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The systemic immune-inflammation index is associated with an increased risk of incident cancer—A population-based cohort study

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Several studies found that the systemic immune-inflammation index (SII) is a prognostic factor for mortality in patients with solid tumors. It is unknown whether an increased SII in generally healthy individuals reflects a risk for developing cancer. Our objective was to investigate the association between the SII and incident cancers in a prospective cohort study. Data were obtained from the Rotterdam Study; a population-based study of individuals aged ≥45 years, between 2002 and 2013. The SII at baseline was calculated from absolute blood counts. The association between the SII and the risk of any solid incident cancer during follow-up was assessed using Cox proportional hazard models. Individuals with a prior cancer diagnosis were excluded. Data of 8,024 individuals were included in the analyses. The mean age at baseline was 65.6 years (SD 10.5 years) and the majority were women. During a maximum follow-up period of 10.7 years, 733 individuals were diagnosed with cancer. A higher SII at baseline was associated with a 30% higher risk of developing a solid cancer (HR of 1.30 [95% CI; 1.11–1.53]), after adjustment for age, sex, socioeconomic status, smoking, BMI and type 2 diabetes. The absolute cumulative 10-year cancer risk increased from 9.7% in the lowest quartile of SII to 14.7% in the highest quartile (p-value = 0.009). The risk of developing cancer was persistent over time and increased for individuals with the longest follow-up. In conclusion, a high SII is a strong and independent risk indicator for developing a solid cancer.

Key words: circulatory marker, inflammatory marker, systemic immune-inflammation index, etiology, cancer risk
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Introduction

In 1863, Virchow observed the presence of leukocytes in neoplastic tissues and hypothesized an association between inflammation and cancer.[1] Since then, various theories regarding this presumed association have been proposed.[2–5] One theory suggests that low-grade, chronic inflammation increases the risk of cancer.[3] For example, a *Helicobacter pylori* infection is associated with gastric cancer, inflammatory bowel disease with colorectal cancer and tobacco smoke, in addition to being carcinogenetic, can induce chronic inflammation and is associated with lung cancer.[3,6] Alternatively, inflammation is considered a consequence, rather than the cause, of cancer.[1]

Inflammatory markers in blood can be used as biomarkers to study these hypotheses. Well-known inflammatory markers include C-reactive protein, erythrocyte sedimentation rate and white blood cell count.[7–11] A relatively novel inflammatory marker in this respect is the systemic immune-inflammation index (SII).[12]

It is an index that incorporates the absolute blood counts of neutrophils, lymphocytes as well as platelets, by multiplying the platelet count by the ratio of neutrophil and lymphocyte counts. Several studies found that the SII is a prognostic factor in patients with solid cancers, such as hepatocellular carcinoma, colorectal and pancreatic cancer.[12–14] So far, it is unknown whether an increased SII also is a marker for developing incident cancer in healthy individuals.

What's new?

The systemic immune-inflammation index (SII) incorporates blood counts of neutrophils, lymphocytes, and platelets. Several studies have found that the SII can help to predict mortality in patients with solid tumors. Might the SII also be useful in evaluating future cancer risk? In this prospective epidemiologic study, the authors found that an increased SII is independently associated with as much as a 30% higher risk of a future diagnosis of a solid cancer. These results indicate that inflammatory cells could play a role in the etiology of cancer. Further research is needed.

We hypothesized that when inflammatory cells play a role in the etiology of cancer, individuals with higher levels of inflammation, as measured by the SII, over a longer period of time are at a higher risk to develop cancer. Therefore, the objective of our study was to assess the relationship between SII levels at baseline and the subsequent risk of developing a solid cancer in a prospective, population-based cohort.

Methods

Study setting

The study was embedded in the Rotterdam Study, an ongoing prospective cohort study in community-dwelling elderly in the Ommoord suburb of the city of Rotterdam in the Netherlands. The rationale and design have been previously been described.[15] Briefly, in 1989, inhabitants aged 55 years and older were invited to participate. The original cohort was enrolled between 1989 and 1993 of whom 7,983 participated (78%). A second cohort of 3,011 persons (67% participation) was enrolled between 2000 and 2001. In 2006, a third cohort with 3,932 persons of 45 years and older were enrolled (65% participated). This resulted in an overall study population of 14,926 individuals aged 45 years and above.

Study population

Baseline values of the SII were measured at the earliest study center visit at which a leukocyte differential count was available: the fourth visit of the first cohort (January 2002–July 2004; n = 3,550), the second visit of the second cohort (July 2004–December 2005; n = 2,468) and the first visit of the third cohort (February 2006–December 2008; n = 3,932; see Supporting Information Fig. S1).[16] Data of individuals with missing granulocyte, lymphocyte or platelet counts or of individuals with a diagnosis of cancer (except nonmelanoma skin cancer) prior to the initial blood count at baseline were excluded (n = 687, see Fig. 1).

Assessment of the SII

Fasting blood samples were collected at the study center and full blood count measurements were performed immediately after blood draw. These measurements included absolute counts of granulocytes, lymphocytes and platelets and were performed using the COULTER® Ac·T diff2™ Hematology Analyzer (Beckman Coulter, San Diego, CA).

The SII was calculated from the platelet (P; $\times 10^9$/l), granulocyte, as a proxy for neutrophils (N; $\times 10^9$/l) and lymphocyte (L; $\times 10^9$/l) blood counts, using the following formula: SII = P × N/L.[12] Both the neutrophil-to-lymphocyte-ratio (NLR = N/L) and the platelet-to-lymphocyte ratio (PLR = P/L) were also calculated.

Collection of other variables

The following variables were considered as potential confounding factors: age, sex, socioeconomic status (high/intermediate/low), smoking status (current/former/never) and body mass index (BMI; kg/m^2). Individual characteristics were determined at baseline by interview or at the study center. Status on prevalent type 2 diabetes was ascertained from general practitioners' records (including laboratory glucose measurements), hospital discharge letters and serum glucose measurements at the study center. Diabetes was defined, according to the WHO guidelines, as a fasting glucose ≥7.0 mmol/l or use of glucose lowering medication.[17]

Assessment of outcome

The outcome of interest was the incident diagnosis of cancer. Cancer cases were identified from general practitioners' medical records (including hospital discharge letters), the Dutch Hospital Data registry and regional histopathology and cytopathology registries. Cases were coded independently by two physicians and classified according to the International Statistical Classification of Diseases, 10th revision (ICD-10) and the International Classification of Primary Care, 2nd edition (ICPC-2).[18,19] Information on cancer was available up till January 1, 2013. Only pathologically verified cases were used in the analyses. Incident solid cancers were defined as any primary malignant tumor, except nonmelanoma skin cancers or hematological malignancies.

Dates of death were obtained through the Netherlands Personal Records Database (BRP) and the causes of death were obtained from general practitioners' records or hospital discharge letters and coded similarly as morbidity.[18,19]

Statistical analysis

We explored all three biomarkers (NLR, PLR and SII) and compared models including the three biomarkers using the Akaike Information Criterion (see Supporting Information Table S1).[20] We found that the SII performed the best, therefore only the results comprising the SII were reported. Participants were divided into quartiles based on the SII established at baseline. Differences between the quartiles were assessed with ANOVAs for normally distributed continuous variables and with χ^2-tests for categorical variables. We estimated the absolute risk of being diagnosed with a solid cancer for each quartile of the SII using the cumulative incidence. Differences across the strata were tested using Gray's tests.[21–23]

The relationship between the SII level at baseline and the risk of any solid cancer during follow-up was assessed using Cox proportional hazard models (separate analyses were performed for

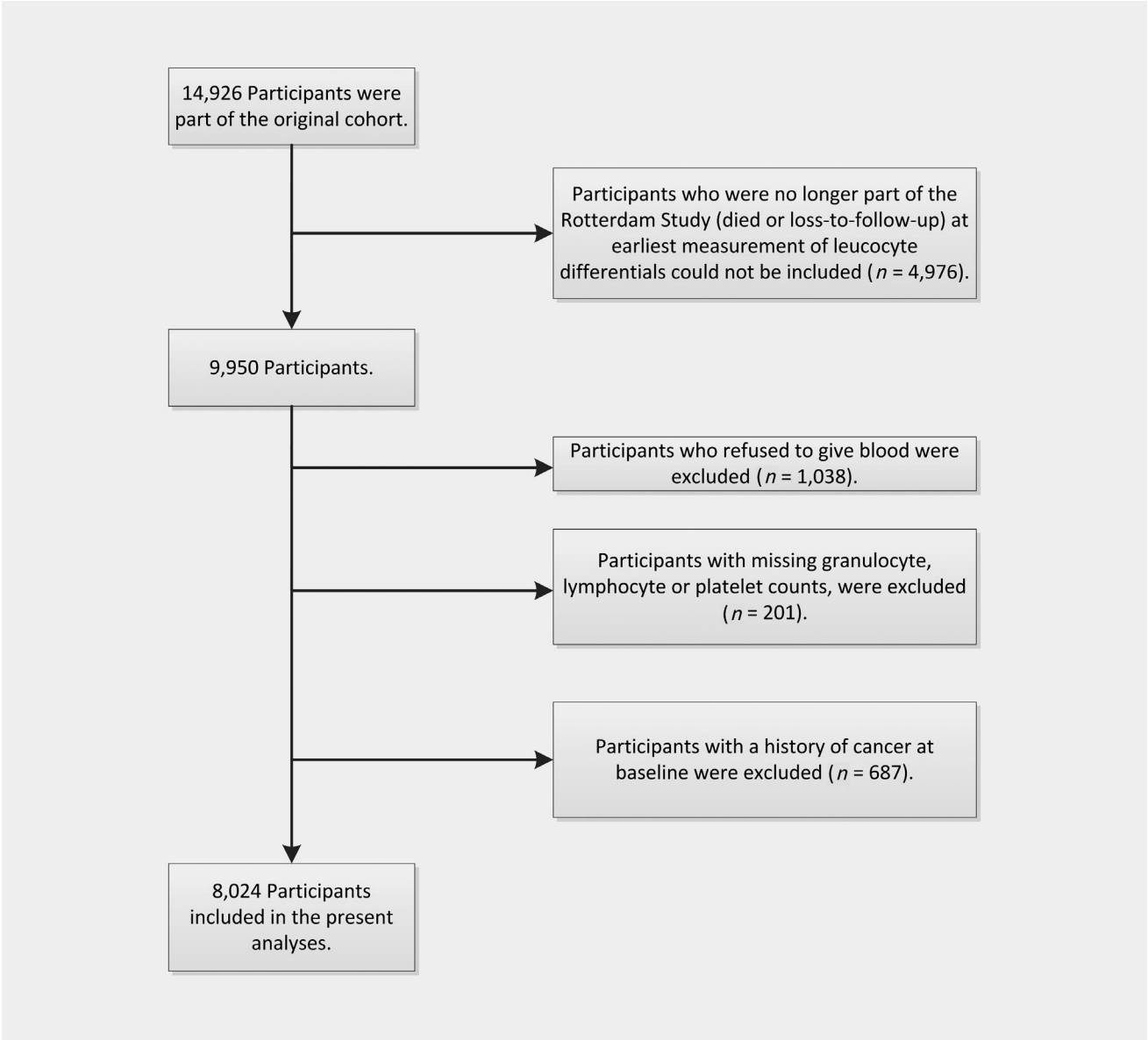

Figure 1. Flowchart of the study population inclusion.

breast, prostate, colorectal, lung and bladder cancer). For each individual, follow-up was defined in years, from the baseline date as described above, until the date of cancer diagnosis, death or end of study period (January 1, 2013), whichever came first.

The results are reported as hazard ratios (HR) and 95% confidence intervals (CI). The SII was log-transformed prior to being entered in any of the analyses. The proportional hazard assumption was assessed for all variables, using the Kaplan–Meier estimates for the categorical variables and the Schoenfeld's residuals for the continuous variables.[24]

All analyses were adjusted for previously mentioned cancer risk factors, that is, age, sex, SES, smoking status, BMI and diabetes. Variables were added to the crude model in a stepwise approach when a variable changed the effect estimate by more than 10% or when a variable was considered clinically relevant.[25] Effect modification was assessed for smoking and BMI by adding an interaction variable to the model and was considered statistically significant at a p-value <0.10.

First, we analyzed the SII as a continuous variable. Then, to assess whether there was a quartile-effect relationship, we stratified the SII into quartiles, in which the lowest one was taken as a reference category.

To explore whether the SII could be a marker of yet undetected disease we repeated the analysis only assessing the risk of cancer in the first 6 months of follow-up. To investigate whether the overall effect was not solely due to an inflammatory response to undetected cancers, and in fact a case of reverse causality, we additionally performed an analysis in which data of individuals with a

follow-up of less than 6 months, 2 years, 5 and 8 years, respectively, were subsequently excluded.

Statistical significance of associations was accepted at a *p*-value <0.05. All analyses were performed using SPSS software (Version 21.0) and SAS (Version 9.4, SAS Institute, Cary, NC).[26]

Results

General characteristics of the study population

Data of 8,024 individuals were included in the analyses (see Fig. 1). The mean age at baseline was 65.6 years (standard deviation [SD] 10.5 years) and 57.3% were women (*n* = 4,597). The mean BMI was 27.1 kg/m^2 (SD 4.1), 20.4% was a current smoker (*n* = 1,632), 48.6% a former smoker (3,897) and 10.9% had diabetes at baseline (*n* = 872). The median SII was 455 (IQR: 339–618). Population characteristics for each quartile of the SII can be found in Table 1.

The total follow-up was 53,582 person-years with a maximum of 10.7 years per person; for more than three-quarters of the participants, the follow-up period was at least 5 years. Completeness of follow-up at January 1, 2013, was 98.7%.

Development of a solid cancer

In total, 733 individuals (9.1%) developed a solid cancer during follow-up. The most frequent cancers were: colorectal (*n* = 123, 16.8%), prostate (*n* = 112, 15.3%), breast (*n* = 99, 13.5%), lung (*n* = 95, 13.0%) and bladder cancer (*n* = 83, 11.3%). Other solid cancers included esophagus, kidney, pancreas, melanoma and gastric cancer.

A higher SII at baseline was associated with a 43% increased risk of a solid cancer in the univariable analysis (HR: 1.43; 95% CI 1.22–1.67) and a 30% increased risk when adjusted for cancer risk factors mentioned above (HR 1.30; 95% CI: 1.11–1.53; see Tables 2 and 3). The effect of the SII was not modified by either smoking or BMI.

In the stratified analysis, the risk was higher in each subsequent quartile, with a significantly higher risk in the fourth quartile in comparison to the lowest quartile (HR: 1.39, 95% CI; 1.12–1.72), with a significant trend over the quartiles (*p*-value = 0.002, see Table 3).

The absolute 5- and 10-year risk of being diagnosed with a solid cancer were 5.4 and 9.7% in the lowest quartile compared to 7.2 and 14.7% in the highest quartile, respectively (see Fig. 2).

The risk of developing a solid cancer after a high baseline SII was significantly higher within the first 6 months after baseline, with a HR of 2.00 (95% CI; 1.09–3.67). The risk was persistent over time and increased for individuals with longer follow-up times (see Table 3).

Next, we assessed the effects for the five major cancers in this population (colorectal, prostate, breast, lung and bladder

Table 1. General cohort characteristics at baseline for each quartile of the SII

	Systemic immune-inflammation index				
Characteristic	Q1	Q2	Q3	Q4	*p*-value
	‹339	339–455	456–618	›618	
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Total	2,006	2,006	2,006	2,006	
Sex					
Male	915 (45.6)	854 (42.6)	837 (41.7)	821 (40.9)	‹0.001
Female	1,091 (54.4)	1,152 (57.4)	1,169 (58.3)	1,185 (59.1)	
Age (in years)					
Mean (SD)	65.0 (9.9)	64.9 (10.2)	65.5 (10.6)	67.2 (11.0)	‹0.001
Smoking[1]					
Current	346 (17.2)	388 (19.3)	440 (21.9)	458 (22.8)	‹0.001
Former	987 (49.2)	1,001 (49.9)	937 (46.7)	972 (48.5)	
Never	649 (32.4)	595 (29.7)	600 (29.9)	547 (27.3)	
SES[1]					
High	392 (19.5)	413 (20.6)	387 (19.3)	339 (16.9)	0.009
Intermediate	830 (41.4)	854 (42.6)	830 (41.4)	805 (40.1)	
Low	758 (37.8)	718 (35.8)	764 (38.1)	827 (41.2)	
BMI (in kg/m^2)[1]					
Mean (SD)	27.0 (3.7)	27.2 (4.1)	27.2 (4.2)	27.1 (4.5)	0.133
DM status					
Yes	187 (9.3)	208 (10.4)	220 (11.0)	257 (12.8)	0.004
No	1,819 (90.7)	1,798 (89.6)	1,786 (89.0)	1,749 (87.2)	

[1]Unknown: SES (*n* = 107, 1.3%), smoking (*n* = 104, 1.3%), BMI (*n* = 146, 1.8%).
Abbreviations: SES, socioeconomic status; BMI, body mass index; DM, diabetes mellitus.

Table 2. Univariate Cox proportional hazard regression for the association between baseline characteristics and diagnosis of a solid cancer

	Univariable analysis		
Clinical variable	**HR**	**Lower 95% CI**	**Upper 95% CI**
Cohort			
RS-I	Reference		
RS-II	0.92	0.78	1.09
RS-III	0.43	0.35	0.53
Female	0.58	0.50	0.67
Age (in years)	1.03	1.03	1.04
SES			
High	Reference		
Intermediate	1.07	0.86	1.32
Low	1.15	0.93	1.42
Smoking			
Never	Reference		
Former	1.52	1.27	1.83
Current	1.71	1.38	2.13
DM	1.62	1.33	1.98
BMI (in kg/m^2)	1.01	0.99	1.03
SII			
Logarithm	1.43	1.22	1.67

Abbreviations: SES, socio-economic status; DM, type II diabetes status; BMI, body mass index; SII, systemic immune-inflammation index; HR, hazard ratio; CI, confidence intervals.

cancer). These effects were similar for colorectal, prostate lung and bladder cancer, but we found null results for breast cancer (see Supporting Information Fig. S2).

Discussion

The association between inflammation and cancer is well known, and only partly understood as a result of its complex nature.[2–4] On the one hand, inflammation is thought to induce cancer, but on the other hand, it may also be secondary to a systemic inflammatory response to yet-undetected tumor and accumulated DNA-damage. In both occasions, the products of inflammatory processes can be considered as potential biomarkers.[2–5,9] These markers have a prognostic and potentially also a predictive value in solid cancers.[27,28]

To the best of our knowledge, this is the first study on the etiological association between the SII and incident cancers in the general population. The SII is a relatively new composite measure of the neutrophil, lymphocyte and platelet counts in the peripheral blood.[12] Neutrophils were traditionally considered innocent bystanders in the cancer setting. More recently, it has been assumed, however, that neutrophils may be important in tumor initiation, progression and metastasis.[29,30] Pro-metastatic effects of platelets are attributed to the adhesion of platelets to tumor cells, thereby providing a shield protecting

Table 3. Multivariable Cox proportional hazard regression for the association between baseline levels of the SII with the development of a solid tumor

	Total follow-up		Follow-up › 6 months		Follow-up ›2 years		Follow-up ›5 years		Follow-up ›8 years	
SII	**HR[1]**	**95% CI**	**HR[1]**	**95% CI**	**HR[1]**	**95% CI**	**HR[1]**	**95% CI**	**HR[1]**	**95% CI**
Q1	Reference		Reference		Reference		Reference		Reference	
Q2	1.13	0.91–1.42	1.11	0.88–1.40	1.12	0.86–1.45	1.23	0.81–1.88	1.19	0.40–3.55
Q3	1.23	0.98–1.53	1.19	0.95–1.49	1.26	0.97–1.62	1.56	1.05–2.34	1.73	0.64–4.63
Q4	1.39	1.12–1.72	1.33	1.07–1.66	1.37	1.07–1.77	1.82	1.22–2.71	2.92	1.15–7.36
Logarithm	1.30	1.11–1.53	1.26	1.07–1.50	1.27	1.05–1.54	1.48	1.10–1.99	2.20	1.12–4.32
p-value for trend	0.002		0.010		0.009		0.001		0.009	

Number of patients/cohort: 692/7703 for the total follow-up period, 646/7643 for follow-up ›6 months, 508/7406 for follow-up ›2 years, 213/6014 for follow-up ›5 years and 44/2360 for follow-up ›8 years.
[1]Adjusted for cohort, sex, age (years), socioeconomic status (high/intermediate/low), smoking status (current/former/never), BMI (body mass index, kg/m^2) and Type II diabetes status.
Abbreviation: SII, systemic immune-inflammation index.

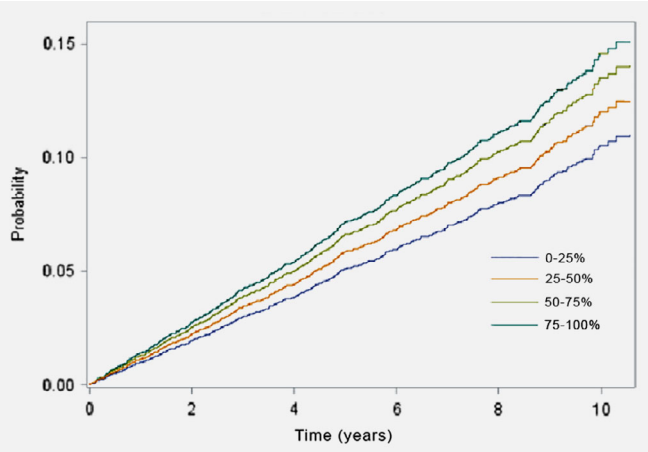

Figure 2. Absolute risk of being diagnosed with a solid cancer for each quartile of the SII. [Color figure can be viewed at wileyonlinelibrary.com]

against cell death, but also to platelet-derived factors that enable cells to migrate from the bloodstream into visceral organs.[31,32] Lymphocytes, on the other hand, are thought to have an antitumor effect through their ability to specifically target and then kill cancer cells.[33,34] From this, it would logically follow that individuals with increased levels of neutrophils and platelets and/or decreased levels of lymphocytes are at a higher risk of developing cancer.

The results of the present analyses indicate that individuals from the general population who have higher levels of the SII at baseline are more likely to be diagnosed with a solid cancer during follow-up. We showed an increased risk for each subsequent quartile. When exploring the association between the SII and risk of cancer over time, it appeared that the risk increased within the first 6 months of follow-up. This effect could reflect a systemic immune response to a cancer that is already present, however yet undetected. Whether the SII could function as a biomarker for early detection should be further explored. Studies exploring the effect of changes in the SII over time would be especially insightful. Although we would be cautious in using this marker as a screening tool since it is a general inflammatory marker and is therefore nonspecific.

Despite the fact that the risk is increased in the first 6 months of follow-up, the overall effect cannot merely be explained by reverse causality. The risk persisted after exclusion of data individuals with a follow-up of 6 months or less and increased when we subsequently evaluated the risk for individuals with a follow-up period of more than 2, 5 or even 8 years of follow-up. This phenomenon supports the hypothesis that chronic inflammation is a risk factor for cancer development. Interestingly, both the innate and adaptive immune systems seem to be involved. In which the innate immune system seems to be activated, whereas the adaptive immune system seems to be downregulated. However, whether the inflammatory cells contained in the SII play a causal role in the initiation or the further development of solid tumors remains to be elucidated. Furthermore, chronic inflammation can be induced by environmental factors. Both smoking and a high BMI are associated with this type of inflammation. Yet we found no effect modification by either of these factors.[3]

To see whether the found effect could be attributed to any specific cancer, we performed a secondary analysis in which alternately the five major solid tumors (colorectal, prostate, breast lung and bladder cancer) in this population were taken as an endpoint. The effect was present for colorectal, bladder and lung cancer, but was only statistically significant for prostate cancer. We found no effect for breast cancer which may have been due to lack of power, or to differences in tumor biology.

Strengths and limitations

We showed a relationship between the SII and the diagnosis of a solid cancer in a prospective, population-based cohort, with a long term follow-up of a large number of people. This setting is the design of choice for assessing a relationship between blood levels and the risk of cancer. The association remained robust after adjustment for potential confounders, of which we collected detailed information, and was substantiated by the significant dose-effect relationship as well as an increase of the risk over time.

Ideally, we should have related the SII to the different disease stages. We would hypothesize that individuals with a higher level at baseline were more likely to be diagnosed with metastasized disease and those with relatively lower levels with local disease.[27] Unfortunately, information on stage at diagnosis was not available.

Another limitation was that we had only a single measurement. Multiple measurements over a longer time period would allow for more precise measurement and a better understanding of the association. One would be able to better assess whether the SII increases in time up to the diagnosis and could also be used as a marker for early detection.

Finally, the design of our study did not allow for the assessment of a potential prognostic potential of the SII, although from literature, it is known the SII also has prognostic value.[12,13] Recently, some studies have also shown that related inflammatory markers, such as the neutrophil-to-lymphocyte ratio may have a predictive value.[28,35] In the future markers such as the SII could help guide therapeutic choices in patients, especially in immunotherapy.[36,37]

In conclusion, the SII is an independent risk indicator for a future diagnosis of a solid cancer on the shorter and longer term. Future studies should further explore and validate this association.

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Ethics Statement

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalog number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

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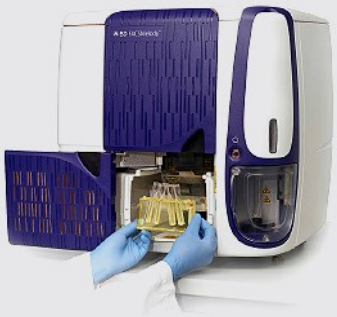

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