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Fundamental Analysis of the Role of Aging on Breast Cancer

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Abstract

Cancer is one of the most overwhelming diseases and takes place with upper frequency as we age. As a matter of fact, age is one of the most significant risk issues for most solid cancers. It is very problematic to explain what relates aging to cancer, regarding the existence of multiple dissimilar cancers, the time required for their expansion, and the multi-hit theory of carcinogenesis. Breast cancer is a heterogeneous distortion appearing in younger women has progressively come to be the focus of deep study, and often dispute, over the past decade. Medical experiments and biomarker findings show that late-onset breast cancers rise more gradually and are physically less violent than early-onset breast cancers, even when controlled for hormone receptor and growth factor receptor expression. Although it is assumed that immune system plays a key role in controlling the cancer progress and evolution within its ability to mount a suitable response, it also favors cancer progress by taking part in the growth of chronic inflammation. The obvious imbalance between retaining a fairly reactive innate immune response and evolving a severely altered adaptive immune response with aging leads to the low-grade inflammatory status usually observed in the elderly, supporting the conclusion that the biology of breast cancer is age-dependent. Therefore, in the present study, we discuss our emerging knowledge of the biology of (breast) cancer coming from aging at both the pathologic and the genomic level. We clarify the potential role of aging on breast cancer biology, and how even current knowledge might advance the clinical management of breast cancer patients.

Key words: *Aging, Cancer, Breast cancer, Immune system, Inflammaging.*

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1. Introduction

One of the most overwhelming diseases is cancer and takes place with upper frequency as we age. As a matter of fact, age is one of the most significant risk issues for most solid cancers [1]. This may be regarded inconsistent given that the aging process might be presumed to provoke the progress of cancer, as a minimum to some extent. This denotes that cellular senescence is not in itself adequate to stop cancer progression for the period of aging and may even, regarding current experimental data, contribute to it [2], accompanied by other influences encompassed the age-related dysregulation of homeostatic systems. One such dysregulated system is the immune response.

The literature demonstrates that breast cancer has a sole pathophysiology according to age. Younger patients have a higher frequency of estrogen receptor-negative, higher-grade tumors and older patients have a higher rate of estrogen receptor-positive, low-grade tumors [3,4,5,6,7]. The data in the literature also reflects that mammography attributes using standardized descriptors can envisage the histology of breast cancer [8,9]. Numerous findings have revealed the possibility of envisaging the prospect of invasive breast cancer versus DCIS using patient traits and mammographic results [10,11], by treating age groups uniformly. In the present study, we will illustrate the recent understanding of the connection between aging, immunity, and cancer according fundamentally to data from human aging analyses. We also show that the inherent age-based differences in breast cancer pathophysiology will influence the predictive ability of these models, resulting in differential accuracy and distinct predictive features based on age.

In line with what mentioned above, we sought to ask a very relevant question: Is age a prognostic and/or predictive factor among patients with early-stage breast cancer? Due to the growing importance in concentrating the possibly unnecessary analysis and treatment of certain breast cancers, we were motivated to examine this question.

2. Review of the Related Literature

The risk of getting breast cancer increases with age. The table below shows the percentage of women who will get breast cancer over different time periods. The time periods are based on the woman's current age. For example, go to current age 60. The table shows 3.48% of women who are now 60 years old will get breast cancer sometime during the next 10 years. That is, 3 or 4 out of every 100 women who are 60 years old today will get breast cancer by the age of 70 [12].

Current Age	10 Years	20 Years	30 Years
30	0.44	1.88	4.07
40	1.45	3.67	6.83
50	2.29	5.56	8.76
60	3.48	6.89	8.90
70	3.88	6.16	N/A

Table 1.Percent of U.S. Women Who Develop Breast Cancer over 10-, 20-, and 30-Year Intervals According to Their Current Age, 2009–2011

2.1 Aging

Aging is in consort with dysregulation of most of the body's heavily interconnected and related homeostatic systems. Based on the current view, aging is not a disease, while some would like to regard it as such. This dysregulation is an enduring process that makes aging individuals more vulnerable to pathologies that the young can overcome, finally culminating in the appearance of eminent age-associated diseases such as cancer, cardiovascular diseases, metabolic diseases, and neurodegenerative diseases. The precise nature and causes of aging are still unknown [12,13].

The meaning of aging is similarly very challenging, revealing our partial knowledge of the various aspects of this very compound procedure. The meaning of aging relies on the viewpoint that we have on its causes. As a matter of fact, some theories delineate aging by taking the viewpoint of genetic determination, demonstrated by the evolutionary attitude to aging, whereas others support the accumulation of the results of dangerous proceedings over time, which subsequently decreases the reserves obtainable for adaptation to such damage accumulation caused. Whatever the exact cause, this is a universal, inevitable process that leads permanently to death in mammals [13]. Nevertheless, particular facets of this procedure are dependent on either intrinsic or extrinsic modulation, resulting in large interindividual differences in longevity and vulnerability to different age-related diseases such as cancer. In this context, we can define aging as simultaneous or successive changes in several interrelated physiological systems, leading to the exhaustion of an individual's reserves and, as such, rendering the organism more vulnerable to different stresses [13].

2.2 Breast Cancer

The gigantic bulk of human malignancies are age-associated cancers, showing occurrence rates that increase exponentially with age during adulthood such that over 75% of all invasive cancers occur in vulnerable people's age 55 years or older [14]. Although total age-adjusted US cancer occurrence rates have increased about 15% during the past three decades, breast cancer age-adjusted occurrence rates have increased approximately 23% to a current level of ~130 cases per 100,000, signifying ~180,000 new cases annually [15]. thus, approximately 80% of all breast cancers arise in women over age 50; and the 10-year prospect of developing invasive breast cancer increases from less than 1.5% at age 40, to about 3% at age 50 and over 4% by age 70, producing a cumulative lifetime risk of 13.2% or 1 in 8 [16]. Noteworthy are the near identical increases in age-specific occurrence rates for each of the four ER/PR subsets during premenopausal years and the significantly different inflections near age 50; only the two ER-positive breast cancer subtypes (ER-positive/PR-positive, ER-positive/PR-negative) show ever increasing rates during postmenopausal years, whereas ER-negative breast cancers show a minor decrease in occurrence rates after age 50 [17]. With the exception of medullary breast cancer, which fits an early age unimodal model across all racial groups regardless of steroid receptor status, all histopathologic breast cancer subtypes demonstrate similar bimodal age density distributions within each racial group. As well, when this statistical method was applied to a separate published set of breast cancer cases

molecularly sub-classified by gene expression microarrays (total 122 Stanford/Norway cases) into luminal (subtypes A and B) or non-luminal (basal and HER2-positive) types, both molecular types exhibited bimodal age-at-diagnosis distributions, with the luminal cases appearing most like ER-positive late-onset breast cancers and the non-luminal cases appearing most like ER-negative early-onset breast cancers [17].

In spite of established consciousness that breast and other cancers are mainly age-related diseases and that aging predisposes to diseases like cancer, geroscience is still in its infancy [18] and is only beginning to notify oncology about the cancer–aging relationship [10]. As a result, emergent molecular and cellular hypotheses set forth to justify the cancer–aging relationship are of interest but remain largely untested [19].

Moving forward, there are several points to consider. Breast cancer is a disease of aging, with a median age at diagnosis of 61 years [20]. As such, one may choose to look at these data from the other side of the age spectrum- i.e., that women aged > 40 years, including elders with adequate cardiac reserve, derive similar benefit from chemotherapy and trastuzumab as their younger counterparts.

2.3 Immune System

Although immune system involvement was disputed until recently, experimental and human patient data now propose that the immune system has a critical role in the natural history of cancer [21]. The universal agreement that the immune system is a biologically significant procedure in carcinogenesis is reflected by its inclusion in the set of cancer hallmarks. This reinforces the distinguished fact that cancer does not develop in isolation as a result of mutations, but that both the macro- and micro-environment also play key roles [22]. Among the first immune cells to meet cancer cells, natural killer (NK) cells may be the most important within the action of their receptors leading to increased interferon gamma secretion. This makes tumor cells be demolished, and their fragments are engulfed by macrophages and dendritic cells (DCs). These cells then become activated to secrete many cytokines and chemokines, leading to activation of B and T cells, which in turn further activate the innate immune response. These cells, antibodies, and cytokines can eliminate tumor cells and create immune memory cells. Collectively, this should lead to the formation of an immune memory to specific tumor antigens.

Tregs (CD4+ FOXP3+) not only are very vital for the interaction between the immune system and cancers, they but also are essential for the impendent of autoimmunity. However, these cells are raised in the peripheral blood and tumors of cancer patients. In several cases, their increased density in the tumor environment indicates a poor prognosis [23]. While tregs are too vital for maintaining immune system homeostasis, they may also play a role in the advancement and continuation of several types of cancer. It should also be mentioned that Tregs may also have a role in suppressing tumor development by regulating inflammation [24]. It seems essentially obvious that the Janus-type behavior of Tregs in regard to tumors relies on the environment in which they are acting.

All of these data demonstrate that with aging alterations in both arms of the immune system, as well as in their efficient cooperation, contribute to altered protection against different challenges, the development and maintenance of inflammation, and increased susceptibility to disease [25].

Conclusion

There is no doubt that aging is the foremost risk factor for the development of various diseases including cancers. Understanding the mechanisms regulating aging is crucial for comprehending the incidence of these different diseases. While the low-grade inflammation related with aging can be a conventional factor linking aging to these diseases, and thus strictly deleterious, this may be essential for survival since it ensures that the elderly are likely to be able to react to aggressive inflammatory factors much more straightforwardly than they would be able to if they had an immune response similar to that of young people. Thus, understanding the collaboration between this low-grade inflammation and its shift toward pathogenic pathways not only in the cells but also in the microenvironment can provide the key to why aging is the most significant risk factor for these diseases. Clinical observations and biomarker studies indicate that late-onset breast cancers grow more slowly and are biologically less aggressive than early-onset breast cancers, even when controlled for ER receptor expression, supporting the conclusion that the biology of breast cancer is age-dependent. Therefore, recognizing the actual mechanism inspiring aging may support to delay the onset of these pathologies and may eventually extend the healthiest life span possible with aging.

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