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Recommendations and metaanalyses

French recommendations for assessing and managing the risk of cancer before the initiation of targeted therapies for chronic rheumatic inflammatory diseases

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ABSTRACT

Objective: Chronic inflammatory rheumatic diseases (CIRDs) are associated with a higher risk of cancer due to persistent inflammation, immune dysregulation, and immunomodulatory therapies. The growing use of targeted therapies necessitates systematic cancer risk assessment prior to treatment initiation.
Objective: To develop practical recommendations for cancer risk assessment and management before initiating targeted therapies in patients with CIRDs, while balancing therapeutic benefits with oncologic safety.
Methods: Conducted under the French Society of Rheumatology, this initiative followed standardized procedures. A multidisciplinary task force was established, including rheumatologists, oncologists, pulmonologists, gynecologists, and patient representatives. Two systematic literature reviews (2005–2024) were performed to assess cancer risk in CIRD patients under conventional and targeted DMARDs.

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Recommendations were formulated based on evidence synthesis and expert consensus, with multiple voting rounds to establish levels of agreement.
Results: The task force proposed three overarching principles and eight evidence-based recommendations. It advocated the application of general population cancer screening programs, adapted to the specific needs of immunocompromised patients with CIRDs. These adaptations may involve earlier and/or more frequent screening. Recommendations also support systematic risk assessment before initiating therapies, reinforced preventive strategies like HPV vaccination and smoking cessation, and at least one dermatologic evaluation during follow-up. Decisions regarding higher-risk therapies, such as JAK inhibitors and abatacept, should involve multidisciplinary discussions.
Conclusion: These recommendations provide a practical, individualized framework for cancer risk assessment in CIRD patients. By integrating adapted screening, prevention, and shared decision-making, they aim to optimize patient safety while preserving disease control.

1. Introduction

Chronic inflammatory rheumatic diseases (CIRDs), such as rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), and psoriatic arthritis (PsA), are characterized by persistent inflammation and immune system dysregulation. These conditions not only compromise patients' quality of life but also significantly increase the risk of certain cancers compared to the general population. The association between CIRDs and malignancies is multifaceted, involving disease-specific mechanisms, lifestyle factors, and the effects of immunomodulatory therapies. For instance, RA is associated with a 20% overall increase in cancer risk, particularly hematological malignancies and lung cancer, with additional contributions from smoking and chronic systemic inflammation [1,2]. Conversely, some cancers, such as breast and endometrial cancer, appear less frequent in RA patients, a phenomenon requiring further investigation into hormonal and immune factors [1].

Targeted therapies for CIRDs, which include biologic and synthetic targeted disease-modifying anti-rheumatic drugs (b/tsDMARDs), have transformed disease management but also raised concerns about their potential impact on cancer risk. These treatments may alter immune surveillance, increasing susceptibility to certain malignancies, such as non-melanoma skin cancers and cervical cancer [3–5]. Such risks necessitate a proactive approach to cancer risk assessment and prevention. Current evidence highlights the importance of regular cancer screening and tailored strategies for high-risk populations, including patients on long-term immunosuppressive therapies [6,7].

This article aims to provide recommendations for assessing and mitigating cancer risk in patients with CIRDs, aiming to balance the therapeutic value of targeted treatments with their potential oncologic hazards while promoting preventive and management strategies.

2. Methods

The recommendations were conducted on behalf of the French Society of Rheumatology and followed the 2014 EULAR Standardized Operating Procedures (SOPs) [8].

After receiving approval from the French Society of Rheumatology, the convenor (JA) established a steering committee that included two methodologists (AM and RS) and three fellows (OF, MB, GMdF), who conducted the systematic literature reviews (SLRs).

Subsequently, the remaining task force members were invited, making a total of 16 participants, including 9 university hospital rheumatologists, 1 private practice rheumatologist, 2 pulmonologists with an expertise in lung cancer, 1 gynecologist with a subspeciality on cervical cancer, 1 oncologist and 2 patient representatives and members of patient associations.

The steering committee defined the research questions of the SLRs. Under the guidance of the methodologists, the 3 fellows performed two SLRs. The first focused on the evaluation of risk of cancer of csDMARDs and b/tsDMARDs in patients with RA (MB and OF, Prospero no CRD42024524728). The second addressed the overall prevalence of cancer in patients with SpA (including PsA) and the risk of cancer of csDMARDs and b/tsDMARDs in patients with SpA (GMdF and OF, Prospero no CRD42024596902). These SLRs included studies published from 2005 until 2024 and are published separately. The results of the SLRs were discussed with the steering committee first and the task force afterwards.

At the task force meeting in November 2024, the SLRs were first presented, and their findings were discussed. In addition to the evidence from the SLRs, expert opinion was considered when formulating overarching principles and recommendations. Recommendations were edited according to the comments made, followed by formal voting. Consensus was reached if $\geq$ 75% of the members voted in favor of the recommendations in the first (or $\geq$ 67% and $\geq$ 50% in a second and third) round. Finally, each task force member indicated his or her level of agreement (LoA) through an online survey (numerical rating scale ranging from 0 = 'do not agree at all' to 10 = 'fully agree'). The mean of the LoA was presented. The draft of the manuscript was sent to all task force members for review. The final manuscript was approved by all authors and by the French Society of Rheumatology executive board.

3. Results

3.1. Overarching principles

The task force defined three overarching principles of cancer risk management in CIRDs (Table 1).

3.1.1. The risk of certain cancers is higher in patients with CIRDs compared to the general population. This should be considered in the management of these patients

Patients diagnosed with RA face an increased risk of developing certain types of cancer compared to the general population. This heightened risk is reflected in a standardized incidence ratio (SIR) that indicates a 20% higher overall cancer risk [1]. Notably, the highest incidence was observed for tobacco driven cancer such as lung cancer (SIR 1.41), bladder cancer (SIR 2.38), skin cancer including melanoma (SIR 1.37), and hematologic malignancies, including diffuse large B-cell lymphoma (SIR 1.79) and Hodgkin's lymphoma (SIR 2.73) [1,2]. This increased risk of hematologic malignancy is primarily attributed to the chronic inflammation and immune system dysregulation that are characteristic of RA [9].

The association between RA and lung or bladder cancer is partly explained by smoking, a well-established shared risk factor for both conditions. However, immunological factors specific to RA likely

Table 1
Overarching principles and recommendations.

	Level of Agreement (SD)
Overarching principles	
A. The risk of certain cancers is higher in patients with chronic inflammatory rheumatic disorders compared to the general population. This should be considered in the management of these patients	
B. Cancer risk in patients with CIRDs is primarily mediated by traditional risk factors, which are more prevalent in this population. Chronic inflammatory rheumatism itself and its treatments may contribute to cancer risk	
C. The risk of cancer should be regularly assessed in patients with CIRDs during follow-up and systematically before initiating disease-modifying anti-rheumatic therapies	
Recommendations	
1. The rheumatologist, together with the primary care physician, must ensure that patients with CIRDs undergo organized cancer screening programs recommended for the general population	9.4 (0.7)
2. Smoking cessation must be systematically encouraged to reduce the risk of cancer.	10 (0)
3. Disease activity should be optimally controlled in order to reduce the risk of lymphoma, especially in patients with rheumatoid arthritis	9.4 (0.9)
4. Given the increased risk of cervical cancer in patients with CIRDs, they should be screened more closely than recommended for the general population	9.5 (0.7)
5. In patients under the age of 26 years, it is recommended to check HPV vaccination and to propose catch-up vaccination if not completed	9.6 (0.6)
6. Patients with CIRDs receiving disease-modifying anti-rheumatic therapies should visit a dermatologist at least once during their follow-up to evaluate the risk of skin cancer. The dermatologist will define the follow-up modalities.	9.9 (0.5)
7. In patients with a history and/or genetic predisposition to cancer, the use of JAKi and abatacept should only be considered in the absence of suitable treatment alternatives and contingent on a collegial decision	9.4 (0.7)
8. In patients aged 65 years or older, and/or in those who currently smoke or have smoked for a long time in the past, the use of JAKi should only be considered when suitable treatment alternatives are absent and contingent upon a collegial decision	8.9 (0.9)

CIRDs: chronic inflammatory rheumatic diseases, HPV human papillomavirus; JAKi: JAK inhibitors; SD: standard deviation.

contribute to this increased risk independently of smoking. Chronic systemic inflammation induces cellular damage and dysregulated tissue repair processes, which could potentially lead to malignant transformation [10]. Lymphomas, particularly diffuse large B-cell lymphoma and Hodgkin's lymphoma, are significantly more prevalent in patients with RA. This relationship is strongly linked to persistent immune activation [10–12]. Continuous stimulation of lymphoid tissue in the context of autoimmune activity may facilitate lymphomagenesis. Furthermore, the immune dysregulation characteristic of RA has been shown to impede the body's ability to effectively suppress the development of these malignancies [1]. The potential for viral oncogenesis, particularly through Epstein-Barr virus reactivation, to further augment the risk of Hodgkin's lymphoma has also been investigated.

Notably, certain cancers seem to occur at lower frequencies in RA patients compared to the general population, e. g breast cancer (SIR 0.91), endometrial cancer (SIR 0.77), and pancreatic cancer (SIR 0.90) [1,13]. The underlying mechanisms behind these observations may involve hormonal and immune factors. For instance, early menopause and a younger age at first pregnancy, both associated with an increased risk of RA, are also linked to a lower risk of breast cancer. Similarly, the hyperactive state of the immune system in RA may enhance surveillance against certain malignancies, thereby reducing their prevalence. However, the precise mechanisms underlying this reduced cancer risk in RA patients remain poorly understood and warrant further investigation.

The relationship between axSpA or PsA and cancer has drawn increasing attention due to the potential risks associated with both diseases and their treatments. While evidence suggests that the overall cancer risk in these populations is not significantly different from that of the general population, notable variations in risk exist depending on cancer type, patient demographics, and disease subtype [14]. In axSpA, the overall cancer risk remains comparable to that of the general population [14]. However, certain cancers demonstrate increased prevalence in specific subgroups. Specifically, hematological malignancies, including lymphomas and multiple myeloma, have been observed to exhibit elevated risks, with SIR ranging from 1.36 to 2.10 across various studies [14,15]. This increased risk is particularly pronounced among older populations, as evidenced by studies conducted on Taiwanese cohorts [15]. Furthermore, an elevated risk has been observed for breast cancer in women with axSpA, particularly among elderly Taiwanese populations, where chronic inflammation and genetic predispositions may play a contributory role [15–17]. However, the risks associated with other malignancies are less pronounced. For instance, colorectal, lung, bladder, prostate, ovarian, cervical, and gastrointestinal cancers did not have a higher prevalence compared to the general population [14,18]. Nonetheless, there is a slightly elevated risk of kidney cancer, and some data suggest a potential increased risk of thyroid cancer, though evidence remains inconclusive and requires further investigation.

In PsA, there is some evidence of a modestly increased risk of non-melanoma skin cancers (NMSC), with a reported relative risk (RR) of 2.46 [19]. However, this increase is often attributed to the associated psoriasis and its treatments, such as phototherapy, rather than PsA itself [14]. Conversely, no consistent increase in melanoma or other solid tumors has been observed [19]. A higher prevalence of hematological malignancies, including lymphomas, has been reported in certain studies, though these findings are not universally confirmed [20]. Notably, risks associated with solid tumors, such as breast or colorectal cancers, do not appear elevated in PsA populations [14].

Large-scale registries and observational studies, such as the Swedish and Danish biologics registers and the ASAS-COMOSPA study, provide valuable insights but also highlight inconsistencies. For instance, while some studies suggest a protective effect against colorectal cancer in axSpA patients possibly due to oral NSAIDs regular consumption, others indicate potential increased risks for renal carcinoma and hematologic malignancies [20]. These discrepancies are likely attributable to methodological differences, variations in patient populations, and differing treatment regimens.

3.1.2. Cancer risk in patients with CIRDs is primarily mediated by traditional risk factors, which are more prevalent in this population. Chronic inflammatory rheumatism itself and its treatments may contribute to cancer risk

The increased cancer risk observed in patients with CIRDs is attributed to a multifaceted interplay among traditional risk factors as in general population (Table 2), disease-specific mechanisms,

Table 2
Cancer risk factors in the general population.

Risk factors	Description	Proportions of cancers related to each risk factor
Aging	Increased risk due to cumulative cell damage and decreased DNA repair over time	Not specified
Genetic factors	Some people inherit genetic mutations increasing their cancer risk	< 10%
Tobacco smoking	Leading cause of cancer due to carcinogenic substances in tobacco	19.8%
Alcohol consumption	Increases the risk of multiple cancers	8.0%
Unhealthy diet	Poor nutrition contributes to cancer development	5.4%
Overweight & obesity	Excess body weight is associated with several types of cancer	5.4%
Infections	Viruses and bacteria like HPV, hepatitis B, and H. pylori can trigger cancer	4.0%
Occupational exposure	Contact with hazardous substances like asbestos increases cancer risk	3.6%
UV radiation (sun & tanning beds)	Prolonged exposure to ultraviolet radiation increases the risk of skin cancer	3.0%
Ionizing radiation	Exposure to radon or medical diagnostic radiation can contribute to cancer	1.8%
Lack of physical activity	Less than 30 minutes of daily activity is linked to increased cancer risk	0.9%
Hormonal treatments	Some hormone therapies may slightly increase cancer risk	0.6%
Not breastfeeding	Breastfeeding may offer protective benefits against breast cancer	0.5%
Fine particles (air pollution)	Airborne pollutants contribute to cancer risk	0.4%

Source: https://www.ameli.fr/assure/sante/themes/cancers/facteurs-risques-prevention.

and therapeutic interventions. A particularly significant risk factor for cancer in RA is smoking, which is strongly associated with lung and bladder cancers. Beyond its role in cancer development, smoking is a known driver of RA pathogenesis, promoting chronic inflammation and exacerbating systemic immune dysregulation [1]. Furthermore, research has demonstrated a correlation between smoking and poorer outcomes in patients initiating biologics for inflammatory diseases [21]. Other traditional risk factors for cancer in these diseases include advanced age, obesity, and environmental exposures (Table 2). Advanced age has been shown to increase cumulative exposure to DNA damage and decrease immune surveillance, both of which have been linked to heightened cancer susceptibility. Obesity, along with its association with systemic inflammation and elevated levels of pro-inflammatory adipokines, amplifies cancer risk. Environmental factors, such as exposure to pesticides, have also been implicated [22].

Chronic inflammation significantly contributes to cancer development. Prolonged immune activation has been shown to cause DNA damage, genomic instability, and epigenetic modifications that favor malignant transformation [14]. In RA, patients with high disease activity face an increased risk of developing hematological malignancies, such as diffuse large B-cell lymphoma [23]. Similar associations have been observed between axSpA or PsA and cancers, including multiple myeloma and lymphomas, although the evidence supporting these associations is less conclusive [24].

The role of therapeutic interventions in modulating cancer risk is a complex issue. Tumor necrosis factor inhibitors (TNFi) are generally considered safe regarding cancer risk; however, some studies have linked their use, like all immunosuppressants, to an increased risk of certain cancers, including non-melanoma skin cancers (NMSC) and cervical cancer [1,6,25]. Similarly, Janus Kinase inhibitors (JAKi) are subject to specific precautions following a Pharmacovigilance Risk Assessment Committee (PRAC) safety signal regarding a potential increased risk of cancer, although conclusive evidence is still lacking. [26,27]. Abatacept has also been implicated in potentially increasing cancer risk, but further research is required to validate these observations [1,28–30]. Its mechanism of action, which involves inhibiting T-cell activation, contrasts with that of certain anticancer immunotherapies that aim to stimulate or unleash T-cell responses against tumors.

By altering immune surveillance and regulatory mechanisms, immunomodulatory therapies can facilitate the emergence of cancers in susceptible individuals. This is particularly evident in malignancies associated with viral infections and dysplastic cell detection, as seen in cervical and skin cancers. The impact of immunosuppressive therapies on cervical cancer related to Human papillomavirus (HPV) is particularly concerning. These therapies reduce immune surveillance, impairing the clearance of high-risk oncogenic HPV strains like HPV-16 and HPV-18. Persistent infections increase the likelihood of progression to cervical intraepithelial neoplasia and eventually invasive cervical cancer. Studies have demonstrated that patients receiving DMARDs, including methotrexate, TNFi, and JAKi, exhibit a higher prevalence of persistent HPV infections compared to the general population [31]. While there are no data available for other treatments, a general immunosuppressive effect may contribute to an increased risk of persistent infection. This risk is exacerbated by disease-related immune dysfunction, particularly in RA, which further weakens the immune response to HPV [4]. NMSC are the most prevalent malignancies associated with immunomodulatory therapies. The increased risk is primarily attributed to the suppression of immune mechanisms that detect and eliminate dysplastic skin cells. This immunosuppressive effect facilitates the development of NMSC, including both basal cell carcinoma and Squamous cell carcinoma. Recent studies have emphasized the need for vigilant skin monitoring and preventive strategies for patients undergoing long-term immunosuppressive treatments [32,33].

3.1.3. The risk of cancer should be regularly assessed in patients with CIRDs during follow-up and systematically before initiating disease-modifying anti-rheumatic therapies

Cancer risk assessment forms a critical element of managing patients with CIRDs, particularly during follow-up and prior to starting DMARDs. This proactive strategy is backed by the complex relationship among chronic inflammation, immunosuppressive treatments, and cancer development [3,10]. A thorough medical history, baseline imaging, and laboratory markers may be part of the evaluation. A dedicated time for cancer risk assessment can be suggested annually during consultations or as part of a systematic global review. This evaluation could also involve another healthcare professional in collaboration with the rheumatologist, ensuring comprehensive and efficient care. The frequency of cancer screenings for these patients can generally follow the guidelines for the general population, but individualized adjustments may be necessary. Risk factors like previous malignancies, comorbidities (e.g., diabetes or cardiovascular disease) [34], lifestyle choices (such as smoking or alcohol consumption), and specific disease characteristics may require a more tailored

Table 3
Organized and under evaluation cancer screening in the French general population.

Organized general population cancer screening			
Cancer	Target population	Screening method	Frequency
Breast cancer	Women aged 50 to 74 years	Bilateral mammography with double reading	Every 2 years
Colorectal cancer	Men and women aged 50 to 74 years	Immunological stool test	Every 2 years
Cervical cancer	Women aged 25 to 65 years	Cervical smear or HPV test	- 25–29 years: 2 smears one year apart, then one every 3 years if normal - 30–65 years: HPV test 3 years after the last smear, then every 5 years
Screening strategies under evaluation			
Cancer	Target population	Screening method	Frequency
Prostate cancer	No systematic organized screening	Individual screening based onPSA and rectal examination	Based on shared decision-making with a physician
Lung cancer	No organized screening IMPULSION national pilot program (Implementation of lung cancer screening by CT scan in the general population), 2025, French National Cancer Institute	Low-dose chest CT scan	Not determined

approach. Importantly, this evaluation should be conducted systematically before starting conventional or targeted DMARDs because of the effects of immunomodulation on the risk of certain cancers. Chronic immunosuppression can heighten the likelihood of malignancies, underlining the importance of careful pre-treatment assessment.

Treatment decisions are also critical, as certain treatments may influence cancer risk [26,35]. For instance, JAKi and abatacept should be used with caution in patients with identified high-risk of cancer, while anti-cytokine therapies or rituximab may be preferred in the absence of evidence demonstrating a detrimental effect on cancer risk. Meanwhile, multidisciplinary collaboration involving rheumatologists, oncologists and other organ specialists treating cancer is essential to balance effective disease management with oncologic safety. This collaborative approach fosters shared decision-making, ensuring that patients receive comprehensive information regarding the benefits and risks associated with proposed treatments [3].

4. Recommendations

The task force defined 8 recommendations of cancer risk management in CIRDs. The list of the recommendations, including the level of agreement based on voting by the task force, is shown in Table 1. The recommendations follow a logical sequence and they are not listed in sequence of importance. All recommendations are discussed in detail below.

4.1. The rheumatologist, together with the primary care physician, must ensure that patients with CIRDs undergo organized cancer screening programs recommended for the general population

The recommendation to ensure that patients with CIRDs participate in organized cancer screening is particularly important due to their increased risk profile. As shown in Table 3, general population screening protocols must be directly applied to this group with some adaptations for some. In France, for breast cancer, biennial mammography for women aged 50 to 74 years remains a cornerstone of early detection and should be systematically implemented for patients with CIRDS; and this should be complemented by regular breast self-examination. Similarly, after 50 years of age, colorectal cancer screening using a biennial fecal immunology test is critical. Cervical cancer screening through cytology or HPV testing varies by age but should follow a more frequent schedule, as detailed in recommendation 4, which outlines specific adaptations for immunocompromised patients. Regarding prostate cancer, while there is no organized population screening, individual discussions about PSA testing based on shared decision-making can be considered. It is vital to recognize that these screening recommendations are evolutionary, reflecting ongoing advancements in medical knowledge and technology; thus, the modalities and intervals may be subject to future modifications to optimize cancer detection in both the general population and those with CIRDs.

Lung cancer screening is an evolving field in France. While there is currently no general recommendation for low-dose chest CT screening for lung cancer, pilot programs, such as IMPULSION (Implementation of lung cancer screening by CT scan in the general population), initiated in 2025 by the French National Cancer Institute (INCA), are evaluating its feasibility in high-risk groups. This approach is particularly relevant for patients with CIRDs, which often face a higher burden of smoking-related diseases and pulmonary complications, such as interstitial lung disease and bronchial pathology, especially in RA. Epidemiological data suggest that the excess lung cancer risk associated with smoking decreases substantially 10–15 years after cessation and may approach that of never-smokers after approximately 20 years, depending on age and duration of prior exposure [36,37]. Despite the lack of formal recommendations, the increased risk in patients with CIRDs makes them a population of significant interest for future screening initiatives.

4.2. Smoking cessation must be systematically encouraged to reduce the risk of cancer

Smoking cessation is a fundamental strategy for enhancing health outcomes in patients with CIRDs. The well-established association between smoking and RA underscores the imperative to target tobacco use to mitigate disease-related complications and improve patient outcomes. Smoking is also a risk factor for

RA-associated pulmonary conditions, including interstitial and bronchial lung diseases, and it increases the risk of lung cancer-already elevated in RA patients due to systemic inflammation. In addition to its role in lung cancer, tobacco use has been linked to various other types of cancer, including bladder, oral cavity, esophageal, pancreatic, and kidney cancer [38]. Beyond cancer, smoking adversely impacts cardiovascular health by accelerating atherosclerosis development, which increases the risks of myocardial infarction and stroke [39]. These risks are exacerbated in RA patients, who already face heightened cardiovascular vulnerability due to chronic inflammation [40]. Additionally, smoking cessation is critical not only for reducing the risk of malignancies and cardiovascular disease but also for improving RA treatment efficacy. Research indicates that smokers with RA demonstrate a reduced response to disease-modifying antirheumatic drugs (DMARDs), including biologics like TNFi, compared to non-smokers [41]. The cessation of smoking has been shown to enhance treatment response, leading to better disease control and an improved quality of life [42].

To achieve successful smoking cessation, comprehensive programs employing diverse tools such as nicotine replacement therapies, behavioral counseling, prescription medications like varenicline or bupropion, and digital tools should be adopted. Additionally, vaping may serve as a transitional aid in some cases. Tailoring these interventions to individual needs ensures sustainable outcomes and maximizes health benefits. Integration of smoking cessation efforts into the management of RA has been demonstrated to result in substantial benefits, including the reduction of cancer and cardiovascular risks, while optimizing treatment responses [43].

4.3. Disease activity should be optimally controlled in order to reduce the risk of lymphoma, especially in patients with rheumatoid arthritis

Optimal disease activity control in RA is essential for lowering the risk of lymphoma, particularly given the increased susceptibility observed in RA patients. Chronic inflammation and immune dysregulation, which are hallmark features of uncontrolled RA, significantly contribute to lymphomagenesis. Studies indicate that poorly managed RA patients have a higher incidence of lymphomas compared to the general population, with diffuse large B-cell lymphoma and Hodgkin's lymphoma being especially prevalent [2,10].

The advent of targeted therapies, such as biological and synthetic DMARDs, has significantly transformed the management of RA. These therapies effectively reduce systemic inflammation and halt disease progression, thereby potentially mitigating the risk of malignancies associated with chronic immune activation. For instance, TNFi and other biologics have been linked to a decreased risk of certain lymphomas when RA is well-controlled, although some concerns remain regarding treatment-specific risks [11,35,44].

Moreover, recent evidence highlights a downward trend in the incidence of non-Hodgkin's lymphomas among RA patients during the era of modern biologics, suggesting that effective control of inflammation reduces oncogenic triggers [20]. Nonetheless, certain therapies like rituximab, often used in patients with severe RA or those at high risk of lymphoma, have been associated with a higher incidence of hematological malignancies, particularly multiple myeloma [1,20,30].

Physicians managing RA must remain vigilant regarding these risks and implement regular cancer screenings for high-risk individuals, especially those with prolonged disease activity or who are on immunosuppressive therapies. Early detection and optimal control of RA activity are key strategies for reducing cancer morbidity and improving patient outcomes.

4.4. Given the increased risk of cervical cancer in patients with CIRDs, they should be screened more closely than recommended for the general population

Individuals diagnosed with CIRDs face a significantly higher risk of developing cervical cancer compared to the general population. Research has shown a heightened risk ranging from 49% to 80% [6,45]. This increased risk is especially notable among women undergoing long-term immunomodulatory therapies, including corticosteroids, methotrexate, and targeted b/tsDMARDs, which hinder the immune system's ability to effectively eliminate HPV infections [1]. Moreover, the progression from cervical high-grade intraepithelial lesions (HGIL) to cervical cancer may occur more quickly in these patients, necessitating enhanced vigilance and tailored screening strategies [6].

A Swedish cohort study [6] involving over 40,000 women revealed that the risk of low-grade lesions, which are not precancerous, in untreated patients with RA was 53% higher (HR 1.53; 95% CI [1.23–1.89]) compared to the general population, while the risk of HGIL was 39% higher (HR 1.39; 95% CI [1.16–1.66]). Furthermore, the risk of HGIL increased further among patients under immunosuppressive treatment, with hazard ratios exceeding 2.0 for specific treatments such as azathioprine. An Australian cohort study also reported a 23% increase in cervical intraepithelial lesion risk among autoimmune patients compared to healthy controls [46]. Further evidence underscores the risks in other immunosuppressed populations, including patients living with HIV, those with systemic lupus erythematosus, and organ transplant recipients, who also necessitate intensive surveillance. For instance, a 5.5-fold elevated risk of HPV infection has been observed in HIV-positive patients, along with a substantially heightened risk of cervical intraepithelial lesion, with HGIL exhibiting up to 11.6 times the probability of occurrence [1,20,47,48]. A similar elevated risk has been observed in patients with systemic lupus erythematosus. The odds ratio (OR) for HPV infection in these patients is 2.87 (95% CI 2.20–3.76), and the likelihood of HGIL is even higher [49]. Furthermore, organ transplant recipients exhibit a substantially elevated risk of developing cervical cancer (2-fold), vulvar cancer (22-fold), and anal cancer (5-fold), thereby underscoring the pervasive threat posed to immunocompromised individuals [50].

The existing literature suggests that cervical cancer screening for women with compromised immune systems, including those with CIRDs, could be tailored based on age. In the general population programs, cervical cancer screening begins at 25 years of age. However, this starting age may need to be reevaluated for patients with juvenile idiopathic arthritis (JIA) or similar conditions, as many of these individuals undergo several years of immunosuppressive treatment prior to the age of 25, which raises their risk of HPV persistence and progression HGIL or cervical cancer earlier than in the general population [45].

Before age 30, cytology (Pap smear) is recommended in France because of the transient nature of HPV infections in younger women and the lower likelihood of progression to HGIL or cervical cancer. An annual cytological examination may be advised, as currently recommended for immunosuppressed women, such as organ transplant recipients [6,51]. This strategy is guided by the higher prevalence of HPV infection and the increased likelihood of persistent lesions in these populations. After age 30, HPV testing is typically viewed as more suitable due to its higher sensitivity and specificity for detecting high-risk HPV strains associated with HGIL and cervical cancer [1,52]. The ideal frequency of HPV testing in this demographic remains undetermined; however, intervals shorter than 5 years may be appropriate, considering the need to balance

Table 4
Situations requiring adaptation of general population cancer screening protocols in patients with chronic inflammatory rheumatic diseases (CIRDs).

Cancer	Target population	Screening method	Frequency	Special features of patients with CIRDs	Prevention
Cervical cancer	Women aged 25 to 65 years with CIRDs receiving DMARDs	Cervical smear or HPV test	Suggested frequency - 25–29 years: annual smear - 30–65 years: HPV test every 3 years Annual screening recommended for immunocompromised patients (e.g. HIV, organ transplant, etc.)	Screening closer than that recommended for the general population should be considered	Includes HPV vaccination for girls and boys (11–14 years old, with catch-up possible up to 19 years old): general population and immunocompromised individuals In patients under 26 years of age, the HPV vaccination status must be verified, and catch-up vaccination offered if not done
Non-melanoma skin cancer	All patients with CIRDs receiving DMARDs	Clinical examination	At least once during their follow-up Follow-up modalities will be defined by the dermatologist	At least 1 systematic screening	Optimal photoprotection Self-skin check for screening

DMARDs: disease modifying anti-rheumatic drugs; CIRDs: chronic inflammatory rheumatic diseases; HPV: human papillomavirus; HIV: human immunodeficiency virus; JIA: juvenile idiopathic arthritis.

reducing unnecessary interventions and ensuring early detection of high-grade lesions [45] (Table 4). A 3-years interval might be a good compromise in this specific population.

The relevance of screening beyond the age of 65 for women with CIRDs merits consideration, given the persistent risk of cervical lesions in immunosuppressed populations [53]. However, the utility of continued screening at this age is influenced by factors such as postmenopausal atrophic changes, which can complicate both sample collection and result interpretation but also diagnostic performances of colposcopy. These changes may reduce the reliability of cytology and HPV testing, raising questions about the cost-effectiveness and diagnostic yield of screening in older women [1,54].

4.5. In patients under the age of 26 years, it is recommended to check HPV vaccination and to propose catch-up vaccination if not completed

The HPV vaccination is a crucial preventive measure against HPV infections, which are a leading cause of cervical dysplasia, cervical cancer, and other HPV- related malignancies. The vaccine is most effective when administered before exposure, typically during adolescence, which explains the recommendation to vaccinate individuals up to 26 years old, ideally before starting DMARDs (Table 4). This timing maximizes the immunogenic response, ensuring robust antibody production and long-term protection against high-risk HPV strains. For patients with CIRDs, particularly children and adolescents with JIA, the vaccine' s role is even more critical. In this population, it is recommended to vaccinate as early as possible, specifically before the initiation of DMARDs (vaccination possible from age 9). Several studies have shown that the bivalent HPV vaccine is both safe and immunogenic in this group, despite slightly lower antibody titers compared to healthy controls [55,56]. These findings support the updated 2019 EULAR recommendations, which advocate for HPV vaccination in immunocompromised individuals due to its protective benefits and minimal adverse effects, even among those on immunosuppressive therapies [45]. However, the advantages of catch-up vaccination in older individuals are more limited. As age increases, the likelihood of prior HPV exposure rises, and the immune system's capacity to produce a strong vaccine response declines, especially in those over 26 years of age or with existing immunodeficiencies. Research indicates that older individuals often show suboptimal antibody responses to the vaccine, diminishing its effectiveness in preventing HPV- associated diseases [45]. These findings highlight the critical importance of timely vaccination during adolescence and early adulthood, as catch-up programs for older patients may offer only marginal benefits.

4.6. Patients with CIRDs receiving disease-modifying anti-rheumatic therapies should visit a dermatologist at least once during their follow-up to evaluate the risk of skin cancer. The dermatologist will define the follow-up modalities

Patients with CIRDs who are treated with DMARDs are at an increased risk for certain types of skin cancer due to immunosuppression. Therefore, a dermatological evaluation is recommended to identify individual risk factors and guide appropriate surveillance. Importantly, this evaluation should not delay the initiation of the DMARD therapy, which is critical for disease control and long-term outcomes (Table 4).

Several studies have shown an increased risk of NMSC, particularly basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), as well as melanoma, in patients with RA, AxSpA, and PsA [1,57–59]. This heightened risk is partly due to chronic inflammation and immune dysregulation associated with these diseases, as well as the immunosuppressive effects of certain treatments like methotrexate, thiopurines, TNFi, abatacept, and JAKi.

A meta-analysis of 21 studies indicated a higher risk of melanoma in patients with RA (SIR = 1.23; 95% CI 1.01-1.49) [5]. Similarly, a French nationwide cohort study utilizing health insurance data found an increased melanoma risk in patients with RA compared to the general population (SIR = 1.37; 95% CI 1.29–1.46) [1]. In axSpA, a US Medicare-based cohort study reported a significantly higher incidence of melanoma than in the general population (IRR = 1.77; 95% CI 1.53-2.07) [16]. Another US database study confirmed an elevated risk of both melanoma (OR = 1.59; 95% CI 1.30-1.95) and SCC (OR = 1.48; 95% CI 1.24-1.78) in these patients [60].

Despite this well-documented risk, systematic skin cancer screening for all patients remains controversial, as there is no clear evidence that it significantly reduces melanoma-related mortality.

Given constraints in accessing dermatological care, it is crucial to prioritize screening efforts for high-risk individuals. To address this challenge, some authors have proposed a risk-stratification algorithm to help clinicians prioritize dermatological referrals. This model considers the CAP score (a simple clinical tool combining skin cancer history, age, and phototype), as well as treatment-associated risks. Although this approach has not yet been fully validated, it suggests that patients with a high CAP score (defined as age > 50, history of non-melanoma skin cancer, and skin phototype I or II), or those treated with high-risk DMARDs should be referred to a dermatologist for screening, while lower-risk patients could rely on education and self-surveillance initially before seeing a dermatologist at a later stage [61]. Regardless of their risk level, all patients should be educated on regular skin self-examinations using the ABCDE rule (Asymmetry, Border irregularity, Color variations, Diameter > 6 mm, Evolution). In addition, rigorous photoprotection is essential, including avoiding sun exposure during peak hours, wearing protective clothing, and applying high-SPF sunscreen (Table 4). Rheumatologists should play a proactive role in integrating these preventive measures into routine patient care, ensuring that those most at risk receive appropriate screening and follow-up.

4.7. In patients with a history and/or genetic predisposition to cancer, the use of JAKi and abatacept should only be considered in the absence of suitable treatment alternatives and contingent on a collegial decision

In patients with a history of cancer that poses a significant risk of recurrence or a confirmed genetic predisposition, the use of JAKi and abatacept must be approached with caution. The ORAL Surveillance trial highlighted an increased risk of malignancies in patients with age > 50 years and at least one additional CV risk factor treated with tofacitinib compared to TNFi [62]. Of particular significance is the observation that this heightened risk became evident after a period of 18 months, underscoring the need for prolonged follow-up to accurately assess long-term safety. These findings necessitate the implementation of additional real-world studies that encompass all JAKi within their approved indications, incorporating comprehensive follow-up and detailed data on patients exposed to multiple prior targeted therapies, as cumulative treatment regimens may potentially influence cancer risk profiles.

For abatacept, emerging evidence suggests a potential association with an increased malignancy risk, particularly in high-risk populations. A population-based cohort study assessed the cancer risk associated with abatacept as an initial bDMARD in RA compared to other bDMARDs. The study reported a modest but statistically significant increase in overall cancer risk (adjusted hazard ratio [HR]: 1.17, 95% CI 1.06–1.30), particularly for non-melanoma skin cancer (HR: 1.20, 95% CI 1.03–1.39) [63]. Another analysis of a French claims database indicated an elevated risk of cancer among patients exposed to abatacept, particularly lung cancer (standardized incidence ratio [SIR]: 2.10, 95% CI 1.69–2.59), highlighting a specific signal that necessitates further investigation to clarify causal associations [1]. Despite these findings, the number of studies exploring the association between abatacept and cancer risk remains insufficient to draw definitive conclusions. The mechanisms underlying these potential risks could be related to abatacept's role in modulating T-cell activation, which might affect immune surveillance against tumor cells. However, current evidence is often limited by small sample sizes and potential confounding factors, such as baseline cancer risk or prior exposure to multiple therapies. To enhance our understanding, it is critical to conduct long-term studies that evaluate cancer risks with abatacept across broader patient populations and extended follow-up periods. Additionally, assessing the impact of prior bDMARD exposure and cumulative treatment on cancer risk will help refine safety profiles and support more informed clinical decisions.

If no suitable alternatives are available, the initiation of JAKi or abatacept should be conditioned on a collegial decision (Fig. 1). This decision-making process involves a multidisciplinary review to contextualize the risks and formally document the absence of alternative therapies in the medical file. This ensures a thoughtful and collaborative assessment while supporting rheumatologists in their discussions with patients, facilitating shared decision-making. While these procedural recommendations aim to prioritize patient safety, the task force acknowledges the constraints they impose on clinical practice. Should subsequent data substantiate a more reassuring safety profile for JAKi or abatacept, these measures may be reconsidered and streamlined accordingly.

4.8. In patients aged 65 years or older, and/or in those who currently smoke or have smoked for a long time in the past, the use of JAKi should only be considered when suitable treatment alternatives are absent and contingent upon a collegial decision

For patients at risk of cancer, prescribing JAKi should rely on the absence of appropriate therapeutic alternatives and the results of a collaborative decision-making process. This recommendation is based on the guidance provided by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) and includes additional criteria for patient evaluation.

Specifically, heightened caution is advised for individuals aged 65 years or older, as well as those individuals aged 50 to 74 years who are current or former smokers having quit within the past 10 years, with a smoking history of at least 15 cigarettes per day for 25 years, or at least 10 cigarettes per day for 30 years [64].

Furthermore, this recommendation emphasizes the previously identified factors, such as a personal history of cancer or genetic predispositions, ensuring a thorough cancer risk evaluation before the initiation of treatment. A detailed algorithm is proposed to guide the evaluation and decision-making process, integrating criteria such as age, smoking history, and other predisposing factors. This algorithm supports careful consideration of JAKi treatment under specific conditions (Fig. 1). For patients who meet these criteria, systematic assessments, including population-specific cancer screenings and customized monitoring strategies, are recommended to minimize potential risks while ensuring that the benefits of JAKi are carefully weighed.

5. Discussion

Patients with rheumatoid arthritis (RA) and other CIRDs face a higher risk of developing cancer compared to the general population [65]. Managing cancer risk in these patients, particularly those treated with targeted therapies, is complex and requires careful balancing of chronic inflammation effects and oncological risks. Effective control of disease activity is crucial, as uncontrolled inflammation is a well-known factor in the development of malignancies, including lymphomas [1,10]. Poorly-controlled RA specifically correlates with an increased incidence of diffuse large B- cell lymphoma and Hodgkin' s lymphoma [1,2]. These findings highlight the significance of adequately treating inflammatory arthritis to lower the risks of both cancer and irreversible joint damage [1,10]. Managing oncological risks in these patients also entails aligning cancer screening protocols with the unique needs of those who are immunocompromised. Although general population screening protocols provide a solid framework, adaptations are essential for individuals with CIRDs [6,45]. For instance, cervical

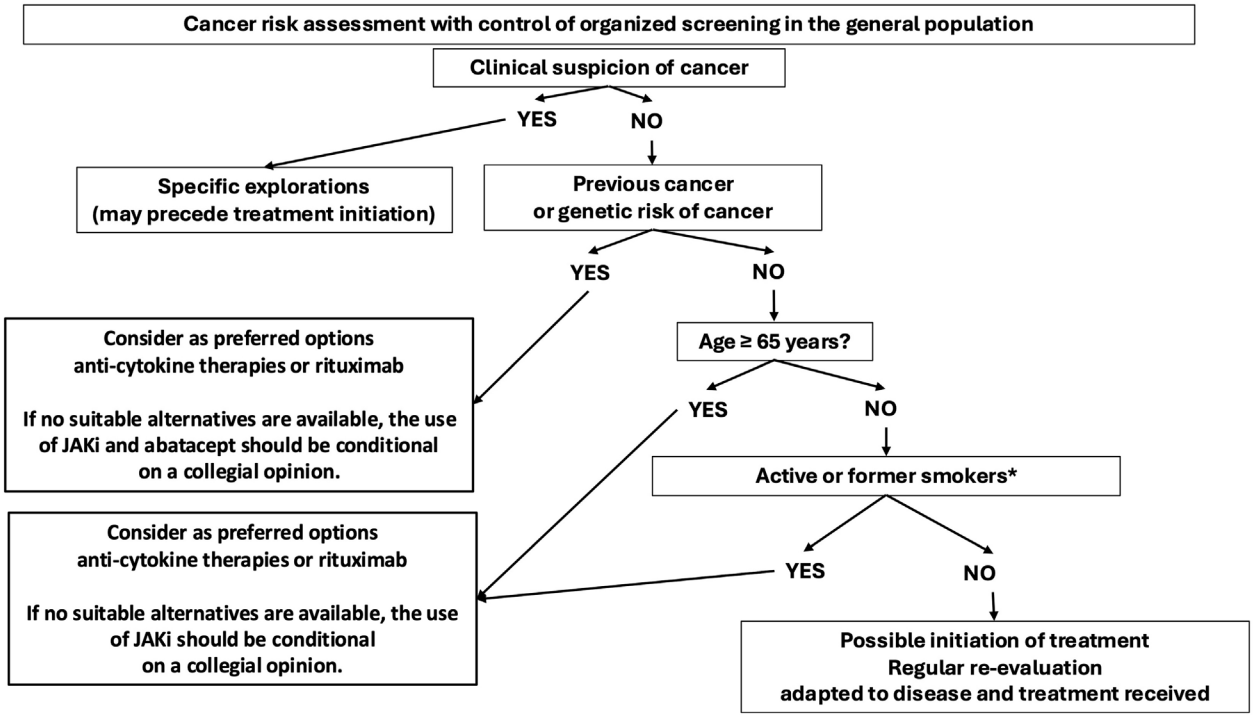

Fig. 1. Algorithm for assessing cancer risk before considering the prescription of a targeted therapy. JAKi: JAK inhibitor; PY: patient-year; TNFi: Tumor Necrosis Factor inhibitors; IL6Ri: IL6 receptor inhibitors. * Former smokers having quit within the past 10 years, with a smoking history of at least 15 cigarettes per day for 25 years, or at least 10 cigarettes per day for 30 years.

cancer screening should occur more frequently in patients receiving immunosuppressive therapies due to their heightened risk of persistent high-risk HPV infections [6,45]. Moreover, skin cancer screening, especially for non- melanoma skin cancers, should be thorough in this demographic, as long-term immunosuppressive therapy is linked to a higher prevalence of basal cell carcinoma and squamous cell carcinoma [3]. Likewise, while there is currently no universal recommendation for lung cancer screening in the general population in France, and screening cannot yet be recommended outside of validated or soon-to-be-validated criteria, low-dose CT scans may, in the future, prove beneficial for high-risk groups. Should a national screening program for current and former smokers be implemented, it will likely be necessary to consider extending eligibility criteria to other at-risk populations, such as patients with RA. Finally, multidisciplinary care involving oncologists and rheumatologists is critical to optimizing cancer prevention strategies and customizing screening protocols to reflect each patient's individual risk profile. This tailored approach ensures early detection of malignancies while alleviating the burden of unnecessary procedures on patients already managing the complexities of chronic disease [3,45].

The role of JAKi in managing CIRDs has raised specific concerns [26]. These risks are particularly pronounced in older patients, smokers, and those with predisposing factors, prompting regulatory agencies to restrict the use of JAKi in these populations (European Medicines Agency, 2023). However, these findings underscore the critical need for additional data specific to the four approved JAKi to better understand their safety profiles across different rheumatic and autoimmune diseases, with sufficient follow-up durations. The available evidence largely stems from studies conducted in RA, with limited data on other conditions. Expanding research to these populations is crucial, as the pathophysiological mechanisms of chronic inflammation and immune dysregulation may vary across diseases and influence cancer risks differently. Additionally, the median follow-up durations in current studies are often insufficient to capture long-term risks. Many cancers, particularly solid tumors, may take several years to develop following the initiation of therapy. Studies with extended follow-up, ideally exceeding five years, are necessary to determine whether there is a time-dependent increase in cancer incidence associated with JAKi. For each JAKi, further data are needed to address specific gaps, as currently, no differences between the various JAKi are reflected in treatment recommendations. Tofacitinib, for which robust data are available from ORAL Surveillance, requires additional validation of whether the observed risks are consistent in diseases beyond RA and at lower doses. Baricitinib has limited long-term safety data outside of RA, which remains its only approved indication among CIRDs. This restricts our understanding of its potential oncologic risk profile in broader rheumatologic populations and underscores the need for further research in diverse clinical settings and over extended follow-up periods. Upadacitinib, although approved for multiple conditions, requires further data to clarify its long-term risk profile, especially in high-risk populations like smokers or those with a history of malignancy. Filgotinib, with its selective inhibition of JAK 1, raises theoretical expectations of reduced off- target effects, but this needs verification through long-term studies, particularly outside RA.

It is also essential to determine whether there is a pathophysiological mechanism linking JAKi to increased cancer risks. JAKi interfere with multiple pathways involved in immune surveillance and tumorigenesis, including interferon signaling and cytokine-mediated immune responses. These effects may impair the immune system's ability to detect and eliminate dysplastic or cancerous cells, potentially increasing the risk of oncogenesis. For example, suppression of natural killer cells or cytotoxic T-cell activity [66,67], which play critical roles in tumor immunity, may explain some of the observed risks. Interestingly, the ORAL Surveillance study did not demonstrate a dose-response relationship for malignancy risk with tofacitinib, suggesting that the cancer risk might not solely depend on the degree of JAK inhibition. Instead, it could

Table 5
Research agenda.

Research agenda
1. Do CIRDs modify the clinical presentation or progression of certain cancers?
2. What are the specific cancer risks (breast, kidney, thyroid, lymphatic) in patients with axSpA and PsA?
3. How do different JAKi vary in their associated cancer risks based on their selectivity?
4. What are the long-term safety profiles of abatacept and other non-TNF biologics in terms of cancer risk?
5. Are there differences in cancer risk based on the duration and cumulative dose of DMARDs?
6. Do some chronic inflammatory rheumatic disease therapies offer protective effects against certain cancers?
7. What are the barriers to adherence to cancer screening programs among patients with CIRDs?
8. How effective is thoracic low-dose CT screening in reducing lung cancer mortality in patients with CIRDs?
9. What are the epidemiological patterns and underlying mechanisms of anal, vulvar, and oropharyngeal cancers in immunosuppressed populations?
10. What are the most appropriate screening methods for different types of cancers, considering patient age and risk factors?
11. What tools (biomarkers, artificial intelligence, advanced imaging) could improve cancer detection in patients with CIRDs?
12. Should screening for urogenital cancers (cervical, prostate, bladder) be intensified in this population?
13. What is the role of targeted HPV testing in screening and early detection of oropharyngeal cancers?
14. What strategies can improve HPV vaccination awareness and uptake, particularly in immunosuppressed individuals?
15. How can awareness and engagement in HPV vaccination and cancer screening be improved for immunosuppressed individuals?
16. Cancer risk should also be evaluated in other immune-mediated inflammatory diseases (IMIDs), considering distinct immunosuppressants, repeated CT scans (e.g. for the evaluation of Interstitial Lung Disease), and disease-specific factors such as HPV-related risk in lupus

involve patient-related factors, such as pre-existing carcinogenic exposures like smoking or cumulative inflammatory burden. Mechanistic studies are urgently needed to clarify these interactions and identify biomarkers to predict which patients are at higher risk of developing malignancies under Janus kinase inhibitor therapy.

Similarly, abatacept has been implicated in potentially increasing cancer risks, particularly non-melanoma skin cancers and invasive malignancies, although the data remain inconsistent [3]. Abatacept's mechanism of action, which involves T-cell co-stimulation modulation, may theoretically impair immune surveillance against cancer cells [68]. Despite these concerns, abatacept still has a place in selected patients, particularly those with contraindications to other treatments, provided there is careful patient selection and monitoring. Further research, as detailed in the research agenda below, is necessary to clarify the long-term risks associated with both abatacept and Janus kinase inhibitors.

Beyond the clinical and mechanistic understanding of cancer risk, it is equally important to consider the patient perspective in navigating these complex decisions. While the clinical recommendations outlined above provide a comprehensive and evidence-based framework for cancer risk management in patients with CIRDs, it is essential to integrate the patient perspective to ensure their relevance and applicability in real-world settings. Beyond clinical data and screening protocols, managing oncological risks in immunosuppressed populations also involves addressing psychological, emotional, social, and cultural factors that shape patient experiences and decision-making processes. Patients are not only recipients of care but also essential partners in the decision-making journey. Incorporating a more human and collaborative dimension into the recommendations could help transform them from a set of clinical directives into tools for shared decision-making. Patients should be empowered to actively participate in discussions about cancer risks and screening strategies, with space given to their concerns, values, and life circumstances. Moreover, communication about potential cancer risks and preventive strategies must be nuanced. While transparency is crucial, it is equally important to balance information delivery with the potential psychological burden it may cause. Patients often face multiple layers of anxiety — stemming from their disease, treatment side effects, and now, the possibility of malignancy. Excessive focus on risk without appropriate context and reassurance may lead to increased distress and reduced adherence to therapeutic strategies. These insights, provided by patient advocates, highlight the need to tailor cancer risk communication in a compassionate and individualized manner. Clinicians should foster open, empathetic dialogue, ensuring that patients feel heard, supported, and actively involved in every step of their care. Future guidelines should explicitly encourage this collaborative approach, making space for patient narratives alongside clinical evidence to optimize both health outcomes and patient well-being.

Future research must address several knowledge gaps, including clarifying cancer risks in axial axSpA and PsA, particularly for malignancies such as breast, kidney, thyroid, and lymphatic cancers, which are essential for guiding clinical practice. It should also specify the differential cancer risks associated with JAKi based on their selectivity, the long-term safety profiles of abatacept and other non-TNFi biologics, and the efficacy of low-dose CT screening in reducing lung cancer mortality in CIRD populations.

Future research should focus on understanding the epidemiology and mechanisms underlying other HPV-related cancers, including anal, vulvar, and oropharyngeal cancers among immunosuppressed populations. Moreover, it is essential to define the most appropriate screening methods for each type of cancer, considering patient age and risk factors. For instance, while cytology and HPV DNA testing remain standard for cervical cancer, the potential role of high-resolution anoscopy for anal cancer and targeted HPV testing for oropharyngeal cancers requires further investigation to establish tailored screening protocols. This personalized approach could help optimize early detection strategies and improve outcomes in this high-risk population. Future research should also integrate strategies to enhance HPV vaccination awareness and uptake, especially given its critical role in preventing HPV-related malignancies in immunosuppressed individuals.

The research agenda below outlines these priorities, providing a roadmap for addressing critical uncertainties (Table 5).

These recommendations offer a comprehensive framework for managing cancer risks in patients with CIRDs, emphasizing the need for personalized, multidisciplinary strategies. They underscore the importance of tailored cancer screening protocols, proactive risk assessment, and effective disease control to reduce oncological risks linked to inflammation and immunosuppressive therapies. Recommendations such as improving HPV vaccination coverage, particularly among at-risk populations, and systematically tackling smoking cessation reflect the proactive approach needed for these patients. Given the rapid evolution of therapeutic options, continuous guideline updates and targeted research will be essential to refine risk mitigation and optimize patient with CIRD outcomes.

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