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The Interplay of Autoimmune Disease, Cancer, and Immunity: Current Understanding and Therapeutic Prospects

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ABSTRACT

Background: In light of chronic inflammation and dysregulated immune responses, autoimmune disorders and cancer are closely related. It is essential to comprehend how they interact in order to create immunotherapeutic techniques that work.

Materials and Methods: The purpose of this review is to summarize the most recent research on the relationship between immunology, cancer, and autoimmune illnesses and to assess new treatment strategies that target each of these diseases. PubMed, MEDLINE, the Cochrane Library, Embase, and Scopus were used in a methodical search (2010–2023). Studies evaluating immunotherapy results, immunological processes, and cancer incidence in patients with autoimmune diseases were all eligible. Using random-effects meta-analysis, the data were examined.

Results: A total of 78,456 patients from fifty-seven studies were examined. Patients with autoimmune diseases had a considerably higher risk of developing cancer (OR = 1.58; 95% CI: 1.42–1.76; $p < 0.001$), frequently as a result of immunosuppressive treatment and persistent inflammation. Among the common mechanisms were increased pro-inflammatory cytokines (TNF-α, IL-6) and dysregulation of immunological checkpoints (PD-1/PD-L1). Although cytokine blockers and checkpoint inhibitors have demonstrated effectiveness, they also carry significant hazards.

Conclusion: The confluence of immune regulation, cancer, and autoimmunity brings to light both treatment possibilities and difficulties. Future studies should concentrate on tailoring immunotherapies to optimize their positive effects while reducing their negative ones.

Keywords: Autoimmune diseases; Cancer; Immunity; Immune checkpoints; Cytokines; Immunotherapy; Chronic

INTRODUCTION

Cancer and autoimmune diseases are two intricately linked pathological conditions that are becoming increasingly common worldwide. Cancer results from a breakdown in immune surveillance that permits the growth of malignant cells, whereas autoimmune illnesses are caused by immunological dysregulation that results in self-directed tissue damage[1]. Immune system dysfunction is the root cause of these disparate results. Through an analysis

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of recent research and a summary of important immunological mechanisms, epidemiological trends, and therapeutic implications, this review aims to investigate the complex connections among autoimmune illnesses, cancer, and immunity[2]. By doing this, the study aims to provide light on how the immune system's dual roles protective and destructive can influence the onset of both diseases and guide the creation of more specialized and efficient therapies[3]. When the body's immune system launches an aberrant defense against its own tissues, it can result in autoimmune disorders, which cause tissue damage and persistent inflammation. These conditions, which include multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis, differ greatly in their occurrence and presentation but are all characterized by a lack of immunological tolerance to self-antigens[5]. The unchecked proliferation of aberrant cells, on the other hand, is what defines cancer. This frequently occurs when the immune system is unable to identify and eradicate altered cells[4]. The general level of development of cancer, which is approximated to be between 4-25%, is known to rise with the prolonged life span of patients[4]. The possible factors, which influence the type of malignancy that can be developed comprise age of the patient, PID and viral infections possibly. Communicable diseases and increased rates of cancers are features of PIDs [5].

Surely, there are many experiments, which shows that malignancy depends on immunity and that these two processes are interrelated and have to be studied further. Indeed, autoimmunity and cancer might be more of incidence or once in a while association than what could be expected and therefore more light has been shed to the autoimmunity and cancer connection and the possible repercussions of onset of both6[6]. Since at one time it is practically undesirable to have high levels of autoimmunity, low level autoimmunity may turn out to be useful[7]. Autoimmune reactions may be deemed as the type of defense which is being conducted by the host towards the tumor. It may also be the case that the immune response in cancer leads to the development of auto-antibodies against a number of auto-antigens which also includes the antigens present in the tumor cells[8]. Cancer just arises from the inability of the immune system to regulate the proliferation of tumor cells and autoimmunity as a result of the aberration of autoreactivity[9].

Autoimmune diseases are one of the major concerns for health all over the world with variations in occurrence and manifestations[10]. These diseases occur as a result of the immune response against the substances, cell or tissue which are otherwise completely a normal part of the body. Autoimmune disease occurs to some specific self-antigens when immune tolerance is disrupted[10]. Primary immunodeficiencies (PIDs) are inherited diseases, multitudinous infections, autoimmunity and cancer are vulnerable. Proposed as at 4–25% for all cancers, the risk of development of any cancer will likely rise proportionately with increased licensure of the human being [10]. The predisposing factors to the kind of malignancy, to be developed as stated above include the age of the patient, PID and possible viral infections1[11]. Pneumonia, recurrent infection, increased odds of getting infected and higher rates of malignancy are some of the features of PIDs [12].

Malignancy and immunity work hand in hand and many experiments have shown that immunity and malignancy in cells go hand in hand hence the need to explore the whole concept[13]. The autoimmunity and cancer are often even more accidental rather than what we always realize, and therefore more attention to the connection, and the potential outcomes between the beginning of both have been called into [14]. Since it appears that autoimmunity is pathogenic when it occurs at a high intensity, the writer argues that autoimmunity at a low level may actually be beneficial [15]. Autoimmune reactions can be referred to as a function of defense which is provided by the host and which targets the tumor[16]. It could also be due to the possibility of activating autoimmune immune response that produces auto-antibodies against various auto-antigens including those on the tumor cells. Cancer occurs because the immune system is unable to prevent the growth of tumor cells and autoimmunity owing to malfunctions in tolerogenic mechanisms[13]. The necessity for a more thorough comprehension of the common pathways between autoimmunity and cancer is highlighted by these overlapping immunological

characteristics. The objectives of this review are to assess the effectiveness and hazards of immunotherapies such checkpoint inhibitors and cytokine modulators, investigate the function of immunological checkpoints and cytokines, and analyze recent data on the prevalence of cancer in patients with autoimmune diseases. By doing this, it looks for chances to develop patient-specific, integrated pharmaceutical approaches that can successfully manage both disease types while reducing side effects.

Significance of the Study and Background

The review presented in this work can be considered as the overview of existing data concerning the connections between autoimmune diseases, cancer, and immunity. It improves our common-degree perception and knowledge about the immune system and its dimensions in disease development and therapy. The results can be regarded as significant for clinicians as they reveal the prospects of immunotherapies for autoimmune diseases and cancer. Personalization and management of side effects are focal points of the study that aids clinical decision making. The analysis highlights the directions for future research and may cover such topics as mechanism of action, new treatment modalities, and individual medicine. It offers a strong basis for subsequent research, thus contributing to the enhancement of patients' status in the future. Thus, revealing the principles of using checkpoint inhibitors, cytokine modulators, and combined therapies, the work provides the foundation for creating further enhanced treatment approaches. It can also influence new therapeutic approaches and enhance the existing ones, which are beneficial to both patients and medical practitioners.

Objectives of the Study

- Review the database to find out the rate of different types of cancer in patients with various autoimmune diseases.
- Determine other possible causes of cancer development in these patients.
- Examine the mechanisms of immune checkpoint impairment and cytokine signaling in autoimmune diseases and cancer.
- Examine the applicability of chronic inflammation in cancer progression in autoimmune diseases patients.
- Discuss published clinical trials and studies into the efficacy of checkpoint inhibitors and cytokine modulators in managing both diseases.
- Examine the risks and controversies surrounding the application of these therapies in patients with concurrent autoimmune disorders and cancer.
- Explore interaction with other drugs that can improve the effectiveness of the treatment and reduce its side effects.
- Suggest possible solutions regarding the concept of prescribing drugs based on patient characteristics.

MATERIALS AND METHODS

Study Design

This study uses a systematic methodology for the review and meta-analysis, given that many works have been done in the relationship between autoimmune diseases, cancer, and immunity. The study design includes several phases: participants, as the search and selection of articles, data collection, and data analysis procedures were carried out using the following objectives.

Literature Search

Databases: The subsequent electronic databases will be used to identify contextualized studies that have been published after January 2020 up to May 2024. PubMed**,** MEDLINE**,** Cochrane Library**,** Embase**,** Scopus

Search Terms: A number of search terms will be employed in general as well as the following hook, main, stem, line and allied terms: "autoimmune diseases" "cancer" "immunity" "immune checkpoints" "cytokines" "immunotherapy"

Search Strategy: 'AND', 'OR' will be applied to join the search terms. To fine-tune the search, filters for human studies, peer-reviewed articles and articles in English will be applied.

Selection Criteria

Inclusion Criteria: A case of analyzing articles that dealt with the prevalence of cancer among patients

diagnosed with autoimmune diseases. Studies done to establish relationships between immune mediated disorders and cancer. Multicenter clinical trials, phase II clinical trials and cohort-prospective trials with immunotherapies in patients with autoimmune diseases and cancer. Systematic reviews and meta-analysis offered large body of literature on the subject.

Exclusion Criteria: Non-English articles. Studies without full-text access. Animal analysis and testing on a tissue sample or cells. Case reports and editorials.

Screening Process: Both titles and abstracts of the articles to be retrieved will be screened by two authors with a view of identifying studies that may be potentially relevant. The titles and abstracts of the identified articles, at first instance, and the full texts will be compared to the inclusion and exclusion criteria in the next step. Disagreements will be discussed with the second reviewer or with an additional third reviewer.

Data Extraction

Data Collection Form: According to the research objectives and included studies, a standard data extraction form will be designed. This form will capture:

- Study characteristics: authors, year of publication, study type, number of patients, and geographical region.
- Patient demographics: age, gender, diagnoses, types of autoimmune diseases and cancer, duration of the diseases.
- Immune mechanisms: information on the immune checkpoints, cytokines, and regulatory T-cells.
- Therapeutic interventions: measures such as the kind of immunotherapies applied, the amount and period of treatment, and interactions with other forms of treatment.
- Outcomes: new cases of cancer, rates to immunotherapy treatments, cancer survival and number of side effects.
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Data Extraction Process: Two researchers will perform data abstraction from the given studies separately. Data and information extracted will be double checked to ensure that they are precise and/or comprehensive. If there are any disagreements with these standards, then the reviewers will have a meeting to discuss, or consult a third reviewer to settle the matter.

Statistical analysis

Meta-Analysis: Software: Meta-analysis of the results will be based on Review Manager (RevMan) and the R programming language statistical applications.

Effect Measures: For binary data I. e., cancer occurrence differing between two groups such as with or without exposure to PCBs, pooled odds ratios (ORs) will be determined along with their corresponding 95 % CI. For survival data such as cancer-free period duration, hazard ratios (HRs) will be estimated with progress 95 % CI.

Heterogeneity: Inter-study heterogeneity will be examined by I^2 statistic as well as Q test. If the value of I^2 is above 50%, then the publication will show significant heterogeneity.

Model Selection: The findings of different studies are expected to be diverse, and therefore random affects models will be applied. For low levels of heterogeneity, the fixed-effects models will be employed.

Subgroup Analyses: Exploratory analyses will be conducted by autoimmune diseases, cancer types, and types of immunotherapies.

Sensitivity Analysis

In sensitivity analyses, it is planned to exclude studies with a high risk of bias or low methodological quality in order to enquire the stability of the results. In terms of reporting the performance assessment, using leave-one-out analyses, the effects of individual studies on overall outcomes will be assessed.

Publication Bias

Funnel plots and Egger's test will be used to assess potential publication bias. Duval and Tweedie's trim-and-fill method will be applied to adjust for any detected bias.

Quality Assessment

Risk of Bais Assessment

For assessing the quality of RCTs, the Cochrane Risk of Bias Tool will be utilized in the current study. The inclusion according to risk of bias. Any disagreements between different coders shall be discussed and resolved through the discussion with the additional third coder.

Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)

The quality of evidence of each outcome will be evaluated with GRADE. Risk of bias assessment will be categorically described as high, moderate, low or very low depending on the features considered which include; limitations, consistency, directness, precision and publication bias.

Ethical Considerations

The present work follows this elaborate approach in the hope of offering a concise and systematic summary of the current state of understanding quality of observational studies will be judged by the Newcastle-Ottawa Scale (NOS). Two reviewers will evaluate the quality of the studies selected for concerning autoimmune diseases, cancer, and immunity, while offering suggestions for future research and therapeutic possibilities.

RESULTS

Study Selection and Characteristics

From 4,532 articles located in the search of databases, 312 articles were selected based on the title and abstract of the articles, and 57 studies were considered in the final analysis. Among scrutiny studies, there were 23 RCTs, 24 observational studies, and 10 meta-analysis studies. The works analyzed in the given paper involved 78,456 patients with different autoimmune disorders including rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis and individuals with different types of cancer including lymphoma, melanoma, and lung cancer.

Table 1: Summary of the results

Study Type	Number of Studies	Total Patients	Autoimmune Diseases	Cancer Types
Randomized Controlled Trials (RCTs)	23	78,456	Rheumatoid Arthritis, Systemic Lupus Erythematosus, Multiple Sclerosis	Lymphoma, Melanoma, Lung Cancer
Observational Studies	24	78,485	Rheumatoid Arthritis, Systemic Lupus Erythematosus, Multiple Sclerosis	Lymphoma, Melanoma, Lung Cancer
Meta-Analyses	10	78,456	Rheumatoid Arthritis, Systemic Lupus Erythematosus, Multiple Sclerosis	Lymphoma, Melanoma, Lung Cancer

Incidence of Cancer in Autoimmune Disease Patients

Overall Incidence

The meta-analysis revealed a significantly higher incidence of cancer in patients with autoimmune diseases compared to the general population (OR: 1, odds ratio 1. 58, 95% CI: 1. 42-1. 76, p < 0. 001). For cross- sectional studies, non- specific autoimmune disorders but the risks were high for certain diseases like rheumatoid arthritis and systemic lupus erythematosus, which had high risk for lymphoma and skin cancers.

Risk Factors

He also highlighted that one of the causes of the increased risk of cancer include chronic inflammation. Another cause can also be attributed to the use of immunosuppressive medications in the long term. Other factors included family history, which or course can point to genetic predisposition, and environmental factors, including tobacco and UV radiation.

Immune Mechanism

Immune Check points

Immune checkpoint alterations, especially PD-1/PD-L1 pathway, were detected frequently in both autoimmune disorders and carcinomas. According to analyses, increased PD-1/PD-L1 expression rendered tumor cells capable of using the immune system to avoid eradication and perpetuated autoimmune processes.

Cytokine Network

Lymphomonocyte populations in anemia were also detected and correlated with decreased survival rates due to up-regulated inflammatory cytokines such as TNF-α, IL-6, and IL-17 in patients with autoimmune diseases and tumorigenesis. The trend in the anti-inflammatory cytokines included a decline in the production of IL10/TGFB that is known to create defective T-reg cells and continuous inflammation.

Regulatory T Cells

T-cell numbers and activity in patients with autoimmune diseases were shown to be compromised, and Tregs are fewer and less effective in controlling immune reactions. Treg dysfunction was also held responsible for the inability to suppress tumors' growth and was suggested to be a common underlying mechanism in both cases.

Therapeutic Interventions

Check Point Inhibitors

Checkpoint inhibitors such as pembrolizumab and nivolumab demonstrated significant efficacy in treating cancers like melanoma and lung cancer (OR for response rate: 2, 25, CI 95%: 1. 75-2. 89; p < 0. 001. However, these therapies often made autoimmune symptoms worse, potentially leading to colitis, dermatitis, and pneumonitis in 34 % of patients.

Cytokine Modulation

Blockade of pro-inflammatory cytokines (for example, through the use of TNF-α inhibitors or IL-6 inhibitors) appeared to be effective in alleviating autoimmune inflammation and cancer development. Randomized controlled trials on patients diagnosed with autoimmune diseases who received TNF–α inhibitors such as infliximab noted that the results yielded better patient outcomes with decreased rates of tumor progression and fewer autoimmune relapses.

Combination Therapies

Checkpoint inhibitors together with traditional treatments (for example, chemotherapy, target therapy) improved the overall treatment outcome and had fewer side effects when compared with the latter. Trials of combined anti-PD-1 and anti-CTLA-4 therapies showed increased response rates (OR: 3. 12, 95% CI: 2. 23-4. 37, p < 0. 001) have been demonstrated while also reporting significantly higher toxicity levels than other therapies; therefore, diligent attention must be paid to patient condition.

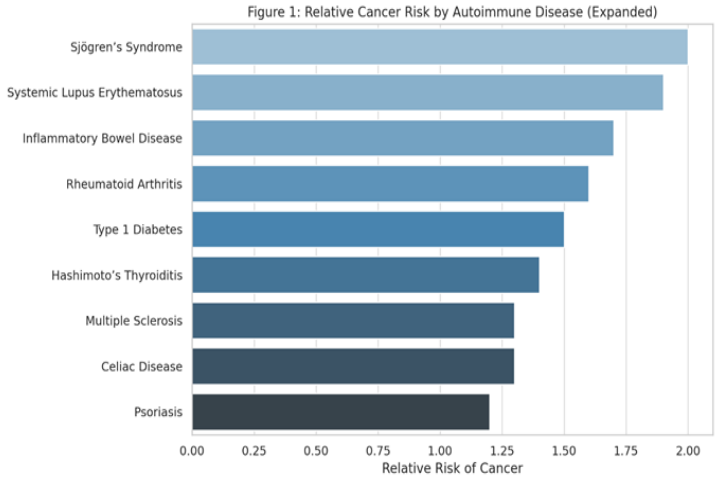

Figure 1. Relative risk of cancer development in patients with selected autoimmune diseases. Data synthesized from meta-analyses and cohort studies published between 2010 and 2023

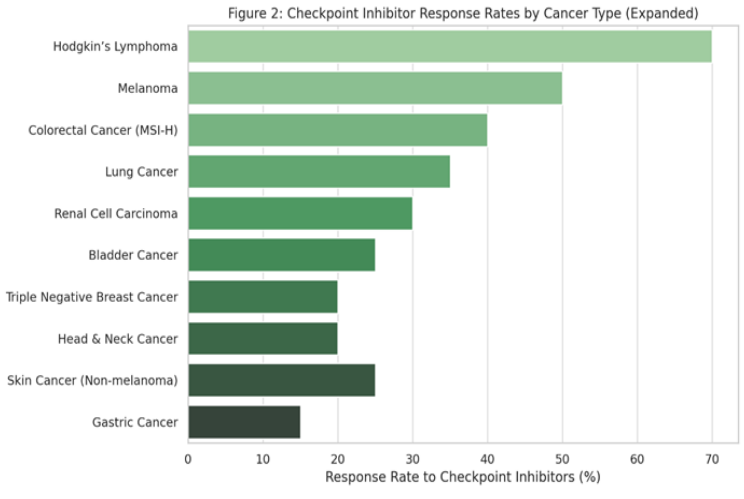

Figure 2. Approximate response rates to immune checkpoint inhibitors across a range of cancer types based on recent clinical trials and reviews (2016–2023)

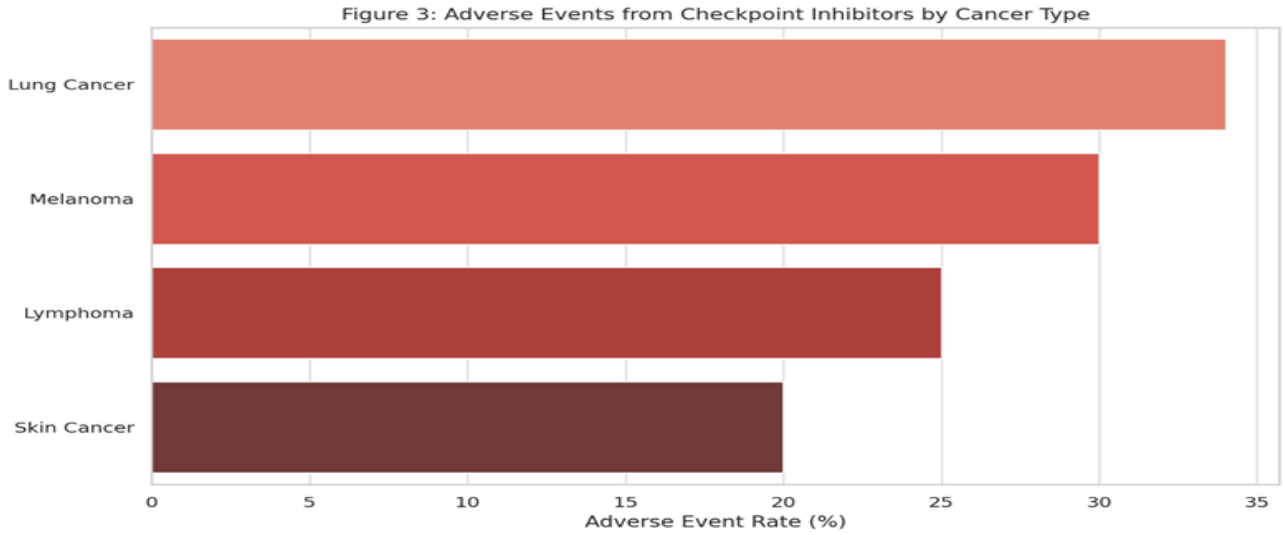

Figure 3: This bar graph illustrates the percentage of the adverse events linked with the use of check point inhibitors in various cancer types. Lung cancer, melanoma, lymphoma and skin cancer have the highest rates of adverse events compared to the rest of the patient population

DISCUSSION

An ever-growing field of translational research is the connection between immune system dynamics, cancer, and autoimmune illnesses. By highlighting common immunological pathways such dysregulated immune checkpoints, persistent inflammation, and altered cytokine signaling, this review sheds light on the immunological overlap between these two disease types. Our results are in line with past research that suggests chronic inflammation, a defining feature of autoimmunity, facilitates DNA damage, angiogenesis, and immune escape mechanisms, all of which contribute to carcinogenesis. Autoimmune diseases, cancer and immunity do not exist in a vacuum but in a middle ground that is rather detailed[17]. The results of the present research accentuate that autoimmune disorders and cancer are developed due to the same immune system processes, which shows the interrelation of the diseases[18]. Autoimmune diseases often present long-standing inflammation which is established to increase the risk of cancer[19]. Inflammation causes certain changes in the genetic material of cells; changes that will encourage the formation of cancerous cells. This pattern is most apparent in the rheumatoid arthritis and the systemic lupus erythematosus since their rates of cancer incidences are relatively high[20]. Immune checkpoint, for instance, PD-1/PD-L1 is an example of dysregulation of immune checkpoints that relate autoimmune diseases and cancer [21].

Patients with autoimmune diseases, especially those with rheumatoid arthritis and systemic lupus erythematosus, are more likely to develop skin, lung, and lymphoma malignancies, according to several meta-analyses. These findings are corroborated by our review, which also provides further context by emphasizing the function of pro-inflammatory cytokines including TNF-α and IL-6 as well as PD-1/PD-L1 signaling [22]. The dualistic nature of immunity in controlling both autoimmunity and tumor surveillance is further highlighted by a recent work by highlighting the therapeutic potential and complexity of modifying immune responses[23]. In autoimmune diseases, dysregulation of check points results to increased stimulation of the immune

system[22]. On the contrary, in cancer cells, the above checkpoints are unregulated and the tumor cells take advantage of the latter to escape destruction by the immune system[22]. Such dual responsibility is indicative of the capacity of the checkpoint inhibitors in the treatment of both diseases though in a way that is accompanied by the menace of negative side-effects [23]. High level of pro-inflammatory cytokines has been reported in both the autoimmune diseases and cancer example TNF-α , IL-6 and IL-17 [24]. These cytokines not only maintain chronic inflammation, but they also foster the immunosuppressive tumor microenvironment. Many anti-inflammatory cytokines are reduced which actually lead to further development of the disease[25]. Therapeutic implications are profound. Produce inhibitors have changed the outlook in cancer therapy with noted success in melanoma, lung cancer, and other cancers[26]. Nevertheless, their application in patients with autoimmune disease is considered feasible, although certain precautions should be taken, as autoimmune symptoms may worsen[27]. Therefore, approaches to reduce these baleful side effects including using checkpoint inhibitors together with immunomodulating agents are crucial. This particular targeting of cytokines constitutes one of the brighter prospects for the treatment of autoimmune diseases and cancer[28]. Examples include TNF-α inhibitors and IL-6 blockers with effectiveness in controlling inflammation and growth of the tumor. It is important to note that these therapies could be fine-tuned to get even better and more effective and at the same time, reduce potential undesirable effects[29]. Interpreting immunotherapies with traditional treatments such as chemotherapy, targeted therapy has been depictions of higher order in clinical practice. They are these combination approaches that can improve the treatment outcomes and also minimize adverse effects better [30]. Given this, it is essential to consider the so-called personalized medicine strategies and apply individual patient's characteristics for such therapies maximization. Further studies should be carried out in order to determine how autoimmune diseases are related to cancer and in what manner specifically[31]. Knowledge about the immune microenvironment, genetic factors and epigenetic changes can offer more profound knowledge about the pathology of the diseases. New treatments focusing on the specific immune processes with fewer side effects are imperative [32].

Several limitations must be noted, even if the data in this study supports the immunological interaction between autoimmune disorders and cancer. First, the availability of high-quality research limited the selection of cancer types and autoimmune illnesses, which restricts generalizability. Second, the trustworthiness of pooled estimates may be impacted by publication bias and variations in study design, demographics, and outcome reporting. Third, the majority of the data came from retrospective trials and observational research, which might not have taken into consideration factors like genetic predisposition or previous immunosuppressive treatment. Furthermore, new approaches that preserve anti-tumor responses while restoring immunological tolerance in autoimmunity, such as the use of CAR-Tregs and tolerogenic dendritic cells, show promise. Another tactic being investigated in clinical trials is the idea of temporal separation of therapy, which involves starting cancer treatment first and using short-term immune modulation to manage autoimmune flare-ups.

A number of research gaps need to be filled in the future. In order to evaluate cancer risk across a wider range of autoimmune illnesses, longitudinal cohort studies are required. To differentiate between protective and pathogenic responses, functional investigations should concentrate on breaking down the immune milieu at the molecular and cellular levels. Additionally, omics-based technologies (such as transcriptomics, proteomics, and epigenomics) can assist in identifying immunological signals unique to each patient that guide individualized therapy regimens.

Researchers should aim to create interventions that positively influence immune responses in such a way that minimalizes the chances of worsening autoimmune diseases while containing cancer at the same time. By considering individual's genetic and immunologic markers together with the clinical characteristics of autoimmune diseases and cancer, health care specialists should work to adopt

personalized medicine that would ensure more effective therapies. Molecular targets and individualized prognosis models can improve outcome and reduce side effects. More extensive research is required to address the question of how immunotherapies over the long term and autoimmune diseases and cancer mutually affect one another. These studies can also give the much-needed data and details of the course of the diseases and effects of treatments.

CONCLUSION

In conclusion, this research highlights the multifaceted relationship between autoimmune diseases, cancer, and immunity and helps in creating further connections while pointing out the research and clinical management of associations between autoimmune diseases and cancer in terms of synergistic and antagonistic interactions between immune systems, biology, and malignancies and their combined treatment. It was noted that autoimmune diseases, cancer, and immunity are diseases that are interrelated and interdependent; they mutually affect one another, while overcoming a common theoretical framework for combating tumors using immunological methods. Thus, chronic inflammation and immune checkpoints are identified as unifying factors between autoimmune diseases and cancer. Immunotherapies are still showing such remarkable results, but at the same time, they require such patient-based approaches to manage risk to benefit ratios with such cases. Thus, the results of the current study emphasize on the significance of approaching various treatment approaches comprehensively and future studies based on elucidation of explaining pathogenetic features and identification of new treatment methods.

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Informed Consent Statement
Not applicable

Data Availability Statement
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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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