A Systematic Review and Meta-Analysis to Inform Cancer Screening Guidelines in Idiopathic Inflammatory Myopathies

Authors

Alexander G.S. Oldroyd

NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

Centre for Musculoskeletal Research, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

Centre for Epidemiology Versus Arthritis, University of Manchester, Manchester, UK

Department of Rheumatology, Salford Royal NHS Foundation Trust, Salford, UK

Andrew B. Allard

Royal National Hospital for Rheumatic Diseases, Royal United Hospitals Bath NHS Foundation Trust, Bath, UK

Jeffrey P. Callen

Division of Medicine, Department of Medicine, University of Louisville, Louisville, Kentucky, USA

Hector Chinoy

NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

Centre for Musculoskeletal Research, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

Department of Rheumatology, Salford Royal NHS Foundation Trust, Salford, UK

Lorinda Chung

Division of Immunology and Rheumatology, Department of Medicine and Dermatology, Stanford University, Stanford, California, USA

Palo Alto Health Care System, Palo Alto, California, USA

David Fiorentino

Department of Dermatology, School of Medicine, Stanford University, Stanford, California, USA

Michael D. George

Division of Rheumatology, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Division of Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Patrick Gordon

Department of Rheumatology, King's College Hospital NHS Foundation Trust, London, UK

Kate Kolstad

Division of Immunology and Rheumatology, Department of Medicine and Dermatology, Stanford University, Stanford, California, USA

Drew J.B. Kurtzman

Department of Dermatology, Wright State University, Dayton, Ohio, USA

Pedro M. Machado

Centre for Rheumatology and Department of Neuromuscular Diseases, University College London, London, UK

National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre, University College London Hospitals National Health Service (NHS) Trust, London, UK

Department of Rheumatology, Northwick Park Hospital, London North West University Healthcare NHS Trust, London, UK

Neil J. McHugh
Department of Pharmacy and Pharmacology, University of Bath, Bath, UK

Anna Postolova
Department of Immunology and Rheumatology, Stanford Health Care, Stanford, California, USA

Albert Selva-O'Callaghan
Systemic Autoimmune Unity, Vall D'Hebron General Hospital, Universitat Autonoma de Barcelona, Barcelona, Spain

Jens Schmidt
Department of Neurology, Neuromuscular Centre, Göttingen, Germany

Sarah Tansley
Department of Pharmacy and Pharmacology, University of Bath, Bath, UK
Royal National Hospital for Rheumatic Diseases, Royal United Hospitals NHS Foundation Trust Bath, Bath, UK

Ruth Ann Vleugels
Harvard Medical School, Boston, Massachusetts, USA
Department of Dermatology, Brigham and Women's Hospital, Boston, Massachusetts, USA

Victoria P. Werth
Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania, USA
Division of Dermatology, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, Pennsylvania, USA

Rohit Aggarwal
Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Corresponding author:
Rohit Aggarwal MD MS
Medical Director, Arthritis and Autoimmunity Center (Falk)
Associate Professor of Medicine
Co-director, UPMC Myositis Center
Division of Rheumatology and Clinical Immunology
University of Pittsburgh
3500 Terrace Street, BST S 700, Pittsburgh, PA
aggarwalr@upmc.edu
https://orcid.org/0000-0001-7531-8038

Abstract

Objectives

To identify clinical factors associated with cancer risk in the idiopathic inflammatory myopathies (IIMs) and to systematically review the existing evidence related to cancer screening.

Methods

A systematic literature search was carried out on Medline, Embase and Scopus. Cancer risk within the IIM population (i.e. not compared to the general population) was expressed as risk ratios (RR) for binary variables and weighted mean differences (WMD) for continuous variables. Evidence relating to cancer screening practices in the IIMs were synthesised via narrative review.

Results

Sixty nine studies were included in the meta-analysis. Dermatomyositis subtype (RR 2.21), older age (WMD 11.19), male gender (RR 1.53), dysphagia (RR 2.09), cutaneous ulceration (RR 2.73), and anti-transcriptional intermediary factor-1 gamma positivity (RR 4.66) were identified as being associated with significantly increased risk of cancer. Polymyositis (RR 0.49) and clinically amyopathic dermatomyositis (RR 0.44) subtypes, Raynaud's phenomenon (RR 0.61), interstitial lung disease (RR 0.49), very high serum creatine kinase (WMD -1189.96) or lactate dehydrogenase (WMD -336.52) levels, and anti-Jo1 (RR 0.45) or anti-EJ (RR 0.17) positivity were identified as being associated with significantly reduced risk of cancer. Nine studies relating to IIM-specific cancer screening were included. Computed tomography (CT) scanning of the thorax, abdomen and pelvis appeared to be effective in identifying underlying asymptomatic cancers.

Discussion

Cancer risk factors should be evaluated in patients with IIM for risk stratification. Screening evidence is limited but CT scanning could be useful. Prospective studies and consensus guidelines are needed to establish cancer screening strategies in IIM patients.

Keywords

- Myositis
- Muscle
- Autoantibodies
- CT scanning
- Neoplasia
- Epidemiology
- Meta-analysis

Key messages

- IIM cancer risk factors include: dermatomyositis, older age, male gender, dysphagia, cutaneous ulceration, anti-TIF1gamma
- Cancer screening evidence is limited but CT scans may be useful
- Findings from this study can inform IIM-specific cancer screening guidelines

Introduction

Idiopathic inflammatory myopathies (IIMs) are chronic multisystem autoimmune conditions that may cause muscle inflammation (myositis), skin manifestations and interstitial lung disease (ILD)(1,2). Adult onset IIMs are associated with increased risk of cancer. A recent meta-analysis of such studies reported a standardised incidence ratio (SIR) of 4.66 for dermatomyositis (DM) and 1.75 for polymyositis (PM)(3). The generally accepted definition of cancer associated myositis (CAM) is malignancy within 3 years of IIM onset. Cancer remains the leading cause of death for adults with IIM(4–6).

Around one in four patients are diagnosed with cancer within three years before or after IIM onset(4), however risk varies according to the presence/absence of certain factors(7). Unfortunately, the data regarding risk factors is largely derived from retrospective studies with small populations, thus limiting the ability to form robust conclusions and extrapolate to the wider population.

Meta-analysis of existing evidence could synthesise results across studies and identify factors associated with cancer in IIM populations, thus potentially accounting for biases, such as publication bias and outlier studies. Further, assimilation of evidence relating to cancer screening specific to CAM could provide an evidence base informing clinical screening practices and facilitate the formulation of cancer screening guidelines.

The International Myositis Assessment and Clinical Studies Group (IMACS), the largest international group for scientific studies in myositis, began a special interest group to develop evidence-based cancer screening guidelines for newly diagnosed IIM patients. This meta-analysis forms an important component in guideline formation. Therefore, the overall aim of this study is to identify risk factors associated with CAM using meta-analysis, and to systematically review existing evidence relating to CAM screening approaches.

Methods

We performed a systematic review of factors associated with cancer in IIM populations and screening practices. Evidence pertaining to factors associated with cancer were assimilated via meta-analysis. Results of studies relating to cancer screening in IIM populations was assimilated into a narrative review. Study selection, data extraction, quality assessment, data synthesis and analysis were all carried out in adherence to PRISMA guidelines (see Supplementary Material for PRISMA checklist)(8).

Data sources

A systematic literature search was carried out on Medline via PubMed, Embase via OVID and Scopus. The following were used to identify appropriate studies: "myositis", "neoplasm", "screening". Full length peer reviewed articles published in English language before the 8th of January 2020 were included. Case reports, letters and conference abstracts were excluded. References of each identified study were also examined for further appropriate studies.

Study selection

Studies were included in the risk factor meta-analysis if they provided data on at least one risk factor, included at least 10 IIM study subjects, and provided data on an IIM control group. It is important to note that risk factors were assessed in comparison to each study's wider IIM population, not the general healthy population. Eligible IIM subtypes included DM, PM, anti-synthetase syndrome (ASS), immune-mediated necrotising myopathy (IMNM) and clinically amyopathic DM (CADM). Data relating to inclusion body myositis was excluded due to the relationship with cancer being distinct from that of other IIM subtypes(4). Only the study with the largest cohort was included where repeated studies utilised the same cohort data, where identifiable.

For the review of screening practices, studies that assessed at least one cancer screening approach/modality in an IIM population were included.

Data extraction

Each eligible article was independently reviewed by two reviewers. The title and study abstracts were reviewed to assess eligibility/ineligibility. Preliminary full text reviews were carried out where eligibility/ineligibility could not be decided using the title and abstract alone. Full text review of each eligible article was carried out by a single reviewer. Extracted data included study type, population studied, sample size, risk factors evaluated, number of cases (i.e. those with risk factors), controls (i.e. those without risk factors), number of cases and controls diagnosed with cancer (excluding non-melanotic skin cancers). Available data (e.g. mean, standard deviation, median, range) on continuous risk factors, such as age, in those with/without cancer was also collected. A second reviewer reviewed selected studies to ensure accuracy of data extraction. The quality of studies and bias assessment was carried out using the GRADE system developed by the Scottish Intercollegiate Guidelines Network, where each study was given a quality assessment of either "very low", "low", "moderate" or "high"(9). Studies were excluded if they were deemed to be of "low" or "very low" quality or subject to a high risk of bias according to the GRADE system. Agreement of both reviewers was required to remove a study according to bias. The decision of study inclusion/exclusion was made by a third reviewer in the case of differing assessments.

Data synthesis and analysis

Meta-analysis was carried out for each risk factor where data from at least two eligible studies was available. Investigated factors included IIM subtypes, demographics, clinical features, laboratory parameters and auto-antibodies. The denominator used in cancer risk estimation for each factor was the remaining IIM population of each study, not the general population. The cancer risk associated with individual ASS-related autoantibodies (anti-Jo1, anti-PL7, anti-PL12, anti-EJ, anti-OJ, anti-KS) was considered. Subsequently, the risk associated with the presence of any ASS-related autoantibody was calculated by combining studies that compared risk against non-ASS IIM controls. Risk ratios (RRs) were calculated for binary variables (e.g. presence of ILD). The weighted mean difference (WMD) for each continuous variable (e.g. age) was calculated by comparing means and standard deviations. The mean and standard deviation was calculated from studies that reported only median and range using methods described by Hozo *et al*(10).

The small number of studies that reported the utility of cancer screening approaches in IIM populations precluded a meta-analysis, therefore a narrative review was carried out.

Heterogeneity and study sample size analysis

Heterogeneity was assessed using the standard chi-squared test and I^2 statistic. Further analysis was carried out for factors with very high levels of heterogeneity (I^2 >75%). Influence analysis ("leave-one-out") was carried out to identify outlier studies, i.e. those with extreme effect sizes, and thus substantially contributing to heterogeneity. A study was considered an outlier if it fulfilled the cut off criteria proposed by Viechtbauer *et al*(11).

Egger's test was used to assess the influence of study cohort size on calculated effect sizes(12). "Trim and fill" was used to calculate adjusted effect sizes for factors with significant (<0.05) Egger's test p-values(13).

All analysis was carried out using the statistical programme R(14), and the meta(15) and metafor(16) packages.

Results

A total of 7,030 articles were initially identified via the literature search and 141 were reviewed for eligibility following removal of ineligible papers, duplicates, case reports and reviews (Figure 1). Sixty seven studies were included in the risk factor meta-analysis (Figure 1) and 9 in the screening narrative review (two studies were included in both the meta-analysis and systematic review). Table 1 displays the summary RRs and WMDs calculated for each risk factor. See Supplementary Material for forest plots for each risk factor and further details of each study (Supplementary Table 1).

IIM subtypes

DM was significantly associated with a higher risk of cancer, compared to other IIM subtypes(17,18,27–36,19,37–40,20–26). PM(17,18,27,28,30,31,33–38,19,39,40,20–26) and CADM(28,35,41) were found to be associated with significantly lower risk for cancer compared to remaining IIM subtypes. ASS subtype was a non-significant factor, however data from only two eligible studies were available(21,42). Insufficient data was available to perform meta-analysis on data relating to IMNM.

Clinical Factors including demographics and laboratory values:
Demographics

Older age at time of IIM onset was found to be significantly associated with increased risk of cancer(21,22,44–53,28,54,29,32,33,36,39,42,43). The mean age of IIM onset in cancer cases was 59 years, compared to 49 years in the non-cancer cases. Male gender was found to be significantly associated with higher risk of cancer, compared to female gender(17,18,32–34,36,38,39,41–44,21,45–54,22,55–59,25–30).

Clinical risk factors

Sufficient data were available to quantify the cancer risks associated with dysphagia, cutaneous ulceration, Raynaud's and ILD. Dysphagia, which was typically not objectively defined across the majority of studies, was significantly associated with higher risk of cancer(22,25,49,56,59,60,26,29,32,33,39,43,46,47). Cutaneous ulceration was also significantly associated with higher risk of cancer(45,46,49,50,53). Analysis revealed that the presence of Raynaud's was associated with a significantly lower risk of cancer(22,25,59,26,29,30,39,41,45,46,50). The presence of ILD, which was typically diagnosed via computed tomography (CT) scanning, was also associated with a significantly lower risk of cancer(22,26,45,46,56,59,28–30,32,33,35,39,43).

Laboratory values

Lower CK(22,27,29,32,33,38,39,43,46,53) values were significantly associated with increased cancer risk, therefore, conversely, very high values were associated with lower risk of cancer. It is important to note however, that the mean CK level in cancer cases (2,402 IU/L) was still raised compared to normal values, but lower than the non-cancer group (3,557 IU/L). Similarly, lower LDH(22,32,33,38,39,46,53) values (mean LDH 766 U/L) were found to be associated with increased cancer risk as compared to higher LDH values (mean LDH 1078 U/L). Both ALT(29,38,53) and ESR(22,29,33,38,43,45) levels were found to be non-significant factors, and insufficient data was available for aspartate aminotransferase and aldolase.

Auto-antibodies

Anti-transcriptional intermediary factor-1 gamma (anti-TIF1γ) positivity was significantly associated with increased cancer risk(21,31,63–71,37,41,44,48,58,60–62). Anti-nuclear matrix protein 2 (anti-NXP2) positivity was a non-significant factor(21,37,76,61,62,68,71–75). Large proportions of the "control" cohorts in studies of anti-NXP2-positive cohorts were comprised of anti-TIF1γ-positive cases. We repeated meta-analysis after removing anti-TIF1γ-positive cases. The RR of anti-NXP2 using data from six studies with anti-TIF1γ cases excluded was 1.47 (95% CI 0.57, 3.80, I^2 0.00%), again indicating that positivity for anti-NXP2 is a non-significant factor for cancer relative to other autoantibody subtypes(21,37,62,68,71,73).

Analysis was carried out for each individual ASS-related autoantibody. Anti-Jo-1(21,22,77,25,26,29,33,46,59,62,71) and anti-EJ(21,62,71,78,79) were significantly associated with reduced cancer risk. Positivity for anti-PL7(21,62,71,78,79), anti-PL12(21,62,71,78,79), anti-OJ(21,71,78,79) and anti-KS(71,79) were non-significant factors, although limited by small number of studies. Analysis revealed that the presence of any ASS-related autoantibody was significantly associated with lower risk of cancer(21,22,25,26,29,33,59,62,70,71).

Positivity for other autoantibodies, including anti-3-hydroxy 3-methylutaryl coenzyme A reductase (anti-HMGCR)(21,62,71,80,81), anti-signal recognition particle (anti-SRP)(62,71,80), anti-small ubiquitin-like modifier-1 activating enzyme (anti-SAE1)(21,62,71), anti-melanoma differentiation-associated gene 5 (anti-MDA5)(21,44,48,62,71) or anti-Mi2(21,41,58,62,64,71), were identified as non-significant factors for cancer. Both MSA negativity(21,30,45,62,71) and ANA positivity(22,26,54,56,82,28,30,39,41,43,46,50,53) were non-significant factors.

Heterogeneity and publication bias
Table 1 displays the standard chi-squared test results and I^2 statistic for heterogeneity of each analysed factor. Influence analysis aimed to identify "outlier" studies for risk factors with very high (>75%) heterogeneity. One study each fulfilled the outlier criteria for CK(53), ESR(45) and ALT(53). Adjusted WMD after removal of data from outlier publication was calculated and did not change overall relationships (Supplementary Table 2).
Significant publication bias was observed with "any ASS-antibody". Adjusted RR following "trim and fill" analysis with six added studies was 0.46 (95% CI 0.23, 0.93).

Cancer screening utility review
Nine studies(40,45,83–89) relating to utility of cancer screening approaches in IIM populations were identified. Table 2 displays the details of each study. A total of 90 cancers were identified via screening across 1,033 patients. Studies were carried out across a number of countries, including the USA, Canada, Taiwan, China, France and Spain, and widely ranging intervals between IIM onset/diagnosis and screening were reported. All but one study was retrospective. Study population sizes ranged between 14 and 400. A wide variety of cancers were diagnosed, including but not limited to breast cancer, squamous cell carcinoma, multiple myeloma, ovarian cancer, lymphoma, lung cancer and oesophageal cancer.
The utility of "blind screening" (i.e. investigations carried out in the absence of target symptoms) was reported by Leatham et al(85) and Sparsa et al(45). Leatham et al identified 17 out of 48 cancer patients diagnosed with cancer via "blind" screening modalities after DM onset. CT scanning of the thorax, abdomen or pelvis detected the most cancer diagnoses (6/17, 38%), followed by mammography (3/17, 18%). Sparsa et al reported the identification of 30 cancers via 122 investigations. Thirty five investigations were "directed" (i.e. initiated due to the presence of target symptoms) and resulted in the identification of 19 (54%) cancers. In contrast, 87 investigations were "blind" and identified 11 (13%) cancers. Again, CT scanning of the thorax, abdomen and pelvis was the single investigation that detected the most cancers (5/18, 28%).
The utility of ^{18}F-FDG PET/CT was reported by Maliha et al(84) and Selva-O'Callaghan et al(88). Maliha et al reported that ^{18}F-FDG PET/CT scans revealed no further cancer diagnoses and actually lead to more biopsies, compared to "conventional" screening (see Table 2 for details). Similarly, Selva-O'Callaghan reported that single ^{18}F-FDG PET/CT scans were comparable to large number of conventional screening investigations, which included complete physical examination, laboratory tests (complete blood count and serum chemistry panel), thoraco-abdominal CT scan, tumour markers (CA125, CA19-9, CEA, PSA), gynaecological examination, ovarian ultrasonography and mammography.
The screening utility of CA125 was demonstrated by Amoura et al(89) and Whitmore et al(87). Amoura et al demonstrated that increased levels were significantly associated with subsequent cancer diagnoses (OR 29.7, 95% CI 8.2, 106.6, p-value <0.0001). Whitmore et al also demonstrated the utility of normal values - no study participant with normal CA125 levels were subsequently diagnosed with cancer during the study period. In contrast, Lim et al concluded that CA125 testing was not useful for detection of cancer(40). Eighteen participants had raised CA125 levels and only one (6%) was subsequently diagnosed with cancer. Additionally, 53 participants had normal CA125 levels and two (4%) were diagnosed with cancer.
Both Amoura et al and Lim et al reported the screening utility of CEA, CA15-3 and CA19-9 (Table 2). Raised CEA or CA15-3 levels were not associated with cancer in each study. Raised CA19-9 levels were

significantly associated with cancer in the study by Amoura *et al* - 11 cases had raised levels and three subsequently developed cancer (OR 4.5, 95% CI 1.00, 18.7, p-value 0.018). Raised CA19-9 levels were not found to be associated with cancer in the study by Lim *et al*, however. Of note, Amoura *et al* reported that three cases had raised levels of both CA19-9 and CA125 and all of these were subsequently diagnosed with cancer (OR 86.3, 95% CI 4, 1832, p-value <0.0001). Lim *et al* also reported no association between raised AFP levels and cancer. Interestingly, Lim *et al* reported an association between CA15-3 levels and the development of ILD - 8 (89%) of the 9 patients with increased CA15-3 levels were diagnosed with ILD.

Discussion

This meta-analysis has quantified the relationship between 30 clinical factors and the risk of cancer in IIM patients. Fifteen factors significantly associated with cancer risk were identified. Existing evidence relating to the utility of cancer screening in IIM populations was also reviewed, providing information useful for the future formation of cancer screening guidelines.

DM, increasing age, male gender, dysphagia, cutaneous ulceration and the presence of anti-TIF1γ were all associated with increased cancer risk. The magnitude of risk of cancer was greatest for those positive for anti-TIF1γ, with a fourfold increased risk. For LDH and CK, very high LDH or CK values were associated with reduced cancer risk.

PM and CADM subtypes were associated with lower risk of cancer compared to other subtypes. However, the risk of cancer in PM and CADM cases may be reduced, but the risk is still raised compared to the general population, as previously identified(3).

ASS subtype was a non-significant factor for cancer, however this was based on data from only two studies. The presence of ILD or any ASS-related antibody, in particular anti-Jo1 and anti-EJ, were significantly associated with lower cancer risk. ASS is characterised by ILD and the presence of any ASS-related antibody, therefore it may be concluded that ASS patients are at significantly lower cancer risk, compared to other IIM subtypes.

Insufficient evidence was available to include IMNM subtype in the meta-analysis. However, meta-analysis was possible for anti-SRP and anti-HMGCR, both IMNM-specific autoantibodies. Positivity for either anti-SRP or anti-HMGCR were non-significant factors for cancer. Additionally, very high CK levels, which are also typically observed in IMNM cases, was associated with reduced cancer risk. A small number of studies have reported increased risk of cancer in IMNM patients compared to the general population, however the risk may be dependent on autoantibody status as reported by Allenbach *et al*(80), where anti-HMGCR positivity was associated with increased cancer risk and anti-SRP positivity was not. An increased cancer risk associated with anti-HMGCR positivity compared to the general population was however not found by Tiniakou *et al*(90). Overall, the relationship between IMNM and cancer remains unclear, and further research in larger cohorts is warranted.

Anti-NXP2 positivity was not associated with cancer in this meta-analysis even after removal of anti-TIF1γ positive cases, where possible. Previous studies have however highlighted the increased risk of anti-NXP2 positivity compared to the general population, for example Yang *et al* reported a cancer risk SIR of 8.14 compared to the general population(21). It is perhaps therefore still appropriate to consider anti-NXP2 positivity a cancer risk factor when considering comparison to the general population. Further research to fully delineate the cancer risk associated with anti-NXP2 positivity is warranted.

Few previous studies have investigated the utility of cancer screening approaches in IIM populations, however a number of conclusions can be drawn.

Firstly, imaging of internal organs via CT scanning of the thorax, abdomen and pelvis appeared to yield a high proportion of cancers. CT scanning is a readily available low cost investigation and therefore represents a potentially useful method of screening.

Secondly, CA125 levels may potentially be useful in stratifying patients' ovarian cancer risk. It is important to note, however, that the evidence is overall weak, with only three studies reporting relevant results.

Thirdly, neither of the two included studies demonstrated that ^{18}F-FDG PET/CT scanning lead to a higher yield of cancer diagnosis (84,88). The study by Selva-O'Callaghan et al, however, indicated that ^{18}F-FDG PET/CT scanning was comparable to a wide panel of extensive screening investigations in ability to detect cancers. This indicates that a single ^{18}F-FDG PET/CT scan may potentially negate the need for numerous investigations. It is important to note the small population sizes in the studies by Maliha et al and Selva-O'Callaghan et al and non-stratification according to the presence of risk factors, thus precluding extrapolation of utility of ^{18}F-FDG PET/CT in IIM patients with risk factors. The higher number of biopsies performed following ^{18}F-FDG PET/CT without subsequent cancer diagnoses, as reported by Maliha et al, is also a potential disadvantage. ^{18}F-FDG PET/CT can provide potentially useful IIM-specific clinical information relating to ILD and myositis(91). Further, a single ^{18}F-FDG PET/CT scan can result in lower "out of pocket expenses" for patients (US $127 less), compared to a broad panel of screening investigations (i.e. CT, tumour markers, faecal occult blood, mammography, ovarian ultrasonography) (92). However, a small but potentially important radiation exposure of 25 mSv si associated with an ^{18}F-FDG PET/CT scan, compared to 14-19 mSv with a standard whole body CT scan (93). ^{18}F-FDG PET/CT may therefore represent a cost-effective single investigation that can identify underlying malignancy and detect ILD and myositis, thus removing the need for further multiple screening investigations. Further evidence is, however, required to fully delineate the role of ^{18}F-FDG PET/CT scanning as a screening strategy for cancer in IIM patients.

As previously mentioned, all results and findings in this study pertain only in comparison to IIM patients, not the general population. Future research and meta-analysis may consider delineating the cancer risk of appropriate factors in comparison to the general population.

One major potential limitation to this study is the varying MSA detection methods employed by different studies. This introduces the risk of varying accuracy of MSA detection, thus affecting the calculated effect sizes. Further, substantial heterogeneity potentially limits the clinical translation of variables studied. Publication bias was observed with any ASS-related antibody, thus highlighting potential inaccuracy of calculated effect sizes. Recent advances in understanding raise the possibility that PM cases may actually represent other subtypes, such as IMNM or other neuromuscular disorders(94–96), thus potentially limiting the accuracy of the estimated cancer risk associated with PM. Calculation of the cancer risk associated with connective-tissue disease-associated IIM ("overlap IIM") was not possible due to varying classification. A number of potential risk factors such as ethnicity, arthralgia, arthritis and fever were not included in this meta-analysis due to unavailability of objective data. No studies addressed whether or not repeated cancer screening is beneficial in identifying cancer; evidence on this important topic will impact screening practices, especially in patients where no cancer was diagnosed via initial screening. The potential interaction of the presence of multiple risk factors and their impact upon stratification of cancer risk in IIM has never been evaluated. The small number of studies that report the utility of cancer screening investigations highlights the need for further research in this area.

Conclusion

This meta-analysis has quantified the risk of cancer associated with a large number of clinical risk factors and MSAs, which can inform cancer screening practices for IIM patients. In addition, the systematic review of available evidence related to utility of cancer screening investigations, although limited, can also inform clinical decisions and aid guideline development in this area. Overall, these results can inform the development of cancer screening guidelines, thus potentially leading to earlier cancer diagnosis and improved patient outcomes.

Contributions

R.A. conceived and designed the study. A.O., M.D.G., D.K., S.T., A.A., A.P. and K.K. carried out the literature review and data extraction. A.O. carried out all data analysis. A.O. lead manuscript preparation. All authors reviewed results, critically appraised the manuscript and approved the final version.

Data availability statement

There are no new data associated with this article.

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Table 1 - Meta-analysis results, including calculated effect sizes, heterogeneity and publication bias for each factor

Domain	Factor	RR/WMD (95% CI)	GRADE certainty rating*	Heterogeneity p-value	I²(%)	Egger's test (p-value)
Subtype†	DM	2.21 (1.78, 2.77)	Moderate	0.134	24.8	0.162
	PM	0.49 (0.37, 0.65)	Moderate	0.061	34.0	0.603
	CADM	0.44 (0.20, 0.97)	Low	0.751	0.0	-
	ASS	0.28 (0.00, 6554.79)	Low	0.017	82.4	-
Demographics	Age	11.19 (9.29, 13.08)	High	0.001	56.1	0.859
	Male gender	1.53 (1.34, 1.75)	High	0.101	24.2	0.081
Clinical features	Dysphagia	2.09 (1.21, 3.60)	High	<0.0001	83.6	0.310
	Cutaneous ulceration	2.73 (1.33, 5.59)	Moderate	0.389	3.1	-
	Raynaud's	0.61 (0.39, 0.95)	Moderate	0.698	0.0	0.055
	ILD	0.49 (0.32, 0.76)	High	0.011	52.3	0.381
Blood parameters	CK	-1189.96 (-2132.74, -247.18)	Moderate	<0.0001	84.5	0.182
	LDH	-336.52 (-514.40, -158.64)	Moderate	0.093	44.8	-
	ALT	36.29 (-313.18, 385.77)	Low	0.001	85.5	-
	ESR	4.4 (-6.2, 14.9)	Low	0.028	60.2	-
Autoantibodies	Anti-TIF1γ	4.68 (3.37, 6.48)	High	<0.0001	68.8	0.543
	Anti-NXP2	1.16 (0.73, 1.87)	Moderate	0.278	17.4	0.271
	Anti-SAE1	1.59 (0.33, 7.74)	Low	0.217	34.5	-
	Anti-HMGCR	0.55 (0.19, 1.61)	Low	0.277	21.6	-
	Anti-MDA5	0.17 (0.02, 1.28)	Low	0.457	0.0	-
	Anti-Mi2	1.05 (0.28, 3.92)	Low	0.381	5.6	-
	Anti-SRP	0.40 (0.14, 1.21)	Low	0.790	0.0	-
	Any ASS antibody	0.41 (0.26, 0.64)	High	0.746	0.0	<0.001
	Anti-Jo1	0.45 (0.25, 0.84)	High	0.700	0.0	0.051
	Anti-PL7	0.68 (0.15, 3.07)	Low	0.541	0.0	-
	Anti-PL12	1.59 (0.89, 2.86)	Low	0.789	0.0	-
	Anti-EJ	0.17 (0.07, 0.44)	Low	0.964	0.0	-
	Anti-OJ	1.56 (0.68, 3.52)	Low	0.870	0.0	-
	Anti-KS	1.23 (0.05, 30.12)	Very low	0.717	0.0	-
	MSA negative	0.89 (0.50, 1.59)	Low	0.073	50.4	-
	ANA positivity	0.91 (0.58, 1.41)	Low	<0.0001	75.0	0.113

RR = risk ratio, WMD = weighted mean difference, CI = confidence interval, DM = dermatomyositis, PM = polymyositis, CADM = clinically amyopathic dermatomyositis, ASS = anti-synthetase syndrome, ILD = interstitial lung disease, CK = creatine kinase, LDH = lactate dehydrogenase, ALT = alanine transaminase, ESR = erythrocyte sedimentation rate, TIF1γ = transcriptional intermediary factor-1 gamma, NXP2 = nuclear matrix protein 2, SAE1 = small ubiquitin-like modifier-1 activating enzyme, HMGCR = 3-hydroxy 3-methylutaryl coenzyme A reductase, MDA5 = melanoma differentiation-associated gene 5, SRP = signal recognition particle, MSA = myositis specific autoantibody, ANA = anti-nuclear antibody

*Grading of Recommendations, Assessment, Development and Evaluations certainty rating: very low (the true effect is probably markedly different from the estimated effect), low (the true effect might be markedly different from the estimated effect), moderate (the authors believe that the true effect is probably close to the estimated effect), high (the authors have a lot of confidence that the true effect is similar to the estimated effect)

†The risk of cancer for each IIM subtype is estimated against each study's wider IIM population, not the general population

Table 2 - Details of identified studies reporting utility of cancer screening investigations in IIM populations

	Country	Study type	IIM subtypes included	Population size	Screening modality assessed	Timing of screening	No. cancer cases identified	Control modality	No. cancer cases identified	Comments
Kidambi et al(84)	USA	Retrospective	DM	79 Upper GI endoscopy - 47	Upper and lower GI endoscopy	Mean 6.8 years (SD 6.6) after DM onset	0 2 cases of Barrett's oesophagus 10 adenoma	NA	NA	

				Lower GI endoscopy - 67						
Maliha et al(85)	Canada	Retrospective	DM (31), PM (1), overlap (25), IBM (1), Orbital (1), unspecified subtype (4)	63	¹⁸F-FDG PET/CT	"Average" time of 9 months after IIM diagnosis	0	"Conventional" - physical and gynaecological examination, CBC, serum biochemistry, LFTs, serum protein electrophoresis, urinalysis, CXR, gastroscopy, colonoscopy, CT of thorax, abdomen and pelvis, mammography, endovaginal USS, serum tumour markers	3 - breast cancer via mammography, squamous cell carcinoma via examination, multiple myeloma via blood tests	¹⁸F-FDG PET/CT lead to more biopsies compared to conventional screening (8 vs 5)
Leatham et al(86)	USA	Retrospective	DM	400		Median 4.2 years (IQR 1.7, 8..6) between symptom onset and screening	29 cancers across 27 patients diagnosed after DM onset. 17 cancers (16 patients) diagnosed by blind screening. CT abdomen - 4 Mammography - 3 CBC - 3 Colonoscopy - 2 PSA - 2 CT thorax - 1 CT pelvis - 1	NA	NA	2 cancers (breast cancer and DLBCL) were diagnosed via repeat "blind screening". Increasing age was only identified cancer risk factor.
Huang et al(87)	China	Retrospective	DM and PM	129 PM (30), DM (99)	WBMRI	Mean disease duration of 30.8 months (SD 47.9, range 10 days to 19 years)	5 (all DM) 3 NPC 1 ovarian 1 thyroid cancer	NA	NA	
Whitmore et al(88)	USA	Retrospective	DM	14	Serum CA-125	Median disease duration of 15.5 months (range 7 to 24)	4 ovarian cancer	NA	NA	Pre-diagnosis serum CA-125 levels were found to be higher in 2 (50%) of ovarian cancer cases. Normal serum CA-125 levels were seen in all controls.
Sparsa et al(46)	France	Retrospective	DM and PM	40	History, physical and pelvic examination, CBC, ESR, general chemistry screen, LFTs, CXR, mammography, CT TAP, upper and lower GI endoscopy, "small bowel radiologic examination", thyroid imaging, MRI, PET-CT, cancer-associated antigens, bone marrow biopsy, laparotomy	Not reported for whole cohort. Screening occurred between 12 months prior to and 8 months after IIM onset in cancer cases	Total of 122 investigations - 30 revealed malignancy. 35 tests were "directed" - 19 (54%) were positive 87 tests were "blind" - 11 (13%) were positive	NA	NA	CT TAP revealed most "blind" screening cancers - 5/18 (28%) were positive
Selva-O'Callaghan et al(89)	Spain	Prospective	49 DM 6 PM	55	¹⁸F-FDG PET/CT	Within 6 months period after IIM diagnosis	Positive in 7 cases (1 false-positive), negative in 44 cases (3 false-negatives) and inconclusive in 4 cases	CT abdomen and pelvis, mammography, gynaecologic examination, ovarian USS, tumour markers (CA-125, CA-19.9, CEA, PSA)	Positive in 9 cases (2 false-positive) - 5 breast, 1 lung, 1 pancreas, 1 vagina, 1 colon, Negative in 46 cases (2 false-negatives)	¹⁸F-FDG PET/CT PPV was 86%, NPV was 94%
Amoura et al(90)	France	Retrospective	50 DM 52 PM	102	CEA > 5ng/ml CA15-3 >25 units/ml CA19-9 >37 units/ml CA125 >35 units/ml	Not reported	CEA - increased in 4 patients - no cancer diagnoses	NA	NA	

						CA15-3 - increased in 22, 2 cancer diagnoses CA19-9 - increased in 11 patients - 3 cancer diagnoses CA125 - increased in 8 patients - 5 cancer diagnoses CA19-9 and CA125 were both increased in 3 patients - all 3 were diagnosed with cancer			
Lim et al(41)	Taiwan	Retrospective	98 DM 53 PM	152	CEA > 5ng/ml CA125 >35 units/ml CA19-9 >34 units/ml CA15-3 >25 units/ml AFP >12ng/ml	Mean 6.1 years (SD 5.7) after IIM onset	CA15-3 - increased in 9 patients - no cancer diagnoses CA125 - increased in 18 patients - 1 cancer diagnosis CA19-9 - increased in 10 - 1 cancer diagnosis AFP - increased in 4 - no cancer diagnoses CEA - increased in 8 - 3 cancer diagnoses			8 (89%) of the 9 with elevated CA15-3 levels developed ILD

IIM = idiopathic inflammatory myopathy, DM = dermatomyositis, GI = gastro-intestinal, SD = standard deviation, NA = not applicable, PM = polymyositis, IBM = inclusion body myositis, ^{18}F-FDG PET/CT = fluorodeoxyglucose positron emission tomography/computed tomography, CBC = complete blood count, LFT = liver function tests, CXR = chest X-ray radiograph, USS = ultrasound scan, IQR = inter-quartile range, PSA = prostate specific antigen, DLBCL = diffuse large B-cell lymphoma, WBMRI = whole body magnetic resonance imaging, NPC = nasopharyngeal carcinoma, ESR = erythrocyte sedimentation rate, CT TAP = computed tomography thorax, abdomen and pelvis, CEA = carcinoembryonic antigen, PPV = positive predictive value, NPV = negative predictive value, AFP = alpha fetoprotein, ILD = interstitial lung disease
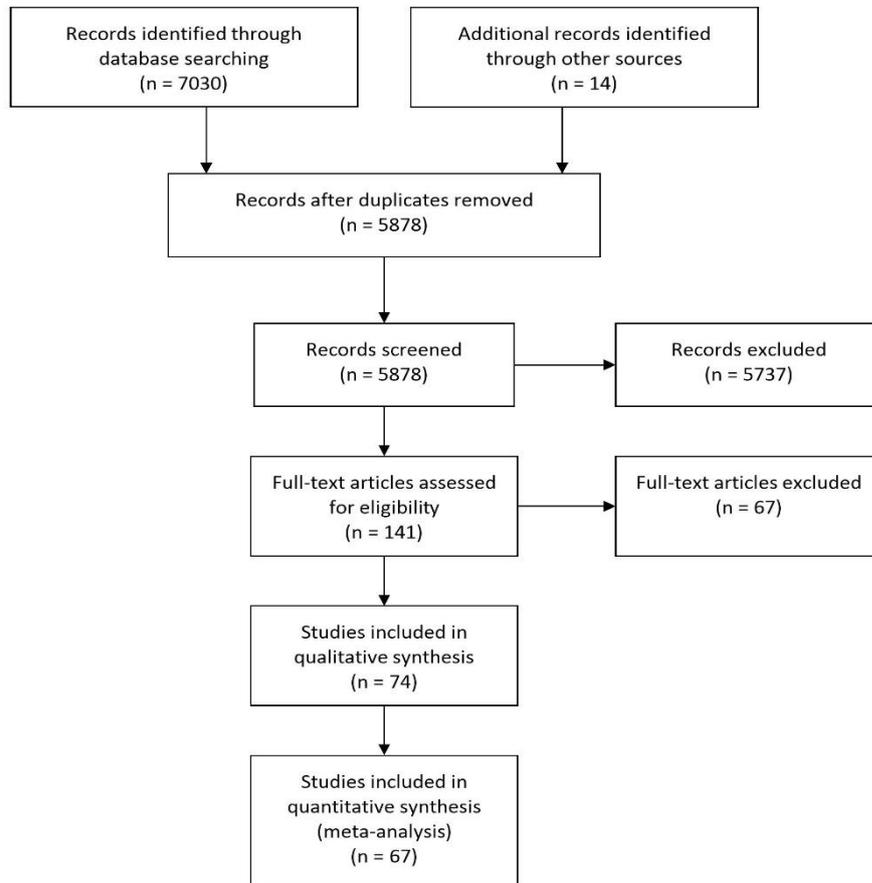
Figure 1 – PRISMA flow diagram