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Association between proteinuria and incident colorectal cancer: analysis of a nationwide population-based database

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ABSTRACT

Objectives This study aimed to assess whether adults with proteinuria were at a higher risk of incident colorectal cancer (CRC) than those without proteinuria using a large-scale population-based database.

Design A retrospective observational study.

Setting The JMDC Claims Database, an administrative health claims database, was used. Data were collected between 2005 and 2020.

Participants We selected records of participants (n=3 543 705) who underwent health check-ups, including physical examinations, blood tests and urine dipstick tests. We excluded participants who were aged <20 years (n=25 577), had a history of CRC, colorectal disease, renal disease and renal replacement therapy (n=114 888), or had missing data on medications (n=170 145), cigarette smoking (n=14 835), alcohol consumption (n=366 414) or physical activity (n=106 550). Finally, we analysed 2 745 296 participants.

Main outcome measures The primary outcome was CRC at any stage.

Results Participants were categorised as having no proteinuria (n=2 435 872), trace proteinuria (n=231 153) or positive proteinuria (n=78 271). Over a mean follow-up period of 1189±914 days, 10 615 CRC diagnoses were recorded. The incidence of CRC (95% CI) was lowest in participants without proteinuria (11.7; 95% CI, 11.5 to 11.9 per 10 000 person-years), followed by trace proteinuria (12.5; 95% CI, 11.7 to 13.3 per 10 000 person-years) and positive proteinuria (16.1; 95% CI, 14.6 to 17.7 per 10 000 person-years). After multivariable adjustment, compared with no proteinuria, HRs for incident CRC were 1.20 (95% CI, 1.12 to 1.29) and 1.23 (95% CI, 1.11 to 1.36) for trace and positive proteinuria, respectively. The association between proteinuria and incident CRC existed in participants after multiple imputations for missing data, with a follow-up period of ≥365 days, regardless of age, sex, obesity, hypertension, diabetes mellitus and estimated glomerular filtration rate.

Conclusions Trace and positive proteinuria were associated with a greater risk of incident CRC. Assessment of proteinuria could help identify individuals at an increased risk of CRC.

Strengths and limitations of this study

- ► The strengths of our study include the use of a large-scale population-based database.
- ► We conducted a semiquantitative assessment of proteinuria using the urine dipstick test.
- ► We identified colorectal cancer using International Classification of Diseases, 10th Revision codes, and recorded diagnoses of the administrative database are generally considered less well validated.

INTRODUCTION

Proteinuria is a major indicator of chronic kidney disease (CKD) and is reportedly associated with incident cardiovascular disease.[1–3] Furthermore, several epidemiological studies have shown that proteinuria is associated with an elevated incidence of cancer. Considering the presence of shared pathological mechanisms between proteinuria and specific cancers, such as common risk factors (obesity, hypertension and diabetes mellitus), chronic inflammation and oxidative stress, the possible links among proteinuria, CKD and cancer could be pathologically plausible. Although previous cohort studies reported the clinical association between CKD (defined using estimated glomerular filtration rate (eGFR)) and incident cancer, the results of these studies lacked consistency.[4–6] In the subgroup of older men, CKD was associated with a higher risk for incident lung and urinary tract cancers.[4] Similarly, CKD was reported a higher renal and urothelial cancer risk.[5] On the other hand, another cohort reported that CKD with diabetes mellitus was not related to incident overall cancer.[6] Therefore, clinical evidence on the association between CKD and the risk of developing cancer is conflicting and controversial.[4–6] Colorectal cancer (CRC) is one of the most common types of cancer. It is

the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide, with an estimated 1.8 million new cases and 861 000 deaths annually, according to the GLOBOCAN data.[7] In the USA, there are approximately 150 000 newly diagnosed cases of CRC, and around 54 000 Americans die annually due to CRC.[8] In Japan, CRC is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths (https://ganjoho.jp/reg_stat/statistics/stat/summary.html). Considering the high burden of CRC, identifying people at a high risk of this type of cancer is essential from a public health viewpoint. However, no definitive aetiology has been identified for CRC, such as hepatitis B or C virus in liver cancer or human papillomavirus in cervical cancer; therefore, an effective screening method for identifying people at a high risk of CRC is warranted. It would be clinically and epidemiologically important to clarify whether assessing proteinuria in the general population would help identify people at a high risk of developing CRC. In this study, we aimed to evaluate the association between proteinuria and incident CRC using a nationwide population-based database.

METHODS

This database is available for anyone who purchases it from JMDC (https://www.jmdc.co.jp/en/index).

Study population

This retrospective observational study analysed data from the JMDC Claims Database (JMDC, Tokyo, Japan) between January 2005 and April 2020.[9–14] The JMDC has contracts with more than 60 insurers and includes health insurance claims records data of insured individuals who are primarily employees of relatively large companies in Japan. The JMDC Claims Database includes health check-up data on medical history, status of medications, laboratory tests and dipstick urine tests, as well as clinical follow-up data from claims records using the International Classification of Diseases, 10th Revision (ICD-10) coding. For the current analyses, we selected records of participants (n=3 543 705) who underwent health check-ups, including physical examinations, blood tests and urine dipstick test. We excluded participants who were aged <20 years (n=25 577), had a history of CRC, colorectal disease, renal disease and renal replacement therapy (n=114 888), or had missing data on medications for hypertension (n=169 239), diabetes mellitus (n=698), or dyslipidaemia (n=208), cigarette smoking (n=14 835), alcohol consumption (n=366 414) or physical activity (n=106 550) (figure 1).

This study was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because all data in the JMDC Claims Database were anonymised and de-identified. All data were compliant with the International Conference on Harmonisation guidelines.[15]

Urine dipstick test, other measurements and definitions

Urine dipstick protein was rated on a 5-point scale: negative, trace, +, ++, +++, and we categorised the study participants as no proteinuria, trace proteinuria (10–20 mg/dL) or positive proteinuria (≥30 mg/dL, urine dipstick protein ≥ +). Information on cigarette smoking (current

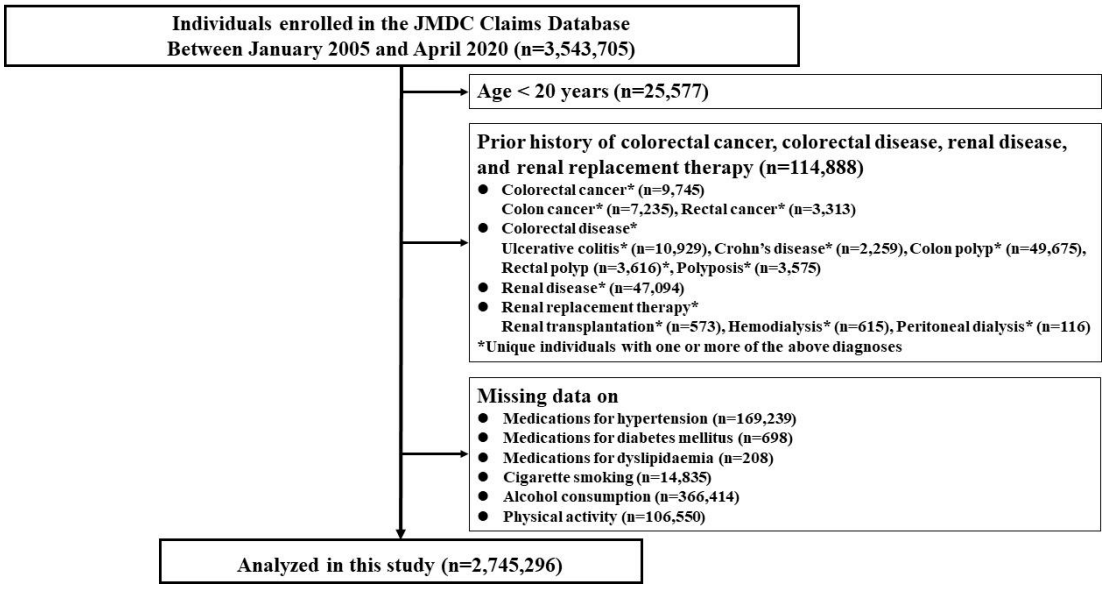

Figure 1 Flowchart. For the current analyses, we selected records of individuals (n=3 543 705) who underwent health check-up including physical examination, blood test and urine dipstick test enrolled in the JMDC Claims Database between January 2005 and April 2020. We excluded individuals <20 years of age (n=25 577), those with history of colorectal cancer (International Classification of Diseases 10th Revision codes C18, C19, C20), colorectal disease, renal disease and renal replacement therapy (n=114 888), and missing data on medications for hypertension (n=169 239), diabetes mellitus (n=698) or dyslipidaemia (n=208), cigarette smoking (n=14 835), alcohol consumption (n=366 414) and physical activity (n=106 550). After all exclusion criteria were applied, data from 2 745 296 individuals were analysed in this study.

or non-current) and alcohol consumption (daily or not daily) was self-reported. Obesity was defined as a body mass index of ≥25 kg/m^2. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg or use of blood pressure-lowering medications. Diabetes mellitus was defined as a fasting glucose level of ≥126 mg/dL or the use of glucose-lowering medications. Dyslipidaemia was defined as a low-density lipoprotein cholesterol level of ≥140 mg/dL, high-density lipoprotein cholesterol level of <40 mg/dL, triglyceride level of ≥150 mg/dL or use of lipid-lowering medications. Physical inactivity was defined as not engaging in 30 min of exercise two or more times a week or not walking for ≥1 hour per day.[16] eGFR was calculated using the following glomerular filtration rate equation designed for the Japanese population: eGFR=194 × (serum creatinine level)$^{-1.094}$ × (age)$^{-0.287}$ (×0.739, if woman).[17]

Outcomes

Data on outcomes were collected from the period between January 2005 and April 2020. The primary outcome was CRC at any stage (ICD-10 codes: C18, C19 and C20). We collected information on the primary outcomes from the claim records included in the JMDC Claims Database. The JMDC Claims Database could track the individual's clinical information (such as diagnosis of CRC) even if the individual sees different medical providers as long as they retain the same insurance coverage.

Statistical analysis

Descriptive statistics are reported as medians (IQRs) for continuous data and numbers (proportions) for categorical data. The statistical significance of the differences across the three groups based on proteinuria was determined using analysis of variance for continuous data and χ^2 tests for categorical data. We conducted Cox regression analyses to identify the association between proteinuria and the subsequent risk of CRC. HRs were calculated in an unadjusted model (Model 1), an age-adjusted and sex-adjusted model (Model 2) and after adjustment for potential confounders, including age, sex, obesity, hypertension, diabetes mellitus, dyslipidaemia, current cigarette smoking, alcohol drinking and physical inactivity (Model 3). We checked the proportional hazard assumption using Schoenfeld residual tests. We conducted seven sensitivity analyses. First, we imputed missing data for covariates using multiple imputation with chained equations and 20 iterations on the assumption of missing at random, as previously described.[14 18 19] HRs and SEs were obtained using Rubin's rules. Second, to minimise the potential effect of latent CRC, we excluded participants whose observational period for CRC was <365 days. Third, we excluded participants who were diagnosed with CRC but had no confirmed treatment history. We defined colon resection (procedure code: K719), colorectal mucosal resection (procedure code: K721), rectal resection (procedure code: K740) and others (procedure codes: K726, K728, K732, and K736) as surgery for CRC, and the use of fluorouracil, irinotecan, oxaliplatin or capecitabine as chemotherapy for CRC. Fourth, we included the use of non-steroidal anti-inflammatory drugs (NSAIDs) in the multivariable model. We defined the use of NSAIDs (ATC-code: M01A) within 90 days from the health check-up date. Fifth, we divided participants into three groups according to predicted urine albumin-to-creatinine ratio (pACR) (<30 mg/g, 30–299 mg/g, ≥300 mg/g) and examined the association of pACR category with incident CRC using multivariable analysis. We calculated pACR using the following conversion equation for urine dipstick protein adjusted for sex, hypertension and diabetes mellitus: pACR=exp (2.0373+0.7270 (if trace) + 1.6775 (if +) + 3.2622 (if ++) + 4.5435 (if >++) + 0.0822 (if woman) + 0.27249 (if diabetes mellitus) + 0.33627 (if hypertension)).[20] Sixth, we performed subgroup analyses stratified by age (≥50 years vs <50 years), sex, obesity, hypertension, diabetes mellitus and eGFR (≥60 mL/min/1.73 m^2 vs <60 mL/min/1.73 m^2). Seventh, we analysed the relationship of proteinuria with the risk for C18, C19 or C20, separately. Statistical significance was set at p<0.05. Statistical analyses were performed using the SPSS software V.25 (IBM Corp) and Stata V.17 (StataCorp).

Patient and public involvement

Study participants were not involved in the design, or conduct, or dissemination plans of this study.

RESULTS

Clinical characteristics

The characteristics of the study participants (n=2 745 296) are shown in table 1. The mean age was 45.2±11.1 years, and 1554705 participants (56.6%) were men. Using the results of the urine dipstick test at the health check-up, participants were categorised as having no proteinuria (n=2 435 872), trace proteinuria (n=231 153) or positive proteinuria (n=78 271). Compared with those without proteinuria, participants with trace or positive proteinuria were more likely to be men. The prevalence of obesity, hypertension, diabetes mellitus, dyslipidaemia and cigarette smoking increased with proteinuria.

Proteinuria and incident CRC

During a mean follow-up period of 1189±914 days, there were 10615 incident CRC diagnoses (C18, C19 and C20 accounted for 8591 (80.9%), 374 (3.5%) and 3021 (28.5%), respectively, and 1249 participants had two or more diagnoses). The incidence (95% CI) of CRC was the lowest in participants without proteinuria (11.7 (95% CI, 11.5 to 11.9) per 10000 person-years), followed by trace proteinuria (12.5 (95% CI, 11.7 to 13.3) per 10000 person-years) and positive proteinuria (16.1 (95% CI, 14.6 to 17.7) per 10000 person-years). In the unadjusted model (Model 1) and age-adjusted and sex-adjusted model (Model 2), trace proteinuria and positive proteinuria were associated with a higher risk of CRC events than no proteinuria. After multivariable adjustment for covariates, the HRs (95%

Table 1 Characteristics of study population

	Proteinuria category			
	No (n=2 435 872)	Trace (n=231 153)	Positive (n=78 271)	P value
Age, years	45 (39–53)	43 (37–51)	45 (38–54)	<0.001
Men, n (%)	1 360 816 (55.9)	142 049 (61.5)	51 840 (66.2)	<0.001
Obesity, n (%)	573 631 (23.5)	64 424 (27.9)	30 803 (39.4)	<0.001
Body mass index, kg/m^2	22.3 (20.2–24.8)	22.6 (20.3–25.3)	23.6 (20.7–27.1)	<0.001
Hypertension, n (%)	441 789 (18.1)	45 311 (19.6)	27 331 (34.9)	<0.001
Systolic blood pressure, mm Hg	118 (107–128)	117 (107–128)	123 (110–136)	<0.001
Diastolic blood pressure, mm Hg	72 (65–81)	72 (65–81)	76 (67–86)	<0.001
Diabetes mellitus, n (%)	96 347 (4.0)	13 930 (6.0)	13 994 (17.9)	<0.001
Glucose, mg/dL	91 (85–98)	93 (86–100)	95 (87–109)	<0.001
Dyslipidaemia, n (%)	951 922 (39.1)	92 976 (40.2)	38 991 (49.8)	<0.001
Low-density lipoprotein cholesterol, mg/dL	118 (98–140)	118 (97–140)	120 (98–143)	<0.001
High-density lipoprotein cholesterol, mg/dL	62 (52–74)	60 (50–72)	57 (48–70)	<0.001
Triglyceride, mg/dL	81 (57–121)	83 (57–125)	96 (63–153)	<0.001
Cigarette smoking, n (%)	599 820 (24.6)	67 439 (29.2)	25 789 (32.9)	<0.001
Alcohol consumption, n (%)	559 086 (23.0)	51 402 (22.2)	18 157 (23.2)	<0.001
Physical inactivity, n (%)	1 277 150 (52.4)	123 729 (53.5)	42 782 (54.7)	<0.001

Data are expressed as number (percentage) or median (IQR). P values were calculated using χ^2 tests for categorical variables and the analysis of variance for continuous variables. We analysed 2 745 296 participants. Participants were divided into three groups according to dipstick urine test at health check-up; no proteinuria, trace proteinuria and positive proteinuria.

CIs) for CRC events were 1.20 (95% CI, 1.12 to 1.29) for trace proteinuria and 1.23 (95% CI, 1.11 to 1.36) for positive proteinuria, respectively, compared with those without proteinuria (figure 2). We checked the proportional hazard assumption by Schoenfeld residual tests, and there was no breach of this hypothesis. The Schoenfeld residual global test also showed no breach of that hypothesis (p=0.66 for trace proteinuria and p=0.07 for positive proteinuria).

Sensitivity analyses

First, we analysed 3 403 240 participants after multiple imputations for missing data. During the follow-up period, 12 943 CRC events occurred. In these participants, trace proteinuria (HR, 1.19; 95% CI, 1.12 to 1.27) and positive proteinuria (HR, 1.25; 95% CI, 1.15 to 1.38) were both associated with an elevated incidence of CRC compared with no proteinuria (online supplemental table 1). Second, we excluded participants whose follow-up period for CRC was <365 days and analysed 2 263 006 participants with a follow-up period of ≥365 days. In these participants, compared with no proteinuria, trace proteinuria (HR, 1.20; 95% CI, 1.11 to 1.28) and positive proteinuria (HR, 1.24; 95% CI, 1.11 to 1.37) were associated with a greater risk of CRC ((online supplemental table 2)). Third, among 10 615 participants with a CRC diagnosis, we confirmed treatment for CRC (surgery or chemotherapy)

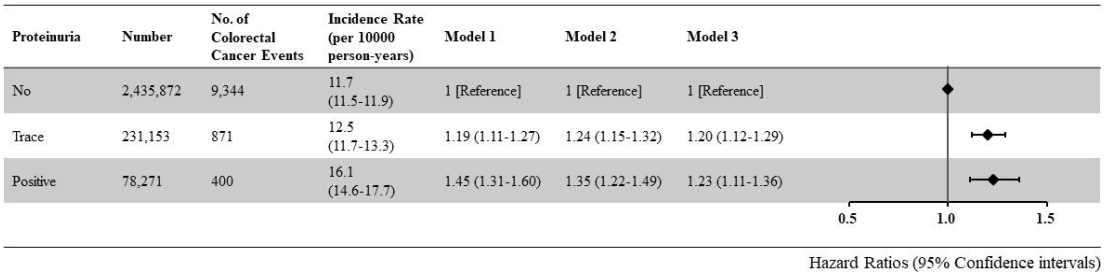

Figure 2 The association between proteinuria and incident colorectal cancer. We analysed 2 745 296 participants. The incidence rate was per 10 000 person-years. Unadjusted and adjusted HRs (95% CIs) associated with the proteinuria group are shown. Model 1 is unadjusted. Model 2 includes adjustment for age and sex. Model 3 includes adjustment for age, sex, obesity, hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, alcohol consumption and physical inactivity.

Table 2 The frequency of events, corresponding incidence rates and HRs for colorectal cancer events after excluding participants diagnosed with colorectal cancer but no treatment history confirmed

	Proteinuria category		
	No (n=2 433 494)	Trace (n=230 931)	Positive (n=78 183)
No. of colorectal cancer events	6966	649	312
Incidence rate (per 10 000 person-years)	8.7 (8.5 to 8.9)	9.3 (8.6 to 10.1)	12.5 (11.2 to 14.0)
Model 1 (unadjusted)	1 (reference)	1.19 (1.10 to 1.29)	1.52 (1.36 to 1.70)
Model 2	1 (reference)	1.24 (1.14 to 1.34)	1.40 (1.25 to 1.57)
Model 3	1 (reference)	1.20 (1.10 to 1.30)	1.26 (1.12 to 1.41)

We excluded 2688 participants diagnosed with colorectal cancer but no treatment history for colorectal cancer confirmed. The incidence rate was per 10 000 person-years. Unadjusted and adjusted HRs (95% CIs) associated with the proteinuria group are shown. Model 1 is unadjusted. Model 2 includes adjustment for age and sex. Model 3 includes adjustment for age, sex, obesity, hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking, alcohol consumption and physical inactivity.

in 7927 participants (74.7%). We excluded 2688 participants who were diagnosed with CRC but not confirmed as undergoing treatment for CRC. Even in this model, compared with no proteinuria, trace proteinuria (HR, 1.20; 95% CI, 1.10 to 1.30) and positive proteinuria (HR, 1.26; 95% CI, 1.12 to 1.41) were associated with a higher incidence of CRC (table 2). Fourth, even after adjustment for the use of NSAIDs, our primary results did not change (online supplemental table 3). Fifth, we investigated the relationship between pACR and incident CRC using multivariable analysis. The risk of CRC increased with pACR (online supplemental table 4). Sixth, the relationship between proteinuria and incident CRC was present in all subgroups (figure 3). Seventh, the association of proteinuria with a greater risk for CRC development was consistent in all CRC subsites separated by C18, C19 or C20 (online supplemental table 5).

DISCUSSION

In this nationwide analysis of a health claims database that had adults who underwent health check-ups, including the dipstick urine test, those with trace and positive proteinuria had a higher risk of incident CRC events than those with no proteinuria, even after adjusting for multiple potential confounders. This association was consistent in all subgroups stratified by age, sex, obesity, hypertension, diabetes mellitus or eGFR.

Several previous studies have examined the relationship between proteinuria and CRC, and the results are conflicting. Jørgensen *et al* studied 5425 participants without diabetes mellitus or previous cancer in the Tromsø study, and showed that an elevated albumin-to-creatinine ratio was not associated with incident CRC.[21] Analysis of the Third National Health and Nutrition Examination Survey, which included 6112 adults aged ≥50 years, demonstrated that urinary albumin-to-creatinine ratio was associated with a higher risk of cancer-related mortality; however, it was not associated with mortality due to CRC.[22] A recent study using the Korean National Health Insurance System data reported that proteinuria was associated with the incidence of CRC (HR, 1.11; 95% CI, 1.07 to 1.15).[23] However, the analysis of the Korean National Health Insurance System data included adults who took medications such as renin-angiotensin system

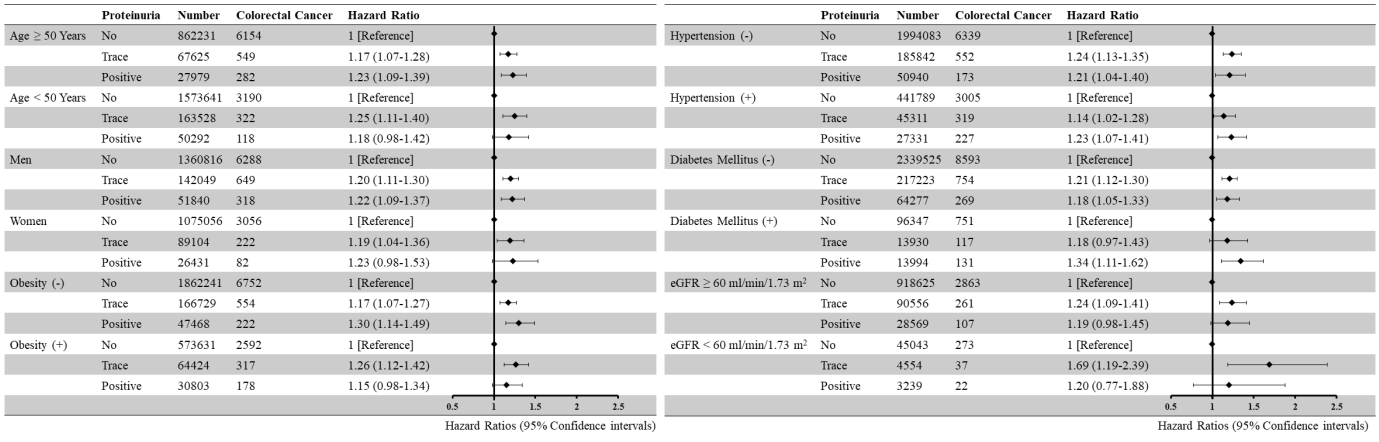

Figure 3 Subgroup analyses. We performed subgroup analyses by age (≥50 years vs <50 years), sex, obesity, hypertension, diabetes mellitus and eGFR (≥60 mL/min/1.73 m^2 vs <60 mL/min/1.73 m^2) in the multivariable model. Adjusted HRs (95% CIs) associated with the proteinuria group and the forest plot were shown. eGFR, estimated glomerular filtration rate.

inhibitors, which could have influenced the results. Further, other potential factors such as colorectal polyps or inflammatory bowel disease were not considered. The current study extends our knowledge by demonstrating that both trace and positive proteinuria might be associated with an elevated CRC risk using a large-scale population-based database. Furthermore, univariate and multivariable analyses revealed a possible dose-dependent relationship between proteinuria and incident CRC. Trace and positive proteinuria were associated with a higher risk of CRC in all subgroups. Interestingly, in a subgroup of participants with eGFR <60 mL/min/1.73 m^2, the HRs for both trace and positive proteinuria did not change. Therefore, eGFR did not affect the relationship between proteinuria and incident CRC, and proteinuria could influence the incidence of CRC independently of renal function. Several factors such as colorectal polyps, inflammatory bowel disease and some renal diseases are known to increase the risk of CRC. For example, membranous nephropathy can coexist with CRC.[24] However, even after excluding participants with a history of these diseases, an association between proteinuria and an elevated risk of CRC remained.

In the current study, proteinuria preceded the development of CRC. However, the precise pathological mechanisms underlying this association remain unclear. Because of the nature of observational studies, our study is insufficient to infer a causal relationship between proteinuria and incident CRC. Several possible explanations, such as chronic inflammation and oxidative stress, could be suggested. However, further investigations are required to clarify the underlying mechanisms for our results. Furthermore, whether efforts to reduce proteinuria, such as the administration of renin-angiotensin system inhibitors, could reduce the future risk of CRC should be examined. Although randomised clinical trials would be the best strategies for this purpose, such trials might not be feasible because of time, costs and ethical concerns. Studies using large-scale epidemiological cohort data or administrative claims databases might be more feasible starting points to establish this evidence.

Our results might have several clinical implications. CRC is a common type of cancer and a major cause of mortality. Therefore, early detection and therapeutic intervention for CRC are essential. From this viewpoint, the assessment of proteinuria in the general population could be helpful in identifying individuals who are at a high risk of CRC. Furthermore, if future investigations could demonstrate a lower incidence of CRC attributable to treatment for proteinuria, population-level efforts for proteinuria detection and control would be more strongly warranted.

The strengths of our study include the use of a large-scale population-based database with health check-up records and clinical outcomes. This study also has several limitations. Although we conducted a semiquantitative assessment using the urine dipstick test in this study, the latest guidelines recommend quantitative assessment for proteinuria using calculation of the random urine protein-to-creatinine ratio, urine albumin-to-creatinine ratio and 24 hours urine collection testing.[25 26] Because we used the random spot urine assessed at a single occasion in this study, we need to acknowledge the possibility of misclassification. We conducted a multivariable Cox regression analysis that included variables such as obesity, hypertension and diabetes mellitus. However, the possibility of unmeasured confounders and residual bias remained. For example, eating red meat can increase the risk of both CRC and proteinuria. However, the JMDC Claims Database does not include information on dietary components. Individuals included in the JMDC Claims Database are primarily employees of relatively large Japanese companies. Therefore, our results might have been subject to selection bias (eg, healthy worker bias). The JMDC Claim Database does not include information on region or socioeconomic status. Further research is necessary to generalise our findings. The sensitivity analysis, which excluded participants with follow-up periods of <365 days, confirmed our main findings. However, the observational period of this study was relatively short for the epidemiological study on cancer, and we were unable to eliminate the possibility of including undetected CRC at baseline, which could have affected the study results. Further studies with longer observational periods are required to validate our results. We identified CRC using ICD-10 codes, and recorded diagnoses of administrative database (including JMDC Claims Database) are generally considered less well-validated. Thus, there remains uncertainty regarding the accuracy of the diagnosis of CRC. However, the validity of the diagnoses of the administrative claims data were reported to be high in Japan. For example, the sensitivity and specificity of cancer diagnoses in the administrative database in Japan were 83.5% and 97.7%, respectively.[27] Further, we confirmed that three-quarters of the participants diagnosed with CRC underwent surgery or chemotherapy for CRC, and the association between proteinuria and incident CRC did not change even after excluding participants who were diagnosed with CRC but had no confirmed history of treatment. Detailed information on clinical assays used for the measurement of proteinuria and laboratory tests are not available because the details of the testing methods used in health check-ups are left up to each institute.

CONCLUSIONS

Trace and positive proteinuria are associated with a greater risk of incident CRC compared with no proteinuria. Assessment of proteinuria using the dipstick urine test could help identify people with an elevated risk of future CRC.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was conducted according to the ethical guidelines of the University of Tokyo (approved by the Ethical Committee of The University of Tokyo: 2018-10862).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement This database is available for anyone who purchases it from JMDC. (https://www.jmdc.co.jp/en/index).

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