CC/2017/10

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

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

1. COC members have considered a sequence of papers looking at dietary IGF-I and the risk of cancer.

2. At the last meeting, members considered a draft statement summarising the issue. This was designed to be a short summary but linking to the original discussion papers for detailed consideration. Members made a number of comments and suggestions. It was agreed that a short lay summary should be prepared to accompany the revised statement; this is attached at Annex A. The revised statement which includes some updates is attached at Annex B, to note the tables at the back of the statement need some further checking which will be completed prior to publication.

Questions for the Committee

3. Members are asked to comment on:

a) the lay summary

b) the overall structure and content of the draft statement.

Secretariat

July, 2017

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Annex A to CC/2017/10

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

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

Draft lay summary

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Lay summary: circulating levels of Insulin-like growth factor- I and the risk of cancer

Insulin-like Growth Factor- (IGF)-I is a growth factor involved in the normal growth and development of body tissues. IGF-I is a short protein chain (peptide) made up of 70 amino acids and is largely produced in the liver. The structure of IGF-I is identical in humans, cattle and pigs so that IGF-I originating from other species would be active in humans.

IGF-I concentrations in the blood vary depending on factors such as age, gender and diet. IGF-I is also present in animal tissues and is likely to occur in foods from animal sources such as meat and milk, although few data are available for foods other than milk.

As a peptide, IGF-I is likely to be digested by gastric enzymes in the same way as other proteins and very little is thought to be absorbed intact. This means that IGF-I present in food would not be expected to be active within the body in the way that IGF-I produced endogenously (by the body itself) would be.

It has been suggested that IGF-I may be involved in the development of cancer. This is because it is known to cause cells to proliferate (divide) as part of its normal function and may also inhibit apoptosis (programmed cell death of damaged cells). It is also known that individuals with acromegaly (a condition of excess growth) have elevated levels of growth hormone and IGF-I and also have an increased risk of colorectal cancer.

IGF-I is found in cows' milk, with the highest levels being present in the colostrum, the first milk produced after the calves' birth. The IGF-I levels present in milk depend on the breed of cow and decline rapidly once the cow has been milked several times. Cows treated with the hormone bovine somatotropin (BST) produce higher concentrations of BST in their milk, so concerns have been expressed that this could increase the risk of cancer in consumers who drank the milk.

COC review

The COC reviewed the available data considering an extensive database of studies that assessed circulating IGF-I levels and risk of breast, prostate, lung and colorectal cancer. They also examined the effect of diet (including milk consumption) on IGF-I concentrations in the blood, and considered the studies which linked diet, IGF-I concentrations and cancer risk. A variety of background information on IGF-I was also considered. The COC considered that as a protein it was unlikely that there would be absorption of intact IGF-I by the majority of consumers.

An estimate was made of the possible exposure to IGF-I from the diet. This showed that even if all relevant foods contained IGF-I at the same concentration as one of the higher values measured in milk, and, that consumers were eating high levels of all IGF-I containing foods, the amount of IGF-I they could consume would still be significantly lower (less than 2%) than the IGF-I produced by the body.

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Increased circulating levels of IGF-I are associated with an increased risk of certain cancers, however, many factors influence IGF-I concentration in the blood and since tumours are also able to produce their own growth factors, the explanation for this association is unclear.

Very few of the available human studies have linked cancer risk, diet and circulating IGF-I concentrations but where this has been done, there is no indication of any association, with milk consumption, which if anything, reduced risk.

The COC noted that there were a number of limitations to the available studies; these included a lack of information on diet, ethnicity and changes in IGF-I concentrations over time, with the majority of studies measuring it only at the start of the study.

Overall, it was concluded that on the basis of the available evidence, IGF-I in the diet would not expected to increase the risk of cancer in consumers.

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Annex B to CC/2017/10

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

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

Revised statement

Secretariat

July 2017

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

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

Background

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

These can be accessed here: [*link to be inserted prior to publication*]

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 most recently by the Veterinary Products Committee (VPC) at a meeting in 2008. They considered it unlikely, based on the normal concentration of endogenous IGF-I in the blood, that enough IGF-I could be absorbed from the gut lumen by drinking milk to increase the circulating amount of endogenous IGF-I sufficient to have any effects on tissues. However, the possibility that dietary IGF-I could cause cell proliferation of the gut mucosae with the potential of increasing cancer could not be excluded.

IGF-I and cancer

5. There are a number of reasons that IGF-I 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-I. These individuals also have a high prevalence of colorectal neoplasia (VPC, 1999). 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-I.

7. IGF-I 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-I (Pollak *et al*., 1992).

IGF-I: identity, structure and physiological control.

9. IGF-I 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-I is highly conserved in mammalian species and is identical in humans, cattle and pigs (European Commission, 1999).

10. In the circulation, IGF-I is bound to one of six 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-I since changes to IGFBP-3 concentrations could alter the IGF-I:IGFBP-3 ratio and changing the circulating concentration of free IGF-I, the active form.

11. The rate of secretion of IGF-I 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

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

of hormones including insulin, growth hormone (GH), oestrogen, testosterone and thyroid hormones (Yu and Rohan, 2002). IGF-I production in humans was estimated to be 9.95 mg/day (Guler *et al*., 1989).

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

13. In circulation, IGF-I 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-I is prone to degradation in the bloodstream whereas the ternary complex is more stable (Wu *et al*, 2008). IGFBP-3 protease releases the IGF-I so it can then leave the bloodstream and act on surrounding tissues; the free IGF-I may then bind to smaller binding proteins such as IGFBP-4 which can cross the vascular barrier but protect the IGF-I on the journey to the target tissues. The action of IGFBP-4 protease released by the target tissue makes the IGF-I available to receptors. Tissue-specific regulation of IGFBP proteolysis may provide a mechanism for controlling the bioavailability of IGF-I to receptors through the effects of local growth factors.

Analysis of IGF-I and IGFBP-3

14. IGF-I 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-I which might not necessarily reflect the availability of IGF-I to receptors. In some cases IGF-I was removed from its binding proteins, usually by acid-alcohol extraction. However, it was not always clear whether this has been conducted.

15. Renehan *et al.* (2003) reported that higher concentrations of IGF-I 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 between studies, caution should be exercised when comparing analytical results, since many papers report only IGF-I 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-I and its binding proteins

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

19. The circulating levels of IGF-I and its binding proteins vary depending on factors such as age, gender, 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-I 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-I levels decline to around a third to a half of peak levels, gradually declining with age thereafter. IGF-I 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-I concentrations are summarised in Table 1 of CC/2012/16 and given in the summary tables for individual studies. For the purposes of illustration, average IGF-I concentrations were reported to be 80-200, 200-500, 290 and 160 ng/ml in pre-pubertal children, pubertal children, 20 y old humans and 70 y old humans respectively (Juul *et al*., 1994a; Juul *et al*., 1994b; Perdue, 1984).

20. There are fewer data available on the circulating levels of IGF-I binding proteins. In healthy adults, IGFBP-3 remained fairly constant but as with IGF-I 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-I (Rajaram *et al*., 1997).

22. Serum levels of IGF-I 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-I levels (Thissen *et al*., 1994).

23. IGF-I has also been measured in saliva, gastric juice, jejunal chime, 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-I

24. It has been noted (European Commission, 1999) that about 3% of the IGF-I 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-I in *in vitro* assays (Burrin, 1997; European Commission, 1999).

Dietary exposure of humans to IGF-I

25. With the exception of milk, there are few data available on concentrations of IGF-I 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-I was measured in the first post-partum milking, and this reflects the high level of IGF-I that is known to occur in colostrum (Ginjala and Pakkanen, 1998). The levels of IGF-I 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-I 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-I, through consumption of maternal milk and to have a greater exposure of the luminal side of the gut to IGF-I than is the case in older individuals. The higher concentration of IGF-I found in colostrum provides neonates with a high dietary intake of IGF-I. It is feasible that this high exposure and bioavailability of IGF-I in neonates is related to a normal physiological role of IGF-I in the growth and development of the newborn.

28. Exposures in human neonates will vary depending on the feeding regimen, as only infants fed human milk would be exposed to IGF-I, since formula does not contain IGF-I. 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-I 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-I in the tissues of experimental animals. For example, IGF-I 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-I has been estimated in Table 1 below:

Table 1: Chronic exposure assessment for IGF-I 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-I 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 a concentration of 101 µg/kg[4] 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-I in toddlers is 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-I 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-I would be less than 1% of endogenous production[5]. 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 IGF-I production it has not been possible to compare it with dietary exposure.

[4] The highest reported concentration in milk from the 5th post-partum milking of Ayrshire cows.
[5] The reference for the estimate of 10,000 µg/day was not given, but it may have been taken from Guler *et al*., 1989.

The effect of dietary components on IGF-I concentrations

33. A number of studies in both humans and animals have indicated that serum IGF-I 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-I but not necessarily with increases in growth hormone levels. Although the increased permeability of the gut in newborns may mean that IGF-I is more likely to be absorbed intact, higher IGF-I 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-I 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-I 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-I levels. Conversely, malnutrition is associated with lower levels of IGF-I.

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.

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-I levels.

Milk

39. In general and as noted above, formula fed babies have higher levels of circulating IGF-I than breast fed babies, and where the formula has a higher protein content, the levels of circulating IGF-I are higher still (Socha *et al*., 2011). Supplementation of the diet with whole milk has been shown to increase IGF-I 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-I 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 a low fat/high fibre diet interventions were not shown to significantly affect IGF-I levels.

Absorption, distribution, metabolism and excretion of IGF-I

40. IGF-I 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-I might pass through the gut without being broken down. Concentrations of IGF-I in the gut lumen are likely to be lower than the levels in the blood since IGF-I levels are lower in jejunal chime and plant-derived foods do not contain IGF-I, this would dilute the concentration of IGF-I in the gut lumen so passive absorption of IGF-I is not anticipated since any absorption of IGF-I from the gut lumen would need to operate against a concentration gradient. This suggests that, even if the IGF-I was not digested, it would be unlikely to be absorbed to any significant extent.

41. There are few data on oral dosing in humans has. In the single available study, Mero *et al*., (2002) gave 12 adult volunteers I^{123} labelled recombinant IGF-I; serum samples were taken 60 minutes after dosing and were subjected to gel electrophoresis. It was concluded that the IGF-I was fragmented during circulation since no radioactive IGF-I was eluted at the positions of free IGF-I or the IGF-I binding proteins, only smaller molecules being detected.

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

43. Parenterally administered IGF-I 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-I remained in the bloodstream bound to IGFBPs.

44. It is expected that IGF-I 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-I in milk, saliva, digestive juices and bile also occurs. Free IGF-I is rapidly removed from plasma (elimination half-life < half-an-hour), but protein-binding can considerably slow down the elimination (EMEA, 2007).

Direct effects of IGF-I on the gut

46. Studies of the trophic effects of IGF-I 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

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concentration of 750 ng/ml IGF-I 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-I

47. Toxicological studies of recombinant human (rh) IGF-I 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-I 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-I than in normal mice or transgenic mice that had injections of IGF-I. rhIGF-I was not genotoxic in an *in vitro* cytogenetics assay and in an *in vivo* micronucleus test.

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

Epidemiology studies: cancer and IGF-I

49. A number of human studies have examined the relationship between blood IGF-I 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-I 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[6] (Cancer Research UK, 2017a). Most women develop breast cancer when post-menopausal but around 20% of cases occur in pre-menopausal women. Breast

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

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-I concentrations and breast cancer is discussed in detail in CC/2012/06.

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

52. The results of the prospective studies investigating levels of IGF-I and breast cancer risk are also inconsistent. Some studies report an association between IGF-I 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-I 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-I and oestrogen positivity in the cancer.

54. It has been suggested that high levels of IGFBP-3 are protective by reducing the concentration of free IGF-I 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-I 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-I can be produced by tumours. The results are inconsistent, with many studies reporting no difference in IGF-I levels between prostate cancer cases and controls but a similar number reporting elevated IGF-I levels in prostate cancer cases compared to controls.

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-I are associated with a

modest increase in risk of prostate cancer, though in the former study this was only for low grade prostate cancer. The results of studies analysing the association between IGF-I levels and cancer stage and/or severity also appear to be inconsistent.

58. A total of five meta-analyses have been performed on the available data and all have reported a positive association between IGF-I levels and the risk of prostate cancer (Shi *et al*., 2001; Renehan *et al*., 2004; Morris *et al*., 2006; Roddam *et al*., 2080; 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-I 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-I concentrations and colorectal cancer is discussed in detail in CC/2016/01.

61. Patients with acromegaly and thus elevated growth hormone and IGF-I 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-I levels in patients with colorectal cancer and controls have reported both increased levels of IGF-I 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-I and colorectal cancer risk are also inconsistent. Some studies report an association between IGF-I 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-I 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-I 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-I concentrations and breast cancer is discussed in detail in CC/2016/01.

67. Studies comparing circulating serum or plasma IGF-I levels in patients with lung cancer and controls have reported increased, decreased and no difference in the levels of IGF-I 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-I and lung cancer risk are also inconsistent. Some studies report an association between IGF-I 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-I 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-I and cancer risk only have baseline IGF-I levels 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-I 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-I but not IGFBP-3 increased over time in prostate cancer cases but not controls (2-5 years before diagnosis and within one year of diagnosis) suggesting that IGF-I could be a tumour marker. Soubry *et al*. (2012) reported an association between colorectal adenoma and increasing IGF-I level or IGF-I: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-I production dominated that from other tissues so that it was unlikely that IGF-I production by a tumour would significantly increase circulating IGF-I levels.

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Renehan et *al*, (2001) reported that IGF-I and IGFBP-3 levels were unaffected by removal of colorectal adenomas.

Diet, IGF-I 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 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-I 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-I, but intakes of red meat, poultry and fish were not associated with plasma IGF-I levels – see Table 3 below. Non-drinkers of milk who had the highest tertile ratio[7] of IGF-I to IGFBP-3 (i.e. higher levels of free IGF-I) 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-I/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-I/IGFBP-3 ratio, despite a moderate positive influence of milk or dairy food on circulating IGF-I levels.

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

	IGF-I/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)

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

Tertile 3	13/17	1.59 (0.55-4.64)	16/29	1.43 (0.59-3.51)	16/39	1.05 (0.41-2.69)
				$P_{interaction}$ = 0.03 *		
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)	21/46	1.00 (0.43-2.36)
				$P_{interaction}$ = 0.18 *		
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 *		

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

76. The association between colorectal cancer risk with serum IGF-I, 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-I concentrations by conditional logistic regression. Possible confounders that were considered for to use for adjustment included body mass index, 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-I 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-I 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-I 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.

Conclusions of the Committee

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

General conclusions on IGF-I

IGF-I in the gut - general

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

79. It has been suggested that a truncated form of IGF-I missing several amino acids might be more potent than IGF-I 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.

80. It is highly unlikely that dietary IGF-I 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-I in colostrum indicates that it may be involved in the maturation of the neonatal gut.

IGF-I in food

81. IGF-I 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-I 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-I has been estimated to be 10,000 µg/day, dietary IGF-I 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-I are not available.

The effect of diet on circulating IGF-I concentrations

82. A number of epidemiological and intervention studies have indicated that IGF-I 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-I (rhIGF)

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

84. Several clinical studies of rhIGF-I 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-I caused any cancer in treated patients.

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

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

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86. The results of the available studies assessing the risk of cancer related to circulating IGF-I 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-I contributes to circulating levels is uncertain.

iii) The control subjects were sometime 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-I levels.

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

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

IGF-I and breast cancer

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

88. The results of the twenty one prospective studies investigating levels of IGF-I and breast cancer risk are also inconsistent. Some studies report an association between IGF-I 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.

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

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

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

IGF-I and prostate cancer

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

93. 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-I levels and prostate cancer stage and/or severity also appear to be inconsistent.

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

95. 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.

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

IGF-I and colorectal cancer

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

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

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

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

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

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

IGF-I and lung cancer.

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

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

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

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

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

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

Studies linking cancer risk and dietary IGF-I

109. 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-I concentration and cancer risk. From the limited data available, milk consumption was either protective against colorectal cancer for individuals with high circulating IGF-I or there was no association between colorectal cancer risk with increasing IGF-I levels associated with consumption of dairy calcium, dairy proteins and other food components.

Overall conclusion

110. There is insufficient evidence to draw any firm conclusions as to whether exposure to dietary IGF-I is associated with an increased incidence of cancer in consumers. However, the data indicate that the levels of IGF-I consumed are likely to be low and that IGF-I 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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Annex A

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

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

Search strategy

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Annex B

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

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

Summary tables of epidemiology studies.

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

Subjects	Number of subjects	Variables matched or controlled for	How was IGF-I measured and was it free?[8]	Association between IGF-I levels and breast cancer	Main results	Reference
Retrospective studies						
Breast cancer patients treated with tamoxifen	69 patients-		Not stated – probably RIA	-	It was noted that tamoxifen treatment caused a reduction in serum IGF-I (1.4 u/ml to 0.9 U/ml	Pollak *et al*., 1992
French breast cancer patients, aged 20-80	47 cases; 134 controls	Age	RIA on plasma and acid ethanol extract of plasma.	Positive	Higher median levels of total and free IGF-I in cases (152 ng/ml and 26) 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.	RIA ?? Free	Positive	Elevated IGF-I in pre-menopausal patients (p = 0.025) but not in post-menopausal patients. RR=7.34 for IGF-I/IGFB-3 ratio, comparing upper and lower quintiles. [check levels] No differences in IGFBP-3. IGF-I/IGFBP-3 ratio significantly higher in pre-menopausal cases compared to controls only.	Bruning *et al*., 1995
Chinese breast cancer patients (age not given)	63 cases; 27 controls with benign breast disease.		RIA after acid extraction	None	No significant difference between IGF-I in cases (149 ng/ml) and controls (174 ng/ml). High IGFBP-1 and 3 associated with increased risk, IGFBP-2 with reduced risk (p <0.05) [check paper].	Ng *et al*., 1998
US pre-menopausal	99 cases; 99 controls	Age, weight.	RIA after acid extraction	None	No significant association between IGF-I and cancer ORS (p > 0.05, but OR;95%CI	Del Giudice *et al*., 1998

[8] Free IGF-I is measured by, for example, acid-ethanol extraction of plasma or serum which removes binding proteins.

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Subjects	Number of subjects	Variables matched or controlled for	How was IGF-I measured and was it free?[8]	Association between IGF-I levels and breast cancer	Main results	Reference
breast cancer patients (mean age 42.6 y)	with non-proliferative breast disease				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".	
US breast cancer patients, aged <40 to 49	94 cases 76 controls	Age, area of residence.	Commercial immunoradio-metric assay	Positive	Increased breast cancer risk in upper two tertiles of IGF-I levels as compared with the lower tertile (OR=2.4 & 1.8). Decreased risk or cancer in upper two tertiles of IGFBP-3 compared to the lowest. Women with high IGF-I and low IGFBP-3 at higher risk than low IGF-I and high IGFBP-3 Check CIs	Bohlke *et al*., 1998
US women mean age 74 (54.6 at recruitment)	45 cases 393 controls	??	RIA stated not to cross react	None	IGF-I 120.22 ng/ml in cases; 126.96 ng/ml in controls. Not significantly different. Check CIs	Jernström & Barrett-Connor., 1999
US women mean age 52 (largely African-American or Hispanic)	130 cases 42 controls	??	RIA after acid extraction	Positive	IGF-I 111.9 ng/ml in cases; 92.1 ng/ml in controls. Significant (*p* = 0.019) Check CIs	Vadgama *et al*., 1999
NZ women undergoing surgery for breast lesions	12 benign 31 malignant + matched controls	Age	RIA after acid extraction	None	IGF-I 150.9 ng/ml in benign disease cases; 142 ng/ml in matched controls, 128 ng/ml in cancer patients and 126 ng/ml in matched controls. Not significantly different.	Holdaway *et al*., 1999
US breast cancer patients, aged <40 to 49	83 cases 69 controls	??	Commercial immunoradio-metric assay	None	IGF-I 161.52 ng/ml in cases and 157.95 ng/ml in controls. Not significantly different. No differences in IGFBP-3 between groups.	Mantzoros *et al*., 1999
Breast cancer patients aged	75 cases; 75 controls	??	Commercial immunoradio-	None	No association between IGF-I and breast cancer in pre- or post-menopausal women	Petridou *et al*., 2000

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Subjects	Number of subjects	Variables matched or controlled for	How was IGF-I measured and was it free?[8]	Association between IGF-I levels and breast cancer	Main results	Reference
<45 to >75 y			metric assay of serum samples			
Black & white American women aged 31-67 y	40 cases:40 controls	Age, ethnicity, menopausal status, IGFBP-3		Positive	Adjusted OR=2.00 for women with greater than the median level of IGF-I (OR=6.31 for free IGF-I)	Li *et al*., 2001
Chinese breast cancer patients, aged 48.5±8.3 y	300 cases; 300 controls	Age and menopausal status	Commercial ELISA	Positive	Plasma IGF-I was higher in cases (143 ng/mL) than in controls (127 ng/mL) IGFBP-3 also significantly higher in cases than controls 4340 and 4030 ng/ml.	Yu *et al*., 2002
Taiwanese women aged 24-72	297 cases; 593 controls	"Matching factors" and IGFBP-3	Commercial immunoradio-metric asay	Positive	High IGF-1 associated with increased risk of pre but not postmenopausal breast cancer (OR 1.86). No association with IGFBP-3.	Wu *et al*, 2009.
US women aged 25-79	184 cases; 522 controls	Ethnicity ??	Commercial IGF-I (IGFBP-3 blocked) RIA	Positive	IGFBP-3 associated with increased risk of breast cancer. No association for IGF-I in Hispanic women, but association in NHW women	Rollison *et al*, 2010.
Prospective studies						
Female nurses (USA) aged 30-55 y	397 cases; 620 controls	Age	ELISA	Positive	RR=7.28 in pre-menopausal women ≤50y with IGF-I>207 ng/ml, compared to those with IGF-I<158ng/ml. No association for whole group or post-menopausal women	Hankinson *et al*., 1998
Female nurses (USA) aged 30-55 y	800 cases; 1129 controls	??	ELISA after acid extraction	Positive	RR=2.5 in pre-menopausal women ≤50y with IGF-I>187ng/mL, compared to those with IGF-I<176ng/mL. No association in post-menopausal women.	Schernhammer *et al*., 2005 (update /expansion of Hankinson *et al*., 1998)
Female Nurses aged 25-42y	317 cases; 634 controls	"breast cancer risk factors"	Commercial ELISA after acid extraction	None	No association between IGF-1, IGFBP-I or IGFBP-3 and breast cancer risk in largely pre-menopausal women.	Schernhammer *et al.,* 2006
American	115 cases;	Age, menopausal	RIA after acid	Positive	Adjusted RR=2.3 in women ≤50y with	Toniolo *et al*.,

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Subjects	Number of subjects	Variables matched or controlled for	How was IGF-I measured and was it free?[8]	Association between IGF-I levels and breast cancer	Main results	Reference
women aged 35-65 y	486 controls	status, stage of menstrual cycle at blood sampling.	extraction		IGF-I>265ng/mL, compared to those with IGF-I<168ng/mL	2000
American women "pre-menopausal"	138 cases; 259 controls		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-I and IGFBP-3 levels.	Extension of above study. Rinaldi *et al*., 2005a
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"	Commercial ELISA on plasma or serum	Positive but not significant when adjusted for IGFBP-3	Mean levels 301.5 and 293.6 ng/ml in cases and controls. OR 1.41 for highest vs lowest quintile, lower if adjusted.	Rinaldi *et al*., 2005b - re-analysis of Toniolo *et al*., 2000, Kaaks *et al*., 2002, Muti *et al* 2002.
Italian women aged 35-69 y	133 cases; 532 controls	"various social and physiological variables"	Commercial immunoradio-metric assay of free and total IGF-I	Positive	Adjusted RR=3.12, comparing upper & lower quartiles of free IGF-I	Muti *et al*., 2002
American breast cancer patients, aged 19-73 y	126 cases (66 pre-menopausal); 126 controls	Age, date of examination, length of follow up for matching. Insulin, glucose, BMI, IGFBP-3.	Commercial immunoradio-metric assay after acid extraction	Positive	Elevated IGF-I and IGFBP-3 were associated with raised risk of breast cancer in pre-menopausal women. Elevated IGFBP-2 was associated with reduced breast cancer risk in post-menopausal women.	Krajcik *et al*., 2002
Dutch women aged 29-73	513 cases; 987 controls	??	Commercial immunoradio-metric assay after acid extraction	None	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.	Kaaks *et al.,* 2002
Swedish women aged 20-69 at	149 cases; 333 controls	??	Commercial immunoradio-metric assay	None	No association between IGF-1, IGFBP-1,-2,-3 or IGF-I/IGFBP-3 ratio and breast cancer risk in post-menopausal women.	Keinan-Boker *et al.,* 2003

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Subjects	Number of subjects	Variables matched or controlled for	How was IGF-I measured and was it free?[8]	Association between IGF-I levels and breast cancer	Main results	Reference
enrolment. Mean age 57 in study.			after acid extraction			
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	No association between IGF-I and risk but there was an association between IGF-II and IGFBP-3 and breast cancer risk in post-menopausal women with ER positive tumours.	Grønbæk *et al.,* 2004
Guernsey women, ≥35 at recruitment, mean age 57 at diagnosis	117cases (70 pre-menopausal) ; 350 controls	??	Commercial ELISA	None	Non-significant association for IGF-I adjusted for IGFBP-3 in pre-menopausal women. Association between IGFBP-3 adjusted for IGF-1 and breast cancer risk in premenopausal women. No associations in post-menopausal women	Allen *et al.,* 2005
European women aged 50 or more at diagnosis	243 cases (152 pre-menopausal); 243 controls	Age, IGFBP-3, ??	ELISA	Positive	No overall association, but an association between IGF-1 adjusted for IGFBP-3 and post-menopausal breast cancer risk in the youngest premenopausal women and oldest post-menopausal women.	Rollison *et al.,* 2006
European women aged 35-69	1081 cases (370 pre-menopausal); 2098 controls	??	Commercial ELISA after acid extraction	Positive	Association between IGF-1 and IGFBP-3 and breast cancer risk in post-menopausal women (OR 1.38), but no association in pre-menopausal women.	Rinaldi *et al.,* 2006
Swedish women 19-43y	212 cases; 369 controls	??	Commercial immunoradio-metric assay	Positive	Association between IGF-I and increased risk (OR 1.7) but not with IGF-II.	Lukanova *et al*., 2006
Swedish women 19-43y	244 cases; 453 controls	??	Commercial chemiluminescence based immunoassay	Positive	Association between IGF-I and increased risk (OR 1.73; 95% CI 1.14-2.63).	Chen *et al*., 2010. Same cohort as above.
Swedish women 22-	719 cases; 1434	??	Commercial chemiluminesce	None	No association between IGF-I and increased risk (OR 1.08; 95% CI 0.80-	Toriola *et al*., 2011. Same

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Subjects	Number of subjects	Variables matched or controlled for	How was IGF-I measured and was it free?[8]	Association between IGF-I levels and breast cancer	Main results	Reference
37y	controls		nce based immunoassay		1.47).	cohort as above.
Australian women aged 27-75y at baseline	423 cases; 1901 controls	??	Commercial ELISA	Positive	No overall association but IGF-1 and IGFBP-3 associated with increased breast cancer risk in older women (HR 1.61 for women aged >60).	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 overall association but modest increase in risk associated in women aged <50	Vatten *et al*., 2008
US women aged 54-74	835 cases; 816 controls	??	Commercial ELISA for total and free IGF-I	Positive	Free IGF-1 associated with a modest (but not linear) increase risk in postmenopausal women not using HR. No associations for total IGF-I or IGFBP-3.	Gunter *et al*, 2009.
US women aged 55-74	389 cases; 470 controls	BMI, estradiol, ??	Commercial ELISA for total IGF-I	None? (Authors considered positive but not statistically significant)	IGF-1 and IGF-I/IGFBP-3 associated with increased risk of postmenopausal breast cancer (OR 1.28 for IGFI) No association with IGFBP-3.	Schairer *et al*, 2010.
Meta analysis of five studies	-		-	*Positive*	*High levels of IGF-I & IGFBP-3 were associated with increased risk of pre-menopausal breast cancer eg (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-I 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-I 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*	*Key et al., 2010*

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Subjects	Number of subjects	Variables matched or controlled for	How was IGF-I measured and was it free?[8]	Association between IGF-I levels and breast cancer	Main results	Reference
					increased risk of (oestrogen positive) breast cancer, but not of (oestrogen-negative) breast cancer	

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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-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
Retrospective studies						
American men (age not known)	32 cases; 6 controls (male) 6 controls (female)	Radioimmuno assay	None	Age	IGF-I and IGFBP-3 not elevated in prostate cancer patients. Levels? 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)	Radioimmuno assay after acid extraction	None	-	IGF-I 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? 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))	Radioimmun oassay	None	-	IGF-I and IGFBP-3 not elevated in prostate cancer patients Levels? IGFBP-2 higher in cases.	Ho and Baxter, 1997
Greek men, 38.5% aged <69 y, 34.6% aged 70-74 y & 26.9% aged >75 y	52 cases; 52 controls with BPH	Commercial radioimmuno-assay after ethanol extraction	Positive	Age	Unadjusted OR=1.71 for 60 ng/ml increment of serum IGF-I, comparing IGF-I in prostate cancer cases with controls Levels?	Mantzoros, *et al*., 1997
Swedish men, aged <80 y	210 cases; 224 controls	Commercial Immuno-radiometric assay. No interference	Positive	Age, height, BMI, total energy intake	IGF-I higher in cases than controls (158.4 ng/ml vs 147.4 ng/ml) $p = 0.02$ Significant association between IGF-I and prostate cancer risk (OR; 95%CI = 1.51; 1.0-2.26, $p = 0.04$). Stronger	Wolk, *et al*., 1998

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
		detected			association for men aged <70 y (OR= 2.93;1.43-5.97). No difference in IGFBP-3 levels (2688 ng/ml and ?? Levels?	
Austrian white men aged 56-79 y, with elevated PSA	Cohort of 245, with 74 developing prostate cancer	Commercial immuno-radiometric assay	Positive	-	IGF-I 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
Swedish men aged 69.9±6.3 y	208 cases; 70 controls	Commercial immuno-radiometric assay	None	Age, height, BMI.	No associations between IGF-I or IGFBP-3 and prostate cancer (158 and 152 ng/ml and 2664 ± 1041 and 2556 ± 783 ng/ml respectively in cases and controls), Positive association of IGFBP-1 levels and cancer risk.	Signorello, *et al.,* 1999
UK men aged 69.9±6.3 y	37 cases; 57 controls	Commercial (?) Immuno-radiometric assay	None	Age	No associations between IGF-I levels and prostate cancer (202 and 181.3 ng/ml in cases and controls).	Cutting, *et al.,* 1999
Greek men, mean age 67 and 69 y	34 cases; 131 BPH controls	Commercial immune radiometric assay	None	Total PSA, free PSA, PSA/IGF-I ratio	No difference between IGF-I in BPH and cancer patients (104.8 and 116.3 ng/ml).	Koliakos, *et al.,* 2000
German men (mean age 66 or 64)	171 cases; 67 controls	Radioimmunoassay and chemi luminescence	None	Age, testosterone, anti-androgen treatment	No difference between IGF-I levels in prostate cancer patients and controls (158.6 ng/ml vs 159.1 ng/ml by chemiluminescence and 150.5 vs 168.1 ng/ml by RIA).	Kurek, *et al*., 2000
US men (age not reported)	57 cases; 39 controls	Commercial active IGF-I ELISA	Negative	Age	IGF-I levels were lower in prostate cancer patients (125 ± 58 ng/ml) than in controls (158 ± 71 ng/ml) p = 0.019	Baffa, *et al*., 2000

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
US men aged 62 and 63y controls	38 cases; 40 controls	Commercial ELISA or radioimmunoassay.	None	"Patient and specimen variations"	No differences in IGF-I levels between cases and controls. IGFBP-3 levels lower in cases Levels? IGFBP-2 levels lower in cases.	Yu, *et al*., 2001
Canadian men, aged 52-75 y	84 cases; 75 controls (BHP patients)	Commercial active IGF-I ELISA	Positive	Age, IGFBP-3 (intact, fragment, total), free & total PSA	Prostate cancer patients had higher levels of IGF-I (126.6 ± 4.9 ng/mL *vs.* 101.2 ± 5.5 ng/ml, p <0.001) and intact IGFBP-3 (1480 ± 680 ng/ml *vs*. 1120 ± 720 ng/ml, p <0.001)	Khosravi, *et al*., 2001
Chinese men aged 71.9±7.5 y	112 cases; 306 controls	Commercial ELISA after acid-ethanol extraction	Positive	IGFBP-I, IGFBP-3, 5α-androstane-3α, 17β-diol glucuronide, sex hormone binding globulin, weight, height, BMI, waist-to-hip ratio	Higher risk of prostate cancer in upper vs lower quartiles of IGF-I levels, (OR; 95%CI =2.63;1.19-5.79, significant positive trend, p=0.01). Prostate cancer risk was inversely related to levels of IGFBP-3 (0.54;0.26-1.15, non-significant trend, p > 0.08. Risk elevated for higher IGF-I: IGFBP-3 ratio (2.51:1.32-4.75). For localised disease there were significant trends for IGF-I (15.73; 3.04-81.94, p=0.001) and IGF-I:IGFBP-3 (6.30; 1.96-20.24, p<0.001). For advanced disease there were significant trends for IGF-I:IGFBP-3 (2.53;1.11-5.78, p<0.003) and IGFBP-1.	Chokkalingam, *et al.,* 2001
Check details	120 cases 44 controls				IGF-I levels lower in pre-operative patients and patients with lymph and bone metastases than healthy controls (151.1, 156.4, 153.4 and 171.3 ng/ml) IGFBP-3 levels lower in patients with bone metastases IGFBP-2 levels lower in cases.	Shariat *et al*, 2002

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
Canadian men, mean aged 65 y cases-63 y controls	244 cases; 408 controls	ELISA	None until corrected for age and PSA	Age	No difference in mean IGF-I (176.1 ± 58.3 and 178.7± 54.7 ng/ml) and IGFBP-3 levels (2724 ± 647 and 2673 ± 589 ng/ml) cases and controls respectively. Inverse relationship between IGF-I and cancer risk when age-adjusted.	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); 232 BPH controls	Commercial immune-radiometric assay	None	PSA, IGFBP-3, IGF-I/PSA ratio, IGFBP-3/PSA ratio, age , BMI, smoking	IGF-I higher in advances cancer cases than controls (171.8 vs 140.6 ng/ml, p = 0.01). IGFBP-3 lower (1790 ng/ml) in advanced cases compared to localised cases (2090 ng/ml) or BPH controls (2110 ng/ml).	Miyata *et al*., 2003
Italian men median age 68 and 65 y	171 cases: 174 BPH controls	Commercial ELISA	Positive	Human glandular Kallikrein (hK2), PSA, free/total PSA, hK2/PSA	IGF-I higher in prostate cancer (142 ng/ml) compared to controls with BPH (143 ng/ml)	Scorilas *et al*., 2003
Malaysian men mean age 70 68 (cases, BPH) and 57 (controls)	25 cases: 45 BPH, 69 controls	Commercial ELISA	None	-	No significant differences in IGF-I between the 3 groups (98.3 ± 39.3, 119.3 ± 31.1; 119.36.1 ng/ml respectively). 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	24 localised cases, 19 metastasised cases: 45 BPH	Immuno-radiometric assay	None	-	IGF-I levels similar in all groups (138.3 ± 58.2, 137.7 ± 39.0 and 147.7 ± 4.42 respectively). IGFBP-3 levels lower in metastasised group compared to BPH controls	Aksoy *et al*., 2004

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
	controls				(1795.6 ± 305.6 vs 2196.0 ± 505.7 ng/ml, *p* = 0.005)	
British men, mean age 62y	176 cases; 324 controls	Commercial ELISA	Positive associations stronger for advanced-stage prostate cancer	Age, GP practice, recruitment date, IGFBP-3, smoking. Other variables BMI, class, exercise, alcohol use, did not affect the model and were not used.	IGF-I 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. IGFBP-3 not associated with risk. IGF-II associated with increased risk.	Oliver *et al*., 2004
Austrian men, median age 67 and 69 y	156 cases; 271 controls	Immuno-radiometric assay	None	-	IGF-I levels similar in both groups (166 ± 6.1 ng/ml and 159 ± 4.5 ng/ml).	Marszalek *et al*., 2005
Arab men 15- 90 y.	30 cases; matched controls	Immuno-radiometric assay	Positive	Age	IGF-I levels higher in cases (127.60 ± 85.19 vs 70.09 ± 63.56 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 ELISA	None when adjusted	Age, PSA, ethnic background, digital rectal examination.	IGF-I levels higher in HGPIN cases than controls (130.2 vs 118.8 ng/ml, *p* = 0.01) IGFBP-3 levels non-significantly higher in HGPIN cases than controls (2393.9 vs 2276.0 ng/ml, *p* = 0.06)	Nam *et al*., 2005
Chinese men (mean age 65y) with total PSA of 4/-10 ng/ml.	281 cases 503 controls	ELISA following acid ethanol precipitation	Positive	-	IGF-I higher in cases than controls (219 vs 178 ng/ml, *p* = 0.001) No difference in IGFBP-3 levels (2715 vs 2694 ng/ml, *p* = 0.32)	Zhigang *et al*., 2007
Men in Belarus	? controls, prostate		None	-	No significant differences between levels of IGF-I (99.2 ± 34.4, 119.2 ±	Povelitsa & Nazarov. 2008

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
	cancer, BPH, BPH + neoplasia				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.	
Prospective studies						
US male physicians aged 40 to 84 y	152 cases; 152 controls	Commercial ELISA	Positive	Age, smoking, duration of follow up.	IGF-I associated with increased risk RR;95%CI =2.41;1.23-4.74, (adjusted (for IGF-II, IGFBP-3, *p* = 0.001)	Chan*, et al*., 1998a
US male physicians aged aged 40-84 y	530 cases; 534 controls	Commercial ELISA	None for all prostate cancer; Positive for advanced-stage prostate cancer	Age, smoking, IGFBP-3, BMI considered but not used.	For the new cases, there was no association between IGF-I and total prostate cancer risk. For advanced stage prostate cancer there was a positive association with IGF-I (RR;95%CI of 5.1; 2.0-13.3, *p* trend = 0.002) and a negative association with IGFBP-3 (0.2:0.1-0.6, , *p* trend = 0.01) comparing upper and lower quartiles	Updated in Chan *et al*., 2002
US health plan members, aged 40-80 y	Cohort of 765. 45 cases; 179 controls	Radioimmunoassay	None	Age, interval between serum collection and diagnosis	No association between IGF-I and prostate cancer (RRs of 0.62, 0.70, and 0.81 for 2nd to 4th quartiles). Additional analysis by conditional logistic regression also negative.	Schaefer, *et al*., 1998
US (mainly) white middle class men, aged 64.8±8.9 y	72 cases; 137 controls	Commercial radio-immunoassay	Positive	Age, length of sample storage, IGF-II, IGFBP-3, PSA	High IGF-I and low IGF-II were associated with high risk of prostate cancer. Adjusted OR;95%CI for IGF-I = 3.1;1.1-8.7. No association with IGFBP-3 (0.71;0.3-1.7)	Harman, *et al.,* 2000
Swedish men. Median age = 59.7 y.	149 cases; 298 controls	Commercial immuno-radiometric assay after acid	Positive	Age, date of survey, residency, IGFBP-3, BMI, smoking	Mean IGF-I higher in cases (229 vs 214 ng/ml, *p* = 0.02) IGFBP-3 also higher in cases (2611 vs 2498 ng/ml, *p* = 0.04)	Stattin, *et al*., 2000

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
		extraction			IGF-I and IGFBP-3 were positively associated with prostate cancer with respective OR; 95%CIs of 1.72; 0.93-3.19, *p* = 0.006 and 1.83; 0.98-3.24 *p* = 0.007 respectively.	
Swedish men. Median age = 59.9 y.	281 cases; 560 controls	Commercial immune-radiometric assay after acid extraction	Positive. Association stronger in younger men	Age, IGFBP-3, BMI, smoking	Mean IGF-I higher in cases (218 vs 208 ng/ml, *p* =?) IGFBP-3 also higher in cases (2422 vs 2360 ng/ml, *p* = ?) IGF-I associated with prostate cancer, highest vs lowest quartile OR= 1.67;1.02-2.72, *p* trend = 0.05 (reduced by adjustment of IGFBP-3 to 1.47; 0.81-2.64)	Extended in Stattin, *et al*., 2004
Finnish men aged 55-67	179 cases 174 BPH 268 normal histology	Commercial ELISA after acid extraction	None	Age, IGFBP-3, PSA, prostate volume	No association between IGF-I and prostate cancer after adjustment for prostate volume (OR; 95% CI = 0.57; 0.28-1.16). 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, ELISA	None	Age. No other confounders (smoking, marital status, education) "mattered".	No difference in IGF-I (119.8 ng/ml and 118.4 ng/ml, OR: 95%CI = 0.7; 0.2-2.23) or IGFBP-3 levels (1042.5 ng/ml and 1022.6 ng/ml, OR:95%CI=1.1; 0.3-3.8) between prostate cancer patients and controls respectively.	Lacey, *et al*., 2001
Finnish male smokers (ATBC cohort)	100 cases: 400 controls	Commercial ELISA	None	Age, BMI, intervention group, time between blood draws, IGFBP-3	No association between IGF-I and IGFBP3 levels and risk (OR;95%CI = 0.52;0.23-1.16 for fourth vs first quartile).	Woodson *et al*., 2003
Dutch men, aged 65-≥80 y	201 cases; 201 controls	Immuno-radiometric assay	None	Log total IGF-I, log free IGF-I, IGFBP-3, PSA density, PSA density of	No difference between total (133.9 vs 135.6) and free IGF-I (0.711 vs 0.712 ng/ml) or IGFBP-3 (3488.9 vs 3556.7 ng/ml) at baseline between cases and	Janssen *et al*., 2004

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
				transition zone, age at baseline, log PSA at each visit.	controls.	
American men, aged 65-≥80 y	174 cases; 174 controls	Immuno-radiometric assay after acid ethanol precipitation	None	Ethnicity, year of entry, age at entry, year of blood draw. (Marital status, education, aspirin use, NSAID use, waist-hip-ratio assessed but not used) IGFBP-3, PSA.	No Association (RR; 95%CI =0.67; 0.37-1,25) lowest vs highest quartile. Mean ± SD levels were 157.7 ± 94.5 and 163.2 ± 77.7 ng/ml in cases and controls. Small decrease in risk with increasing IGFBP-3 levels (0.65; 0.35-1.20). Mean ± SD levels were 3101 ± 924 and 3210 ± 843 ng/ml in cases and controls.	Chen *et al*., 2005
French men, aged 65-≥80 y	100 cases; 400 controls	Chemi luminescent assay (no interference from IGFBPs	None	Age, intervention group, IGF variables, smoking, BMI, alcohol intake. Stratified by PSA level.	No association with IGF-I (lowest vs highest quartile OR;95%CI = 1.83; 85-3.95) or IGFBP-3 (lowest vs highest quartile OR;95%CI = 0.42; 0.12-1.52)	Meyer *et al*., 2005
US men	462 cases 462 controls	Commercial ELISA, no further details	Positive, but became non-significant on further adjustment	Age, IGFBP-3, PSA, time, year & season of blood draw. Other prostate cancer risk factors assessed but not presented.	Higher IGF-I associated with increased prostate cancer risk (OR; 95% CI for top vs bottom quartile 1.37; 0.76- 2.49, *p* trend = 0.05). 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	1331 cases 1331 controls	Commercial ELISA, no further details	Positive	Age, IGFBP-3. Other prostate cancer risk factors assessed but not presented.	Association between IGF-I, 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. Mean IGF-I levels higher in cases (205 vs 197 ng/ml *p* = 0.0001)	Nimptsch *et al*., 2010 Extension of above study by Platz et al., 2005.

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
					Association between IGFBP-3, and total prostate cancer risk (OR; 95% CI top vs bottom quartile 1.41;1.12-1.78, *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-I	
British men	141 cases 423 controls	Commercial ELISA, no further details	None	Age, duration of sample storage. BMI, smoking, alcohol consumption	No association between IGF-I, and prostate cancer risk (OR;95% CI top vs bottom quartile =1.37; 0.92- 2.03, *p* = 0.62). Association reduced by adjustment for IGBP-3. Median levels 122 and 124 ng/ml. No association for IGFBP-3 (1.40: 0.77-2.55). Median levels 3200 and 3200 ng/ml.	Morris *et al*., 2006
Men resident in Australia	524 cases 1826 controls	Commercial ELISA, no further details	None	Country of birth, alcohol consumption. Other variables assessed (BMI, smoking, energy intake) but not used).	No association between IGF-I, and prostate cancer risk (OR; 95% CI top vs bottom quartile 1.07; 0.79- 1.46). Cancer risk associated with increased IGFBP-3 at baseline (*p* trend ≥ 0.08, HR;95%CI = 1.70; 1.15-2.52 for doubling of IGFBP-3 level.	Severi *et al*., 2006
European men from 10 countries (EPIC cohort)	630 cases 630 controls	ELISA following acid ethanol precipitation	Positive- Became non-significant if adjusted for IGFBP-3	IGFBP-3 Other variables assessed (BMI, smoking, alcohol, exercise, marital status) but not used).	Small association between IGF-I and risk (highest vs lowest third, OR; 95%CI =1.35;0.99-1.28, *p* trend = 0.08) but became non-significant when adjusted for IGFBP-3 (1.39; 1.01-1.89, *p* trend ≥ 0.12) IGFBP-3 not associated with risk. (ORs	Allen *et al*., 2007

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
					??)	
European from the EPIC cohort	1542 cases 1542 controls	ELISA following acid ethanol precipitation. Some samples analysed by immunoassay	Positive	Matched by age, study centre, duration of follow up, time of sampling, duration of fasting at sampling.	IGF-I levels associated with increased risk (OR;95%CI = 1.69;1.35-2.13, *p* trend = 0.0002) Mean IGF-I levels 156.49 and 151.1 ng/ml in cases and controls respectively (*p* = 0.001)	Extended in Price *et al*., 2012
Men from PLCO cohort (US)	727 cases 887 controls	ELISA following acid ethanol precipitation	None	Times since initial screen, year of blood draw. IGFBP-3, IGF-I/IGFBP-3. Other variables assessed (BMI, height, diabetes, family history, smoking, activity, nutrients, study centre) but not used).	Small association between IGF-IGBP3 molar ratio in obese men (OR:95%CI = 2.3:1.10-5.01, *p* trend = 0.04) highest vs lowest quartile) risk higher for aggressive disease (2.80; 1.11-7.08)	Weiss *et al*., 2007
US and Canadian men	96 cases and 412 controls	Commercial ELISA, no further details	None	Age, region, ethnicity.	No association between IGF-I, IGFBP-3 and prostate cancer risk overall (OR;95%CI = 1.26; 0.66- 2.41 P = highest vs lowest quartile) or by ethnic group. Mean levels of IGF-I cases and controls were 236 and 228, 240 and 228, and 231 and 226 ng/ml in Black, White and Asian men. No consistent association between IGFBP-3 and risk. Mean levels of IGFBP-3 were 3725 and	Borugian *et al*., 2008

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
					3688, 4027 and 3911, and 3670 and 3772 ng/ml in Black, White and Asian cases and controls respectively.	
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-I as compared with those with low IGF-I. The OR was 1.26;1.03-1.54 for IGFBP-3. P values*	*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-II 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	-		*Positive*		*Increased concentrations of IGF-1 were associated with an increased risk of*	*Rowlands, et al. 2009*

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Association between IGF-I levels and prostate cancer	Variables the study controlled, analysed or matched for?	Main results	Reference
fourteen prospective and 20 retrospective studies					*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.*	

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

Subjects	Number of subjects	How was IGF-I measured and was it free[9]?	Variables study controlled, matched or analysed for	Association between IGF-I 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-I	Gender, age, educational level.	None	Mean ± SEM IGF-I levels not significantly different -80.25 ± 5.05 and 78.83 ± 4.76 ng/ml in cases and controls. Highest two tertiles of IGF-I and IGF-II associated with increased risk compared to lowest (OR;95%CI = 5.2;1.0-26.8 p value?) 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-I (190 vs 169 ng/ml) and lower IGFBP-3 (3220 vs 3470 ng/ml) in those with high-risk adenomas, compared with those with no cancer or low-risk adenomas. Check levels	Renehan, *et al*., 2001
Japanese men	157 cases 311 controls		Self Defence Force rank, hospital, smoking, IGFBP-3, glucose	Positive after additional adjustment	Modest positive association with IGF- I (OR;95%CI = 1.8: 1.0-4.5, *p* trend = 0.06). Minimal reduction in risk if high IGFBP-3. Association less marked for advanced adenomas. ORs for this?	Teramukai *et al.*, 2002.
Adults aged	239 cases; 517 controls	ELISA		None	No difference between IGF-I (Mean ± SEM 121.4 ± 4.8 and 130.7 ± 3.9 ng/ml for cases	Keku *et al.,* 2005

[9] In many studies, it is unclear whether the IGF-I 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.

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Subjects	Number of subjects	How was IGF-I measured and was it free[9]?	Variables study controlled, matched or analysed for	Association between IGF-I levels in blood and colorectal cancer	Main results	Reference
					and controls, IGF-II or IGFBP3 (3177 ± 8) and 3255 ± 51 ng/ml for cases and controls). IGF-I lower in male cases than controls (126.6 ± 5.7 and 145.8 ± 6.3 ng/ml	
US adults attending for colonoscopy	164 cases 614 controls	-	Alcohol intake, waist/ hip ratio	Negative	Plasma IGFBP-3 not associated with adenoma risk. Tissue IGFBP-3 mRNA was higher in cases. ORs for this?	Keku *et al*., 2008
US adults Caucasian, Japanese and Native Hawaiian	554 cases; 786 controls	ELISA following acid alcohol extraction to give free IGF-I	Age, race, ethnicity, sex, recruitment site. Energy, smoking, oestrogen use alcohol intake, folate intake BMI, waist and hip circumference	None	IGF-I 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 (DHS cohort)	167 adults	ELISA	Age, race, gender	Negative	No effect of IGF-I (OR;95%CI = 0.7;0.3-1.5), IGF-II or IGFBP-3 (1.0; 0.5-2.1) on recurrent adenoma risk.	Kang *et al*., 2013
Chinese adults (17-83 y)	24 polyps 13 CRC 13 controls	ELISA	-	Positive for adenomatous polyps and colorectal cancer	IGF-I 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)	Zhang *et al*., 2013
Turkish adults	48 cases 30 controls	ELISA	Age, BMI, visceral fat, waist circumference homeostasis metabolic	Positive	IGF-I levels higher in carcinoma and adenoma cases compared to controls (Mean ± SD, 184.6 ± 61.6, 177 ± 87.6 and 108.9 ± 45.3 ng/ml respectively)	Erarslan *et al*., 2014

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Subjects	Number of subjects	How was IGF-I measured and was it free[9]?	Variables study controlled, matched or analysed for	Association between IGF-I levels in blood and colorectal cancer	Main results	Reference
			assessment method			
US males	126	ELISA	Age, smoking	Negative	No association between IGF-I, IGF binding proteins and number or types of polyp. ORs?	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-I and IGFBP3 higher in cases than controls in both groups (levels ?). Significant association between IGF-I 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.	Ochs-Balcom *et al*., 2014
Prospective studies						
American male physicians, aged 40-84 y	193 cases; 318 controls	ELISA	Age, smoking, BMI, alcohol	Positive	IGF-I 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-II Negative association with IGFBP-3 levels (RR=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;	ELISA. Results stated to be consistent with those following acid chromatography	Age, fasting status, month of sampling, alcohol intake, BMI, IGF-I and IGFBP-3 adjusted for each other.	None	No significant association between plasma IGF-I and colorectal cancer. Negative association with IGFBP-3 *p* > 0.05).	Giovannucci, *et al*., 2000

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Subjects	Number of subjects	How was IGF-I measured and was it free[9]?	Variables study controlled, matched or analysed for	Association between IGF-I levels in blood and colorectal cancer	Main results	Reference
	107 controls.					
American women aged 35-65 y	102 cases; 200 controls	Double antibody immuno radiometric assay after acid ethanol extraction to give free IGF-I	Menopausal status, age, date of recruitment, time of blood sampling	None	No significant association between plasma IGF-I (OR:95%CI = 1.88, *p* trend = 0.25 or IGFBP-3 (2.46, *p* trend = 0.19) and colorectal cancer. Negative trend with IGFBP-1.	Kaaks, *et al.*, 2000
Chinese men aged 45-65 y	125 cases; 661 controls	Commercial radio-immunoassay. Unclear if free	Residence, age, time of blood sampling, age, weight, smoking, alcohol	None	No significant association between plasma IGF-I and colorectal cancer (OR:95%CI = 1.52; 0.82-2.85, *p* trend > 0.5). IGFBP-3 ?? Positive associations with IGF-II and IGFBP-2.	Probst-Hensch, *et al.,* 2001
Swedish men and women aged 30-70 y	110 colon + 580 rectal cancer cases; 336 controls	Double antibody immuno radiometric assay	Sex, age, sub-cohort, date of blood sampling, fasting time.	None	No significant trends, but IGF- & IGFBP-3 levels had a slight positive association with colon cancer (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.	Palmqvist, *et al.,* 2002
American female nurses aged 35-55 y	182 cases; 364 controls	ELISA	Age, date of blood sampling, fasting status, smoking	Positive	Positive association between IGF-I and colorectal cancer when adjusted for IGFBP-1 (RR=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 Increased risk with high IGF-I/IGFBP-3 molar ratio	Wei, *et al.,* 2005
Adults	202 cases; 256 controls	ELISA	Age, race, education, polyp	Positive	IGF-I, IGF-I/IGFBP3 and insulin levels associated with adenoma, particularly	Schoen *et al.,* 2005

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Subjects	Number of subjects	How was IGF-I measured and was it free[9]?	Variables study controlled, matched or analysed for	Association between IGF-I levels in blood and colorectal cancer	Main results	Reference
			history, aspirin use, NSAID use, smoking family history of CRC		severe adenoma. OR;95%CI = 1.7;1.0-2.9, *p* trend =0.05, top vs bottom quartile for IGF-I	
UK adult males	147 cases 440 controls	ELISA	Age, smoking, alcohol, BMI	None	No associations with colorectal cancer for IGF-I (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).	Morris *et al*., 2006
Japanese men and women aged 40-69 y	375 cases; 750 controls	Total IGF-I by immuno-radiometric assay.	Smoking, alcohol, BMI, exercise, family history of CRC	None	IGF-I, IGFBP-1 and IGFBP-3 were not associated with colorectal cancer Split into men, women, colon, rectum- overall figure?	Otani, *et al*.,, 2007
American post-menopausal women aged 50-79 y	438 cases; 816 controls	Total and free IGF-I by ELISA	Age, smoking, race/ethnicity physical activity, waist circumference, NSAID use, alcohol use, family history of CRC	Positive	The trend associating free IGF-I with colorectal cancer was of borderline significance (HR;95%CI = 1.35; 0.92-1.98, *p* trend = 0.05).	Gunter, *et al*., 2008
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-I, IGFBP-3 or IGF-I/IGFBP-3 ratio ORs??	Max, *et al*., 2008
Adults from polyp prevention trial	375 recurrent adenoma cases;	Radio-immunoassay	Age, gender, body mass index, intervention group, aspirin,	Negative	Risk of adenoma recurrence reduced at high IGF-I (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)	Flood *et al*., 2008

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Subjects	Number of subjects	How was IGF-I measured and was it free[9]?	Variables study controlled, matched or analysed for	Association between IGF-I levels in blood and colorectal cancer	Main results	Reference
	375 controls		smoking, ethnicity, and education		levels.	
Males from Wheat Bran Fibre Trial	299 no controls		Smoking history, BMI, alcohol use, family history of CRC	Negative	IGF-I reduced the risk of adenoma recurrence (OR;95%CI = 0.55;0.29-1.01 and 0.49;0.26-0.91 for first vs second and third quartiles, *p* trend = 0.02).	Jacobs *et al*., 2008
Adults 40-69 from JACC cohort	101 cases 303 controls	Immuno-radiometric assay	Area, age, BMI, cholesterol, smoking, alcohol, energy intake, protein intake.	Negative	No effect on CRC mortality with IGF-I (OR;95%CI= 1.01; 0.49-2.10), IGF-II or IGFBP-3 (1.22; 0.63-2.38) levels. P trend =	Suzuki *et al*., 2009
European	1121 cases; 1121 control	Free IGF-I 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	Slight association of IGF-I with colon cancer (not rectal cancer) in young (<50y) participants or those with low milk intakes. RR for an increase in serum IGF-I of 100 ng/mL = 1.43; 1.13-1.93. p trend No association with IGFBP-3.	Rinaldi, *et al*., 2010
US adults (HPFS and NHS cohort)	499 cases; 993 controls	ELISA	Smoking, alcohol intake, dietary intakes of red meat, processed meat, methionine, folate, calcium, family history of	Positive	Risk associated with high IGF-I/IGFBP3 reduced by higher 25(OH)D levels.	Wu *et al*., 2011

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Subjects	Number of subjects	How was IGF-I measured and was it free[9]?	Variables study controlled, matched or analysed for	Association between IGF-I levels in blood and colorectal cancer	Main results	Reference
			CRC			
Japanese adults	1520		Age, screening period, fasting duration, smoking, alcohol, family history of CRC, NSAID use, height, energy intake.	Positive	Increased IGF-I associated with colorectal adenoma in men (OR;95% CI =1.63; 1.08-2.48) but not women (OR;95% CI =0.79; 0.44-1.43)	Yamaji *et al*., 2012 (abstract only)
Adults aged > 49y from IRAS cohort	143 individuals; 24 with polyps	Radioimmunoassay	Age, centre, race/ethnicity, gender, BMI, IGF-I and IGFBP-3 adjusted for each other.	Positive	Increasing IGF-I (OR;95% CI =3.81; 1.30-10.8, "ever increase" vs "no increase" and IGF-I/IGFBP3 over a decade associated with polyps.	Soubry *et al*., 2012
US adults (PLCO cohort)	764 cases; 775 controls	ELISA	Age, race, sex, year of blood draw, BMI, smoking and education	Positive	Higher IGF-I at baseline associated with increased risk of colorectal adenoma (OR:95%CI for highest vs lowest 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-I/IGFBP3 also associated with increased risk.	Gao *et al*., 2012
Meta-analysis of five studies	-			*Positive*	*IGF-I levels were positively associated with colorectal cancer (OR;95%CI = 1.58;1.11-2.27 p trend), whereas IGFBP-3 (0.77; 0.36-1.66) and IGF-I/IGFBP-3 ratio were less clearly associated*	*Renehan, et al., 2004*
Meta-analysis of eight studies				*Positive*	*Positive association between IGF-I levels and risk of colorectal cancer (1.37;1.05-1.78)* *No association with IGFBP-3 (0.98; 0.64-*	*Morris, et al., 2006*

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Subjects	Number of subjects	How was IGF-I measured and was it free[9]?	Variables study controlled, matched or analysed for	Association between IGF-I levels in blood and colorectal cancer	Main results	Reference
					1.51) p values	
Meta-analysis of ten studies	-			*Positive*	*Moderately positive association between IGF-I 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) p values*	*Rinaldi, et al., 2010*
Meta-analysis of nineteen studies	-			*Positive*	*Moderately positive association between IGF-I 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-I 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) p values*	*Yoon et al., 2015*

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

Subjects	Number of subjects	How was IGF-I measured and was it free?	Variables study controlled, matched or analysed for	Association between IGF-I levels and lung cancer	Main results	Reference
Retrospective studies						
Males	37 cases 25 controls	Radioimmunoassay	-	Positive	IGF-I higher in patients	Bhatavdekar *et al.,* 1994 [abstract only]
Korean lung cancer patients	41 cases SCLC=9, NSCLC = 32) 20 controls	IGF by Radioimmunoassay, IGFBPs by Western blotting		Negative	Levels of IGF-I (207.9 ± 62.6 vs 281.3 ± 53.9 ng/ml, p <0.01) and IGFBP-3 lower in lung cancer patients[10].	Lee *et al*., 1999
Americans (white, black & hispanic), aged 60.6 to 63.4 y	204 cases; 218 controls		Age, sex, ethnicity, smoking status.	Positive	IGF-I 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-II. Negative association with IGFBP-3 (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		Age, sex, ethnicity, smoking status.	Positive	OR=2.06, comparing risks in upper and lower quartiles of IGF-I. Negative association with IGFBP-3.	Wu *et al*., 2000 Same population as above study
Chinese patients	78 cases , 35 with benign lung disease 14 controls			Positive	IGF-I levels higher in patients 570.67 ± 185.80, 466.53 ± 142.42 and 427.66 ± 141.19 ng/ml. No significant differences in IGFBP-3 between groups.	Wang, *et al*., 2004 Abstract only (original in Chinese).
Lung cancer patients	24 cases; 12 controls	Free IGF-I measured by two site immuno-radiometric		None (in serum)	IGF-I and IGFBP-3 lower in the epithelial lining fluid of patients. Serum IGF-I non-significantly lower in cases than controls (126.9 ± 63.4 vs 167.6 ± 56.5 ng/ml)	Ünsal *et al*., 2005

[10] Units given as “Arbitrary densometric units” so have not been included.

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Variables study controlled, matched or analysed for	Association between IGF-I levels and lung cancer	Main results	Reference
		assay.			Serum IGFBP-3 also non-significantly lower (2277.6 614.0 vs 2874.7 ± 861.9 ng/ml)	
Korean patients	77 cases advances NSCLC	ELISA		Negative	IGF-I associated with improved prognosis and survival.	Han *et al*., 2006
Polish patients	38 cases (25 NSCLC) 10 No controls	ELISA		Positive	IGF-I higher (123.6 ± 43.4 vs 74.2 ± 12 ng/ml, $p < 0.05$) in patients compared with healthy controls. IGF-II also higher.	Izycki *et al*., 2006
German adults	34 patients 13 controls	ELISA. It was noted that the quotient of each sample was calculated.		None	No differences in IGF-I 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-I 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	Associated with overall survival	Vlachostergios *et al*., 2011
Chinese adults	80 NSCLC patients 45 BPL controls	ELISA	No	Positive	Pre-operative IGF-I associated with tumour size and poor prognosis IGF-I levels higher than in BPL controls (21.59 ±9.04 vs 12.37 ± ng/ml, p= 0.0003)	Fu *et al*., 2013
Prospective studies						
American women aged 32 to 70 y	93 cases; 186 controls		Age, date of blood sampling, menopausal status, day of	None	No difference in IGF-I level (129.8;119.8-140.6 ng/ml in cases and 131;123.5-139 ng/ml in controls, p =0.84)	Lukanova, *et al*., 2001

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Variables study controlled, matched or analysed for	Association between IGF-I levels and lung cancer	Main results	Reference
			menstrual cycle smoking status.		No association between lung cancer and levels of IGF-I (OR;95%CI = 0.79; 0.29-2.19, *p* = 0.53 top vs bottom quartile) and IGFBP-1, -2 & -3 (0.77;0.34-1.74, *p*= 0.93). Mean IGFBP=3 levels 4387 and 4413 ng/ml in cases and controls.	
Chinese men aged 45 to 64 y	230 cases 659 controls	??	Age, residence, time of sample collection	Negative	Reduced risk associated with high IGF-I and IGFBP-3 (ORs 0.70; 0.45-1.10 *p* trend = 0.36 & 0.52;0.31-0.88 *p* trend = 0.04 , respectively, comparing upper & lower quartiles).	London, *et al*., 2002
Heavy smokers (aged 50 to 69 y) or asbestos workers (aged 45 to 69 y) in USA.	159 cases; 297 controls	??	Age, gender, ethnicity, year of enrolment, year of blood sampling, smoking status	None	IGF-I levels non-significantly higher in cases (158 and 153 ng/ml, *p* = 0.52). No significant association between IGF-I 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 (30700 and 29400 ng/ml, *p* = 0.17) Positive association for IGFBP-3: (OR=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-I measured by immune-radiometric assay	Area, gender, age, smoking, BMI, IGFBP-3	Positive	Increased IGF-I 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	Wakai *et al*., 2002

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Variables study controlled, matched or analysed for	Association between IGF-I levels and lung cancer	Main results	Reference
					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).	
Male smokers (Finland) from ATBC cohort.	200 cases; 400 controls	??	Age, intervention arm, BMI, years of smoking	None	No significant association between IGF-I (OR; 95%CI = 0.76:0.39-1.49, highest vs lowest quartile) or IGFBP-3 (OR; 95%CI = 0.71:0.35-1.47) and lung cancer.	Ahn *et al*., 2006
UK male professionals	167 cases; 498 controls	ELISA	BMI, alcohol, smoking	None	No significant association between IGF-I (OR; 95%CI = 1.21;0.62-2.35, *p* trend= 0.45, highest vs lowest quartile) IGF-2 or IGFBP-3 (1.70; 0.87-3.30, *p* trend= 0.06 and lung cancer	Morris *et al*., 2006
Meta-analysis of four studies	-			*None*	*No association between IGF-I and lung cancer when results from all 4 studies are considered. OR=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 values?*	*Renehan, et al., 2004*
Meta-analysis of five studies	-	-	-	*None*	*No significant association between IGF-I (OR; 95%CI = 1.02; 0.80-1.31) or IGFBP-3 (0.98; 0.61-1.58) and lung cancer p values?*	*Morris et al., 2006*
Meta-analysis of six studies	-			*None*	*No association between IGF-I and lung cancer (OR; 95%CI = 0.87; 0.60-1.13). Inverse association between IGFBP-3 and lung cancer risk (OR;*	*Chen, et al., 2009*

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Subjects	Number of subjects	How was IGF-I measured and was it free?	Variables study controlled, matched or analysed for	Association between IGF-I levels and lung cancer	Main results	Reference
					95%CI = 0.68; 0.48-0.88) p values?	
Meta-analysis of six studies	*-*			*None*	*No association between IGF-I 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*

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