## Impact of red cell distribution width on future risk of cancer and all-cause mortality among cancer patients – the Tromsø Study

Red cell distribution width (RDW) has recently been associated with the risk of cardiovascular disease and all-cause mortality.[1,2] The underlying mechanisms remain unresolved, but high levels of RDW may be caused by inflammation or poor nutritional status.[3] Inflammation and malnutrition are known risk factors of cancer, and chronic inflammation may lead to cancer in several organs.[4,5]

Recent case control studies have shown associations between RDW and colon cancer and malign biliary obstruction.[6,7] In addition, RDW has been shown to predict cancer in patients with unintentional weight loss, and to be associated with poor prognosis in patients with lung cancer and multiple myeloma.[8-10] Since active malignancy is accompanied by a prolonged inflammatory response, and inflammatory processes influence RDW,[3,5,11] the retrospective design of these previous studies makes it impossible to determine whether high RDW is causally related to cancer development. As limited knowledge exists regarding the association between high RDW and future cancer development or disease activity, we thus performed a large prospective population-based study to assess the impact of RDW on future risk of incident cancer, cancer stage and mortality among cancer patients.

Participants were recruited from the fourth survey of the Tromsø Study conducted in 1994-95. A detailed description of the study design and population has been published elsewhere.[12] The regional committee of medical and health research ethics approved the study, and all 25 383 included subjects gave their written consent to participate. Baseline information was collected by self-administered questionnaires, blood samples and a physical examination.[1] Incident cancer diagnosis, grade and site, as well as mortality among the cancer patients, were recorded from the date of enrolment through to the end of follow-up on December 31, 2010. All cancer diagnoses in the Norwegian population are registered in the Cancer Registry of Norway, and information about cancer in the cohort was obtained by linkage to the cancer registry using a unique 11-digit personal identification number. In a recent evaluation of data quality, the Cancer Registry of Norway had a completeness of 98.8%, with 94% of the cases being histologically verified.[13] Information on mortality was obtained by linkage to the national Cause of Death Registry at Statistics Norway.

Statistical analyses were carried out with STATA, version 13 (Stata corporation, College Station, TX, USA). For analyses of the association between RDW and cancer, person-time of follow-up was calculated from the date of enrolment to the date when cancer was first diagnosed, to the date when the participant died or moved from the municipality of Tromsø, or to the end of the study period, whichever came first. Cox proportional hazard regression models were used to obtain crude, sex-adjusted, and multivariable adjusted hazard ratios (HR) with 95% confidence intervals (CI) for incident cancer according to RDW levels. The lowest RDW quartile was used as the reference category in the Cox models, and age was used as the timescale. The multivariable model included BMI, smoking, white blood cell count and haemoglobin.

For analysis of the association between RDW and all-cause mortality among cancer patients, person-time was calculated from the date of cancer diagnosis to the date of death, date of migration or the end of the study period. The three lower RDW quartiles were merged and used as the reference category in the mortality analysis.

In total, 1 191 men and 1 114 women were diagnosed with cancer during 332 575 person-years of follow-up (median 15.7 years). The mean RDW levels were 12.8% for men and 12.9% for women. In our hospital laboratory, the reference range for RDW is 11.7-14.5%. Previously, we have published data on baseline characteristics across categories of RDW.[2] Age, white blood cell counts, proportion of smokers and subjects with anaemia increased with higher categories of RDW, whereas the haemoglobin concentration decreased. The proportion of subjects with anaemia, defined as haemoglobin levels <12.0 g/dL in females and <13.0 g/dL in men, was higher in women than in men in all RDW categories, while the proportion of smokers showed a more pronounced increase across RDW quartiles in men than in women.

The multivariable-adjusted risk of cancer was 30% higher in men in the highest compared with the lowest RDW quartile (HR 1.30, 95% CI 1.07-1.59) (Table 1), and men with RDW above the 95$^{th}$ percentile (RDW ≥14.3%) had an 83% higher cancer risk (HR 1.83, 95% CI 1.43-2.22). Apparently, there was no significant association between RDW and the risk of cancer in women (HR upper *versus*

**Table 1.** Sex-specific incidence rates (IRs) and hazard ratios (HRs) with 95 % confidence intervals (CIs) for incident cancer according to quartiles (Q), and above the 95$^{th}$ percentile, of red cell distribution width (RDW).

| RDW (%) | Person-years | Events | Crude IR* (95% CI) | Crude HR (95% CI) | Multiadjusted HR** (95% CI) |
|---|---|---|---|---|---|
| Men | 156 591 | 1191 | 7.61 (7.19-8.05) | | |
| Q1 (11.0-12.3) | 40 081 | 146 | 3.64 (3.10-4.28) | ref | ref |
| Q2 (12.4-12.7) | 43 257 | 236 | 5.46 (4.80-6.20) | 1.03 (0.84-1.27) | 1.02 (0.83-1.26) |
| Q3 (12.8-13.1) | 35 731 | 288 | 8.06 (7.18-9.05) | 1.15 (0.94-1.40) | 1.12 (0.91-1.38) |
| Q4 (13.2-30.5) | 37 522 | 521 | 13.89 (12.74-15.13) | 1.40 (1.15-1.69) | 1.30 (1.07-1.59) |
| >95$^{th}$perc. (14.3-30.5) | 6 037 | 157 | 26.00 (22.24-30.40) | 1.94 (1.54-2.46) | 1.83 (1.43-2.33) |
| Women | 175 984 | 1114 | 6.33 (5.97-6.71) | | |
| Q1 (10.7-12.3) | 46 047 | 215 | 4.67 (4.09-5.34) | ref | ref |
| Q2 (12.4-12.7) | 44 529 | 269 | 6.04 (5.36-6.81) | 1.02 (0.85-1.23) | 1.01 (0.84-1.21) |
| Q3 (12.8-13.2) | 42 797 | 287 | 6.71 (5.97-7.53) | 0.99 (0.83-1.19) | 0.95 (0.80-1.14) |
| Q4 (13.3-24.5) | 42 610 | 343 | 8.05 (7.24-8.95) | 1.14 (0.96-1.36) | 1.09 (0.91-1.31) |
| >95$^{th}$perc. (14.6-24.5) | 9 155 | 57 | 6.22 (4.80-8.07) | 1.06 (0.79-1.42) | 1.12 (0.82-1.52) |

*Incidence rates are per 1000 person-years; **adjusted for body mass index, smoking, white blood cell count and hemoglobin levels at baseline. Age as time-scale.*

Table 2. Incidence rates (IRs) and hazard ratios (HRs) with 95 % confidence intervals (CIs) for cancer stage by quartiles (Q) of red cell distribution width (RDW) stratified by gender and age (women only).

| RDW (%) | Person-years | Events | Crude IR* (95% CI) | Crude HR (95% CI) | Multiadjusted HR** (95% CI) |
|---|---|---|---|---|---|
| Men | | | | | |
| **Localized** | 156 591 | 461 | 2.9 (2.7-3.2) | | |
| Q1-3 (11.4-13.1) | 119 069 | 289 | 2.4 (2.2-2.7) | ref | ref |
| Q4 (13.2-19.6) | 37 522 | 172 | 4.6 (3.9-5.3) | 1.07 (0.88-1.30) | 1.09 (0.89-1.33) |
| **Regional spread** | 156 591 | 274 | 1.7 (1.6-2.0) | | |
| Q1-3 (11.5-13.1) | 119 069 | 159 | 1.3 (1.1-1.6) | ref | ref |
| Q4 (13.2-30.5) | 37 522 | 115 | 3.1 (2.6-3.7) | 1.27 (0.99-1.62) | 1.15 (0.89-1.49) |
| **Distal metastasis** | 156 591 | 235 | 1.5 (1.3-1.7) | | |
| Q1-3 (11.2-13.1) | 119 069 | 118 | 1.0 (0.8-1.2) | ref | ref |
| Q4 (13.2-18.3) | 37 522 | 117 | 3.1 (2.6-3.7) | 1.58 (1.21-2.05) | 1.35 (1.03-1.77) |
| Women <55 years | | | | | |
| **Localized** | 130 949 | 260 | 2.0 (1.8-2.2) | | |
| Q1-3 (11.4-13.1) | 102 210 | 201 | 2.0 (1.7-2.3) | ref | ref |
| Q4 (13.2-19.8) | 28 739 | 59 | 2.1 (1.6-2.6) | 0.96 (0.72-1.28) | 1.00 (0.74-1.36) |
| **Regional spread** | 130 949 | 146 | 1.1 (0.9-1.3) | | |
| Q1-3 (11.3-13.2) | 102 210 | 112 | 1.1 (0.9-1.3) | ref | ref |
| Q4 (13.3-18.2) | 28 739 | 34 | 1.2 (0.8-1.7) | 1.00 (0.68-1.47) | 1.02 (0.68-1.53) |
| **Distal metastasis** | 130 949 | 93 | 0.7 (0.6-0.9) | | |
| Q1-3 (11.1-13.2) | 102 210 | 67 | 0.7 (0.5-0.8) | ref | ref |
| Q4 (13.3-17.2) | 28 739 | 26 | 0.9 (0.6-1.3) | 1.22 (0.78-1.92) | 1.14 (0.70-1.84) |
| Women ≥55 years | | | | | |
| **Localized** | 45 034 | 216 | 4.8 (4.2-5.4) | | |
| Q1-3 (11.4-13.2) | 31 163 | 135 | 4.3 (3.7-5.1) | ref | ref |
| Q4 (13.3-17.3) | 13 872 | 81 | 5.8 (4.7-7.3) | 1.28 (0.97-1.69) | 1.23 (0.93-1.64) |
| **Regional spread** | 45 034 | 137 | 3.0 (2.6-3.6) | | |
| Q1-3 (11.4-13.2) | 31 163 | 97 | 3.1 (2.6-3.8) | ref | ref |
| Q4 (13.3-18.0) | 13 872 | 40 | 2.9 (2.1-3.9) | 0.88 (0.61-1.27) | 0.88 (0.60-1.28) |
| **Distal metastasis** | 45 034 | 127 | 2.8 (2.4-3.4) | | |
| Q1-3 (11.7-13.2) | 31 163 | 78 | 2.5 (2.0-3.2) | ref | ref |
| Q4 (13.3-15.5) | 13 872 | 49 | 3.5 (2.7-4.7) | 1.34 (0.94-1.92) | 1.30 (0.89-1.88) |

*Incidence rates are per 1000 person-years; **adjusted for body mass index, smoking, white blood cell count and hemoglobin level at baseline. Age as time-scale.*

lower quartile: 1.09, 95% CI 0.91-1.31) (Table 1). However, stratification of women according to age (≥55 years) revealed that women of post-menopausal age had a similar risk of incident cancer as did men in the same age group. Women older than 55 in the highest RDW quartile had a 22% higher risk of incident cancer than women in the three lower quartiles (HR 1.22, 95% CI 1.02-1.45) (data not shown).

There was an association between high RDW and increased risk of regional and distal metastasis at the time of diagnosis in men and women of post-menopausal age (Table 2). In men, a 1% increase in RDW was associated with a 21% increased risk of regional cancer spread (HR 1.21, 95% CI 1.11-1.33) and a 19% increased risk of distal metastasis (HR 1.19, 95% CI 1.06-1.33) after multivariable adjustment (*data not shown*). The risk estimates were essentially similar in women.

On average cancer patients were followed for up to 3.9 years after the initial cancer diagnosis (range 1 day to 15 years). The association between RDW and death after cancer diagnosis is shown in Table 3. During this period, 500 (46%) female and 590 (51%) male patients died. Male cancer patients within the highest RDW quartile had a 25% higher risk of death during follow-up than men in the three lower quartiles (HR 1.25, 95% CI 1.05-1.49) after multivariable adjustment. The association between RDW and mortality disappeared after further adjustment for advanced cancer stage at diagnosis (HR quartile 4 *versus* quartiles 1-3: 1.09, 95% CI 0.91-1.30). There was a similar trend among women, though the risk estimate was not statistically significant (HR quartile 4 *versus* quartiles 1-3: 1.18, 95% CI 0.97-1.43).

Our findings are in part supported by previous studies on the association between RDW and cancer.[6-9] In a case-control study, RDW was higher in 225 patients with colon cancer compared to 494 cancer-free controls,[6] and was reported to be a useful tool to differentiate between benign and malign causes of biliary obstruction.[7] As occult cancer may affect RDW through low-grade inflammation, we excluded 131 participants who were diagnosed with cancer within one year after the inclusion date, resulting in a mean time from inclusion to diagnosis of 9 years. Further, sensitivity analysis was performed by extending the exclusion interval from one to two years from study inclusion to cancer diagnosis (excluding an additional 127 subjects) without affecting the risk estimates for cancer by RDW. Moreover, adding the time from baseline to cancer diagnosis as an extra adjustment variable did not alter the results. Thus, our findings demonstrate a clear temporal sequence between exposure (RDW) and outcome (incident cancer).

While there was no association between RDW and cancer among women younger than 55, women older than 55 had a similar risk to men. The prevalence of iron deficiency anaemia is higher in pre-menopausal than post-menopausal women,[14] and RDW is strongly associated with iron deficiency anaemia.[15] Within the highest RDW

**Table 3.** Sex-specific hazard ratios (HRs) with 95 % confidence intervals of death following a cancer diagnosis (n=2305) according to quartiles (Q) of red cell distribution width (RDW).

| RDW (%) | Person-years | Events | Crude HR (95% CI) | Model 1* (95% CI) | Model 2^ (95% CI) |
|---|---|---|---|---|---|
| Men | 4 192 | 590 | | | |
| Q1-3 (11.2-13.1) | 2 440 | 266 | ref | ref | Ref |
| Q4 (13.2-30.5) | 1 752 | 324 | 1.41 (1.19-1.67) | 1.25 (1.05-1.49) | 1.09 (0.91-1.30) |
| Women | 4 721 | 500 | | | |
| Q1-3 (11.1-13.2) | 3 374 | 318 | ref | ref | Ref |
| Q4 (13.3-20.7) | 1 321 | 182 | 1.21 (1.01-1.46) | 1.18 (0.97-1.43) | 1.06 (0.87-1.30) |

**Model 1 is adjusted for body mass index, smoking, white blood cell count and hemoglobin level; ^model 2: model 1 + regional and distal metastasis; age is time-scale in both models.*

quartile in our cohort, 22% of women younger than 55 had anaemia, while the corresponding proportion was 7% in older women. Moreover, stratification of the cohort according to anaemia status and adjustment for haemoglobin concentration did not influence the risk estimates for cancer by RDW (*data not shown*). Our findings indicate that anaemia, and iron deficiency in particular, is probably not the underlying link between high RDW and cancer risk. We suggest that mechanisms other than anaemia and iron deficiency without anaemia, such as worsened health conditions with subsequent low-grade inflammation, may link high RDW to cancer risk. Alternatively, endogenous sex-hormones may protect pre-menopausal women from the risk of cancer among those with high RDW.

RDW was associated with advanced cancer stage and worsened prognosis among cancer patients in our study. Accordingly, elevated RDW was associated with more advanced cancers and worse prognosis in a study of 146 patients with multiple myeloma,[10] and a correlation was found between elevated RDW, cancer stage and prognosis among lung cancer patients.[9] In the present study, the apparent association between RDW and mortality in cancer patients was substantially weakened after adjustment for regional and distal metastasis at cancer diagnosis. These findings suggest that the correlation between high RDW and cancer-related mortality could be explained by the association between high RDW and more advanced cancer stages at diagnosis.

We found a dose-dependent relation between RDW and future risk of cancer in men and in women of post-menopausal age. The apparent association between RDW and case-fatality disappeared after adjustment for cancer stage, suggesting that the relation is explained by the ability of RDW to predict advanced cancers. Further studies are warranted to confirm our original findings, and to explore the underlying mechanism or mechanisms.

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