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ORIGINAL RESEARCH

Fibrotic Marker Galectin-3 Identifies Males at Risk of Developing Cancer and Heart Failure

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ABSTRACT

BACKGROUND Cancer and heart failure (HF) are the leading causes of death in the Western world. Shared mechanisms such as fibrosis may underlie either disease entity, furthermore it is unknown whether this relationship is sex-specific.

OBJECTIVE We sought to investigate how fibrosis-related biomarker galectin-3 (gal-3) aids in identifying individuals at risk for new-onset cancer and HF, and how this differs between sexes.

METHODS Gal-3 was measured at baseline and at 4-year follow-up in 5,786 patients of the PREVEND (Prevention of Renal and Vascular Endstage Disease) study. The total follow-up period was 11.5 years. An increase of ≥50% in gal-3 levels between measurements was considered relevant. We performed sex-stratified log-rank tests and Cox regression analyses overall and by sex to evaluate the association of gal-3 over time with both new-onset cancer and new-onset HF.

RESULTS Of the 5,786 healthy participants (50% males), 399 (59% males) developed new-onset cancer, and 192 (65% males) developed new-onset HF. In males, an increase in gal-3 was significantly associated with new-onset cancer (both combined and certain cancer-specific subtypes), after adjusting for age, body mass index, hypertension, smoking status, estimated glomerular filtration rate, diabetes mellitus, triglycerides, coronary artery disease, and C-reactive protein (HR: 1.89; 95% CI: 1.32-2.71; $P < 0.001$). Similar analyses demonstrated an association with new-onset HF in males (HR: 1.77; 95% CI: 1.07-2.95; $P = 0.028$). In females, changes in gal-3 over time were neither associated with new-onset cancer nor new-onset HF.

CONCLUSIONS Gal-3, a marker of fibrosis, is associated with new-onset cancer and new-onset HF in males, but not in females. (J Am Coll Cardiol CardioOnc 2023;■:■–■) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

ECM = extracellular matrix

eGFR = estimated glomerular filtration rate

gal-3 = galectin-3

GI = gastrointestinal

HF = heart failure

RCV = reference change value

TME = tumor microenvironment

Cancer and heart failure (HF) are among the leading causes of death in the Western world.[1,2] Recent studies elucidated that these 2 disease entities are in fact more intertwined than initially thought. Numerous shared risk factors and pathophysiological mechanisms are thought to underlie this relationship, 1 of which is fibrosis.[3,4]

Fibrosis is the process of excessive extracellular matrix (ECM) buildup in response to (chronic) tissue injury.[5,6] Consequently, fibrosis causes loss of function and perturbations in normal physiology.[6] Interestingly, fibrosis seems to exert sex-specific effects: it has been observed that the incidence of cardiovascular disease, and more generally cardiac remodeling, is significantly lower in premenopausal females than in age-matched males.[6-8] Similar to HF, cancer is also deemed a fibrotic disease entity. ECM deposition, remodeling and stroma stiffening are all characteristics of fibrosis seen in tumors and the tumor microenvironment (TME).[9] As with HF, the sex-specific mechanisms in this process are beginning to be unraveled.[9] In addition to the epidemiological evidence that, for example, cancer incidence is higher in males than in females, it has been postulated that also on a cellular level, cancer indeed differs between sexes: fibrosis-associated processes are observed to be higher expressed in male cancer patients.[9]

Galectin-3 (gal-3), a lectin of the β-galactoside-binding class, is a biomarker of fibrosis and has been studied in both preclinical and clinical settings in various fibrotic disease entities, including cancer and HF.[10-12] The association between gal-3 and HF is well-established in the literature, and it has been demonstrated that increased levels of gal-3 are associated with HF and HF severity.[13,14] In cancer, however, the role of gal-3 is less understood, but recent studies have demonstrated that in certain prevalent cancers, such as gastrointestinal (GI) cancer, increased levels of gal-3 are observed.[15-17]

Given the sex differences that play a role in both cancer, HF, and fibrosis, we hypothesized that a biomarker such as gal-3 may also exhibit different effects in males and females.[18-21] Therefore, we investigated the association of serial measurements of gal-3 with 2 fibrotic disease entities: new-onset cancer and new-onset HF in both sexes.

METHODS

STUDY DESIGN. This was a post hoc analysis performed with data from the PREVEND (Prevention of Renal and Vascular Endstage Disease) study, a prospective cohort study conducted in the north of the Netherlands. In total, 8,592 people were enrolled, with an enrichment based on microalbuminuria (defined as >10 mg/L).[22] We excluded patients with missing baseline status, or follow-up status, missing gal-3 measurements at baseline and/or follow-up, patients with non-Caucasian ethnicity, as we cannot assume similar biological effects of gal-3 in all ethnicities, and patients with prevalent cancer or HF (Supplemental Figure 1). A full list of inclusion and exclusion criteria for the PREVEND study is presented elsewhere; ethical approval was obtained from the local medical ethics committee of the University Medical Center Groningen, and the study was carried out in accordance with the Declaration of Helsinki.[22]

GAL-3 MEASUREMENTS. Blood samples were drawn and measured at baseline and 4-year follow-up. Gal-3 was measured using an enzyme-linked immunosorbent assay by BG Medicine. The intra-and interassay coefficients are reported elsewhere.[14] We evaluated the prognostic value of gal-3 levels at baseline, as well as the association of a relevant increase in gal-3 level, which was defined as an increase of 50% or more in gal-3 level at follow-up compared with baseline gal-3 level. This is based on the reference change value (RCV) of gal-3. RCV is the difference between 2 consecutive measurements that must be surpassed for a change to constitute a clinically significant change.[23] In HF, the literature demonstrated a RCV of ±25% for gal-3; literature concerning RCV and new-onset cancer was less abundant.[23] Therefore, the value of a doubling in RCV (ie, ≥50%) was explored in this study.

CANCER DIAGNOSIS. An extensive registration of cancer diagnoses per patient was provided by the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA).[24] We excluded all pre-existing cancers (ie, before baseline; n = 163). All cancer subtypes were used for all-type cancer analyses; subtype analyses were performed for the most common cancer subtypes (Supplemental Table 1). We censored all nonmelanoma skin cancers (n = 531). If patients developed multiple cancers over time, we examined the data of the first diagnosed cancer.

HF DIAGNOSIS. HF diagnoses were made by an endpoint adjudication committee based on clinical signs, symptoms, and objective evidence retrieved from patient files to assess the presence of new-onset HF or HF at baseline.[25,26] Each individual case was validated by 2 different experts (RdB) through an

anonymous validation process as described elsewhere.[26] We excluded all patients with pre-existent HF (n = 11).

STATISTICAL ANALYSIS. Normally distributed data are presented as mean ± SD, non-normally distributed data are presented as median with 25th and 75th percentiles (IQR), and categorical data are presented as n (%). Between-group differences were tested with Student's *t*-test (2 groups) or analysis of variance (≥3 groups) for normally distributed data, whereas Mann-Whitney *U* test or Kruskal-Wallis test was used to compare non-normally distributed data. Between-group differences for categorical data were tested with Pearson's chi-square test. In order to validate whether gal-3 presents similar behavior in other disease entities, we evaluated the prognostic role of a relevant increase (≥50%) in gal-3 per sex for both new-onset cancer and new-onset HF. Data were visualized with cumulative hazard plots and were quantified using the HR with 95% CI after performing Cox proportional hazard regression analyses. After checking whether proportional hazard assumptions were met, we adjusted for confounders based on the directed acyclic graph created for this study; to ensure similar analyses, we used the same model for both disease entities (Supplemental Figure 2). In line with the current literature, we also evaluated the association of gal-3 per doubling (ln_2), per SD, and per quartile analysis. All data were analyzed using STATA/SE14 (StataCorp) and GraphPad Prism (version 8.4.2, GraphPad Software). A *P* value ≤0.05 was considered statistically significant for all analyses but interaction term analyses, where a *P* value of ≤0.10 was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS. Levels of gal-3 at baseline and follow-up were available in 5,786 patients, who were included for present analyses. Sex was distributed evenly in the study population, females (n = 2,915 [50%]) and males (n = 2,871 [50%]) (Table 1). Males were on average older than females (50 ± 12 years vs 48 ± 11 years; $P < 0.001$), had a higher body-mass index (BMI) (25.9 kg/m^2 [IQR: 23.7-28.2 kg/m^2] vs 25 kg/m^2 [IQR: 22.5-28.1 kg/m^2]; $P < 0.001$), and had a higher systolic and diastolic blood pressure at baseline (131/76 mm Hg vs 118/70 mm Hg; $P < 0.001$). Resting heart rate was higher in females compared with males (70 beats/min [IQR: 60-74 beats/min] vs 66 beats/min [IQR: 64-76 beats/min]; $P < 0.001$). Estimated glomerular filtration rate (eGFR) was higher in females than in males (98.0 mL/min/1.73 m^2 [IQR: 84.9-107.0 mL/min/1.73 m^2] vs 96.1 mL/min/1.73 m^2 [IQR: 85.7-108.0 mL/min/1.73 m^2]; $P = 0.007$).

TABLE 1 Baseline Characteristics of Patient Population

	Male (n = 2,871)	Female (n = 2,915)	*P* Value
Demographics			
Age, y	50 ± 12	48 ± 11	<0.001
BMI, kg/m^2	25.9 (23.7-28.2)	25 (22.5-28.1)	<0.001
SBP, mm Hg	131 (120-143)	118 (109-134)	<0.001
DBP, mm Hg	76 (70-82)	70 (64-76)	<0.001
HR, beats/min	66 (60-74)	70 (64-76)	<0.001
eGFR, mL/min	96.1 (84.9-107.0)	98.0 (85.7-108.0)	0.007
Laboratory parameters			
NT-proBNP, pg/mL	22.9 (10.1-50.2)	51.1 (28.4-85.1)	<0.001
Creatinine, serum, μmol/L	90 (83-98)	75 (69-81)	<0.001
Cholesterol, mmol/L	5.6 (4.9-6.3)	5.5 (4.8-6.3)	0.014
hsCRP, mg/L	1.2 (0.5-2.6)	1.3 (0.6-3.2)	0.006
Gal-3 baseline, ng/mL	10.6 (8.9-12.6)	11 (9.1-13.3)	<0.001
Gal-3 follow-up, ng/mL	11.3 (8.9-14)	11.7 (9.1-14.7)	<0.001
Relevant change in gal-3	291 (10.1)	288 (9.9)	0.75
Medical history			
Hypertension	794 (27.7)	882 (30.3)	0.029
Hypercholesterolemia	488 (17.0)	333 (11.4)	<0.001
Cerebrovascular accident	22 (0.8)	17 (0.6)	0.40
Diabetes mellitus	34 (1.2)	30 (1.0)	0.57
Myocardial infarction	119 (4.2)	21 (0.7)	<0.001

Values are mean ± SD, median (IQR), or n (%).

BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; gal-3 = galectin-3; HR = heart rate; hsCRP = high sensitivity C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure.

Laboratory parameters demonstrated a higher level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in females (51.1 pg/mL [IQR: 28.4-85.1 pg/mL] vs 22.9 pg/mL [IQR: 10.1-50.2 pg/mL] in males; $P < 0.001$), as well as a higher level of high-sensitivity C-reactive peptide (hsCRP). Serum creatinine and cholesterol were higher in males (Table 1).

Lastly, hypertension was the only comorbidity that was more common in females than males. Hypercholesterolemia, (history of) cerebrovascular accident, and the presence of diabetes mellitus were more common in males. In males, myocardial infarction was 4 times more common than in females (119 [4.2%] vs 21 [0.7%]; $P < 0.001$) (Table 1).

GAL-3 AND SEX. Gal-3 levels at both baseline (11 ng/mL [IQR: 9.1-13.3 ng/mL] vs 10.6 ng/mL [IQR: 8.9-12.6 ng/mL]; $P < 0.001$) and follow-up (11.7 ng/mL [IQR: 9.1-14.7 ng/mL] vs 11.3 ng/mL [8.9-14.0 ng/mL]; $P < 0.001$) were significantly higher in females compared with males (Table 1). The number of patients that demonstrated a relevant increase (≥50% at follow-up gal-3 compared with baseline gal-3) in gal-3 was evenly distributed among sex (291 [10.1%] males vs 288 [9.9%] females; $P = 0.75$).

TABLE 2 Cox Regression Analysis According to Subtype of Cancer

	Unadjusted		Model 1[a]	
Type of Cancer	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Males				
All-type, n = 234				
Gal-3 baseline	1.03 (1.00-1.05)	0.017	0.99 (0.95-1.02)	0.45
Relevant increase[b]	2.02 (1.44-2.82)	<0.001	1.89 (1.32-2.70)	<0.001
Gastrointestinal, n = 73				
Gal-3 baseline	1.01 (0.96-1.06)	0.69	0.95 (0.88-1.03)	0.23
Relevant increase	2.66 (1.53-4.63)	0.001	2.29 (1.24-4.23)	0.008
Lung/trachea, n = 36				
Gal-3 baseline	1.01 (0.95-1.08)	0.67	0.96 (0.86-1.08)	0.54
Relevant increase	2.71 (1.23-5.94)	0.013	2.80 (1.24-6.32)	0.014
Kidney/urinary tract, n = 54				
Gal-3 baseline	1.05 (1.01-1.08)	0.005	1.01 (0.95-1.08)	0.73
Relevant increase	1.90 (0.93-3.88)	0.080	1.58 (0.74-3.39)	0.24
Females				
All-type, n = 165				
Gal-3 baseline	1.03 (1.00-1.06)	0.083	0.99 (0.95-1.04)	0.78
Relevant increase	0.84 (0.48-1.44)	0.52	0.90 (0.51-1.60)	0.73
Gastrointestinal, n = 34				
Gal-3 baseline	1.01 (0.93-1.09)	0.82	0.94 (0.83-1.06)	0.30
Relevant increase	1.19 (0.42-3.89)	0.74	1.45 (0.50-4.17)	0.49
Lung/trachea, n = 15				
Gal-3 baseline	1.04 (0.95-1.13)	0.41	1.03 (0.90-1.18)	0.67
Relevant increase	2.23 (0.63-7.91)	0.21	2.83 (0.77-10.36)	0.12
Kidney/urinary tract, n = 13				
Gal-3 baseline	1.07 (1.00-1.13)	0.047	1.07 (0.95-1.20)	0.27
Relevant increase	N/A	N/A	N/A	N/A
Breast, n = 76				
Gal-3 baseline	1.02 (0.97-1.07)	0.36	0.98 (0.92-1.06)	0.66
Relevant increase	1.05 (0.51-2.19)	0.90	0.97 (0.44-2.13)	0.94

[a]Model 1: adjusted for age, BMI, coronary artery disease, diabetes mellitus, smoking status, hypertension, inflammation, triglycerides and eGFR. [b]Relevant increase: an increase of ≥50% of follow-up gal-3 compared with baseline gal-3 level.

Abbreviations as in Table 1.

NEW-ONSET CANCER. During a follow-up of 11.5 years, 399 patients developed new-onset cancer. There were a greater number of cancer events among males (n = 234) than females (n = 165) (**Figure 1**, Supplemental Figure 3). New-onset GI cancer was the most common cancer subtype (n = 107 [26.8%]), followed by cancer of the kidney and urinary tract (n = 67 [16.8%]) and lastly incident lung cancer (n = 51 [12.8%]); the remaining new-onset cancer subtypes (n = 174 [43.6%]) were dispersed over various subtypes of cancer that precluded subtype-specific analyses.

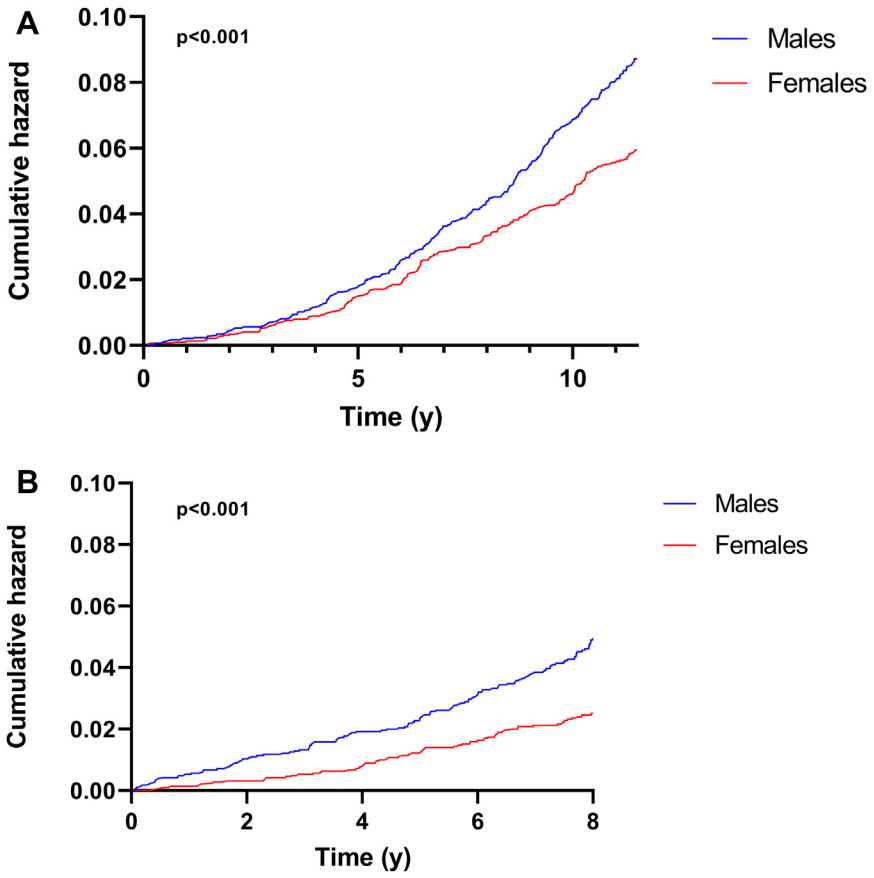
Baseline gal-3 levels were associated with new-onset cancer and cancer of the kidney and urinary tract among males in unadjusted analyses, though this association was not significant after multivariable adjustment. A relevant increase in gal-3 levels was associated with all-type new-onset cancer (HR: 1.89; 95% CI: 1.32-2.70; $P < 0.001$), GI cancer (HR: 2.29; 95% CI: 1.24-4.23; $P = 0.008$), and cancer of the lung and trachea (HR: 2.80; 95% CI: 1.24-6.32; $P = 0.014$) (**Table 2**) in males; these associations remained independent of adjustment for potential confounders (age, BMI, coronary artery disease, diabetes mellitus, smoking status, hypertension, inflammation, triglycerides, and eGFR). There was statistical evidence that the association between a relevant increase in gal-3 and new-onset cancer was greater in males compared with females (*P* value for interaction between male sex and relevant gal-3 increase: $P = 0.007$).

In females, we only observed an association between baseline gal-3 levels and new-onset cancer of the kidney and urinary tract (HR: 1.07; 95% CI: 1.00-1.13; $P = 0.047$), but the sample size was too small to allow for adequate analyses in a multivariable regression. In contrast to males, a relevant change in gal-3 was not associated with any new-onset cancer type in females (**Table 2**).

Males with a relevant increase in gal-3 levels demonstrated a higher cumulative hazard for new-onset cancer of all cancer types, as well as GI cancer, cancer of the trachea and lung, and cancer of the kidney and urinary tract (**Figures 2A and 3**) (log-rank for all analyses $P < 0.001$). Additional gal-3 analyses are presented in Supplemental Table 3, and numbers at-risk for **Figures 1-3** are presented in Supplemental Table 4.

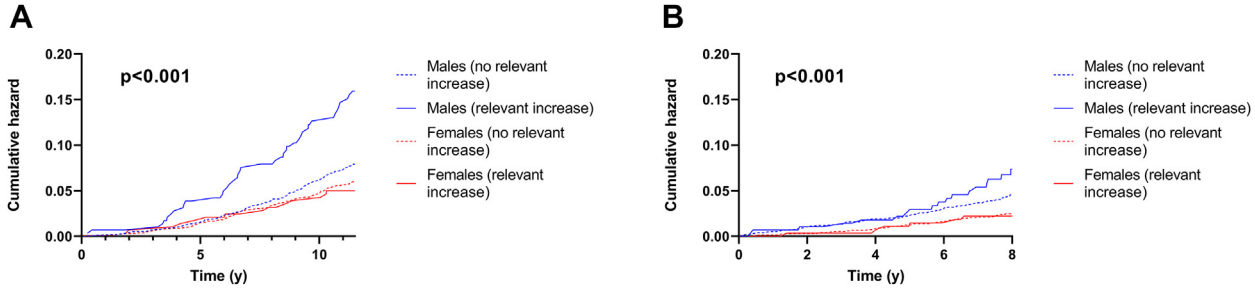
NEW-ONSET HF. In total, 192 patients developed new-onset HF, 125 (65%) of which were males, and 67 (35%) were females. Of these 192 patients, 114 (59.7%) had a left ventricular ejection fraction lower than 40%; 77 patients (40.3%) had a left ventricular ejection fraction >40% (**Table 3**). In HF, gal-3 demonstrated comparable results as in cancer, in both males and females (**Figures 1 and 2**, Supplemental Figure 3). A relevant increase in gal-3 was also more indicative of new-onset HF in males than in females (**Figure 2B**). In a multivariable model that was adjusted for age, BMI, coronary artery disease, diabetes mellitus, smoking status, hypertension, inflammation, triglycerides, and eGFR, a relevant increase in gal-3 was significantly associated with new-onset HF in males (HR: 1.77; 95% CI: 1.07-2.95; $P = 0.028$) (**Table 4**), however, we found no statistical evidence for a significant interaction between a relevant gal-3 increase and male sex (*P* for interaction: $P = 0.286$. Additional gal-3 analyses are presented in Supplemental Table 3.

FIGURE 1 New-Onset Cancer and New-Onset HF According to Sex



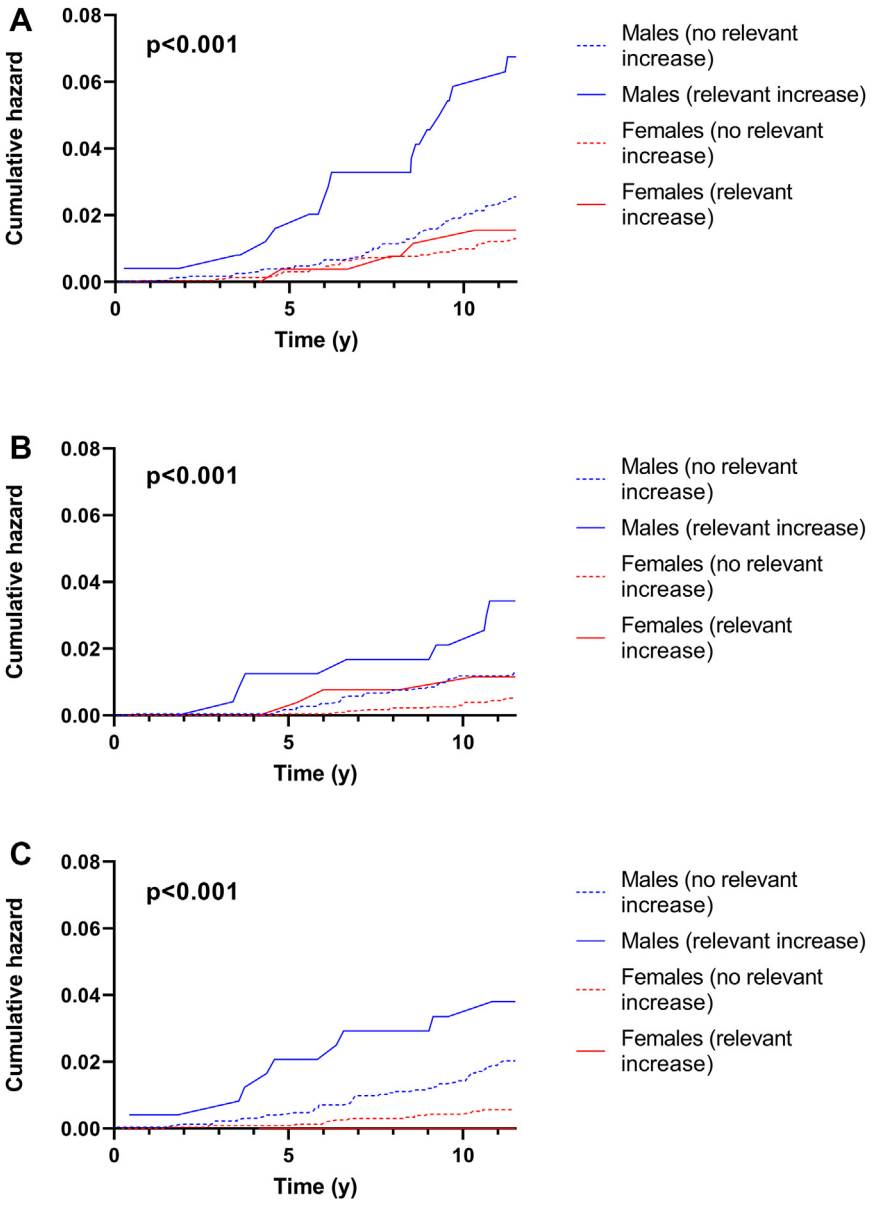
Cumulative hazard plots depicting the cumulative hazard of new-onset cancer **(A)** and new-onset heart failure (HF) **(B)** per sex. Males are represented by an **unbroken blue line**; females are represented by an **unbroken red line**. Significance was tested by log-rank test.

FIGURE 2 Changes in Gal-3 Levels and New-Onset Cancer and New-Onset HF



Cumulative hazard plots demonstrating the cumulative hazard of new-onset cancer **(A)** and new-onset heart failure (HF) **(B)** per sex. Males who underwent a relevant increase in galectin-3 (gal-3) are represented by an **unbroken blue line**; males who did not are represented by a **dashed blue line**. Females who underwent a relevant increase in galectin-3 are represented by an **unbroken red line**; females who did not are represented by a **dashed red line**. Significance was tested by log-rank test.

FIGURE 3 **Changes in Gal-3 Levels and New-Onset Cancer Types**



Cumulative hazard plots demonstrating the cumulative hazard of a panel of 3 subtypes of new-onset cancer: **(A)** gastrointestinal cancer; **(B)** lung and trachea cancer; and **(C)** kidney and urinary tract cancer. Males who underwent a relevant increase in galectin-3 (gal-3) are represented by an **unbroken blue line**; males who did not are represented by a **dashed blue line**. Females who underwent a relevant increase in galectin-3 are represented by an **unbroken red line**; females who did not are represented by a **dashed red line**. Significance was tested by log-rank test.

DISCUSSION

We demonstrated notable sex differences in the association of gal-3 with new-onset cancer and new-onset HF. Increases in gal-3 over time were after covariate adjustments associated with new-onset cancer and new-onset HF in males, but not in females (Central Illustration).

GALECTIN-3 AND NEW-ONSET CANCER. The associations of gal-3 with new-onset cancer and sex-specific differences are not widely discussed in the

TABLE 3 Characteristics of Patients With New-Onset HF

Clinical Sign/Symptom	N = 192
Angina pectoris	65 (33.9)
Fluid retention	80 (41.7)
Left ventricular hypertrophy	31 (16.2)
Nocturia	21 (10.9)
Orthopnea	42 (21.9)
Palpitations	35 (18.2)
Pulmonary edema	24 (12.5)
Raised jugular venous pressure	12 (6.3)
Reduced exercise tolerance	109 (56.8)
Shortness of breath	150 (78.1)
Tachycardia	37 (19.3)

Values are n (%).
HF = heart failure.

TABLE 4 Cox Regression Analysis for New-Onset HF

	Unadjusted		Model 1[a]	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All n = 192				
Gal-3 baseline	1.05 (1.03-1.07)	<0.001	1.00 (0.97-1.04)	0.85
Relevant increase[b]	1.31 (0.86-2.01)	0.21	1.50 (0.97-2.32)	0.067
Males, n = 125				
Gal-3 baseline	1.05 (1.03-1.07)	<0.001	1.03 (0.99-1.07)	0.100
Relevant increase	1.54 (0.93-2.54)	0.090	1.77 (1.07-2.95)	0.028
Females, n = 67				
Gal-3 baseline	1.05 (1.02-1.09)	0.002	0.95 (0.89-1.03)	0.21
Relevant increase	0.90 (0.39-2.09)	0.82	1.14 (0.49-2.67)	0.77

[a]Model 1: adjusted for age, BMI, coronary artery disease, diabetes mellitus, smoking status, hypertension, inflammation, triglycerides and eGFR. [b]Relevant increase: an increase of ≥50% of follow-up gal-3 compared with baseline gal-3 level.
Abbreviations as in Table 1.

literature. The TME is composed of a combination of blood vessels, ECM, and immune cells. It is thought that fibrosis plays a role in cancer initiation by (dys) regulating the TME.[27] In the TME, gal-3 suppresses T-cell activation by binding the T-cell receptor, resulting in immunosuppression and thus facilitating tumor growth.[28]

Moreover, previous studies showed that elevated levels of gal-3 were observed in patients with GI tumors, which could provide scientific ground as to why a relevant change in gal-3 is associated with new-onset GI cancer.[29-31] However, these associations concern prevalent cancer, rather than new-onset cancer, and are based on a single time measurement rather than serial measurement of gal-3.

Furthermore, our incidence data are supported by existing literature as there is a higher cancer incidence in males compared with females.[1] The finding that females have increased levels of gal-3 is also in agreement with existing literature. Although the reason for this remains to be elucidated, it could potentially be explained by sex-specific differences in fat mass: there is a robust association between fat mass and gal-3, and in this way, females—who have higher fat distribution than males—may have higher levels of gal-3.[32-35] In addition, sex hormones may be key players in fibrogenesis, possibly influencing disease progression.[6] Lastly, from a more philosophical and societal point of view, it may be argued that given the underrepresentation of females in (pre)clinical trials, we simply lack adequate background information to provide a solid explanation.[6]

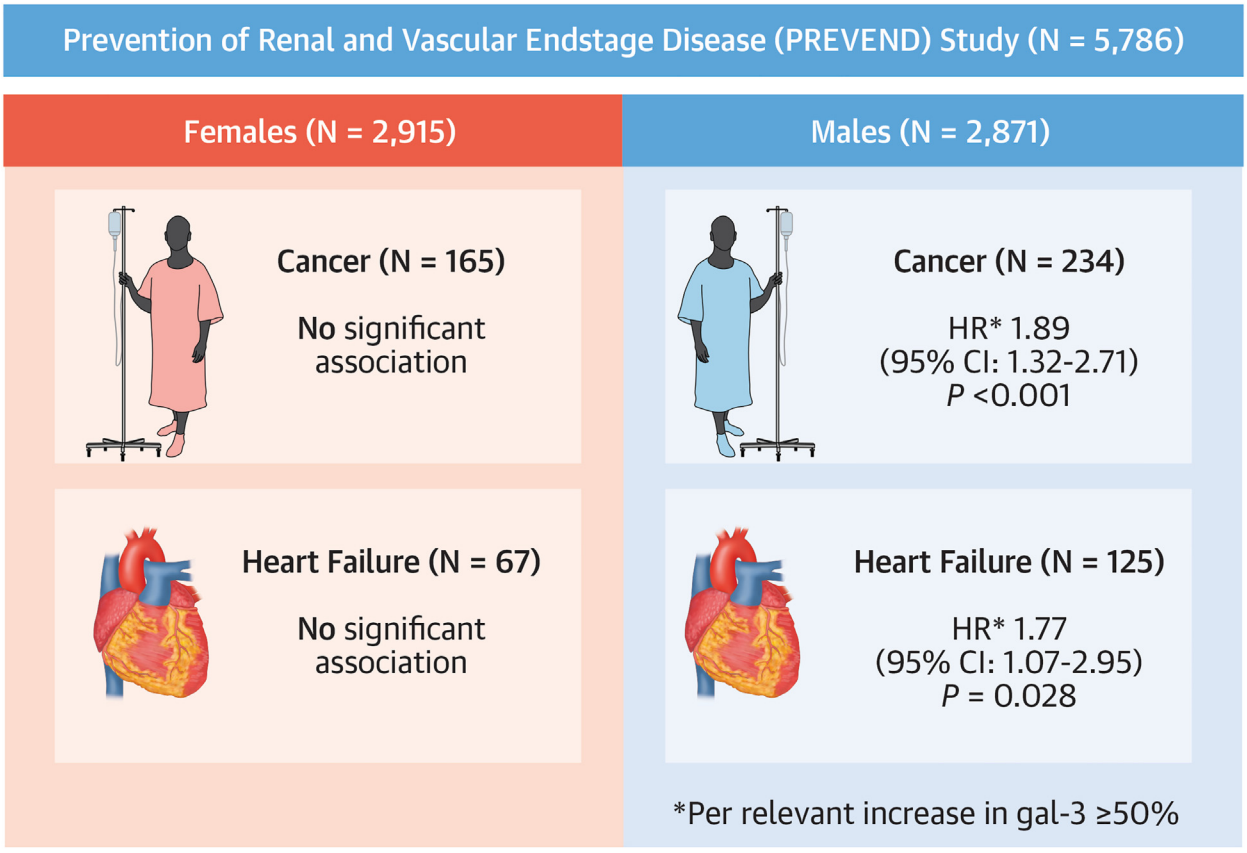
GAL-3 AND NEW-ONSET HF. Gal-3 has been shown to be a prominent marker for cardiovascular disease. In HF, fibrosis predominantly results from either direct cardiac injury during a myocardial infarction or increased ventricular remodeling caused by perturbations in hemodynamic workload.[36] Consequently, collagen deposition in the ECM increases and cardiac stiffening ensues, causing a detrimental decline in cardiac functioning.[37]

The notion that serial measurements of gal-3 bear greater value in indicating new-onset HF than single time measurements has been demonstrated before.[14,38] In similar fashion, Ghorbani et al[38] found that serial measurements were also associated with new-onset HF in the Framingham Heart Study. Our study demonstrates that increases over time are indicative of new-onset HF in males, but not in females.

STUDY STRENGTHS AND LIMITATIONS. Our current study evaluated the sex-specific association of (changes in) gal-3 with 2 fibrotic disease entities: new-onset cancer and new-onset HF. Recent literature is predominantly focused on the role of gal-3 in prevalent disease entities and does not dive into sex-specific properties. Furthermore, our data also revealed that a relevant increase in gal-3 over time is more indicative of new-onset cancer and new-onset HF, even after adjustment, than contemporary analyses.

When compared with models using increases in baseline (log_2/log_{STD}) gal-3, our new model (relevant increase; double RCV) demonstrates stronger associations with both clinical endpoints, and is easy to use in the clinical setting. The lack of a statistically significant interaction for new-onset HF could be a consequence of being underpowered because there were one-half as many people with new-onset HF as new-onset cancer. For better (sex-specific) identification of these patients, prospective studies are still needed.

CENTRAL ILLUSTRATION **Galectin-3 is Associated With New-Onset Cancer and Heart Failure in Males**



van den Berg PF, et al. J Am Coll Cardiol CardioOnc. 2023;■(■):■–■.

Galectin-3 is associated with new-onset cancer and heart failure in males. The HR for new-onset cancer is depicted **below** the cancer pictogram, and the HR for new-onset HF **below** the heart pictogram. Males and females are represented by their respective sex pictogram. gal-3 = galectin-3.

There is also some discrepancy in the lack of association when gal-3 levels are not modelled as relevant change but as doubling, increase per SD, or quartile-analyses. We believe this is due to the fact that the increases in gal-3 measurements between baseline and follow-up were relatively small, and those modalities do not identify the relevant group at risk. Furthermore, a lack of sensitivity exists when strict criteria, such as a doubling in gal-3 or increase in SD, are applied. Moreover, the relatively small numbers per cancer type may have caused underpowering in this regard. In addition, the underlying pathophysiology of both diseases, as well as the context in which we utilized gal-3 (ie, as a marker of fibrosis) might play a role. Lastly, the increase per SD and quartile analysis is rather group-based than individual-based (which is the case with our relevant change approach), thus also providing an explanation for lack of significant findings in that regard.

The reason why serial increases in gal-3 appear to be differentially associated with both endpoints in males as compared with females remains to be studied. Studies targeting gal-3 inhibition have been ongoing in HF already, but in cancer, this has been less intensely studied.[32,39,40] Based on the outcomes of this study, we suggest that gal-3 may be a suitable target for dual therapy,[32,40] and it would be worth investigating the dual beneficiary effect of gal-3 inhibition in 2 fibrotic disease entities, and to investigate to what extent this effect is sex-specific.

The current study has some limitations. Although patients were selected based on the presence of

microalbuminuria, the PREVEND cohort represents a fairly young cohort, as for example reflected by the relatively low prevalence of prostate cancer. The incidence of new-onset HF is relatively low, which potentially represents a lack of power. It also is worth noting that some of the new-onset cancer and new-onset HF cases could have occurred before the 4-year follow-up, which warrants the notion that our data should be interpreted as associations with increase in gal-3 rather than as a predictive analysis. Therefore, further validation of these results is required, especially in a prospective setting.

CONCLUSIONS

A clinically relevant increase in gal-3, a marker of fibrosis, is associated with new-onset cancer and new-onset HF especially in males, but not in females. This may motivate the development of novel medical therapeutical options in both the field of oncology and cardiology.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE OR COMPETENCY IN PATIENT CARE: The pathophysiology of cancer and HF shares numerous common mechanisms, including fibrosis. The increase of gal-3 identifies males at risk of developing new-onset cancer and new-onset HF; whereas in females, no association was found between an increase in gal-3 and either disease entity. In the era of personalized medicine, it is inevitable that sex-specific differences will play an increasing role in tailoring treatment to optimize their effect.

TRANSLATIONAL OUTLOOK: Future research is still needed to assess the role of fibrosis and fibrosis-associated markers for new-onset cancer and new-onset HF, and to understand the sex-related differences in these diseases and associated (fibrotic) biomarkers. Fibrosis may be a common therapeutic target for cancer and HF. Further validation of our results and elaboration of our findings in a prospective setting are needed.

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APPENDIX For supplemental figures and tables, please see the online version of this paper.