Editorial Commentary

Breast Cancer, Age, and Hypertension
A Complex Issue

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It has been estimated that 124 cases of breast cancer occur annually per 100,000 women in the United States alone, and 23.5 of 100,000 die every year despite the advances in therapeutic options that took place over the past decades. The absolute estimates for 2011 show 230,480 new cases, with 39,520 unexpected fatal cases.1 This establishes breast cancer as the most frequent malignancy and at the same time the second leading cause of cancer mortality in women.

The risk of fatal outcome in women treated for breast cancer is related to cancer biology, which determines the choice of and response to therapy, as well as to comorbid conditions and age. Age plays a special role in epidemiological considerations because it is regarded to be the strongest predictor of both morbidity and mortality in both sexes, irrespective of baseline medical status. However, ways by which ageing affects prognosis in a patient diagnosed with breast cancer have not yet been fully elucidated.

Hypertension is the most important modifiable risk factor for vascular events. According to the World Health Organization, it is the top leading cause of death in all societies, irrespective of level of income. Hypertension has been found to lead to accelerated senescence of the cardiovascular system, a notion confirmed by observations from hypertensive animals of an increased turnover of cells, and reduced half-life of DNA, accompanied by the presence of shorter telomere fragments in kidneys of spontaneously hypertensive rats.2 On the other hand, prevalence of hypertension implies that a large proportion of cancer patients, especially those at older ages, have essential hypertension at the time of diagnosis of cancer.

Antihypertensive Medications and Cancer

Over the past 2 decades, a heated discussion was fueled by reports linking particular classes of antihypertensive medica-
tions to increased incidence of cancer. Early reports zeroed in on dihydropyridine calcium channel blockers, the more recent ones on angiotensin II receptor antagonists. However, in neither case did careful examination of available evidence lend support to the notion that antihypertensive medications could be associated with clinically important increase in risk of cancer.3 On the other hand, some data coming from recent observational studies show that for some specific cancer types (ie, urinary bladder cancer), treated hypertensive patients and normotensive subjects have similar risk, whereas untreated hypertensive patients tend to have significantly lower risk of cancer.4 A large observational study showed the possibility of increased risk of breast cancer in women treated for hypertension.5 The possible explanation of both findings may rest on the fact that untreated hypertensives have higher generation of reactive oxygen species (ROS), when compared with treated hypertensive patients or normotensive subjects.6 The greater level of ROS generation may, in turn, promote apoptosis of cancer cells, at least at early stages of hypertensive disease.5 It is, however, likely that longer-standing disease through advanced cellular senescence might have cancer promoting effects, making it difficult at the moment to disentangle marginal effects of medications and the disease per se on risk of cancer.2,5,6 This is supported by a recent observation that indicated that disulphiram, a compound used for treatment of alcoholism, can induce ROS generation in breast cancer cells and promote their apoptosis.7 On the contrary, antihypertensive medications decrease ROS generation. Our own observation lent support to this by showing that hypertensive patients treated with diuretics have increased ferric-reducing ability of plasma.8 This has potentially beneficial effects on the cardiovascular system, but, in view of the abovementioned data, might, to an as-yet unknown degree, impede the apoptotic mechanisms that guard against development of cancer.

Hypertension as a Mediator of Age-Related Risk

Seen in this context, the finding published in this issue of Hypertension by Jung et al10 that hypertension mediates the age-related disparity in survival of patients with metastatic breast cancer gains special importance. Briefly, between 1999 and 2008, the authors followed vital status of 553 women (median survival of 3.3 years) with metastatic breast cancer. By the end of the study, 47.9% patients were still alive. Patients aged >51 years had 43% greater risk of death (95% confidence interval, 11–84) as compared with their younger counterparts. The presence of hypertension (47 of 223 patients aged ≤51 years and 190 of 330 aged >51 years) influenced survival adversely, rendering risk of death 45%
(95% confidence interval, 12–89) greater in those affected with it, even after adjustment for age and other important factors. The effect of age on survival was no longer significant after adjustment for hypertension or hypertension-augmented Charlson comorbidity score (hCCS). hCCS or hypertension were strong predictors of age-survival relationship among metastatic breast cancer patients, explaining survival disparity between younger and older patients by 44% and 40%, respectively. The findings by Jung et al provide evidence that hypertension hurts rather than protects patients affected with malignancy.

The authors could further their research by performing analyses concentrating on causes of death (cancer versus vascular) and the occurrence of any nonfatal vascular events during follow-up. Another issue of potential interest would be to look at data regarding the type, age group distribution, duration, and efficacy of antihypertensive therapy in 237 (42.9% of the entire group) hypertensive women. This is important in view of possible confounding between hypertension, antihypertensive medications, and risk of mortality due to cancer and cardiovascular events. Third, an analysis related to type of adjuvant anticancer therapeutics used would be of interest as well.

The authors are justified in concluding that omission of hypertension in CCS imposes a limitation on its use. Hypertension, through the cellular senescence it induces and through its age dependence, shares at least some pathophysiologic features with cancer and ageing. This establishes hypertension as a possible mediator of risk of shorter survival in older patients with metastatic breast cancer. It is of note that Jung et al base their findings on a population with low comorbidity on average. One is left to speculate that in patients with greater overall level of comorbidity, weight of 1 assigned to hypertension would not affect the overall index sufficiently, and thus the prognostic information of hypertension would be obtunded by overall poor status of the patient and greater weights assigned to such phenomena as complicated diabetes mellitus and renal disease (each assigned the weight of 2) or advanced liver disease (weight of 3). Similarly, in patients with types of cancer other than metastatic breast cancer, especially those with short expected survival times imposed by the malignancy, long-term effects of hypertension might not reveal themselves. Even with these reservations, the authors justly conclude that hypertension should be included in comorbidity information on breast cancer patients and that such information should be used to plan supportive strategies.

Breast Cancer Adjuvant Therapy and Hypertension: Practical Implications
The previously mentioned issue of anticancer adjuvant therapies assumes special importance in the context of Jung et al’s findings. Ever since the introduction of both radiation and chemotherapy to deal with remnant breast cancer cells, it was clear that such regimens have high potential to damage cardiovascular system, both in short and long term. Highly dependent on the particular mode of action, the damage may range from venous thromboembolism (tamoxifen), through direct cytotoxic effects on heart (most agents with an exception of endocrine therapy, ie, tamoxifen), and stimulation of hypertension (mostly alkylating agents and inhibitors of angiogenesis, ie, bevacizumab). As described by Jones et al in their multiple hit hypothesis, at early stages of breast cancer, the combination of an insult by aggressive anticancer regimens and impact of accumulated cardiovascular risk factors is responsible for the winding up of a vicious circle of vascular damage. Fortunately, interventions aiming at fighting cardiovascular risk factors (including hypertension) have been found to be on the whole effective in conferring protection to the patient. Both medications (such as angiotensin-converting enzyme inhibitors) and exercise were found at least partially to revert toxic effects of breast cancer adjuvant chemotherapy on the heart and vessels, thus making it possible for the patient to continue with the anticancer regimen. The finding by Jung et al indicates that hypertension is a risk factor for age-related shortening of survival of metastatic breast cancer patients, and thus the logical approach is to treat hypertension in accordance to current practice guidelines. However, further research is needed to check whether the abovementioned risk is completely reversible on antihypertensive therapy, and whether risk reduction is linked with blood pressure lowering per se.

Take-Home Message
The importance of findings by Jung et al rests on showing that in patients with metastatic breast cancer, hypertension affects survival, just as it does in the general population, and that it serves as mediator of age-related decrease of survival times. Although hypertension-augmented CCS may not reflect that risk sufficiently in populations with a high level of comorbidity or in populations where the principal pathology imposes short survival, it seems to be a useful predictive tool in patients with metastatic breast cancer and possibly other malignancies with longer expected survival times. Due cardiovascular vigilance is warranted in the course of anticancer adjuvant therapy of breast cancer, with home blood pressure measurement and planned follow-up assessment of cardiovascular status. Prompt initiation of therapeutic measures based on current guidelines is likely to reduce further morbidity and mortality in patients in whom breast cancer concurs with hypertension. These therapies should consist of both lifestyle modifications and adequate use of antihypertensive medications. Further research into pathophysiology of the cancer-hypertension-age triad is needed to open new options for even more adequate prevention and therapy.

Disclosures
None.

References


