Microcytosis as a risk marker of cancer in primary care: a cohort study using electronic patient records.

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ABSTRACT

Background: Microcytosis, smaller than normal red blood cells, has previously been identified as a possible early risk marker for some cancers. The role of microcytosis across all cancers has not been fully investigated.

Aim: To examine cancer incidence in a cohort of patients with microcytosis, with or without accompanying anaemia

Design and setting: Cohort study of patients aged ≥40 years using UK primary care electronic patient records.

Methods: The 1-year cancer incidence was compared between cohorts of patients with a mean red cell volume of < 85fL (low) or 85fL-101fL (normal). Further analyses examined gender, age-group and cancer site, and haemoglobin values.

Results: 497 out of 12,289 patients with microcytosis had a new cancer diagnosis within 1 year (4.0%, 95% confidence interval 3.7 to 4.4), compared to 1,465 of 73,150 without microcytosis (2.0%, CI 1.9 to 2.1). In males, 298 out of 4,800 with microcytosis developed cancer (6.2%, CI 5.5 to 6.9), compared to 940 out of 34,653 without (2.7%, CI 2.5 to 2.9). In females with microcytosis, 199 out of 7,489 developed cancer (2.7%, CI 2.3 to 3.1), compared to 525 out of 38,497 without (1.4%, CI 1.3 to 1.5). In patients with microcytosis but normal haemoglobin, 86 out of 2,637 males (3.3%, CI 2.6 to 4.0) and 101 out of 5,055 females (2.0%, CI 1.6 to 2.4) were diagnosed with cancer.

Conclusions:

Microcytosis is a predictor of underlying cancer even if haemoglobin is normal. Although a benign explanation is more likely, clinicians in primary care should consider simple testing for cancer in unexplained microcytosis, particularly in males.

Keywords: Microcytosis; Cancer; Primary Health Care; General Practice; diagnosis

How this fits in

Microcytosis has long been recognised with iron deficiency and with haemoglobinopathies. Similarly, iron deficiency has been identified as a feature of some cancers, particularly colorectal. However, the relationship between microcytosis and other cancers was largely unknown, including the importance of microcytosis without anaemia. This study has found an overall cancer risk in those aged ≥40years of 6.2% in males and 2.7% in females, with colorectal and lung cancer the most frequent. Further, even with a normal haemoglobin, microcytosis represents a small – but real – risk of underlying cancer.

Introduction

There were 163,444 deaths from cancer in the UK in 2016,(1) accounting for more than a quarter (28%) of all UK deaths.(2) Whilst cancer survival rates are improving, the UK still lags behind many other economically developed countries internationally(3, 4) and has generally lower survival rates than comparable European countries.(5) These differences are due in part to delays in diagnosis,(3) with cancers in the UK diagnosed at a later stage compared to other European countries.(6) The NHS long term plan, released in 2019, targets that by 2028 the proportion of cancers diagnosed at stages 1 and 2 will rise from around half now to three quarters.(7) It is important for primary care clinicians to recognise features of possible cancer in order to investigate appropriately.(8)

Some previous primary care research studies have found a number of blood test features to be associated with cancer that could act as early risk markers. These include: thrombocytosis,(9) raised inflammatory markers,(10) hypoalbuminaemia(11) and hypercalcaemia.(12) Thrombocytosis was more commonly associated with patients who had lung and colorectal cancers, and one third of the patients with lung or colorectal cancer and thrombocytosis had no other symptoms indicating malignancy.(9) A study into early detection of multiple myeloma in primary care found an association between myeloma and macrocytosis. (13)

Previous studies have recently identified microcytosis (smaller than normal red blood cells) as a potential early risk marker for certain cancers including: lymphoma,(14) oesophago-gastric,(15) colorectal,(16) and kidney cancer.(17) These risks were independent of any anaemia. The precise role of microcytosis in primary care across all cancers is not currently known, particularly in patients without anaemia. This study aims to investigate the role of microcytosis as a risk marker for all cancers.

Methods

Data sources

This cohort study used electronic patient records from the Clinical Practice Research Datalink (CPRD) which holds anonymised primary care records from a network of over 1,400 UK practices. It includes information on symptoms, referrals and laboratory tests.(18) The cases for this study were derived from the control sample of previously published CPRD studies.(12,19) CRPD cases were patients aged ≥40 years with a record of cancer at 1 of 13 cancer sites between 2000 and 2009. Each case was matched to five controls with no record of the cancer of interest at the diagnosis date of the case, but could have any other cancer. Matching was done by sex, practice and year of birth. (12, 19)

Patient sample

108,993 patients were studied with a mean cell volume (MCV) result between 2006 and 2008 and who were aged ≥40 years at the time of testing. We chose 2006 as a starting point to account for the introduction of the Quality and Outcomes Framework, and the NICE Guideline, Referral for Suspected Cancer in 2005,(20) and a cut off of 2008 allowed for one year follow up for looking at cancer diagnoses. Patients were grouped into either: microcytosis or a normal MCV. An upper boundary for microcytosis was chosen as 85 femtolitres (fL) due to the common use of that value as a threshold in UK practice, though 80fL is commonly used in North America.(21) Patients with MCV values below 50fl were excluded, for two reasons: the result could have been erroneous, and even if not, clinically such patients are likely to warrant investigation on such an extreme finding alone. The index date was defined as the date of the first MCV result. A comparison sub-cohort of patients with a normal MCV, defined as 85-101fL, were used with the same age and date criteria. Values above 101fL were defined as macrocytosis and were therefore excluded. Haemoglobin values reported on

the same day as the MCV were also identified. We excluded patients diagnosed with cancer (other than non-melanoma skin cancer) before the index date from both study and comparison groups.

Cancer outcomes

New diagnoses of cancer (other than non-melanoma skin cancer) within 1 year of the index date were found by searching the patient records, using a previously published list of cancer codes (available from authors on request).

Statistical methods and analysis

The primary analysis was the 1-year cancer incidence, expressed as a percentage (with 95% confidence intervals) for patients in the microcytosis group and for the normal MCV group. This one-year incidence could be regarded as a positive predictive value for microcytosis.

Further sub-analyses were performed by sex, age-group and cancer site. Additional analyses examined the incidence in patients with a second MCV test result within 3 months and 6 months of the index test; the incidence in the microcytosis group if the upper threshold were lowered to 80fL, and the period between test date and cancer diagnosis. Cancer incidences in patients with microcytosis with or without anaemia are also reported. Anaemia was defined as below 13.0g/dl for males and below 11.5g/dl for females. Analyses were performed using Stata 15.

Results

After all exclusions, there were 85,439 participants: 12,289 with microcytosis and 73,150 with a normal MCV. (Figure1) In the microcytosis cohort, the median age was 73 years (interquartile range= 64 to 81); 4,800 were male (39.1%). In the normal cohort there were 73,150 patients, with a median age of 71 (63 to 79) and 34,653 being male (47.4%).

Figure 1 here

Cancer diagnoses

497 patients in the microcytosis group had a cancer diagnosis, representing a 1-year cancer incidence of 4.0% (CI 3.7 to 4.4). In the normal group 1,465 patients were diagnosed with cancer, a 1-year cancer incidence of 2.0% (CI 1.9 to 2.1). The median age at cancer diagnosis in the microcytosis group was 76 years (interquartile range= 70 to 83) and for the normal group it was 75 (68 to 81).

Gender

The 1-year cancer incidence was higher in males for both groups with 298 of 4,800 males with microcytosis (6.2%, CI 5.5 to 6.9), and 199 of 7,489 females (2.7%, 2.3 to 3.1). In males with a normal MCV 940 of 34,653 were diagnosed with cancer (2.7%, 2.5 to 2.9), and 525 of 38,497 females (1.4%, 1.3 to 1.5). (Table 1). The cancer incidence with microcytosis was higher than with a normal MCV across both age groups, the highest cancer incidence being in males over 70 with microcytosis, with 225 out of 3,008 developing cancer (7.5%, 6.6 to 8.5).

Table 1 here

Cancer sites

The cancer sites for the two genders are shown in Figure 2. Cancer sites that made up a greater proportion of cancers diagnosed in the microcytosis cohort than the normal cohort were: colorectal (113, 23%), lung (67, 13%), lymphoma (24, 5%), kidney (22, 4%) and stomach (15, 3%).

Figure 2 here

In the microcytosis cohort, 3,187 participants had a second MCV result within 3 months of the index date (74.6% of these also showed microcytosis). In those who remained microcytic 175 out of 2,377 were diagnosed with cancer (7.4%, CI 6.3 to 8.5) compared to 27 of 809 (3.3%, CI 2.2 to 4.8) in those whose second MCV was within the normal range. Similar figures were found for repeat blood test within six months.

Reanalysis using 80fL as the upper limit for the microcytosis group increased the cancer incidence in those with an 'abnormal' result to 190 out of 2940 overall (6.5%, 5.6 to 7.4), with 120 of 1,101 males (10.9%, 9.1 to 12.9) and 70 of 1,839 females (3.8%, 3.0 to 4.8). In the microcytosis group, the median period between the index date and cancer diagnosis was 80 days, whereas in the normal MCV group the median period to cancer diagnosis was 113 days.

Concomitant anaemia

2,162 of 4,799 (45%) males and 2,433 of 7,488 (32%) females in the microcytosis group also had anaemia at the index date. Two cases apparently had a second blood test on the index date yielding

a discordant result. These two were omitted from this sub-analysis. In those with microcytosis and anaemia, 212 of 2,162 males (9.8%, CI 8.6 to 11.1) and 98 of 2,433 females (4.0%, 3.3 to 4.9) were diagnosed with cancer. In those with microcytosis and normal haemoglobin, 86 of 2,637 males (3.3%, 2.6 to 4.0) and 101 of 5,055 females (2.0%, 1.6 to 2.4) were diagnosed with cancer within a year. Colorectal cancer was the most common cancer in all females and males with microcytosis and anaemia, whereas in males with microcytosis only, prostate was the most common. (Table 2)

Table 2 here

Discussion

Summary

This study is the first to report the incidence of cancer in patients with microcytosis compared to those with a normal MCV in primary care across all cancer types. The overall 1-year cancer incidence in those with microcytosis was 4.0%, (3.7 to 4.4), compared to 2.0% (1.9 to 2.1) in those with a normal MCV. The difference was more marked in males, with 6.2% (5.5 to 6.9) of microcytic patients developing cancer, and only 2.7% (2.3 to 3.1) of females doing so. Individual cancers that were disproportionately more common with microcytosis were colorectal, lung, lymphoma, kidney and stomach. In patients who had microcytosis but with normal haemoglobin, 3.3% (2.6 to 4.0) of men and 2.0% (1.6 to 2.4) of women had a diagnosis of cancer within a year.

Strengths and limitations

The large size of this study is a key strength, as well as the setting in primary care - where patients often present symptoms that could trigger cancer investigation. The study is largely representative of the UK population, other than the matching to a previous cancer case population. This may have increased the cancer risk in the population, but should have done so equally for those with microcytosis and their comparison group. The study is reliant on the quality of CRPD data: however since 2000, laboratory test data has been automatically transmitted to most GP practices (16) which considerably reduces the chance of transcription error. We do not know why the blood test was taken. Blood tests are commonly performed in primary care for many different reasons: around 1 in 4 of the adult UK population have a full blood count in any one year.(16) Even so, the quarter of the over 40s population who have had a blood test and so are expected to be a somewhat more ill population. This is why the comparison cohort used were patients with a 'normal' MCV result rather

than the untested population. We used an upper threshold of 85fL to define 'microcytosis' - a conservative choice, though reflecting common UK practice.

Comparison with existing literature

The results of this study largely agree with previous CPRD studies that found that microcytosis was associated with: non-Hodgkin lymphoma,(14) oesophago-gastric cancer(15) and kidney cancer.(17) The association between microcytosis and colorectal cancer reported from another case-control study (16) also supports our findings. No primary care study has reported cancer incidence with microcytosis across all cancers, or in patients with normal haemoglobin. Secondary care studies of microcytosis concentrate on iron-deficiency anaemia and possible causes of the anaemia, and we could find no reports on microcytosis unaccompanied by anaemia.

Implications for research and practice

Although the risk of cancer with microcytosis is above the 3% figure that NICE recommend for urgent cancer investigation, general practitioners have in house tests to help in this situation. This increased risk is made up of a small number of cancers - particularly colorectal - as shown in figures 2a and 2b. There seems to be no effect for some other cancers, for example, breast. For general practitioners, an MCV is only reported alongside the haemoglobin value. Anaemia accompanied by microcytosis strongly suggests iron-deficiency, and so measurement of iron stores (which were too few in our study for reliable analysis) would be the usual next step. If iron deficiency is identified, its cause will be sought, which would generally involve examining for gastro-intestinal blood loss. This diagnostic pathway does not remove the need to enquire about other symptoms suggestive of one of the malignancies we report here, particularly lung cancer. What this study changes however, is for patients with microcytosis but without anaemia. Some may be iron-deficient, simplifying the

investigation strategy. It seems sensible for all these patients also to be offered faecal immunochemical testing for hidden gastrointestinal blood loss, plus a chest X-ray if respiratory symptoms suggest lung cancer is possible. In such a way, the small number of patients whose microcytosis has been caused by cancer could receive a more timely diagnosis, whilst not exposing the majority to unnecessary referral and invasive testing.

Conclusion

Patients in primary care with microcytosis may harbour cancer, with colorectal and lung cancers the most probable. Most of the relevant initial investigations are available in primary care allowing initial assessment of possible cancer to be performed rapidly.

Funding: This research arises from the CanTest Collaborative, which is funded by Cancer Research UK [C8640/A23385]. Funding was provided by the National Institute for Health Research (NIHR), through the NIHR Policy Research Unit in Cancer Awareness, Screening, and Early Diagnosis and NIHR Programme Grants for Applied Research (Grant Reference Number RP-PG-0608-10045). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health and Social Care, other government departments or arm's length bodies.

Ethical approval: Independent Scientific Advisory Committee – protocol 09-110

Competing interests: William Hamilton was clinical lead on the 2015 revision of the NICE guidance on investigation of suspected cancer. His contribution to this article is in a personal capacity, and does not represent the view of the Guideline Development Group, or of NICE itself. Rhian Hopkins, Sarah Bailey and Elizabeth Shephard have declared no competing interests.

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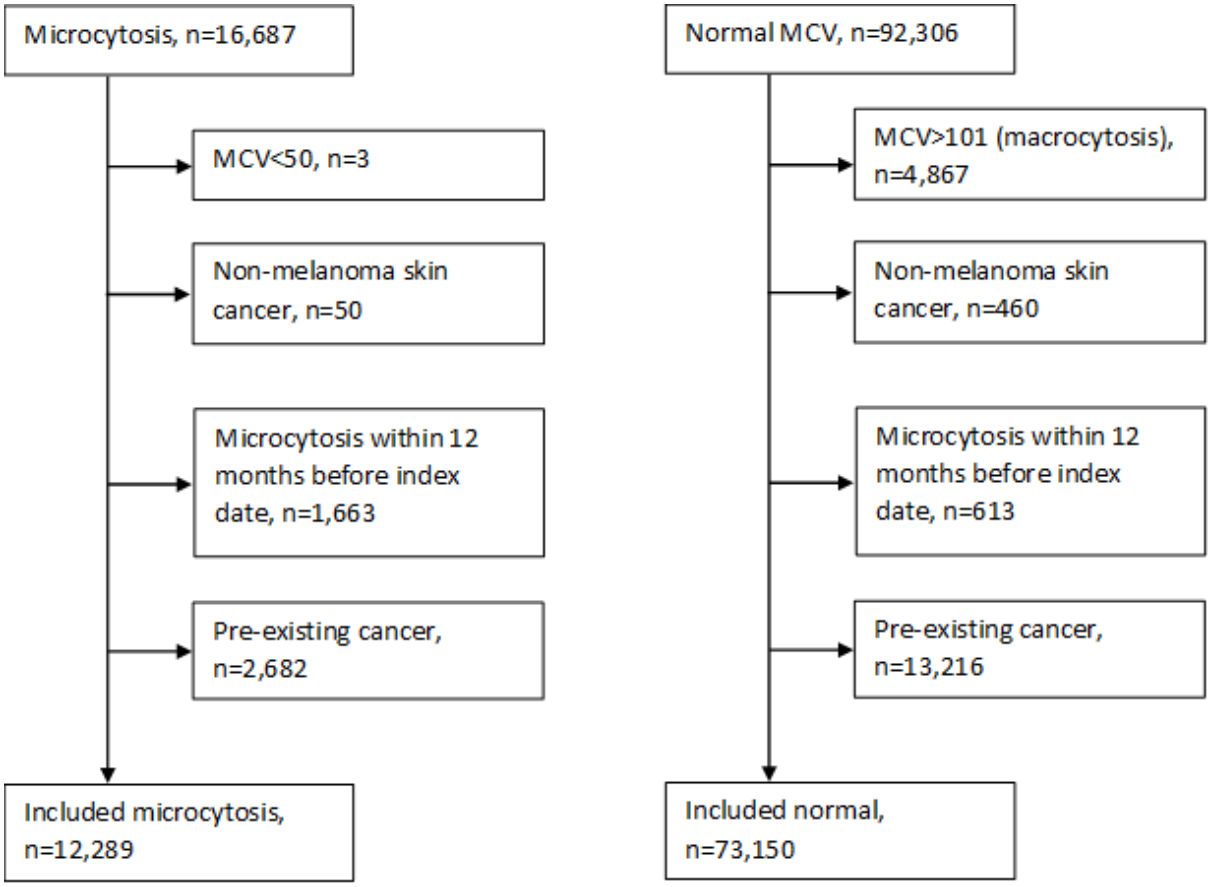


Figure 1. Exclusions flow diagram showing the number of patients excluded for having an MCV less than 50, MCV over 101, non-melanoma skin cancer, microcytosis in the 12 months before index date, or pre-existing cancer, and the number included in the microcytosis and normal MCV cohorts.

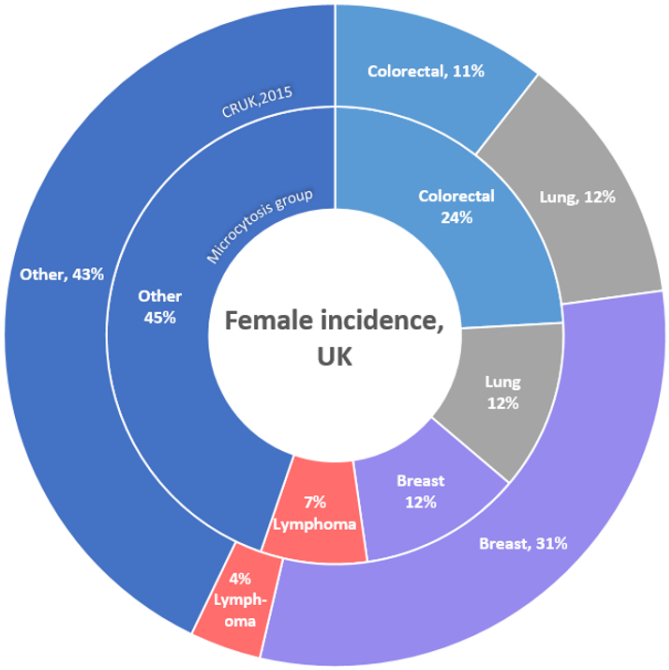
	Microcytosis			Normal MCV		
	Number in cohort	**With cancer**	**Cancer incidence (95%CI)**	**Number in cohort**	**With cancer**	**Cancer incidence (95%CI)**
Males	4,800	298	6.21% (5.54 to 6.93) *	34,653	940	2.71% (2.54 to 2.89)
Females	7,489	199	2.66% (2.30 to 3.05)	38,497	525	1.36% (1.25 to 1.48)
Aged 40-69	4,647	125	2.69% (2.24 to 3.20)	32,631	437	1.34% (1.22 to 1.47)
Aged 70+	7,642	372	4.87% (4.40 to 5.37) *	40,519	1,028	2.54% (2.39 to 2.69)

* Incidence above 3% NICE threshold for referral

Table 1. The number of patients in the cohort, the number with cancer and the cancer incidence for males, females, 40-69 year olds, and over 70 year olds, in both the microcytosis and normal MCV cohorts.

	Male		Female	
	Microcytosis and anaemia n=2,162 (%)	**Microcytosis only n=2,637 (%)**	**Microcytosis and anaemia n=2,433 (%)**	**Microcytosis only n=5,055 (%)**
	No cancer 1,950 (90%)	**No cancer 2,551 (97%)**	**No cancer 2,335 (96%)**	**No cancer 4,954 (98%)**
1	Colorectal, 56 (2.6%)	Prostate, 27 (1.0%)	Colorectal, 34 (1.4%)	Colorectal, 14 (0.3%)
2	Prostate, 28 (1.3%)	Lung, 15 (0.6%)	Breast, 10 (0.4%)	Lung, 14 (0.3%)
3	Lung, 28 (1.3%)	Colorectal, 9 (0.3%)	Lung 10 (0.4%)	Breast, 13 (0.3%)

Table 2. The 3 most common cancer sites in males and females both with microcytosis and anaemia, and with microcytosis only, the number and percentage of the group without cancer, and the number and percentage with cancer at each site.



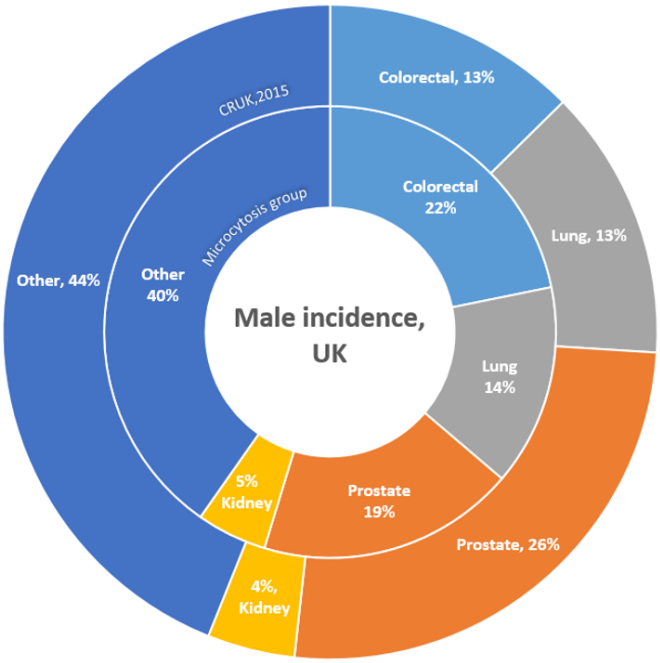


Figure 2a. The most commonly diagnosed cancer types in females with microcytosis compared to the general UK female population. The inner ring shows the proportions of the most common cancer types in the microcytosis cohort. The outer ring shows the proportions of incidences of these types in the general population in 2015.

Figure 2b. The most commonly diagnosed cancer types in males with microcytosis compared to the general UK male population. The inner ring shows the proportions of the most common cancer types in the microcytosis cohort. The outer ring shows the proportions of incidences of these types in the general population in 2015.