History, Biology, and Health Inequities: Emergent Embodied Phenotypes and the Illustrative Case of the Breast Cancer Estrogen Receptor

How we think about biology—in historical, ecological, and societal context—matters for framing causes of and solutions to health inequities. Drawing on new insights from ecological evolutionary developmental biology and ecosocial theory, I question dominant gene-centric and ultimately static approaches to conceptualizing biology, using the example of the breast cancer estrogen receptor (ER).

Analyzed in terms of its 4 histories—societal, individual (life course), tumor (cellular pathology), and evolutionary—the ER is revealed as a flexible characteristic of cells, tumors, individuals, and populations, with magnitudes of health inequities tellingly changing over time.

This example suggests our science will likely be better served by conceptualizing disease and its biomarkers, along with changing magnitudes of health inequities, as embodied history—that is, emergent embodied phenotype, not innate biology. (*Am J Public Health.* 2013;103:22–27. doi:10.2105/AJPH.2012.300967)

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HOW WE IN PUBLIC HEALTH think about biology—in historical, ecological, and societal context—has everything to do with how we frame causes of and solutions to health inequities. The dominant paradigm for the past century has placed genes and gene frequency at the center of biological phenomena, including disease and disease rates.[1–5] Reflecting this orientation, funding priorities for the US National Institutes of Health (NIH) emphasize genomics,[6,7] even for social inequalities in health. For example, within the 46 pages on "Minority Health and Health Disparities" allotted in the NIH's most recent biennial 732-page report to the US Congress, the terms "genome," "genomic," "genetic," and "gene" appear 87 times, whereas "social determinants of health" and "discrimination" each occur once, "socioeconomic" 7 times, "poverty" twice, and "racism" not at all.[6]

During the past 2 decades, however, a fast-emerging body of biological research has been challenging the dominant gene-centric paradigm, which emphasizes that genome composition is determined at conception, by providing robust novel evidence that nothing in biology makes sense except in the light of history[8]: evolutionary, developmental, ecological, and societal.[1–4,9–14] Termed "ecological evolutionary developmental biology" (or "eco-evo-devo"),[1] a central thesis, building on ideas of norms of reaction,[1–4,9,10] is that "the same genotype can generate different phenotypes depending on what cues are present in the environment"[1(p10)]—hence, "bodies express ecology."[9(p3)] Providing novel evidence that environments not only "select" (or filter) variation but also construct it,[1–4,9,10] well-known "textbook" nonhuman illustrations of developmental plasticity in embryos and phenotypic flexibility in adults range from temperature-dependent sex determination in turtles[1,2,10] to socially induced sex change in adult fish[1,2,15] to massive changes in adult migratory birds' gizzard size and muscle type depending on where they are in the course of their migratory cycle.[9] Among humans, one salient example is the differential adult health status exhibited by identical twins reared together but whose social class trajectories in adult life diverge.[16]

What relevance, if any, might this broader, more historical and more dynamic framing of biology—only just now making headway into the public health literature[1,5,11–13]—have for understanding and addressing health inequities? To foster discussion and debate, I consider the illustrative case of the breast cancer estrogen receptor (ER), selected because it offers a useful example for thinking through issues of history, biology, and health inequities more generally (see the box on the next page).

In brief, the breast cancer ER is a biological trait of critical clinical and public health importance, since women (and men) whose breast tumors are ER positive can be treated with antiestrogenic drugs (e.g., tamoxifen and raloxifene), and hence have better survival than patients whose tumors are ER negative.[17–19] Of note, ER is not exclusive to breast tissue. Present in people and other vertebrates, it is a steroid receptor, chiefly located in the nucleus but also in cell membranes. In its 2 different forms, ERα and ERβ, it is centrally involved in regulation of cell growth and cell death (apoptosis) throughout the body, including the reproductive, immune, skeletal, cardiovascular, and central nervous systems.[19–22] A defining feature is that ER, like any steroid receptor, has the dual ability to bind to DNA regulatory elements while at the same time its own activity is modulated by substances that attach to it (i.e., ligands).[20–22]

Drawing on the ecosocial theory of disease distribution and its focus on how we literally embody, biologically, our societal and ecological context,[5,23,24] I systematically address the 4 histories of the breast cancer ER: societal, individual, pathological, and evolutionary. The evidence reviewed suggests that our science will likely be better served by conceptualizing the breast cancer ER—and by implication, other biomarkers and health outcomes—as "emergent embodied phenotypes" (see the box on the next page), in contrast to prevailing frameworks that treat biological traits as the deterministic readout of a genetic "program."[1–4,9,10]

CONVENTIONAL VIEWS OF THE BREAST CANCER ESTROGEN RECEPTOR

Most studies on breast cancer ER status, like other mainstream

Four Sets of Historically Informed Questions to Ask When Investigating Embodied Health and Disease Biomarkers and Outcomes, as Framed by the Construct of "Emergent Embodied Phenotype"

Question 1: Societal history. What data exist on historical trends in the average population rates of—and health inequities in—the embodied biomarker or outcome? (For example, between and within countries and regions, defined geopolitically and in relation to societal divisions involving property, power, resources, and discrimination, including socioeconomic position, race/ethnicity, indigenous status, gender, sexuality, disability, nativity, and immigrant status.)

Question 2: Individual (life course) history. What is the "natural"—and "unnatural"—history of the embodied biomarker or outcome across a person's life course? Does its expression change over time for a given course of illness, or across repeat bouts of an illness? Does its expression vary by the societal groups considered in Question 1 (i.e., display health inequities)?

Question 3: Pathological/cellular history. What is the "natural"—and "unnatural"—history of the embodied biomarker analyzed at the level of the tissue(s) involved? Does its expression change over the course of the disease? Or vary by the societal groups considered in Question 1 (i.e., display health inequities)?

Question 4: Evolutionary history. What is known—and debated—about the evolutionary history of the embodied biomarker or outcome under analysis? What insight does this history provide regarding the likely dynamics of expression, within and across individuals, historical generations, and societal groups?

research on risk factors for disease,[5] typically investigate risk factors for breast cancer ER status ahistorically, as if it were a fixed trait of tumors.[17,18,25–28] Identified risk factors for ER-positive tumors are late age at menarche, delayed age at first birth, higher parity, breastfeeding, postmenopausal obesity, and use of hormone therapy (estrogen plus progestin); for ER-negative tumors, they are premenopausal or younger age at diagnosis and being a carrier for *BRCA1* (a harmful mutation of breast cancer susceptibility gene 1).[17,25–28] In US research especially (but not exclusively), "race" is also listed, whereby ER-positive tumors are stated to occur more frequently among White women of European ancestry than among women of African and Asian descent, differences typically inferred to be genetically driven.[26–28] Underpinning such inferences is the longstanding but erroneous belief[5,29,30] that humanity can be divided into biologically discrete races—a stance still explicitly argued by some scientists,[31,32] but not supported by contemporary evidence.[33–35] Also emphasized in the global literature[26,27,36] (albeit based on scanty data[37,38]) is the on-average younger age at diagnosis (associated with more aggressive, ER-negative disease) among women in developing as compared with developed countries. Another claim, expressed in various reviews, is that "populations with a low SES [socioeconomic status] are more likely to develop an ER-negative disease than populations with a high SES."[26(p1113)]

Does, however, an historically informed analysis support these assertions and their underlying causal premises?

USING 4 HISTORIES TO QUESTION THE STATUS QUO

Four different types of history challenge conventional accounts of the epidemiology of the breast cancer ER: societal, life course, pathological, and evolutionary. I consider these 4 dynamic aspects of history in turn, each of which is integral to the history of every breast tumor.

History 1: Societal Dynamics

The first history, at the societal level, concerns trends in the rates of and inequities in cause-specific mortality and morbidity. Such information has long proven critical to understanding determinants of both population health and health inequities,[5,39–41] even as it is often overlooked in the rush for the next latest discovery and dismissed as merely descriptive. Yet it is these data that reveal that observed disparities in ER status are historically contingent and dynamic, not fixed.

Jump back, first, to the middle-third of the 20th century, a time predating both the discovery of the ER[42] and its clinical use for guiding breast cancer treatment.[41–45] This period also precedes the widespread rise of mammographic screening[45,46] and hormone therapy.[47–49] It consequently was a time when breast cancer incidence and mortality rates more closely paralleled each other, compared with their divergence now because of changes in both screening and treatment.[45,50] As shown in Table 1, contrary to current findings, in 1931, premenopausal mortality rates (indicative of early onset disease, more likely to be ER negative) were lower (and with a less steep age-related increase) among UK women married to men in working-class occupations than among those whose husbands had professional occupations; by 1971, however, these rates were nearly equivalent.[51] Similarly, in the United States, premenopausal mortality rates in 1930 were virtually the same for White women and women of color,[52] a pattern that continued well in the 1960s.[50] Moreover, in both countries in the 1930s, the proportion of breast cancer deaths among women younger than 50 years was far higher than that observed today[50–52] (as would be expected, given shorter life expectancy[53]). Although such data must be interpreted cautiously, given possible misclassification (likely differential) of cause of and age at death, social class, and race/ethnicity, the most likely bias involves census undercount of more impoverished persons and persons of color, thereby shrinking their denominators.[50,54] Hence, the data in Table 1, if anything, present an inflated estimate of risk among women subject to social adversity—suggesting even less resemblance to contemporary patterns.

Further challenging ahistorical approaches to analyzing and interpreting racial/ethnic and social class disparities in ER status are results of a recently published study, the first to test statistically trends in the White versus Black

TABLE 1—Changing Socioeconomic and Racial/Ethnic Inequalities in Breast Cancer Mortality Among Women Aged 25 to 54 Years in the United Kingdom and the United States: Early 1930s to Early 1970s

Time Period	Social Group	Breast Cancer Mortality (Deaths/100 000 Population)		
		Premenopausal, Aged 25–34 Y	Premenopausal, Aged 35–44 Y	Perimenopausal, Aged 45–54 Y
	United Kingdom			
1931[51(p187)]	Social class I + II: women married to men in professional, managerial, and technical occupations	3.4	22.8	60.6
	Social class III: women married to men in skilled occupations	3.0	20.3	54.6
	Social class IV + V: women married to men in partly skilled and unskilled occupations	2.8	16.5	43.5
1971[51(p187)]	Social class I + II: women married to men in professional, managerial, and technical occupations	4.0	24.9	63.5
	Social class III: women married to men in skilled occupations	4.2	25.8	62.9
	Social class IV + V: women married to men in partly skilled and unskilled occupations	4.7	25.0	62.9
	United States			
1930[52]	White	2.9	18.1	45.1
	Non-White	5.3	16.2	37.3
1940[50]	White	. . .	19.2	47.5
	Non-White	. . .	21.8	47.5
1950[50]	White	. . .	20.8	47.1
	Non-White	. . .	20.8	45.3
1956–1961[52]	White	3.8	19.5	50.5
	Non-White	5.3	24.1	48.8
1965[50]	White	. . .	20.2	51.9
	Non-White	. . .	24.2	50.8

Note. For the age-specific breast cancer mortality rate among US women aged 25 to 34 years, data from on-line publications are not available for the years 1940, 1950, and 1965. Regarding racial/ethnic terms as used in the US sources, the non-White population in the United States until 1960 was overwhelmingly composed of Black Americans, who constituted 95.2% of non-Whites in 1930, 95.6% in 1940, 95.5% in 1950, 92.1% in 1960, and 88.7% 1970.[50]

odds ratio for ER-positive breast cancer, that examined US women diagnosed from 1992 through 2005 with incident invasive disease.[55] A key finding was that the age-adjusted odds ratio rose from 1992 to 2002 and then leveled off, and actually fell among women aged 50 to 69.[55] The most plausible explanation is that these results reflect the socially patterned abrupt decline in hormone therapy use following the July 2002 publication of results of the Women's Health Initiative.[47–49,56] This study found that hormone therapy did not protect against (and may have elevated) risk of cardiovascular disease; at the same time, it reconfirmed prior evidence that hormone therapy increased risk of breast cancer, and especially ER-positive breast cancer.[56] As a result, hormone therapy use dropped precipitously among the women most likely to use it: White affluent women with health insurance who were sufficiently healthy not to have any contraindications against use.[47,48,57,58] They accordingly experienced a drop in prevalence of ER-positive tumors not observed among women who did not use hormone therapy, thus reducing the White versus Black odds of ER-positive tumors.[55] Current social inequalities in ER status are precisely that: current, not invariant; the larger point is that contemporary findings should always be evaluated in light of historical trends.

History 2: Individual Dynamics

Comparing risk across historical generations provides one kind of insight; comparing risk over the course of an individual's life course—that is, individual history —offers another.[41,59] Here, the case of women with repeat occurrences of breast cancer is particularly instructive—especially because all exposures occurring prior to the first tumor are common to both tumors. Since at least the mid-1980s, studies have repeatedly documented considerable discordance in ER status, independent of treatment status, among women with repeat diagnoses of breast cancer—both tumors arising from metastases and those occurring as new primary malignancies.[60,61] For example, recent evidence from large US and international studies indicates that women whose initial primary tumor was ER positive are equally likely to have their second primary tumor be ER positive or ER negative.[60] Moreover, among women who are *BRCA1* or *BRCA2* carriers, discordance of ER status between the first and second tumor is as high as 70% for those whose initial tumor was ER positive (for *BRCA1* carriers) and as high as 48% for those whose initial tumor was ER negative (for *BRCA2* carriers).[62] The finding that new second primary tumors, and even metastatic tumors, can differ in ER expression, even among *BRCA1* and *BRCA2* carriers, underscores that ER status cannot be construed as a fixed trait of individuals.

History 3: Tumor Dynamics

Still a third history pertains to that of the tumor itself (or, more broadly, cellular pathology). At issue is the well-known concept of the "natural history" of disease,[63–65] modified by recognition that the course of disease is not simply "natural" but can vary

by individuals' societal and ecological context.[45,63–65] Additionally, like many diseases, breast cancer is not simply one disease; there are a variety of types, with heterogeneity expressed at the molecular as well as clinical and epidemiological levels of analysis.[18,19,66] Relevant to treatment and prognosis, breast tumors can be distinguished not only by such well-known clinically relevant features as whether they are positive versus negative for ER, progesterone receptor, and HER2 (human epidermal growth factor receptor 2), but also (reflecting new technological advances) by molecular subtypes based global gene expression (e.g., luminal, HER2-enriched, basal-like, and normal breast-like).[18,19,66]

Current work on clonal competition, however, clarifies that it is erroneous to assume a tumor is only of one type.[67] Instead, as increasingly emphasized in clinical oncology research, especially on drug-resistant tumors, intertumor heterogeneity—whether for ER status or at the molecular level—changes over time.[18,19,66] New experimental evidence additionally suggests that ER-negative tumors (once thought to be permanently ER negative) can be induced to reexpress ER.[17,66,68] Although the idea of tumor as "emergent phenotype" has appeared in the carcinogenesis literature for at least half a century,[66,69,70] it nevertheless is largely absent from public health research regarding etiology—which continues to treat ER status as a fixed characteristic linked to other innate individual characteristics,[25–28] rather than reflecting what the tumor predominantly happens to be when detected and biopsied. As the evidence shows, however, the history of a tumor and its constituent cells matters—not only for treatment and prognosis but also for etiologic analysis and inference.

History 4: Estrogen Receptor Evolution

Lastly, consider the contemporary relevance of the evolutionary history of the ER and other nuclear receptors,[20–22,71–76] a topic of lively investigation and debate.[73–76] New evidence amassed in the past decade indicates that nuclear receptors evolved about 635 million years ago, long before any organisms had endocrine systems, and are ubiquitous in animals but not present in fungi, plants, or choanoflagellates. This evidence further suggests that the postulated ancestral estrogen-related receptor (also referred to as the ancestral steroid receptor, AncSR1) gave rise to the vertebrate ER (which uniquely has the ability to bind estradiol) as well as orthologs found in other metazoans (e.g., mollusks, annelids, amphioxus, and hagfish). One salient leading hypothesis is that the ancestral estrogen-related receptor (for which no steroid ligand had yet evolved) initially functioned as a xenobiotic sensor, detecting substances exogenous to the organism that could be eaten or required detoxification.[73–76] Another leading hypothesis is that subsequent diversification of steroids and nuclear steroids receptors in vertebrates enabled the occurrence and control of complex physiological processes during the development and adult life of vertebrate organisms—including a hormonally regulated reproductive system, one that in mammals features the mammary glands, the very organs that give the class Mammalia its name.[20–22,73,74]

The relevance of this history to the breast cancer ER is the ER's evolved sensitivity to extracellular signals.[20–22,71–76] Thus, ER expression, far from being fixed, can change over time, repeatedly. Its expression can be altered by both shifting hormonal levels (whether endogenous, as in the case of pregnancy, or exogenous, as per exposure to hormone therapy or to xenoestrogens) and by nonhormonal exposures (e.g., involving methylation).[19–21,61,77] ER status is thus a flexible characteristic of cells; vertebrate cells' evolved capacity is to change their ER status, which consequently is contingent, not fixed. The evolutionary history of ER helps illuminate why this flexibility exists.

CONSIDERING HEALTH AND DISEASE AS EMERGENT PHENOTYPE

In conclusion, as this case of the breast cancer ER reveals, history matters—deeply, at multiple levels and time scales—to claims about disease etiology and causes of health inequities. In particular, these findings challenge static and gene-centric approaches to biology and etiology, including approaches that treat measured biomarkers as primarily reflections of innate biology and observed inequities in their distributions as fixed. A new raft of work in ecological evolutionary developmental biology is providing compelling evidence that organisms' phenotypes are emergent and flexible.[1,2,9,10] The 4 histories considered here—societal, individual, pathological, and evolutionary—and the levels they span are at play in every case and every population rate of disease; they are concurrent, not sequential. To see disease and its biomarkers, along with changing magnitudes of health inequities, as embodied history[5] (i.e., emergent phenotype, not innate biology) offers a radically different, inclusive, and promising perspective for public health and clinical medicine alike. ■

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Suicide, Guns, and Public Policy

Suicide is a serious public health concern that is responsible for almost 1 million deaths each year worldwide. It is commonly an impulsive act by a vulnerable individual. The impulsivity of suicide provides opportunities to reduce the risk of suicide by restricting access to lethal means.

In the United States, firearms, particularly handguns, are the most common means of suicide. Despite strong empirical evidence that restriction of access to firearms reduces suicides, access to firearms in the United States is generally subject to few restrictions.

Implementation and evaluation of measures such as waiting periods and permit requirements that restrict access to handguns should be a top priority for reducing deaths from impulsive suicide in the United States. (*Am J Public Health.* 2013; 103:27–31. doi:10.2105/AJPH.2012.300964)

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"Knowing is not enough; we must apply. Willing is not enough; we must do."[1a]

–Johann Wolfgang von Goethe

SUICIDE IS A COMPLEX

behavior involving the intentional termination of one's own life. The prevalence, causes, means, and prevention of suicide have been extensively studied and widely reported.[1b–4] The World Health Organization (WHO) has identified suicide as a serious public health concern that is responsible for more deaths worldwide each year than homicide and war combined,[5] with almost 1 million suicides now occurring annually. In 2007, the Centers for Disease Control and Prevention (CDC) reported that 34 598 Americans died by suicide, far more than the 18 361 murders during the same period.[6] Among Americans younger than 40 years, suicide claimed more lives (n = 13 315) than any other single cause except motor vehicle accidents (n = 23 471).[6]

Psychiatric disorders are present in at least 90% of suicide victims, but untreated in more than 80% of these at the time of death.[7] Treatment of depression and other mood disorders is therefore a central component of suicide prevention. Other factors associated with suicidal behavior include physical illness, alcohol and drug abuse, access to lethal means, and impulsivity. All of these are potentially amenable to modification or treatment if recognized and addressed. It is important to distinguish between impulsivity as a personality trait and the impulsivity of the act of suicide itself. It is not generally appreciated that suicide is often an impulsive final act by a vulnerable individual[8] who may or may not exhibit the features of an impulsive personality.[9]

The impulsivity of suicide provides opportunities to reduce suicide risk by restriction of access to lethal means of suicide ("means restriction"). Numerous medical organizations and governmental agencies, including the WHO,[5] the European Union,[10] the Department of Health in England,[11] the American College of Physicians,[12] the CDC,[4,13] and the Institute of Medicine,[14] have recommended that means restriction be included in suicide prevention strategies. In the United States, firearms are the most common means of suicide,[15] with a suicide attempt with a firearm more likely to be fatal than most other means.[16] In a study of case fatality rates in the northeastern United States, it was found that 91% of suicide attempts by firearms resulted in death.[17] By comparison, the mortality rate was 84% by drowning and 82% by hanging; poisoning with drugs accounted for 74% of acts but only 14% of fatalities. Many studies have shown that the vast majority of those who survive a suicide attempt do not go on to die by suicide. A systematic review of 90 studies following patients after an event of self-harm found