Circulating Insulin-like Growth Factor-I Concentrations and Risk of 30 Cancers: Prospective Analyses in UK Biobank

Anika Knuppel[1], Georgina K. Fensom[1], Eleanor L. Watts[1], Marc J. Gunter[2], Neil Murphy[2], Keren Papier[1], Aurora Perez-Cornago[1], Julie A. Schmidt[1], Karl Smith Byrne[3], Ruth C. Travis[1], and Timothy J. Key[1]

ABSTRACT

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

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

Introduction

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

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

Materials and Methods

Study population

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

[1]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom. [2]Section of Nutrition and Metabolism, International Agency for Research on Cancer, Lyon, France. [3]Genetic Epidemiology Group, International Agency for Research on Cancer, Lyon, France.

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

R.C. Travis and T.J. Key contributed equally to this article.

Corresponding Author: Anika Knuppel, University of Oxford, Richard Doll Building, Oxford OX3 7LF, United Kingdom. Phone: 4418-6528-9247; E-mail: anika.knuppel@ndph.ox.ac.uk

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

Exposure and outcome assessment, and covariates

Nonfasting blood samples were collected from all participants at recruitment. Between 2012 and 2013, participants who lived within a 35-km radius of the UK Biobank Co-ordinating Centre in Stockport, England were invited to participate in additional repeat blood collection to remeasure the same analytes as at baseline, and thus enable correction for regression dilution bias (∼20,000 participants, 21% response rate). Of these, 14,149 met our inclusion criteria (as of March 3, 2019; https://biobank.ctsu.ox.ac.uk/~bbdatan/Repeat_assessment_doc_v1.0.pdf). Blood samples were centrifuged and serum was stored at −80°C (29). Serum concentrations of IGF-I were measured using Chemiluminescence Immunoassays (DiaSorin Liaison XL, analytic range 1.3–195 nmol/L). Measurements were conducted at a purpose-built laboratory for UK Biobank in Stockport, England (as of June 4, 2020; http://www.ukbiobank.ac.uk/wp-content/uploads/2013/12/ukb_biomarker_panel_final_website_Oct2013_CLMS.pdf) and the average within-laboratory coefficients of variation (ratio of the SD to the mean) were 6.03% for low concentrations, 5.29% for medium concentrations, and for 6.18% for high concentrations (as of December 20, 2019; https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/serum_biochemistry.pdf).

Data on cancer diagnoses were provided by the Medical Research Information Service of the National Health Service (participants resident in England or Wales) and the Information Services Division of the National Health Service Scotland (participants resident in Scotland; https://biobank.ndph.ox.ac.uk/crystal/crystal/docs/CancerLinkage.pdf). The endpoints were first incident cancer diagnosis or cancer first recorded in death certificates, and we reported results for cancers at sites with more than 100 incident cases in the sample [all coded using the 10th revision of the World Health Organization's International Statistical Classification of Diseases (ICD-10)]: oral (C00–14), lip and oral cavity (C00–06), oropharynx (C09–10), esophagus (C15), adenocarcinoma of esophagus (C15, morphology codes ICD-O-3 8140–8573), squamous cell carcinoma of esophagus (C15, 8050–8082), stomach (C16), colorectum (C18–20) including colon (C18) and rectum (including rectosigmoid junction; C19–20), liver (C22), gallbladder and biliary tract (C23–24), pancreas (C25), lung (C34), lung (C34) in never smokers, malignant melanoma (C43), mesothelioma (C45), breast in women (C50), endometrium (C54), ovary (C56), prostate (C61), kidney (C64–65), bladder (C67), brain (C71), thyroid (C73), lymphatic and hematopoietic tissues (C81–96) and the subgroups non-Hodgkin lymphoma (NHL; C82–85), multiple myeloma (C90), and leukemia (C91–95), and the NHL subtypes follicular lymphoma (C82) and diffuse NHL (C83).

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

Statistical analysis

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

To investigate the role of potential confounders, a minimally adjusted model was fitted (model 0) stratified by sex, age group (<45, 45–49, 50–54, 55–59, 60–64, and ≥65 years), geographical region (London, North-West, North-East, Yorkshire and Humber, West Midlands, East Midlands, South-East, South-West, Wales, and Scotland), and Townsend deprivation index (fifths, unknown). In model 1, we additionally adjusted for ethnicity (White, Asian, Black, mixed race or other, and 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, and ≥60 metabolic equivalent hours per week, and unknown), height (continuous), alcohol consumption (<1.0, 1.0–4.9, 5.0–9.9, 10.0–14.9, 15.0–19.9, 20.0–24.9, and ≥25.0 g/day, nondrinker, and unknown), smoking status and intensity (never, former, current <15 per day, current ≥15 per day, current intensity unknown, and unknown), and body mass index (BMI, <18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30–32.4, 32.5–34.9, and ≥35.0 kg/m^2). In women, model 1 was additionally adjusted for hormone replacement therapy use (never and ever), oral contraceptive pill use (never and ever), parity and age at first birth (nulliparous; 1–2, <25; 1–2, 25–29; 1–2, ≥30; and 1–2, unknown; ≥3, <25; ≥3, 25–29; ≥3, ≥30 years; and ≥3, unknown; and unknown), interaction between menopausal status (pre-, post-, and unknown) and BMI.

Measurement error and within-person temporal fluctuations when using only one baseline IGF-I measurement can result in the underestimation of the real association between IGF-I and cancer risk (31, 32). Therefore, HRs were corrected for this regression dilution bias using data from a subsample of 6,711 women and 7,438 men with IGF-I measurements made in second blood samples collected during follow-up on average 4.3 years (SD, 0.9 years) after recruitment. Log HRs and SEs were divided by the sex-specific regression dilution ratios (0.74 for women and 0.80 for men) obtained from the subsample by dividing the difference in mean IGF-I concentrations between the 5th and 1st quintiles at resurvey by the equivalent difference at baseline (31, 32).

To assess the role of other biomarkers related to IGF-I and cancer risk sensitivity analyses were conducted additionally adjusting model 1 for serum concentrations of C-reactive protein, glycated hemoglobin, sex hormone–binding globulin, and testosterone (fifths, unknown) as these biomarkers have been shown to interrelate with the IGF-I system (model 2; ref. 33). To assess the role of sun exposure and sun sensitivity as potential confounders of the IGF-I melanoma skin cancer association, sensitivity analyses were conducted additionally adjusting model 1 for skin color (very fair, fair, light olive, dark olive, and brown/black), hair color (blond, red, light brown, dark brown, and black), skin reaction to sun exposure (get very tanned, moderately tanning, mildly/occasionally tanning, and never tanning only burning), and sunburn

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)
BMI (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		
Nonsmoker	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)
Nondrinker	29,120	20.8 (5.9)
Unknown	312	20.4 (5.7)
Physical activity (metabolic equivalent hours/week)		
<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: N/A, not available; Q1, lowest quintile; Q5, highest quintile.

before age 15 (never and ever).To assess heterogeneity by follow-up time, sex, and age at biomarker assessment, four sensitivity analyses were conducted: (i) analyses were stratified by above and below 3.89 years of follow-up, the median follow-up time of any cancer case (interquartile range, 2.06–5.54; max., 8.86 years) and compared on the basis of competing risk; (ii) multivariable adjusted models with and without an interaction term for sex and (iii) age group at blood collection (<55 and ≥55 years) were compared using likelihood ratio tests.

Results

A total of 23,412 participants (5.9%) were newly diagnosed with any type of malignant cancer (excluding nonmelanoma skin cancer, C44) during a mean follow-up of 6.9 (SD, 1.27) years (Supplementary Table S1 shows the median follow-up time by cancer site). Mean circulating IGF-I concentration was 21.6 nmol/L (SD, 5.6).

IGF-I concentrations were higher in participants who were men, younger, taller, of Black compared with White ethnicity, had a BMI between 22.5 and 27.5 kg/m^2 compared with a lower and higher BMI, who were more affluent, had a higher level of attained education, had moderate alcohol intake, and did not smoke, and in women who had never used hormone replacement therapy, had used the oral contraceptive pill, were younger when they first gave birth, and were premenopausal (**Table 1**).

Figure 1 depicts estimated HRs and 95% CIs of each cancer site associated with higher serum IGF-I concentrations (per 5 nmol/L), ranked by effect size (all subtypes estimates are presented in Supplementary Table S2). In multivariable adjusted models (model 1), with correction for regression dilution bias, there were positive associations between IGF-I concentrations and thyroid cancer (HR per 5 nmol/L higher concentration 1.18; 95% CI, 1.01–1.37), multiple myeloma (HR, 1.13; 95% CI, 1.01–1.27), breast cancer in women (HR, 1.11; 95% CI, 1.07–1.15), prostate cancer (HR, 1.08; 95% CI, 1.05–1.12), colorectal

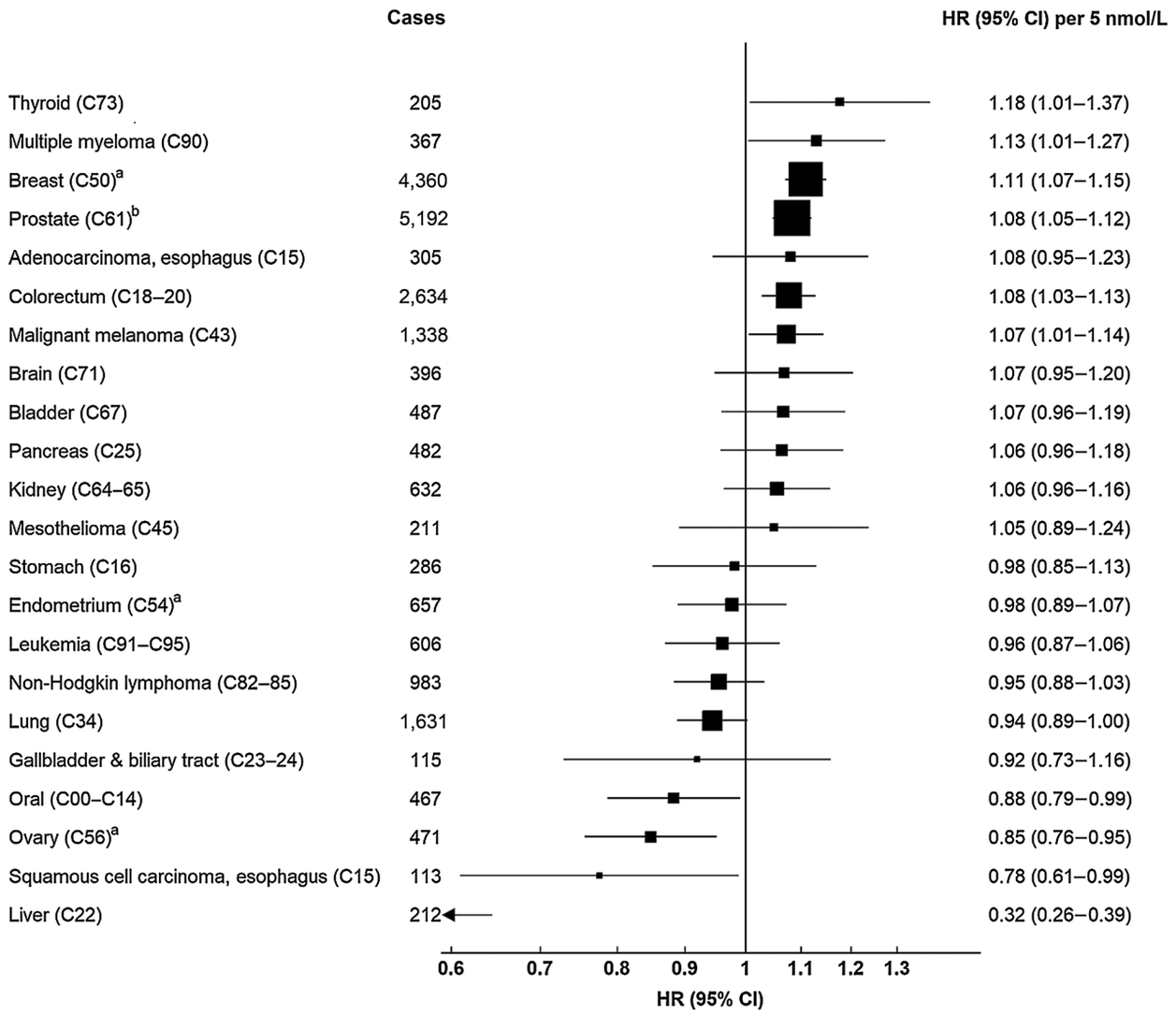

Figure 1.

HRs and 95% CIs for cancer risk per 5 nmol/L higher IGF-I concentration by cancer site ($n = 394{,}388$), corrected for regression dilution bias. HRs are represented by squares, with their 95% CIs as horizontal lines; the size of the squares is inversely proportional to the variance of the log HR. The filled arrow signifies where the CI extends beyond the reported HR range on the *x*-axis. [a]Analyses restricted to women ($n = 217{,}519$). [b]Analyses restricted to men ($n = 188{,}135$). All associations stratified for sex, age group (<45, 45–49, 50–54, 55–59, 60–64, and ≥65 years), geographical region (London, North-West, North-East, Yorkshire and Humber, West Midlands, East Midlands, South-East, South-West, Wales, and Scotland), and Townsend index (quintiles and unknown), and adjusted for age (underlying time variable), ethnicity (White, Asian, Black, mixed race or other, and unknown), educational level (college or university degree/vocational qualification, national examination at ages 17/18, national examination at age 16, and other qualification or unknown), total physical activity (<10, 10–19, 20–39, 40–59, and ≥60 metabolic equivalent hours per week, and 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, and ≥25.0 g/day, nondrinker, and unknown), smoking status and intensity (never, former, current <15 cigarettes per day, current ≥15 cigarettes per day, current intensity unknown, and unknown), and BMI (<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, and ≥35.0 kg/m^2), and in women: hormone replacement therapy use (never and ever), oral contraceptive pill use (never and ever), parity, age at first birth (nulliparous; 1–2, <25; 1–2, 25–29 years; 1–2, ≥30; and 1–2, unknown; ≥3, <25; ≥3, 25–29; ≥3, ≥30 years; and ≥3, unknown; and unknown), interaction between menopausal status (pre-, post-, and unknown), and BMI; and corrected for regression dilution using regression dilution ratios of 0.74 for women and 0.80 for men.

cancer (HR, 1.08; 95% CI, 1.03–1.13), and malignant melanoma (HR, 1.07; 95% CI, 1.01–1.14), and inverse associations between IGF-I concentrations and risks of liver cancer (HR, 0.32; 95% CI, 0.26–0.39), squamous cell carcinoma of the esophagus (HR, 0.78; 95% CI, 0.61–0.99), ovarian (HR, 0.85; 95% CI, 0.76–0.95), and oral cancer (HR, 0.88; 95% CI, 0.79–0.99). Associations were similar when analyzed using sex-specific fifths of IGF-I concentration (see Supplementary Table S2). Sensitivity analyses additionally adjusted for serum concentrations of C-reactive protein, glycated hemoglobin, sex hormone–binding globulin, and testosterone found qualitatively similar results (see Supplementary Table S2). Additional adjustment for sun exposure and sun sensitivity variables did not change the IGF-I association with malignant melanoma (HR, 1.08; 95% CI, 1.01–1.15; see Supplementary Table S2).

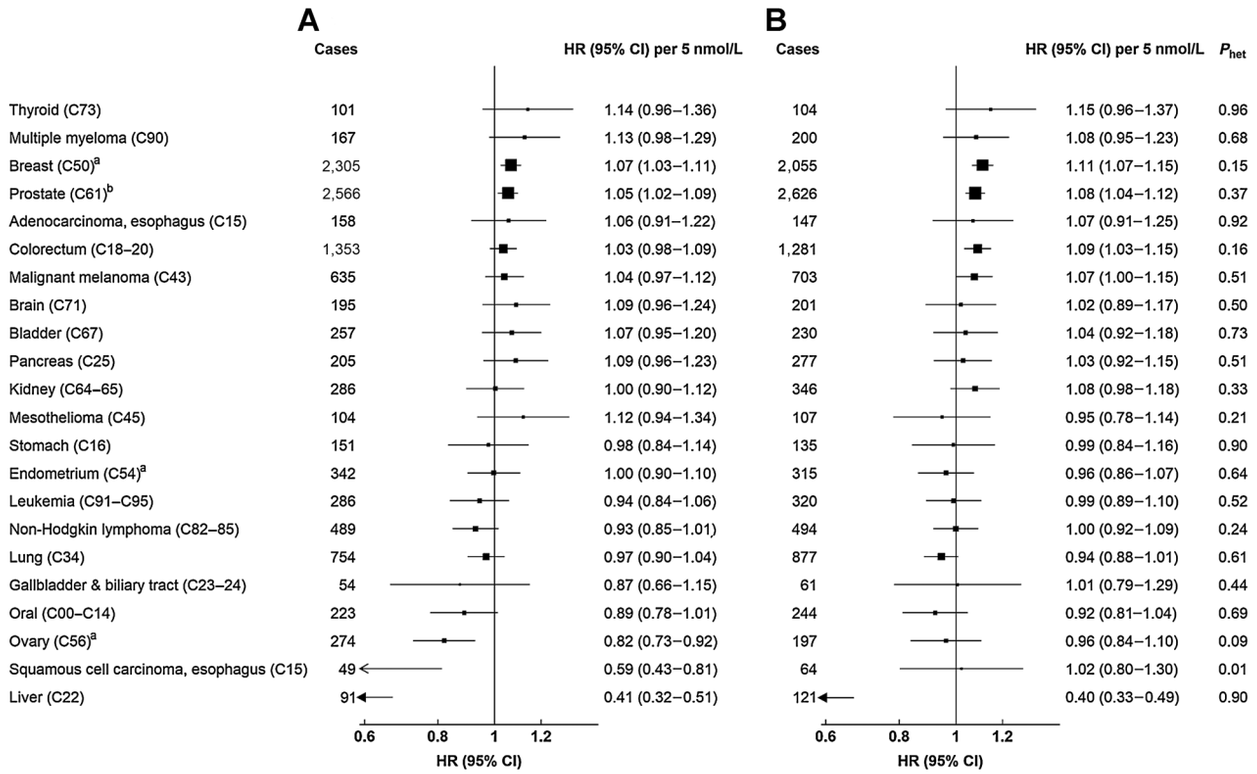

Figure 2.

HRs and 95% CIs for cancer risk per 5 nmol/L higher IGF-I concentration by cancer site stratified by follow-up time at diagnosis (<3.89 years, **A**; ≥3.89 years, **B**; $n = 394{,}388$). HRs are represented by squares, with their 95% CIs as horizontal lines, the size of the squares is inversely proportional to the variance of the log HR. $P_{heterogeneity}$ (P_{het}) 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 CI is outside that range. [a]Analyses restricted to women ($n = 217{,}519$). [b]Analyses restricted to men ($n = 188{,}135$). All associations stratified for sex, age group (<45, 45–49, 50–54, 55–59, 60–64, and ≥65 years), geographical region (London, North-West, North-East, Yorkshire and Humber, West Midlands, East Midlands, South-East, South-West, Wales, and Scotland), and Townsend index (quintiles and unknown), and adjusted for age (underlying time variable), ethnicity (White, Asian, Black, mixed race or other, and unknown), educational level (college or university degree/vocational qualification, national examination at ages 17/18, national examination at age 16, and other qualification or unknown), total physical activity (<10, 10–19, 20–39, 40–59, and ≥60 metabolic equivalent hours per week and 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, and ≥25.0 g/day, nondrinker, and unknown), smoking status and intensity (never, former, current <15 cigarettes per day, current ≥15 cigarettes per day, current intensity unknown, and unknown), BMI (<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, and ≥35.0 kg/m^2), and in women: hormone replacement therapy use (never and ever), oral contraceptive pill use (never and ever), parity, age at first birth (nulliparous; 1–2, <25; 1–2, 25–29; 1–2, ≥30; and 1–2, unknown; ≥3, <25; ≥3, 25–29; ≥3, ≥30 years; and ≥3, unknown; and unknown), interaction between menopausal status (pre-, post-, and unknown), and BMI.

Figure 2 and Supplementary Table S3 show associations stratified by 3.89 years. The inverse association with squamous cell carcinoma of the esophagus was restricted to cases diagnosed within the first few years of follow-up with no association after that (HR, 0.59; 95% CI, 0.43–0.81 in cases diagnosed <3.89 years follow-up and HR, 1.02; 95% CI, 0.80–1.30, ≥3.89 years follow-up; $P_{heterogeneity} = 0.01$; **Fig. 2**). For the other cancers, there was limited evidence for heterogeneity by follow-up time, although there was a suggestion of a weaker association with ovarian cancer when restricted to cases diagnosed after 3.89 years of follow up (HR, 0.82; 95% CI, 0.73–0.92 in cases diagnosed <3.89 years follow-up and HR, 0.96; 95% CI, 0.84–1.10, ≥3.89 years follow-up; $P_{heterogeneity} = 0.09$). There was little evidence for differences by sex, except that sex-specific analyses showed an inverse association between IGF-I and NHL only in women (HR, 0.88; 95% CI, 0.80–0.97 in women and HR, 1.03; 95% CI, 0.96–1.12 in men; $P_{heterogeneity} = 0.01$); and a stronger inverse association between IGF-I and liver cancer in men (HR, 0.33; 95% CI, 0.26–0.40 in men and HR, 0.56; 95% CI, 0.45–0.71 in women; $P_{heterogeneity} < 0.01$; see Supplementary Fig. S2 and Supplementary Table S3). Similarly, there was little evidence for differences in the associations by age at blood collection (<55 and ≥55 years; Supplementary Fig. S3 and Supplementary Table S3), with the exceptions of the associations of IGF-I with bladder cancer (HR, 0.70; 95% CI, 0.52–0.96 for age <55 years and HR, 1.09; 95% CI, 1.00–1.19 for age ≥55 years; $P_{heterogeneity} = 0.01$) and brain cancer (HR, 1.25; 95% CI, 1.05–1.49 for age <55 years and HR, 1.00; 95% CI, 0.89–1.11 for age ≥55 years; $P_{heterogeneity} = 0.03$).

Discussion

In this large British cohort study, higher serum IGF-I concentration was associated with increased risks of thyroid cancer, malignant melanoma, and multiple myeloma, in addition to the expected positive associations with colorectal, breast, and prostate cancer. Higher IGF-I concentration was also associated with lower risks of oral, liver, ovarian cancer, and squamous cell carcinoma of the esophagus; these observed inverse associations may be influenced by reverse causality, and although the average follow-up time was relatively short there was

significant evidence of this bias for squamous cell carcinoma of esophagus. When considering multiple testing using Bonferroni correction (19 tests based on the main cancer sites, not including subsites, $P < 0.0026$), the associations with ovarian, thyroid, colorectal, colon, breast, prostate, and liver cancer remained statistically significant (34).

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

The inverse association found between IGF-I concentration and liver cancer is similar to findings from case–control studies nested in the α-Tocopherol, β-Carotene Cancer Prevention Study of male smokers and in EPIC, in which those with the lowest IGF-I concentrations had a greater risk (13, 14). However, in the EPIC study this association was attenuated after additional adjustment for biomarkers of liver damage (13). A further nested case–control study, the Japan Collaborative Cohort Study, found an inverse but nonstatistically significant association between IGF-I and liver cancer (12). Although we found no evidence for reverse causality in analyses stratified by follow-up time, the follow-up time might have been too short to investigate reverse causality robustly for liver cancer, which might be particularly susceptible to this bias because the majority of circulating IGF-I is produced by the liver (38). Case–control studies suggest that low serum IGF-I concentrations might be caused by decreased hepatic reserve in nonalcoholic fatty liver disease, liver cirrhosis, and hepatocellular carcinoma (39). Thus, low serum IGF-I levels could be an indicator for compromised liver health that in turn increases the risk of liver cancer, or liver cancer could lead to changes to serum IGF-I several years before a liver cancer is diagnosed.

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

In-line with earlier research from nested case–control studies, we found no association between total IGF-I and lung (5, 6), bladder (21), pancreatic (16), biliary tract (15), and endometrial cancer (18, 19), and our findings do not support an inverse association that has been observed in a nested case–control study of male smokers between IGF-I concentrations and kidney cancer (20). Subgroup analyses suggested additional associations between IGF-I and a decreased risk of NHL in women, a decreased risk of bladder cancer, and an increased risk of brain cancer in participants aged under 55 years. Previous studies of the association between IGF-I and NHL and bladder cancer found no evidence for an association (21, 25), and findings from previous studies on brain cancer were mixed (22, 23).

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

This study shows that IGF-I concentration is positively associated with the risks of colorectal, breast, and prostate cancer, as well as thyroid cancer and possibly with malignant melanoma and multiple myeloma. IGF-I was inversely associated with the risks of liver and ovarian cancer, perhaps related to reverse causation bias. The findings suggest that IGF-I is important in the development of several, but perhaps not all, types of cancer, and more research is needed for less common cancers, and employing Mendelian randomization and other approaches to assess causality.

Disclosure of Potential Conflicts of Interest

J.A. Schmidt reports grants from Cancer Research UK during the conduct of the study. R.C. Travis reports grants from Cancer Research UK (programme grant paid via University of Oxford) during the conduct of the study and World Cancer Research Fund (project grant funding paid via University of Oxford until 2019) outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

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Authors' Contributions

A. Knuppel: Data curation, formal analysis, investigation, visualization, methodology, writing-original draft, writing-review and editing. **G.K. Fensom:** Data curation, methodology, writing-review and editing. **E.L. Watts:** Data curation, methodology, writing-review and editing. **M.J. Gunter:** Investigation, methodology, writing-review and editing. **N. Murphy:** Investigation, methodology, writing-review and editing. **K. Papier:** Data curation, investigation, methodology, writing-review and editing. **A. Perez-Cornago:** Resources, writing-review and editing. **J.A. Schmidt:** Investigation, writing-review and editing. **K. Smith Byrne:** Investigation, writing-review and editing. **R.C. Travis:** Conceptualization, supervision, investigation, methodology, project administration, writing-review and editing. **T.J. Key:** Conceptualization, supervision, funding acquisition, investigation, writing-review and editing.

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