inconsistent.

103. Overall, conclusions could not be drawn with regard to dietary IGF-1 exposure and colorectal cancer risk.

IGF-1 and lung cancer.

104. Although lung cancer is considered to be largely preventable with smoking and industrial exposures being major risk factors, it has been suggested that IGF-1 may act with tobacco carcinogens to promote lung cancer and that it could also be involved in tumour de-differentiation.

105. The twelve retrospective studies comparing circulating serum or plasma IGF-1 levels in patients with lung cancer and controls which have been considered have reported increased, decreased and no difference in the levels of IGF-1 in cancer patients compared to controls. Since cancers may produce their own growth factors, the results are difficult to interpret.

106. The results of the six prospective studies investigating levels of IGF-1 and lung cancer risk are also inconsistent. Some studies report an association between IGF-1 but the majority report no association.

107. Five meta-analyses have also been performed. These produced results which generally did not show any association.

108. Results for an association with IGFBP-3 are also inconsistent, but some data indicate an inverse association.

109. Overall, conclusions could not be drawn with regard to dietary IGF-1 exposure and lung cancer risk.

Studies linking cancer risk and dietary IGF-1

110. Although there are numerous epidemiology studies assessing the link between diet and cancer risk, there are very few studies which have attempted to link both dietary exposure, circulating IGF-1 concentration and cancer risk. From the limited data available, milk consumption was either protective against colorectal cancer for individuals with high circulating IGF-1 or there was no association between colorectal cancer risk with increasing IGF-1 levels associated with consumption of dairy calcium, dairy proteins and other food components.

Overall conclusion

111. There is insufficient evidence to draw any firm conclusions as to whether exposure to dietary IGF-1 is associated with an increased incidence of cancer in consumers. However, the data indicate that the levels of IGF-1 consumed are likely to be low and that IGF-1 is likely to be broken down in the gut and not absorbed to any significant extent. Thus the risk, if any, is likely to be low.

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Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATBC	Alpha Tocopherol Beta Carotene
BMI	Body Mass Index
BPI	Benign Prostate Hyperplasia
BST	Bovine Somatotropin
BW	Body Weight
CI	Confidence Intervals
COC	Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment
CRC	Colorectal cancer
DSL	Diagnostic Systems Limited
EDTA	Ethylenediaminetetraacetic Acid
ELISA	Enzyme Linked Immunosorbent Assay
EMEA	European Medicines Agency
EPIC	European Prospective Investigation into Cancer and Nutrition
EU	European Union
FSA	Food Standards Agency
GH	Growth Hormone
HPFS	Health Professionals Follow Up Study
HRT	Hormone Replacement Therapy
IGF	Insulin-like Growth Factor
IGFBP	IGF Binding Protein
IQR	Inter Quartile Range
IRR	Incidence Rate Ratio
i.v.	intra-venous
kg	Kilogramme
µg	Microgramme
mg	Milligramme
ml	Millilitre
mRNA	messenger Ribonucleic Acid
NDNS	National Diet and Nutrition Survey

NHS	National Health Service
ng	Nanogramme
NOEL	No Observed Effect Level
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSCLS	Non-small cell lung cancer
OR	Odds Ratio
PLCO	Prostate, Lung, Colorectal, and Ovarian screening trial.
PSA	Prostate Specific Antigen
rh	Recombinant Human
RIA	Radioimmunoassay
RR	Relative Risks
s.c.	Sub-cutaneous
SCLC	Small cell lung cancer
SD	Standard Deviation
SEM	Standard Error of the Mean
US	United States
VMD	Veterinary Medicines Directorate
VPC	Veterinary Products Committee
WCRF	World Cancer Research Fund

Annex A

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

Statement on possible carcinogenic hazard to consumers from insulin-like growth factor-1 (IGF-1) in the diet

Search strategy

Details of literature search

1. Question to be addressed: “Does the ingestion of IGF-I in the diet cause an increased risk of cancer in consumers?”

2. The starting point for obtaining documents on the dietary effects of IGF-I was the book “Your Life In Your Hands” by Jane Plant. All cited articles that referred to IGF-I were obtained. These articles were often not primary references to original research, so the original reports that were cited in the articles were obtained also.

3. Several searches of the literature were performed on computer by the FSA’s Information Unit. The databases searched included PubMed and the British Library ETOC. Several combinations of keywords were used, including:
- IGF-I (title) AND food,
- IGF-I (title) AND cancer (all fields) filtered by Cancer Cells,
- IGF-I (title) factor AND digestion OR breakdown,
- IGF-I (title) AND absorption, IGF-1 (title) OR insulin-like growth factor AND gut AND lining OR lumen.

4. Less formal searches were also performed using Google.

5. Articles were chosen from the results of the literature search according to the relevance of their titles and/or abstracts to:
- concentrations of IGF-I in foodstuffs,
- endogenous levels of IGF-I
- association of endogenous IGF-I levels with cancers,
- association of eating particular foods with cancer risks,
- toxicological or pharmacokinetic studies of IGF-I,
- possible mechanisms of action.

6. The selected articles were obtained. Further relevant articles were cited in the articles that had been obtained and copies of these too were ordered.

7. It was not possible to obtain original copies of the full reports of toxicological studies submitted in support of the authorisation of use of IGF-I as a medicine for human patients. However, published summaries of the studies were available.

8. Not all of the obtained articles were cited in the discussion papers prepared by the Secretariat. Some did not meet the selection criteria, despite their titles. Some repeated information given elsewhere. Wherever possible, the primary source of information was used.

Annex B

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

Statement on possible carcinogenic hazard to consumers from insulin-like growth factor-1 (IGF-1) in the diet

Summary tables of epidemiology studies.

Table B1: Summary of results of epidemiology studies of breast cancer risk associated with IGF-1 and related substances

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
Retrospective studies						
Breast cancer patients treated with tamoxifen or placebo	69 patients-		Not stated – probably radio immunoassay (RIA)	-	It was noted that tamoxifen treatment caused a reduction in serum IGF-1 (1.4 U/ml in treated group compared to 0.9 U/ml in controls, *p*= 0.02)	Pollak *et al*., 1992[10]
French breast cancer patients, aged 20-80 (only those > 35y analysed)	47 cases; 134 controls	Age	Laboratory RIA on plasma and acid ethanol[11] extract of plasma.	Positive	Higher median levels of total and free IGF-1 in cases (152 and 26 ng/ml) than in controls (115 and 20 ng/ml).	Peyrat *et al*., 1993
Dutch breast cancer patients aged 38-75 y	150 cases; 441 controls	Age, menopausal status, family history, pre-menopausal BMI, height, waist to hip ratio, albumin, C-peptide, testosterone, c-reactive protein.	Laboratory RIA.	Positive	Elevated IGF-1 in pre-menopausal patients (*p* = 0.025) but not in post-menopausal patients[12]. RR; 95%CI =7.34; 1.67-32.16 for IGF-1:IGFB-3 ratio, comparing upper and lower quintiles. No differences in IGFBP-3. IGF-1:IGFBP-3 ratio significantly higher in pre-menopausal cases compared to controls only.	Bruning *et al*., 1995

[9] Free IGF-1 is the biologically active form.
[10] Original study published as Pollak *et al*. 1990
[11] Acid-ethanol extraction removes binding proteins and improves the accuracy of the assay.
[12] Group mean concentrations not given for IGF-1 or IGFBP-3.

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
Chinese breast cancer patients (age not given)	63 cases; 27 controls with benign breast disease.	Commercial RIA	RIA after acid extraction	None	No significant difference between IGF-1 in cases (149 ng/ml) and controls (174 ng/ml) High IGFBP-1 and 3 associated with decreased risk, IGFBP-4 with increased risk (p <0.05)	Ng *et al*., 1998
US pre-menopausal breast cancer patients (mean age 42.6 y)	99 cases; 99 controls with non-proliferative breast disease	Age, weight.	RIA after acid extraction	None	No significant association between IGF-1 and cancer ORs (p > 0.05, but OR; 95%CI of 2.05; 0.93-4.53, p= 0.07 for comparison of highest quintile of IGFBP-3 levels versus the lowest quintile "approaching significance".	Del Giudice *et al*., 1998
US breast cancer patients, aged <40 to 49	94 cases 76 controls	Age, age at first birth, age at menarche, height, BMI, log oestradiol, ethnicity, parity, family history.	Commercial immunoradio-metric assay	Positive	Increased breast cancer risk in upper two tertiles of IGF-1 levels as compared with the lower tertile (OR; 95%CIs =2.4; 1.0-5.6 and 1.8; 0.7-4.6[13]). Decreased risk of cancer in upper two tertiles of IGFBP-3 compared to the lowest (0.4;0.2-1.0 and 0.7;0.3-1.7). Women with high IGF-1 and low IGFBP-3 at higher risk than low IGF-1 and high IGFBP-3.	Bohlke *et al*., 1998
US women mean age 74 (54.6 at recruitment) from Rancho Bernardo study	45 cases 393 controls	Age, age at menarche, age at menopause, no of liver births, current weight or weight gain.	RIA stated not to cross react	None	Mean ± SD IGF-1 120.22 ± 40.64 ng/ml in cases; 126.96 ± 53.97 ng/ml in controls. Not significantly different. Also, not significantly different when analysed by logistic regression (p = 0.44).	Jernström & Barrett-Connor., 1999

[13] *P* values not stated

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
US women mean age 52 (largely African-American or Hispanic)	130 cases 42 controls	Hormone treatment, smoking, height, BMI, age, age at menarche, age at menopause.	Commercial RIA after acid extraction	Positive	Mean ± SEM IGF-1 111.9 ± 6.6 ng/ml in cases; 92.1 ± 6.4 ng/ml in controls. Significant (p = 0.019). IGF-1 levels higher in pre-menopausal women with recurring compared to non-recurring breast cancer (157 ± 16 vs 104 ± 9 ng/ml, p= 0.01) but not in post-menopausal women (88.8 ± 14 vs 97.4 ± 10 ng/ml) No differences in IGF-1 levels in breast cancer patients of different ethnicities.	Vadgama *et al*., 1999
NZ women undergoing surgery for breast lesions	12 benign 31 malignant + matched controls (for both conditions)	Age	RIA after acid extraction	None	IGF-1 150.9 and 142 ng/ml in benign breast disease cases and controls and 128 and 126 ng/ml in breast cancer patients and controls. Not significantly different. IGFBP-3 higher in women with benign breast disease (3600 ± 700 ng/ml compared to controls (2700 ± 600 ng/ml) or cancer patients (2700 ± 500 ng/ml), p = 0.001 Free IGF (1 and 2) lower in women with benign breast disease	Holdaway *et al*., 1999

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
US breast cancer patients, aged <40 to 49	83 cases 69 controls		Commercial immunoradio-metric assay	None	Mean ± SE IGF-1 = 161.52 ± 5.48 ng/ml in cases and 157.95 ± 7.45 ng/ml in controls. Not significantly different. No differences in IGFBP-3 between groups (3321.67 ±.46.51 and 3343.04 ± 49.56 ng/ml respectively)	Mantzoros *et al*., 1999
Breast cancer patients aged <45 to >75 y	75 cases; 75 controls	Age, residence.	Commercial immunoradio-metric assay of serum samples	None	No association between IGF-1 and breast cancer in pre- or post-menopausal women. Mean ± SE IGF-1 = 182.1 ± 13.3 ng/ml in cases and 197.3 ± 15.9 ng/ml in controls (p = 0.47) for pre-menopausal women and 144.0 ± 7.1 and 141.6 ± 7.0 for post-menopausal women (p = 0.81)	Petridou *et al*., 2000
Black & white American women aged 31-67 y	40 cases:40 controls	Age, ethnicity, menopausal status, IGFBP-3	Commercial DSL ELISA	Positive for free IGF-I	OR; 95%CI =2.00; 0.43-9.28 p = 0.376 for women with greater than the median level of IGF-1 and 6.31; 1.03-38.72, p = 0.047 for greater than the median level of free IGF-1. OR; 95%CI for greater than the median level of total IGFBP-3 = 0.89; 0.38-2.13, p= 0.420. Median (range) 106 (40-253) and 97 (39-202 ng/ml) for total IGF-1, 1.2 (0.1-2.7) and 0.9 (0.2-2.6) ng/ml for free IGF-1 and 3020 (1130-4910) and 2720 (1360-4480) ng/ml IGFBP-3 in cases and controls respectively.	Li *et al*., 2001

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
Chinese breast cancer patients, aged 48.5±8.3 y	300 cases; 300 controls	Age, menopausal status, BMI, age at menarche, age at first live birth, waist: hip ratio, history of fibroadenoma, family history of breast cancer and IGF-I or IGFBBP-3.	Commercial DSL ELISA	Positive. The effect was stronger in pre compared to post-menopausal women.	For all women[14], median (range) plasma IGF-1 was higher in cases (143 (31-334) ng/ml) than in controls (127 (34-350) ng/ml) $p < 0.001$ Partially adjusted OR; 95% CI = 1.95; 1.18-3.23, top vs bottom tertile, p_{trend} = 0.009. This reduced when adjusted for IGFBP-3 1.49; 0.85-2.59, p_{trend} = 0.199. IGFBP-3 also significantly higher in cases than controls 4340 (2100-9767) and 4030 (1513-10740) ng/ml, $p < 0.001$. Partially adjusted OR; 95% CI = 3.00; 1.70-5.31, top vs bottom tertile, p_{trend} = 0.009. This reduced when adjusted for IGF-1, 2.50; 1.37-4.58 p_{trend} = 0.004.	Yu *et al*., 2002

[14] Additional analyses by menopausal status were presented in the paper.

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
Taiwanese women aged 24-72	297 cases; 593 controls	Date of enrolment, fasting status. "Matching factors" and IGFBP-3	Commercial DSL immunoradio-metric assay	Positive	High IGF-1 associated with increased risk of pre but not post- menopausal breast cancer. Adjusted OR; 95% CI = 1.45; 0.83-2.19, p_{trend} = 0.454 top vs bottom tertile for all women, 1.86; 1.01-3.44, p_{trend} = 0.040 for pre-menopausal women and 1.53; 0.75-3.10, (p_{trend} = 0.235 for post-menopausal women. No association with IGFBP-3. Adjusted OR; 95% CI = 0.81; 0.51-1.28, p_{trend}= 0.361 top vs bottom tertile for all women, 0.92; 0.50-1.69, p_{trend} = 0.770 for pre-menopausal women and 0.66; 0.32-1.3.7, p_{trend} = 0.271 for post-menopausal women.	Wu *et al*, 2009.

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
US women aged 25-79	184 cases; 522 controls	Age, study centre, ethnicity education, recent hormone exposure, BMI, parity, total energy expenditure, total calories and cholesterol.	Commercial IGF-1 (IGFBP-3 blocked) RIA	Positive	IGF-1 associated with increased risk: OR; 95% CI = 1.92; 1.07-3.43, p_{trend} = 0.05 (top vs bottom quartile) for all women. When analysed by menopausal status or ethnicity, this was significant only in post-menopausal or non-hispanic white (NHW) women. IGFBP-3 associated with increased risk of breast cancer: 3.04; 1.63-5.67, p_{trend} = 0.05 for all women. When analysed by menopausal status or ethnicity, this was significant only in post-menopausal or NHW women. The IGF-1: IGFBP-3 ratio was not significant for any group.	Rollison *et al*, 2010.
Prospective studies						
US women aged 30-55 y from Nurses' Health Study	397 cases; 620 controls	Age, time of blood draw, fasting status, month of blood sampling, menopausal status, use of post-menopausal hormones.	Commercial DSL ELISA	Positive for pre-menopausal women aged < 50 y at baseline only.	RR; 95%CI = 0.85; 0.53-1.39, *p* trend = 0.63 and 0.99; 0.65-1.50, *p* trend = 0.86 for post-menopausal women and all women, top vs bottom quintile. 7.28; 2.40-22.0, *p* trend = 0.01 in pre-menopausal women ≤ 50 y top vs bottom tertile. Median (range) IGF-1 = 206 (77.6-425 ng/ml, in cases compared to 175 (84.9-320) ng/ml in controls, *p*= 0.009. No differences in levels in cases and controls for whole group or post-menopausal women	Hankinson *et al*., 1998

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
US women aged 30-55 y from Nurses' Health Study	800 cases; 1129 controls	Age, time of blood draw, fasting status, month of blood sampling, menopausal status, use of post-menopausal hormones.	Commercial DSL ELISA after acid extraction	Positive for pre-menopausal women aged < 50 y at baseline only	RR; 95%CI = 1.0; 0.7-1.5, *p* trend = 0.59 for post-menopausal women, top vs bottom quintile and 1.60; 1.0-2.5, *p* trend = 0.07 for pre-menopausal women, top vs bottom tertile. 2.5; 1.4-4.3, *p* trend = 0.01 in pre-menopausal women ≤ 50 y top vs bottom tertile. Median (range) IGF-1 187 (135-264) ng/mL in cases compared to 176 (128-253) ng/ml in controls. No differences in levels in in cases and controls for all, post-menopausal or all premenopausal women.	Schernhammer *et al*., 2005 (update / expansion of Hankinson *et al*., 1998)
US women aged 25-42 y from Nurses' Health Study II	317 cases; 634 controls	Age, time of blood draw, fasting status, month of blood sampling, menopausal status, luteal day, ethnicity.	Commercial ELISA after acid extraction	None	Median (range) IGF-1 = 230 (153-346) and 239 (135-341), 242 (164-352) and 249 (150-350) and, 260 (167-367) and 258 (151-350) ng/ml in cases and controls for all, premenopausal or pre-menopausal aged ≤ 50 women. No association between IGF-1, IGFBP-I or IGFBP-3 and breast cancer risk in largely pre-menopausal women. RR: 95%CI = 1,0; 0.73-1.37, *p* trend = 0.77, top vs bottom quartile for IGF-1 and 1.07; 0.79-1.45, *p* trend = 0.76 for IGFBP-3.	Schernhammer *et al.,* 2006

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
American women aged 35-65 y	115 cases; 486 controls	Age, menopausal status, stage of menstrual cycle at blood sampling. Further adjustments for history of benign breast disease, family history of breast cancer, parity	RIA after acid extraction	Positive in women < 50 y only.	Adjusted OR; 95%CI =2.3; 1.07-4.94, *p* trend = 0.03, top vs bottom quartile in women ≤ 50y and 1.60; 0.91-2.81, *p* trend = 0.09 and 0.95; 0.49-1.86, *p* trend = 0.87 in all pre-menopausal and post-menopausal women respectively. Mean (SE) IGF-1 = 196.0 (3.78) and 200.4 (2.60) ng/mL in cases and controls for all women, For IGFBP-3 = 2.17; 0.99-4.76 *p* trend = 0.09, 1.18; 0.66-2.08, *p* trend = 0.63, and1.08; 0.54-2.16, *p* trend = 0.63, in pre-menopausal women ≤ 50y, all pre-menopausal and post-menopausal women respectively.	Toniolo *et al*., 2000
American women “pre-menopausal”	138 cases; 259 controls	Age, menopausal status, date of baseline blood sampling, assay method, functional IGFBP-3.	In house RIA or 2 commercial ELISAs after acid extraction	Positive	Variable ORs depending on assay and adjustments used. Increased risk in women with elevated IGF-1 and IGFBP-3 levels. For example, adjusted OR; 95%CI =1.93; 1.00-3.72, *p* trend = 0.02, top vs bottom quartile IGF-1. For IGFBP-3, 2.03; 1.09-3.76 *p* trend = 0.02, top vs bottom quartile.	Extension of above study. Rinaldi *et al*., 2005a

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
US, Swedish and Italian women pre-menopausal aged 35-47	220 cases; 434 controls	Age at menarche, BMI, family history, and benign breast disease + matching criteria of study cohort, age, menopausal status, date of baseline blood sampling,	Commercial DSL ELISA on plasma or serum	None	Mean (range, 5 and 95th) levels of IGF-1 =301.5 (174.1-444.2) and 293.6 (165.7-450.1) ng/ml in cases and controls. OR 1.41; 0.75-2.63, *p* trend = 0.15, for highest vs lowest quintile IGF-1, lower if adjusted for IGFBP-3. Mean (range) levels of IGFBP-3 = 3683 (2425-5089) and 3588 (2347-4872) ng/ml in cases and controls. OR 1.77; 0.97-3.24, *p* trend = 0.09, for highest vs lowest quintile IGFBP-3, lower if adjusted for IGF-1.	Rinaldi *et al*., 2005b - re-analysis of Toniolo *et al*., 2000, Kaaks *et al*., 2002, Muti *et al* 2002.

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
Italian women aged 35-69 y	133 cases; 532 controls	Matched for age, menopausal status, daylight saving period at recruitment, recruitment centre and recruitment period. Also adjusted for BMI, social and economic status and reproductive variables	Commercial DSL immunoradio-metric assay of free and total IGF-1	Positive in pre-menopausal women only.	No differences in IGF-1 levels: Mean (± SD) IGF-1 = 170.1 (± 55.2) and 158.8 (± 59.8) ng/ml in pre-menopausal cases and controls and 123.9 (± 44.3) and 130.1 (± 50) in postmenopausal cases and controls. Adjusted RR; 95%CI =3.12; 1.13-8.60, *p* trend = 0.01, comparing upper & lower quartiles of total IGF-1 in pre-menopausal women and 0.58; 0.24-1.36, *p* trend = 0.25. Free IGF-1 not associated. Mean (± SD) IGFBP-3 levels significantly higher in pre-menopausal cases compared to controls 3754 ± 965.1 and 3549.2 ± 753.4 ng/ml, $p < 0.05$. 3690 ± 1025.6 and 3739.8 ± 806 in post-menopausal cases and controls. Adjusted RR = 2.31; 0.97-5.53, *p* trend = 0.02 and 0.73; 0.30-1.75, *p* trend = 0.25	Muti *et al*., 2002

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
American breast cancer patients, aged 19-73 y	126 cases of which 66 were pre-menopausal and 126 controls	Age, date of examination, length of follow up for matching. Insulin, glucose, BMI, IGFBP-3.	Commercial DSL immunoradio-metric assay after acid extraction	Positive in pre-menopausal women in adjusted model but not if adjusted for IGFBP-3.	No differences in IGF-1 levels - Mean (± SD) IGF-1 = 258 (± 86) and 244 (± 90) ng/ml in pre-menopausal cases and controls and 227 (± 71) and 243 (± 76) in postmenopausal cases and controls. Fully adjusted OR; 95%CI = 2.01; 0.33-12.4, *p* trend = 0.25, adjusted 3.49; 0.65-18.7, *p* trend = 0.05 in premenopausal women top vs bottom quartile. Fully adjusted 1.22; 0.21-6.78, *p* trend = 0.74 in post-menopausal women. IGFBP-3 higher in cases compared to controls: 2510 ± 700 and 2310 ± 670 ng/ml in pre-menopausal *p* =0.04 and lower in cases compared to controls 2220 ± 530 and 2420 ± 660 ng/ml, *p* =0.04 in post-menopausal women. Adjusted OR; 95%CI = 5.28; 1.13-24.7, *p* trend = 0.033, and 0.44; 0.15-1.28 *p* trend = 0.10 pre and post-menopausal women top vs bottom quartile. Elevated IGFBP-2 was associated with reduced breast cancer risk in post-menopausal women.	Krajcik *et al*., 2002

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
Swedish women aged 29-73 from study cohorts, based in 2 towns (Malmö and Umeå). Analysed as 3 groups, 2 single cohorts and combined.	513 cases; 987 controls	Age, date of blood donation, use of exogenous hormones, menopausal status.	Commercial immunoradio-metric assay after acid extraction	None	IGF-1 levels higher in cases in Umeå cohort only[15]. Small association between IGF-1 and breast cancer risk in post-menopausal women (OR s 1.73 to 1.9) in 1 of 3 cohorts only; reduced when adjusted for hormone use. No association in pre-menopausal women. No differences in IGBP-3 levels between cases and controls. No association with breast cancer risk.	Kaaks *et al.,* 2002
Dutch women from Prospect-Epic and Monitoring Project on Cardiovascular disease risk factors (PPHV) cohorts. Mean age 57 and post-menopausal status.	149 cases; 333 controls	Cohort, age, place of residency and date of enrolment. Further adjustment for BMI, age at menarche, age at first full term delivery and IGFBP-3:IGF-1.	Commercial DSL immunoradio-metric assay after acid extraction	None	No association between IGF-1 and breast cancer risk, OR;95%CI = 0.7; 0.3-1.5, top vs bottom quartile, p trend not given Also, no association between IGFBP-3, 1.4; 0.6-3.4 IGFBP-1, -2, and IGF-1/IGFBP-3 ratio also not associated with breast cancer risk in post-menopausal women.	Keinan-Boker *et al.,* 2003

[15] Further details are available in the paper.

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
Danish women aged 50-64	412 cases; 397 controls	Parity, age of first birth, benign tumours, BMI, education, alcohol and HRT duration	Non-competitive time-resolved immunofluoro-metric assay (DELFIA) after acid extraction.	None	Median (5-95th percentile) for IGF-1= 126 (78-203) in cases and 124 (76-187) in controls. No association between IGF-1 and risk IRR[16]; 95%CI = 0.97; 0.87-1.08 per 25 unit increase. IGFBP-3 concentrations 4,157 (2,996-5,564) in cases and 4,063 (2,865-5,470) in controls. IRR =1.13; 1.02-1.26 per 500 unit increase.	Grønbæk *et al.,* 2004

[16] Incident rate ratio

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
Guernsey women, ≥35 at recruitment, mean age 57 at diagnosis	117cases of which 70 were pre-menopausal and 350 controls	Age, date of blood collection, menopausal status. Further adjustment for BMI, age at menarche, age at first birth, IGFBP-3.	Commercial DSL ELISA	None	No differences in IGF-1 levels - Mean (inter-quartile range) IGF-1 = 171 (142-205) and 170 (141-203) ng/ml in pre-menopausal cases and controls and 125 (98-178) and 128 (103-162) ng/ml in postmenopausal cases and controls. Non-significant association for IGF-1 adjusted for IGFBP-3 in pre-menopausal women OR; 95%CI= 1.71; 0.74-3.95, *p* trend = 0.21 top vs bottom tertile. No association in post-menopausal women, 0.73; 0.29-1.84, *p* trend = 0.52 No differences in IGFBP-3 levels – IGFBP-3 = 4709 (3906-5346) and 4764 (4294-5374) ng/ml in pre-menopausal cases and controls and 4626 (3850-5374) and 4543 (3933-5374) ng/ml in postmenopausal cases and controls. IGFBP-3 associated with decreased risk in premenopausal women, 0.60; 0.29-1.24, *p* trend = 0.02, association reduced when adjusted for IGF-1. No associations in post-menopausal women	Allen *et al.,* 2005

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
European women aged 50 or more at diagnosis from CLUE I and CLUE II cohorts	243 cases of which 152 were pre-menopausal and 243 controls	Age, menopausal status, date of blood draw, ethnicity, freeze/ thaw history of sample. Further adjusted for IGFBP-3,	Commercial DSL ELISA	Positive for youngest pre-menopausal women	No difference in IGF-1 levels[17]. No overall association, OR; 95%CI = 1.60; 0.85-3.02 *p* trend = 0.30 and 1.55; 0.61-3.94 *p* trend = 0.48 in pre- and postmenopausal women, top vs bottom tertile. Association with increased risk in the youngest (25-35y) premenopausal women, 5.31; 0.85-13.13, *p* trend = 0.01 No difference in IGFBP-3 levels. No overall association, OR; 95%CI = 0.69; 0.36-1.34 *p* trend = 0.73 and 1.17; 0.48-2.84 *p* trend = 0.36 in pre- and post-menopausal women.	Rollison *et al.,* 2005
European women aged 35-69 from EPIC cohort	1081 cases of which 370 were pre-menopausal and 2098 controls	Age, menopausal status, time of day of blood draw, phase of menstrual cycle (where relevant) and fasting status. Further adjustment for BMI, age at first full term pregnancy, number of full term pregnancies, age at menarche and previous use of oral contraceptives.	Commercial DSL ELISA after acid extraction	Positive for post-menopausal women.	IGF-1 not associated with increased risk in all cases (Fully adjusted OR; 95%CI = 1.29; 0.98-1.68, *p* trend = 0.34 or pre-menopausal women (1.03; 0.60-1.77, *p* trend = 0.81) but associated with increased risk in post-menopausal women, 1.38; 1.02-1.86, *p* trend = 0.01, top vs bottom quintile. Increased IGFBP-3 associated with increased risk in all cases, (fully adjusted = 1.29; 0.98-1.70 *p* trend = 0.05) and post-menopausal women (1.44; 1.04-1.98 *p* trend = 0.01) but not pre-menopausal women (0.92; 0.55-1.70 *p* trend = 0.69).	Rinaldi *et al.,* 2006

[17] IGF-I and IGFBP-3 levels presented in paper by separate age groups only.

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
Swedish women 19-43 y from the Northern Sweden Maternity cohort	212 cases; 369 controls	Parity, age at blood draw, date of blood draw, eligibility (gestational age).	Commercial immunoradio-metric assay	Positive	Association between IGF-1 and increased risk (OR; 95%CI =1.7; 1.1-2.7 *p* trend = 0.02). The risks were increased in primiparous compared to multiparous women (2.2; 1.1-4.4, *p* trend = 0.02 and 1.4; 0.7-2.8, *p* trend = 0.26, top vs bottom tertile). No association with IGF-2.	Lukanova *et al*., 2006
Swedish women 19-43 y Same cohort as above	244 cases; 453 controls	Age, date of blood draw, gestational age,	Commercial chemiluminescence based immunoassay	Positive	IGF-1 was significantly higher in cases (140.55 and 132.96 ng/ml respectively, *p* <0.03) Association between IGF-1 and increased risk (OR 1.73; 95% CI 1.14-2.63, *p* < 0.009). The effect was stronger in women ≤ 25 y and > 30 compared to women aged 25-30 y and in women where cases were diagnosed less than 15 y from blood sampling	Chen *et al*., 2010.
Finnish women 22-37y Finnish Maternity Cohort	719 cases; 1434 controls	Age, date of blood draw.	Commercial chemilumine-scence based immunoassay	None	No differences in mean (10^{th} and 90^{th} percentile) IGF-1 levels - 133.7 (94.9-198.0) and 134.7 (94.5-195.0) ng/ml cases and control respectively. No association between IGF-1 and increased risk (OR 1.08; 95% CI 0.80-1.47, *p* trend 0.68, top vs bottom quintile).	Toriola *et al*., 2011.

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
Australian women aged 27-75y at baseline Melbourne Collaborative cohort study	423 cases; 1901 controls	Age, menopausal status. Further adjustment for country of birth, age at menarche, parity, duration of lactation, oral contraceptive use, hormone replacement use, physical activity, alcohol consumption, smoking, education BMI and IGFBP-3.	Commercial DSL ELISA	Positive in post-menopausal women only.	No differences in mean (95% CI) IGF-1 levels - 161 (156-167) and 160 (157-163) ng/ml cases and controls respectively. No overall association for IGF-1 (Fully adjusted HR; 95%CI = 0.95; 0.65-1.40 *p* trend = 0.80 top vs bottom quartile or pre-menopausal women (0.83; 0.49-1.38, *p* trend = 0.57) but positive in post-menopausal women (1.59; 1.03-2.44, *p* trend = 0.05). No differences in IGFBP-3 levels - 3100 (3033-3167) and 3058 (3028-3092) ng/ml in cases and controls respectively. No overall association for IGFBP-3 (1.09; 0.78-1.53) *p* trend = 0.50 or for pre or post-menopausal women (0.73; 0.42-1.26, *p* trend = 0.20 and 1.42; 0.92-2.19, *p* trend = 0.06. IGFBP-3 associated with increased breast cancer risk in women aged >60 (1.6; 1.03-2.55, *p* trend = 0.02.	Baglietto *et al.,* 2007
Norwegian women aged 40-42	325 cases; 647 controls	IGFBP-3, age, year of blood collection.	RIA after acid extraction	Positive	No differences in median (range) IGF-1 levels 205 (38-461) and 202 (53-419) ng/ml in cases and controls respectively. No overall association (OR; 95%CI = 1.46; 0.93-2.32, top vs bottom quintile, *p* trend = 0.15.	Vatten *et al*., 2008

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
US women aged 54-74 from Womens Health Initiative cohort	835 cases; 816 controls	Randomly chosen controls. Further adjustment for age, ethnicity, alcohol consumption, smoking, family history of breast cancer, parity, age at menopause, age at menarche, age at first child's birth, use of oral contraceptives, use of NSAIDs, use of hormone replacement therapy, education, oestradiol levels, physical activity and BMI.	Commercial ELISA for total and free IGF-1	None	No association with total or free IGF-1. HR;95%CI = 1.21; 0.85-1.72, *p* trend = 0.15 and 1.06; 0.77-1.54, *p* trend = 0.67 respectively No association with IGFBP-3- 0.77; 0.55-1.08	Gunter *et al*, 2009.
US women aged 55-74 from Prostate, Lung, Colorectal, and Ovarian screening trial. (PLCO) cohort	389 cases; 470 controls	Age at randomization, date of blood sampling. BMI, oestradiol.	Commercial DSL ELISA for total IGF-1	None (Authors considered it positive but not statistically significant – the *p* values are not given)	No differences in mean (95% CI) IGF-1 levels - 209 (203-215) and 205 (198-213) ng/ml cases and controls respectively. IGF-1 associated with increased risk of postmenopausal breast cancer (OR; 95%CI = 1.28;0.67-2.44, for IGFI) No differences in mean (95% CI) IGFBP-3 levels - 4580 (4493-4668) and 4579 (4500-4657) ng/ml cases and controls respectively. No association with IGFBP-3.	Schairer *et al*, 2010.

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-1 measured and was it free?[9]	Association between IGF-1 levels and breast cancer	Main results	Reference
US women aged 31-89 with breast cancer from HEAL study	600 cases	BMI, ethnicity, tamoxifen use at blood draw, treatment at diagnosis, IGFBP-3.	Commercial radio immunoassay	Positive	Mortality increased with higher IGF-1 - HR; 95% CI = 3.10; 1.21-7.93, *p* trend = 0.02, highest *vs*. lowest quintile and IGF-1/IGFBP-3 ratio (2.83; 1.25-6.36, *p* trend = 0.01. No dose response relationship noted.	Duggan *et al*., 2013
Meta-analyses						
Meta-analysis of five studies	-		-	*Positive*	*High levels of IGF-1 & IGFBP-3 were associated with increased risk of pre-menopausal breast cancer (OR 1.96), but not of post-menopausal breast cancer (OR 0.97) other analyses performed.*	*Renehan et al., 2004*
Meta-analysis of sixteen studies	-		-	*Positive*	*IGF-1 levels higher for risk in post-menopausal women only (OR 1.39).*	*Shi et al., 2004*
Meta-analysis of seven studies	-		-	*Marginally positive*	*Higher levels of IGF-1 but not IGFBP-3 group were associated with increased risk of pre-menopausal breast cancer (OR 1.74).*	*Sugumar et al., 2004*
Meta-analysis of seventeen studies	-		-	*Positive*	*IGF-1 weakly positively associated with increased risk in pre-menopausal women and strongly positively associated with increased risk in post-menopausal women. IGF-1 positively associated with increased risk of (oestrogen positive) breast cancer, but not of (oestrogen-negative) breast cancer*	*Key et al., 2010*

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Table 2: Summary of results of epidemiology studies of prostate cancer risk associated with IGF- and related substances

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
Retrospective studies						
American men (age not known, but described as elderly)	32 cases; 6 controls (male) 6 controls (female)	Radioimmuno-assay (RIA)	Age	None	No difference in IGF-1 levels. IGF-1 Mean ± SD, IGF-1 = 151 ± 42 ng/ml in cases and 138 ± 31 ng/ml in controls No difference in IGFBP-3 levels. Mean ± SD, IGFBP-3 = 13.1 ± 0.8 arbitrary units/mm in cases and 13.2 ± 1.8 in controls. IGFBP-2 higher in cases.	Cohen, *et al.,* 1993
Israeli men, aged 68.5 ± 3.4 y	14 cases; 10 controls (4 with elevated PSA)	RIA after acid extraction	None	None	IGF-1 not elevated in prostate cancer patients, but IGFBP-3 was decreased (68.2 ± 9.1% vs 95.4 ± 0.9% of total serum proteins). Levels not given IGFBP-2 higher in cases.	Kanety, *et al*., 1993
Australian men, aged 60-83 y	16 cases; 15 controls (8 with benign prostate hyperplasia (BPH))	RIA	None	None	IGF-1 not elevated in prostate cancer patients. Mean ± SEM = 139 ± 25 in cases with high prostate specific antigen (PSA), 140 ± 45 in cases with normal PSA and 124 ± 18 in BPH controls. IGFBP-3 not elevated in prostate cancer patients. Mean ± SEM = 2434 ± 270 in cases with high PSA, controls 3201 ± 555 in cases with normal PSA and 2871 ± 386 in BPH controls IGFBP-2 higher in cases.	Ho and Baxter, 1997

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
Greek men, 38.5% aged <69 y, 34.6% aged 70-74 y & 26.9% aged >75 y	52 cases; 52 controls with BPH; 52 healthy controls	Commercial RIA after ethanol extraction	Age, town of residence, height, BMI, schooling, Sex Hormone Binding Globulin, other hormones analysed	Positive	IGF-1 significantly higher in cases compared to healthy controls. Mean (SD) levels of IGF-1 = 160.3 (68.2), 146.0 (68.2) and 124.7 (58.6) ng/ml in cases, BPH controls and controls respectively. Unadjusted OR; 95%CI =1.71; 1.00-3.73, *p* = 0.05 for 60 ng/ml increment of serum IGF-1, comparing IGF-1 in prostate cancer cases with controls.	Mantzoros, *et al*., 1997
Swedish men, aged <80 y	210 cases; 224 controls	Commercial DSL Immuno-radiometric assay.	Age, height, BMI, total energy intake	Positive	Mean (SD) IGF-1 higher in cases than controls (158.4 (53.8) ng/ml vs 147.4 (47.6) ng/ml) *p* = 0.02 Significant association between IGF-1 per 100 ng/ml as a continuous variable and prostate cancer risk (OR; 95%CI = 1.51; 1.0-2.26, *p* = 0.04). Stronger association for men aged <70 y (OR= 2.93;1.43-5.97). No difference in IGFBP-3 levels (2688 (1037) and 2518 (774) ng/ml) No association between IGFBP-3 per 150 ng/ml as a continuous variable and prostate cancer risk (OR; 95%CI = 1.31; 0.95-1.82, *p* = 0.10).	Wolk, *et al*., 1998
Austrian white men aged 56-79 y, with elevated PSA	Cohort of 245 sequential patients, with 74 developing prostate cancer	Commercial DSL immuno-radiometric assay	-	Positive	Mean (±?[18]) IGF-1 level was greater (*p* = 0.03) in prostate cancer patients (176 ± 26 ng/ml) than in those having no prostate cancer (136 ± 23 ng/ml).	Djavan, *et al*., 1999

[18] Not stated whether it is SD or SE

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
Swedish men aged 69.9±6.3 y	208 cases; 70 controls	Commercial DSL immuno-radiometric assay	Age, height, BMI.	None	No differences in mean ± SD IGF-1, 158 ± 53.8 and 152 ± 53.3 ng/ml in cases and controls. No differences in mean ± SD IGFBP-3, 2664 ± 1041 and 2556 ± 783 ng/ml in cases and controls Positive association of IGFBP-1 levels and cancer risk.	Signorello, *et al.,* 1999 Related to study by Wolk *et al*, 1998.
UK men aged 69.9 ± 6.3 y	37 cases; 57 controls Consecutive patients	Commercial Immuno-radiometric assay	Age	None	No difference in mean ± SD IGF-1, 202 ± 64. 1 and 181.3 ± 64.1 ng/ml between cases and controls.	Cutting, *et al.,* 1999
Greek men, mean age 67 and 69 y	34 cases; 131 BPH controls Consecutive patients	Commercial immuno-radiometric assay	Total PSA, free PSA, PSA/IGF-1 ratio	None	No difference between mean ± SD IGF-1 in BPH and prostate cancer patients (104.8 ± 62.3 and 116.3 ± 67.8 ng/ml respectively).	Koliakos, *et al.,* 2000
German men (mean age 66 or 64)	171 cases; 67 controls	Radioimmunoassay and chemi luminescence	Age, testosterone, anti-androgen treatment	None	No difference between mean ± SD IGF-1 levels in prostate cancer patients and controls (158.6 ± 66.5 ng/ml vs 159.1 ± 58.4 ng/ml respectively).	Kurek, *et al*., 2000
US men (age not reported)	57 cases; 39 controls	Commercial DSL active IGF-1 ELISA	Age, weight, PSA	Negative	Mean IGF-1 levels were lower in prostate cancer patients (125 ± 58[19] ng/ml) than in controls (158 ± 71 ng/ml) $p = 0.019$	Baffa, *et al*., 2000

[19] It is not stated whether this was an SD or SEM, the statistical test used was a student's t test.

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
US men aged 62 and 63y controls	38 cases; 40 controls (in remission)	Commercial DSL ELISA or radioimmuno-assay.	"Patient and specimen variations"	None	No differences in IGF-1 levels between cases and controls at first or subsequent serial sample. Median (range) 107.7 (38.9-161.7) and 110.2 (46.6-213.1) ng/ml. p= 0.777 for cases and controls for first sample. IGFBP-3 levels significantly lower in cases - 4091 (2526-7121) and 4768 (2953-6773) ng/ml, p = 0.044 IGFBP-2 levels lower in cases in third and fourth samples only.	Yu, *et al*., 2001
Canadian men, aged 52-75 y	84 cases; 75 controls (BHP patients)	Commercial DSL active IGF-1 ELISA	Age, IGFBP-3 (intact, fragment, total), free & total PSA	Positive	Prostate cancer patients had higher mean ± SEM levels of IGF-1 (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)	Khosravi, *et al*., 2001

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
Chinese men aged 71.9 ± 7.5 y	112 cases; 306 controls	Commercial DSL ELISA after acid-ethanol extraction	IGFBP-I, IGFBP-3, 5α-androstane-3α, 17β-diol glucuronide, sex hormone binding globulin, weight, height, BMI, waist-to-hip ratio	Positive	Mean: 95%CI IGF-I levels higher in cases compared to controls – 138.6; 129.1-148.0 and 123.7; 118.9-128.4 ng/ml respectively, *p*= 0.05. Higher risk of prostate cancer in upper vs lower quartiles of IGF-1 levels, (OR; 95%CI =2.63; 1.19-5.79, *p*=0.01). No difference in IGFBP-3 levels in cases compared to controls – 2777.5; 2634.8-2916.2 and 2792.0; 2701.0-2883.1 ng/ml , *p* =0.85. Prostate cancer risk was non-significantly, inversely related to levels of IGFBP-3 (0.54; 0.26-1.15, trend: *p* > 0.08. Risk elevated for higher IGF-1:IGFBP-3 ratio For localised disease there were significant trends for IGF-1 (15.73; 3.04-81.94, *p*=0.001) and IGF-1: IGFBP-3 ratio. For advanced disease there were significant trends for IGF-1: IGFBP-3 ratio and IGFBP-1.	Chokkalingam, *et al.,* 2001
US men 61.8 ± 7.2 y	120 cases 44 controls 19 men with metastases in lymph nodes and, 10 men with bone metastases.	Commercial DSL ELISA		None	IGF-1 levels non-significantly lower in pre-operative patients and patients with lymph and bone metastases than healthy controls (median level = 151.1, 156.4, 153.4 and 171.3 ng/ml respectively) IGFBP-3 levels lower in patients with bone metastases than those with lymph metastases (3239, 3344, 2989, 2555 ng/ml in cases, controls, lymph metastases and bone metastases respectively) IGFBP-2 levels lower in cases.	Shariat *et al.*, 2002

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
Canadian men, mean aged 65 y cases-63 y controls	244 cases; 408 controls with benign conditions. From consecutive patients.	ELISA	Age, PSA, prostate volume.	None until corrected for age and PSA then negative	No difference in mean IGF-1 (176.1 ± 58.3 and 178.7 ± 54.7 ng/ml) *p*= 0.57 Inverse relationship between IGF-1 and cancer risk when age-adjusted OR; 95%CI = 0.4; 0.2-0.7, *p* = 0.001. No difference in mean IGFBP-3 levels (2724 ± 647 and 2673 ± 589 ng/ml) cases and controls respectively, *p* = 0.3. Inverse relationship between IGFBP-3 and cancer risk when age-adjusted OR;95%CI= 0.6; 0.36-1, *p* = 0.001.	Ismail *et al*., 2002
Japanese men, mean age 69.8y localised cases-and controls and 71.3y advanced cases	112 cases (84 advanced, 28 localised); 32 BPH controls	Commercial immuno-radiometric assay	PSA, IGFBP-3, IGF-1/PSA ratio, IGFBP-3/PSA ratio, age , BMI, smoking	Positive for advanced cases only.	IGF-1 higher in advanced cancer cases than controls (Mean ± SD = 171.8 ± 40.4 vs 140.6 ± 42.5 ng/ml, *p* < 0.01) but not localised cases (166.7 ± 73.9 ng/ml). No association between IGF-1 and cause specific or relapse free survival IGFBP-3 lower (1790 ± 500 ng/ml) in advanced cases compared to localised cases (2090 ± 580 ng/ml) or BPH controls (2110 ± 580 ng/ml) *p* < 0.05. No association between IGFBP-3 and cause specific or relapse free survival	Miyata *et al*., 2003
Italian men median age 68 and 65 y	171 cases: 174 BPH controls	Commercial DSL ELISA	Human glandular Kallikrein (hK2), PSA, free/total PSA, hK2/PSA	Positive	Mean ± SE IGF-1 higher in prostate cancer (142 ± 8.1 ng/ml) compared to controls with BPH (103 ± 7.3 ng/ml) –significance not stated. High IGF-1 predictive of cancer only when corrected for PSA	Scorilas *et al*., 2003

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
Malaysian men mean age 70 68 (cases, BPH) and 57 (controls)	25 cases: 45 BPH, 69 controls	Commercial DSL ELISA	-	None	No significant differences in IGF-1 between the 3 groups (Mean ± SD - 98.3 ± 39.3, 119.3 ± 31.1; 119.36.1 ng/ml respectively p = 0.776 for BPH. p = 0.054 for prostate cancer compared to controls). IGFBP-3 significantly lower in prostate cancer cases (2691 ± 1105 ng/ml, p = 0.029) and BPH cases (2618 ± 816, p = 0.029) compared to controls (3116 ± 618 ng/ml).	Lopez *et al*., 2004
Turkish men aged 51-79 y (controls) and 53-85 y (cases).	24 localised cases, 19 metastasised cases: 45 BPH controls	Commercial DSL Immuno-radiometric assay	-	None	IGF-1 levels similar in all groups (138.3 ± 58.2, 137.7 ± 39.0 and 147.7 ± 4.42 ng/ml respectively). IGFBP-3 levels lower in metastasised group compared to BPH controls (1795.6 ± 305.6 vs 2196.0 ± 505.7 ng/ml, p = 0.005)	Aksoy *et al*., 2004
British men, mean age 62 y	176 cases; 324 controls	Commercial DSL ELISA	Age, GP practice, recruitment date, IGFBP-3, smoking. Other variables BMI, class, exercise, alcohol use, did not affect the model and were not used.	Positive associations stronger for advanced-stage prostate cancer	Mean; 95%CI IGF-1 levels higher in cases (130.7; 125.8-135.9 vs 121.2; 117.4-125.2 ng/ml, p < 0.003) IGF-1 associated with increased risk (OR: 95%CI = 3.00; 1.50-6.01, p trend = 0.005) upper vs lower quartiles adjusted for IGFBP-3 and smoking. No difference in mean:95%CI levels 3311.0; 3161.3-3467.7 and 3220.1;3102.6 and 3342.0 ng/ml in cases and controls respectively, p < 0.3) IGFBP-3 not associated with increased risk (OR: 95%CI = 0.8, 0.29-1.15, p trend = 0.3). IGF-2 associated with increased risk.	Oliver *et al*., 2004

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
Austrian men, median age 67 and 69 y	156 cases; 271 controls	Commercial DSL Immuno-radiometric assay	-	None	Median ± SE IGF-1 levels similar in both groups (154.5 ± 6.0 ng/ml and 153 ± 4.5 ng/ml, $p < 0.33$).	Marszalek *et al*., 2005
Arab men 15-90 y.	30 cases; matched controls	Commercial DSL Immuno-radiometric assay	Age	Positive	IGF-1 levels higher in cases (127.60 ± 85.19 vs 80.77[20] ± 51.69 ng/ml, $p < 0.01$) IGFBP-3 lower in cases (783.4 ± 37.18 vs 897.2 ± 44.72 ng/ml, $p < 0.01$)	Kehinde *et al*., 2005
Canadian men, aged 64 and 65 y	103 cases high grade prostatic interstitial neoplasia (HGPIN); 205 controls	Commercial DSL ELISA	Age, PSA, ethnic background, digital rectal examination.	Positive	IGF-1 levels higher in HGPIN cases than controls (130.2 vs 118.8 ng/ml, $p = 0.01$) OR; 95%CI for HGPIN = 1.95; 1.0-3.7, top vs bottom quartile $p = 0.04$ IGFBP-3 levels non-significantly higher in HGPIN cases than controls (2393.9 vs 2276.0 ng/ml, $p = 0.06$) OR; 95%CI for HGPIN = 2/04; 1.1-3.9, top vs bottom quartile, $p = 0.03$	Nam *et al*., 2005

[20] The way the data are presented makes precise comparison difficult. Concentrations have been presented as mean ± SD for all cancer patients compared to the 30 patients aged 60-69 y since the control data are given as 10 y splits rather than as the whole group.

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
Chinese men (mean age 65 y) with total PSA of 4/-10 ng/ml.	281 cases 305 controls (including normal histology, BPH, and other non-malignant diseases such as prostatitis and PIH)	Commercial DSL ELISA following acid ethanol precipitation	-	Positive	Mean ± SD IGF-1 higher in cases than controls (219 ± 65.27 vs 178 ± 54.9 ng/ml, p = 0.001). Univariate analysis for predicting cancer, crude OR; 95%CI = 3.15; 1.21-6.13, p =0.02. No difference in IGFBP-3 levels (2715 ± 588.4 vs 2694 ± 587.8 ng/ml, p = 0.32) Univariate analysis for predicting cancer 1.36; 0.74-31.5, p =0.85.	Zhigang *et al*., 2007
Men in Belarus	Controls, prostate cancer, BPH, BPH + neoplasia		-	None	No significant differences between levels of IGF-1 (99.2 ± 34.4, 119.2 ± 32.2, 111.2 ± 32.2, 152.0 ± 51.4 ng/ml) & IGFBP-3 (5589 ± 260, 5553 ± 514, 5421 ± 449, 5236 ± 827 ng/ml) in patients and those in controls.	Povelitsa & Nazarov. 2008
Prospective studies						
US male physicians aged 40 to 84 y (PHS study)	152 cases; 152 controls	Commercial DSL ELISA	Age, smoking, duration of follow up.	Positive	IGF-1 higher in cases than controls (269.4 vs 248.9, p = 0.03). IGF-1 associated with increased risk RR;95%CI =2.41;1.23-4.74, top vs bottom quartile (adjusted for IGF-2, IGFBP-3, p = 0.001) No difference in IGFBP-3 levels (not stated) p= 0.95. No association with IGFBP-3 =0.41;0.17-1.03, top vs bottom quartile (adjusted for IGF-2, IGF-1, p = 0.09)	Chan*, et al*., 1998

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
US male physicians aged 40-84 y	530 cases; 534 controls	Commercial DSL ELISA	Age, smoking, IGFBP-3, BMI considered but not used.	Positive for advanced-stage prostate cancer only	For the new cases, there was no association between IGF-1 and total prostate cancer risk *p* trend = 0.39 (results not given in paper). For advanced stage prostate cancer there was a positive association with IGF-1 (RR;95%CI of 5.1; 2.0-13.3, *p* trend = 0.002, top vs bottom quartile) but not early stage disease – 1.2; 0.7-2.2, *p* trend = 0.27. There was a negative association with IGFBP-3 for advanced (0.2:0.1-0.6, *p* trend = 0.01) but not early stage cancer (1.0; 0.6-1.8, *p* trend = 0.80.	Chan *et al*., 2002 - update of Chan *et al*., 1998.
US health plan members, aged 40-80 y	Cohort of 765. 45 cases; 179 controls	Radioimmunoassay	Age, interval between serum collection and diagnosis	None	No association between IGF-1 and prostate cancer (RR; 95%CI 0.81; 0.36-1.80, top vs bottom quartile, *p*= 0.74). Additional analysis by conditional logistic regression also negative.	Schaefer, *et al*., 1998
US men (mainly white) age 64.8 ± 8.9 y 65.7 ± 9.7 y 49.1 ± 6.1 y	72 cases; 127 controls 76 non-age-matched controls with normal prostate volume.	Commercial radio-immunoassay	Age, length of sample storage, visit date, IGF-2, IGFBP-3, PSA	Positive	High IGF-1 associated with high risk of prostate cancer. Adjusted OR; 95%CI for IGF-1 = 3.1; 1.1-8.7 top vs bottom tertile, multivariate analysis[21]. No association with IGFBP-3 (0.71;0.3-1.7) Low IGF-2 associated with increased risk 0.20; 0.07-0.59	Harman, *et al.,* 2000

[21] Stated to be significant but p values not given for the multivariate analyses

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
Swedish men. Median age = 59.7 y.	149 cases; 298 controls	Commercial immuno-radiometric assay after acid extraction	Age, date of survey, residency, IGFBP-3, BMI, smoking	Positive	Mean IGF-1 higher in cases (229 vs 214 ng/ml, *p* = 0.02). IGF-1 positively associated with prostate cancer with OR; 95%CI of 1.72; 0.93-3.19, *p* = 0.006 IGFBP-3 higher in cases (2611 vs 2498 ng/ml, *p* = 0.04). IGFBP-3 positively associated with cancer risk - 1.83; 0.98-3.24 *p* = 0.007	Stattin, *et al*., 2000
Swedish men. Median age = 59.9 y.	281 cases; 560 controls	Commercial immune-radiometric assay after acid extraction	Age, IGFBP-3, BMI, smoking	Positive. Association stronger in younger men	Mean ± SD IGF-1 significantly higher in cases (218.6 ± 78.1 vs 207.8 ± 78.3 ng/ml, *p* = 0.04) IGF-1 associated with prostate cancer, highest vs lowest quartile OR= 1.67;1.02-2.72, *p* trend = 0.05 (Non-significant when adjusted for IGFBP-3 - 1.47; 0.81-2.64, *p* trend = 0.3) IGFBP-3 also higher in cases (2422 ± 548 vs 2360 ± 555 ng/ml, *p* = 0.03) IGFBP-3 also associated with prostate cancer, 1.30;0.84 - 2.03, *p* trend = 0.03 (Non-significant when adjusted for IGF-1 - 1.04; 0.63 – 1.74, *p* trend = 0.24)	Extended in Stattin, *et al*., 2004

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
Finnish men aged 55-67	179 cases 174 BPH 268 normal histology	Commercial DSL ELISA after acid extraction	Age, IGFBP-3, PSA, prostate volume	None	No difference in mean ± SE IGF-1 between cases and benign controls 183 ± 5 and 94 ± 5 ng/ml respectively, $p = 0.094$. No positive association between IGF-1 and prostate cancer after adjustment for prostate volume (OR; 95% CI = 0.57; 0.28-1.16). No difference in mean ± SE IGFBP-3 between cases and benign controls 4558 ± 100 and 4526 ± 56 ng/ml respectively $p = 0.948$. No association between IGFBP-3 and prostate cancer (1.24; 0.68-2.24)	Finne, *et al*., 2000
US men, aged 58-86 y	30 cases; 60 controls	Commercial DSL ELISA	Age. No other confounders (smoking, marital status, education) "mattered".	None	No difference in IGF-1 between cases and controls (119.8 ng/ml and 118.4 ng/ml respectively) OR: 95%CI = 0.7; 0.2-2.23, p trend = 0.5, top vs bottom quartile. No difference in IGFBP-3 levels between cases and controls (1042.5 ng/ml and 1022.6 ng/ml respectively) OR: 95%CI=1.1; 0.3-3.8, p trend = 0.5)	Lacey, *et al*., 2001

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
Finnish male smokers (ATBC cohort) aged 50 -69 y at baseline	100 cases: 400 controls	Commercial DSL ELISA	Age, BMI, intervention group, time between blood draws, IGFBP-3/IGF-1	None	No difference in mean ± SD IGF-1 levels between cases and controls at baseline - 146.5 ± 52.5 and 146.7 ± 50.9 ng/ml respectively $p = 0.41$). No association between IGF-1 and risk (OR; 95%CI = 0.52; 0.23-1.16, p trend = 0.16) for fourth vs first quartile). No difference in mean ± SD IGFBP3 levels between cases and controls (2502.0 ± 746.3 ng/ml and 2398.6 ± 635.8 ng/ml respectively, $p = 0.17$) No association with risk: 1.93; 0.83-4.49, p trend = 0.06.	Woodson *et al*., 2003
Dutch men, aged 65-≥80 y	201 cases; 201 controls	Immuno-radiometric assay	Log total IGF-1, log free IGF-1, IGFBP-3, PSA density, PSA density of transition zone, age at baseline, log PSA at each visit.	None	No difference between total (133.9 vs 135.6, $p = 0.81$) and free IGF-1 (0.711 vs 0.712 ng/ml, $p = 0.67$)) at baseline between cases and controls. No difference in IGFBP-3 (3488.9 vs 3556.7 ng/ml $p = 0.28$) Changes in IGF-1 and IGFBP-3 between baseline and measurement 4 years later did not predict risk[22].	Janssen *et al*., 2004

[22] Presented as box plots.

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
American men, aged 65-≥80 y	174 cases; 174 controls	Immuno-radiometric assay after acid ethanol precipitation	Ethnicity, year of entry, age at entry, year of blood draw, BMI, insulin. (Marital status, education, aspirin use, NSAID[23] use, waist-hip-ratio assessed but not used) IGFBP-3, PSA.	None	No difference in mean ± SD lGF-1 levels in cases and controls 157.7 ± 94.5 and 163.2 ± 77.7 ng/ml.. No association (RR; 95%CI =0.67; 0.37-1,25, *p* = 0.45) lowest vs highest quartile. No difference in mean ± SD levels were 3101 ± 924 and 3210 ± 843 ng/ml in cases and controls respectively. Small decrease in risk with increasing IGFBP-3 levels (0.65; 0.35-1.20, *p* = 0.11).	Chen *et al*., 2005
French men, aged 65-≥80 y SU.VI.MAX study	100 cases; 400 controls	Chemi luminescent assay (stated that no interference from IGFBPs with this method)	Age, intervention group, IGF variables, smoking, BMI, alcohol intake. Stratified by PSA level.	None	No difference in mean ± SD lGF-1 levels in cases and controls: 154 ± 42 and 150 ± 47 ng/ml respectively, *p* = 0.43. No association with IGF-1 (OR;95%CI = 1.80; 0.76-4.27, *p* trend = 0.13 lowest vs highest quartile, fully adjusted model) No difference in mean ± SD lGFBP-3 levels in cases and controls - 4059 ± 752 and 4172 ± 883 ng/ml respectively, *p* = 0.24. No association with IGFBP-3 (lowest vs highest quartile OR; 95%CI = 0.40; 0.10-1.60)	Meyer *et al*., 2005

[23] NSAID: Non-steroidal anti-inflammatory drug

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
US men, median age of cases = 68.6 Health Professionals Follow up study.	462 cases 462 controls	Commercial DSL ELISA	Age, IGFBP-3, PSA, time, year & season of blood draw. Other prostate cancer risk factors assessed but not presented.	Positive, but became non-significant on further adjustment for IGFBP-3	Mean ± SD lGF-1 levels higher in cases than controls: 181 ± 56 and 173 ± 54 ng/ml respectively, *p* = 0.02. Higher IGF-1 associated with increased prostate cancer risk (OR; 95% CI for top vs bottom quartile 1.37; 0.92- 2.03, *p* trend = 0.05). Mean ± SD lGFBP-3 levels in cases than controls - 3003 ± 751 and 2905 ± 757 ng/ml respectively, *p* = 0.03 IGFBP-3 also non-significantly associated with increased, risk (1.62; 1.01-2.46 for top vs bottom quartile, *p* trend = 0.08).	Platz *et al*., 2005
US men Health Professionals Follow up study.	1331 cases 1331 controls	Commercial ELISA, no further details	Age, IGFBP-3. Other prostate cancer risk factors assessed but not presented.	Positive	Mean IGF-1 levels higher in cases (205 vs 197 ng/ml *p* = 0.0001) Association between IGF-1, and total prostate cancer risk (OR; 95% CI top vs bottom quartile 1.41; 1.12-1.78, *p* trend = 0.001). Stronger association for low than high grade tumours. Association between IGFBP-3, and total prostate cancer risk (OR; 95% CI top vs bottom quartile 1.58; 1.24-2.01, *p* trend = 0.003). Mean IGFBP-3 levels higher in cases (3632.6 vs 3536.9 ng/ml, *p* = 0.001). This became non-significant when adjusted for IGF-1	Nimptsch *et al*., 2010 Extension of above study by Platz et al., 2005.

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
British men BUPA study	141 cases 423 controls	Commercial DSL ELISA	Age, duration of sample storage. BMI, smoking, alcohol consumption	None	Median levels of IGF-1 = 122 and 124 ng/ml in cancer cases (all types) and controls. No association between IGF-1, and prostate cancer risk (OR; 95% CI top vs bottom quartile =1.37; 0.92-2.03, *p* trend = 0.62). Association reduced by adjustment for IGBP-3. Median levels 3200 ng/ml for cases and controls. No association for IGFBP-3 (1.40; 0.77-2.55, *p* trend = 0.42).	Morris *et al*., 2006
Men resident in Australia	524 cases 1826 controls	Commercial DSL ELISA	Country of birth, alcohol consumption. Other variables assessed (BMI, smoking, energy intake) but not used).	None	Median levels of IGF-1 = 168 and 176 ng/ml in cases and controls. No association between baseline IGF-1, and prostate cancer risk (HR; 95% CI top vs bottom quartile 1.07; 0.79- 1.46, *p* trend = 0.5). Median levels of IGFBP-3 = 2972 and 2944 ng/ml in aggressive and non-aggressive cases respectively and 2972 ng/ml in controls. Increased risk with higher IGFBP-3 at baseline (1.49; 1.11-2.00, *p* trend ≥ 0.008).	Severi *et al*., 2006

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
European men from 10 countries (EPIC cohort)	630 cases 630 controls	Commercial DSL ELISA following acid ethanol precipitation	IGFBP-3 Other variables assessed (BMI, smoking, alcohol, exercise, marital status) but not used).	None	No difference in mean; 95%CI IGF-1 = 168; 163-173 and 162; 156-167 ng/ml in cases and controls, *p* = 0.08 Small association between IGF-1 and risk (highest vs lowest tertile, OR; 95%CI =1.35; 0.99-1.28, *p* trend = 0.08) No difference in mean;95%CI IGFBP-3 = 3711; 3648-3777 and 3674; 3611-3740 ng/ml in cases and controls respectively ng/ml, *p* = 0.38 IGFBP-3 not associated with increased risk 1.22; 0.92-1.64, *p* trend = 0.38)	Allen *et al*., 2007
European from the EPIC cohort	1542 cases and 1542 controls	Commercial DSL ELISA following acid ethanol precipitation. Some samples analysed by immunoassay	Matched by age, study centre, duration of follow up, time of sampling, duration of fasting at sampling.	Positive	Mean; 95%CI IGF-1 156; 154-159 and 151; 148-53 ng/ml respectively (*p* = 0.001) IGF-1 levels associated with increased risk (OR; 95%CI = 1.69; 1.35-2.13, highest vs lowest quartile, *p* trend = 0.0002)	Extended in Price *et al*., 2012

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
Men from PLCO cohort (US)	727 cases 887 controls	ELISA following acid ethanol precipitation	Times since initial screen, year of blood draw. IGFBP-3, IGF-1:IGFBP-3. Other variables assessed (BMI, height, diabetes, family history, smoking, activity, nutrients, study centre) but not used).	None	No association of IGF-1 with risk OR; 95%CI: 1.12; 0.79-1.60, highest vs lowest quartile, $p = 0.28$. Risk higher for aggressive disease in obese men only (2.80; 1.11-7.08, $p = 0.03$). Small association between IGF-1:IGFBP3 molar ratio in obese men (OR; 95%CI = 2.3; 1.10-5.01, p trend = 0.04)	Weiss *et al*., 2007
US and Canadian men. Mean ages range from 67.1 to 71.2 y depending on group.	96 cases and 412 controls	Commercial ELISA, no further details	Age, region, ethnicity.	None	Mean ± SD IGF-1 =236 ± 75, 240 ± 84 and 231 ± 80 ng/ml in Black, White and Asian cases and 228 ± 74, 228 ± 74 and 226 ± 86 ng/ml in the respective controls. No association between IGF-1 and prostate cancer risk overall (OR; 95%CI = 1.26; 0.66- 2.41 $p = > 0.05$ highest vs lowest quartile) or by ethnic group. Mean levels 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. No consistent association between IGFBP-3 and risk, 1.35; 0.15-6.59 $p = > 0.05$.	Borugian *et al*., 2008

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables the study controlled, analysed or matched for?	Association between IGF-1 levels and prostate cancer	Main results	Reference
Meta-analyses						
Meta-analysis of 14 studies	-			*Positive*	*OR; 95% CI for prostate cancer was 1.47; 1.23-1.77 among men with high IGF-1 as compared with those with low IGF-1. The OR was 1.26; 1.03-1.54 for IGFBP-3.*	*Shi, et al., 2001*
Meta-analysis of six studies	-			*Positive*	*High concentrations of IGF-1 were associated with an increased risk of prostate cancer (comparing 75th with 25th percentile, OR=1.49; 1.14-1.95, p trend* = 0.003*).* *For IGFBP-3 the overall OR was 0.95; 0.70-1.28*	*Renehan, et al. 2004*
Meta-analysis of nine studies.	-	-		*Positive*	*High concentrations of IGF-1 were associated with an increased risk of prostate cancer (OR; 95%CI, highest vs lowest quintile 1.31; 1.03-1.67). Association more positive with low grade disease. There was no association between IGF-2 or IGFBP-3 and prostate cancer (1.05; 0.82-1.35 for IGFBP-3)*	Morris *et al*., 2006
Meta-analysis of twelve studies	-			*Positive*	*High concentrations of IGF-1 were associated with an increased risk of prostate cancer (OR; 95% CI, highest vs lowest quintile= 1.38;1.19-1.60, p trend <0.001).*	*Roddam, et al. 2008*
Meta-analysis of fourteen prospective and 20 retrospective studies	-			*Positive*	*Increased concentrations of IGF-1 were associated with an increased risk of prostate cancer (Overall, OR; 95% CI = 1.21;1.07-1.36, p= 0.003) per standard deviation increase in peptide. Association more positive with more aggressive disease.* *For IGFBP-3 the overall OR was 0.88-0.79-0.9, p trend = 0.02, a slightly protective effect.*	*Rowlands, et al. 2009*

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Table 3: Summary of results of epidemiology studies of colorectal cancer risk associated with IGF-1 and related substances

Subjects	Number of subjects	How was IGF-1 measured and was it free[24]?	Variables study controlled, matched or analysed for	Association between IGF-1 levels in blood and colorectal cancer	Main results	Reference
Retrospective studies						
Greek adults	41 cases; 50 controls	Immuno-radiometric assay consistent with methods used to extract free IGF-1	Sex, age, educational level.	None	Mean ± SEM IGF-1 levels not significantly different 80.25 ± 5.05 and 78.83 ± 4.76 ng/ml in cases and controls. Highest two tertiles of IGF-1 and IGF-2 associated with increased risk compared to lowest (OR; 95%CI = 5.2; 1.0-26.8) IGFBP-3 levels 2950 ± 150 and 2790 ± 110 ng/ml in cases and controls.	Manousos *et al*., 1999
English men and women aged 55-64 y	60 men and 40 women (42 high and 11 low risk adenomas, and 47 normal).	Radio immunoassay	Age, sex, current use of hormone replacement therapy, smoking, BMI, aspirin use	Positive (for high-risk adenomas)	Higher IGF-1 (190 vs 168 or 169 ng/ml, p = 0.06) and lower IGFBP-3 (3220 vs 3460 or 3490 ng/ml p = 0.05) in those with high-risk adenomas, compared with those with no cancer or low-risk adenomas.	Renehan, *et al*., 2001

[24] In many studies, it is unclear whether the IGF-1 measured was free or attached to binding proteins since the experimental details are not always provided. The majority of studies use commercially available ELISA kits, which may or may not involve an acid alcohol extraction step to remove the binding proteins.

Subjects	Number of subjects	How was IGF-1 measured and was it free[24]?	Variables study controlled, matched or analysed for	Association between IGF-1 levels in blood and colorectal cancer	Main results	Reference
Japanese men	157 cases 311 controls	Commercial immuno-radiometric assay	Self Defence Force rank, hospital, smoking, IGFBP-3, glucose	Not significant	Modest positive association with IGF- I (OR; 95%CI = 1.8; 1.0-4.5, *p* trend = 0.06). Levels of IGF-1 = 77, 79 and 81 ng/ml in control, all and advanced adenomas. Minimal reduction in risk if high IGFBP-3. Association less marked for advanced adenomas (1.7; 0.6-4.6, *p*= 0.37) Levels of IGFBP-3 = 2920, 2960 and 3801 ng/ml in control, all, and advanced adenomas.	Teramukai *et al.*, 2002.
Adults aged	239 cases (one or more adenomatous polyps); 517 controls (no polyps)	DSL ELISA After acid ethanol extraction	Age, sex, NSAID use	None	No difference between IGF-1 (Mean ± SEM 121.4 ± 4.8 and 130.7 ± 3.9 ng/ml for cases and controls, IGF-2 or IGFBP3 3177 ± 8 and 3255 ± 51 ng/ml for cases and controls). IGF-1 lower in male cases than controls (126.6 ± 5.7 and 145.8 ± 6.3 ng/ml, *p* = 0.02)	Keku *et al.,* 2005
US adults attending for colono-scopy	164 cases (one or more adenomatous polyps) 416 controls (no polyps)	-	Alcohol intake, waist/ hip ratio	None	Plasma IGFBP-3 not associated with adenoma risk (OR; 95%CI = 1.0; 0.5-1.9, *p* = 0.88). Mean (SEM) levels 2012 (68) and 2001 (43) in cases and controls. Tissue IGFBP-3 mRNA was higher in cases.	Keku *et al*., 2008

Subjects	Number of subjects	How was IGF-1 measured and was it free[24]?	Variables study controlled, matched or analysed for	Association between IGF-1 levels in blood and colorectal cancer	Main results	Reference
US adults Caucasian, Japanese and Native Hawaiian	554 cases; 786 controls	ELISA following acid alcohol extraction	Age, race, ethnicity, sex, recruitment site. Energy, smoking, oestrogen use alcohol intake, folate intake BMI, waist and hip circumference	None	IGF-1 not associated with adenoma risk OR; 95%CI = 0.83; 0.54-1.27, *p*= 0.26 (lowest vs highest quartile) IGFBP-3 not associated with adenoma risk 0.78; 0.51-1.19, *p*=0.37 (lowest vs highest quartile)	Le Marchand *et al.* 2010
US adults (Diet and Health Study cohort)	167 adults	Commercial DSL ELISA	Age, race, sex	Negative	No effect of IGF-1 (OR; 95%CI = 0.7; 0.3-1.5), IGF-2 or IGFBP-3 (1.0; 0.5-2.1) on recurrent adenoma risk. Levels of IGF-1 = 4.88 and 4.90 ng/ml in individuals with recurrent and non-recurrent adenomas. Levels of IGFBP-3 = 7.81 and 7.78 ng/ml in recurrent and non-recurrent.	Kang *et al*., 2013
Chinese adults (17-83 y)	24 polyps 13 CRC 13 controls	Commercial ELISA	Age, sex	Positive for adenomatous polyps and colorectal cancer	IGF-1 levels higher in adenomatous polyp and CRC cases compared to controls (Mean ± SD, 200.96 ± 55.92, 218.77± 88.93 and 98.37 ± 24.99 respectively, *p* <0.001)	Zhang *et al*., 2013
Turkish adults	48 cases 30 controls	Commercial ELISA	Age, BMI, visceral fat, waist circumference homeostasis metabolic assessment method	Positive	IGF-1 levels higher in carcinoma and adenoma cases compared to controls (Mean ± SD, 184.6 ± 61.6 *p* <0.0001, 177 ± 87.6 and 108.9 ± 45.3 ng/ml, *p* <0.00 respectively)	Erarslan *et al*., 2014

Subjects	Number of subjects	How was IGF-1 measured and was it free[24]?	Variables study controlled, matched or analysed for	Association between IGF-1 levels in blood and colorectal cancer	Main results	Reference
US males	126 healthy males, 69 with no polyps and 57 with polyps	Commercial ELISA	Age, smoking	Negative	No association between IGF-1 (112.1 and 105.9 ng/ml in individuals with no polyps and polyps respectively), IGF binding proteins (685.9 and 69.3 ng/ml in no polyps and polyps respectively) and number or types of polyp.	Comstock *et al.,* 2014
US adults	410 cases 1070 controls	ELISA	Age, sex, family history, smoking, NSAID, BMI.	Negative in Caucasians Positive in African-Americans	IGF-1 and IGFBP3 higher in cases than controls in both groups. Caucasians – mean (SD) IGF-1 =119.0 (40.7) and 122.9 (41.2) ng/ml in cases and controls. African-Americans = 109.8 (40.8) and 106.9 (41.2) in cases and controls. Caucasians – mean (SD) IGFBP-3 =3727.7 (839) and 3868.4 (801) ng/ml in cases and controls. African-Americans = 3448.6 (933.7) and 3446.8 (840.7) in cases and controls. Association between IGF-1 and CRC risk in African Americans only (OR: 95%CI = 1.68; 1.06-2.68 and 1.68; 1.05-2.71 for second and third tertiles (*p* trend = 0.12). Stated to be a threshold effect.	Ochs-Balcom *et al*., 2014

Subjects	Number of subjects	How was IGF-1 measured and was it free[24]?	Variables study controlled, matched or analysed for	Association between IGF-1 levels in blood and colorectal cancer	Main results	Reference
Prospective studies						
American male physicians, aged 40-84 y	193 cases; 318 controls	Commercial DSL ELISA	Age, smoking, BMI, alcohol	Positive	IGF-1 associated with increased risk RR; 95%CI = 2.51; 1.15-5.46, *p* trend = 0.02, highest vs lowest quintile. No association with IGF-2 Negative association with IGFBP-3 levels (RR; 95%CI = 0.28; 0.12-0.66, *p* trend = 0.005).	Ma, *et al*., 1999 & 2001
American female nurses, aged 35–55 y	79 adeno-carcinoma cases 158 controls 90 intermediate or late stage adenoma 90 controls 107 early stage adenoma cases; 107 controls.	ELISA. Results stated to be consistent with those following acid chromato-graphy	Age, fasting status, month of sampling, alcohol intake, BMI, IGF-1 and IGFBP-3 adjusted for each other.	Positive for some stages	No overall association, but non-significant association between plasma IGF-1 and intermediate/late stage colorectal cancer. top vs bottom tertile RR; 95%CI 2.18; 0.94-5.08, *p* trend = 0.10 Negative association with IGFBP-3 RR; 95%CI = 0.28; 0.10-0.83, *p* > 0.05, *p* trend = 0.04	Giovannucci, *et al*., 2000

Subjects	Number of subjects	How was IGF-1 measured and was it free[24]?	Variables study controlled, matched or analysed for	Association between IGF-1 levels in blood and colorectal cancer	Main results	Reference
American women aged 35-65 y	102 cases; 200 controls	Double antibody immuno radiometric assay after acid ethanol extraction to give free IGF-1	Menopausal status, age, date of recruitment, time of blood sampling	None	No significant association between plasma IGF-1 (top vs bottom quintile OR; 95%CI = 1.88; 0.72-4.91, *p* trend = 0.25 or IGFBP-3 (2.46; 1.09-5.57, *p* trend = 0.19) and colorectal cancer. Mean (SD) IGF-1 =181.3 (172.0-190.6) and 188.0 (176.4-201.4) ng/ml and IGFBP-3 2922 (2842-3002) and 3012 (2904-3135) in cases and controls respectively. Negative trend with IGFBP-1.	Kaaks, *et al*., 2000
Chinese men aged 45-65 y	125 cases; 661 controls	Commercial DSL radio-immunoassay.	Residence, age, time of blood sampling, age, weight, smoking, alcohol	None	No significant association between plasma IGF-1 and colorectal cancer (top vs bottom quintile OR; 95%CI = 1.52; 0.82-2.85, *p* trend = 0.24). IGFBP-3 1.72; 0.91-3.25, *p* trend = 0.13. The associations weakened with further adjustment. Positive associations with IGF-2 and IGFBP-2.	Probst-Hensch, *et al.,* 2001

Subjects	Number of subjects	How was IGF-1 measured and was it free[24]?	Variables study controlled, matched or analysed for	Association between IGF-1 levels in blood and colorectal cancer	Main results	Reference
Swedish men and women aged 30-70 y	110 colon + 580 rectal cancer cases; 336 controls	Commercial DSL double antibody immuno radiometric assay	Sex, age, sub-cohort, date of blood sampling, fasting time.	None	No significant trends, but IGF-1 & IGFBP-3 levels had a slight positive association with colon cancer (top vs bottom quartile OR; 95%CI = 2.47; 0.93-6.53, *p* trend = 0.08) and a slight negative association (OR; 95%CI = 0.43; 0.11-1.59, *p* trend = 0.23) with rectal cancer. Mean (SD) IGF-1 =198.7 (188.1-209.3) and 200.4 (192.6.-208.2) ng/ml and IGFBP-3 2595 (2490-2696) and 2585 (2504-2666) ng/ml in cases and controls respectively.	Palmqvist, *et al.,* 2003
American female nurses aged 35-55 y - from Nurses' health study	182 cases; 364 controls	Commercial DSL ELISA	Age, date of blood sampling, fasting status, smoking	Positive	Positive association between IGF-1 and colorectal cancer when adjusted for IGFBP-1 (RR; 95% CI = 2.17; 0.96-4.88, *p* trend = 0.03) comparing upper and lower quartiles. No association with IGFBP-3 (0.81; 0.38-1.7, *p* trend = 0.12 Median (interquartile range) IGF-1 =156.7 (123.5-206.1) and 147.1 (111.3 -192.5) ng/ml and IGFBP-3 4049 (3479-4952) and 4060 (3849-4952) ng/ml in cases and controls respectively. Increased risk with high IGF-1/IGFBP-3 molar ratio	Wei, *et al.,* 2005

Subjects	Number of subjects	How was IGF-1 measured and was it free[24]?	Variables study controlled, matched or analysed for	Association between IGF-1 levels in blood and colorectal cancer	Main results	Reference
Adults	202 cases; 256 controls	Radio-immunoassay after acid-ethanol extraction	Age, race, education, polyp history, aspirin use, NSAID use, smoking family history of CRC	Positive	IGF-1, IGF-1/IGFBP3 and insulin levels associated with adenoma, particularly severe adenoma. OR; 95%CI = 1.7; 1.0-2.9, *p* trend =0.05, top vs bottom quartile for IGF-1 Mean IGF-1 ± SD = 132.3 ± 46.6, 126.3 ± 48.4 and 117.1 ± 44.6 ng/ml and Mean IGFBP-3 ± SD = 3294 ± 735, 3155 ± 709 and 3179 ± 695 ng/ml in advanced adenoma cases, non- advanced adenoma cases and controls respectively.	Schoen *et al.,* 2005
UK adult males	147 cases 440 controls	Commercial DSL ELISA	Age, smoking, alcohol, BMI	None	No associations with colorectal cancer for IGF-1 (OR; 95%CI = 1.10; 0.56-2.18, *p* trend =0.65, top vs bottom, IGFBP-1 and IGFBP-3 (0.72; 0.37-1.37 *p* trend =0.46). Median (interquartile range) IGF-1 =122 (88-164) and 124 (190-60) ng/ml and IGFBP-3 3200 (2600-3800) and 3200 (2700-3800) ng/ml in cases and controls respectively.	Morris *et al*., 2006

Subjects	Number of subjects	How was IGF-1 measured and was it free[24]?	Variables study controlled, matched or analysed for	Association between IGF-1 levels in blood and colorectal cancer	Main results	Reference
Japanese men and women aged 40-69 y	375 cases; 750 controls	Total IGF-1 by commercial immuno-radiometric assay.	Smoking, alcohol, BMI, exercise, family history of CRC	None	No associations with colorectal cancer for IGF-1 (OR; 95%CI = 0.83; 0.40-1.7 *p* trend = 0.91 men and 0.83; 0.38-1.8 *p* trend = 0.60 women, top vs bottom quartile), IGFBP-1 and IGFBP-3 (1.40; 0.65-2.8 *p* trend = 0.6 men and 1.1; 0.53-2.3 *p* trend = 0.74 women, top vs bottom quartile). Median (interquartile range) IGF-1 =172 (137-206) men, 160 (129-190) women and 154 (136 -204) men and 159 (121-197) women ng/ml and IGFBP-3 4520 (3995-5170) men and 4870 (4320-5490) women and 4450 (3895-5050) men and 4885 (4260-5440) ng/ml in cases and controls respectively.	Otani, *et al*., 2007
American post-meno-pausal women aged 50-79 y from Women's Health Initiative study	438 cases; 816 controls	Total and free IGF-1 by Commercial DSL ELISA	Age, smoking, race/ethnicity physical activity, waist circumference, NSAID use, alcohol use, family history of CRC	Positive	The trend associating free IGF-1 with colorectal cancer was of borderline significance (HR; 95%CI = 1.35; 0.92-1.98, *p* trend = 0.05) top vs bottom quartile. No significant association with IGFBP-3, 0.98; 0.70-1.38. Total mean ± SD IGF-1 123.2 ± 49.0 and 119.8 ± 48.4 ng/ml, free IGF-1 0.33 ± 0.36 and 0.32 ± 0.36 and IGFBP-3 4114.2 ± 812.8 and 4081.1 ± 745.3 in cases and controls respectively.	Gunter, *et al*., 2008

Subjects	Number of subjects	How was IGF-1 measured and was it free[24]?	Variables study controlled, matched or analysed for	Association between IGF-1 levels in blood and colorectal cancer	Main results	Reference
Finnish male smokers, aged 50-69 y (ATBC cohort)	134 cases; 400 controls	ELISA	Smoking history, BMI, fibre intake, hypertension, physical activity	None	No association with IGF-1, (OR; 95%CI = 0.92; 0.49-1.70, *p* trend = 0.90, top vs bottom quartile), IGFBP-3 (0.98; 0.51-1.88 *p* trend = 0.85) or IGF-1/IGFBP-3 ratio Median (interquartile range) IGF-1 = 137 (109-165) and 139 (113 -175) ng/ml and IGFBP-3 2300 (1920-2753) and 2338 (1952-2827) ng/ml in cases and controls respectively.	Max, *et al*., 2008
Adults from polyp prevention trial	375 recurrent adenoma cases; 375 controls	Commercial radio-immunoassay	Age, sex, body mass index, intervention group, aspirin, smoking, ethnicity, and education	Negative	Risk of adenoma recurrence reduced at high IGF-1 (OR; 95%CI = 0.65; 0.41-1.01, *p* trend = 0.02, top vs bottom quartile) and IGFBP3 (0.66; 0.42-1.05, *p* trend = 0.14) levels.	Flood *et al*., 2008
Males from Wheat Bran Fibre Trial	299 no controls	Commercial DSL ELISA	Smoking history, BMI, alcohol use, family history of CRC	Negative	IGF-1 reduced the risk of adenoma recurrence (OR; 95%CI = 0.49; 0.26-0.91 for first vs third quartiles, *p* trend = 0.02). No association with IGFBP-1 or IGFBP-3 = 1.17; 0.59- 2.37 for first vs third quartiles, *p* trend = 0.65	Jacobs *et al*., 2008

Subjects	Number of subjects	How was IGF-1 measured and was it free[24]?	Variables study controlled, matched or analysed for	Association between IGF-1 levels in blood and colorectal cancer	Main results	Reference
Adults 40-69 from Japan Collabora-tive Cohort study. (JACC) cohort	101 cases 303 controls	Commercial Immuno-radiometric assay	Area, age, BMI, cholesterol, smoking, alcohol, energy intake, protein intake.	None	No effect on CRC mortality with IGF-1 (OR; 95%CI = 1.01; 0.49-2.10, *p* trend =0.35, top vs bottom tertile), IGF-2 or IGFBP-3 (1.22; 0.63-2.38, *p* trend =0.16, top vs bottom tertile) levels. Total mean ± SD IGF-1 130.8 ± 52.0 and 134.2 ± 8.3 ng/ml, and IGFBP-3 3020 ± 750 and 3120 ± 890 ng/ml in cases and controls respectively.	Suzuki *et al*., 2009
European	1121 cases; 1121 control	Commercial DSL Free IGF-1 ELISA following acid alcohol extraction	BMI, ratio of waist to hip circumference, height, smoking status, education, physical activity, alcohol intake, dietary intakes of red meat, processed meat, dairy products, fruit, vegetables and fibre	Positive for colon cancer. None for rectal cancer	No overall association with IGF-1 (OR; 95%CI = 1.11; 0.83-1.48, top vs bottom quintile) or total IGFBP-3 1.14; 0.80-1.61, top vs bottom quintile). Slight association of IGF-1 with colon cancer (not rectal cancer) in young (<50y) participants or those with low milk intakes. RR for an increase in serum IGF-1 of 100 ng/mL = 1.43; 1.13-1.93. Total mean; 95%CI IGF-1 211.0; 121.8-330.9 and 207.0; 113.8-334.9 ng/ml, and IGFBP-3 4099.0; 2787.3-5580.2 and 4026.6; 2844.5-5464.1 ng/ml in cases and controls respectively.	Rinaldi, *et al*., 2010

Subjects	Number of subjects	How was IGF-1 measured and was it free[24]?	Variables study controlled, matched or analysed for	Association between IGF-1 levels in blood and colorectal cancer	Main results	Reference
US adults (Health Professio-nals Follow up Study and Nurses' Health Study cohort)	499 cases; 992 controls	Commercial DSL ELISA	Smoking, alcohol intake, dietary intakes of red meat, processed meat, methionine, folate, calcium, family history of CRC	Positive	Risk associated with high IGF-1/IGFBP3 reduced by higher 25(OH)D levels. IGF-1 significantly higher in cases compared to controls (OR; 95%CI for IGF-1 = 1.37; 1.05-1.78 and 1.52; 1.11-2.07 high vs low IGF-1 for colorectal and colon cancer respectively). No association with IGFBP-3 = 0.96; 0.74-1.26 and 0.91; 0.68-1.25 for colorectal and colon cancer respectively)[25]. Total mean ± SD IGF-1 185 ± 96.7 and 175 ± 66.3 ng/ml (p = 0.02), and IGFBP-3 4352 ± 1025 and 4291 ± 1013 ng/ml (p = 0.02) in cases and controls respectively. No differences in milk consumption between groups.	Wu *et al*., 2011
Japanese adults	1520	Commercial reagents used to measure total IGF-1.	Age, screening period, fasting duration, smoking, alcohol, family history of CRC, NSAID use, height, energy intake.	Positive	Increased IGF-1 associated with colorectal adenoma in men (OR; 95% CI =1.63; 1.08-2.48, top vs bottom quartile, p = 0.02) but not women (OR; 95% CI =0.79; 0.44-1.43, p = 0.52). No association between IGFBP-3 and colorectal adenoma in men or women 1.42; 0.94-2.14, p = 0.10 and 1.31; 0.76-2.29, p = 0.58 respectively.	Yamaji *et al*., 2012

[25] P values not given for this part of the analysis.

Subjects	Number of subjects	How was IGF-1 measured and was it free[24]?	Variables study controlled, matched or analysed for	Association between IGF-1 levels in blood and colorectal cancer	Main results	Reference
US adults aged > 49y from Insulin Resistance and Atherosclerosis study (IRAS) cohort	143 individuals; 24 with polyps	Commercial radioimmuno assay	Age, centre, race/ethnicity, sex, BMI, IGF-1 and IGFBP-3 adjusted for each other.	Positive	Increasing IGF-1 (OR; 95% CI =3.81; 1.30-10.8, “ever increase” vs “no increase” and IGF-1/IGFBP3 over a decade associated with polyps. No associations at individual time points	Soubry *et al*., 2012
US adults (PLCO cohort)	764 cases; 775 controls	Commercial DSL ELISA	Age, race, sex, year of blood draw, BMI, smoking and education	Positive	Higher IGF-1 at baseline associated with increased risk of colorectal adenoma (OR; 95%CI for highest vs lowest quartile was 1.80; 1.30-2.47, *p* trend = 0.02). IGFBP-3 not associated with risk of CRC (1.32; 0.98-1.79, *p* trend = 0.05) IGF-1/IGFBP3 also associated with increased risk. No significant differences between cases and controls for mean IGF-1 (206.6 ±75.8 and 196.6 ±71.7 ng/ml) or IGFBP-3 (4483.3 ± 887.9 and 4420.4 ± 866.0)	Gao *et al*., 2012
Meta-analyses						
Meta-analysis of five studies	-			*Positive*	*IGF-1 levels were positively associated with colorectal cancer (OR; 95%CI = 1.58; 1.11-2.27), whereas IGFBP-3 (0.77; 0.36-1.66) and IGF-1/IGFBP-3 ratio were less clearly associated*	*Renehan et al., 2004*

Subjects	**Number of subjects**	**How was IGF-1 measured and was it free[24]?**	**Variables study controlled, matched or analysed for**	**Association between IGF-1 levels in blood and colorectal cancer**	**Main results**	**Reference**
Meta-analysis of eight studies				*Positive*	*Positive association between IGF-1 levels and risk of colorectal cancer (1.37; 1.05-1.78)* *No association with IGFBP-3 (0.98; 0.64-1.51)*	*Morris et al., 2006*
Meta-analysis of ten studies	-			*Positive*	*Moderately positive association between IGF-1 levels and risk of colorectal cancer (RR; 95%CI= 1.07; 1.01-1.14 or 1.13; 0.97-1.32 depending on method used)*	*Rinaldi et al., 2010*
Meta-analysis of nineteen studies	-			*Positive*	*Moderately positive association between IGF-1 levels and risk of colorectal cancer (OR; 95%CI= 1.25; 1.16-2.04). Risk more marked for colon cancer and in Caucasians*	*Chi et al., 2013*
Meta-analysis of twelve studies	-			*Positive for advanced colorectal carcinoma only*	*Moderately positive association between IGF-1 levels and risk of advanced colorectal adenoma (OR; 95%CI= 2.21; 1.08-4.52). but not non-advanced (0.89; 0.55-1.45)*	*Yoon et al., 2015*

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Table 4: Summary of results of epidemiology studies of lung cancer risk associated with IGF-1 and related substances

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables study controlled, matched or analysed for	Association between IGF-1 levels and lung cancer	Main results	Reference
Retrospective studies						
Males	37 cases 25 controls	Radioimmuno-assay	Unclear how controls obtained. Age, smoking status, dietary factors, occupation and clinical details "were recorded".	Positive	IGF-1 higher in patients: Controls - 33.33 ± 8.32 ng/ml Early stage - 211.68 ± 73.10 ng/ml ($p < 0.01$) Late stage - 134.11 ± 24.06 ng/ml ($p < 0.05$)	Bhatavdekar *et al.,* 1994
Korean lung cancer patients	41 cases of which small cell lung cancer (SCLC) = 9, and non-small cell lung cancer (NSCLC) = 32) 20 controls	IGF by Radioimmuno-assay, IGFBPs by Western blotting	Age and sex matched.	Negative	Levels of IGF-1 (207.9 ± 62.6 vs 281.3 ± 53.9 ng/ml, p <0.01) and IGFBP-3 lower in lung cancer patients[26].	Lee *et al*., 1999

[26] IGFBP-3 units given as "Arbitrary densometric units" so have not been included.

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables study controlled, matched or analysed for	Association between IGF-1 levels and lung cancer	Main results	Reference
Americans (white, black & hispanic), aged 60.6 to 63.4 y	204 cases; 218 controls	Commercial DSL Immunoassay with acid ethanol extraction.	Age, sex, ethnicity, smoking status.	Positive	IGF-1 (mean; 95%CI cases 166.3; 156-176.5 vs controls 143.4; 135.5-151.3 ng/ml) associated with increased risk (OR; 95%CI =2.06; 1.19-3.56, *p* trend =0.01, top vs bottom quartile). No association with IGF-2. Negative association with IGFBP-3 (mean; 95%CI cases 37.0; 35.7-38.3 vs controls 37.6; 36.3-38.9 µg/ml[26]) (0.48; 0.25-0.92, *p* trend = 0.5)	Yu, *et al*., 1999
Americans (white, black & hispanic), aged 60.6 to 63.4 y	183 cases; 227 controls	Commercial Immunoassay	Age, sex, ethnicity, smoking status, BMI, family history of cancer.	Positive	IGF-1 (mean; 95%CI cases 166; 156-177 vs controls 143; 135-150 ng/ml, 0.002). Adjusted OR; 95%CI = 2.13; 1.20-3.78 upper vs lower quartiles of IGF-1. Negative association with IGFBP-3. mean; 95%CI cases 3674; 3539-3809 vs controls 3745; 3623-3867 ng/ml[27], = 0.714). Adjusted OR=0.59; 0.33-1.05 upper vs lower quartiles of IGF-1. Mean IGF-1 levels and IGF-1:IGFBP-3 ratio non-significantly higher in advanced disease	Wu *et al*., 2000 Same population as above study[28]

[27] Units as given in the respective paper- Wu *et al*, 2000 seems more plausible.
[28] Study designed to include mutagen sensitivity in the analysis.

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables study controlled, matched or analysed for	Association between IGF-1 levels and lung cancer	Main results	Reference
Chinese patients	78 cases , 35 with benign lung disease 14 controls			Positive	IGF-1 levels higher in lung cancer patients 570.67 ± 185.80, compared to patients with benign lung disease and healthy controls 466.53 ± 142.42 and 427.66 ± 141.19 ng/ml respectively. No significant differences in IGFBP-3 between groups.	Wang, *et al*., 2004 Abstract only (original in Chinese).
Lung cancer patients	24 cases; 12 controls who had undergone bronchoscopy for other indications.	Free IGF-1 measured by two site immuno-radiometric assay.		None (in serum)	IGF-1 and IGFBP-3 lower in the epithelial lining fluid of patients. Serum IGF-1 non-significantly lower in cases than controls (126.9 ± 63.4 vs 167.6 ± 56.5 ng/ml) Serum IGFBP-3 also non-significantly lower (2277.6 ± 614.0 vs 2874.7 ± 861.9 ng/ml)	Ünsal *et al*., 2005
Korean patients	77 cases advanced NSCLC, 21 healthy controls	Commercial DSL ELISA	Sex, stage, histology, Eastern Co-operative Oncology Group (ECOG) PS, smoking status	Negative	IGF-1 associated with improved prognosis and survival.	Han *et al*., 2006
Polish patients	38 cases (25 NSCLC) 10 healthy controls	ELISA	-	Positive	IGF-1 higher (123.6 ± 43.4 vs 74.2 ± 12 ng/ml, $p < 0.05$) in patients compared with healthy controls. IGF-1 levels increased after chemotherapy. IGF-2 also higher in cases.	Izycki *et al*., 2006

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables study controlled, matched or analysed for	Association between IGF-1 levels and lung cancer	Main results	Reference
German adults	34 patients 13 controls	ELISA. It was noted that the quotient of each sample was calculated.		None	No differences in IGF-1 or IGFBP-3 between patients and healthy controls (limited analytical data provided)	Matuschek *et al*., 2011
US adults	100 NSCLC patients	Immunobeads	Sex, ethnicity, smoking, histology and fasting status.	None	No association between IGF-1 and IGFBP-3 and prognosis.	Shersher *et al*., 2011
Greek adults	77 NSCLC patients	Total by radio-immunoassay	Age, smoking, weight loss, metastasis, histologic sub type.	None	IGF-1 associated with overall survival	Vlachostergios *et al*., 2011
Chinese adults	80 NSCLC patients 45 Benign Pulmonary Lesion (BPL) controls	Commercial DSL ELISA	No	Positive	Pre-operative IGF-1 associated with tumour size and poor prognosis IGF-1 levels higher than in BPL controls (21.59 ± 9.04 vs 12.37 ± 4.51 ng/ml, p= 0.0003)	Fu *et al*., 2013

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables study controlled, matched or analysed for	Association between IGF-1 levels and lung cancer	Main results	Reference
Prospective studies						
American women aged 32 to 70 y	93 cases; 186 controls	Commercial DSL radioimmunoassay after acid ethanol precipitation.	Age, date of blood sampling, menopausal status, day of menstrual cycle smoking status.	None	No difference in IGF-1 level (Mean; SD) 129.8; 119.8-140.6 ng/ml in cases and 131; 123.5-139 ng/ml in controls, *p* =0.84) No association between lung cancer and levels of IGF-1 (OR; 95%CI = 0.79; 0.29-2.19, *p* = 0.53 top vs bottom quartile) and IGFBP3 (0.77; 0.34-1.74, *p*= 0.93). No association of risk with levels of IGFBP1 or 2. Mean IGFBP=3 levels 4387 and 4413 ng/ml in cases and controls (*p*= 0.80).	Lukanova, *et al*., 2001
Chinese men aged 45 to 64 y	230 cases 659 controls	Commercial radioimmuno-assay	Age, residence, time of sample collection, smoking status	None	Non-significant reduced risk associated with high IGF-1 (OR; 95%CI = 0.70; 0.45-1.10 *p* trend = 0.36). Mean (IQR) IGF-1 123 (117-129) in cases and 127 (124-129) ng/ml in controls. Reduced risk with high IGFBP-3 (0.52; 0.31-0.88, *p* trend = 0.04) upper vs lower quartiles) Mean (IQR) IGFBP-3 1793 (1730-1856) in cases and 1863 (1538-2160) ng/ml in controls.	London, *et al*., 2002

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables study controlled, matched or analysed for	Association between IGF-1 levels and lung cancer	Main results	Reference
Heavy smokers (aged 50 to 69 y) or asbestos workers (aged 45 to 69 y) in USA.	159 cases; 297 controls	Commercial DSL ELISA	Age, sex, ethnicity, year of enrolment, year of blood sampling, smoking status	None	IGF-1 levels non-significantly higher in cases (158 and 153 ng/ml, *p* = 0.52). No significant association between IGF-1 and lung cancer (OR: 95%CI =0.64; 0.31-1.33, *p* = 0.29 upper vs lower quartiles). IGFBP-3 levels non-significantly higher in cases (30,700 and 29,400 ng/ml, *p* = 0.17) Positive association for IGFBP-3: (OR; 95%CI = 2.35; 1.13-4.92, *p* = 0.03 upper vs lower quartiles).	Spitz, *et al*., 2002
Individuals in the JACC study	194 cases 9351 controls	Free IGF-1 measured by immuno-radiometric assay	Area, sex, age, smoking, BMI, IGFBP-3	Positive	Increased IGF-1 associated with increased risk of lung cancer death (1.74: 1.08-2.81, *p* = 0.043). The risk reduced when only cases with > 3 yrs follow up included (1.32: 0.78-2.21, *p* = 0.41). High IGFBP-3 associated with decreased risk (0.67; 0.45-1.21, *p* = 0.037). The risk reduced further when only cases with > 3 yrs follow up included (0.50: 0.31-0.80, *p* = 0.002).	Wakai *et al*., 2002

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables study controlled, matched or analysed for	Association between IGF-1 levels and lung cancer	Main results	Reference
Male smokers (Finland) from ATBC cohort.	200 cases; 400 controls	Commercial DSL ELISA	Age, intervention arm, BMI, years of smoking	None	No significant association between IGF-1 and lung cancer (OR; 95%CI = 0.76; 0.39-1.49, highest vs lowest quartile); mean ± SD = IGF-1 137.2 ± 52.3 and 145.5 ± 52.0 ng/ml in cases and controls Or, for IGFBP-3 and lung cancer mean ± SD = 2228 ± 650 and 2369 ± 640 ng/ml in cases and controls (OR; 95%CI = 0.71; 0.35-1.47).	Ahn *et al*., 2006
UK male professionals	167 cases; 498 controls	ELISA	BMI, alcohol, smoking	None	No significant association between IGF-1 and lung cancer (OR; 95%CI = 1.21; 0.62-2.35, *p* trend= 0.45, highest vs lowest quartile) IGF-2 or IGFBP-3 and lung cancer (1.70; 0.87-3.30, *p* trend= 0.06)	Morris *et al*., 2006
Meta-analyses						
Meta-analysis of four studies	-			*None*	*No association between IGF-1 and lung cancer when results from all 4 studies are considered. OR; 95%CI =1.01; 0.49-2.11, lowest vs highest.* *Reduced IGFBP-3 was not associated with increased risk (0.83; 0.38-1.84) p = 0.001*	*Renehan, et al., 2004*
Meta-analysis of five studies	-	-	-	*None*	*No significant association between IGF-1 (OR; 95%CI = 1.02; 0.80-1.31) or IGFBP-3 (0.98; 0.61-1.58) and lung cancer*	*Morris et al., 2006*

Subjects	Number of subjects	How was IGF-1 measured and was it free?	Variables study controlled, matched or analysed for	Association between IGF-1 levels and lung cancer	Main results	Reference
Meta-analysis of six studies	-			*None*	*No association between IGF-1 and lung cancer (OR; 95% CI = 0.87; 0.60-1.13, p= 0.14).* *Inverse association between IGFBP-3 and lung cancer risk (OR; 95%CI = 0.68; 0.48-0.88 p = 0.52)*	*Chen, et al., 2009*
Meta-analysis of six studies	-			*None*	*No association between IGF-1 and lung cancer (OR; 95%CI, 1.05; 0.80-1.37, p = 0.74). Inverse non-significant association between IGFBP-3 and lung cancer risk (0.96; 0.59-1.56, p = 0.87).*	*Cao, et al., 2012*

References (Annex B, Table 4)

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