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Monocyte number associated with incident cancer and mortality in middle-aged and elderly community-dwelling Danes

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ABSTRACT

Background: Monocytes play an important role in innate immunity and exhibit prognostic value in some cancers. It was hypothesised that activation of the innate immune system through mobilisation of monocytes to tissue macrophages develops an inflammatory state associated with increased risk of cancer and mortality.

Methods: To test this hypothesis monocyte number was measured in a sample of 669 Danish men (59%) and women (41%) aged 55 to 75 years who were free of any known prevalent cancer or cardiovascular disease. The population was followed for 6.3 years, during which period incident cancers and deaths were compiled from validated national registries.

Results: Fifty-two subjects developed cancer and 83 subjects died during follow-up. The upper quintile of monocyte number (median 0.44×10^9/L, lower quintile <0.33, upper quintile >0.60) was associated with an increased risk of cancer (hazard ratio [HR] 2.00 [95% CI 1.12–3.57]) and deaths (HR 1.67 [1.03–2.72]) in univariate analyses, after correction for age and gender (cancer HR 2.15 [1.20–3.86] and death HR 1.63 [1.00–2.67]), and following additional correction for smoking habits, diabetes, systolic blood pressure, and total cholesterol (cancer HR 2.00 [1.10–3.70] and death HR 1.30 [0.78–2.16]). COX regression models, with inclusion of the aforementioned explanatory variables and added heart rate variability, alcohol use, and CRP, revealed monocyte count (per 0.1×10^9/L increase) to be independently associated with incident cancer (HR 1.12 (1.05–1.19)) and death (HR 1.13 (1.06–1.19)).

Conclusions: In healthy middle-aged and elderly community-dwelling Danes circulating monocytes independently predicted incident cancer and mortality.

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1. Introduction

The monocyte, which plays a major role in innate immunity, constitutes about 5% of the circulating white blood cell pool and exhibits a short half-life in the circulation of a few hours.[1,2] The monocyte migrates into other tissues of the body, where it transforms into a long-lived macrophage. Thus, the circulating level of monocytes may reflect increased production of tissue macrophages. The activation of the innate immune system is associated with increased secretion from extravascular mononuclear phagocytic cells of cytokines, lysozymes, and thromboxanes.[1,3] Of particular interest is the fact that the number of circulating monocytes and their secretory products exhibit prognostic value in various cancers, renal disease, cardiovascular disease and community-acquired pneumonia, where an increased level of monocytes has robustly been associated with fatal outcome.[4–9]

A state of low-grade inflammation, often measured by hs-CRP (high sensitive C-reactive protein), has been associated repeatedly with a poor prognosis in the general population in terms of longevity,[10–13] although not always significantly.[14] Monocyte level is associated with poor outcome in various cancer forms, but CRP level is not.[4,7,8,15] Low-grade inflammation is characterised by increased release of certain cytokines and endothelial factors associated with increased level of mononuclear phagocytic cells.[3] Thus, increased concentration of monocytes may in part reflect a state of low-grade inflammation that may potentially play a role in longevity and cancer development.

The aim of the present study was therefore to evaluate whether a high plasma monocyte level carries prognostic information in terms of mortality and incident cancers in a relevant population of middle-aged and older individuals of 50 to 75 years of age, who were free of any known cardiovascular disease and cancer at the time of monitoring.[16]

2. Materials and methods

2.1. Population

This study is part of the Copenhagen Holter study, which aimed to address the value of 24-h Holter recording in the risk assessment of middle-aged and elderly men and women in relation to other risk factors.

The Central Office of Civil Registration, Ministry of the Interior, identifies each person in Denmark by a unique registry number. This number enabled the present study to perform an epidemiological survey of subjects living within two well-defined postal regions in Copenhagen. All men aged 55, and all men and women aged 60, 65, 70 and 75 years received a questionnaire ($n = 2969$) about cardiovascular risk factors, use of medications and medical history. The overall aim of the Copenhagen Holter Study was to evaluate the prognostic value of different Holter variables in the population. For the study to have enough power, a population with a higher level of atherosclerotic risk burden was aimed for. Thus, women under 60 were not included and a higher proportion of subjects with several risk factors were included. Exclusion criteria for this study were: manifest ischemic heart disease, i.e. a history of acute myocardial infarction (AMI), coronary revascularisation, angina pectoris; other manifest cardiac diseases, i.e. congestive heart failure, valvular heart disease, congenital heart disease, arrhythmic heart disease including permanent atrial fibrillation, and medical treatment for any heart disease; history of stroke; cancer; other significant or life-threatening diseases, e.g. cirrhosis hepatitis, renal insufficiency needing dialysis, and chronic lung disease needing home-oxygen therapy. All together, 669 subjects participated in this study (Fig. 1). All participants were subjected to a physician-based interview, physical examination including anthropometric measurements, fasting laboratory testing, and 48-h Holter monitoring. These subjects were ranked according to

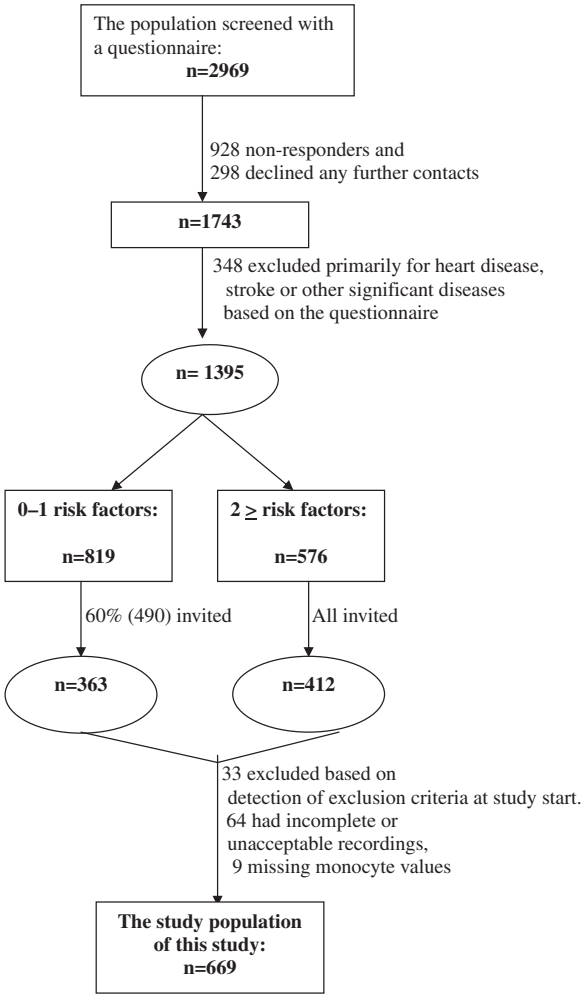

Fig. 1 – Selection of the study population from two postal areas in the north-western part of Copenhagen, Denmark. Risk factors for cardiovascular disease were identified and included: hypertension, diabetes mellitus, smoking habits, familial history of cardiac disease, i.e. sudden death or AMI in a parent or sibling before the age of 60, obesity (body mass index [BMI] > 30 kg/m^2), and known hypercholesterolaemia.

the number of the following self-reported risk factors: hypertension, diabetes mellitus, smoking habits, familial history of cardiac disease i.e. sudden death or AMI in a parent or sibling before the age of 60, obesity (body mass index [BMI] > 30 kg/m^2), and known hypercholesterolaemia. The study was initiated in April 1998, and the last subject was included in June 2000. The follow-up was performed in April 2005.

2.2. Laboratory testing

Blood sampling was carried out between 7:00 and 10:00 a.m. after an overnight fast of at least 8 h. Venous blood was collected in evacuated glass tubes. Plasma and serum samples were separated immediately after collection by centrifuging at 2000*g* for 15 min, and stored at −70 °C. Differential counting of the white blood cell types was measured with the PENTRA 120 Automated Hematology Analyzer (ABX Diagnostics, Montpellier, France). Monocyte number exhibited a within-run coefficient of variance (CV) of 4.2% to 14.7% depending on its concentration. Standard analyses including blood glucose and cholesterol measurements were performed immediately on a Hitachi 7170 automated analyzer (Tokyo, Japan). High sensitive C-reactive protein (hs-CRP) was measured with an immunofluorescence technique using the KRYPTOR immunoassay system manufactured by B.R.A.H.M.S (Saint-Ouen, France) in 2003. Within-assay CV was 2.1% to 5.1%, and detection range 0.06 to 200 μg/ml. NT-proBNP was measured by electrochemiluminescence technique using Elecsys 2010 provided by Roche (Basel, Switzerland), detection range: 0.6–4,130 pmol/L, CV within-run: 1.9–2.7%.

2.3. Definition of variables

Blood pressure was measured by a mercury manometer after at least 10 minutes of rest. Diabetes mellitus was defined as known diabetes or fasting plasma glucose of $\geqslant$7.0 mmol/l. Holter recording for 48 h was made by two-channel Space Labs tape recorders (9025, Space Labs, Inc., Redwood, WA, USA). Analysis of Heart Rate Variability (HRV) was carried out using the FT3000 Medical Analysis and Review Station. From the 48-h Holter recording, the first 24 h were selected for analyses (2nd to 25th hour). Analysis was performed by trained personal at the Holter laboratory of the Copenhagen University Hospital, Hvidovre, Denmark. Time domain components of HRV were measured, and the following parameters were identified: mean value and standard deviation for the mean time between normal-to-normal intervals (MEANNN and SDNN).

For CRP, a value of 3 μg/ml or more was considered 'high' according to the current guidelines.[10,11]

2.4. End-points

'Data on death and cancer were obtained through the Danish National Patient Register and the Danish Cancer Registry. All deaths and hospital admissions and discharges in Denmark are reported to this registry within two weeks. Hospital admissions were additionally studied from hospital discharge letters. We did not use combined end-points; thus, a subject who had a cancer diagnosis and eventually died during follow-up, was not censored after the cancer diagnosis, but contributed to both the cancer and the mortality end-points.

2.5. Ethics

Before inclusion all the participants gave their written informed consent. The study was approved by the regional ethics committee for the city of Copenhagen and Frederiksberg. The Declaration of Helsinki was complied with.

2.6. Statistical analysis

Statistical analyses were performed using the SAS statistical software programme (version 9.1). For normally distributed variables mean and standard deviations (SD) are presented, otherwise median values and inter-quartile ranges are presented. The variable of interest is monocyte count in relation to its association to incident cancer and overall mortality, and all other variables are risk factors for which adjustments are made. Survival in different groups were evaluated by the method of Kaplan–Meier and compared by log-rank test. Cox proportional hazard models were used to evaluate risk factor-adjusted associations of variables of interest with death or cancer. The assumption of proportional hazards was assessed by visual judgment of the log-minus-log survival plots. In addition to the main parameters of interest, the following covariates of potential prognostic importance were pre-selected for evaluation in the Cox models when death was the end-point: age, sex, smoking, serum cholesterol, systolic arterial blood pressure, and diabetes mellitus. When cancer was the end-point gender, age, smoking, CRP, alcohol usage, and heart rate variability were selected for adjustments in the Cox models. Spearman's correlation coefficients are presented to assess correlation between the variable of interest and the other continuous variables in the data set. A multivariate association model with both forward and backward selection evaluated the association of monocytes and other white blood cell lines with end-points including selected confounders. In forward or backward selection/elimination procedures $p < 0.05$ was used as the criterion for entering and staying in the model.

3. Results

A total of 669 community subjects where included (Fig. 1) with an average age of 64.5 years (Table 1). Twenty percent of the participants had $>0.60 \times 10^9$ monocytes per litre. The range of monocytes was 0.14×10^9 cells/L to 3.9 and the range of white blood cells was 2.0×10^9 cells/L to 14.9. The monocyte number was higher in males and smokers (Table 2). Monocyte number was positively associated with increased CRP and the number of other subtypes of white blood cells, but negatively associated with HDL cholesterol (Table 3). A linear regression analysis including monocyte number as a dependent variable and smoking habits, CRP, gender and HDL cholesterol as independent variables showed that only smoking and CRP were independently associated with monocyte number (data not shown).

Table 1 – Baseline characteristics of the community-dwelling subjects with no apparent cancer or cardiovascular disease (n = 669).

Co-variables	
Age (years)	64.5 (6.8)
Female	276 (41%)
Diabetes mellitus	75 (11%)
Smokers	310 (46%)
BMI	26.2 (4.2)
P-albumin (g/l)	43.2 (3.0)
P-hs-CRP (μg/ml)	2.5 (1.1–4.6)
P-pro-BNP (pg/ml)	58 (31–117)
P-triglyceride (mg/dL)	115 (79.6–159.3)
B-monocyte ($\times 10^9$/l)	0.44 (0.34–0.56)
B-basophils ($\times 10^9$/l)	0.06 (0.04–0.08)
B-eosinophils ($\times 10^9$/l)	0.21 (0.21–0.30)
B-lymphocytes ($\times 10^9$/l)	2.0 (1.59–2.43)
B-neutrophils ($\times 10^9$/l)	3.35 (2.66–4.14)
P-cholesterol (mg/dl)	235 (40.8)
P-HDL cholesterol (mg/dl)	58.3 (46.6–69.9)
P-creatinine (mg/dl)	1.05 (0.22)
P-glucose (mg/dl)	104.4 (30.6)
SDNN24H	124.8 (25.1)

BMI, body mass index; hs-CRP, high-sensitive C-reactive-protein; pro-BNP, pro-brain natriuretic peptide, SDNN24, SD of beat to beat interval during 24 h HOLTER monitoring. For normally distributed variables mean (SD) and for not normally distributed variables median (Q1–Q3) are presented. Categorical variables are presented by proportions.

3.1. *Follow-up and event rates*

The median follow-up time was 76 months (interquartile range 4 months). During follow-up 82 subjects (12%) died and 52 (8%) developed cancer. Cancer diagnoses comprised pulmonary including bronchial (n = 14), breast (n = 9) gastro-intestinal including liver and pancreatic (n = 8), genitourinary including prostate (n = 6), skin including melanomas (n = 5), haematological including lymphomas (n = 4), and other unspecified primary sites (n = 6), respectively. The three most prevalent cancers (pulmonary, breast and gastro-intestinal) were distributed in quintiles as Q1 2/3/3; Q2 0/2/1; Q3 3/1/1; Q4 4/1/0; and Q5 5/2/3 respectively. Of the 52 subjects who developed cancer during follow-up, 29 subjects (56%) died. Fig. 2 shows the incidence of death and cancer in quintiles of monocytes and Fig. 3 shows Kaplan–Meier survival curves according to the quintiles of monocytes. The upper quintile of monocyte number was associated with an increased rate of both death and cancer, in univariate analysis and also after adjustment for relevant covariates (Table 4), although the significance of this association for death was lacking after multiple adjustments. Using quartiles instead of quintiles did not significantly change the results, such that the upper quartile of monocyte number displayed similar results to the upper quintile of monocyte number (data not shown), but the impression was that quintiles reflected the optimal separation of data. Also, monocyte number as a continuous variable was a significant predictor of death and cancer (Table 5).

Further adjustments for diabetes, LDL cholesterol and HDL cholesterol in addition to the other covariates mentioned in Table 5 did not change the results and monocytes remained a significant predictor of cancer in the model (per 0.1×10^9/L, HR: 1.12, 95% CI: 1.05–1.20, $p = 0.0009$). In a forward selection model with all these variables only gender and monocytes remained in the model as significant predictors of cancer: HR for monocytes: per 0.1×10^9/L, 1.13, 95% CI: 1.06–1.20, $p = 0.0001$ and HR for male gender: per 0.1×10^9/L, 0.53, 95% CI: 0.30–0.94, $p = 0.03$. If we excluded the 29 subjects who died after an established cancer diagnosis from the mortality analyses, this did not change the results presented in Table 5.

We suspected a J-shaped association between cancer rate and monocyte number based on visual inspection of Fig. 2. Supplementary and explorative analyses showed that if the

Table 2 – Correlation of monocyte number with selected categorical variables in the study population.

Categorical variables	Median values, unit 10^9/L (Interquartile range)
Gender[*]	
Female	0.42 (0.20)
Male	0.45 (0.23)
Smoking[**]	
No	0.40 (0.19)
Yes	0.48 (0.23)
Diabetes	
No	0.43 (0.25)
Yes	0.44 (0.21)

[*] $p < 0.005$.
[**] $p < 0.0001$.

Table 3 – Correlation of monocyte number with other continuous variables in the study population.

Continuous variables	Spearman correlation coefficients
P-albumin	−0.045
B-leukocytes	0.636[***]
B-neutrophils	0.494[***]
B-eosinophils	0.367[***]
B-basophils	0.248[***]
Erythrocyte volume fraction	0.187[***]
P-creatinine	0.070
P-glucose	0.020
P-cholesterol	−0.087[*]
P-HDL cholesterol	−0.131[**]
P-LDL cholesterol	−0.052
P-hs CRP	0.270[***]
P-Pro-BNP	−0.014
Systolic blood pressure	0.033
Body mass index	0.026
SDNN24H	−0.068

HDL cholesterol = high-density lipoprotein cholesterol; LDL cholesterol = low-density lipoprotein cholesterol; hs CRP = high-sensitive C-reactive-protein; pro-BNP = pro-brain natriuretic peptide.
[*] $p < 0.05$.
[**] $p < 0.001$.
[***] $p < 0.0001$.

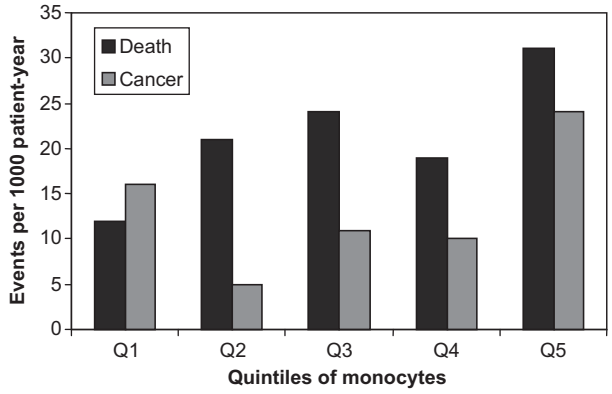

Fig. 2 – Death and incident cancer corresponding to quintiles (Q) of monocytes in 699 community-dwelling subjects during 6.3 years of follow-up. Q1 ($n = 144$) $\leqslant 0.32 \times 10^9$/L; Q2 ($n = 130$) $> 0.32 \times 10^9$/L and $\leqslant 0.40 \times 10^9$/L; Q3 ($n = 134$) $> 0.40 \times 10^9$/L and $\leqslant 0.47 \times 10^9$/L; Q4 ($n = 138$) $> 0.47 \times 10^9$/L and $\leqslant 0.60 \times 10^9$/L; Q5 ($n = 123$) $> 0.60 \times 10^9$/L. Hazard ratio per 0.10×10^9/L increase in monocyte number: death 1.12 ($p < 0.001$) and cancer 1.13 ($p < 0.001$).

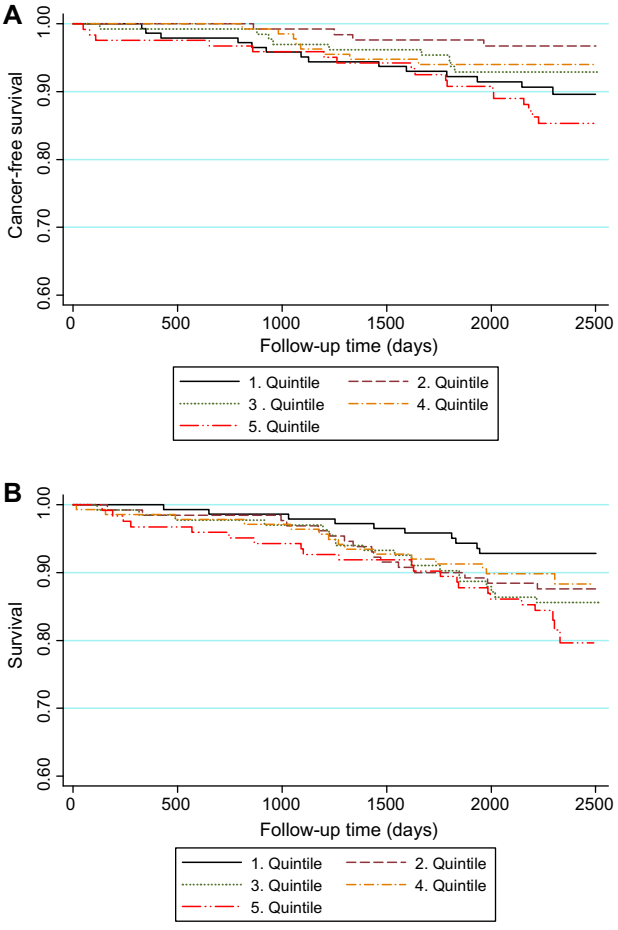

Fig. 3 – Kaplan–Meier plots of cancer-free survival (A) and total mortality (B) according to quintiles of monocyte number during a median follow-up of 6.3 years in community-dwelling subjects ($n = 699$).

Table 4 – Cox proportional hazard models for prediction by the upper quintile of the monocyte number of incident cancer and mortality.

	Death Hazard ratio (95% CI)	Cancer Hazard ratio (95% CI)
Univariate	1.67 (1.03–2.73)*	2.00 (1.12–3.57)**
Gender and age-adjusted	1.64 (1.00–2.67)*	2.15 (1.20–3.86)*
Multivariate	1.30 (0.78–2.16)	2.00 (1.10–3.70)*

Multivariate adjustment for death as the end-point: gender, age, smoking, cholesterol, systolic blood pressure, and diabetes.
Multivariate adjustment for cancer as end-point: gender, age, smoking, CRP, alcohol usage, and heart rate variability.
* p-Value < 0.05.
** p-Value < 0.01.

second quintile of the monocyte number was taken as a reference both the first and the fifth quintiles predicted cancer after adjustments for age, gender, smoking, CRP, alcohol usage and HRV. In this analysis the first quintile of monocyte number ($<0.33 \times 10^9$ cells/L) compared with the second quintile of monocyte number was associated with an increased risk of cancer (HR: 3.2, 95% CI: 1.1–8.9, $p = 0.037$) and the fifth quintile of monocyte number ($>0.60 \times 10^9$ cells/L) was also associated with an increased risk of cancer (HR: 3.9, 95% CI: 1.3–12.1, $p = 0.015$). By contrast both the third and the fourth quintile were not associated with an increased risk of developing cancer during follow-up (HR: 1.8, 95% CI: 0.53–5.8, $p = 0.35$) and (HR: 1.50, 95% CI: 0.44–5.20, $p = 0.51$). If monocyte quintiles 2 to 4 were taken as a normal reference, the univariate analyses of a difference between the reference and the first quintile according to incident cancer only showed an insignificant trend (HR: 1.88, 95% CI: 0.96–3.70, $p = 0.067$); however, the fifth quintile remained significant (HR: 2.71, 95% CI: 1.43–5.14, $p = 0.0023$). These analyses support the possibility of a J-shaped association between monocyte number and incident cancer. There were no inter-

Table 5 – Cox proportional hazard models for prediction by monocyte number as a continuous variable of incident cancer and mortality.

	Death Hazard ratio (95% CI)	Cancer Hazard ratio (95% CI)
Univariate	1.12 (1.07–1.17)***	1.14 (1.07–1.21)***
Gender and age-adjusted	1.12 (1.07–1.17)***	1.13 (1.07–1.20)***
Multivariate	1.13 (1.06–1.19)***	1.12 (1.05–1.19)***

Multivariate adjustment for death as the end-point: gender, age, smoking, cholesterol, systolic blood pressure, and diabetes.

Multivariate adjustment for cancer as the end-point: gender, age, smoking, CRP, alcohol usage, and heart rate variability.
Hazard ratio is given per 0.1×10^9/L increment of monocyte number (IQR of monocytes 0.22×10^9/L)
*** $p < 0.001$

actions between monocyte number and smoking, gender, or CRP with regard to incident cancer and death.

3.2. Other white blood cell lines versus mortality and incident cancer

Total white blood cell (WBC) number was associated with mortality after adjustment for sex and age (per 0.1×10^9/L, HR: 1.18, 95% CI: 1.06–1.31, $p = 0.002$) and so was neutrophils number (per 0.1×10^9/L, HR: 1.26, 95% CI: 1.1–1.44, $p = 0.0007$). This was not reproduced by lymphocytes (per 0.1×10^9/L, HR: 1.12, 95% CI: 0.84–1.48, $p = 0.43$) or basophils (per 0.1×10^9/L, HR: 2.74, 95% CI: 0.14–55.2, $p = 0.51$), or eosinophils (per 0.1×10^9/L, HR: 2.60, 95% CI: 0.74–9.12, $p = 0.14$). After further adjustment for other covariates (from Table 4) WBC number became insignificant in the model (per 0.1×10^9/L, HR: 1.06, 95% CI: 0.95–1.19, $p = 0.30$), and so did neutrophils (per 0.1×10^9/L, HR: 1.12, 95% CI: 0.96–1.31, $p = 0.16$). In forward and backward selection models adjusted for age and gender and with monocytes, total white blood cell number and neutrophils included in the model, monocytes maintained the strongest association with mortality in all of these models. No white blood cells other than monocytes were associated with incident cancer in univariate or in age- and gender-adjusted models.

4. Discussion

The hypothesis that circulating monocytes carry prognostic information in middle-aged and elderly subjects living in the community in terms of mortality and incident cancer was substantiated by the data presented here. In addition, the association of monocyte number with CRP level and their inverse correlation with HDL cholesterol would suggest that monocyte number reflects increased activation of the innate immunity of mononuclear phagocytic tissue cells, whose secretion of various cytokines to the circulation would confer dyslipidemia and a clinical state of low-grade inflammation.[1,3]

Of interest was the independence of the prognostic value of monocytes for incident cancer in apparently healthy individuals between 50 and 75 years of age in particular after adjusting for the effects of gender, age, smoking, CRP, alcohol usage, and heart rate variability. The results should be validated in future studies, but the present data indicate monocyte number to be a likely candidate for the prognostic biomarker of incident cancer in addition to its established significance as a prognostic marker in specific cancer diseases. Forward selection analyses including several candidate markers for incident cancer, i.e. gender, age, smoking, CRP, alcohol usage, and heart rate variability, revealed that only monocyte number and female gender were significantly independently associated with the endpoint. This observation is compatible with the results from the Women's Health Study, which stated that CRP is not predictive of incident cancer in women.[17] This was suggested because CRP was not associated with the prevalent hormone-related incident cancers forms in women, e.g. breast cancer and ovarian cancer.[18] It is a limitation of the present study that it did not achieve enough power to determine which cancer forms could be predicted and to detect whether monocyte number might add value to the prediction of female cancers; this issue should be addressed in future studies, which should include larger samples of subjects for the purpose of adequately addressing these topics. The perspective laid down by the present findings is that a simple measurement of blood monocyte concentration would be a likely candidate to include in algorithms aimed at predicting cancer diseases. Speculatively, the mechanisms behind the independent association with incident cancer by monocyte number might be related to an insidious progression of preclinical cancer disease involving activation of innate immunity.[19]

Longevity was inversely correlated to monocyte number in the present study and monocytes were found to provide independent prognostic value to mortality together with previously established risk factors of death such as age (per definition), gender, smoking habits, cholesterol, systolic blood pressure, and diabetes. Centenarians of good health have been found to exhibit low levels of systemic inflammation and relatively high levels of HDL cholesterol and low levels of total cholesterol, suggesting a mechanistic relationship for longevity.[20,21] Indeed, beneficial lipidemia is associated with a low level of plasma cytokines[3] and this scenario may in part be facilitated by an innate immune system in 'standby mode,' as reflected by a normal number of monocytes. Indirect evidence of the value of addressing low-grade inflammation was achieved recently showing that statin therapy could decrease CRP and LDL cholesterol levels and reduce mortality[22] in healthy individuals from the background population.

White blood cell number has shown predictive significance in the development of diabetes[23] and cardiovascular disease[24] and has also shown a weak association with incident cancers in postmenopausal women.[25] However, many of the various circulating cytokines, which have been related to detrimental prognosis in community-acquired pneumonia and various cancers[26] including risk of cardiovascular disease[27,28] and diabetes[3] are in fact proteins secreted specifically by tissue macrophages originating from blood monocytes. In accordance, the present study indicated that the number of neutrophils was associated with all-cause mortality, but this association disappeared after correction by monocyte number. In fact monocytes were the only WBC sub-type amongst neutrophils, lymphocytes, basophils, and eosinophils, which independently showed prognostic value in terms of mortality and incident cancer disease.

Explorative analyses suggested that the lower quintile of circulating monocytes of these community subjects might relate to adverse outcome in terms of incident cancer. Although the association showed a strong trend in a proportional Cox hazard model, which was corrected for relevant covariates, towards a higher rate of incident cancer amongst subjects with a lower quintile for monocyte number than in subjects with a normal level of monocytes, as defined by the second quintile for monocyte number, the result requires further investigation. This notion should be evaluated in studies with sufficient power to address this interesting interaction. The clinical rationale for this inter-

action of low monocyte number and incident cancer is that a low number of monocytes may signify malfunction of the immune system, which has been suggested to be associated with increased susceptibility towards cancer development.[29,30] It is by definition obvious that this trend towards a J-shaped curve of monocyte number for the prediction of incident cancer would decrease the strength of the otherwise significant association of a high monocyte number and incident cancer in the analyses presented above. It is likely, therefore, given that such a J-shaped interaction can be validated, that the predictive strength of a high number of monocytes in the prediction of incident cancer is even greater than the results have indicated of the present study.

The strengths of this study include the usefulness of validated registries available in Denmark for mortality and incident cancer diagnoses and the low migration rate of the population under study. Amongst the limitations are the rather low number of participants, making invalid the discriminative strengths of monocyte levels in predicting individual cancers, and the fact that this population consisted of subjects of Caucasian ethnicity, making it doubtful whether the results would apply to other races.

In conclusion it was shown that monocyte number is associated with incident cancer and mortality in middle-aged and elderly subjects who did not display apparent cardiovascular disease or cancer at baseline. Future studies should consider evaluating monocyte number as a prognostic candidate for incident cancer and mortality, a hypothesis that is substantiated by the results of the present study.

Conflict of interest statement

None declared.

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