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A Guideline-Created Unfreedom for Women with Breast Cancer

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Abstract

Paul Farmer has used the term "structural violence" to describe offenses against human dignity and restrictions that increase human suffering and death. Amartya Sen talks of such conditions as "unfreedoms": institutional structures that push some into the abyss. While clinical practice guidelines are an institutional structure commonly considered constructive in facilitating high quality and equitable care, review suggests that for one large group of women with breast cancer the opposite is true—the specific guidelines create an "unfreedom."

Keywords: Treatment guidelines; Breast cancer; Equity; Oophorectomy

The clinical practice guidelines of three major cancer organizations strongly influence global medical practice. Their current guidelines for the systemic treatment of hormone-sensitive breast cancer in pre-menopausal women, which promote a drug regimen that is unaffordable and impractical for most women in the world needing treatment, are an example of structural violence in cancer medicine. In recommending drug use over widely-available ovary-removal surgery, which is at least equivalent in efficacy and is a higher-quality treatment, the guidelines constrain agency and contribute to 100,000 women's deaths globally each year. By ignoring the important roles that poverty, human rights, education, and corrupt governance play in the practice of clinical medicine, these guidelines create a sanctioned "unfreedom."

Everyone has the right "to share in scientific advancement and its benefits". Universal Declaration of Human Rights. Article 27.

"It may be difficult for us to imagine how restricted a life so many of our fellow human beings lead". Amartya Sen (1, p.xi)

In "Pathologies of Power," his plea for health care as a human right, Paul Farmer uses specific patient examples to show how "the right to survive is trampled in an age of great affluence," and to provide greater understanding of the complex realities of clinical medicine and of "our tolerance of societal abominations" [1]. Farmer has used the term "structural violence" to describe offenses against human dignity and restrictions that increase human suffering and death. As Farmer writes, Amartya Sen talks of such conditions as "unfreedoms": institutional structures that push some into the abyss [1]. From his extensive field experiences with lethal communicable diseases, Farmer has borne witness to the difficult social and economic challenges that most patients with serious medical conditions face in the world. His focus has been more on circumstances in low- and middle-income countries than on examples of pathologies of power in high-income countries. Such examples are, however, becoming more painfully frequent, particularly around rapidly rising costs of generic pharmaceutical drugs. This communication explores the consequences for poor women everywhere of one specific clinical practice guideline from three major high-income country cancer organizations, and possible explanations for the guidelines' narrow focus.

New Data Show that an Old Treatment is of the Highest Quality

Surgical oophorectomy as a breast cancer treatment in pre-menopausal women was first used by Beatson over a century ago, and was only pushed aside when short-term and reversible treatment with luteinizing hormone-releasing-hormone (LHRH) agonist drugs (which suppress ovarian function) became possible around 1990. During the 1990s, however, clinical trial data were developed for the sub-group of patients benefiting from hormonal therapies—that is patients with hormone sensitive tumors--showing that at least 5 years of LHRH treatment was optimal. Through this period to the present, LHRH drugs plus tamoxifen or surgical oophorectomy plus tamoxifen have been considered equivalently effective additional (adjuvant) treatments in women with operable breast cancer [2-6]. Five years of treatment with these approaches are associated with a 33% increase in survival after ten years [7].

Recently, new data in both adjuvant and metastatic studies have suggested that the efficacy of surgical oophorectomy is very low in women found, on the days of their surgery, to be in prolonged follicular phases of their cycles (beyond 14 days), with low progesterone levels [8,9]. If this sub-group of women is excluded, then for all other women greater benefits can be expected than have been reported for this intervention.

Further, new data also show that the bone mineral density (BMD) safety profile of surgical oophorectomy plus tamoxifen is better than that of all other adjuvant treatments, where continuous bone loss is seen in all sites [10]. Specifically, with this treatment over 2 years, no loss of BMD at all in the hip was observed, while modest loss of BMD in the lumbo-sacral spine was seen in the first year only [10]. Loss of BMD is usually treated with bisphosphonate medicines, which are expensive and are toxic for women with poor oral hygiene.

In most of the world, surgical care, including surgical oophorectomy, can be safely provided for all patients in need through free public health mechanisms. In contrast, costs for drugs are out-of-pocket for most women in the world. LHRH drugs cost an average of $150 a month in low- and middle-income countries and many more times this figure in high-income countries; everywhere there are also administrative and indirect treatment costs.

In these circumstances, surgical oophorectomy plus tamoxifen is a better treatment for women everywhere because on multiple measures of quality it compares very favorably with LHRH plus tamoxifen treatment [11,12]. Globally, there are approximately 500,000 annual new cases of hormone-sensitive breast cancer in pre-menopausal women; 400,000 of these cases are among women in low- and middle-income countries (LMIC). Among these women after 10 years, half survive with surgery alone, while over 80% survive with surgery and optimal hormonal adjuvant therapy (7). In LMIC the overwhelming majority of these women receive no or limited and relatively ineffective adjuvant therapy, because it is unaffordable or impractical for them. Thus, instead of 320,000 LMIC women surviving 10 years, perhaps 220,000 live this long, and 100,000 unnecessary deaths occur.

A Treatment Unfreedom for Premenopausal Women with Hormone Sensitive Breast Cancer Everywhere

Clinical practice guidelines from high-income countries are believed to play major roles in promoting high-quality, evidence-

based care. As a consequence, practitioners worldwide look to such statements from respected organizations for guidance in their treatment choices. There are statements from three organizations that pertain to the question of adjuvant hormonal treatment for premenopausal women with hormone sensitive breast cancer, in particular relative to the place of surgical oophorectomy plus tamoxifen as a treatment option. In the update of the guideline from the American Society of Clinical Oncology (ASCO), ovarian ablation (including surgical oophorectomy) is completely omitted from the text and the guideline altogether [13]. In the guidelines from the European Society of Medical Oncology (ESMO), there is lack of clarity about the place of surgical oophorectomy, which is but cursorily mentioned and not discussed; clearly LHRH + tamoxifen treatment is favored [14]. In the widely-cited NCCN clinical practice guidelines, surgical oophorectomy is listed but not discussed [15]. The ASCO guideline and other statements by this organization make clear that its "guidelines are developed for implementation across health settings" [13,16]. Farmer suggests that such language needs to be followed by a clause: "By the way, we *really* mean everybody" [1]. In summary, three major breast cancer treatment guidelines now omit, or make but passing reference to, surgical oophorectomy plus tamoxifen as a major, equitable treatment option for women, despite organizational statements of commitments to cost-effectiveness and global cancer victims [13]. These guidelines and statements, all limiting choice, constitute structural violence against women globally who need affordable treatment. Not promoting a very effective treatment most women in the world can actually receive, and promoting only an expensive drug approach, perpetrates an act which can be fairly called an unfreedom. These actions are occurring in the face of calls from the Institute of Medicine (IOM) for equity in medical care: "The quality of medical care must be consistent across all patients, irrespective of gender, ethnicity, socio-economic status and other personal characteristics" [17]. In these contexts, laments about the poorer outcomes for breast cancer in low- and middle- income countries deserve the Pogo admonition: "We have met the enemy and he is us" [18].

Dissecting the Circumstances of the Creation of this "Unfreedom"

Guideline content

Guideline creation processes clearly focus on efficacy. In scientific and associated lay press reports, we often see a statistically significant but small increase in efficacy touted despite its uncertain or very limited clinical significance. The efficacy focus offers a narrow perspective on the impact of a treatment and ignores other metrics assessed as important by the IOM [17]. As an example, the ASCO guideline almost dismissively lists harms from ovarian suppression in parentheses, and the consequences of these are never discussed—e.g., the bone loss associated with these treatments which mandate another costly pharmaceutical intervention--bisphosphonates [13]. Organizationally, ASCO has clearly expressed resistance to an approach using multiple metrics [16]. In this regard, ASCO is out of step with IOM thorough consideration of safety issues (like BMD toxicity), patient-centered care, timeliness, value, and equity [17]. Further, this ASCO guideline, in now omitting mention of ovarian ablation altogether, is inconsistent with other organizational values [12]. It is important here to not confound separate issues—Surgical oophorectomy plus tamoxifen as an appropriate first option for women everywhere, based on efficacy and multiple metrics; Surgical oophorectomy plus tamoxifen as an equitable intervention because it is attainable worldwide; and surgical oophorectomy plus tamoxifen as a particularly high-value intervention which is important in low- and middle-income counties, but realistically, important everywhere.

Understanding the Practice of Medicine in Low- and Middle-Income Countries (LMIC)

In discussions of cancer care globally, there appears to be a genuine lack of awareness of circumstances in LMICs and the impact of high-income country guidelines, along with slighting of the important roles that poverty, human rights, education, the absence of responsible governance, and corruption play in the practice of clinical medicine, resulting in equity-insensitive, out-of-touch recommendations. There has been an initiative that resource-based guidelines are an appropriate approach to assisting LMIC [15,19]. This idea is based on perceptions of benefits from National Cancer Control Plans—a top-down approach to achieving change in medical practice [20]. Interestingly, such a widely-promoted approach has not been operative in high-income countries, where guidelines have come from professional organizations, not governments. To whom are such resource-based guidelines directed? Do authors perceive that governments will somehow mandate following such guidelines? Separate from serious concerns that such efforts are naïve about how medicine is practiced and how social change in medicine occurs globally, one can say that these efforts are clearly works in progress--the NCCN presentation in alternately bold and light print is confusing, the choices they posit are not justified, and discussion is absent [15]. For example, the NCCN resource-based guidelines (authored without a single member from LMIC) suggest oophorectomy alone without consideration of the benefits (such as bone mineral density preservation) of combined hormonal therapies (ovarian-targeting and endocrine) [10,15]. Does NCCN really wish to suggest, indeed promote, a double standard of care? In addressing cancer care in LMIC, we need much bigger and broader thinking that reflects deeper understanding of the multiple overpowering societal issues. We need i. entrepreneurial, local, initially small, country-specific approaches; ii. institutional—hospital and medical school, and professional society community-based models; and iii. local in-country leadership--"bottom-up" efforts, all three of which are carefully evaluated [21].

Understanding Life Circumstances of Patients in LMIC

In Pathologies of Power, Farmer reluctantly bears witness with specific patient studies because of respect for the silence in which the poor often suffer, the apparent lack of effect of such stories, and his awareness that he can give but partial accounts [1]. However, my own experience over the past 25 years with women suffering from breast cancer in south and Southeast Asia has been that they willingly talk about their difficult circumstances. My sense from the often-positive reactions that readers have to Katherine Boo's comprehensive account of life in a poor slum in Mumbai is that in fact such reports are increasing awareness of the details of the lives of citizens at the bottom of the pyramid and are heightening concern with rising inequity [22].

In our adjuvant oophorectomy trial, we had several sites in the Philippines [8]. In interviewing women about their participation in the trial, the following volunteered life account was typical:

"My first husband was stabbed and killed. I have two kids with him, and when he died I peddled goods for us to survive (crying)". She goes on to tell about her child's avoidable illness and protracted hospitalization, her mother's premature death with associated loss of family income, and finally breast cancer [23].

In this trial, our experience about the important role that out-of-pocket expenses play in Filipino decisions about health care parallels that found in the IARC breast cancer screening study which was abandoned because women with breast abnormalities would not seek help out of concerns with unaffordable treatment costs [24].

These accounts were similar to those of Bangladeshis recruited to our metastatic oophorectomy trial [9]. Asked about their "late"

presentations, women volunteered that they had "no choice": their families had limited money; seeking treatment was impractical; there were never any affordable treatments available for them; they had no permission from their families to seek personal health care; and finally, their personal financial priorities were for food for their children and school uniforms and supplies for their children—most importantly for their girls. The filmmaker Saiful Huq Omi captured this dilemma in a brief documentary Moriyam's Story [25].

Conclusions

This exploration of the absence of promotion for the well-documented, high-quality surgical oophorectomy plus tamoxifen treatment for pre-menopausal women with hormone receptor positive, operable breast cancer suggests several factors are at play. Most importantly, the narrow perceptions of quality assessment in guidelines creation, the ignoring of broad organizational values, and the absence of due diligence by high-income country experts in suggesting guidelines for low- and middle-income countries perpetuate this "unfreedom" [21]. "The culture of medicine will have to be transformed" if we are to be true to our values and measurably improve outcomes for poor women with breast cancer worldwide [26].

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