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Enhanced surgery-induced angiogenesis among premenopausal women might partially explain excess breast cancer mortality of blacks compared to whites: An hypothesis

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Abstract There is excess breast cancer mortality for African-Americans (AA) compared to European-Americans (EA) of 1.5–2.2 fold that first appeared in 1970s and has been worsening since. This disparity may not be explained solely by reduced access to medical care. We proposed that surgery to remove a primary tumor induces angiogenesis of distant dormant micrometastases in 20% of premenopausal node-positive patients. This hypothesis helps explain the reduced benefit of mammography for women aged 40–49. Interestingly, for AA the average age at diagnosis is 46 while for EA it is 57. The resultant increased proportion of AA premenopausal breast cancer suggests a possible explanation for the AA/EA excess mortality. Early detection, which began in the 1970s, is more effective in postmenopausal women than in premenopausal women. Since AA breast cancer is mostly premenopausal and EA breast cancer is mostly postmenopausal, it might be anticipated that starting in the 1970s because of surgery-induced early mortality, outcome would be superior for EA compared to AA.

Introduction

Analysis of a mature breast cancer database of 1173 early stage patients led us to propose that surgery to remove a primary tumor can result in acceleration of metastasis development by inducing proliferation of quiescent single

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tumor cells and angiogenesis of dormant micrometastases. The latter phenomenon is clinically significant in approximately 20% of premenopausal women with node-positive disease.[1–3] This proposed surgery-induced angiogenesis is associated with node positive patients compared to node negative patients by a ratio of 5:1 and premenopausal patients compared to postmenopausal patients by a ratio of 2:1.

The proposed mechanisms are growth factors produced in response to wounding and also the removal of the primary, as occurs in animal models where the primary exerts homeostatic effects (e.g. by angiogenesis inhibitors). Most of these relapses occur within 10 months of surgery for patients untreated with adjuvant therapy and result in a surge in mortality at 2–3 years.

While this mechanism is well documented in experimental systems, there is not yet direct evidence that it occurs in breast cancer. However, the necessary elements of this mechanism, (1) a bimodal hazard of relapse, (2) long-term dormancy of breast cancer and (3) a transient surge of proangiogenic and growth factors post surgery, have been described in a number of other studies.[4–24]

We have reported that this surgery-induced early surge in breast cancer mortality could explain the mammography paradox, a counterintuitive excess mortality in the first 6–8 years after starting screening in randomized trials to determine the value of early detection for women aged 40–49. This effect is not apparent for women aged 50–59. In long-term follow-up, the expected advantage of early detection eventually appears in both age groups although it remains difficult to exclude the possibility that the younger cohort are benefiting by incident screening episodes once they have passed the menopause. According to our calculations, surgery-induced angiogenesis would produce 0.1 deaths per 1000 young women 2–3 years after the start of screening. Both the magnitude and timing of the early mortality surge agree with data from randomized clinical trials conducted in several countries and over some decades of time.

Suggestions about the racial connection

This information was presented in the September 2005 issue of the *International Journal of Surgery*[25] and triggered several letters to the editor. Two of these letters have caused us to investigate whether this effect might also have relevance to the reported difference in breast cancer outcome for black women compared to white women. That is the subject of this hypothesis essay.

A letter from one of us (I.G.), a clinician treating breast cancer in Africa, pointed out that surgery-induced angiogenesis might explain the very high early mortality and also the generally poor outcome of patients in that part of the world.[26] Also noted was that African patients typically present to clinics in their early 40s, and a high percentage have node-positive status and locally advanced disease. It is common for an African woman to first seek alternative treatment after detecting a lump due to fears of ''provoking'' the tumor. Often after palliative surgery and chemotherapy there is unexplained very rapid disease progression.[27,28]

The other letter that focused our attention was from an African-American (AA) attorney who informed us that it is a commonly held belief by AA women that ''cancer spreads when the air hits it'' or words to that effect.[29] This attorney suggested that what we described might provide a scientific explanation for that belief.

The ''cancer spreads when the air hits it'' notion is believed by 61% of AA and 29% of European Americans (EA).[30] It has some similarity to the ''provoking'' that African women associate with conventional treatment. The ''air hits it'' myth is frequently dismissed as a superstitious fable with no scientific foundation and also has been associated with belief systems of persons of ''low socioeconomic status''.[31]

Myths seldom lack any connection with reality. Could it be that AA believe in the myth twice as frequently as EA because they observe it twice as often? Is it possible that the effect we found in the all-white (Milan) database is amplified somehow in AA and especially Africans?

Data from epidemiology

Anderson, Jatoi and colleagues[32,33] have studied the subject of the AA excess mortality compared to EA. There is a mortality disadvantage of 1.5–2.2 fold that first appeared in US Surveillance Epidemiology and End Results (SEER) data in the mid 1970s and has been widening since.[32–36] As mammographic early detection first started in the mid 1970s and has been more and more widely used since then, researchers suggested a connection between the two events.

An initial hypothesis was that the mortality disparity was explainable based on a two-tiered access to medical care in the US. This hypothesis was tested by analyzing the racial disparity within the US Department of Defense (DoD), where everyone including spouses has equal access to free medical care. Two papers published in 2003 examined this and came to different conclusions. One paper said equal access to early detection would eliminate the mortality difference[36] and the other reported that racial disparity in mortality has been widening even in the DoD system,[33] so one cannot easily dismiss the problem as reduced access to medical care. Other biology-based factors should be investigated.

Interestingly, epidemiological data show that at less than age 57, AA have higher mortality from breast cancer compared to EA, but over age 57, that relationship is actually reversed.[32] Moreover, it is important to observe that the age that breast cancer is diagnosed differs between AA and EA women. For AA, the average age of presentation is 46 while it is 57 for EA. So AA breast cancer is mainly premenopausal while EA breast cancer is mainly postmenopausal. Other ethnicities also have different peak incidental ages. For US Hispanics, the average age of presentation is 50 years.[36] As mentioned, in Africa the median age is the early 40s. For Jordanian women, the average age is the middle 40s.[37] There is a wide range among Asian-Americans. Filipino- and Hawaiian-American women most frequently are diagnosed between age 21 and 49 while Japanese- and Chinese-American women are most frequently diagnosed age 50–59 and 60–69, respectively.[38] This information is listed in Table 1.

Table 1 The age at which breast cancer is diagnosed varies among the various racial and ethnic groups as indicated

Racial/Ethnic group	Age at which breast cancer is diagnosed
European-Americans	Average: 57 years
African-Americans	Average: 46 years
Africans (Nigeria)	Average: early 40s
Hispanic-Americans	Average: 40s
Jordanians	Average: 50 years
Hawaiian-Americans	Mode:21—49 years
Filipinos	Mode:21—49 years
Chinese-Americans	Mode: 50—59 years
Japanese-Americans	Mode: 60—69 years

These data have been reported in slightly different formats.

Hypothesis

In the light of our findings, we suggest a possible partial explanation of the racial disparity as follows. Since early detection is apparently more effective in postmenopausal women than in premenopausal women and AA breast cancer is basically premenopausal while EA breast cancer is postmenopausal, it may be expected that starting in the 1970s, mortality will be superior for EA compared to AA. This would mean that early detection protocols, which were tested and optimized mainly on white women both in the US and Europe (most trials were in Sweden), may be suboptimal for AA women among others and especially for African women.

We do not intend to oversimplify this subject, but it seems clear to us that at least part of the phenomenon of widening mortality difference between AA and EA in the United States can be explained on the assumption of surgery-induced metastasis acceleration (mainly the angiogenesis-driven acceleration) for premenopausal node-positive breast cancer patients. This also might provide a partial explanation of why breast cancer outcome in Africa is so often unfavorable.

Moreover, it should also be considered that breast cancer is influenced by the hormone milieu of the host woman, mainly in premenopause. Indeed, breast cancer sex hormone receptor-content that is a main factor predicting outcome, varies during each menstrual cycle[39] as does vascular endothelial growth factor (VEGF) content.[40] Differences between AA and EA women have been reported. Luteal phase estradiol levels are higher in AA women than in EA women.[41,42] AA women undergo menarche earlier than EA women.[43] AA also tend to cycle more rapidly than their Caucasian counterparts.[44] Each of these differences in the cycle and its hormones could contribute to outcome differences, especially since it is reported that the outcome of premenopausal breast cancer also depends upon the hormonal milieu as reflected by the menstrual cycle phase at the time of its resection.[45]

Suggested tests of hypothesis

The most obvious test of the hypothesis would be a direct investigation of the mortality pattern following the ex novo introduction of mammography screening in a not previously screened mixed population. The comparison of mortality rates among the four subsets (black—no mammography; white—no mammography; black—mammography; white—mammography) would provide the most persuasive answer to the question.

Lacking this direct (and unrealistic) comparison, we should pursue some less direct clues. As the main factor resulting in early recurrence and death for premenopausal patients is proposed to be the angiogenesis switch of avascular micrometastases, according to the hypothesis, we suggest to focus tests keying upon this biology. Three research areas could be investigated: microvessel density, angiogenesis inhibition, and genetic polymorphism.

Microvessel density

Angiogenesis assessment in invasive breast cancer formalin-fixed paraffin-embedded specimens to study microvessel densities using monoclonal antibodies to CD31, CD34 and human factor VIII related antigen (FVIIIRAg) have been found to be significantly associated with patient survival ($P = 0.008$, $P = 0.0014$ and $P = 0.007$, respectively).[46] The level of neovascularization in a tumor depends on the net effect of total angiogenic stimulation and inhibition occurring in a tumor and other nonangiogenic factors like oxygen and nutrient consumption rate of the tumor cells.[47] Surgery may disturb this balance by removing the source of angiogenic inhibition. Therefore microvessel density counting with CD31/CD34 staining could be done in both patients who have had biopsies and are coming for definitive surgery and in patients whose tumors have recurred or relapsed (to compare these with previous excision biopsies). Cross-racial comparisons of micro-vessel densities in breast cancers resected from premenopausal AA and EA node-positive women should be done. Also, animal experiments with and without the administration of preoperative antiangiogenic agents and assessing microvessel density on the final pathology may be carried out. This will give more histological tissue for microvessel density assessment than is possible with core biopsies in patients. We could correlate this with recurrence and survival of the laboratory animal.

Angiogenesis inhibition

The expressions of angiogenesis inhibitors like thrombospondin-1[48] in a serial fashion before and after surgery could be done, to see if surgery really has an effect on their levels. One shall then compare the magnitude of such an effect in premenopausal/postmenopausal and black/white women and relate this to survival and recurrence. It might be useful to relate findings to the histopathologic and microvascular pattern of the initial tumor to see if different tumor types have different potentials for angiogenic inhibition.

Genetic polymorphism

Genetic polymorphism relating to genes controlling angiogenesis may be associated with differential effects on tumor progression and patient survival.[17] For example,

Andreassen et al. reported that genetic polymorphism in transforming growth factor beta 1(TGFB1) was associated with differential tissue sensitivity to radiotherapy,[49] and Carey et al.[50] reported that a basal-like subtype invasive breast cancer is more prominent in AA than EA. We could compare specific angiogenesis related genotypes in the different ethnic populations and survival following surgery for breast cancer.

Concluding remarks

In conclusion, we suggest that the observed race-related changes in breast cancer mortality may, in part, stem from screening and subsequent resection of poor-prognosis breast cancers among AA premenopausal women, which negatively impacts the host cancer balance in a subset of these women. The mammography screening introduction should be considered as a probe revealing biologic features of the host—disease balance in AA and EA, as reflected by the change in mortality dynamics. This conceptual approach is analogous to using CMF adjuvant chemotherapy given after resection as a probe to study the postsurgical recurrence dynamics, which provide information about the underlying structure of the recurrence pattern of patients undergoing surgery alone.[51]

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Conflict of interest
None.

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