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COMMENTARY

Tackling the clinical complexity of breast cancer

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Abstract

Clinical complexity (CC) is an increasingly recognized feature of internal medicine patients who are often characterized by complex needs determined by both biological (i.e. intrinsic to the patient or disease biology) and non-biological (i.e. socioeconomic, cultural, environmental, behavioural) factors. Breast cancer, one of the most common malignancies worldwide, certainly represents an example of a complex disease. Nonetheless, the concept itself of CC and its possible determinants in breast cancer have been poorly addressed. We herein provide our view about the possible factors triggering CC, the key issues of CC and the related unmet needs in breast cancer.

Keywords: cancer, internal medicine, multimorbidity, oncology.

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Commentary

Although a precise definition has yet to be agreed on,[1] the concept of clinical complexity (CC) has certainly drawn increasing attention in clinical medicine,[2–4] especially in the general and internal medicine settings.[5–7] Of note, the term 'complex' applied to clinical medicine is not used as the mere and general synonym of 'difficult to understand', but rather it defines the essential features of a complex system, including non-linearity, unpredictability, adaptivity and context sensitivity, in which countless variables interact with each other and this interaction determines a certain outcome.[8,9] Hence, a complex system can be tentatively defined as "*a network of individual variables from whose dynamic interaction new properties of the system itself emerge, and where the observable outcomes are something more and different than the sum of its single parts*".[1] In practice, the main determinants of CC may be divided into biological (that is, intrinsic to the patient or to disease biology) and non-biological (that is, socioeconomic, cultural, environmental, behavioural).[1]

Unfortunately, at present, there are no validated tools or frameworks able to capture and measure CC in relation to specific disease-related outcomes. Nonetheless, as shown by several scientific campaigns claiming a more holistic, patient-centred and precise approach to medicine (for example, Choosing Wisely, 4P medicine (predictive, personalized, preventive and participatory)),[10,11] there seems to be a compelling need for more inclusive, non-disease focused and multidisciplinary healthcare. This is particularly true in oncology, which, according to the American College of Physicians, is an internal medicine subspecialty,[12] requiring a broad knowledge of both biological and non-biological factors causing cancer and its clinical consequences. The concept of CC well applies to oncology, especially considering the massive advancements made in understanding the molecular and physiopathogenic bases of carcinogenesis,[13] the unprecedented development of novel treatments, including immunotherapy,[14] and the complex needs of cancer patients.[15] Above all, from this point of view, breast cancer (BC) undoubtedly represents a prototype of complex disease.

BC is the most common malignancy in women[16] and, in 2020, regardless of sex, it was the most common malignancy worldwide, accounting for roughly 12% of all malignancies, hence representing a major global healthcare issue.[17] It is well known that early BC, that is, confined to the breast or only spread to the axillary lymph nodes, is a curable disease, whilst advanced, metastatic disease is not curable.[16] Nevertheless, thanks to novel treatments and recent improvements, it may become a chronic disease and a relevant comorbidity.[18] Biologically, BC is a heterogenous condition, characterized by different histological subtypes and by the expression of key proteins, namely hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2). Additionally, BC is usually

a highly mutated neoplasia, especially triple-negative BC,[19] favouring cancer proliferation through apoptosis inhibition and oncogenesis enhancement. Several predisposing mutations also increase the risk of developing BC, including, amongst others, *BRCA1* and *BRCA2*, and sexual chromosome number abnormalities such as Klinefelter syndrome. The improvement in the knowledge of the biological complexity of BC has recently led to the development of novel treatments such as the use of trastuzumab-deruxtecan for $HER2^+$ BC[20] and immunotherapy or sacituzumab govitecan for triple-negative BC.[21] HR-positive metastatic disease is a good example of the possibility to extend survival expectations with well-tolerated, active and effective treatments such as those targeting cyclin-dependent kinases 4/6.[22] It is worth noting how studies also demonstrated improved quality of life, indicating the low global toxicity of this novel drug class.[23]

Surprisingly, whilst the biological complexity of BC has been widely recognized and addressed, the biological complexity of patients with BC and non-biological factors are still overlooked. For example, in clinical trials, specific sub-analysis for patients with multimorbidity, older age, cognitive impairment or other common conditions are lacking. Progression-free survival curves are typically not stratified according to the aforementioned variables. Moreover, in the oncological setting, the currently available scores of multimorbidity, such as the Cumulative Illness Rating Scale and the Charlson Comorbidity Index, are unlikely to capture and grade the real burden of multimorbidity in cancer patients. This is because patients with an oncological disease would immediately fall into a high severity score, and hence minor, yet clinically significant, survival differences would be missed. In most cases, clinical decisions are therefore taken according to expert-based consensus – when present – rather than based on solid evidence as in the case of the management of BC in elderly patients.[24] In face of the growing incidence of BC in patients aged more than 70 years old, the higher mortality compared to younger patients highlights a major health disparity and is possibly due to a delayed diagnosis of BC, frailty and multimorbidity.[25] A possible solution to these issues could lie in the reshaping and attributing more value and significance to phase IV, postmarketing trials. Indeed, phase III trials must be conducted in a rigorous way and cannot reproduce the real-life setting. At the same time, we have no instruments, at present, for defining precise endpoints for phase IV trials, including patients with different needs and patient-reported outcomes.

Patients' needs, personal preferences, beliefs and concerns about medications are other essential features that could affect the overall management of BC. For example, surgery as a therapy for BC and hormone therapy represents a massive psychological toll, as they alter one's body image and deeply affect intimacy, sexuality and fertility.[26] This, in turn, may lead to depression, anxiety, treatment refusal or non-adherence, suicide, and, broadly speaking, to poor mental health and decreased quality of life. According to the most recently published review on this matter, several methodological issues undermine the studies conducted so far assessing health-related quality of life in patients with BC.[26]

Regarding non-biological factors, several characteristics were found to be associated with a variable risk of developing BC and of having poorer outcomes. For example, obesity, a high-in-fat diet, diabetes mellitus and lack of physical activity were found to be associated with BC and may be associated with worse outcomes.[27] Hormone replacement therapy and use of hormone-based contraceptives are other risk factors that should be considered. Finally, a high socioeconomic status is associated with an increased risk of having a diagnosis of BC but with lower mortality. The apparently lower incidence of BC in patients with lower socioeconomic factors can be attributable to the lack of adherence to screening programmes in this population.[28] Table 1 summarizes the main variables determining CC in BC, along with some examples about how these factors could affect the management or outcomes of BC. It is worth noting that almost all biological and non-biological factors determining CC in BC are influenced by both BC per se and by the ongoing BC treatments (for example, sex and gender, genetics, multimorbidity, frailty, stigmatization and resilience). These variables could represent the basis for developing ad hoc CC indexes or tools that should be properly designed and prospectively validated in this setting. In fact, it is unlikely that a universal CC index could be used in any clinical setting but rather a validation is needed for specific conditions, as in the case of BC.

To conclude, although biological complexity of BC has been deeply studied and this has led to a paradigm shift from considering BC as a lethal disease to a chronic comorbidity, this has not been paralleled by a deep dissection of patient-related and non-biological factors influencing the overall management of BC. Actually, BC represents a typical example of chronic disease, and future studies, also including consensus papers or guidelines, should look at BC from an internal medicine viewpoint rather than considering it as a sole specialistic, oncologic disease. This could provide important novel insights into the management of BC, including treatment of multimorbidity in BC and proper drug prescription to avoid potential interactions. The involvement of all stakeholders implied in the treatment of BC, including patients themselves, is key for tackling the complexity of this condition. Novel instruments and novel phase IV trial designs should be developed to achieve this goal.

Table 1. Biological and non-biological factors, their variables, and practical examples that determine the clinical complexity of breast cancer.

Factors	Main variables	Examples
Biological, cancer related		
Histopathology	Preinvasive or invasive; luminal A or B, basal-like; ductal, lobular, mucinous, metaplastic, others	Different treatments and prognosis according to histopathology
Immunohistochemistry	Oestrogen and progesterone receptors, human epidermal growth factor receptor 2; triple-negative (if all the above are negative)	Different treatments and prognosis according to immunohistochemistry
Genetic mutations	*TP53*, *PIK3CA*, *MYC*, *PTEN*, *CCND1*, *ERBB2*, *FGFR1*, *GATA3*	Different treatments and prognosis according to genetic mutations
Metastatic disease	Lymph nodes, distant organs	Different treatments and prognosis according to disease progression
Biological, patient related		
Age	Paediatric *versus* adult *versus* elderly	Older age as a risk factor
Sex and gender	Female sex, male sex, sexual chromosomes alterations, transgenderism	Genetic factors more common in men; transgender people (male to female) taking hormone therapy have a similar risk of breast cancer as in women; Klinefelter syndrome associated with breast cancer
Genetic predisposition	BRCA1, BRCA2, PALB2, CHEK2; other genetic syndromes	Increased risk due to specific mutations; first-degree family history of breast cancer increases the risk
Ethnicity	White, Black, Hispanic, Asian	Breast cancer more common in white women and the Western world
Fertility, contraception and sexuality	Women of childbearing age, menopause, use of contraceptive pills	Different risks of developing more aggressive disease; preserving fertility in younger patients; sexual and intimacy issues due to therapies
Stigmatization, resilience and body image	Society and partner/peer stigmatization; high or low resilience; poor body image due to surgery	Stigmatization may lead to isolation, depression, and poor outcomes; resilience should be strengthened for preventing poor outcomes and improving body image
Comorbidity or multimorbidity	Copresence of other acute and/or chronic conditions	Multimorbidity deeply affects therapeutic choices, the risk of adverse events, prognosis; osteoporosis may worsen due to treatments
Frailty and mental health	Frail *versus* non-frail individuals; cognitive impairment, psychiatric illnesses	Frailty and cognitive impairment as a barrier for treatments; reactive depression and anxiety may increase the risk of poor outcomes
Non-biological		
Environmental	Difficult access to healthcare, pollution, hormones	Increased risk of breast cancer in polluted areas and patients exposed to female sex hormones
Socioeconomic	Low income, lack of health insurance, need for a caregiver, living alone	Poor socioeconomic status and living alone are associated with worse prognosis
Cultural	Level of education, language barriers, ethnic minority	Diagnostic delay may be caused by low level of education and other cultural barriers
Behavioural	Smoking, alcohol, addictions, lack of physical activity, unhealthy diet, non-adherence to medications and health screening programmes	Smoking, alcohol abuse and high-fat diet are associated with increased risk of breast cancer and its complications; screening programmes reduce mortality

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