Thrombocytosis as a Risk Marker for Future Cancer

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Biography

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Jason Duval is a native of Oregon where he majored in Biology at Oregon State University. After completion of his undergraduate degree, he moved to Albany to work as a Medical Assistant at an Ear Nose and Throat clinic for three years and worked part time as a Health Services Coordinator for Community Outreach. He then moved to Hillsboro and obtained his Master's Degree in Physician Assistant Studies from Pacific University in August of 2021.

Abstract

Background: Cancer remains a leading causes of death worldwide. Identifying cancer earlier on and initiating treatment before late stage progression can occur, has proven to improve patient outcomes. Invasive biopsy procedures and extensive workups are usually required for a definitive diagnosis. Developing a screening protocol for the utilization of thrombocytosis as an early detection marker for cancer could potentially shorten diagnosis timelines and allow for faster treatment initiation leading to better overall patient outcomes. This review evaluates the efficacy of viewing thrombocytosis in adult patients as an early risk marker in regard to lifetime incidence of all cancer diagnoses.

Methods: An exhaustive search of the literature was performed using the following databases: PubMed, Web of Science, CINAHL. Keywords used in the search were: Thrombocytosis AND cancer AND incidence AND "primary care." Eligibility criteria were applied to the search results. Non-published studies, studies performed before 1990, and studies published in a language other than English were excluded. To be included, study subjects must have been 18 years of age or older and without previous cancer diagnoses. The risk of bias assessment was performed using critical appraisal forms provided by JAMA evidence.

Results: The search yielded 13 studies after duplicates were removed. Seven studies were screened for relevance. Of these 7 studies, 3 met eligibility criteria. These studies showed that cancer incidence is increased in patients with thrombocytosis as well as those with borderline, but subthreshold, thrombocytosis. A systematic review study included calculated likelihood ratios which found that thrombocytosis was a predictor of cancer in all sites except breast.

Conclusion: Our findings suggest a positive association between isolated thrombocytosis and the lifetime incidence of cancer in general. General practitioners who have patients with isolated thrombocytosis should further investigate and evaluate for possible cancer in order to initiate treatment as soon as possible. This could potentially improve overall patient outcomes including patient survival and quality of life.

Keywords: *Thrombocytosis, cancer, incidence*, *primary care, risk marker, platelet count, platelets, cancer diagnosis*

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List of Abbreviations

CBC..... Complete Blood Count
CPRD.....Clinical Practice Research Datalink
ECM.....Extracellular matrix
LR.....Likelihood Ratio
NCRAS.....National Cancer Registration Service
PPV.....Positive Predictive Value
QUADAS-2.....Quality Assessment of Diagnostic Accuracy Studies-2
UK.....United Kingdom

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BACKGROUND

Cancer remains a leading cause of death in the US today, with trachea, bronchus, lung, colon, and rectal cancers being the most common in adults in 2012.[1] It is generally accepted that delays in recognition and diagnosis of these cancers ultimately leads to a delay in initiating treatment, which allows for disease progression and patient harm.[2] It is the responsibility of the healthcare provider to utilize everything at their disposal to minimize patient harm and provide effective care to these patients in order to improve patient survival and quality of life.

This review evaluates the efficacy of viewing thrombocytosis in adult patients as an early risk marker in regard to lifetime incidence of all cancer diagnoses. The purpose of this study is to establish the relationship between thrombocytosis and cancer incidence in order for general practitioners to identify cancers earlier in their patients and therefore allow them to initiate treatment earlier and improve overall patient outcomes. Our aim is to answer the clinical question: Can patients with thrombocytosis have a higher lifetime incidence of new cancer diagnoses than those with normal platelet counts?

METHODS

For this critically appraised topic, an exhaustive search of the literature was performed using MEDLINE-PubMeb, Web of Science, and CINAHL. The search was conducted using the following terms: *Thrombocytosis, Cancer, Incidence*, and *"primary care."* References cited by qualifying articles were also screened for inclusion. To be included, articles must have evaluated the incidence of cancer in patients with thrombocytosis or a high-normal platelet count, who were 18 years of age or older and who did not have a previous cancer diagnosis. Other inclusion criteria required that the article be published after 1990, in English, and use only human subjects. Articles that focused on only a single cancer type (e.g. Colorectal, kidney, etc.) were excluded from the review. A risk of bias assessment for each article that met inclusion criteria was performed using JAMA evidence critical appraisal worksheets.[3]

RESULTS

The initial search yielded 17 articles for our review. An additional 2 articles were found by screening the bibliographies of qualifying studies. After eliminating duplicates and applying our eligibility criteria, there were 3 articles[2,4,5] that remained. (See Figure 1.) These 3 articles consisted of 2 prospective cohort[2,4] studies and 1 systematic review.[5] (See Tables 1,2.)

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

In the first cohort study, Ankus et al randomly selected 10 000 patients from the Clinical Practice Research Datalink (CPRD), a database that compiles primary care patient records from approximately 7% of the United Kingdom (UK) population. Eligibility criteria were then applied to these 10 000 subjects, which included a platelet count between 325 to 399 x 10^9/L, age greater than or equal to 40 years at the time of the platelet count, and no previous cancer diagnosis prior to the platelet count. This yielded a sample of 2704 individuals. This sample was then stratified into 3 subgroups based on platelet count:

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

Patient records were then searched for a new cancer diagnosis in the year after the initial platelet index using the CPRD as well as the English National Cancer Registration Service (NCRAS) in order to establish the 1-year cancer incidence for each of the 3 subgroups.[4]

Group 1 (platelet count 325 – 349 x 10^9 /L) was comprised of 1439 subjects. The median age at platelet index was 69.4 years old and 22.8% were male. In this group, 38 subjects were diagnosed with

cancer within 1 year of their platelet index, a 2.6% (95% CI 1.9-3.6) incidence.[4]

Group 2 (platelet count 350 - 374 x 10^9 /L) was comprised of 779 subjects. The median age at platelet index was 72.0 and 21.1% were male. In this group, 29 subjects were diagnosed with cancer within 1 year, a 3.7% (95% CI 2.5-5.3) incidence.[4]

Group 3 (platelet count 375 – 399 x 10^9 /L) was comprised of 486 subjects. The median age at platelet index was 71.7 and 24.3% were male. In this group, 25 subjects were diagnosed with cancer within 1 year, a 5.1% (95% CI 3.4-7.5) incidence.[4]

Additionally, Ankus et al ran a chi-square test that showed a significant relationship between platelet count and cancer diagnosis ($P < 0.01$). After stratifying the subgroups by sex, they also found that cancer incidence was consistently higher in men. Based on the above results, Ankus et al concluded that "patients with higher platelet counts were more likely to be diagnosed with cancer than those with lower counts". Ankus et al makes note that this is the "first study to consider cancer risk with a platelet count in the high normal range," citing that all previous studies have only evaluated cancer risk in patients with thrombocytosis (>400 x 10^9 /L).[4]

Bailey et al (2017): Clinical relevance of thrombocytosis in primary care: a prospective cohort study of cancer incidence

using English electronic medical records and cancer registry data

In the second cohort study, Bailey et al (2017) randomly selected 50 000 patients who had had a complete blood count (CBC) taken from the same CPRD database as Ankus et al. This sample was then divided into 2 cohorts, patients with thrombocytosis (>400 x 10^9 /L) and patients with a normal platelet count (150 – 400 x 10^9 /L). For patients in the thrombocytosis cohort with multiple CBC's on file, the count that first showed thrombocytosis was used as the index platelet count and date. Using the CPRD and the NCRAS, the records of these 2 cohorts were then evaluated for new cancer diagnoses. The primary analysis of the study was to report the 1-year incidence of cancer as a percentage, as this would be equivalent to the positive predictive value (PPV) of thrombocytosis for cancer for the thrombocytosis cohort.[2]

The thrombocytosis cohort included 31 261 patients who all met the following criteria: no history of previous thrombocytosis, age >40 years at time of thrombocytosis, no previous history of cancer, and thrombocytosis detected from 2000-2013. The median age of the thrombocytosis cohort was 67.9 years, and 69.8% were female.[2]

The comparison cohort was matched to a random selection of 10 000 patients from the thrombocytosis cohort, and after exclusion criteria were applied (history of pre-existing cancer or

thrombocytosis), consisted of 7969 patients. These patients were matched by age (within 5 years), sex, and practice. These comparison patients also had a CBC done between 2000 and 2013, and their first platelet count in this period must have fallen in the "normal" range, defined as 150 – 400 x 10^9 /L. The index date for this cohort was the platelet count measured nearest to the index date of their matched counterpart in the thrombocytosis cohort. The median age of the comparison cohort was 68.3 years and 67.4% were female.[2]

The 1-year cancer incidence for patients in the thrombocytosis cohort was 11.6% for males, and 6.2% for females. Approximately one-third of these cancer diagnoses were made at least 3 months after the patient's platelet index date. Comparatively, the 1-year cancer incidence of patients in the comparison cohort was 4.1% for males, and 2.2% for females.[2]

Bailey et al (2017) also showed that the risk of cancer increased with increasing platelet count and that across all ages, patients with thrombocytosis were at a higher risk than those with a normal platelet count. This risk was further increased in patients aged >70 years.[2]

Further analysis revealed that patients with a second platelet count taken within 6 months of the first showing continued thrombocytosis that was even higher or at the same level as their first, had a 1-year cancer incidence of 18.1% for males and 10.1% for

females. Even for patients whose second platelet count decreased, but still classified as thrombocytosis, showed an increased 1-year cancer incidence for both males and females of 19.1% and 7.3%, respectively. This analysis shows that the greatest risk of cancer is in those who display repeated elevated platelet levels.[2]

Cancer staging data were not available for all cancers diagnosed in each of the cohorts. Of the cancer diagnoses made in the thrombocytosis cohort, staging data was available for 47.6%. Of these, 49.2% of cancers diagnosed were early stage, as compared to 50.8% late stage. In the comparison cohort, 54.6% of the cancer diagnoses had staging data available. Of these, 62.6% were classified as early stage, and 37.4% as late stage. The 49.2% of early stage cancers detected in the thrombocytosis cohort equate to 575 cancer diagnoses where thrombocytosis may have been the earliest detected risk marker.[2]

Bailey et al (2017) found that the most common sites of cancer in in the thrombocytosis cohort were lung and colorectal. Bailey et al (2017) reports no significant difference in symptom reporting between the 2 cohorts in the month before their index platelet count. Of the patients with thrombocytosis who were diagnosed with lung cancer, 35.7% had no symptoms that would prompt investigation according to current guidelines other than their thrombocytosis. This was the same

case for 32.9% of the patients diagnosed with colorectal cancer. This shows that for approximately one-third of all lung and colorectal cancers, thrombocytosis has a potential to serve as a reliable risk marker, even in the absence of other symptoms, that should trigger a clinician to further investigate for underlying malignancy.[2]

Bailey et al (2016): How useful is thrombocytosis in predicting an underlying cancer in primary care? a systematic review

In the systematic review, Bailey et al (2016) sought to "identify studies that have investigated whether adults aged ≥40 presenting with thrombocytosis in primary care are at greater risk of cancer than those with normal platelet counts and bring the results together in a narrative synthesis, to answer the general question of whether thrombocytosis is a marker of cancer." They did this by performing an extensive search of the literature using EMBASE (OvidSP), Medline (Ovid), Web of Science, and the Cochrane Library. They also performed forward and backwards citation screening of each of the included articles.[5]

They searched for studies that investigated the association between thrombocytosis and new diagnosis of any cancer type in the primary care setting. Studies were excluded if patients were <40 years of age or if platelet counts were used as a prognostic tool or therapeutic guide in the study. After screening article titles and

abstracts, each qualifying article was reviewed in its entirety for inclusion.

Each qualifying study was then assessed for bias using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool and raw data was extracted. The data from the studies was then used to calculate likelihood ratios (LR) and positive predictive values (PPV). LR represents the "probability of raised platelets in patients with cancer divided by the probability of raised platelets in healthy patients." PPV's were "calculated as the LR multiplied by the prior odds of the disease", which in this case, was determined by primary care incidence data. This calculation method was used because it accounts for the cancer incidence in the general population and therefore allowed the authors to more accurately answer their question.[5]

Bailey et al (2016) found 98 papers in their search of the literature. After duplicates were removed and eligibility criteria were applied, 9 articles remained to be included in their review. They reported overall quality of the studies to be "high" and risk of bias to be "low" after using the QUADAS-2 tool to asses each of them. All 9 studies included in the review were case-control studies and all were comprised of data pulled from the medical records of UK patients.[5]

Each of the 9 studies included in the review assessed the association between thrombocytosis and a specific cancer site. The

sites reported on were: lung, kidney, esophago-gastric, uterine, breast, bladder, pancreatic, ovarian, and colorectal.[5]

Bailey et al (2016) analysis of the data showed that patients with thrombocytosis do in fact have an increased risk of cancer, and that this association is stronger for certain cancer types than others. Bailey et al (2016) reported the strongest PPV for lung and colorectal cancer, 1.63 and 1.39 respectively. Bailey et al (2016) reported likelihood ratios that indicated that thrombocytosis was a predictor of cancer in all evaluated sites except for breast.[5]

DISCUSSION

Our findings suggest that patients with isolated thrombocytosis do have a higher lifetime incidence of new cancer diagnoses as compared to those with normal platelet counts. In addition, Ankus et al[4] showed that this incidence is also increased in patients with borderline thrombocytosis and that the incidence increases as the platelet count increases. Bailey et al (2016)[5] found that thrombocytosis was a predictor of cancer in all sites except breast.

There were several limitations we identified in the 3 studies of interest. In the study conducted by Ankus et al[4], aside from reporting median age, there was no reporting on if or how the patients in the 3 stratified groups were matched for underlying cancer risk. One study included in the systematic review conducted by Bailey et al (2016)[5]

had a small sample of patients with available platelet counts. An author of the review was also an author on all 9 of the studies included in the review. In the study performed by Bailey et al (2017)[2], cancer stage at time of diagnosis was missing for a large portion of patients in the data pool that was reviewed.

With further investigation, we were able to find a recent study that suggests a possible explanation for this apparent association between higher platelet counts and increased incidence of cancer. Gkolfinopoulos et al[6] explains how platelets contribute to the process of developing a metastatic niche through 3 major phases including: "the initial preparation of the metastatic microenvironment by the formation of the extracellular matrix (ECM) and the recruitment of granulocytes; the creation of the neovasculature, which is important for providing the developing tumor with oxygen and nutrients, as well as for clearing away the metabolic waste; and, lastly, the evasion of the immune response by the creation of an immune-suppressive environment around the developing metastasis."[6] Even with this supporting information, we recommend further research be conducted to build upon the physiology behind this association in order to help providers understand the importance of further investigation into their patients with isolated thrombocytosis.

CONCLUSION

There is a clear association between thrombocytosis and the lifetime incidence of cancer in general. General practitioners who have patients with thrombocytosis should further investigate and evaluate for possible cancer in order to initiate treatment as soon as possible. Developing protocols for when and how to further investigate these patients in the medical setting could potentially improve overall patient outcomes including patient survival and quality of life of those diagnosed with cancer worldwide.

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Table 1. Risk of Bias Assessment – Cohort Studies		
	Ankus et al[4]	Bailey et al 2017[2]
Representativeness of sample (selection bias)	Low	Low
Similar prognostic risk (selection bias)	Low	Low
Confounding	Unclear[a]	Low
Assessment of outcome (detection bias)	Low	Low
Incomplete outcome data (attrition bias)	Low	Low
Selective reporting (reporting bias)	Low	Low
Other risks	None	Yes[b]
Overall risk	Low	Low

a= aside from reporting median age of each group, there is no reporting on if additional cancer risk factors were matched between groups
b= cancer stage at time of diagnosis was missing for a large portion of patients in the data pool that was reviewed

Table 2. Risk of Bias Assessment – Systematic Review	
	Bailey et al 2016[5]
A sensible clinical question	Yes
Literature search	Low
High quality studies	Yes[a]
Reproducibility	Yes
Publication bias	Unclear[b]
Outcome reporting	Low
Other potential threats to validity: Was the study apparently free of other problems that could put it at a risk of bias? (has effective subgroup analyses, evaluated quality of evidence appropriately, measures a cumulative effect size)	Low
Overall risk	Low
a= Hamilton et al (5) had a high risk of bias in the "timing and flow" category due to a small subsample of patients with available platelet counts; however overall quality of studies included are high *b= An author of this meta-analysis is also an author on all 9 of the studies included in the meta-analysis. The authors do state that the search strategy and quality assessment were carried out independently of this author however.*	

Figure 1. Summary of Search Results