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Environmental Factors, Lifestyle Risk Factors, and Host Characteristics Associated With Philadelphia Negative Myeloproliferative Neoplasm: A Systematic Review

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Abstract

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell disorders characterized by the overproduction of mature myeloid cells and are often associated with an acquired genetic mutation of *Janus Kinase2V617F*. Various epidemiological studies have indicated associations between environmental factors, lifestyle factors, and host characteristics with developing MPNs. This review aims to collect and summarize the existing information on these risk factors and establish their association with pathogenesis MPNs. Medline, Embase, PubMed, and grey literature were systematically searched using key terms for MPNs, and epidemiological study designs, that is, cross-sectional studies, case-control, and cohort, that investigated the risk factors for MPNs published were identified. Out of the 4621 articles identified, 20 met the selection criteria and were included in this review. Heterogeneity, study reliability, and bias were assessed. A significant association was found between smoking and the development of MPNs. This relationship has been explained by the substantial increase in several proinflammatory mediators and systematic oxidative stress causing hyperstimulation of myeloid compartments leading to the development of MPNs. Obesity was modestly linked with an increased risk of MPNs. The underlying mechanisms have been linked to changes in endocrine, metabolic, and inflammatory systems. No strong association was found between exposure to hazardous substances, that is, benzene and MPNs, but further investigation on the effects of increased levels and duration of exposure on hematopoietic stem cells will be beneficial. Unique individual and host variations have been determined as a modifier of disease pathogenesis and phenotype variations. There is a higher incidence rate of females developing MPNs, specifically ET, than males with higher PV incidence. Therefore, gender contributes to the heterogeneity in myeloproliferative neoplasm. Studies identified as part of this review are very diverse. Thus, further in-depth assessment to explore the role of these etiological factors associated with MPNs is warranted.

Keywords

myeloproliferative neoplasm, myeloproliferative disease, polycythemia vera, essential thrombocythemia, primary myelofibrosis, risk factor, environmental, lifestyle, host characteristics, smoking, obesity, benzene, gender

Introduction

Myeloproliferative Neoplasms (MPNs) are clonal hematopoietic stem cell disorders characterized by increased proliferation of myeloid progenitors leading to an overproduction of mature cells in one or more cell types of the myeloid lineage, causing various complications.[1] The myeloproliferative neoplasms, previously known as a Chronic Myeloproliferative Disease (CMPD), are categorized into subgroups including Chronic Myelogenous Leukemia (CML), Polycythemia Vera

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(PV), Essential Thrombocythemia (ET), and Primary Myelofibrosis (PMF), Chronic Neurophilic Leukemia (CNL), Chronic Eosinophilic Leukemia (CEL), Mast Cell Disease (MCD), MPN unclassified.

In 2008, World Health Organization (WHO) gave these disorders the collective name of Myeloproliferative Neoplasms (MPNs) on their neoplastic nature. WHO categorized MPNs into two groups of Philadelphia (Ph) chromosome-positive or negative by considering clinical behavior, morphologic features, cytogenetics, and molecular changes through advances in molecular biology.[2] The present investigation focuses on three Ph-negative MPN: Essential Thrombocythemia (ET), PV, and PMF.

Until now, the causative mechanism underlying the MPNs is mainly unknown. However, mutations of Janus Kinase 2 (JAK2)V617F in exon 14 were the most frequent molecular abnormality in MPNs, most commonly found in patients with PV, approximately 95%, 50% in ET, and to a lesser extent in PMF. The discovery of this acquired mutation in 2005 revolutionized the diagnosis of MPNs worldwide. JAK2V617F mutation has rarely been detected in other myeloid disorders.[3]

JAK2V617F originates a gain of function mutation causing constitutive activation of the Janus-associated kinase 2 and is now considered as a disease initiating or often called the "driver mutation for the classic MPNs," and it has been a primary diagnostic criterion for these conditions.[4]

Signs and symptoms of MPNs vary but include headaches, excessive sweating, fatigue, bruising, and bleeding. Major vascular complications and thrombotic or hemorrhagic events are amongst the most frequently reported causes of morbidity and mortality in patients with MPNs.[5] Notwithstanding these new insights, little is known about factors related to symptomatic heterogeneity. The progress of MPN-specific Patient-Reported Outcome (PRO) tools has allowed the clinicians to objectively quantify MPN symptom burden and assess the effect of this disease on quality of life. The Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF), Myelofibrosis Symptom Assessment Form (MF-SAF), and MPN-10 have been applied in both clinical and trial settings. It yielded substantial insights into how observed clinical and symptomatic differences can guide clinicians to recognize predictable and unpredictable patterns.

One of the most challenging aspects of these disorders is the patients' diverse clinical features, which could be attributed to specific genetic and epigenetic factors.[6] Aside from the marked JAK2V617F mutation, a range of predisposing factors may contribute to the occurrence of variations in these disorders. These contributing factors can be related to the host/patient, such as individual characteristics, that is, gender, age, ethnicity, comorbidities, immune function, and hormonal imbalance. Another risk factor can be from the external environment, such as contaminants, exposure to hazardous substances, viruses, and unhealthy lifestyle choices, which could be detrimental to an individual's health, such as tobacco smoking, excessive alcohol consumption, and an unhealthy diet.[7] These contributing factors at the presence of the genetic mutation can lead to changes in the pathogenesis or progression of the disease. The severity of the symptoms and complications can also be altered due to the impact of these factors.[3,6]

Using a systematic approach, we aim to identify, review, and collect all known published studies investigating the host, environmental, and lifestyle factors associated with MPNs, in particular, the importance of smoking, diet, chemical exposure, gender for the three subgroups of the Philadelphia chromosome-negative MPNs, PV, ET, and PMF. Besides, this study assessed the quality of the evidence obtained for this review.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline. Meta-analysis was not included.[8]

Literature Search

A systematic literature search was conducted, related studies were identified by searching electronic databases PubMed, Medline, and Embase with the date restrictions of March 2003 to March 2020. In addition, the reference lists and the grey literature, including abstracts published by the American Society of Hematology, European Society of Medical Oncology, European Hematology Association, and American Society of Clinical Oncology, were manually reviewed to identify related studies. Key search terms included *myeloproliferative neoplasms, myeloproliferative diseases, myeloproliferative disorder, polycythemia vera, essential thrombocythemia, primary myelofibrosis, myelofibrosis, predisposing factors, environmental factors and risk factors, smoking, obesity, overweight, diet, hazardous exposure, benzene, and gender.* Complete details of the combination of the keywords used can be obtained from the author.

Study Selection

An article was eligible for inclusion if the participants were diagnosed with one of three Philadelphia negative MPNs subtypes (ET, PV, and PMF) according to WHO 2008 diagnostic criteria. The included studies were conducted between March 2003 and March 2020. The secondary outcome of interest in the studies was incorporating the details on environmental factors, lifestyle risk factors, and host characteristics. Therefore, the articles available in full and abstracts from the publications as mentioned above were included. These abstracts have reported adequate information regarding the topic of interest. Study designs included were epidemiological studies, that is, case-control, cohort, and cross-sectional studies. The included articles were written in English.

Data Extraction

The following data were collected: authors, study design, publication year, journal and journal impact factor, the subtype of MPNs, number of cases and controls, the country where the research has been conducted, risk factors, and key findings. A spreadsheet database of all the extracted information from the chosen article was prepared.

Manual review of filtered records allowed the exclusion of inappropriate and duplicated publications. Both investigators (NA and MIMI) evaluated the full text of selected articles and abstracts independently. If different decisions regarding the eligibility of a study were made, the study in question was jointly reviewed by two investigators, and the final determination was reached by consensus.

Quality Assessment

The case-control and cohort studies' methodological quality was assessed based on the Newcastle–Ottawa Scale (NOS).[9] The NOS is a risk of bias assessment tool for observational studies, and the Cochrane Collaboration recommends it.[9] The NOS is based on three subscale domains: (1) selection of study groups; (2) comparability of groups; and (3) ascertainment of exposure and outcomes for case-control and cohort studies, respectively. In addition, a modified version of the NOS scale for the cross-sectional studies was used.[10] It consists of eight items and assigns a maximum score of nine points for the least risk of bias in the three domains. The studies with a maximum of nine points were defined as high quality. Those with scores 7 to 8 were recognized as the medium quality, and studies scoring less than 7 were classified as low quality.

Statistical Analysis

The content from the systematic review was analyzed qualitatively. As for the articles' quality assessment, a measure of rater's agreement, that is, interrater reliability, on the article quality was carried out using Interclass Correlation Coefficient (ICC). ICC was interpreted, and studies with values less than 0.5 indicate poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability.[11] The findings were reported as ICC with 95% Confidence Intervals (CIs) and *P*-value. Statistical analysis was performed using the SPSS software version 26 (Armonk, NY: IBM Corp.) with an alpha value of 0.05.

Results

A total of 4621 articles from the chosen databases were initially identified (Medline, n = 2725; Embase, n = 1198; PubMed, n = 698). Duplicates were identified and removed, leaving 3792 articles, and from these, 3246 articles were excluded due to irrelevance to the pre-specified inclusion criteria. Title and abstracts of 546 articles were reviewed, and 46 articles met the inclusion criteria. The full text of these articles was reviewed, and 30 were excluded for reasons such as being a review and a meta-analysis and not reporting the outcome of our interest. This review concluded that 16 studies were identified to be relevant and appealing to all the inclusion criteria. These articles include seven cohorts, six case-control, and three cross-sectional studies. Two abstracts were found to be relatable and met the inclusion criteria for this review. One of the included abstracts was cross-sectional studies, and one is a case-control study. The total number of research studies included in this review is twenty. Results of the search strategy are presented in Figure 1.

Quality Assessment

The Newcastle–Ottawa scale scores from both reviewers (NA and MIMI) were collected, and the average was calculated. Regarding quality, studies that received the maximum score of nine, were classified as the high-quality range. The studies which received a score of eight out of nine had recognized them as medium quality. Studies received scores below eight points correlating to low quality. Figure 2 illustrates that 18 studies were included; five are rated high quality, nine medium, and four low quality. The average ICC of all the included studies was calculated to be 0.832. As explained previously, this value lies between 0.7 and 0.9, which indicated good reliability between the rater is regarding the quality of the studies included in this review with a 95% confidence interval of 0.625-0.940, $P = 0.000$.

Lifestyle Factors

Smoking. Out of the eighteen studies included in this review, four case-control studies,[12-15] four cohort,[16–18] and two cross-sectional studies[19,20] have investigated the association and potential contribution of cigarette smoking on development of Philadelphia-negative MPNs.

The study by Sørensen et al. tested this association by comparing MPNs patients to Chronic Lymphocytic Leukemia (CLL) patients. This large single institute case-control study concluded that patients with a history of smoking had approximately a 73% increase in the chance of developing MPNs compared to CLL (OR = 1.64, 95% CI: 1.16-2.30). This finding is statistically significant. In subtype analysis, a significant association was observed for ET (OR = 2.15, 95% CI: 1.38-3.36) and PV (OR = 1.52, 95% CI: 0.92-2.49), also when stratified for gender, the association was significant for females (OR = 2.26, 95% CI: 1.36-3.75) compared to males.[21]

Two sizeable epidemiological case-control studies[13,14] confirmed the previously reported association with smoking. The study, MOSAICC, conducted by McMullin et al., compared individuals with ≥25 pack-years of smoking with never smokers (OR = 3.14, 95% CI: 1.26-7.87). They have also reported a higher risk of developing MPNs in individuals

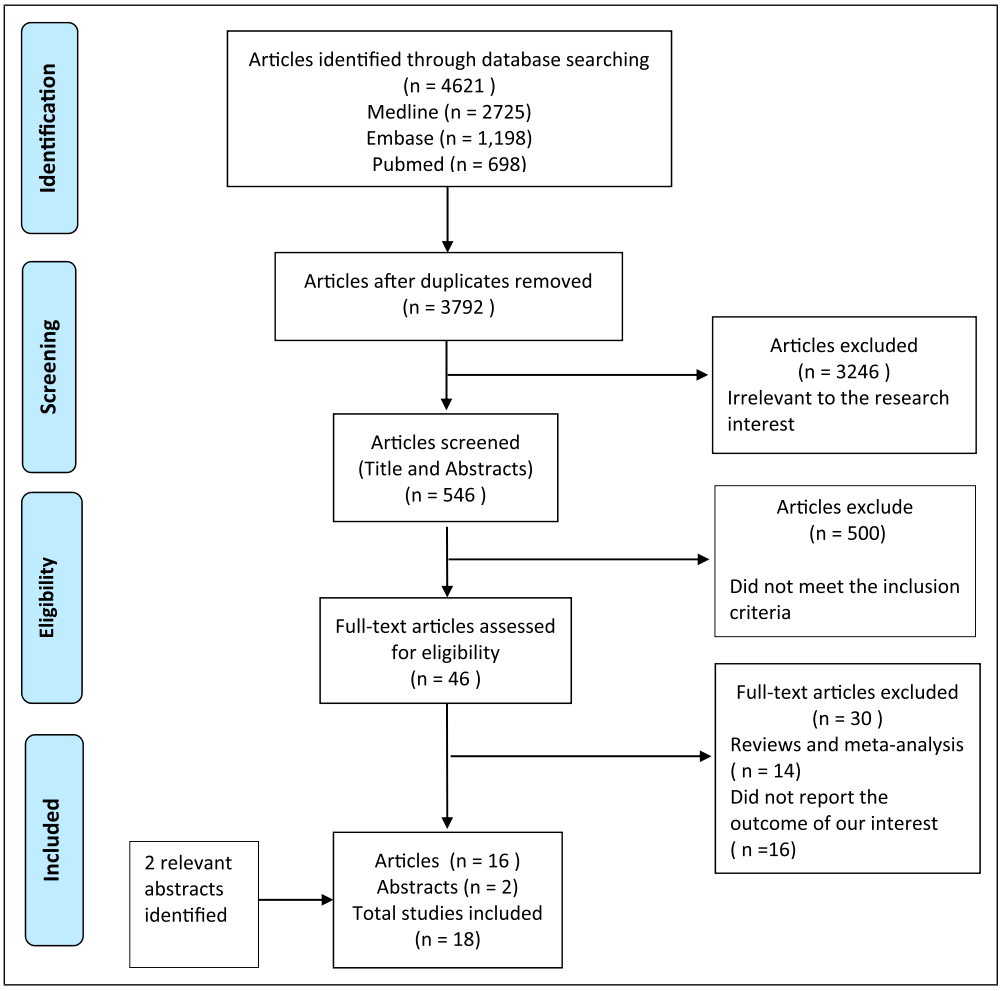

Figure 1. PRISMA flowchart illustrated the flow of information through the different phases of a systematic review. It maps out the number of records identified, included, and excluded and the reasons for exclusions.

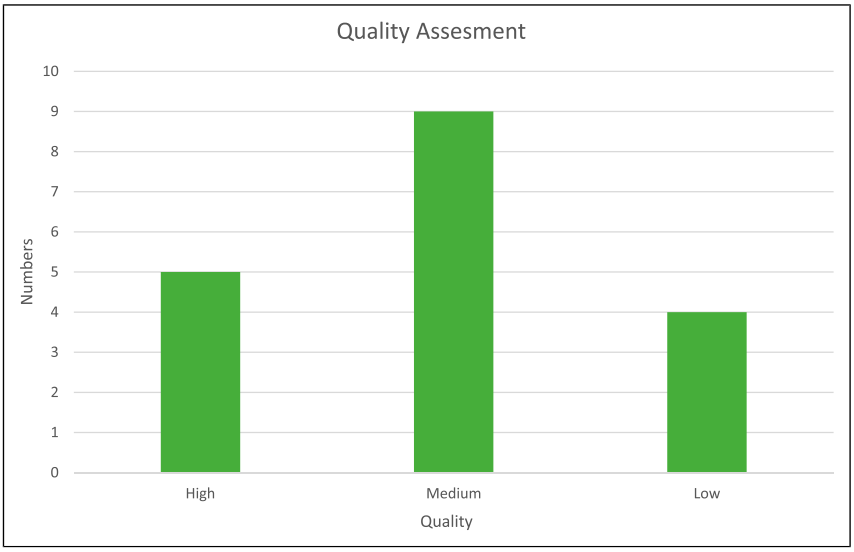

Figure 2. Quality assessment of included articles (Newcastle–Ottawa Scale) demonstrating 5 studies rated high quality, 9 medium, and 4 low quality.

working in occupations with high exposure to environmental tobacco smoke (OR = 2.45, 95% CI: 1.12-5.37).[12] Duncombe et al. have also reported a significantly increased risk of developing MPNs in individuals with high pack-years of smoking (OR = 2.19, 95% CI: 1.03-4.66, $P = 0.01$). When stratified by MPNs subtype, they have described that significant number of cases with PV have been reported to be current smokers (OR = 3.73, 95% CI: 1.06-13.15).[13]

These findings are in line with the results from three extensive prospective cohort studies.[16–18] Pedersen et al. reported the risk of MPNs could be increased by 2.5-fold (95% CI: 1.3-5.0) among daily smokers and 1.9-fold (95% CI: 1.1-3.3) in occasional/ex-smokers.[14] Findings of Iowa woman's health study by Leal et al. [16] conducted on a cohort of 27 370 females and the million woman study by Kroll et al.,[17] a study on 1.3 million middle-aged women, reported that current smokers had a significantly increased risk of developing MPNs—(RR = 1.72, 95% CI: 1.16-2.56) and (RR = 1.98, 95% CI: 1.67-2.35), respectively.[16,17] In subtype analysis, this association was stronger for PV (RR = 2.83; $P = 0.016$) than for ET (RR = 1.32; $P = 0.15$), which is similar to the findings from Duncombe et al. Although this difference was not statistically significant (p-heterogeneity = 0.23),[12] these results are in contrast with Sørensen et al.,[18] where a significant association was observed in subjects diagnosed with ET but not in PV.[21]

A cross-sectional study by Skov et al. aimed to investigate various inflammatory biomarkers such as leukocytes, C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), albumin, fibrinogen, haptoglobin, and fibrin D-dimer, in subjects with MPNs and the impact of smoking on these variables. A positive trend in the increase in these inflammatory biomarkers in the smokers compared with never smokers was reported.[22] This reflects on the hypothesis that smoking significantly impacts circulating inflammatory biomarkers, which could be a contributing factor in developing MPNs.[22]

Two similar studies[15,20] investigated the prevalence and frequency of the clonal hematopoiesis (JAK2V617F mutation) in smokers compared to non-smokers. They have concordantly reported that the JAK2V617F clonal hematopoiesis is significantly higher in current smokers than former smokers and the lowest in the never smokers.[23,24] Weinberg et al. concluded that this association is significant and the difference in mutation frequency can be more than double between the smokers (35.8%) compared to non-smokers (14.8%).[23]

Obesity

Many large cohort and case-control studies have been looking into the biological relationship of obesity with cancer risk, but no concrete evidence has been found. In this review, three cohorts[17,25,26] and one case-control[13] investigating the association of obesity/high BMI as a risk factor for developing MPNs were identified.

A very recent case-control study observed an increased risk of MPNs in individuals who are obese, but the findings were not significant.[12] However, when the analysis was stratified by MPNs subtype, the results showed a significant association between obesity and patients diagnosed with ET (OR = 2.59, 95% CI: 1.02-6.58).[12] Similarly, a large cohort study reported that increasing BMI is not associated with higher risks of MPNs. However, in subtype analysis, it was positively associated with increased risk of ET but not with PV (RR = 1.52 >29.3 - <23.4; $P = 0.042$).[16]

Two other large-scale cohort studies have concluded that obesity in adolescence can significantly increase the risk of developing MPNs. The study by Murphy et al. reported that obese women had a 25% increased risk of MPNs compared with the normal controls (RR = 1.33 95% Cl:1.15-1.52),[19] and Leiba et al. found a strong association between obesity during adolescence and occurrence of MPNs in a cohort of Israeli adolescents (HR = 1.81, 95% CI: 1.13-2.92, $P = 0.014$).[15] According to Murphy et al., increase in BMI is "modestly associated" with increased risk of MPNs.[19]

Environmental Exposure

Benzene exposure. In this review, three case-control studies[27–29] investigating the relationship between exposure to benzene and the risk of developing MPNs were identified. The results and conclusions from these studies were extracted to discover the trend for this association.

The study conducted by Glass et al. investigated the risk of myeloproliferative disease following exposure to low-level benzene in petroleum workers. They have concluded that there is no convincing association between MPNs and low exposure to benzene. However, there is some evidence that exposure over an extended period of 2–20 years before diagnosis may be associated with the increased risk of developing MPNs.[20] These results are preliminary, and more powerful confirmatory studies are essential. A population-based case-control study conducted by Heavner et al. also investigated benzene exposure as a suspected risk factor for MPNs. Their investigation revealed no association between exposure to benzene and the risk of MPNs.[25] Gross-Davis et al.'s findings are consistent with previous studies. They have also reported a lack of association.[26]

Host characteristics

Gender. Disease variability between males and females diagnosed with MPN has been observed. Various studies identify gender as a potential contributing factor in the diversity seen between male and female patients. Two cross-sectional[30,31] and three cohorts[22,26,32] were found, which analyzed the differences in the development of the disease between males and females.

One of the studies focused on the gender differences influencing the vascular complications in patients with MPNs and whether there are also differences in the JAK2V617F

allele burden between men and women with MPNs. They have reported that women have a significantly lower mutational burden, hence, a lower prevalence of homozygous JAK2 clones and less clonal expansion than men. However, despite the lower JAK2V671F allele burden, women have higher vascular complication rates, with 27% of women experiencing vascular complications, compared to 18% of men ($P = 0.09$).[27] Leiba et al. found that the male gender was positively associated with a higher risk of developing MPNs (HR 1.27, 95% CI: 1.03-1.57, $P = 0.028$) compared to females.[15]

Moreover, in subtype analysis by gender, Steins et al. reported that there is an overrepresentation of women diagnosed with ET (26%) and PV (63%) and an underrepresentation of women with PMF (10%) as compared to men PV (54%) and PMF phenotypes (29%) than ET (17%).[27] Besides, Geyer et al. observed the same conclusive results that female patients were more likely to have ET (48.6%) whereas male patients were more likely to have PV (30.3%).[28] A study by Landolfi et al. indicated several gender-related differences in vascular complications and the prevalence of vascular risk factors of PV patients. This study did not have any data about the JAK2 mutant allele burden. However, they have hypothesized that the difference in JAK2V617F allele burden may play a role in some of the observed differences between genders.[29]

An interesting finding regarding gender heterogeneity was discovered when the studies performed a gender stratification to gain more information about the power of gender differences on their primary outcome.

In one of the most recent prospective cohort study, NIH-AARP Diet and Health study on 463 049 participants. Podoltsev and his group reported that smoking was not associated with MPNs in the overall cohort. However, when stratified by sex, it was revealed that there is an increased chance of developing MPNs in women compared the nonsmokers to both former smokers (HR = 1.43 95% Cl: 1.03-2.00; $P = 0.03$) and current smokers (HR = 1.71, 95% Cl: 1.08-2.71; $P = 0.02$).[30]

The results following a gender stratification from this study are in accordance with results from the study,[12] which investigated the same outcome.

Three extensive cohort studies[17,18,25] were all conducted on large cohort of female patients. They concluded that there is a significant association between developing MPNs who are smokers and a modest association with obesity in females.

Discussion

This systematic review of the literature identified various studies investigating the potential associations between the environmental factors, lifestyle factors, and host characteristics with the pathogenesis of MPNs. Tables 1–4 summarize all the key findings from the chosen articles described in this study.

Cigarette smoking and its effects on human health have been the topic of many research studies in the past and present. Various associations with different diseases such as atherosclerosis and chronic heart diseases have been established. Smoking has also been linked to autoimmune diseases such as Crohn's disease and multiple solid malignancies, that is, lung cancer, oral cancers, and hematologic malignancies.[31]

The most substantial evidence found was in those who had a history of high pack-years of smoking and current smokers. The underlying mechanism for the association of diseases and smoking is related to the chronic low-grade inflammatory state and oxidative stress.[31] This relationship has been explained by the excessive increase in the levels of several proinflammatory cytokines, myeloid cells, and in-vivo activation of leukocytes, endothelial dysfunction, and systematic oxidative stress.[32]

The upregulation of JAK-STAT, NF-kB signaling pathways, and several transcription factors in smokers and patients with MPNs have been investigated.[32,33] In the discussion for this significant association,[12] following several studies[13,15,16,20] demonstrated that prevalence and frequency of JAK2V617F mutation are higher in smokers compared to nonsmokers. The increase in inflammatory biomarkers has explained this phenomenon as the result of introducing carcinogens into the body. This will lead to the activation of the JAK2/STAT3 pathway, which ultimately triggers mutation in hematopoietic stem cells and JAK2V617F.[31] Subsequently, upregulation of NF-kB facilitates the clonal expansion of cells with JAK2V617F mutations.[34] Collectively, these studies introduced smoking as a lifestyle risk factor for JAK2V617F mutation, which can play a vital contributing role in MPNs.

There is some ambiguity about the association between smoking and the increased risk of developing MPNs in each subtype. Few studies[12,13] observed statistical significance inpatient with ET but not PV. Whereas another study[17] reported this association to be significant among patients with PV, the risk was insignificant in patients with ET. Hence, further research in the subclassification of MPNs and the association with smoking is warranted.

The prevalence of obesity has increased worldwide. According to the WHO, in 2016, more than 1.9 billion adults were overweight, of whom 13% were obese.[35] Obesity has been associated with many primary health-related conditions, that is, diabetes, chronic heart disease, dyslipidemia, and several primary cancers such as the esophagus, liver, and kidney cancer.[36]

The existing studies on the association between obesity and the risk of developing MPN did not find any significant results. However, obesity cannot be ruled out as a contributing risk factor. The consequences resulting from obesity have been explained in terms of changes in metabolic, endocrinologic, immunologic, and inflammatory systems in the body which may lead to an increase in cell proliferation, cell mutation rate, dysregulate gene function, disturbance in DNA repair, or induce epigenetic changes, favoring the induction of neoplastic transformation.[35] Amongst these changes, secretion of adipokines, hyperinsulinemia, altered insulin-like growth factors, dyslipidemia, and increased inflammatory activity

Table 1. Data Collected From the Studies Investigating the Association Between Smoking and Developing MPNs.

First Author	Year	Design	Country	Gender	Case	Results	Conclusion
Kroll et.al.	2012	Cohort	UK	F	1.3 Million	Statistically significant trend for myelopro life rative disease (OR 1.42 (1.31-1.55)) but not for acute myeloid leukemia (1.10 (0.96-1.26)).	Positive association with smoking comparing frequent smokers with never smokers, the estimated relative risks of MPNs were approximately doubled in comparison to AML.
Pedersen et.al.	2018	Cohort	Denmark	M/F	70	MPN diagnosis for daily smokers was HR 2.5 (95% CI: 1.3-5.0). For ET, PV, MF, and MPN-unclassified, the HRs were 1.8 (95% CI: 0.5-5.8), 1.7 (95% CI: .5-5.8), 4.3 (95% CI: 0.9-19), and 6.2 (95% CI: 1.5-25), respectively. Among occasional/ex-smokers the corresponding HRs were 1.9 (95% CI: 1.1-3.3), 1.5 (95% CI: 0.6-3.7), 0.8 (95% CI: 0.3-2.4), 0.9 (95% CI: 0.2-4.4), and 6.2 (95% CI: 1.8-21).	Positive association beween smoking and all MPNs subtypes
Sørensen et.al.	2015	Case-control	Denmark	M/F	323	(OR = 1.64, 95% CI: 1.16–2.30), Significant in ET (OR = 2.15, 95% CI: 1.38–3.36), positive trend was observed for patients with PV (OR = 1.52, 95% CI: 0.92–2.49), significant for females (OR = 2.26, 95% CI: 1.36–3.75) for males, the association was insignificant (OR= 1.23, 95% CI: 0.77–1.97)	A significant association between a history of smoking and the risk of MPNs compared to CLL.
Duncombe et.al.	2020	Case-control	UK	M/F	106	High pack-years smoking (OR 2.19, 95% CI: 1.03–4.66) and current smoking restricted to PV cases (OR 3.73, 95% CI: 1.06–13.15).	Positive association between smoking and PV.
Leal et.al.	2014	Cohort	USA	F	257	PV was associated with current smoking (RR=2.83; p-trend= 0.016), while ET was not.	Positive association between smoking and PV in women.
Weinberg et.al.	2012	Case-control	Isreal	M/F	81	excess JAK2 mutation in smokers	Positive association between smoking and increased levels of inflammatory biomarkers.
Cordua et al.	2019	Cross-sectional	Denmark	M/F	645	Increasing age, smoking, and alcohol were risk factors for the mutations	Positive association between smoking and increased risk of JAK2 Mutation.
Skov et.al.	2019	Abstract (retrospective cross-sectional)	Denmark	M/F	252	Significantly higher levels of inflammatory biomarkers in smokers compared with never smokers possibly reflecting that smoking has a great impact on circulating levels of these biomarkers.	Positive association between smoking and increased levels of inflammatory biomarkers.
McMillan et.al.	2015	Abstract (Case-control)	UK	M/F	Not available	Positive association between cigarette smoking and MPNs. Participants working in occupations with high exposure to environmental tobacco smoke had an excess risk of MPN(OR 2.45, 95% CI: 1.12-5.37).	Positive association between MPNs and smoking/ environmental tobacco smoke.

Abbreviations: MPN, myeloproliferative neoplasm; PV, polycythemia vera; ET, essential thrombocythemia; JAK2, janus kinase 2; CI, confidence intervals; CLL, chronic lymphocytic leukemia; OR, odds ratio; HR, hazard ratio; RR, relative ratio.

Table 2. Data Collected From the Studies Investigating the Association Between Obesity and Developing MPNs.

First Author	Year	Design	Country	Gender	Cases	Results	Conclusion
Murphy et.al.	2013	Cohort	UK	F	1.3 million	Body mass index was associated with relative risk myeloproliferative syndromes OR 1.32 (1.15-1.52).	Positive association of BMI with the increased risk of developing MPN.
Duncombe et.al.	2020	Case-control	UK	M/F	106	Obesity was linked with ET (OR 2.59, 95% CI: 1.02-6.58).	Positive association between smoking and obesity.
Leal et.al.	2014	Cohort	USA	F	257	ET was associated with body mass index (RR 5 1.52 for >29.3 vs. <23.4 kg/m^2; *P*-trend 5 .042), while PV was not. PV was associated with current smoking (RR 5 2.83; *P*-trend 5 .016), while ET was not.	Positive association between ET with obesity.
Leiba et.al.	2017	Cohort	Isreal	M/F	2516256	A strong association between obesity during adolescence and occurrence of MPNs in a cohort of Israeli adolescents (HR = 1.81, 95% CI: 1.13-2.92, *P* = 0.014).	Positive association beween adolescent obesity and an increased incidence of myeloproliferative neoplasms.

Abbreviations: MPN, myeloproliferative neoplasm; PV, polycythemia vera; ET, essential thrombocythemia; JAK2, janus kinase 2; CI, confidence intervals; CLL, chronic lymphocytic leukemia; OR, odds ratio; HR, hazard ratio; RR, relative ratio.

Table 3. Data Collected From the Studies Investigating the Association Between Exposure to Benzene and Developing MPNs.

First Author	Year	Design	Country	Gender	Cases	Results	Conclusion
Heavner et.al.	2015	Case-control	USA	M/F	54	No evidence of an association between individual-level cumulative exposure and MPN risk (OR 1.0; 95% CI 0.9–1.0).	There was no indication of an association with cumulative PAH exposure.
Glass et.al.	2014	Case-control	Australia, Canada, UK	M/F	30	(OR of 1.79 (95% CI: .68 to 4.74). Spline analyses also showed little indication of a positive relationship between MPD and cumulative exposure (OR 4.40 (95% CI: 1.29 to 15.0).	No convincing association was identified between MPN and low exposure to benzene. Exposure windows of 2–20 years were examined, results do become somewhat more suggestive of an underlying pattern of excess risk.
Gross-Davis et.al.	2015	Case-control	USA	M/F	27	No relationships between MPNs and smoking history, residential history, diet, and lifestyle Behaviors with presumed exposure to aromatic and heterocyclic amines.	No positive association between exposure to benzene and MPNs was reported.

Abbreviations: MPN, myeloproliferative neoplasm; PV, polycythemia vera; ET, essential thrombocythemia; JAK2, janus kinase 2; CI, confidence intervals; CLL, chronic lymphocytic leukemia; OR, odds ratio; HR, hazard ratio; RR, relative ratio.

have been reported as primary underlying mechanisms linking obesity to hematological malignancies.[36]

Consequently, further investigation into the relationship between obesity and MPNs is indispensable. More specifically, stratified subtype analysis and gender differentiation will enable the researchers to find a stronger association between obesity and pathogenesis of MPNs in all subclassifications in both genders.

Benzene is an aromatic hydrocarbon and a natural component of crude oil, gasoline, and tobacco.[37] Individuals who work in the petroleum industry have a higher level of exposure to benzene. A compound such as pesticides, polycyclic

Table 4. Data Collected From the Studies Investigating the Association Between Gender and Developing MPNs

First Author	Year	Design	Country	Gender	Cases	Results	Conclusion
Geyer et.al.	2017	Cross-sectional	Western Europe and USA	M/F	2006	Most female patients were more likely to have ET (48.6% *vs* 33.0%; $P < 0.001$), and most male patients were more likely to have PV (41.8% *versus* 30.3%; $P < 0.001$).	Gender contributes to heterogeneity of MPNs.
Stein et.al.	2011	Cross-sectional	USA	M/F	270	Women ET (43/164: 26%) and PV phenotypes (104/164: 63%) than MF (17/164: 10%) compared to men PV (57/106: 54%) and MF phenotypes (31/106: 29%) than ET (18/106: 17%) ($P = 0.001$). Women were younger at diagnosis, with a median age difference of 6 years ($P = 0.001$).	Women are at higher risk of developing MPNs.
Leiba et al.	2017	Cohort	Isreal	M/F	2516256	Male gender was positively associated with a higher risk of developing MPNs (HR 1.27, 95% CI: 1.03-1.57, $P = 0.028$) compared to females.	Men are at higher risk of developing MPNs
Landolfi et.al.	2012	Cohort	Italy	M/F	1638	Gender-related differences in vascular complications and the prevalence of vascular risk factors of PV patients.	They have hypothesized that the difference in JAK2V617F allele burden may play a role in some of the observed differences between genders. 32
Podoltsev et.al.	2020	Cohort	USA	M/F	490	Increased risk of MPN in women (former smoker vs. non-smokers, HR = 1.43, 95% CI: 1.03-2.00, $P = 0.03$; current smokers vs non-smokers, HR=1/71, 95% CI: 1.08-2.71, $P = 0.02$)	In gender stratification, smoking associated with MPNs in women

Abbreviations: MPN, myeloproliferative neoplasm; PV, polycythemia vera; ET, essential thrombocythemia; JAK2, janus kinase 2; CI, confidence intervals; CLL, chronic lymphocytic leukemia; OR, odds ratio; HR, hazard ratio; RR, relative ratio.

aromatic hydrocarbon (PAH), benzene, and hazardous materials like industrial waste are potent carcinogenic and immunotoxic agents; therefore, they may be associated with various diseases, including cancers, hematological malignancies such as MPNs.[37,38] This has raised the interest of many researchers to delve deeper and investigate these environmental factors and find the pathological link to the development of cancer and hematological disorders.

Recent studies on benzene as a risk factor for hematological malignancies supported that benzene exposure can penetrate cells in the bone marrow, resulting in changes that can potentially lead to acute myeloid leukemia (AML).[39] It has been reported that in individuals exposed to a low benzene concentration daily, there is a stimulation of erythropoietic progenitor cells with independent cytokine growth compared with non-exposed individuals.[40] This spontaneous growth of erythroid progenitor cells is one of the hallmarks of MPNs, especially in polycythemia vera and primary myelofibrosis. However, the findings are not clinically significant to prove an association between exposure to benzene and developing MPNs.[40] The only definite evidence of the association of hematological disease with benzene exposure is acute myeloid leukemia.

The overall conclusion from studies that investigated the association between exposure to benzene and MPNs included in this review is that there is no statistically significant association. However, Glass et al. and several case reports[38,40-42] have reported that benzene is associated with increased risk of MPNs if the exposure time and duration of exposure is extended. The evidence on this association in the literature is inconsistent. Extensive research is required to help us

understand how these exposures may play a role in the etiology of the MPNs.

As previously mentioned, there is diverse variability in phenotypes and clinical features in each disease type. This led the researchers to explore the unique individual and host variations as a modifier of disease pathogenesis. Gender discrepancies within hematologic malignancies are not unique to MPN. Similar differences between males and females have been demonstrated in other disorders such as acute lymphoblastic leukemia, chronic lymphocytic leukemia, and multiple myeloma.[43] Although the discordance's etiological cause remains unclear, sex chromosome, aberrations, aneuploidy, influence of sex hormones, immune-competence, and gene expression may be potential contributors.[44] Investigation of these factors was beyond this study's scope, but future studies would be worth exploring. Gender has been classified as an independent modifier associated with MPNs in several studies. Stein et al. suggested gender differences influence the genotype and clonal expansion resulting in JAK2V617F allele burden variability.[27] Several studies reported a lower allele burden in females than in males. This should be considered when clinically evaluating the allele burden that partly could be responsible for the phenotypic heterogeneity seen in myeloproliferative neoplasm.[43,44]

Study Implications

In this systematic review, multiple online databases were searched using broad search terms for MPNs and epidemiological study designs to identify as many published articles as possible in the time frame of interest. In addition, grey literature and reference lists of identified articles were reviewed to minimize the possibility of missing any relevant studies.

There is heterogeneity in subjects, subtypes, and study designs, and risk factors chosen by each research. Due to the biological similarities of MPNs with some of the hematological malignancies such as leukemia and myelodysplastic syndromes, many studies have grouped these. This can cause misleading disease classification, and because these studies did not concentrate on MPNs alone, there will be a misestimation of the incidence of these diseases. Besides, limitations such as the small sample size in several studies minimized their power to detect acceptable associations between potential risk factors and MPNs. Another limiting factor for this review is that the included studies originate from developed countries such as the UK and the USA, with superior health care infrastructure and cancer registries. Therefore, more accurate incidence and prevalence rates are available. They compared the studies conducted and data received from the general population in developing or undeveloped countries due to the lack of health care resources, diagnostic and registration of rare and complex diseases like MPNs, disease misclassification, and underestimation of the incidence and prevalence rates can occur. Finally, although only a small risk of bias was detected in the included studies using the Newcastle–Ottawa Scale, which detected the reliability and quality of the chosen studies (Figure 2), the introduction of bias for each study is undeniable.

Conclusion

In conclusion, despite the recent improvements in recognition of somatic and germline mutations in patients with MPNs, the critical role of predisposing factors such as environmental factors, lifestyle risk factors, and host characteristics in the pathogenesis and progression of MPNs cannot be eliminated. Evidence collected as part of this review confirmed a strong positive association between cigarette smoking and the pathogenesis of MPNs. Another lifestyle factor investigated was obesity, which some suggested may be classed as a modest contributing factor for MPNs, but further investigation is required to establish the relationship. Exposures to hazardous substances such as benzene may also be associated with MPNs. Exceptionally, levels and duration of exposure can be crucial to the events' outcome; hence, extensive research is required. The hypothesis focuses on lifestyle behaviors such as smoking cessation and weight loss, which could eliminate the mutation's contributing factors. The finite numbers and discrepancies between the conclusions of published studies exploring other environmental factors and lifestyle risk factors propose that extensive, well-designed epidemiological research should be performed.

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