

1 **Title: Circulating insulin-like growth factor-I (IGF-I) concentrations and incidence of**
2 **30 cancers: prospective analyses in UK Biobank**

3 **Author list:** Anika Knuppel¹, Georgina K. Fensom¹, Eleanor L. Watts¹, Marc J. Gunter², Neil Murphy², Keren
4 Papier¹, Aurora Perez-Cornago¹, Julie A. Schmidt¹, Karl Smith Byrne³, Ruth C. Travis^{1*}, Timothy J. Key^{1*}

5 *Contributed equally.

6 **Author affiliations:**

7 ¹ Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK

8 ² Section of Nutrition and Metabolism, International Agency for Research on Cancer, Lyon, France

9 ³ Genetic Epidemiology Group, International Agency for Research on Cancer, Lyon, France

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12 **Corresponding author:** Anika Knuppel, PhD, Cancer Epidemiology Unit, Nuffield Department of Population
13 Health, University of Oxford, Richard Doll Building, Oxford OX3 7LF, UK; telephone number: +44 (0)1865
14 289247; e-mail: anika.knuppel@ndph.ox.ac.uk

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20

21 **Abstract**

22 Circulating insulin-like growth factor I (IGF-I) is positively associated with the risks of colorectal, breast, and
23 prostate cancer, but evidence for other less common cancers is limited. In this study, we investigated
24 associations between serum IGF-I concentrations and incidence of less common cancers in the UK Biobank
25 study. To enable comparison of effect estimates, and as positive controls, both common and less common
26 cancer sites (total 30) were included in an outcome-wide analysis. Data from 394,388 cancer-free
27 participants in the UK Biobank study were analyzed. Multivariable-adjusted Cox proportional hazards models
28 were used to determine associations between baseline serum IGF-I concentrations and cancer incidence,
29 using repeated IGF-I measurements from up to 14,149 participants to correct for regression dilution bias.
30 Higher IGF-I concentration was associated with increased risks of thyroid cancer (hazard ratio per 5 nmol/l
31 higher concentration 1.18; 95% confidence interval 1.01-1.37) in addition to colorectal (1.08; 1.03-1.13),
32 breast (1.11; 1.07-1.15), and prostate cancer (1.08; 1.05-1.12), and reduced risks of ovarian and liver
33 cancer. Mean follow-up was 6.9 years and cannot exclude the possibility that the observed associations may
34 be influenced by reverse causality bias. Additional nominally significant associations with malignant
35 melanoma, multiple myeloma, oral cancer, and esophageal squamous cell carcinoma, did not survive
36 correction for multiple testing. Studies with longer follow-up and pooled analyses are needed to further
37 assess how broad the role of IGF-I is in cancer development.

38 Significance: The results from this outcome-wide analysis are consistent with a positive association of IGF-I
39 with cancers at several sites.

40 **Introduction**

41 Insulin-like growth factor-I (IGF-I) might be associated with cancer risk due to its role in cell proliferation,
42 differentiation, metabolism and apoptosis, and in angiogenesis (1). In large pooled nested case-control
43 studies and meta-analyses, pre-diagnostic circulating IGF-I concentrations have been shown to be positively
44 associated with colorectal cancer (2), breast cancer (3) and prostate cancer (4) and not associated with lung
45 cancer risk (5,6), and there is recent evidence from Mendelian randomization analyses suggesting that the
46 positive associations may be causal (7-9). However, evidence for a role of IGF-I in the development of less
47 common cancers is relatively limited, with some data for cancers of the esophagus (10), stomach (11), liver
48 (12-14), biliary tract (15), pancreas (16), malignant melanoma (17), endometrium (18,19), kidney (20),
49 bladder (21), brain (22,23), thyroid (24), and lymphoma (25). Most of the current evidence for these cancers
50 is derived from a few prospective cohort studies, and associations with risk of cancer at some other sites,
51 such as oral cancers and mesothelioma, have yet to be investigated in prospective analyses.

52 UK Biobank has measured serum concentrations of IGF-I at baseline in ~467,000 participants (93%). The
53 aim of the current study was to investigate the associations between circulating IGF-I concentrations and the
54 incidence of less common cancers in UK Biobank using a comprehensive outcome-wide approach. To
55 enable comparison of effect estimates, and as positive controls, both common and rarer cancer sites were
56 included in the analysis. Furthermore, this approach has the advantages of standardizing definitions and
57 analyses across cancers, allowing an examination of the specificity of findings, and adding evidence for
58 various outcomes simultaneously while eliminating bias in outcome selection based on the results (26).

59 **Materials and Methods**

60 **Study Population**

61 The study was based on data from UK Biobank participants. Of 502,506 adults aged between 39 and 73,
62 who were recruited between 2006 and 2010, 394,388 (78%) participants were included in this study (27,28).
63 Study participants were excluded if they had a prevalent malignant cancer diagnosis (excluding non-
64 melanoma skin cancer, C44), *in situ* breast or non-malignant but potentially serious central nervous system
65 cancers, or zero person-years of follow-up (n=28,431), if their genetically determined sex differed from their
66 reported sex (n=334), if they had missing data on height or weight (n=2,933), current or unknown diabetes
67 status (n=27,208), were current or unknown users of hormone-replacement therapy or oral contraceptives
68 (n=20,987), and if they had missing data on IGF-I concentration (n=28,225) (see Supplementary Figure S1).
69 All participants provided informed written consent at baseline and consented to be followed-up using national

70 record-linkage. The study was approved by the National Information Governance Board for Health and
71 Social Care and the National Health Service North West Multicentre Research Ethics Committee
72 (06/MRE08/65).

73 **Exposure and Outcome Assessment, and Covariates**

74 Non-fasting blood samples were collected from all participants at recruitment. Between 2012 and 2013
75 participants who lived within a 35 km radius of the UK Biobank Co-ordinating Centre in Stockport were
76 invited to participate in additional repeat blood collection to re-measure the same analytes as at baseline and
77 thus enable correction for regression dilution bias (~20,000 participants, 21% response rate). Of
78 these, 14,149 met our inclusion criteria (as of March 3, 2019;
79 https://biobank.ctsu.ox.ac.uk/~bbdatan/Repeat_assessment_doc_v1.0.pdf). Blood samples were centrifuged
80 and serum was stored at -80°C (29). Serum concentrations of IGF-I were measured using chemiluminescent
81 immunoassays (DiaSorin Liaison XL, analytical range 1.3-195 nmol/l). Measurements were conducted at a
82 purpose-built laboratory for UK Biobank in Stockport (as of June 4, 2020; [http://www.ukbiobank.ac.uk/wp-](http://www.ukbiobank.ac.uk/wp-content/uploads/2013/12/ukb_biomarker_panel_final_website_Oct2013_CLMS.pdf)
83 [content/uploads/2013/12/ukb_biomarker_panel_final_website_Oct2013_CLMS.pdf](http://www.ukbiobank.ac.uk/wp-content/uploads/2013/12/ukb_biomarker_panel_final_website_Oct2013_CLMS.pdf)) and the average within-
84 laboratory coefficients of variation (ratio of the standard deviation to the mean) were 6.03% for low
85 concentrations, 5.29% for medium concentrations and for 6.18% for high concentrations (as of December
86 20, 2019; https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/serum_biochemistry.pdf).

87 Data on cancer diagnoses were provided by the Medical Research Information Service of the National
88 Health Service (participants resident in England or Wales) and the Information Services Division of the
89 National Health Service Scotland (participants resident in Scotland)
90 (<https://biobank.ndph.ox.ac.uk/crystal/crystal/docs/CancerLinkage.pdf>). The endpoints were first incident
91 cancer diagnosis or cancer first recorded in death certificates and we report results for cancers at sites with
92 more than 100 incident cases in the sample (all coded using the 10th revision of the World Health
93 Organization's International Statistical Classification of Diseases (ICD-10)): oral (C00-14), lip and oral cavity
94 (C00-06), oropharynx (C09-10), esophagus (C15), adenocarcinoma of esophagus (C15, morphology codes
95 ICD-O-3 8140-8573), squamous cell carcinoma of esophagus (C15, 8050-8082), stomach (C16), colorectum
96 (C18-20) including colon (C18) and rectum (including rectosigmoid junction; C19-20), liver (C22), gallbladder
97 and biliary tract (C23-24), pancreas (C25), lung (C34), lung (C34) in never smokers, malignant melanoma
98 (C43), mesothelioma (C45), breast in women (C50), endometrium (C54), ovary (C56), prostate (C61), kidney
99 (C64-65), bladder (C67), brain (C71), thyroid (C73), lymphatic and hematopoietic tissues (C81-96) and the

100 subgroups non-Hodgkin lymphoma (NHL) (C82-85), multiple myeloma (C90), and leukemia (C91-95), and
101 the NHL subtypes follicular lymphoma (C82) and diffuse NHL (C83).

102 Potential confounders were chosen upon review of the literature and restricted to variables available in UK
103 Biobank. Data on socio-demographic factors, health behaviors, and women-specific factors were collected
104 using a touchscreen questionnaire at baseline; height and weight were measured by trained staff at the
105 baseline assessment center (as of December 20, 2019; [http://www.ukbiobank.ac.uk/wp-](http://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol-1.pdf)
106 [content/uploads/2011/11/UK-Biobank-Protocol-1.pdf](http://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol-1.pdf)). Serum concentrations of C-reactive protein, glycated
107 hemoglobin, sex hormone-binding globulin and testosterone were measured; assay details are reported
108 elsewhere (as of December 20, 2019;
109 https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/serum_biochemistry.pdf accessed).

110 **Statistical Analysis**

111 All analyses were conducted with Stata version 15.1 (30). Hazard ratios (HRs) and 95% confidence intervals
112 (CIs) were estimated for each cancer site of interest using Cox proportional hazards regression models with
113 age as the underlying time variable. The person-years of follow-up were calculated from baseline
114 assessment until the first registration of malignant cancer, date of death due to cancer if not diagnosed
115 previously, date of death, or loss or end of follow-up (31/03/2016 for England and Wales, 31/10/2015 for
116 Scotland), whichever came first. IGF-I concentrations were modelled categorically (sex-specific quintiles) and
117 on the continuous scale (per 5 nmol/l). Missing data in covariates were handled by assigning participants to
118 an 'unknown' category for each respective variable.

119 To investigate the role of potential confounders, a minimally adjusted model was fitted (Model 0) stratified by
120 sex, age group (<45, 45-49, 50-54, 55-59, 60-64, ≥65 years), geographical region (London, Wales, North-
121 West, North-East, Yorkshire and Humber, West Midlands, East Midlands, South-East, South-West and
122 Scotland), and Townsend deprivation index (fifths, unknown). In Model 1, we additionally adjusted for
123 ethnicity (White, Asian, Black, mixed race or other, unknown); educational level (college or university
124 degree/vocational qualification; national examination at ages 17/18; national examination at age 16; other
125 qualification or unknown); total physical activity (<10, 10-19, 20-39, 40-59, ≥60 metabolic equivalent hours
126 per week, unknown); height (continuous); alcohol consumption (<1.0, 1.0-4.9, 5.0-9.9, 10.0-14.9, 15.0-19.9,
127 20.0-24.9, ≥25.0 g/day, non-drinker, unknown); smoking status and intensity (never, former, current <15 per
128 day, current ≥15 per day, current intensity unknown, unknown), and body mass index (<18.5, 18.5-19.9,
129 20.0-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30-32.4, 32.5-34.9, ≥35.0 kg/m²). In women Model 1 was

130 additionally adjusted for hormone replacement therapy use (never, ever); oral contraceptive pill use (never,
131 ever); parity and age at first birth (nulliparous; 1-2, <25; 1-2, 25-29; 1-2, ≥30; 1-2, unknown; ≥3, <25; ≥3, 25-
132 29; ≥3, ≥30 years; ≥3, unknown; unknown); interaction between menopausal status (pre-, post-, unknown)
133 and body mass index.

134 Measurement error and within-person temporal fluctuations when using only one baseline IGF-I
135 measurement can result in the underestimation of the real association between IGF-I and cancer risk
136 (31,32). Therefore, HRs were corrected for this regression dilution bias using data from a subsample of 6711
137 women and 7438 men with IGF-I measurements made in second blood samples collected during follow-up
138 on average 4.3 years (SD 0.9 years) after recruitment. Log HRs and standard errors were divided by the sex-
139 specific regression dilution ratios (0.74 for women and 0.80 for men) obtained from the subsample by
140 dividing the difference in mean IGF-I concentrations between the 5th and 1st quintiles at resurvey by the
141 equivalent difference at baseline (31,32).

142 To assess the role of other biomarkers related to IGF-I and cancer risk, sensitivity analyses were conducted
143 additionally adjusting Model 1 for serum concentrations of C-reactive protein, glycated hemoglobin, sex
144 hormone-binding globulin, and testosterone (fifths, unknown) as these biomarkers have been shown to
145 interrelate with the IGF-I system (Model 2) (33). To assess the role of sun exposure and sun sensitivity as
146 potential confounders of the IGF-I melanoma skin cancer association, sensitivity analyses were conducted
147 additionally adjusting Model 1 for skin color (very fair, fair, light olive, dark olive, brown/black), hair color
148 (blond, red, light brown, dark brown, black), skin reaction to sun exposure (get very tanned, moderately
149 tanning, mildly/occasionally tanning, never tanning only burning), and sunburn before age 15 (never,
150 ever). To assess heterogeneity by follow-up time, sex, and age at biomarker assessment, four sensitivity
151 analyses were conducted: 1) analyses were stratified by above and below 3.89 years of follow-up, the
152 median follow-up time of any cancer case (IQR 2.06, 5.54; max. 8.86 years) and compared based on
153 competing risk, 2) multivariable-adjusted models with and without an interaction term for sex, and 3) age
154 group at blood collection (<55, ≥55 years), compared using likelihood ratio tests.

155 **Results**

156 A total of 23,412 participants (5.9%) were newly diagnosed with any type of malignant cancer (excluding
157 non-melanoma skin cancer, C44) during a mean follow-up of 6.9 (standard deviation = 1.27) years
158 (Supplementary Table S1 shows the median follow-up time by cancer site). Mean circulating IGF-I
159 concentration was 21.6 nmol/l (standard deviation = 5.6).

160 IGF-I concentrations were higher in participants who were men, younger, taller, of Black compared to White
161 ethnicity, had a BMI between 22.5 and 27.5 kgm² compared to a lower and higher BMI, who were more
162 affluent, had a higher level of attained education, had moderate alcohol intake, did not smoke, and in women
163 had never used hormone replacement therapy, had used the oral contraceptive pill, were younger when they
164 first gave birth, and were premenopausal (Table 1).

165 Figure 1 depicts estimated HRs and 95% CIs of each cancer site associated with higher serum IGF-I
166 concentrations (per 5 nmol/l), ranked by effect size (all subtypes estimates presented in Supplementary
167 Table 2). In multivariable adjusted models (Model 1), with correction for regression dilution bias, there were
168 positive associations between IGF-I concentrations and thyroid cancer (HR per 5 nmol/l higher concentration
169 1.18; 95% CI 1.01-1.37), multiple myeloma (1.13; 1.01-1.27), breast cancer in women (1.11; 1.07-1.15),
170 prostate cancer (1.08; 1.05-1.12), colorectal cancer (1.08; 95% CI 1.03-1.13), malignant melanoma (1.07;
171 1.01-1.14), and inverse associations between IGF-I concentrations and risks of liver cancer (0.32; 0.26-
172 0.39), squamous cell carcinoma of the esophagus (0.78; 0.61-0.99), ovarian (0.85; 0.76-0.95), and oral
173 cancer (0.88; 0.79-0.99). Associations were similar when analyzed using sex-specific fifths of IGF-I
174 concentration (see Supplementary Table S2). Sensitivity analyses additionally adjusted for serum
175 concentrations of C-reactive protein, glycated hemoglobin, sex hormone-binding globulin, and testosterone
176 found qualitatively similar results (see Supplementary Table S2). Additional adjustment for sun exposure and
177 sun sensitivity variables did not change the IGF-I association with malignant melanoma (1.08, 1.01-1.15; see
178 Supplementary Table S2).

179 Fig. 2 and Supplementary Table S3 show associations stratified by 3.89 years. The inverse association with
180 squamous cell carcinoma of the esophagus was restricted to cases diagnosed within the first few years of
181 follow-up with no association after that (0.59; 0.43-0.81 in cases diagnosed < 3.89 years follow-up; 1.02;
182 0.80-1.30 ≥ 3.89 years follow-up, $P_{\text{heterogeneity}} = .01$; Fig. 2). For the other cancers, there was limited evidence
183 for heterogeneity by follow-up time, though there was a suggestion of a weaker association with ovarian
184 cancer (0.82; 0.73-0.92 in cases diagnosed < 3.89 years follow-up; 0.96; 0.84-1.10 ≥ 3.89 years follow-up,
185 $P_{\text{heterogeneity}} = .09$). There was little evidence for differences by sex, except that sex-specific analyses showed
186 an inverse association between IGF-I and NHL only in women (0.88; 0.80-0.97 in women; 1.03; 0.96-1.12 in
187 men, $P_{\text{heterogeneity}} = .01$); and a stronger inverse association between IGF-I and liver cancer in men (0.33;
188 0.26-0.40 in men; 0.56; 0.45-0.71 in women, $P_{\text{heterogeneity}} < .01$; see Supplementary Fig. S2 and
189 Supplementary Table S3). Similarly, there was little evidence for differences in the associations by age at
190 blood collection (<55, ≥55 years, Supplementary Fig. S3 and Supplementary Table S3), with the exceptions

191 of the associations of IGF-I with bladder cancer (HR 0.70; 95% CI 0.52-0.96 for age <55 years, 1.09, 1.00-
192 1.19 for age ≥55 years, $P_{\text{heterogeneity}} = .01$) and brain cancer (1.25; 1.05-1.49 for age <55 years; 1.00; 0.89-1.11
193 for age ≥55 years, $P_{\text{heterogeneity}} = .03$).

194 **Discussion**

195 In this large British cohort study, higher serum IGF-I concentration was associated with increased risks of
196 thyroid cancer, malignant melanoma, and multiple myeloma, in addition to the expected positive associations
197 with colorectal, breast, and prostate cancer. Higher IGF-I concentration was also associated with lower risks
198 of oral, liver, ovarian cancer, and squamous cell carcinoma of the esophagus; these observed inverse
199 associations may be influenced by reverse causality, and although the average follow-up time was relatively
200 short there was significant evidence of this bias for squamous cell carcinoma of esophagus. When
201 considering multiple testing using Bonferroni correction (19 tests based on the main cancer sites, not
202 including subsites, $p < 0.0026$) the associations with ovarian, thyroid, colorectal, colon, breast, prostate and
203 liver cancer remained statistically significant (34).

204 Associations with breast, colorectal and prostate cancer have been reported previously in UK Biobank and in
205 separate large nested case-control studies pooling data from several cohort studies (2-4,7-9). Mendelian
206 randomization studies further support that these associations are unlikely to be the result of reverse causality
207 (7-9). The association between IGF-I concentration and thyroid cancer concurs with previous findings of a
208 positive association reported in the European Prospective Investigation into Cancer and Nutrition (EPIC)
209 (24). This association was only slightly attenuated when restricted to later years of follow-up, but reverse
210 causality cannot be ruled out. While investigations of thyroid cancer specimens suggest some local
211 production of IGF-I (35), case-control studies found no large difference in serum IGF-I levels between thyroid
212 cancer cases and controls, which does not support an increase of serum IGF-I levels as a result of thyroid
213 cancer (36). Furthermore, in support of a prospective association, patients with acromegaly, which is
214 characterized by the increased secretion of IGF-I, have been found to have an increased prevalence of
215 thyroid cancer (37). The positive associations we observed of IGF-I with malignant melanoma, and multiple
216 myeloma were not found in previous research (17,25), and might have been due to chance.

217 The inverse association found between IGF-I concentration and liver cancer is similar to findings from case-
218 control studies nested in the α -Tocopherol, β -Carotene Cancer Prevention Study of male smokers and in
219 EPIC, in which those with the lowest IGF-I concentrations had a greater risk (13,14). However, in the EPIC
220 study this association was attenuated after additional adjustment for biomarkers of liver damage (13). A

221 further nested case-control study, the Japan Collaborative Cohort Study, found an inverse but non-
222 statistically significant association between IGF-I and liver cancer (12). Although we found no evidence for
223 reverse causality in analyses stratified by follow-up time, the follow-up time might have been too short to
224 investigate reverse causality robustly for liver cancer, which might be particularly susceptible to this bias
225 because the majority of circulating IGF-I is produced by the liver (38). Case-control studies suggest that low
226 serum IGF-I concentrations might be caused by decreased hepatic reserve in non-alcoholic fatty liver
227 disease, liver cirrhosis, and hepatocellular carcinoma (39). Thus, low serum IGF-I levels could be an
228 indicator for compromised liver health that in turn increases the risk of liver cancer, or liver cancer could lead
229 to changes to serum IGF-I several years before a liver cancer is diagnosed.

230 The inverse associations of IGF-I concentration with oral cancer and squamous cell carcinoma of the
231 esophagus were novel but did not withstand correction for multiple testing. For ovarian cancer, findings from
232 previous nested case-control studies were mixed; some showed no evidence for an association between
233 circulating IGF-I concentration and ovarian cancer risk (40-43), some found a positive association in women
234 diagnosed under 55 years (42,43), and some were in line with the present study and found an inverse
235 association (44) that was slightly stronger in women under 55 years at diagnosis (45,46). In the present
236 study the association was weakened when cases within the first 3.89 years of follow-up were excluded,
237 which suggests that the inverse association may be the result of reverse causality, and this interpretation is
238 supported by several case-control studies in which patients with ovarian cancer had lower circulating IGF-I
239 concentrations at diagnosis (47-49), and a study in ovarian cancer patients that showed that lower circulating
240 IGF-I predicted worse prognosis (50). It is possible that some participants in the present study who were
241 diagnosed with ovarian cancer during early follow-up had subclinical ovarian cancer at the time of baseline
242 measurement which contributed to the lower circulating IGF-I concentrations, for example, via reduced IGF-I
243 liver production because of metastases (51), or early impaired nutritional status and weight loss as a result of
244 the disease (47,52). This hypothesis is further supported by the fact that nearly 60% of women diagnosed
245 with ovarian cancer in UK present at stages 3 or 4 suggesting a late diagnosis (as of June 4, 2020;
246 [https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-](https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/survival#heading-Zero)
247 [cancer/survival#heading-Zero](https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/survival#heading-Zero)).

248 In line with earlier research from nested case-control studies, we found no association between total IGF-I
249 and lung (5,6), bladder (21), pancreatic (16), biliary tract (15), and endometrial cancer (18,19), and our
250 findings do not support an inverse association that has been observed in a nested case-control study of male
251 smokers between IGF-I concentrations and kidney cancer (20). Subgroup analyses suggested additional

252 associations between IGF-I and a decreased risk of NHL in women, a decreased risk of bladder cancer, and
253 increased risk of brain cancer in participants aged under 55 years. Previous studies of the association
254 between IGF-I and NHL and bladder cancer found no evidence for an association (21,25), and findings from
255 previous studies on brain cancer were mixed (22,23).

256 To our knowledge, this is the most comprehensive examination of the associations between circulating IGF-I
257 concentrations and cancer risk to date. It is the first prospective cohort study to investigate associations
258 between pre-diagnostic IGF-I concentrations and risks of oral cancers, mesothelioma, squamous cell, and
259 adenocarcinomas of the oesophagus, and the largest study (based on number of cases) to investigate the
260 associations of IGF-I with cancers of the oesophagus, stomach, endometrium, kidney, and the lymphatic and
261 hematopoietic tissues. Cancer incidence was derived from data linkage, which reduced the risk of outcome
262 misclassification and selective drop-out. Regression dilution bias was addressed using repeated IGF-I
263 measurements from a subsample of participants. UK Biobank had a low initial response rate (5.5%) which
264 raises the risk of selection bias; however, it has been shown that despite a favorable risk profile and lower
265 incidence of cancer in UK Biobank (28) risk factor-endpoint associations are comparable to those found in
266 nationally representative studies with average response rates of 68% (53). While the study was based on
267 larger case counts than many previous studies, it is likely that we did not have enough power to detect
268 associations of IGF-I with the risk of rarer cancers, and differences by ethnicity could not be investigated,
269 due to too few non-white participants in the study. We were not able to investigate associations by tumor
270 subtypes because these data are not yet available. Furthermore, IGF-I related proteins such as IGF-II and
271 IGF binding proteins (IGFBPs) were not measured. Most IGF-I is bound to IGFBPs (54), which play a role in
272 the regulation of IGF-I bioavailability and signaling (55), and IGF-II has also been suggested to be involved in
273 cancer risk (56)(57). The interplay between these factors means that it is possible that the associations
274 observed could partially reflect other aspects of the IGF signaling pathway, as well as IGF-I itself. Despite
275 sensitivity analyses stratifying by follow-up time, reverse causality cannot be ruled out, because the overall
276 follow-up time was short. Residual confounding might also have influenced our findings as a result of
277 imperfectly measured confounders, unmeasured confounders (58), and confounders that were not included
278 as they were specific to certain sites such as *Helicobacter pylori* infection for stomach cancer (59), hepatitis
279 virus infection for liver cancer (60), and auto-immune diseases (61). Finally, we report numerous analyses
280 which increases the risk of chance findings especially in sensitivity analyses.

281 This study shows that, as well as colorectal, breast, and prostate cancer, IGF-I concentration is positively
282 associated with the risk of thyroid cancer and possibly with malignant melanoma and multiple myeloma. IGF-

283 I was inversely associated with the risks of liver and ovarian cancer, perhaps related to reverse causation
284 bias. The findings suggest that IGF-I is important in the development of several but perhaps not all types of
285 cancer, and more research is needed for less common cancers and employing Mendelian randomization and
286 other approaches to assess causality.

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291

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451 **Table 1. Baseline characteristics of included UK Biobank participants**

Characteristics	N	Circulating IGF-I concentration (nmol/l), mean (SD)
IGF-I concentration at baseline	394,388	21.6 (5.6)
IGF-I concentration at follow-up	14,149	21.1 (5.4)
Women	206,253	21.2 (5.6)
Men	188,135	22.0 (5.4)
Age at baseline (years)		
39-44	43,031	24.5 (5.5)
65-73	71,426	19.9 (5.3)
Ethnicity		
White	373,810	21.6 (5.5)
Asian	7,862	21.2 (5.8)
Black	5,791	22.5 (6.1)
Mixed race or other	5,612	22.0 (5.8)
unknown	1,313	21.6 (5.5)
Standing height (quintiles)		
Q1	84,511	20.7 (5.5)
Q5	72,272	22.5 (5.6)
Body mass index (kg/m ²)		
<18.5	1,920	20.0 (5.4)
18.5-19.9	7,711	21.1 (5.6)
20.0-22.4	41,022	21.8 (5.5)
22.5-24.9	84,073	22.1 (5.4)
25.0-27.4	97,212	22.1 (5.4)
27.5-29.9	73,381	21.8 (5.5)
30.0-32.4	43,391	21.1 (5.6)
32.5-34.9	22,456	20.3 (5.6)
≥35.0	23,222	19.0 (5.6)
Socio-economic status (Townsend deprivation index)		
Most affluent (Q1)	80,939	21.9 (5.5)
Most deprived (Q5)	74,896	21.2 (5.7)
Unknown	481	21.7 (5.6)
Qualification		
College or university degree/vocational qualification	238,745	21.9 (5.5)
National examination at ages 17/18	21,644	21.9 (5.6)
National examination at age 16	65,719	21.5 (5.5)
Other/unknown	68,280	20.3 (5.5)
Smoking		
Non smoker	217,519	21.9 (5.6)
Former smoker	133,931	21.2 (5.5)
Current smoker, <15 cigarettes/day	11,931	21.4 (5.6)
Current smoker, ≥15 cigarettes /day	16,261	21.0 (5.7)
Current, intensity unknown	13,386	21.6 (5.5)
Unknown	1,360	20.6 (5.5)
Alcohol intake (grams/day)		
<1.0	42,207	21.2 (5.9)
1.0-4.9	67,970	21.8 (5.7)
5.0-9.9	56,330	22.0 (5.6)
10.0-14.9	57,351	22.0 (5.5)
15.0-19.9	29,516	22.0 (5.4)
20.0-24.9	31,396	21.9 (5.4)
≥25.0	80,186	21.0 (5.2)
Non-drinker	29,120	20.8 (5.9)
Unknown	312	20.4 (5.7)
Physical activity (metabolic equivalent hours /wk)		
<10	86,111	21.3 (5.7)
≥60	88,393	21.5 (5.4)
Unknown	13,045	20.8 (5.6)
Hormone replacement therapy use (in women)		
Never	135,780	21.8 (5.7)
Ever	70,473	20.1 (5.4)
Oral contraceptive pill use (in women)		
Never	39,198	20.4 (5.6)
Ever	167,055	21.4 (5.6)

Parity, age at 1st birth (years; in women)		
≥3, <25	32,801	20.1 (5.5)
≥3, 25-29	12,226	21.2 (5.5)
≥3, ≥30	4,816	21.9 (5.6)
≥3, N/A	114	19.8 (5.8)
1-2, <25	41,636	20.7 (5.5)
1-2, 25-29	29,004	21.4 (5.5)
1-2, ≥30	20,574	22.1 (5.7)
1-2, N/A	27,375	21.4 (5.7)
Nulliparous	37,576	21.8 (5.8)
Unknown	131	20.8 (6.6)
Menopausal status (in women)		
Pre-	50,791	23.5 (5.6)
Post-	145,271	20.3 (5.4)
Unknown	10,191	22.1 (5.8)

Abbreviations: IGF-I = Insulin-like growth factor; Q1 = lowest quintile; Q5 = highest quintile; SD = Standard deviation.

454 **Figure legends**

455

456 **Figure 1. Hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer risk per 5 nmol/l higher**
457 **insulin-like growth factor-I concentration by cancer site (n=394,388), corrected for regression dilution**
458 **bias^c**

459 HRs are presented by squares with their 95%-CIs as horizontal lines, the size of the squares is inversely proportional to
460 the variance of the log HR. The filled arrow signifies where the confidence interval extends beyond the reported HR range
461 on the x-axis.

462 ^a Analyses restricted to women (n=217,519).

463 ^b Analyses restricted to men (n=188,135).

464 ^c Associations stratified for sex, age group (<45, 45-49, 50-54, 55-59, 60-64, ≥65 years), geographical region (London,
465 Wales, North-West, North-East, Yorkshire and Humber, West Midlands, East Midlands, South-East, South-West and
466 Scotland) and Townsend index (quintiles, unknown), and adjusted for age (underlying time variable); ethnicity (White,
467 Asian, Black, mixed race or other, unknown); educational level (College or university degree/vocational qualification;
468 National examination at ages 17/18; National examination at age 16; other qualification or unknown); total physical activity
469 (<10, 10-19, 20-39, 40-59, ≥60 metabolic equivalent hours per week, unknown); height (cm); alcohol consumption (<1.0,
470 1.0-4.9, 5.0-9.9, 10.0-14.9, 15.0-19.9, 20.0-24.9, ≥25.0 g/day, non-drinker, unknown); smoking status and intensity (never,
471 former, current <15 cigarettes per day, current ≥15 cigarettes per day, current intensity unknown, unknown); body mass
472 index (<18.5, 18.5-19.9, 20.0-22.4, 22.5-4.9, 25.0-27.4, 27.5-29.9, 30.0-32.4, 32.5-34.9, ≥35.0 kg/m²) and in women:
473 hormone replacement therapy use (never, ever); oral contraceptive pill use (never, ever); parity, age at first birth
474 (nulliparous; 1-2, <25; 1-2, 25-29 years; 1-2, ≥30; 1-2, unknown; ≥3, <25; ≥3, 25-29; ≥3, ≥30 years; ≥3, unknown;
475 unknown); interaction between menopausal status (pre-, post-, unknown) and body mass index; and corrected for
476 regression dilution using regression dilution ratios of 0.74 for women and 0.80 for men.

477

Figure 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer risk per 5 nmol/l higher insulin-like growth factor-I concentration by cancer site stratified by follow-up time at diagnosis (A: < 3.89 years; B: ≥ 3.89 years; n=394,388)^c

HRs are presented by squares with their 95%-CIs as horizontal lines, the size of the squares is inversely proportional to the variance of the log HR. $P_{\text{heterogeneity}}$ (Phet) comparing associations below and above median follow-up time obtained using competing risks. Arrows signify where confidence limits extend beyond the HR range shown on the x-axis; filled arrows signify where the entire confidence interval is outside that range.

^a Analyses restricted to women (n=217,519).

^b Analyses restricted to men (n=188,135).

^c Associations stratified for sex, age group (<45, 45-49, 50-54, 55-59, 60-64, ≥65 years), geographical region (London, Wales, North-West, North-East, Yorkshire and Humber, West Midlands, East Midlands, South-East, South-West and Scotland) and Townsend index (quintiles, unknown), and adjusted for age (underlying time variable); ethnicity (White, Asian, Black, mixed race or other, unknown); educational level (College or university degree/vocational qualification; National examination at ages 17/18; National examination at age 16; other qualification or unknown); total physical activity (<10, 10-19, 20-39, 40-59, ≥60 metabolic equivalent hours per week, unknown); height (cm); alcohol consumption (<1.0, 1.0-4.9, 5.0-9.9, 10.0-14.9, 15.0-19.9, 20.0-24.9, ≥25.0 /day, non-drinker, unknown); smoking status and intensity (never, former, current <15 cigarettes per day, current ≥15 cigarettes per day, current intensity unknown, unknown); body mass index (<18.5, 18.5-19.9, 20.0-22.4, 22.5-4.9, 25.0-27.4, 27.5-29.9, 30.0-32.4, 32.5-34.9, ≥35.0 kg/m²); and in women: hormone replacement therapy use (never, ever); oral contraceptive pill use (never, ever); parity, age at first birth (nulliparous; 1-2, <25; 1-2, 25-29; 1-2, ≥30; 1-2, unknown; ≥3, <25; ≥3, 25-29; ≥3, ≥30 years; ≥3, unknown; unknown); interaction between menopausal status (pre-, post-, unknown) and body mass index.

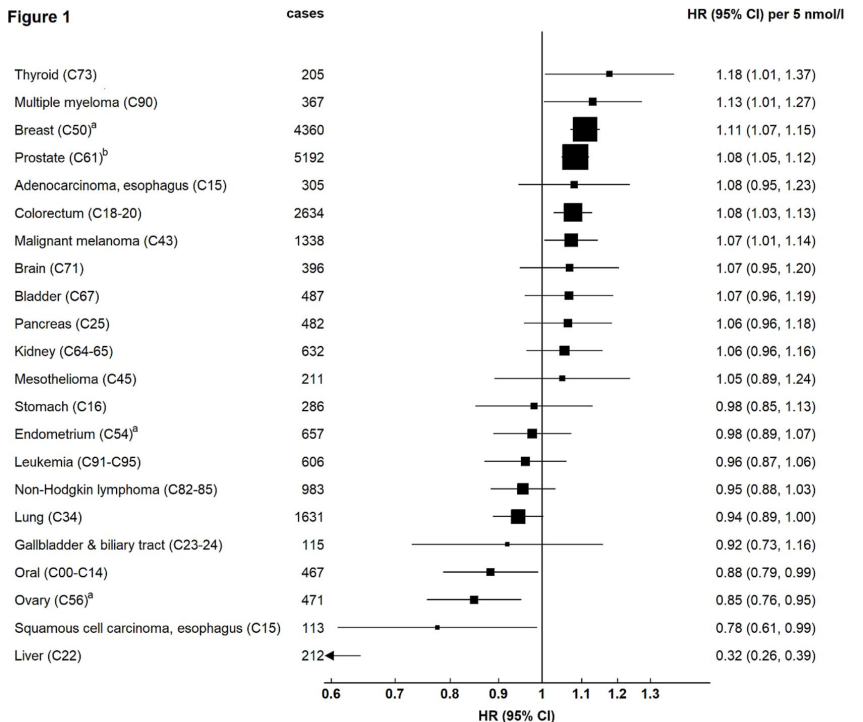


Figure 2

