Cancer incidence in patients with a high normal platelet count: a cohort study using primary care data

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Key messages

- A mildly elevated platelet count may indicate underlying cancer
- The 1 year cancer incidence was 5.1% with a platelet count of 375 – 399 x 10^9/l
- This exceeds the 3% threshold for investigation for cancer (NICE NG12)
- These findings should prompt GPs to suspect cancer where they may not have done
- Cancer incidence was higher in males than in females
- Firm recommendation would require these results to be replicated on a larger scale

Abstract

Background

A platelet count >400×10^9/l (i.e. thrombocytosis) is a recently discovered risk marker of cancer. The risk of undiagnosed cancer in patients with thrombocytosis is 11.6% for men and 6.2% for women; well above the 3% risk threshold set by NICE for cancer investigation. Patients with a platelet count at the upper end of the normal range (325-400x10^9/l) could be at increased risk of undiagnosed malignancy.

Objective

To quantify the risk of an undiagnosed cancer in patients with a platelet count at the upper end of the normal range.

Methods

A primary care-based cohort study using Clinical Practice Research Datalink (CPRD) data from 2000 - 2013. The study sample comprised 2704 individuals stratified by platelet count: 325-349 x 10^9/l; 350-374 x 10^9/l; 375-399 x 10^9/l. Incident cancer diagnoses in the year following that platelet count were obtained from patient records.

Results

Cancer incidence rose with increasing platelet count: 2.6% (95% CI 1.9 to 3.6) in subjects with a count of 325-349x10^9/l; 3.7% (95% CI 2.5 to 5.3) in subjects with a count of 350-374x10^9/l; and 5.1% (95% CI 3.4 to 7.5) in those with a count of 375-399x10^9/l. Colorectal cancer was the most commonly diagnosed type in all three groups. Cancer incidence was consistently higher in males than in females.

Conclusion

These results suggest that clinicians should consider cancer in patients with a platelet count >375x10^9/l, and review the reasons for blood testing and any additional reported symptoms. Until these results are replicated on a larger scale, recommendations for clinical action cannot be made.

Background

Cancer survival in the UK is improving, but generally lags behind that in other European countries.[1,2] Improving earlier diagnosis has been identified as a key strategy to improve survival.[1] A range of research and policy initiatives have aimed to achieve this including public awareness campaigns and two week wait clinics. A valuable approach to achieving earlier diagnosis is to identify signs and symptoms that are associated with underlying malignancy to help GPs select patients for referral for definitive diagnostic testing. Previous approaches to improving cancer diagnosis have included the production of Risk Assessment Tools (RATs) which present the risk of cancer associated with various clinical signs and symptoms. One such sign is thrombocytosis (high platelet count).[3] In the UK, most laboratories report a platelet count of $400x10^9$/l as being the upper end of normal, although lower values have been proposed.[4] Our recent study reported that the positive predictive value of thrombocytosis for detecting any cancer in those aged 40 years and over is 11.6% (95% confidence interval 11.0 to 12.3) in men, and 6.2% (95% CI 5.9 to 6.5) in women.[3] This risk value far exceeds the 3% threshold set in the UK by the National Institute for Health and Care Excellence (NICE) at which patients are recommended for referral for possible cancer.[5] In that study, even mildly elevated platelet counts had a positive predictive value for cancer above 3%. Patients with a platelet count at the upper end of the normal range may also be at increased risk of cancer; identifying these patients in primary care may be the first 'clue' to an undiagnosed malignancy which could help to achieve earlier diagnosis, before other symptoms have developed. In this study, we aimed to quantify the risk of undiagnosed cancer in patients with a platelet count at the upper end of the normal range.

Methods

Data sources

Electronic medical records from the Clinical Practice Research Datalink (CPRD, www.cprd.co.uk) linked with English National Cancer Registration Service (NCRS) data.[6] The CPRD compiles patient records from UK primary care, and holds data on approximately 7% of the UK population. The NCRS for England gathers patient data from screening and imaging services, secondary care patient administration systems, and Hospital Episode Statistics.

Study population

The study sample was a randomly selected 10,000 from the CPRD database (the comparison group from our earlier study[3]) who met the following inclusion criteria:

- First platelet count from 2000 to 2013 was from 150 $\times 10^9$/l to 399 x 10^9/l
- Aged $\geq$40 years at the time of the platelet count

- No cancer diagnosis recorded prior to that platelet count

Exclusion criteria included:

- Aged under 40 years at index date
- Diagnosed with non-melanoma skin cancer (commonly under recorded) after index date

From this sample, patients were selected for the present study who had a platelet count from 325 × 10^9/l to 399 x 10^9/l. The first qualifying platelet count in the study period was designated the 'index date'. Subjects were stratified into three sub-groups:

- Group 1: 325 – 349 x 10^9/l
- Group 2: 350 – 374 x 10^9/l
- Group 3: 375 – 399 x 10^9/l

These ranges were chosen to be narrow enough to enable clinically useful indicators of when a platelet count should prompt further action for suspected cancer, whilst being wide enough to maintain reasonable sample sizes. Subjects were excluded if they had a cancer record prior to their platelet count index date.

Study outcomes and analyses

New cancer diagnoses were determined by searching CPRD records in the year after the platelet index date for any of 2,134 cancer-related codes, organized into 23 common sites. New diagnoses were also obtained from NCRS records; the earliest record was taken as the date of diagnosis.

The one-year cancer incidence (and 95% confidence intervals) was estimated for groups 1–3. The cancer site was identified; where more than one site was recorded, the earliest record was taken as the primary site, and only one cancer diagnosis was recorded per individual. The results were stratified by sex in each group.

It is not possible to determine from CPRD data why blood tests were ordered. Patients' records in the 3 weeks before the index date were searched for codes for single symptoms that should prompt urgent referral in the most recent NICE guidance (NG12).[5] The proportion of subjects with these "alarms" symptoms in the 21 days before their blood test was determined, and compared for subjects with and without a subsequent cancer diagnosis.

Stata version 14.2 was used to execute all analyses.[7] This paper conforms to STROBE reporting guidelines.[8]

Results

The study sample included 2,704 individuals after exclusions (Figure 1). Group 1 (platelet count 325-349x10^9/l) included 1,439 subjects, of whom 328 (22.8%) were male. The median age at the index date was 69.4 years (interquartile range (IQR): 58.3 to 79.2). Cancer was diagnosed in 38 patients within one year, an incidence of 2.6% (95% CI 1.9 to 3.6) (Table 1). Colorectal (n=7, 18%) and lung (n=5, 13%) were the most commonly recorded cancers (Figure 2).

Group 2 (350-374 x10^9/l) included 779 subjects (164 (21.1%) males). The median age at index date was 72.0 (IQR: 59.2 to 80.9). Cancer was diagnosed in 29 patients within one year, an incidence of 3.7% (95% CI 2.5 to 5.3) (Table 1). Colorectal (n=9, 31%) and lung (n=3, 10%) cancers were also the most commonly diagnosed in this cohort (Figure 2).

Group 3 (375-399 x10^9/l) included 486 subjects (118 (24.3%) male). The median age at index date was 71.7 (IQR: 58.9 to 81.3). Cancer was diagnosed in 25 patients within one year, an incidence of 5.1% (95% CI 3.4 to 7.5) (Table 1). Colorectal was the most commonly diagnosed cancer in this cohort (n=7, 28%), followed by lung and prostate cancers (for both, n=2, 7%) (Figure 2).

When the groups were stratified by sex, the cancer incidence was consistently higher in men than in women (Table 2).

In the 21 days before the index test, single symptoms that should trigger an urgent referral under NICE NG12 (so-called alarm symptoms)[5] were recorded for 47 of the 2,704 (1.7%) patients. The proportion reporting an alarm symptom was greater in patients who developed cancer within 1 year of the index test compared to those who did not; 9/92 (9.8%, 95% CI 4.6 to 17.8) versus 38/2,612 (1.5%, 95% CI 1.0 to 2.0) respectively.

Discussion

Cancer incidence increased with increasing platelet count; the risk exceeded 3% in subjects with a platelet count of 375 – 399 x10^9/l. Cancer incidence was consistently higher in men than in women, indicating that baseline platelet levels are higher in women than in men, or that benign causes of raised platelet counts are more common in women. The proportion of males in the sample was just above 20%; this suggests that a higher platelet count is more common in women than in men. The influence of sex on platelet count is poorly understood, and worthy of further research. Colorectal was the most commonly diagnosed cancer type; this is in contrast with our previous work on cancer incidence in patients with a platelet count of >400x10^9/l, in which lung was most commonly diagnosed.[3] In that study, a much higher proportion of lung and colorectal cancers were diagnosed than would be expected given national

incidence data (and a much lower proportion of breast and prostate cancers). In the present study, too few cancers were diagnosed in the sample to make similar comparisons.

Comparison with existing literature

This is the first study to consider cancer risk with a platelet count in the high normal range. All previous studies have used a threshold of ≥400 x 10^9/l when examining the clinical utility of platelet count in diagnosing cancer. In a recent systematic review, thrombocytosis was found to be an independent predictor of four types of cancer in studies of single cancer sites: lung, kidney, oesophago-gastric, and uterine cancer. [9]

Cancer incidence rose with increasing platelet count. Despite the small sample size, it appears that the relationship between cancer risk and platelet counts is monotonic, and begins well in the 'normal' range. The concept of a single threshold defining normality is semi-arbitrary, and based on distributions in the healthy population. Our study population – primary care patients who had a full blood count taken – is a selected population with presumably more ill-heath than the full general population. There are many and varied clinical reasons for taking a full blood count; indeed, at least a quarter of the adult population in any one year has this test.[10] Although our data are from a selected population, having a blood test is unlikely to introduce any bias specifically towards patients who are suspected of having an undiagnosed cancer due to the wide range of reasons for testing. Therefore, it is very unlikely this effect can explain our results, particularly with the clear dose-response effect.

In every platelet count group, males had higher cancer risk compared with females. This is supported by a study suggesting that the normal range for platelet count is higher in females than in males; in that study, the normal upper limit was proposed to be 362 × 10^9/l for males and 405 × 10^9/l for females, supporting our finding that a platelet count in the (350-400) × 10^9/l range should raise more of a red flag for males than for females.[4] If our findings are replicated, it is likely that the threshold platelet count warranting consideration of cancer will be lower in males than in females. In all three groups, colorectal cancer was the most common cancer occurring within one year of the index platelet count. This differs from our previous study, of patients with a platelet count >400 x 10^9/l, where lung cancer was the most commonly diagnosed.[3]

Strengths and limitations

This study uses a robust data source, the CPRD, which has been used extensively in past studies of cancer risk markers.[11–14] The use of NCRS data is a further strength, identifying incident cases that may have been unrecorded in the CPRD. Blood counts are electronically transmitted to the CPRD, reducing the risk of recording error. This study is based on a convenience sample of patients taken from a previous study,[3] resulting in small sample sizes and wide confidence intervals for the risk estimates. The reasons why the blood tests were ordered in the sample are unknown; cancer may have been suspected prior to blood testing. Cancer alarm symptoms accounted for a negligible proportion (1.7%) of all symptoms in

the 3 weeks before the index test, suggesting that cancer was not suspected in the vast majority of patients having blood testing. Cohort 1 had a lower median age than the other two cohorts (69.4 in Cohort 1, 72.0 and 71.7 in Cohorts 2 and 3, respectively) which may have had an impact on the lower proportion of cancer diagnoses in that Cohort. The sample in the present study was too small to investigate the effect of age on the relationship between platelet count and cancer diagnosis; future work should address this.

Conclusions

This study is small, but suggests that the risk of cancer in men with platelet counts >325 x 10^9/l exceeds 3%. For women, the figure is 375 x 10^9/l, though for platelet values in the range 350-374 x 10^9/l the risk is 2.8% (95% CI 1.6 to 4.4), still above the level at which patients would like investigation.[15] This suggests that clinicians should consider a cancer diagnosis in patients with a platelet count above these values. This could lead to earlier diagnosis, potentially at an earlier disease stage, if the patient is referred for further investigation sooner than they would have been had the raised platelet count not been recognized as a risk marker. A clinician receiving a high-normal platelet count should review why the test was done, and what ongoing symptoms the patient is reporting. This finding is currently only a clue towards possible cancer. Until the findings are replicated in a much larger sample, and the specific cancers delineated in greater detail with data on stage at diagnosis, a blanket recommendation for investigation would be premature.

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Ethical approval

Ethical committee approval was given by the Independent Scientific Advisory Committee of the CPRD: reference number 13-007.

Competing interests

WH is an associate editor of Family Practice. The authors declare no other competing interests.

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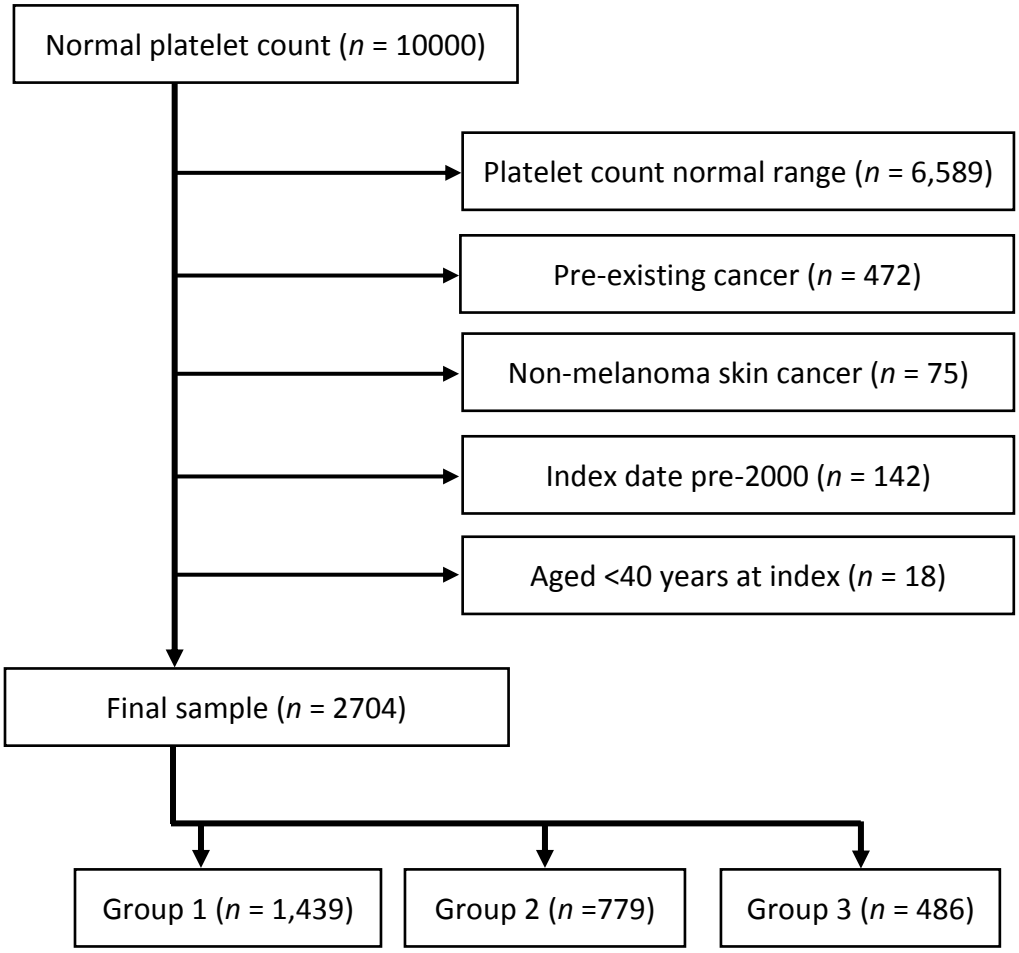

Figure 1: Patient flow diagram to show the number *of subjects* included in *each of* the *platelet count groups*, and the number excluded *from the original study sample.*
Group 1: 325 – 349 x 10^9/l. Group 2: 350 – 374 x 10^9/l. Group 3: 375 – 399 x 10^9/l.

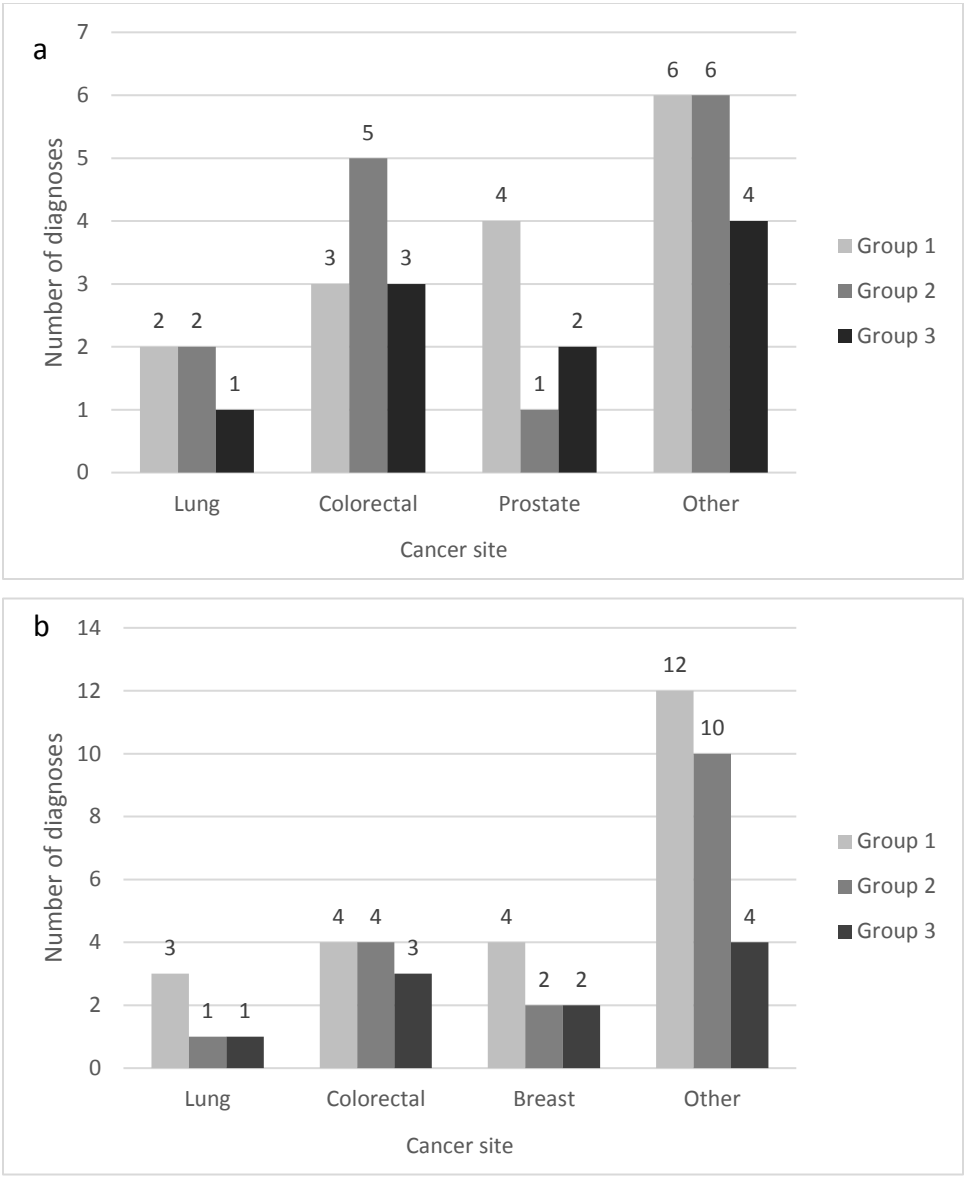

Figure 2. Sites of cancer diagnoses for (a) male and (b) female patients diagnosed with cancer in each of the three platelet count groups. Group 1: 325 – 349 x 10^9/l. Group 2: 350 – 374 x 10^9/l. Group 3: 375 – 399 x 10^9/l.

Table 1. Number of cancers diagnosed in each platelet count group during follow-up and the cancer incidence (%, 95% confidence interval). Group 1: 325 – 349 x 10^9/l. Group 2: 350 – 374 x 10^9/l. Group 3: 375 – 399 x 10^9/l.

Group	Platelet count range (×10^9/l)	Subjects	Number diagnosed with cancer within one year	One year incidence % (95% CI)
1	325–349	1,439	38	2.6 (1.9 to 3.6)
2	350–374	779	29	3.7 (2.5 to 5.3)
3	375–399	486	25	5.1 (3.4 to 7.5)

Table 2. Numbers of cancers diagnosed in each platelet count group during follow-up and the cancer incidence for that group (%, 95% confidence interval), by sex. Group 1: 325 – 349 x 10^9/l. Group 2: 350 – 374 x 10^9/l. Group 3: 375 – 399 x 10^9/l.

Group	Sex	Subjects	Number diagnosed with cancer within one year	One year incidence, % (95% CI)
1	Men	328	15	4.6 (2.6 to 7.4)
	Women	1,111	23	2.1 (1.3 to 3.1)
2	Men	164	12	7.3 (3.8 to 12.4)
	Women	615	17	2.8 (1.6 to 4.4)
3	Men	118	10	8.5 (4.1 to 15.0)
	Women	368	15	4.1 (2.3 to 6.6)

Figure legends

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