Association of Albuminuria and Cancer Incidence

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ABSTRACT

Albuminuria, which is associated with noncardiovascular mortality, might be a result of altered vascular permeability caused by cytokines and other tumor cell products. The aim of this population-based, longitudinal study was to examine whether elevated albumin-to-creatinine ratio (ACR) is associated with cancer incidence. A total of 5425 participants without diabetes or previous cancer in the Tromsø Study were followed; 590 had a first diagnosis of cancer during 10.3 yr of follow-up. The ACR at baseline significantly correlated with the incidence of cancer, even after adjustment for age, gender, body mass index, physical activity, and smoking (P < 0.001). Participants with ACR in the highest quintile were 8.3- and 2.4-fold more likely to receive a diagnosis of bladder cancer and lung cancer, respectively, compared with those with ACR in the lowest quintile after similar adjustments. It is concluded that albuminuria is associated with cancer incidence in individuals without a history of diabetes, macroalbuminuria, or previous cancer and that it might confer risks of varying magnitude for different types of cancer.


Microalbuminuria was originally regarded as an early sign of nephropathy in patients with diabetes, but numerous studies have found that microalbuminuria also predicts all-cause mortality even in individuals without diabetes.1,2 Independent of diabetes, albuminuria has been related to atherosclerosis,3–7 to an increased risk for cardiovascular diseases, and to mortality caused by cardiovascular disease.8–11 It is therefore thought to reflect not only dysfunction of the glomeruli but also generalized vascular dysfunction.

Albuminuria has also been observed in individuals with different kinds of cancers, such as lung, breast, renal cell, colon/rectal, and non-Hodgkin’s lymphoma.12–23 Some studies have indicated that the degree of albuminuria reflects the severity of the disease, with higher levels in patients with metastatic disease and a large tumor burden,12,15,16; therefore, albuminuria has been suggested to be a nonspecific marker of malignancy reflecting a microvascular response (and altered glomerular permeability) to tumor cell products such as cytokines.12,24

In a recent longitudinal, population-based study of community-dwelling elderly individuals, markers of chronic kidney dysfunction were found to predict noncardiovascular mortality (e.g., cancer mortality).25 In another population-based study, urinary albumin excretion also predicted mortality caused by noncardiovascular disease, which could mostly be attributed to malignant neoplasms.9 Although there may be several explanations for these findings, we hypothesized that albuminuria may be related to cancer incidence. Albumin-to-creatinine ratios (ACR) were measured in 5425 individuals who did not have diabetes and were then followed for 10.3 yr with regard to a first diagnosis of cancer. To the best of our knowledge, no previous study has examined this research topic.

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RESULTS

The 5425 individuals who did not have diabetes and were followed with regard to cancer incidence (2545 women, 2880 men) all had participated in the fourth Tromsø survey in 1994/1995, in which the baseline measurements, including measurements of ACR, had been performed. At that time, they were 25 to 84 yr of age and had no previous diagnosis of cancer.

The baseline characteristics of the study group according to ACR quintiles are presented in Table 1. Significant differences between groups were found with respect to age, gender, systolic BP, diastolic BP, ever use of medication for hypertension, glycated hemoglobin, serum creatinine, current use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, prevalent cardiovascular disease, smoking habits, fibrinogen, and white blood cell (WBC) count.

During the 49,120 person-years of follow-up, 590 individuals had a first-ever diagnosis of cancer. Among the individuals who had no cancer diagnosis during follow-up, 397 died and 45 emigrated. The mean follow-up time was 9.1 yr (range 47 d to 10.3 yr).

Figure 1 and Table 2 show that the age- and gender-adjusted risk for cancer increased with increasing levels of ACR, at least in the three upper quintiles of the range for ACR. The trend was slightly attenuated after further adjustments for smoking habits (never smokers, previous smokers/<10 cigarettes per day, previous smokers/≥10 cigarettes per day, current smokers/<10 cigarettes per day, current smokers/10 to 19 cigarettes per day, or current smokers/≥20 cigarettes per day), body mass index, and physical inactivity. ACR was also included in an analysis as a continuous variable (ACR logarithmically transformed). For a 1-SD higher value for the log-transformed

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the participants at baseline in 1994 by ACR quintiles^a</th>
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</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Age (yr; mean [SD])</td>
</tr>
<tr>
<td>Male gender (% [n])</td>
</tr>
<tr>
<td>BMI (kg/m^2; mean [SD])</td>
</tr>
<tr>
<td>Systolic BP (mmHg; mean [SD])</td>
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<tr>
<td>Diastolic BP (mmHg; mean [SD])</td>
</tr>
<tr>
<td>Ever use of medication for hypertension (% [n])</td>
</tr>
<tr>
<td>Glycated hemoglobin (%; mean [SD])</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L; mean [SD])</td>
</tr>
<tr>
<td>Use of ACEI/ARB (% [n])</td>
</tr>
<tr>
<td>Cardiovascular diseases (% [n])</td>
</tr>
<tr>
<td>Physically inactive (% [n])</td>
</tr>
<tr>
<td>Alcohol abstainer (% [n])</td>
</tr>
<tr>
<td>Smoking habits (% [n])</td>
</tr>
<tr>
<td>never smokers</td>
</tr>
<tr>
<td>ex-smokers, &lt;10 cigarettes/d</td>
</tr>
<tr>
<td>ex-smokers, ≥10 cigarettes/d</td>
</tr>
<tr>
<td>current smokers, &lt;10 cigarettes/d</td>
</tr>
<tr>
<td>current smokers, 10 to 19 cigarettes/d</td>
</tr>
<tr>
<td>current smokers, ≥20 cigarettes/d</td>
</tr>
<tr>
<td>Fibrinogen (g/L; mean [SD])</td>
</tr>
<tr>
<td>WBC count (× 10^9/L; mean [SD])</td>
</tr>
</tbody>
</table>

^aMeans and percentages are adjusted for age and gender. Values of age are adjusted for gender, percentages for gender are adjusted for age. ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.
ACR, the age- and gender-adjusted relative risk (RR) for cancer was 1.19 ($P < 0.001$) and was 1.16 ($P < 0.001$) after further adjustments. These results were essentially the same with adjustment for pack-years as an indicator of smoking habits.

The risk for cancer in individuals with microalbuminuria (ACR 2.5 to 25 mg/mmol; $n = 449$) was examined specifically. In these individuals, the risk relative to individuals without microalbuminuria was 1.38 (95% confidence interval 1.08 to 1.77) after multiple adjustments.

Specific analyses were performed with further adjustments for estimated GFR, systolic BP, ever use of medication for hypertension, or current use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers; however, the relationship was very similar after these adjustments. For a 1-SD higher value for the log-transformed ACR, the RR for cancer was 1.17 ($P < 0.001$).

To ensure that severe illness or undiagnosed cancer at the start of follow-up did not influence our results, we performed separate analyses among the individuals who were cancer-free and alive 4 yr after the baseline examination. This analysis included 5058 individuals, 357 of whom received a diagnosis of cancer during follow-up. Table 3 displays the results; it also shows the RR for cancer within the first 4 yr after the baseline measurements. Evidently, exclusion of the first 4 yr of follow-up did not have any major impact on the relationship between ACR and total cancer incidence. Figure 1 also suggests that the relationship was present throughout the follow-up period.

Albuminuria is a result of endothelial dysfunction in the urinary system, and increased ACR may therefore be specifically related to cancers of the kidney and the bladder; however, even after the exclusion of kidney and bladder cancer, the RR for cancer comparing the highest and the lowest quintiles was 1.41 (95% confidence interval 1.07 to 1.84; $P = 0.004$ for trend) after multiple adjustments.

Table 4 displays the distribution of the most frequent cancers ($\geq 35$ cases) that occurred during follow-up (colon/rectal, breast, lung, prostate, and bladder) and the RR for cancer of these sites in relation to ACR level. In addition, results for renal cancer are included. ACR was significantly associated with bladder and lung cancer; tended to be associated with renal cancer.

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**Figure 1.** Estimated age- and gender-adjusted proportion of the cohort without a diagnosis of cancer as a function of follow-up time.

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**Table 2.** RR for cancer at all sites in relation to ACR quintiles$^{a,b}$

<table>
<thead>
<tr>
<th>ACR Quintile (mg/mmol)</th>
<th>N</th>
<th>No. of Cases</th>
<th>RR (95% CI)$^a$</th>
<th>RR (95% CI)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00 to 0.34</td>
<td>1085</td>
<td>92</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>0.34 to 0.47</td>
<td>1085</td>
<td>92</td>
<td>0.99 (0.74 to 1.32)</td>
<td>0.95 (0.71 to 1.27)</td>
</tr>
<tr>
<td>0.47 to 0.66</td>
<td>1085</td>
<td>115</td>
<td>1.24 (0.94 to 1.63)</td>
<td>1.22 (0.91 to 1.58)</td>
</tr>
<tr>
<td>0.66 to 1.11</td>
<td>1085</td>
<td>119</td>
<td>1.24 (0.94 to 1.63)</td>
<td>1.19 (0.90 to 1.56)</td>
</tr>
<tr>
<td>1.11 to 24.82</td>
<td>1085</td>
<td>172</td>
<td>1.68 (1.30 to 2.17)</td>
<td>1.57 (1.21 to 2.03)</td>
</tr>
</tbody>
</table>

$^a$Adjusted for age and gender.

$^b$Adjusted for age, gender, body mass index (BMI), inactivity, and smoking habits (never smokers, ex-smokers/$<10$ cigarettes/d, ex-smokers/$\geq 10$ cigarettes/d, current smokers/$<10$ cigarettes/d, current smokers/10 to 19 cigarettes/d, current smokers/$\geq 20$ cigarettes/d).

**Table 3.** RR for cancer at all sites in relation to ACR at different periods of follow-up$^a$

<table>
<thead>
<tr>
<th>ACR Quintile (mg/mmol)</th>
<th>Follow-up 0 to 4 yr</th>
<th>Start by Year 4 and throughout Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases RR (95% CI)$^a$</td>
<td>No. of Cases RR (95% CI)$^a$</td>
</tr>
<tr>
<td>0.00 to 0.34</td>
<td>37 1.0 (0.5 to 1.3)</td>
<td>55 1.0 (0.7 to 1.5)</td>
</tr>
<tr>
<td>0.34 to 0.47</td>
<td>33 1.0 (0.6 to 1.6)</td>
<td>59 1.4 (0.9 to 1.9)</td>
</tr>
<tr>
<td>0.47 to 0.66</td>
<td>41 1.0 (0.6 to 1.6)</td>
<td>74 1.2 (0.9 to 1.8)</td>
</tr>
<tr>
<td>0.66 to 1.11</td>
<td>48 1.1 (0.7 to 1.7)</td>
<td>71 1.2 (0.9 to 1.8)</td>
</tr>
<tr>
<td>1.11 to 24.82</td>
<td>74 1.5 (1.0 to 2.3)</td>
<td>98 1.6 (1.2 to 2.2)</td>
</tr>
</tbody>
</table>

$^a$Adjusted for age, gender, BMI, inactivity, and smoking habits (never smokers, ex-smokers/$<10$ cigarettes/d, ex-smokers/$\geq 10$ cigarettes/d, current smokers/$<10$ cigarettes/d, current smokers/10 to 19 cigarettes/d, current smokers/$\geq 20$ cigarettes/d).
cancer; but showed no relationship with colon/rectal, breast, or prostate cancer.

Fibrinogen and WBC count were measured in addition to ACR in 5184 individuals. ACR (log-transformed) correlated significantly ($P < 0.001$) with these markers of inflammation ($r = 0.14$ and $r = 0.06$, respectively). Fibrinogen and WBC count correlated with each other ($r = 0.21$, $P < 0.001$). The relationship between ACR and cancer risk was very similar with and without the inclusion of fibrinogen and WBC count in the model. For a 1-SD higher value for the log-transformed ACR, the RR for cancer was 1.16 ($P < 0.001$), after adjustments for age, gender, body mass index, physical inactivity, and smoking habits, and 1.15 ($P < 0.001$), after further adjustments for fibrinogen and WBC count. In the 5000 individuals with measurements of glycated hemoglobin available, the relationship between ACR and cancer risk was similar after adjustment for glycated hemoglobin (data not shown). Exclusion of 342 individuals with glycated hemoglobin levels $\geq 6.0\%$ hardly influenced the results (RR 1.17 and 1.18 for each 1-SD increase in the log-transformed ACR, before and after the exclusion).

**DISCUSSION**

In this population-based study of individuals without diabetes and macroalbuminuria, increasing levels of ACR were associated with an increased incidence of cancer, especially bladder and renal cancer. To the best of our knowledge, no previous study has examined the incidence of cancer in relation to ACR levels in individuals without diabetes of a general population; however, the associations between ACR and cancer risk seem to be in line with the results of studies of individuals on dialysis, who have higher cancer rates than the general population.26,27 Moreover, cystatin C, a marker of chronic kidney dysfunction, has been related to noncardiovascular mortality, including cancer mortality, in community-dwelling elderly individuals. Individuals with prevalent cancer were not excluded, however, in these analyses.25 Two other population-based studies, one of the Norfolk population (United Kingdom)28 and one of the inhabitants of Groningen (Netherlands),9 examined albuminuria as a risk factor for noncardiovascular mortality. The results were conflicting with regard to mortality. The study from Groningen found that death as a result of malignant neoplasms could explain most of the increased noncardiovascular mortality risk, whereas the Norfolk study found no association with cancer death. In both studies, only one single spot-urine sample was analyzed, which leads to larger random errors in the assessment of albuminuria.29 Moreover, the Norfolk study measured albumin concentrations from frozen urine samples, which underestimates the real values and therefore may limit the ability to predict mortality.30

At present, we have no complete explanation for why higher levels of ACR are associated with the risk for cancer. ACR, which is related to renal and endothelial dysfunction, is fre-
quently increased with inflammation,\textsuperscript{31,32} and inflammation has been hypothesized to increase the risk for cancer.\textsuperscript{33} Inflammatory markers, such as WBC count and fibrinogen, have been found to be associated with an increased risk for cancer mortality in individuals without cancer at baseline.\textsuperscript{34–36} Because inflammatory markers were positively related to the ACR level of our participants (Table 1), inflammation might have been a potential explanation for the association with cancer incidence; however, ACR predicted cancer incidence independent of WBC count and fibrinogen.

Albuminuria has been observed in individuals after the detection of various types of cancers.\textsuperscript{12–23} The underlying mechanisms are not known, but albuminuria has been regarded as a paraneoplastic phenomenon (clinical syndromes involving nonmetastatic systemic effects that accompany malignant disease) and a reflection of an inflammatory process. Theoretically, increased glomerular permeability and, thus, albuminuria could be linked to the presence of neoplastic cells through elevated levels of cytokins. A study of patients with non-Hodgkin’s lymphoma showed that urinary albumin excretion was strongly associated with proinflammatory cytokines and suggested that lymphoma cells secrete cytokines that modulate renal leakage of albumin.\textsuperscript{14} In animal models, TNF-\(\alpha\), a cytokine involved in systemic inflammation, has been shown to increase glomerular albumin permeability.\textsuperscript{37} In patients with inflammatory bowel disease, TNF-\(\alpha\) seems to be important in the pathogenesis of microalbuminuria, possibly through TNF-induced damage to the glomerular basement membrane.\textsuperscript{38}

Conversely, albuminuria could also be mediated through decreased tubular reabsorption of filtered albumin.\textsuperscript{39} Indeed, TGF-\(\beta\) may inhibit the megalin-cubilin-mediated endocytosis of albumin in tubular cells \textit{in vitro}.\textsuperscript{40} There is a need for other studies to examine the relationship between ACR and cancer incidence, and if the results are reproduced, then studies examining potential underlying mechanisms are warranted.

In our study, the strength of the associations between ACR and cancer risk persisted largely unchanged when the analysis was restricted to cancers that appeared \(\geq 4\) yr after the baseline examination. This observation reduces the likelihood that the relationship between ACR and cancer incidence was mainly due to early, undiagnosed disease; however, we still cannot totally rule out the possibility that the ACR levels may have been influenced by preclinical disease, especially in case of cancers with a long latency period (\(\geq 4\) yr).

This study indicated that ACR predicts cancer at specific sites. There was a statistically significant relationship with bladder and lung cancer but no relationship with prostate cancer. Smoking was clearly a possible confounder, because it is a widely known predictor of the same cancer sites as those predicted by ACR and is related to ACR as well. Nevertheless, ACR was associated with bladder and lung cancer independent of smoking.

Several studies found that diabetes is associated with a variety of cancers, and in a recent study showing that diabetes predicted cancer mortality, the authors suggested that insulin resistance and hyperinsulinemia may play a role in the pathogenesis of cancer.\textsuperscript{41} Because ACR is associated with diabetes, this could provide a possible link between ACR and cancer. In our study, however, we excluded individuals with diabetes, yet many individuals with type 2 diabetes are not aware that they have the disease. It is therefore reassuring that adjustments for glycated hemoglobin or the exclusion of individuals with glycated hemoglobin \(\geq 6.0\)% (and thus possible cases of diabetes) did not influence our findings.

This study has several strengths. It is a longitudinal, population-based study comprising a large group of individuals with a high attendance rate. Urine samples from the first morning urine from three consecutive days were used to assess albuminuria. A strict definition of albuminuria was used, in that urine samples from all patients were cultured, and patients with bacteriuria were excluded from the analysis. A major limitation of this study is the small number of site-specific cancer cases, and to confirm or refute our results, studies with more statistical power are warranted.

The number of cases in our study was approximately 15% lower than expected on the basis of the national data; however, because individuals with diabetes and macroalbuminuria were excluded and because severely ill individuals are usually underrepresented in population studies, a lower cancer incidence was not unexpected. Although the attendance rate in our study was high (76% of the eligible population), selection bias may have been present; however, if this selection bias should invalidate our findings, then the incidence of cancer would have to be very strongly associated with lower levels of ACR among the nonparticipants. We believe that this is unlikely and that it is more plausible that nonparticipation may have weakened the true relationship between ACR and cancer incidence. Information about cancer incidence was collected in November 2005. It is thus possible that a few cancer cases diagnosed in 2004 had not yet been recorded in the registry, but the likelihood of delayed notification of cancer is regarded to be unrelated to the exposure variable considered.

We conclude that there is a relationship between increasing ACR levels and cancer incidence in individuals without diabetes or macroalbuminuria. The relationship seems to be site specific, but larger samples are needed to examine this topic further. Moreover, studies examining potential underlying mechanisms are required.

**CONCISE METHODS**

The Tromsø Study is a population-based, longitudinal study with repeated health surveys of inhabitants in the municipality of Tromsø, Norway. Originally a cardiovascular study, it now focuses on several chronic and lifestyle-related conditions such as atherosclerosis and diabetes. The regional ethical committee approved the study, and the participants have given informed consent. At the fourth survey in 1994/1995, all inhabitants aged 55 to 74 yr and 5 to 10% random samples of the other 5-yr birth cohorts older than 24 yr were invited to participate in the survey. In the age groups 25 to 54, 55 to 74, and 75 to 84 yr, 1751, 7158, and 148 individuals were eligible for measurement...
of albuminuria and 1205, 5617, and 80, respectively, participated (76% of the eligible population).

Among the 6902 individuals who attended the examination, 110 either withdrew their data or had missing measurements of the ACR. We excluded 239 individuals who reported diabetes and/or use of medication for diabetes, 851 with bacteriuria or hematuria on any day when urine samples were collected or macroalbuminuria (ACR > 25 mg/mmol), and 277 who had a diagnosis of cancer before this survey took place. Thus, 5425 individuals were included in these analyses.

Participants were asked which medication they had used during the past week. Information about smoking habits (never smokers; previous smokers; current smokers; and, for previous and current smokers, number of cigarettes smoked per day), drinking habits (alcohol users versus abstainers), prevalent diabetes, cardiovascular disease (angina pectoris, previous myocardial infarction, stroke), treatment for hypertension, and physical activity was collected from self-administered questionnaires. We categorized the individuals into six groups according to smoking habits: Never smokers, previous smokers/<10 cigarettes per day, previous smokers/≥10 cigarettes per day, current smokers/<10 cigarettes per day, current smokers/10 to 19 cigarettes per day, or current smokers/≥20 cigarettes per day.

Urine samples from the first morning urine from three consecutive days were used to assess microalbuminuria. Albumin and creatinine were measured by turbidimetry on a Cobas Mira S with kits from ABX Diagnostics (Parc Euromedecine, Montpellier, France). The ACR (mg albumin/mmol creatinine) was computed, and the mean of the three ratios was used to assess microalbuminuria. Albumin and creatinine were measured by turbidimetry on a Cobas Mira S with kits from ABX Diagnostics (Parc Euromedecine, Montpellier, France). The ACR (mg albumin/mmol creatinine) was computed, and the mean of the three ratios was used to assess microalbuminuria.

We estimated the RR for cancer among individuals at different ACR levels by use of Cox regression analysis. When ACR was included in an analysis as a continuous variable, the value was logarithmically transformed [log (ACR + 0.1)]. Adjustments were done for age, gender, body mass index, smoking, and physical inactivity. Additional adjustments were done for fibrinogen and WBC count in a separate analysis, for glycated hemoglobin in another, and for other relevant factors in a third.

The Cox analysis also generated curves, adjusted for age and gender and taking censoring into account, describing the proportion of the cohort that had not received a diagnosis of cancer as a function of follow-up time. Two-sided P < 0.05 was considered statistically significant. The data were analyzed using SPSS 14.0 for Windows (SPSS, Chicago, IL).

ACKNOWLEDGMENTS

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DISCLOSURES

None.

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