Cancer risk in patients with IgA nephropathy: a Swedish population-based cohort study

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List of abbreviations:

AER, absolute excess risk; CI, confidence interval; CKD, Chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; HR, hazard ratio; ICD, International Classification of Diseases; IgAN, IgA nephropathy; NMSC, non-melanoma skin cancer; OR, odds ratio; SNOMED, Systematized Nomenclature of Medicine

ABSTRACT

Background. IgA nephropathy (IgAN) is the most common primary glomerulonephritis affecting all ages and both sexes, but there is a lack of studies on its association with cancer and whether it is a paramalignant condition.

Methods. In a Swedish population-based cohort study we compared the risk of cancer among 3,882 biopsy-verified IgAN patients diagnosed during 1974-2011 with 19,341 reference individuals and followed them until 2015. Cox regression was used to estimate hazard ratios (HRs) for cancer in IgAN patients versus controls, and conditional logistic regression assessed the risk of cancer before the IgAN was confirmed.

Results. During a median follow-up of 12.6 years, 488 (12.6%) patients with IgAN and 1,783 (9.2%) matched reference individuals were diagnosed with cancer (HR 1.70; 95% confidence interval, 95%CI, 1.52-1.89). The increased risk was only seen in IgAN patients developing end stage renal disease (ESRD), with an HR of 4.01 (95%CI 3.33-4.82) for any cancer and HR of 2.22 (95%CI 1.79-2.75) when excluding non-melanoma skin cancer (NMSC). Non-ESRD IgAN patients did not have an increased overall cancer risk (HR 1.13; 95%CI 0.99-1.30). There was no increased risk of cancer preceding IgAN diagnosis (odds ratio 1.10; 95%CI 0.92-1.32).

Conclusion. We found no support for IgAN being a paramalignant condition. There was an increased risk of cancer in IgAN patients, but only for those with ESRD. Our results indicate approximately 6 extra cancer case per 100 IgAN patients with ESRD per 10 years, or >17 extra cases if including NMSC as well.

Keywords: cancer risk, epidemiology, IgA nephropathy

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KEY LEARNING POINTS

What is already known about this subject?

-IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide.

-The association between glomerular disease and cancer has long been discussed, and IgAN has been implied to be a potential paramalignant condition.

What this study adds?

-This study is to our knowledge the largest epidemiological study investigating the association between cancer risk in IgAN specifically.

-We did not find any support for increased risk of cancer prior to an IgAN diagnosis, or of IgAN being a paramalignant condition.

-We found an increased risk of cancer in patients with IgAN but confined to those with end stage renal disease and especially in patients who had undergone a kidney transplant.

What impact this may have on practice or policy?

-An IgAN diagnosis does not seem to imply a higher risk of cancer, hence cancer screening does not seem to be needed in the average patient with IgAN.

-We did see a significant increase in cancer among men >60 years at diagnosis, so this subgroup might still merit surveillance.

-With progressive disease the cancer risk increases just as for any patient with kidney failure regardless of aetiology and regular cancer screening should be advocated, foremost in those of high age and in patients with a kidney transplant.

INTRODUCTION

IgA nephropathy (IgAN) is the most common type of primary glomerulonephritis worldwide (1). The clinical presentation varies from asymptomatic, mild disease to acute kidney injury, and progresses to end stage renal disease (ESRD) in 15 to 50% of the cases (2–4).

An association, mainly as a paraneoplastic phenomenon, between glomerular disorders and cancer has long been discussed (5–8). While a recent study supports such an association between glomerulonephritis and cancer (9), there are little data on overall cancer risk in IgAN. A few studies have reported an increased risk specifically of lymphoproliferative disease, kidney and lung cancer in patients with IgAN but these studies have been small or lacked reference groups (10–16).

The aim of this study was to examine the risk of any and site-specific cancers in a large nationwide population-based cohort of individuals with IgAN compared with matched reference individuals.

MATERIALS AND METHODS

Exposure: Definition of IgAN

In this cohort study we defined IgAN as having a record of a kidney biopsy confirming IgAN (diagnosed in 1974–2011) at any of the four pathology departments that evaluate kidney biopsies in Sweden (Stockholm, Gothenburg, Linköping, and Malmö/Lund). Patient charts were reviewed manually or ascertained by local IT departments that searched biopsy records for the IgAN Systematized Nomenclature of Medicine Clinical Term (SNOMED) code D67300 (17). Since this register was set up (18) a random subset of IgAN SNOMED codes has been manually validated by Jarrick et al. against patient charts and biopsy reports. They

found a positive predictive value (PPV) of 95% (95% confidence interval (CI) 92-99%) for the diagnosis (19).

Outcome: Identifying cancer cases

All permanent Swedish residents have a unique personal identity number (20). Through this we linked data on our IgAN patients to the Swedish Cancer Registry (21). More than 96% of all malignancies are reported to the Cancer Register each year and 99% of all cancers are morphologically verified (21). Physicians reporting to the Cancer Register today report the International Classification of Diseases (ICD)-10 code and The Cancer Register then centrally supplements these data with the corresponding ICD-7 code(22). We have primarily used ICD-7 codes for the analyses of overall cancer risk (codes listed in Appendix).

Matched Reference Individuals

The Total Population Register (23) is a register containing data on the birth, death, family, marital status, and migration of all Swedish citizens. Reference individuals, matched for age, sex, calendar year, and county of residence at the time of renal biopsy, were identified by the government agency Statistics Sweden. We used five reference individuals for each individual with IgAN.

There were no exclusion criteria pertaining to the control sampling except that the selected reference individuals had to be alive at the time of matching and not previously diagnosed with biopsy-verified IgAN at the time of matching of the index patient. Hence, our risk-set sampled reference individuals represent a random selection of the Swedish population including individuals with and without other chronic diseases.

Covariates

Diagnoses on smoking, tobacco use and/or chronic obstructive pulmonary disease (COPD) were assessed through relevant ICD codes in the National Patient Register (NPR) (listed in the Appendix) using the personal identity number. The NPR is a national register maintained by the National Board of Health and Welfare in Sweden. It contains data and diagnoses from all specialist medical care (hospitalization or non-primary care outpatient visits)(24). This information was used to adjust for smoking by proxy. Albeit this variable is probably incomplete with regards to smoking, we felt it important to control for smoking as an important risk factor for cancer development.

Data on highest educational level were obtained from the Swedish Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) (25). It was categorized according to length of education (≤9 years compulsory school, 10−12 years, ≥13 years/university and unknown). Education level is a proxy for socioeconomic status, which in turn is acknowledged as a risk factor for a number of other diseases. (26) We used the highest educational level available until the end of follow up, and in children we used their parents´ level.

ESRD was defined as a clinical diagnosis of CKD 5, maintenance dialysis treatment and/or kidney transplantation (see Appendix for definition details).

Exclusion criteria

IgAN patients and reference individuals with a registered cancer in the Cancer Register before the kidney biopsy date and/or study start were excluded from the study. No other exclusion criterion was applied.

Follow-Up

We defined the date of IgAN diagnosis as the day of the first kidney biopsy confirming IgAN.

Follow-up began at biopsy date and the corresponding date in the reference individuals.

Follow-up ended with cancer (event) or death, emigration or on the 31st of December 2015,

whichever occurred first.

Statistical Analyses

We used Cox regression run in strata of each patient and its 5 matched (sex, age, calendar-

year, and county) reference individuals. We further adjusted for smoking and educational

attainment.

To assess reverse causation bias and also to evaluate IgAN as a paramalignant condition, we

performed a sensitivity analysis where we started follow-up one year after IgAN diagnosis.

Further, we also performed a Cox regression analysis with follow-up just for one year after

the IgAN diagnosis.

To examine if the cancer risk was associated with kidney function, we divided the IgAN

cohort further according to ESRD and transplantation status in three different analyses. One

with patients that never reached ESRD or was diagnosed with cancer before reaching ESRD

(i.e. date of ESRD was treated as an additional censoring event), one including only those

who reached ESRD (using ESRD date as start of follow up for both IgAN cases and their

matched reference individuals) and finally one analysis of those who underwent a kidney

transplantation during follow up (similarly using the date of transplantation as start of follow

up for both IgAN cases and reference individuals). The analysis restricted to those with a

kidney transplant was motivated by the further increased risk of cancer in patients on

immunosuppressive medication. In a sensitivity analysis we also analyzed the overall risk

among ESRD patients who had not yet started dialysis treatment or had a kidney

transplantation.

Non-melanoma skin cancer (NMSC) is well known to occur in patients with ESRD and organ transplantation(27,28), therefore we also analyzed cancer risk excluding NMSC in all subgroups.

Conditional logistic regression assessing the Odds Ratio (OR) of prior cancer diagnoses was performed comparing cases and reference individuals. In this analysis all patients from the original cohort and their reference individuals were included. The conditional logistic regressions were not run in strata, hence the analyses were adjusted for age, sex, calendar-year, county, proxy for smoking, and educational attainment.

Ethics

The study was approved by the Stockholm Ethics Review Board (22 January 2014, approval number: 2013/2095–31/2). Because this is a strictly register-based study, the requirement of informed consent was waived by the Board (29).

RESULTS

Background data

Our study cohort consisted of 3,882 patients with IgAN of which 1,117 (29%) were women. Two thirds of the cohort were between 18-59 years old, with approximately the same numbers in the age category <18 years as in > 60 years. They were equally divided in the study entry year categories, and over 50% had a follow up period for more than 10 years. The majority (76%) had an educational level higher than compulsory school (>9 years). In the IgAN cohort 85 (2%) patients had a smoking or tobacco related record in the NPR, compared to 621 (3%) of the reference individuals. Some 1,014 (26%) of the patients with IgAN had or developed ESRD during follow up, and 793 (20%) received a kidney transplant.

Of the reference individuals 11 had ESKD at baseline, and another 33 developed ESRD during follow up. (see Table 1).

Main results

During a median follow-up of 12.6 years, 488 of 3,882 (13%) patients with IgAN were diagnosed with cancer, compared to 1,783 of 19,341 (9%) of the matched reference individuals, corresponding to an adjusted HR (aHR) of 1.68 (95%CI 1.51-1.87).

Excluding the first year of follow up did not change the estimate considerably 1.70 (95%CI 1.53-1.90), and with an aHR for any cancer during first year of follow-up being 1.41 (95%CI 0.91-2.20).

Restricting the cancer diagnoses to all but non-melanoma skin cancer (NMSC) the association was weaker, but still statistically significant 1.31 (95%CI 1.16-1.48). The risk was significantly increased in all subgroup analyses (male vs. female, different age-groups, and calendar years) except in the age category < 18 years (see Table 2, Figure 1, and Supplementary table 1A-B).

Risk of cancer according to kidney function

In the non-ESRD subgroup, 265 of 3,534 (7%) patients with IgAN developed a malignancy, compared to 1,779 of 19,330 (9%) reference individuals, corresponding to an aHR of 1.13 (95%CI 0.99-1.30), hence showing no difference between the IgAN patients and the reference individuals. (see Table 3, Figure 2, and Supplementary table 2).

In the ESRD group, 224 of 984 (23%) patients with IgAN compared to 483 of 4,861 (10%) reference individuals were diagnosed with cancer, resulting in an aHR of 4.01 (95%CI 3.33-4.82), and when NMSC was excluded an aHR of 2.22 (95%CI 1.79-2.75). (see Table 4, Figure 3, and Supplementary table 3).

Restricting the ESRD group to patients with a kidney transplant, the aHR was 4.46 (95%CI 3.64-5.46), while excluding NMSC yielded an aHR of 2.28 (95%CI 1.80-2.88) (see Figure 4 and Supplementary tables 4 A-B).

Of the 327 patients who had not started dialysis treatment or undergone a kidney transplantation before ESRD diagnosis (based on ICD-coding), 12 (3.7%) were diagnosed with cancer before starting dialysis or undergoing transplantation (aHR 2.26; 95%CI 1.09-4.66).

Incidence and Absolut excess risk

In the main analysis we saw an incidence rate (IR) of 7.2 cases of cancer per 1,000 person years in the IgAN cohort when excluding NMSC, compared to 6.3 per 1,000 person years in the reference individuals. This corresponds to an absolute excess risk (AER) of 0.9 extra cases of cancer in the IgAN cohort. In the ESRD and kidney transplantation subgroups the IR was 14.0 and 13.6 cases of cancer per 1,000 person years, and the AER was 5.7 and 6.3 per 1,000 person years, respectively, for the IgAN patients.

Site-specific cancers

The site-specific cancer with the strongest association was by far NMSC in the ESRD and kidney transplantation subgroups, respectively. Excluding NMSC almost halved the excess risk in those subgroups, from aHR 4.01 (95%CI 3.33-4.82) to aHR 2.22 (95%CI 1.79-2.75) in the ESRD subgroup, and from aHR 4.46 (95%CI 3.64-5.46) to aHR 2.28 (95%CI 1.80-2.88) in the kidney transplantation group. In the main analysis the difference when excluding NMSC was not of the same magnitude.

Besides NMSC, cancer in the oral cavity, vulva/vagina, renal/uroepithelial, endocrine glands, colorectal and lymphoproliferative malignancies were the subtypes with the highest HR in both the ESRD and kidney transplantation subgroups. Restricting the analysis to kidney

cancer alone, the aHR in the ESRD subgroup was 11.12 (95%CI 4.60-26.91), compared to 1.65 (95%CI 0.74-3.67) in non-ESRD patients. Cancer of the vulva/vagina was statistically significant in the main analysis, but since all 5 cancer cases in patients with IgAN were in the kidney transplantation strata, and the 6 cases in the control group were from individuals matched to patients in the non-ESRD it was not possible to calculate an aHR according to subgroups.

In ESRD patients who never started dialysis treatment or received a kidney transplant, the only site-specific cancer statistically significantly linked to IgAN was NMSC (aHR 7.57; 95% 1.26-45.44).

The cancer subtypes with the highest AER were NMSC (14.0 and 15.7 per 1,000 person years) renal/uroepithelial (1.7 and 1.7 per 1,000 person years), colorectal (1.2 and 1.4 per 1,000 person years) and cancer in the oral cavity (0.8 and 0.9 per 1,000 person years) in both ESRD and kidney transplantation subgroups, respectively.

Non-ESRD patients did not have an increased risk of *any* cancer (aHR 1.13, 95%CI 0.99-1.30), but had a significantly higher risk of NMSC (aHR 1.90; 95%CI 1.29-2.79), and further for prostate and renal/uroepithelial cancer.

(see Table 2-4, Figures 1-4, and Supplementary table 4A)

Risk of having a cancer diagnosis before IgAN

Of the study start IgAN cohort of 4,037 a total of 155 (4%) had a cancer diagnosis before their IgAN was confirmed. In the reference individuals the number was 707 of 20,048 (4%). The conditional logistics regression showed an adjusted OR of 1.10 (95%CI 0.92-1.32), indicating that there was no increased risk of cancer for the IgAN cohort. (see Supplementary Table 5)

DISCUSSION

In this study we found no support for an increased risk of cancer prior to an IgAN diagnosis or for IgAN being a paramalignant condition. We did find an increased risk of cancer in IgAN patients but confined only to those with ESRD. There was a slight risk increase in those with ESRD without dialysis treatment or transplantation (aHR 2.26), although higher than for those who never developed ESRD (aHR 1.13). The risk increase was especially high in patients who had undergone a kidney transplantation (aHR 4.46).

Comparison to other studies

The association between cancer and glomerulonephritis has been widely discussed and several malignancies have been suggested to be associated with IgAN as paramalignant condition. Most often mentioned is renal cell carcinoma(11,14,30), but also lung cancer (13), larynx (10), esophagus (31), and lymphomas (12,16,32,33). Furthermore, Mustonen *et al* suggest a possible connection between mucosal affection of solid tumors in respiratory, buccal cavity and nasopharynx with higher circulating IgA-levels causing IgA depositions in the kidney (10). Most of these studies are small or consist of case reports lacking statistical power, and in contrast to what these and other studies have implied (5–9,34) we did not see a paramalignant pattern in patients with IgAN and a cancer diagnosis. Most of the cancer diagnoses in our study were not in direct temporal connection with the IgAN diagnosis, nor was there a higher risk of having a cancer diagnosis before the kidney disease. This also partly contrasts to a more recent study by Ryu *et al* (9). These researchers analyzed 1,155 patients with biopsy-verified glomerulonephritis and found an almost three times higher (O/E-ratio 3.42; 95%CI 1.37-5.46) risk for cancer within a month after their kidney diagnosis in patients aged >50 years compared to the general population, although, in their IgAN subgroup they had only 3 cases of cancer in 438 patients and could not confirm a statistically significant

association. Heaf *et al* (34) also examined cancer incidence in patients with biopsy proven glomerulonephritis. They found 911 cancer events in 5,594 patients, with an increased risk of cancer mainly 1 year before or after a glomerulonephritis diagnosis. In that study IgAN patients were not specifically studied but included in a group with more uncommon types of glomerulonephritis, hence the results cannot be completely extrapolated to the IgAN cohort.

Even if potentially not being a paramalignant condition, our results showed an increased risk of cancer in IgAN patients, but only for patients who progressed to ESRD, especially for NMSC and kidney cancer. These elevated risks and sites of cancer in patients with kidney failure is consistent with several previous studies (35–39) and may indicate increased cancer risk regardless of aetiology (40–48). Further supporting that cancer risk increases with function failure rather than within a specific aetiology of the kidney disorder, Xu *et al* examined the correlation between cancer risk and creatinine levels as a part of the Stockholm creatinine Measurements (SCREAM) project. The project included creatinine information from 719,033 individuals >40 years without previous records of cancer. They identified 64,319 cancer events (in 9% of the participants) which revealed a U-shaped association between kidney function loss and risk of cancer. Xu *et al* association was modest in magnitude, and primarily driven by NMSC and urogenital cancers. They concluded that detection bias and/or reverse causation could partly explain an overestimation of the increased risk of cancer in patients with CKD, especially during the first year of follow-up (48).

In more aggressive and rapidly progressive forms of IgAN, that more often end in terminal kidney failure, carcinogenic immunosuppressive medications e.g. cyclophosamide or azathioprine are commonly used (49), and all patients with a kidney transplant will be on multiple immunosuppression regimes. This epidemiological study cannot conclude anything on causality, and we did not have sufficient data to explore the impact of kidney medications

more accurately on cancer risk, although we believe that immunosuppression is the main reason for the increased risk in the ESRD/kidney transplantation group.

In our study we did not find a statistically significant association between IgAN and overall cancer in patients with non-ESRD, except for prostate cancer, renal/uroepithelial cancer and NMSC in men >60 years. This is probably due to detection bias, because of the more frequent health care visits in the IgAN group, and that the disorder will also more often implicate ultrasounds of the kidneys and screening of postrenal obstructions.

There were no major differences in cancer risk or specific cancer subtypes between the ESRD group and those who underwent a kidney transplantation, which is probably explained by the fact that approximately 80% (793 of 1,014) of the ESRD population were transplanted. The cancer subtypes with the strongest association were NMSC, renal/uroepithelial (most distinctive kidney cancer), vulva/vagina, cancer in the oral cavity, endocrine glands, colorectal, and lymphoproliferative malignancies, and this is consistent with several other studies on cancer risk post-kidney transplantation. Our results are fairly similar to those of a recent study by Benoni *et al* examining cancer incidence in patients from the Nordic countries receiving a kidney transplantation (50).

Strengths and Limitations

The main strengths of our study are the large cohort of well-characterized individuals and very long follow-up with a median of 12.6 years. We believe this is the largest study to date examining IgA and cancer. Through the unique personal identity number, we were able to follow-up patients and reference individuals without virtually no loss of follow-up. Further, The Cancer Registry is highly used, validated and with almost complete coverage of all cancers in Sweden.

A limitation in our study could be that it is constrained to patients with biopsy-verified IgAN. However, the fact that approximately one third of our patients were women, and 26% of the IgAN population progressed to ESRD (both proportions consistent with the expected (2)) suggest that our cohort is representative of the average IgAN patient, with a low risk of selection bias.

While our study is representative of the Swedish population, which is predominantly of Caucasian ethnicity, we call for caution when extrapolating of our findings to other countries or ethnically diverse societies. Our ascertainment for smoking from clinical diagnoses is not complete, but we still believe it adds important data on confounding. Nor have we adjusted for other comorbidities or medications.

Finally, there is a risk of detection bias because patients with IgAN are likely to visit healthcare more frequently than the general population, although the main findings were that the non-ESRD patients did not seem to have a higher risk for cancer, or that IgAN is to be considered a paramalignant condition. This lack of association with cancer was further supported in the sensitivity analysis when we excluded the first year of follow up and got almost exactly the same estimate as in the main analysis.

Implication of the findings

That IgAN does not seem to imply a higher risk of cancer, supports the current KDIGO guidelines (49) that cancer screening is not needed in the average patient with IgAN. However, we did see a significant increase in cancer among men >60 years at diagnosis, so this subgroup might still merit surveillance. And with progressive disease the risk increases just as for any patient with kidney failure regardless of aetiology.

In patients with progressive disease and terminal kidney failure, especially those of high age, regular cancer screening should be advocated and directed questions recorded systematically

in patients' medical charts to improve chances of an early detection of any future malignant condition. Skin cancer surveillance should be performed routinely, that is especially importantly after a kidney transplantation since NMSC can metastasize in patients with immunosuppression (27). Our results indicate approximately 6 extra cancer case per 100 IgAN patients with ESRD per 10 years, or >17 extra cases if including NMSC as well.

Conclusion

We found no support for a higher risk of cancer prior to an IgAN diagnosis, or for IgAN being a paramalignant condition. We found an increased risk for cancer in patients with IgAN, but this excess risk was confined only to those who developed ESRD. The risk was foremost increased in patients with a kidney transplant. The association is not interpreted to be IgAN specific, but possibly secondary to kidney function loss and immunosuppression.

AUTHORS' CONTRIBUTIONS

J.R, J.F.L and L.E designed the study. J.R and L.E analyzed the data. J.R made the tables, figure and drafted the paper, with inputs from L.E, J-J.C and J.F.L. L.E supervised the study. All the authors approved the final version of the manuscript. The corresponding author (LE) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

CONFLICT OF INTEREST STATEMENT

Dr Ludvigsson coordinates a study on behalf of the Swedish IBD quality register (SWIBREG) and that study has received funding from Janssen corporation.

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Table 1. Baseline characteristics

Participant characteristics	IgAN n (%)	Controls n (%)
Total	3,882 (100)	19,341 (100)
Matched variables		
Sex		
Female	1,117 (29)	5,508 (29)
Male	2,765 (71)	13,833 (71)
Age (years)		
<18	373 (10)	1,866 (10)
18–39	1,654 (43)	8,244 (43)
40–59	1,337 (34)	6,632 (34)
≥60	518 (13)	2,599 (13)
Calendar year		
Entry year		
1974–1994	1,037 (27)	5,131 (27)
1995–2005	1,614 (42)	8,067 (42)
2006–2015	1,231 (32)	6,143 (32)
Unmatched Variables		
Follow-up (years)		
Mean (SD)	12.8 (8.3)	13.6 (8.4)
<1	80 (2)	240 (1)
1–5	596 (15)	2,705 (14)
5–10	1,020 (26)	4,689 (24)
≥10	2,186 (56)	11,707 (61)
Educational level		
Compulsory school, ≤9 years	844 (22)	4,102 (21)
Upper secondary school, 1-3 years	1,716 (44)	8,690 (45)
University level	1,228 (32)	6,095 (32)
Unknown	94 (2)	454 (2)
Smokers/COPD diagnosis	85 (2)	621 (3)
Kidney function		
End stage renal disease at baseline	348 (9)	11 (0.1)
End stage renal disease during follow up	666 (17)	33 (0.2)
Kidney transplantation during follow up	793 (20)	15 (0.1)

IgAN: IgA nephropathy
SD: Standard deviation
COPD: chronic obstructive pulmonary disease

	IgAN	Controls	Cancer events IgAN	Cancer events Controls	Follow up years IgAN	Follow up years Controls	IR IgAN (95% CI)	IR Controls (95% CI)	HR (95% CI)	aHR* (95% CI)
Any_cancer	3 882 (100%)	19 341 (100%)	488 (12.6%)	1 783 (9.2%)	49 852	262 834	9.8 (8.9-10.7)	6.8 (6.5-7.1)	1.68 (1.51-1.87)	**1.70 (1.52-1.89)**
Any cancer, not NMSC	3 897 (100%)	19 371 (100%)	366 (9.4%)	1 666 (8.6%)	50 828	263 899	7.2 (6.5-7.9)	6.3 (6.0-6.6)	1.30 (1.16-1.47)	**1.31 (1.16-1.48)**
Oral cavity	4 034 (100%)	20 039 (100%)	19 (0.5%)	36 (0.2%)	53 769	279 351	0.4 (0.2-0.5)	0.1 (0.1-0.2)	2.84 (1.59-5.06)	**2.83 (1.58-5.06)**
Solid	3 890 (100%)	19 372 (100%)	472 (12.1%)	1 676 (8.7%)	50 022	263 607	9.4 (8.6-10.3)	6.4 (6.1-6.7)	1.73 (1.55-1.93)	**1.74 (1.56-1.94)**
Hematological	4 025 (100%)	20 015 (100%)	31 (0.8%)	148 (0.7%)	53 731	278 683	0.6 (0.4-0.8)	0.5 (0.4-0.6)	1.31 (0.88-1.96)	1.34 (0.90-2.01)
Lymphoproliferative	4 029 (100%)	20 020 (100%)	23 (0.6%)	122 (0.6%)	53 778	278 822	0.4 (0.3-0.6)	0.4 (0.4-0.5)	1.23 (0.77-1.95)	1.27 (0.80-2.02)
GI-tract	4 017 (100%)	19 971 (100%)	76 (1.9%)	361 (1.8%)	53 584	277 882	1.4 (1.1-1.7)	1.3 (1.2-1.4)	1.24 (0.96-1.61)	1.25 (0.97-1.62)
Gastric	4 037 (100%)	20 041 (100%)	6 (0.1%)	43 (0.2%)	53 928	279 479	0.1 (0.0-0.2)	0.2 (0.1-0.2)	0.73 (0.31-1.75)	0.70 (0.29-1.69)
Colorectal	4 018 (100%)	19 988 (100%)	52 (1.3%)	217 (1.1%)	53 622	278 194	1.0 (0.7-1.2)	0.8 (0.7-0.9)	1.44 (1.05-1.97)	**1.46 (1.06-2.00)**
Liver	4 037 (100%)	20 048 (100%)	7 (0.2%)	29 (0.1%)	53 936	279 547	0.1 (0.0-0.2)	0.1 (0.1-0.1)	1.46 (0.62-3.42)	1.88 (0.77-4.58)
Pancreas	4 037 (100%)	20 047 (100%)	5 (0.1%)	52 (0.3%)	53 931	279 543	0.1 (0.0-0.2)	0.2 (0.1-0.2)	0.61 (0.24-1.56)	0.54 (0.21-1.41)
Lung	4 034 (100%)	20 039 (100%)	8 (0.2%)	117 (0.6%)	53 911	279 355	0.1 (0.0-0.3)	0.4 (0.3-0.5)	0.43 (0.21-0.89)	0.47 (0.22-1.00)
Breast	1 169 (29.0%)	5 781 (28.9%)	21 (1.8%)	152 (2.6%)	16 028	80 085	1.3 (0.7-1.9)	1.9 (1.6-2.2)	0.71 (0.44-1.12)	0.70 (0.44-1.12)
Upper airways	4 034 (100%)	20 043 (100.0%)	3 (0.1%)	13 (0.1%)	53 879	279 515	0.1 (0.0-0.1)	0.0 (0.0-0.1)	1.36 (0.37-4.96)	2.96 (0.65-13.49)
Prostate	2 840 (70.7%)	14 092 (70.6%)	95 (3.3%)	442 (3.1%)	37 114	194 621	2.6 (2.0-3.1)	2.3 (2.1-2.5)	1.40 (1.11-1.77)	**1.42 (1.13-1.80)**
Renal/Urinary	4 027 (100%)	20 004 (100%)	52 (1.3%)	144 (0.7%)	53 680	278 484	1.0 (0.7-1.2)	0.5 (0.4-0.6)	2.22 (1.58-3.12)	**2.29 (1.62-3.23)**
Nervous system	4 032 (100%)	20 018 (100%)	13 (0.3%)	49 (0.2%)	53 796	278 995	0.2 (0.1-0.4)	0.2 (0.1-0.2)	1.38 (0.74-2.58)	1.40 (0.74-2.63)
Endocrine glands	4 027 (100%)	20 025 (100%)	14 (0.3%)	43 (0.2%)	53 776	279 055	0.3 (0.1-0.4)	0.2 (0.1-0.2)	1.65 (0.89-3.05)	1.66 (0.89-3.05)
Penis/Testis	2 856 (70.8%)	14 165 (70.7%)	2 (0.1%)	16 (0.1%)	37 677	197 156	0.1 (0.0-0.1)	0.1 (0.0-0.1)	0.81 (0.18-3.60)	0.79 (0.17-3.63)
Vulva/Vagina	1 176 (29.1%)	5 858 (29.2%)	5 (0.4%)	6 (0.1%)	16 152	81 952	0.3 (0.0-0.6)	0.1 (0.0-0.1)	3.79 (1.15-12.50)	**3.80 (1.13-12.78)**
Cervix/Uterus/Ovaries	1 139 (28.5%)	5 653 (28.5%)	21 (1.8%)	137 (2.4%)	15 575	78 005	1.3 (0.8-1.9)	1.8 (1.5-2.1)	0.74 (0.47-1.18)	0.72 (0.45-1.11)
Melanoma	4 029 (100%)	20 004 (100%)	35 (0.9%)	140 (0.7%)	53 652	278 191	0.7 (0.4-0.9)	0.5 (0.4-0.6)	1.40 (0.95-2.04)	1.36 (0.92-2.00)
Skeleton	4 036 (100%)	20 043 (100%)	1 (0.0%)	1 (0.0%)	53 926	279 513	0.0 (0.0-0.1)	0.0 (0.0-0.0)	5.00 (0.31-79.95)	3.00 (0.19-47.96)
Skin	4 019 (100%)	20 011 (100%)	178 (4.4%)	185 (0.9%)	52 728	278 221	3.4 (2.9-3.9)	0.7 (0.6-0.8)	6.87 (5.42-8.72)	**6.87 (5.40-8.73)**

Table 2. Cancer risk in IgAN patients

IgAN: IgA nephropathy

HR: Hazard Ratio

CI: Confidence interval

IR: Incidence rate per 1,000 person years

NMSC: non-melanoma skin cancer

*Analyses run in strata of cases and 5 (sex, age, calendar-year, and county) matched controls additionally adjusted for smoking and educational attainment

Subgroups cancer	IgAN	Controls	Cancer events IgAN	Cancer events Controls	Follow up years IgAN	Follow up years Controls	IR IgAN (95% CI)	IR Controls (95% CI)	HR (95% CI)	aHR* (95% CI)
Any_cancer	3 534 (100%)	19 330 (100%)	265 (7.5%)	1 779 (9.2%)	41 342	262 623	6.4 (5.6-7.2)	6.8 (6.5-7.1)	1.13 (0.98-1.30)	1.13 (0.99-1.30)
Any cancer, not NMSC	3 540 (100%)	19 357 (100%)	236 (6.7%)	1 664 (8.6%)	41 551	263 638	5.7 (5.0-6.4)	6.3 (6.0-6.6)	1.06 (0.92-1.23)	1.07 (0.92-1.23)
Oral cavity	3 662 (100%)	20 023 (100%)	9 (0.2%)	35 (0.2%)	43 595	279 041	0.2 (0.1-0.3)	0.1 (0.1-0.2)	1.93 (0.88-4.22)	1.94 (0.88-4.27)
Solid	3 542 (100%)	19 361 (100%)	254 (7.2%)	1 672 (8.6%)	41 485	263 395	6.1 (5.4-6.9)	6.3 (6.0-6.7)	1.14 (0.99-1.31)	1.15 (0.99-1.32)
Hematological	3 654 (100%)	19 999 (100%)	16 (0.4%)	148 (0.7%)	43 518	278 365	0.4 (0.2-0.5)	0.5 (0.4-0.6)	0.92 (0.54-1.58)	0.93 (0.54-1.60)
Lymphoproliferative	3 658 (100%)	20 004 (100%)	10 (0.3%)	122 (0.6%)	43 564	278 505	0.2 (0.1-0.4)	0.4 (0.4-0.5)	0.72 (0.37-1.41)	0.74 (0.37-1.45)
GI-tract	3 647 (100%)	19 955 (100%)	47 (1.3%)	361 (1.8%)	43 468	277 564	1.1 (0.8-1.4)	1.3 (1.2-1.4)	1.04 (0.75-1.43)	1.05 (0.76-1.45)
Gastric	3 664 (100%)	20 025 (100%)	5 (0.1%)	43 (0.2%)	43 666	279 160	0.1 (0.0-0.2)	0.2 (0.1-0.2)	0.94 (0.36-2.48)	0.90 (0.33-2.42)
Colorectal	3 648 (100%)	19 972 (100%)	30 (0.8%)	217 (1.1%)	43 498	277 876	0.7 (0.4-0.9)	0.8 (0.7-0.9)	1.08 (0.72-1.61)	1.10 (0.73-1.65)
Liver	3 664 (100%)	20 032 (100%)	6 (0.2%)	29 (0.1%)	43 674	279 229	0.1 (0.0-0.2)	0.1 (0.1-0.1)	1.61 (0.64-4.11)	2.14 (0.80-5.78)
Pancreas	3 664 (100%)	20 031 (100%)	2 (0.1%)	52 (0.3%)	43 669	279 224	0.0 (0.0-0.1)	0.2 (0.1-0.2)	0.36 (0.09-1.54)	0.31 (0.07-1.34)
Lung	3 661 (100%)	20 023 (100%)	5 (0.1%)	116 (0.6%)	43 650	279 047	0.1 (0.0-0.2)	0.4 (0.3-0.5)	0.35 (0.14-0.86)	0.36 (0.14-0.93)
Breast	1 095 (29.9%)	5 779 (29.0%)	17 (1.6%)	152 (2.6%)	13 925	80 032	1.2 (0.6-1.8)	1.9 (1.6-2.2)	0.69 (0.41-1.16)	0.69 (0.41-1.17)
Upper airways	3 661 (100%)	20 027 (100%)	2 (0.1%)	13 (0.1%)	43 622	279 196	0.0 (0.0-0.1)	0.0 (0.0-0.1)	1.57 (0.32-7.80)	5.03 (0.68-37.08)
Prostate	2 544 (69.8%)	14 078 (70.6%)	71 (2.8%)	442 (3.1%)	29 151	194 366	2.4 (1.9-3.0)	2.3 (2.1-2.5)	1.48 (1.13-1.94)	**1.51 (1.15-1.98)**
Renal/Urinary	3 658 (100%)	19 989 (100%)	27 (0.7%)	144 (0.7%)	43 553	278 168	0.6 (0.4-0.9)	0.5 (0.4-0.6)	1.58 (1.00-2.47)	**1.59 (1.01-2.52)**
Nervous system	3 659 (100%)	20 003 (100%)	10 (0.3%)	49 (0.2%)	43 561	278 689	0.2 (0.1-0.4)	0.2 (0.1-0.2)	1.27 (0.63-2.57)	1.25 (0.61-2.56)
Endocrine glands	3 656 (100%)	20 009 (100%)	5 (0.1%)	43 (0.2%)	43 597	278 747	0.1 (0.0-0.2)	0.2 (0.1-0.2)	0.75 (0.29-1.95)	0.76 (0.29-1.97)
Penis/Testis	2 558 (69.9%)	14 151 (70.7%)	2 (0.1%)	16 (0.1%)	29 575	196 900	0.1 (0.0-0.2)	0.1 (0.0-0.1)	0.88 (0.19-3.96)	0.87 (0.19-4.02)
Vuvla/Vagina	1 102 (30.1%)	5 856 (29.2%)	(0.0%)	6 (0.1%)	14 061	81 889	0.0 (0.0-0.0)	0.1 (0.0-0.1)	N/A	N/A
Cervis/Uterus/Ovaries	1 067 (29.4%)	5 651 (28.5%)	16 (1.5%)	137 (2.4%)	13 600	77 941	1.2 (0.6-1.8)	1.8 (1.5-2.1)	0.65 (0.39-1.11)	0.64 (0.38-1.09)
Melanoma	3 656 (100%)	19 988 (100%)	23 (0.6%)	140 (0.7%)	43 472	277 873	0.5 (0.3-0.7)	0.5 (0.4-0.6)	1.15 (0.72-1.82)	1.14 (0.71-1.82)
Skeleton	3 663 (100%)	20 027 (100%)	1 (0.0%)	1 (0.0%)	43 663	279 194	0.0 (0.0-0.1)	0.0 (0.0-0.0)	5.00 (0.31-79.95)	3.00 (0.19-47.96)
NMSC	3 657 (100%)	19 998 (100%)	39 (1.1%)	182 (0.9%)	43 438	277 961	0.9 (0.6-1.2)	0.7 (0.6-0.7)	1.88 (1.29-2.76)	**1.90 (1.29-2.79)**

Table 3. Cancer risk in non-ESRD IgAN patients

IgAN: IgA nephropathy

ESRD: End stage renal disease

CI: Confidence interval

HR: Hazard Ratio

IR: Incidence rate per 1,000 person years

N/A: not able to calculate

NMSC: non-melanoma skin cancer

*Analyses run in strata of cases and 5 (sex, age, calendar-year, and county) matched controls additionally adjusted for smoking and educational attainment

Subgroups cancer	IgAN	Controls	Cancer events IgAN	Cancer events Controls	Follow up years IgAN	Follow up years Controls	IR IgAN (95% CI)	IR Controls (95% CI)	HR (95% CI)	aHR* (95% CI)
Any_cancer	984 (100%)	4 861 (100%)	224 (22.8%)	483 (9.9%)	8 556	53 143	26.2 (22.8-29.6)	9.1 (8.3-9.9)	3.97 (3.30-4.77)	**4.01 (3.33-4.82)**
Any cancer, not_NMSC	1 004 (100%)	4 874 (100%)	131 (13.0%)	446 (9.2%)	9 336	53 447	14.0 (11.6-16.4)	8.3 (7.6-9.1)	2.20 (1.78-2.73)	**2.22 (1.79-2.75)**
Oral cavity	1 066 (100%)	5 105 (100%)	10 (0.9%)	9 (0.2%)	10 247	57 342	1.0 (0.4-1.6)	0.2 (0.1-0.3)	5.55 (2.18-14.11)	**5.36 (2.07-13.84)**
Solid	984 (100%)	4 871 (100%)	219 (22.3%)	452 (9.3%)	8 583	53 367	25.5 (22.1-28.9)	8.5 (7.7-9.3)	4.21 (3.48-5.09)	**4.25 (3.51-5.15)**
Hematological	1 064 (100%)	5 100 (100%)	15 (1.4%)	44 (0.9%)	10 286	57 149	1.5 (0.7-2.2)	0.8 (0.5-1.0)	2.34 (1.25-4.38)	**2.39 (1.26-4.53)**
Lymphoproliferative	1 064 (100%)	5 102 (100%)	13 (1.2%)	35 (0.7%)	10 286	57 197	1.3 (0.6-2.0)	0.6 (0.4-0.8)	2.63 (1.33-5.20)	**2.82 (1.40-5.67)**
GI-tract	1 055 (100%)	5 079 (100%)	29 (2.7%)	105 (2.1%)	10 189	56 916	2.8 (1.8-3.9)	1.8 (1.5-2.2)	1.81 (1.17-2.79)	**1.76 (1.13-2.73)**
Gastric	1 067 (100%)	5 108 (100%)	1 (0.1%)	14 (0.3%)	10 335	57 390	0.1 (0.0-0.3)	0.2 (0.1-0.4)	0.35 (0.05-2.69)	0.32 (0.04-2.56)
Colorectal	1 056 (100%)	5 084 (100%)	22 (2.1%)	58 (1.1%)	10 197	56 995	2.2 (1.3-3.1)	1.0 (0.8-1.3)	2.61 (1.53-4.45)	**2.66 (1.53-4.62)**
Liver	1 066 (100%)	5 110 (100%)	1 (0.1%)	8 (0.2%)	10 335	57 387	0.1 (0.0-0.3)	0.1 (0.0-0.2)	0.92 (0.11-7.93)	1.30 (0.13-13.08)
Pancreas	1 067 (100%)	5 110 (100%)	3 (0.3%)	18 (0.4%)	10 335	57 390	0.3 (0.0-0.6)	0.3 (0.2-0.5)	1.11 (0.31-3.96)	1.21 (0.32-4.56)
Lung	1 067 (100%)	5 105 (100%)	3 (0.3%)	33 (0.6%)	10 334	57 363	0.3 (0.0-0.6)	0.6 (0.4-0.8)	0.76 (0.22-2.59)	0.88 (0.24-3.24)
Breast	199 (18.7%)	980 (19.2%)	4 (2.0%)	31 (3.2%)	2 108	11 312	1.9 (0.0-3.8)	2.7 (1.8-3.7)	0.77 (0.26-2.23)	0.74 (0.25-2.17)
Upper airways	1 067 (100%)	5 108 (100%)	1 (0.1%)	6 (0.1%)	10 330	57 377	0.1 (0.0-0.3)	0.1 (0.0-0.2)	1.07 (0.12-9.62)	1.42 (0.14-14.78)
Prostate	854 (80.9%)	4 071 (80.4%)	25 (2.9%)	154 (3.8%)	8 027	44 867	3.1 (1.9-4.3)	3.4 (2.9-4.0)	1.26 (0.80-1.97)	1.32 (0.84-2.07)
Renal/Urinary	1 055 (100%)	5 091 (100%)	25 (2.4%)	45 (0.9%)	10 200	57 085	2.5 (1.5-3.4)	0.8 (0.6-1.0)	3.81 (2.22-6.56)	**4.12 (2.35-7.22)**
Nervous system	1 065 (100%)	5 102 (100%)	3 (0.3%)	9 (0.2%)	10 308	57 259	0.3 (0.0-0.6)	0.2 (0.1-0.3)	1.96 (0.50-7.57)	2.28 (0.52-10.03)
Endocrine glands	1 063 (100%)	5 098 (100%)	9 (0.8%)	12 (0.2%)	10 251	57 216	0.9 (0.3-1.5)	0.2 (0.1-0.3)	4.23 (1.72-10.43)	**4.46 (1.70-11.71)**
Penis/Testis	863 (81.1%)	4 107 (80.5%)	(0.0%)	2 (0.0%)	8 170	45 669	0.0 (0.0-0.0)	0.0 (0.0-0.1)	N/A	N/A
Vulva/Vagina	201 (18.8%)	995 (19.5%)	5 (2.5%)	(0.0%)	2 095	11 631	2.4 (0.3-4.5)	0.0 (0.0-0.0)	N/A	N/A
Cervix/Uterus/Ovaries	188 (17.8%)	936 (18.5%)	5 (2.7%)	20 (2.1%)	1 970	10 790	2.5 (0.3-4.8)	1.9 (1.0-2.7)	1.33 (0.48-3.69)	1.26 (0.41-3.86)
Melanoma	1 063 (100%)	5 093 (100%)	12 (1.1%)	30 (0.6%)	10 253	57 037	1.2 (0.5-1.8)	0.5 (0.3-0.7)	2.49 (1.22-5.08)	**2.30 (1.11-4.78)**
Skeleton	1 067 (100%)	5 110 (100%)	(0.0%)	(0.0%)	10 336	57 408	0.0 (0.0-0.0)	0.0 (0.0-0.0)	N/A	N/A
NMSC	1 045 (100%)	5 093 (100%)	139 (13.3%)	53 (1.0%)	9 348	57 048	14.9 (12.4-17.3)	0.9 (0.7-1.2)	27.45 (17.49-43.09)	**28.51 (17.90-45.41)**

Table 4. Cancer risk in IgAN patients with ESRD

IgAN: IgA nephropathy
ESRD: End stage renal disease
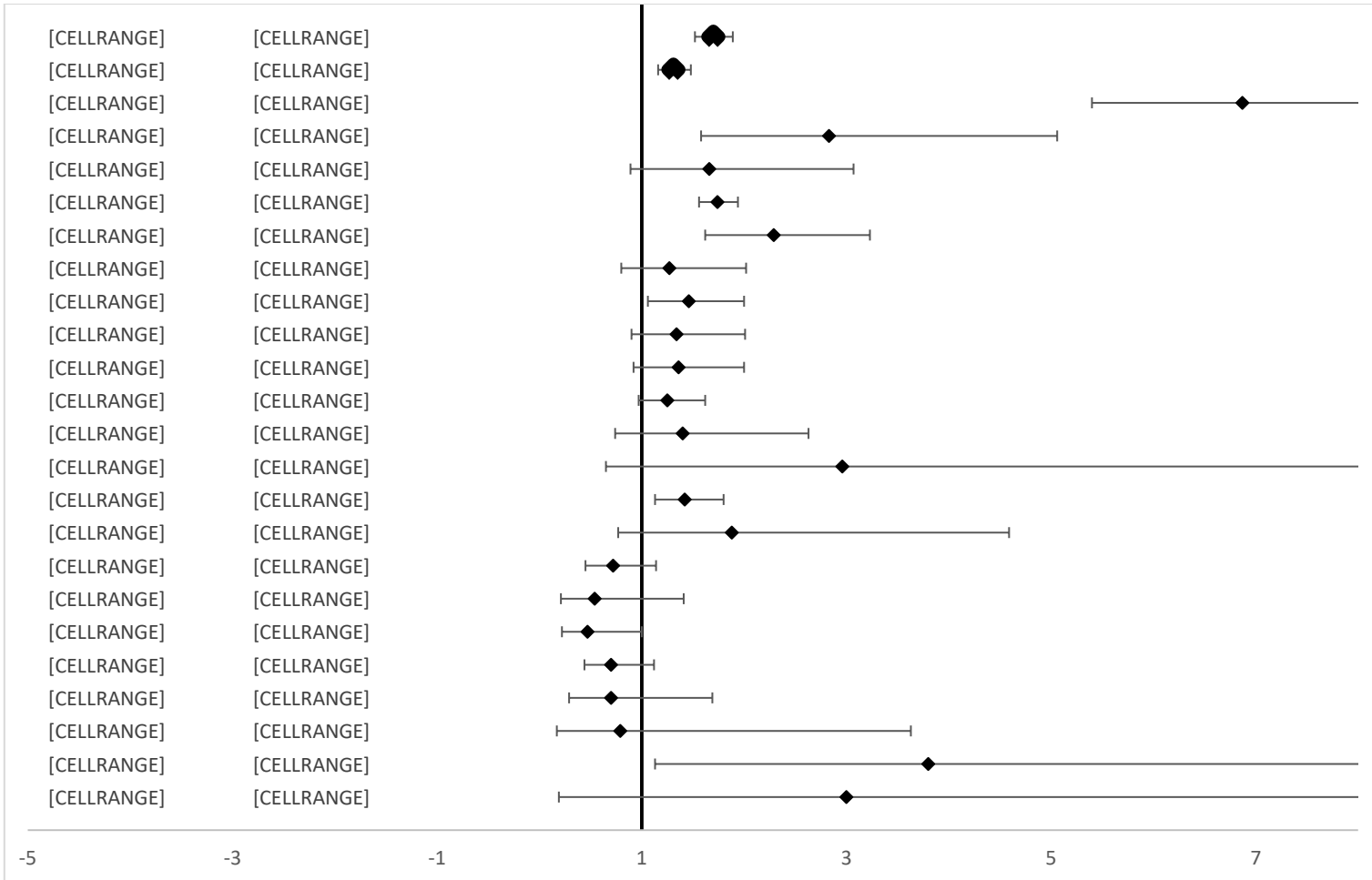CI: Confidence interval
HR: Hazard Ratio
IR: Incidence rate per 1,000 person years
N/A: not able to calculate
NMSC: non-melanoma skin cancer
*Analyses run in strata of cases and 5 (sex, age, calendar-year, and county) matched controls
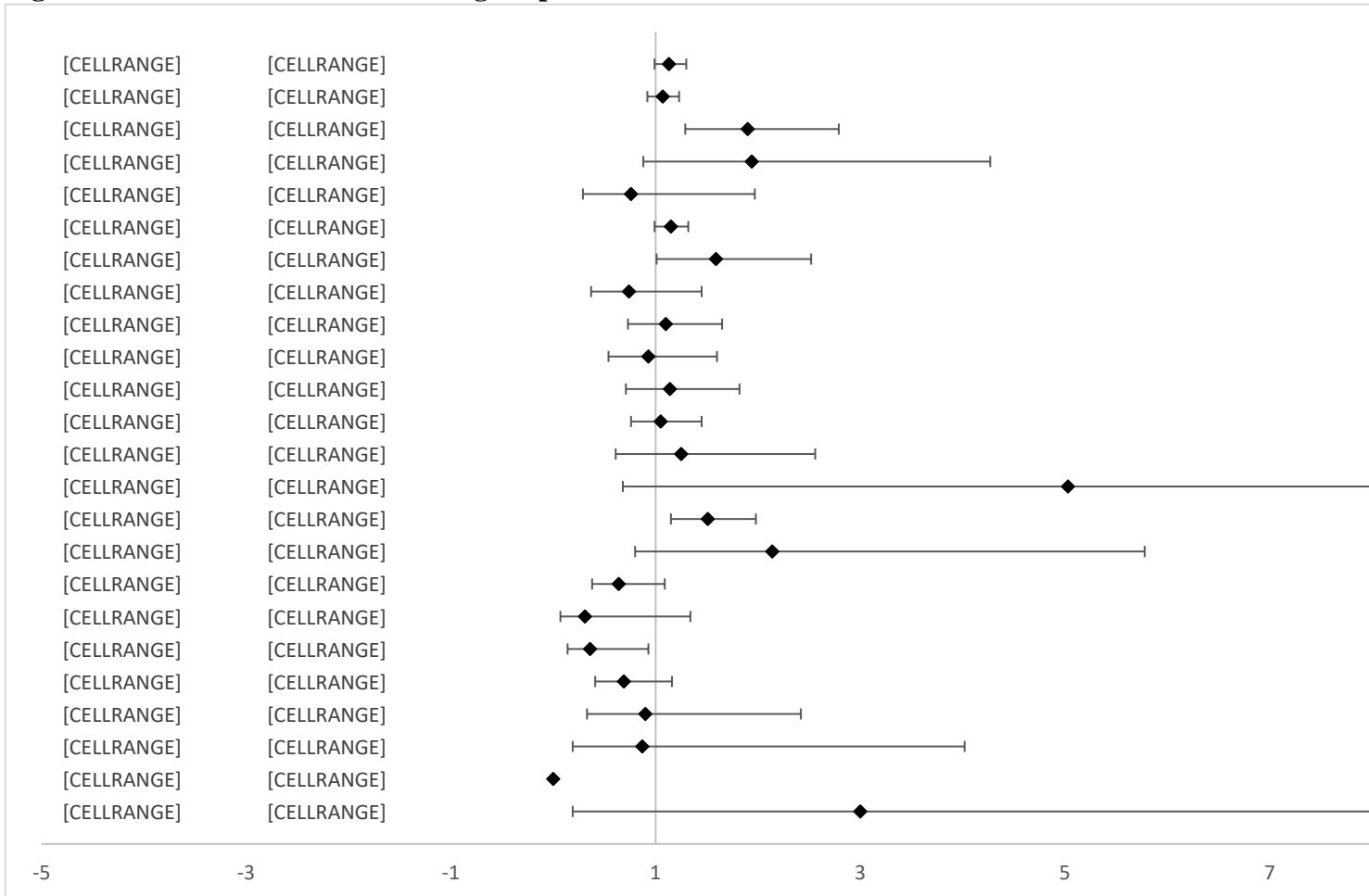additionally adjusted for smoking and educational attainment

Figure 1: Cancer risk in patients with IgAN

IgAN: IgA nephropathy
HR: Hazard Ratio
CI: Confidence interval
NMSC: non-melanoma skin cancer
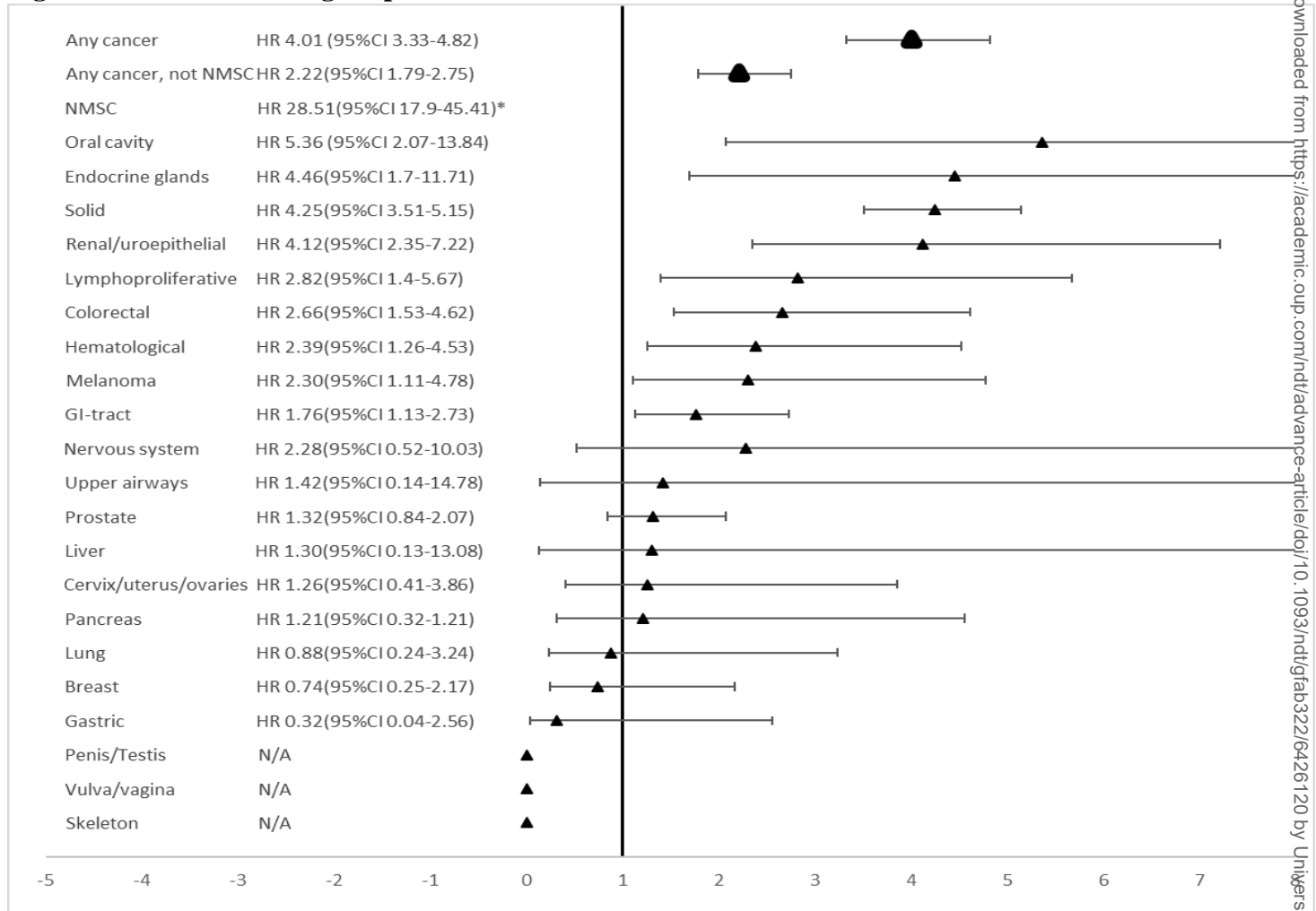GI-tract: gastrointestinal tract

Figure 2: Cancer risk in non-ESRD IgAN patients

IgAN: IgA nephropathy
ESRD: End stage renal disease
HR: Hazard Ratio
CI: Confidence interval
NMSC: non-melanoma skin cancer
GI-tract: gastrointestinal tract
N/A: not able to calculate

Figure 3: Cancer risk in IgAN patients with ESRD

Any cancer	HR 4.01 (95%CI 3.33-4.82)
Any cancer, not NMSC	HR 2.22(95%CI 1.79-2.75)
NMSC	HR 28.51(95%CI 17.9-45.41)*
Oral cavity	HR 5.36 (95%CI 2.07-13.84)
Endocrine glands	HR 4.46(95%CI 1.7-11.71)
Solid	HR 4.25(95%CI 3.51-5.15)
Renal/uroepithelial	HR 4.12(95%CI 2.35-7.22)
Lymphoproliferative	HR 2.82(95%CI 1.4-5.67)
Colorectal	HR 2.66(95%CI 1.53-4.62)
Hematological	HR 2.39(95%CI 1.26-4.53)
Melanoma	HR 2.30(95%CI 1.11-4.78)
GI-tract	HR 1.76(95%CI 1.13-2.73)
Nervous system	HR 2.28(95%CI 0.52-10.03)
Upper airways	HR 1.42(95%CI 0.14-14.78)
Prostate	HR 1.32(95%CI 0.84-2.07)
Liver	HR 1.30(95%CI 0.13-13.08)
Cervix/uterus/ovaries	HR 1.26(95%CI 0.41-3.86)
Pancreas	HR 1.21(95%CI 0.32-1.21)
Lung	HR 0.88(95%CI 0.24-3.24)
Breast	HR 0.74(95%CI 0.25-2.17)
Gastric	HR 0.32(95%CI 0.04-2.56)
Penis/Testis	N/A
Vulva/vagina	N/A
Skeleton	N/A

IgAN: IgA nephropathy
ESRD: End stage renal disease
HR: Hazard Ratio
CI: Confidence interval
NMSC: non-melanoma skin cancer
GI-tract: gastrointestinal tract
N/A: not able to calculate
*Not in graph

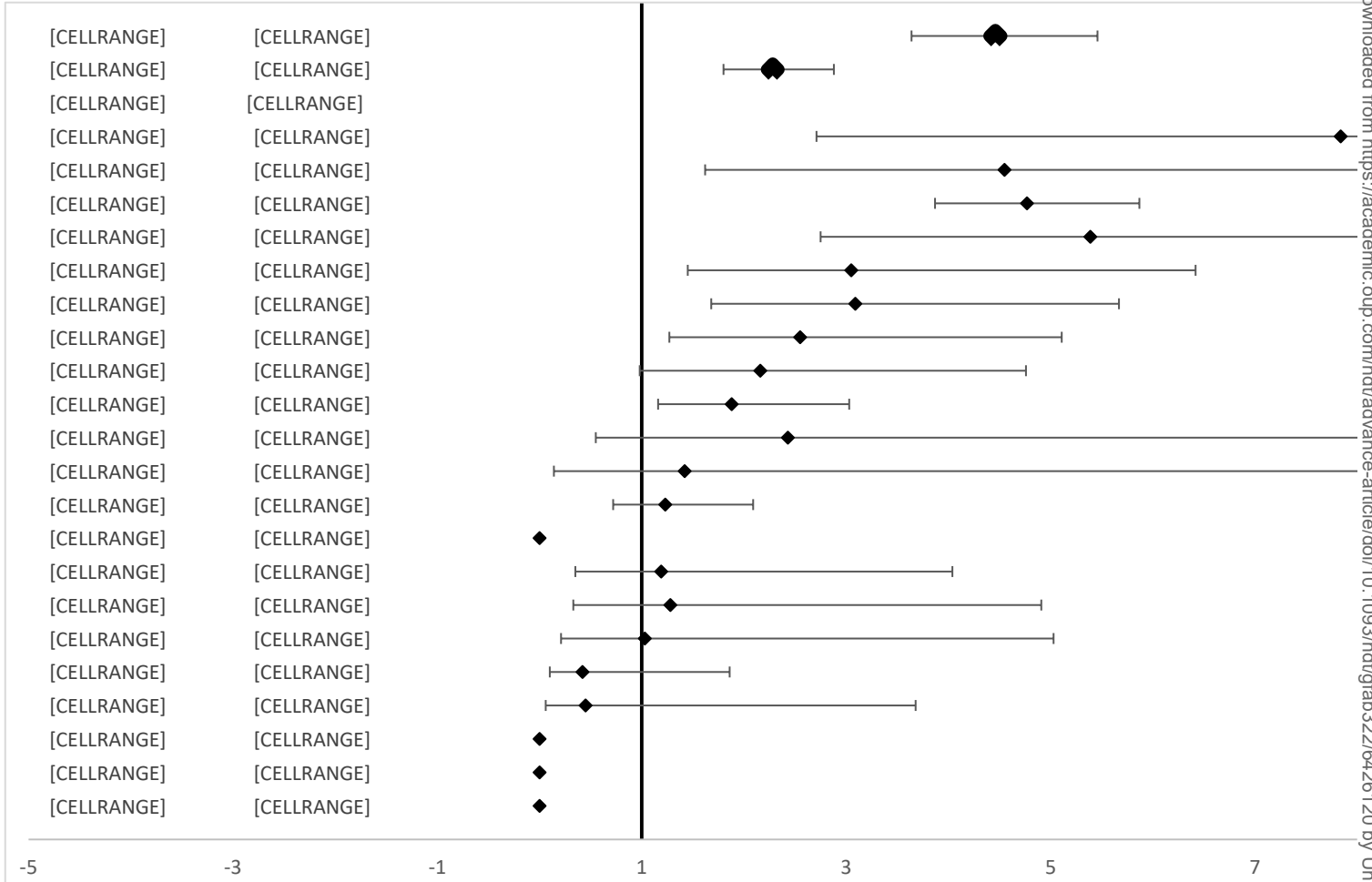**Figure 4: Cancer risk in IgAN patients with kidney transplant**

IgAN: IgA nephropathy
HR: Hazard Ratio
CI: Confidence interval
NMSC: non-melanoma skin cancer
GI-tract: gastrointestinal tract
N/A: not able to calculate
*Not in graph