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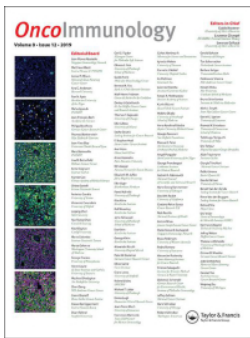
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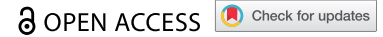


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ARTICLE



Beneficial autoimmunity and maladaptive inflammation shape epidemiological links between cancer and immune-inflammatory diseases

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ABSTRACT

Chronic inflammation drives proliferative responses, hence increasing cellular multiplication with the consequent risk of malignant transformation. Autoimmune responses against self-antigens drive chronic inflammation but may also enhance cancer immunosurveillance with the consequent reduction of tumor incidence and progression. These notions, which have been well established at the preclinical level, may explain the generally positive associations between immune-inflammatory diseases but also some negative associations, for example between breast cancer and rheumatoid arthritis or systemic lupus erythematosus, which have recently been confirmed in a study enrolling close to half a million participants from the UK Biobank.

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Cancer; immunosurveillance; autoimmunity; inflammation

Evermore accurate and expanding archiving of clinical and biological patient data greatly facilitates the discovery of novel epidemiological associations among different diseases. A recent study published in *JAMA Oncology*¹ exploits a large dataset involving 478 753 participants to investigate the relationship between cancers and “immune-mediated diseases”, which is a heterogeneous collection of pathological conditions. Such diseases may be either organ-specific or systemic, involve a mostly inflammatory process without the recognition of specific autoantigens (as this may apply to Crohn's disease, psoriasis, sarcoidosis and ulcerative colitis), an overreaction to exogenous allergens (as this is the case in allergic rhinitis, asthma and celiac disease) or the unwarranted recognition of specific autoantigens with a variable contribution of autoreactive T lymphocytes and autoantibodies. If considered as one single entity, the diagnosis of such “immune-mediated diseases” slightly increases the risk of developing any kind of cancer with a multivariable hazard ratio of 1.08 (95% confidence interval: 1.04–1.12). However, the study in *JAMA Oncology* has sufficient power to unveil more subtle associations between specific immunologically relevant diseases and distinct categories of malignancy that can be either positive or negative.¹

Cancer is the result of two processes, namely (i) the cell-autonomous accumulation of (epi)genetic alterations leading to the activation of oncogenes and the inactivation of tumor suppressor genes, and (ii) the systemic failure of immunosurveillance, i.e. the capacity of innate and cognate immune effectors to recognize and eliminate (pre-)malignant cells.^{2,3} Taken into account the importance of cell-autonomous (epi)genetic

aberrations for carcinogenesis and tumor progression, it is not a surprise that chronic tissue damage coupled to long-term inflammatory processes augments the risk of malignant transformation, based on the well-established notion that each cellular duplication is coupled to the risk of propagating non-repaired mutations and chromosomal aberrations, hence enhancing genomic instability and the risk of developing cancers (Figure 1a).^{4–7} However, there are additional possible links between “immune-mediated disease” and enhanced cancer risk. At a general level, chronic inflammation may drive and accompany tissue senescence, thus facilitating carcinogenesis due to accelerated biological aging.² Moreover, the accumulation of inflammatory cells in inflamed tissues may subvert specific immune responses, hence ultimately abolishing immunosurveillance. For instance, macrophages and granulocytes can inappropriately differentiate into myeloid-derived suppressor cells which impede the activity of cytotoxic lymphocytes.⁸

In specific conditions, autoimmune diseases have been linked to improved immunosurveillance, as exemplified for autoimmune thyroiditis and thyroid cancer,^{9,10} vitiligo and melanoma^{11,12} or non-cirrhotic primary biliary cholangitis and cholangiocarcinoma.¹³ Moreover, in preclinical models, vaccination with normal epithelial cells from the intestine or the mammary gland can induce protective immune responses against colon and breast cancer, respectively, underscoring the possibility that immune responses against (by definition) non-mutated self-antigens can participate to cancer immunosurveillance.^{14,15} The development of human breast cancer becomes also more improbable when histologically normal mammary gland is infiltrated by

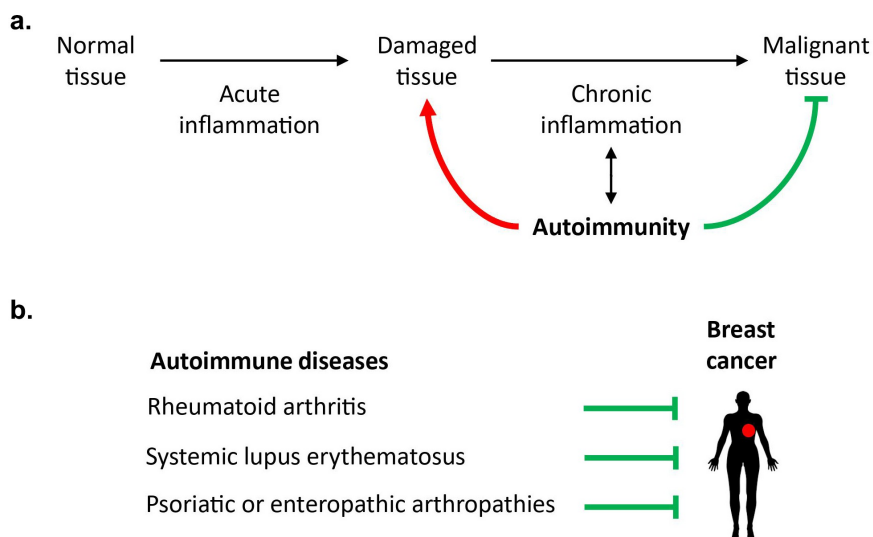


Figure 1. Epidemiological links between systemic autoimmune diseases and breast cancer. (a). Repeated acute inflammatory responses and autoimmune damage can cause chronic inflammation and promote carcinogenesis. By contrast, some autoimmune diseases have been associated with a reduced incidence or progression of cancer, as these pathologies can fuel the immunosurveillance of (pre)malignant cells. (b). Several studies have revealed a negative association between breast cancer and some autoimmune manifestations such as rheumatoid arthritis, systemic lupus erythematosus, and psoriatic or enteropathic arthropathies.

T lymphocytes at a high CD8/FOXP3 ratio,¹⁶ pleading in favor of the hypothesis that even healthy tissues are patrolled by specific T cells to avoid their cancerization.¹⁷

Beyond these examples of organ-specific autoimmune responses that protect against the development or progression of cancers affecting the same organ, accumulating evidence indicates that systemic autoimmunity may reduce the incidence of cancers affecting multiple organs as well. For example, systemic lupus erythematosus (SLE) is associated with a significant reduction of several malignancies (breast, endometrial, prostate, and uterine cancers, melanoma).^{18,19} Rheumatoid arthritis is linked to significantly reduced incidence of breast, colorectal and prostate cancer.^{1,20} Breast cancer is also significantly less frequent in patients with psoriatic or enteropathic arthropathies (Figure 1b).¹ The mechanisms of these effects have not been elucidated but may involve improved immunosurveillance due to the increase in the general immune tonus. Indeed, the presence of a broad repertoire of autoantibody specificities (≥ 3) is related to a particularly strong reduction (by close to 60%) in breast cancer incidence.²¹ Moreover, a cell-penetrating lupus autoantibody that binds single-stranded RNA has been shown to sensitize cancer cells to doxorubicin treatment.²² Lupus-associated anti-ribosomal P autoantibodies reportedly mediate direct pro-apoptotic effects on cancer cells.²³ On top of these considerations, it appears intriguing that the cancer types that are negatively associated with systemic autoimmunity are under particularly strong immunosurveillance.^{24,25}

Nonetheless, other explanations to this epidemiological link between systemic autoimmunity and reduced incidence of specific cancers have been suggested. Thus, anti-inflammatory medications including aspirin may improve anticancer immunosurveillance,^{26,27} contrasting with the effects of glucocorticoids, which subvert immunosurveillance.²⁸ In addition, SLE patients tend to avoid external factors that aggravate the disease (such as sunlight, which is the main trigger of

melanoma)²⁹ as well as endocrine therapies (such as oral contraceptives or hormone replacement therapy),³⁰ perhaps contributing to the reduced incidence of such cancers (Figure 1). Hence, it is not yet clear to which extent the relationship between autoimmunity and reduction of cancer incidence is direct (via immune effects) or indirect (via iatrogenic and behavioral effects). Future studies in suitable mouse models developing spontaneous or experimentally induced autoimmune diseases must dissipate these uncertainties and establish mechanistic links between self-reactive and anticancer immunity.

Disclosure statement

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