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Oestrogen receptors and breast cancer. Are we prepared to move forward? A critical review

Abstract

It is nearly 60 years since the identification of the oestrogen hormone receptor (ER) in breast cancer, a discovery that radically transformed the clinical management of the disease. Hormonal therapy with anti-oestrogens (Tamoxifen and Aromatase inhibitors) antagonise ER function and became the mainstay treatment until today. Around 70% of breast tumours are classified as oestrogen dependent, yet the mechanism of action of other hormones in breast cancer growth both independently and interacting with ER as well as their targeted therapies have yet to find a place in the clinic. In this article, I critically review the scientific literature for the period 1960-2016, examine the rise and persistence of the oestrogen hypothesis as well as the neglect of alternative hormonal explanations. By using Pierre Bourdieu's concepts of the scientific field alongside feminist science scholars to explore the impact of gendered assumptions on science, the analysis provides insight into the dominant role of the oestrogen hypothesis and the struggles for legitimation of different alternative perspectives. I consider these alternative approaches as "internal" struggles for scientific authority, which are in turn, socially determined by "external" gender values that reinforce a binary arrangement of male/female bodies based on fixed molecular hormonal traits.

Key words

breast cancer, hormone therapy, hormone receptors, gender, Bourdieu

Introduction

Contemporary hormone therapy for breast cancer is considered as "one of the most remarkable stories in cancer therapy" (Geisler and Lønning, 2005: 2809). Part of this enthusiasm can be explained by its role as adjuvant therapy after surgery (to prevent recurrence), and to extend years of life in advanced stages of the disease. About 70% of breast cancers are considered to be oestrogen hormone dependant, which places this therapy at the centre of breast cancer clinical management today. Despite its relevance in cancer treatment, its conspicuous association with the gendered hormonal body, and a large body of literature dealing with 'sex hormones', social scientists and feminist scholars alike have paid little attention to how this particular field of cancer treatment has evolved. To begin to fill this gap, in this article I conduct a critical review of the scientific literature related to hormones and breast cancer and explore the main contributions that emerged since the discovery of the oestrogen receptors in the 1960s to 2016. My focus is on how the field developed from a particular oestrogen hypothesis (oestrogen receptors) to explain tumour growth, and how this perspective came to dominate until the present. I consider alternative hypotheses that raised attention to other hormones and their mechanism of action both independently and in relation to oestrogens.

To help explain the trajectory of these developments, I use some of the sociological categories of Pierre Bourdieu, as "thinking tools" rather than a prescriptive construct as proposed by Brubaker (1993), alongside feminist science studies, in particular those that have proposed a return to the technological and scientific matter (atoms, bones, molecules, to name

a few examples) to simultaneously integrate the material, social, and cultural environment through different frameworks (Barad, 2007; Birke, 2000; Fausto-Sterling, 2017; Roy, 2018).

Bourdieu's definition of the scientific field as composed by "forces whose structure is defined by the continuous distribution of the specific capital possessed, at the given moment, by various agents or institutions" and characterised by struggles, where agents and institutions compete for scientific capital (1991: 6–7) will guide my analysis of the specific subfield, i.e. the hormone therapy field (HTF). Bourdieu's theoretical framework and the use of its key concepts (i.e. field, capital, habitus) have allowed social scientists to extend, test, and re-interpret these constructs in different areas of research. The integration of Bourdieu's field theory has however been considered problematic due to his lack of empirical application, as well as his emphasis on the autonomy of the scientific field from external determinants (Camic, 2011; Mathieu and Kleinman, 2011). Bourdieu's notions of gender, on the other hand, have been debated by feminist and gender scholars who have developed an overarching perception that gender has not been systematically analysed, nor in the social order – as hierarchical relations/binary oppositions – or in the different spaces of social life (fields). "Where gender order appears to be universally reproduced on the one hand, gender as an organizing principle remains secondary on the other" (McCall, 1992: 851).

These criticisms in particular seem both to point to Bourdieu's lack of simultaneous attention to what he described as a two-fold relationship in the production of scientific knowledge (Bourdieu, 1990, 298): the "external" factors to which he referred as "the larger social space", the "social order", the "general economic and social conditions", and on the other hand, the "internal" factors operating in the scientific field as an "autonomous world endowed with its own rules of functioning". The latter has constituted the predominant focus of Bourdieu's analysis of science, as Camic has argued, "it is to the *scientific field* that he regularly turns" (Camic, 2011, 277). In this sense, despite the proposition of the existence of

a “relative autonomy” of the scientific field, rather, Bourdieu’s concentration on the internal dynamics of the field endowed it with absolute autonomy as he provided very few clues and little detail on how external forces interact, affect or determine the internal ones. From the perspective of gender, MacCall observes, “the social order is perhaps the most elusive of Bourdieu's concepts” (1992: 839). It is assumed to become internalised as unconscious scientific habitus including those of the “tacit laws of governing the field” (Bourdieu cited in Brubaker, 1993: 230).

Using field analysis to understand the cancer research therapeutic field, Stewart and Rauch (2016) highlight its heteronomous nature, and assert that “It is by no means a ‘pure’ zone of disinterested scholarly activity and scientific discovery” (2016:481). In this review of the literature, I inquire into the autonomy of the HTF in relation to external forces, primarily the relevance of gender for the construction of scientific knowledge and its implications in other sub-fields such as clinical medicine and the pharmaceutical industry. The latter also intersects with strong economic pressures influencing research funding, marketization of anti-cancer drugs, and their access in the healthcare system. The agents of the HTF are laboratory scientists from different disciplines: chemists, molecular biologists and geneticists, cell-biologists, pathologists, pharmacologists as well as medical researchers who tested the new drugs in the clinic. I propose that the HTF’s interactions with the clinic (drug availability, clinical research) can act as a hinge between the “social order” or “external factors” and the internal dynamics of the HTF in their delineation of experimental research and scientific hypothesis, and in the struggle for scientific authority (social capital).

For the social order, I focus on broader societal gender norms that have long permeated the scientific and medical understandings of the hormonal body as sexually specific: oestrogens in women, androgens in men. Feminist biologists such as Fausto-Sterling have reasoned that, “our beliefs about gender affect what kinds of knowledge scientists produce about sex in the

first place" (2000: 3). Yet to take account of these gender-science entanglements and to elaborate an alternative narrative other than "critique" of biological knowledge, implies a disposition to learn (new) discipline-specific ways of knowing and producing scientific facts, to reach out to the phenomena that one seeks to discern, in my case the HTF. In this sense, there is no method for analysing the biological matter, and here my engagement with the HTF is indirect (I am not a specialist trained in this field), but neither this is an attempt to read biology *against* the social. It is rather an attentive reading of scientists' elaborations on tumour biology (and their struggles for social capital), with a focus on "what gets excluded and how those exclusions matter" (Barad, 2007: 30).

As I will argue in this article, hormonal therapy for breast cancer − from key scientific explanations of tumour growth to mainstream drugs and clinical guidelines − has been persistently receptive towards the role of oestrogens (the female 'sex hormone'), but has remained reluctant in recognising the action of other hormones despite more than 40 years evidencing their role on the disease.

Methods

I analyse the period 1960-2016 and concentrate on the key research lines, approaches or contributions to the HTF. Given the considerable amount of existing literature on this topic and period, the following search strategy was designed: firstly, searches were conducted electronically on the Pub Med database for review articles only (available from the 1980s), with added filters for title, English language and the time frame specified above. Search terms included: "o-estrogen/ progesterone/ androgen receptor AND breast cancer". After checking for duplication, the results were as follows: single hormones (o-estrogen 220; progesterone 17; androgen 25; and o-estrogen and progesterone: 14). This was further screened for expert reviews on the status of each hormone receptor and a sample of at least one article per

decade. For the latter, simple historical accounts and reviews of similar content were excluded, unless they explained the development of a new approach which was not described elsewhere in the literature. This allowed for the initial identification of relevant articles. Secondly, snowballing strategy (reference tracking) was used based on the significance given by laboratory scientists and medical researchers to key papers (which informed the basis for their hypothesis, experiments and clinical trials), and by further scanning using the bibliographies of relevant papers I was already aware of drawing on my previous research in hormones and breast cancer (Eraso, 2014, 2018).

In all, I analysed 19 expert reviews in a variety of specialised journals, and 56 original research articles (oestrogen 19; progesterone 13; androgen 19; and combination of hormones 5). Results are presented according to five main research lines in hormonal therapy. In order to reflect critically on the literature, I applied Bourdieu's notions of the scientific field alongside feminist science scholars to explore the impact of gendered assumptions on the HTF.

The oestrogen hypothesis

In 1962, chemists Elwood Jensen and Herbert Jacobson of the University of Chicago identified what is now widely known as oestrogen receptor (ER), an oestrogen-binding protein located in tissues (uterus, vagina, and breast) to which circulating oestrogens interact causing cell division and proliferation (Jensen and Jacobsen, 1962). For their experiment, the researchers administered oestrogen to immature female rats, for which they developed a novel technique, a radioactive oestrogen tracer, which fitted into the small physiologic dose of oestrogen that it is commonly injected into rats. The study showed that the radioactive oestrogen was retained in the uterus and vagina, whilst in other organs was quickly degraded; and that there was an oestrogen binding protein to which the oestrogen hormone binds

producing uterine growth. Subsequent studies (Noteboom and Gorsky,1965; Shyamala and Gorsky, 1969) confirmed the protein structure of the receptor and its location in the nucleus, where it interacted with DNA regulating gene expression. Also, O'Malley's team elucidated the mechanism of nuclear hormone receptors as regulators of nuclear tRNAs producing new protein synthesis. Steroid hormones binding to their receptors thus regulated the transcription of genes through complex pathways (Chan *et al*,1973; O'Malley and McGuire, 1968).

Jensen's discovery was a milestone at the time, since it opened up the possibility to identify which types of cancer could be responsive to hormonal treatment and which ones could not (Jensen et al, 1971), thus reducing the number of unnecessary invasive procedures such as ovariectomy, adrenalectomy, and hypophysectomy, which were known as the main oestrogen-producing glands. More importantly, it also led to a paradigm shift: instead of focusing on blocking the source of oestrogen, it paved the way for the development of new therapies that would block the hormone receptor.

Up until 1962, all studies were concentrated on elucidating the action of oestrogens on their biosynthesis, their enzyme-induced metabolic action on tissues. Confidence in the action of oestrogens, given their ability to alter processes of different kinds, was formidable and easily adopted as an experimental scientific hypothesis[i]. Animal experiments with oestrogen administration rendered immediate, direct observations of palpable organ-changes, as opposed to the mediated way of observing cell phenomena through the microscope, thus strengthening the already extreme confidence in the action of oestrogens as substances (whether exogenous or endogenous) in the development of organs, tissues and physiological action in the female body, including the mitotic action (cells that multiply) associated with cancerous processes. Jensen's study, however, demonstrated that the oestrogen hormone did not experience any chemical change in the process, it was the ER located in the nucleus of the cells in tissues that through complex mechanisms regulated the activity of different genes.

Jensen's "alternative approach", a term he later used to explain his novel hypothesis, left, in his words, the scientific community "surprised" (Jensen et al, 2010: 153). He summed it up with the following statement: study "not what the hormone does to the tissue but what the tissue does to the hormone" (Jensen *et al*, 1966: 133). A focus that displaced the role of the otherwise perceived mighty action of the 'sex hormone' to a position of dependence on the existence of receptors in tissue. Unlike 'sex hormones', tissue − in the scientific language and metaphorical associations used to describe bodily parts at the time − had no sex. We know, however, that oestrogens did not become degendered, and that hormones' action or "messaging" as Celia Roberts has proposed, "is received and responded to within bio-social (as opposed to purely biological) systems or worlds" (2007: 22-23). But decoupling its biological action in breast cancer from an ontological position to one of dependence and subordination opened up a whole new approach to study complex interactions. Some of the implications of these new hypothesis started with the identification of ER properties in human tissue (McGuire and Delagarza, 1973) and will be explored later in this review.

In the next section, I examine the HTF from the perspective of clinical researchers and the pharmaceutical industry as they revealed in the clinic a much more complicated use of therapeutic agents: one that exposed the underlying gender norms that limited, at the time, the autonomy of the HTF.

Androgens in the clinic

Hormone therapy was informed in the 1960s by clinical research going back to the end of the 1930s that reported on the use of oestrogens, progesterone and testosterone. The first clinical use of testosterone to treat breast cancer patients started in 1938 when a gynaecologist, Alfred Loeser, reported that "testosterone had an inhibiting effect" (Loeser, 1940: 481). Hormone therapy was informed by the notion of 'balance', which implied tinkering the dosage of the

antagonist or ‘contra-sexual’ hormone to level out the quantities of hormones circulating in the body. As the use of testosterone propionate and oestrogens expanded in the clinic, standardisation of their use was sought by the Council on Pharmacy and Chemistry (1947-1951), which compared the efficacy of both drugs through a series of clinical-therapeutic evaluations. Objective responses (tumour reduction, metastasis improvements) and subjective responses (sense of wellbeing, pain relief) were evaluated, but in the case of testosterone, the concern to establish a dosage aimed to balancing something else: notions of gender. The masculinising *side effects* that testosterone produced in women, namely hirsutism, deepening of the voice, acne, enlargement of the clitoris, and increased libido, challenged its value as an anti-tumour agent and led to the determination of an optimal dosage that would meet instead three factors, objective and subjective improvements and low “masculinizing action” (Council of Pharmacy, 1951: 475). During this period, female virilisation became a highly debated topic amongst clinical researchers in the United States, and those who deemed it negatively succeed in fuelling a ‘narrative of abandonment’: most oncologists today concur with this view when observing that “androgens have antitumor effects but were abandoned from breast cancer therapy due to their side effects” (Geisler and Lønning, 2005: 2810).

In the decades that followed, experimental clinical research with testosterone, however, did not decline; on the contrary, it was widely stimulated by the pharmaceutical industry that began to focus on testosterone derivatives with a gender objective to which it presented straightforwardly: the development of a substance providing “efficacy without virilization” (Goldemberg, 1973: 1268). The first drug to appear on the market was Fluoximesterone (Halotestin, 1959), a potent anabolic-androgenic steroid whose patent stated, “diminution or elimination of androgenic activity without loss of other properties exhibited by ‘androgens’ ” (Nathan *et al*, 1959: 1395). During the 1960s and 1970s a series of randomized clinical trials were developed to analyse these new compounds and the research group that coordinated

them was the Cooperative Breast Cancer Group (CBCG), sponsored by the National Institutes of Health. The CBCG attempted to overcome the perceived discrepancies between "objective", "subjective" and "masculinizing action", introducing the criteria that characterised the randomised clinical trial (RCT). It developed a single "objective" criteria to test the efficacy of the drugs, which included randomisation, external evaluators and an indicator for disease regression (Goldenberg *et al*, 1973: 1267). According to the strict CBCG protocol, a patient was considered to have an "objective" regression while receiving treatment if more than 50% of all lesions decreased in size while all other lesions remained static; or more than 50% of non-bony lesions decreased in size while all bone lesions remained static and without the appearance of new lesions during therapy (Goldenberg *et al*, 1973: 1267). The women selected for hormone therapy were postmenopausal, and their disease was advanced enough to benefit from surgical and radiotherapeutic treatment. A summary of the clinical trials of the CBCG in the 1960s and 1970s, indicated: similar regression rates (21.5%) for both Stilbestrol [oestrogen] and testosterone propionate (Goldenberg, 1964; Segaloff, 1966); similar efficacy for testosterone propionate and new anabolic androgens, and for the latter a response rate of around 28% (Goldemberg *et al*, 1973; Talley *et al*, 1973). This clear effort in the US context to restrict and prioritize "objective" improvements over "subjective" ones gave androgens a potential role in the clinic. In particular, for clinicians who saw in androgens an effective therapy whose benefits should be safeguarded by scientific protocols rather than professionals' preferences or opinions about their undesirable side effects (masculinizing or virilising). However, it was the subjective perception of clinicians and gynaecologists and their preferences in the use of oestrogens over androgens which played an over-determining factor behind the use of the drug. This is clearly illustrated by a member of the CBCG group, who thus advocated for the use of anabolic-androgenic steroids, "In my view, the virilisation produced by testosterone

propionate makes it a cruel treatment even though it is effective. Since I consider androgenicity sufficiently undesirable to contraindicate using an effective agent [anabolic-androgenic steroid],…." (Gordan, 1969: 41). The development of 'objective' measures for the use of androgens thus became for advocates within the CBCG a way to preserve their use in the clinic, in a context of medical criticism and anxiety about the gender disorders propitiated by the drug. It is worth considering here that the medical literature of the time only referred to the subjective opinions of clinicians in relation to how much virilization could be tolerated in their patients (usually symptoms of hirsutism, a hoarse voice, or increased libido) and that women's decisions in relation to 'androgenicity' were never collected as data or reason for discontinuation.

As for the various non-virilising androgen derivatives of the pharmaceutical industry that were evaluated by the CBCG in the 1960s and 1970s, in many cases with positive results, it can be observed in some medical reports, the implicit questioning of the overestimation of oestrogens over androgens. In 1975, one of the CBCG's managers, Dr Albert Segaloff, reflected, "The largest class of hormones which have been administered are estrogens" (Segaloff, 1975: 133). He also drew attention to the fact that there was only one compound (diethylstilbestrol) which from the 1950s became the "cornerstone" for the treatment of advanced breast cancer. "As opposed to the success in developing androgens with lesser androgenic activity still active against breast cancer, we are not aware of any such estrogen derivatives" (Segaloff 1975: 133) In addition, he questioned the lack of clinical trials on the appropriate dose of oestrogens to be administered, despite oestrogens' known toxicity (nausea, vaginal bleeding, breast soreness, fluid retention, stress incontinence).

The advent of an anti-oestrogen drug (Tamoxifen), which acts on the hormone receptor discovered by Jensen, that was thought to have little toxicity at the time, gave the use of androgens the final blow. As stated by an American oncologist:

> The studies of the Cooperative Breast Cancer Group did not succeed in their quest for the "super" androgen. Although androgens are easy to administer, relatively inexpensive, and have potent anabolic effects, their virilizing properties alarmed many patients and oncologists. Since the advent of the antiestrogens […] androgens have fallen into disfavor. […] The benefits of male hormones are *outweighed* by their alarming virilizing effects (Kaufman, 1981: 196; 198 – my emphasis).

Tackling oestrogen action and synthesis: Anti-oestrogens and aromatase inhibitors

Anti-oestrogen (Tamoxifen): In the mid-1970s the "accidental discovery" of an anti-oestrogen drug marked future developments in the clinical management of hormone-dependant tumours and it further legitimised the persistence of the oestrogen hypothesis, granting it star billing. Tamoxifen (ICI 46,474) became the first cancer target drug due to its ability to block or inhibit ER in mammary cells. The history of Tamoxifen counts it as a random discovery as it first emerged as a contraceptive drug (ICI 46,474) at the Imperial Chemical Industries Pharmaceuticals Division, UK. As an anti-oestrogen for post coital action - the "morning after pill" - ICI 46,474 was soon found to produce the opposite effect (stimulated ovulation) so pharmaceutical interest in this area was quickly abandoned. However, its conversion into a cancer drug was promoted by the British Pharmacologist, Craig Jordan, who between 1972-4 developed a research strategy at the Worcester Foundation for Experimental Biology (WFEB), in Massachusetts, with the aim of assessing the potential action of anti-oestrogens in tumours with positive ER, as identified by Jensen.

The first clinical study comparing the effectiveness of ICI-46,474 with androgens and oestrogens for women with metastatic breast cancer in the UK, gave similar results for the

three drugs, with the advantage of ICI 46,474 having "lower toxicity" in comparison with oestrogens, whilst "the virilizing effect of androgens has not been seen" (Cole *et al*, 1971: 274).

Jordan, however, developed (and tested in rats) another hypothesis, which implied the use of Tamoxifen to prevent recurrence, i.e. not for metastatic/palliative treatment only, but to all ER+ postmenopausal women and for a longer period (more than one year) of medication-taking, an approach he synthesised as "longer was going to be better" at controlling recurrence: Between 1977-78 he presented results demonstrating that, long term, Tamoxifen was a more effective adjuvant therapy (Jordan, 1978). Jordan's promising laboratory results for post-menopausal and pre-menopausal women (Jordan and Allen, 1980) were quickly trialled and extended to the clinic. In fact, like any adjuvant hormonal treatment, the role of Tamoxifen was to prevent recurrence of the disease and to extend years of survival in cancer patients. By 1985 the National Cancer Institute Consensus Conference proposed that Tamoxifen should be the standard treatment for postmenopausal women with ER positive tumour and positive axillary nodes (NIH, 1985).

Another hypothesis Jordan developed at the WFEB was that Tamoxifen might act as a chemoprevention for breast cancer (Jordan, 1976). The finding that contralateral breast cancer was reduced with the administration of Tamoxifen as adjuvant therapy prompted the testing of the drug as a chemopreventive agent. Between 1992-98 Tamoxifen was trialled in the National Surgical Adjuvant Breast and Bowel Project (NSABP) which enrolled 13,800 asymptomatic American women (without cancer) but at high-risk of contracting the disease, and obtained a 50% reduction in cancer incidence in the Tamoxifen-treated group (Fisher *et al*, 1998). An immediate FDA approval (1998) made Tamoxifen the first drug to *prevent* breast cancer.

The WFEB had by then a legendary reputation, specifically with respect to the role of 'female hormones', with the development of the first contraceptive pill (1955), and for pioneering animal *in vitro* fertilization (1959) (Pederson, 2011: 11). By 1971 the National Cancer Act secured the WFEB with an important grant for cancer research, and Edward Jensen was appointed as member of the Scientific Advisory Board. Having Jensen in the institution facilitated Jordan's development of ICI-46,474 into a cancer drug, as Jensen trained Jordan in the (DMBA)-induced rat mammary carcinoma model and the technique to measure ER in animal and human tumours (Jordan and Brodie, 2007). The engagement of the pharmaceutical industry was also crucial in the conversion of Tamoxifen into a cancer drug. ICI bought a US pharmaceutical company which became ICI Americas and "provided human breast cancers for me [Jordan] to establish that tamoxifen blocked, the binding of estradiol to the ER" (Jordan and Brodie, 2007: 9). At the same time, the company recruited Jordan as scientific consultant, "to advocate tamoxifen to clinical trials groups (ECOG and the NSABP) for clinical testing" (Jordan, 2014: R240), the latter trial will boost Tamoxifen to stardom in the 1990s.

Aromatase inhibitors (AIs). Like Tamoxifen, AIs started off as contraceptive drugs and their potential use as an anti-cancer drug was also developed at the WFEB. Experimental studies in animals began in the mid-1970s, and by 1979 one such compound was ready to be tested in the clinic. Yet as Angela Brodie, the lead researcher expressed, "Tamoxifen had by then been shown to be effective and there was a lack of enthusiasm to investigate other approaches, not only at the University of Maryland but also in pharmaceutical companies" (Jordan and Brodie, 2007: 4). AIs work by blocking the conversion, done by the enzyme aromatase, of androgens to oestrogen in body fat, liver, muscles and breast tumours. As such they are anti-oestrogens, alongside Tamoxifen, both targeting different sites and mechanisms − ER action

(Tamoxifen) and oestrogen synthesis (AIs) − and under the same hypothesis of oestrogen-dependence underlying cancer growth.

The AI Formestane was available in 1993, becoming the second breast cancer drug. It was developed for postmenopausal women with ER+ and also for those women whose disease progressed under Tamoxifen. It is worth considering that the principle of aromatisation and of a drug that blocked this process was already existent in testolactone "an altered androgen molecule", trialled first by the CBCG, whose aromatase inhibiting effects were later confirmed in the 1970s. The Brodie's team focused instead on a "non-steroidal" compound with selective action, whereby the drug had no effect over adrenal hormone synthesis. The reception of AIs was subsequently hailed as superior to testolactone precisely for not producing "androgenic effects" (Geisler and Lønning, 2005).

Hormone receptors: Alternative hypotheses

New hypotheses emerged within the discipline of molecular biology and focused on the mechanisms and actions of hormone receptors and their genetic transcription - the ability to regulate gene expression through complex mechanisms which caused uncontrolled cell division and tumours to grow. Stemming from Jensen's research on nuclear receptors and his novel perspective on tissue-action instead of hormone-action, these alternative hypotheses rendered new approaches to the then dominant presence of oestrogen and its receptor. Attention to their long-term development, as seen through a review of the literature, puts into perspective the struggles for legitimation within the HTF. The first results with Tamoxifen also guided this enquiry: in a clinical trial conducted in 1974 it was shown that 45% of women with ER+ did not respond to endocrine therapy (McGuire *et al*, 1977). Based on these unfavourable results, a group led by William McGuire and Kathryn Horwitz of the University of Texas, and Albert Segaloff (CBCG) proposed to investigate the action of other hormones

and their respective hormone receptors. The group first identified the progesterone hormone receptors (PgR) in mammary tumours and their role in predicting endocrine response for ER+ tumours. Their study stablished that the mere existence of ER+ did not indicate responsiveness to hormonal therapy. It was the evidence of hormone action that was needed. PgR, whose expression depends on the action of oestrogens, appeared as a marker of ER functionality, which ensured in turn responsiveness to endocrine therapies (Horwitz *et al*, 1975).

In another seminal study (Horwitz et al, 1975b), the action of hormone receptors of progesterone, prolactin, glucocorticoids, and androgens, as well as the mechanisms of inter-hormonal control were studied *in vitro*. As the authors justified, "the mere presence of ER in a tumor does not guarantee that the tumor will *behave* in a hormone dependent fashion" (McGuire *et al*, 1977: 2936, my emphasis). ER *behaviour* was a term that brought instability and unpredictability to the dominant position of the oestrogen hypothesis. The biology of the mammary tumour thus presented by these researchers, emerged as a space of enormous physiological and chemical variations, whereby a series of hormones played a role, and in which oestrogens appeared only as one piece of the puzzle. However, as Bonnie Spanier has observed in her work on gender ideology in molecular biology, "gene expression" (or in this case ER expression) "increasingly become crystalized into "things", rather than fleshed out as complex processes" (1995: 93). In the following subheadings, I present the different research lines that emerged from attention to these complex processes in tumour biology and how scientist themselves often expressed the constrains of the ER expression (rather than function) as dominant, centralised and hierarchical.

Progesterone and its receptors: Research on progesterone receptors continued, and found a place in the clinic, but only as a biomarker of the functionality of ER+ and its potential response to hormonal treatment: double-positive tumours (ER+ and PgR+) respond better to

Tamoxifen. In relation to the action of progesterone and its receptors, research developments were less auspicious. In the 1990s one of the leading researchers, Horwitz, asked somewhat rhetorically: "But are estrogens the only hormones with a proliferative impact on the breast and on breast cancers?" (Horwitz, 1993: 211). The action of progesterone and progestins in cancer growth rendered some contradictory results as both stimulating and inhibiting tumour growth in animal models and cell lines between mid-1980s and early 1990s (Dao *et al*, 1982; Horwitz and Freidenberg,1985; Kordon *et al*, 1990; Lanari *et al*, 1986). Clinical research with high doses of progestins resulted in similar response rates to the one achieved by Tamoxifen (30%) (Sedlacek, 1988), and found a place in the clinic in the 1980s as a second-line treatment after disease recurrence with Tamoxifen. But the arrival of AIs to the market heralded the demise of progestins as treatment.

The anti-proliferative action of anti-progestins to inhibit tumour growth were also studied (Bakker *et al*, 1987; Bardon *et al*, 1985; Michna et al, 1992). Yet differences in the cell lines used, lab techniques, conditions for cell growth as well as action of different PgR isoforms have been acknowledged as part of the discrepancies regarding its potential action. Clinical research, however, compared to that observed with anti-oestrogens, was very sparse, and above all, slow: 12 years elapsed from the identification of PgR to the first clinical trial with an anti-progestin to treat breast cancer, whilst patient recruitment for the first two trials were considerably low (22 [Maudelonde et al, 1987] and 11 [Bakker et al, 1990] respectively. For ethical reasons, these small trials were conducted on postmenopausal women with metastatic cancer, after conventional therapy (surgery, radiotherapy, and Tamoxifen) had failed. Yet ethics, we can argue, does not explain the clear lack of support for clinical trials and low patient recruitment, which certainly contrasts with those included in the large clinical trials of Tamoxifen (40 RCT by 1992, involving 30,000 patients [Darby *et al*, 2005]). The underlying reason can be found in the drug itself: the anti-progestin RU 486, although scientifically

promising as an anti-cancer agent, was primarily considered an abortive drug, and in the US, the FDA banned its commercial use until the year 2000. Here, a combination of political (anti-abortion groups and politicians) and lack of a foreseeable profit from the pharmaceutical industry that sought no approval, among other actors (Clarke and Montini, 1993), were affecting other medical research areas such as cancer therapeutics. "Where do we begin?" Horwitz asked herself, and countered, "Ensuring that scientists and clinicians have access to antiprogestins, unencumbered by the Byzantine bureaucratic obstacles and the 'antagonistic' political climate currently encountered in the United States, is a good place to start" (Horwitz, 1993: 224). The conclusions of the Institute of Medicine's committee on the clinical uses of anti-progestins for breast cancer were rather demanding in requesting certainty in relation to the specific action of anti-progestins in a way that the anti-oestrogen (Tamoxifen) would have also struggled to offer at the time, i.e. in relation to Tamoxifen resistance and lack of knowledge in its mechanisms of action. The Institute recommended future clinical trials with antiprogestins, but it also warned, "Even if the clinical experience with antiprogestins demonstrates substantial activity with an acceptable toxicity profile, it will still be important to define a unique mechanism or role for the use of antiprogestins as compared to other available endocrine therapies" (Institute of Medicine,1993:47).

Androgens and its receptors: The lack of therapeutic response of tumours classified as ER+ also stimulated experimental research into androgen responsiveness in different human breast cancer cell lines, which advanced the following findings: the clear existence of androgen-responsive tumours, and therefore the usefulness in identifying androgen receptors (AR) – i.e. tumour cells that grow when androgens are administered, or that are inhibited after an anti-androgen –, and the co-existence of ER and AR in the same cell line (Lippman *et al*, 1976). These researchers argued that although the role of androgens in breast cancer was determined, the key problem for its study resided in the limitations of the experimental

models available, i.e. the absence of cell lines that only expressed AR. This important limitation was also recently recognised by Coss *et al* (2014) and Taurilli *et al* (2014).

As studies of ER (and later associated with the expression of PgR) became differentiated in predictive value (likely to respond to hormonal treatment) and prognostic factor (irrespective of treatment, tumours with a particular receptor will have better/worst outcomes), the ER assay for the determination of ER status was recommended by NIH consensus conference in 1979 (Anon, 1979). The AR predictive and prognostic value, however, has yet to have a defined role in the clinic, although they have long been researched (Agoff *et al*, 2003; Bryan *et al*, 1984; Engelsman *et al*, 1974; Isola, 1993; Moinfar *et al*, 2003; Søreide *et al*, 1992). Improving assay techniques to measure the presence of AR also helped expose other relevant factors, primarily, the high occurrence of AR in breast cancer tumours relative to the other two hormones: A study from Norway found that AR "was the sex hormone receptor most frequently found both in primary and secondary breast cancer" − the data for primary tumours was AR (84.9%); ER (72.1%) and PgR (67.1%) (Lea *et al*, 1989: 7162).

Regulation of gene expression by hormone receptors: Research in molecular genetics significantly transformed the understanding of endocrine disorders through work in hormone receptors structure and functions − i.e. regulation of gene expression. Molecular cloning of ER (Green *et al*, 1986) shed light on the genetic organisation of the receptor, providing a functional description of distinct ER action as several domains: the one that bound DNA, that bound hormone, and that activates target genes. Molecular cloning also led to the identification of a second ER isoform, ERβ, with the one discovered earlier renamed ERα (Kuiper *et al*, 1996). Both have different biological functions, thus adding to the complexities of oestrogen action (differential transcriptional activities) in specific tissues (Zhao *et al*, 2008). As feminist scientist Deboleena Roy working at the time recalls, "the stable unitary identity of the estrogen receptor was displaced" causing "a minor endocrinological skirmish

in its day" (2018: 8-9). In addition, O'Malley's team identified new types of molecules named nuclear receptor "coactivators" and "corepressors" that were required for the functioning of hormone receptors and gene regulation (Baniahmad *et al*,1995; Smith *et al*, 1997); and studies also demonstrated that ER nuclear activity was also regulated by epidermal growth factor and insulin-like growth factor type I (Nicholson *et al*, 1999).

Finally, the identification of an oestrogen-binding site (G-protein-coupled receptor) in the cytoplasm and membranes of cells known as "non-nuclear" or "nongenomic", that is, a new membrane-ER, showed to regulate too physiological responses (Filardo *et al*, 2000; Levin *et al*, 2001). Interestingly, some scientists promptly argued against the ER-focus in the clinic by stating, "we can no longer view ER for diagnostic and therapeutic purposes as a simple nuclear transcription factor. The standard for assessing tumor ER status is a simple immunohistochemistry assay detecting nuclear ER. This may need to be challenged" (Schiff et al, 2004: n/p). Renamed G- protein oestrogen receptor (GPER) in 2007 (Prossnitz and Arterburn, 2015), this new receptor was found to be expressed in 50% of breast cancers, indicating poor prognosis in high levels of expression, as well as in patients treated with Tamoxifen an increased risk of endometrial cancers, although a cancer-promoting role has not yet been elucidated (Prossnitz and Barton, 2011).

Complex mechanisms were also advanced in relation to the other steroid hormones and its receptors. The progesterone receptor isoforms A & B discovered in the 1980s, returned evidence of differential mechanism of actions in breast tumours (Graham et al, 1995), ligand-independent actions (Jacobsen et al, 2002), as well as complex-cross talk with ER (Kraus et al, 1995) and growth factor receptors (Pierson-Mullany et al, 2003), though as some scientists have argued, "the clinical significance of PR isoforms is likely vastly under-appreciated" (Hagan and Lange, 2014: 6). In the case of AR, studies from Australia reported that isoforms

may be involved not only in tumour growth/inhibition, but also in responsiveness to endocrine therapies (Birrel *et al*, 1998; Hall *et al*, 1996).

By the year 2000, it seemed like the oestrogen hypothesis in the HTF has been sufficiently complicated, expanded or transcended in the work of many scientific groups though not in clinical ones, where ER assays and anti-oestrogen drugs reigned. A new classification (called "molecular portraits") of tumours based on cell-type and molecular profile, and their predictive and prognostic value has proved that the oestrogen-driven clinical orientation was not just normalizing breast cancer intelligibility, but prescribing action (clinical management). According to this classification, three gene expressions of receptors (ER, PgR HER2/neu), were involved in four distinct malignant subtypes: luminal A and luminal B, human epidermal growth factor receptor 2 (HER2)-enriched, and basal-like cancers (Perou, *et al*, 2000; Sørlie *et al*, 2001). The hormone receptor positive subtypes, luminal A (ER+ PG+) have the best prognosis and alongside luminal B subtype (ER+Pg+and HER2+) account for 70% of breast cancers. The hormone-receptor negative subtypes are considered as presenting a more aggressive disease pattern and worse prognosis, HER2+ account for 20% of cancers, and the basal-like – also labelled "triple negative" for the lack of expression of ER, PG, HER2 – constitute the remaining 10% (Fioretti *et al*, 2014; Ross *et al*, 2009). Clearly, the "molecular portrait" did not incorporate AR gene expression profiling. So, which hormones made it to this classification? And what was "excluded"? It could be summarised by saying that, either a woman has a breast cancer with ER or lacks a "hormone-sensitive cancer". Given that HER2 (Human Epidermal Growth Factor Receptor 2) is not a hormone, and that PgR is only assessed as a biomarker of ER functionality, the value assigned to the "expression" of ER seems the only *voice* that orients endocrine treatment. Tumours expressing HER2 are usually known as "hormone receptor negative", meaning that they do not express ER+ or PgR+. Yet, by virtue of not being tested for AR, their hormonal status is

in fact, misleading: if they were routinely tested for AR, clinical researchers would frequently find that both AR and HER2 are expressed (Higa and Fell, 2013; Niemeier *et al*, 2010). The "molecular portraits" with a centralised control of ER thus seems a good example of what feminist anthropologist Emily Martin called "fitting an interpretation into the facts", in relation to Western's physiology preferences for explanatory models with hierarchical control. "Why not [she questions] instead of an organization with a controller, a team playing a game? (Martin, [1988] 2016: 272).

New perspectives on androgens

From around 2010, attention to the role of AR expression has visibly increased and attempted to re-enter the clinic through a focus on tumours (such as "triple negatives") that did not fall into the recognised categories ER, PgR, HER2, as well as for cases where tumour resistance to hormone therapy drugs had occurred (Garay and Park, 2012). Part of this resurgence steamed from discourses on "personalised medicine", and a conception of breast cancer as caused by complex mechanisms and interactions for which different targeted molecular therapies should be individually used at specific stages of the disease.

A growing body of molecular and genomic studies about the role of AR in breast cancer tumours have provided a rationale for this renewed interest: firstly, the complex interactions or "cross-talk" between ERα and AR signalling pathways have put forward different propositions: that AR operated a "direct inhibition of ERα activity" (Peters, *et al*, 2009: 6131; 6139); and that their interactions explained resistance to Tamoxifen (De Amicis *et al*, 2010; Sikora, 2016). Secondly, the relevance of AR as a prognostic marker, where a meta-analysis concluded that in early breast cancer, "Expression of AR in women with breast cancer is associated with better OS [overall survival] and DFS [disease-free survival] irrespective of coexpression of ER" (Vera-Badillo *et al*, 2014:1).

Clinical trials with AR antagonists (to block the receptor) have tested drugs used for the treatment of prostate cancer in AR+ triple negative tumours (Rampurwala *et al*, 2016). At the same time, other clinical trials are today testing a Selective Androgen Receptor Modulator (SARM), an AR agonist that activates the receptor in women with AR+ and triple negative (NCT02971761) and AR+ER+ tumours (Cancer Research UK, CRUK/15/075). As in previous decades, fear of 'virilisation' still seems to haunt scientists and it well deserves a note of reassurance from trialists: "[SARMs] are a new class of drugs under development for a variety of diseases due to their high specificity for AR, selective anabolic activity, lack of virilizing side effect, and ability to extend androgen therapy to women" (Narayanan *et al*, 2014: 2).

Finally, highlighting both the shortcomings of an ER only clinical focus and the evidence amassed in the past 60 years, some studies are proposing to tackle the interaction of the ER, PgR, AR, and other steroid hormones as a "family" and to treat them with "group therapy" (Sikora, 2016); whilst others propose to consider the "hormonal environments" (ER, PgR, AR) with a focus on the mammary gland developmental stages as it could improve, in the clinical setting, the appropriate AR targeting drugs as inhibitors or activators of androgen action (Tarulli *et al*, 2014: T189, T196).

Discussion and Conclusions

The literature examined for the period 1960-2016 on hormones and breast cancer has identified five main scientific hypotheses, research lines and therapeutic uses within the hormone therapy field (HTF). Drawing on Bourdieu's scientific field analysis, from the findings I conclude that the already existing "oestrogen hypothesis" was further legitimised after the identification of the ER, which became the leading explanatory framework for the aetiology, diagnosis and treatment of breast cancer. I identify this continuity as scientific

habitus "which make possible the choice of objects, the solution of problems, and the evaluation of solutions" (Bourdieu, 1975: 30). In what Jensen emphasised as an "alternative approach" to the mechanism of oestrogen action (through the ER), it is possible to see the recurring value of the association oestrogens-breast cancer, operating at both levels of the HTF: the "internal", where the struggle for specific capital is grounded in the oestrogen hypothesis as a legitimate constituent; and the "external", where the influence of the social order is largely conceived and defined by questions of gender. Against this backdrop, the discovery of ER sounds less revolutionary, as it can be seen as tweaking objects of observation, facilitated by new available techniques (radioactive tracer) and above all, as ratifying legitimised questions: i.e. the oestrogen hypothesis and its enduring causal role in breast cancer since surgeon George Beatson in 1896 observed that by removing the ovaries (the main source of oestrogen production) it improved the clinical condition of women with breast cancer.

The research identified as "androgens in the clinic", offered by the CBCG, revealed a much more complicated use of therapeutic agents and exposed the underlying gender notions that permeated at the time, the social order. The clear effort by the CBCG to evaluate drug efficacy through "objective" improvements over "subjective" and "masculinizing action" gave androgens a potential role in the clinic. However, new androgens (with less *androgenicity*) had to work harder than oestrogens to find a place in the hormonal therapeutic armamentarium. The evidence-based data accumulated in these studies, which confirmed that androgens had a similar effect to oestrogen in remission rates and appeared to have not surpassed the subjective perception (social order- gender notions) of clinicians about their masculinising effects. The administration of androgens questioned the binary of two sexes and it proved an overdetermining factor in the abandonment of androgens in the clinical context, although not in the scientific one. It is possible to extend these contentions to the

assessment of testosterone in women's athletics today and the controversial regulations of international committees banning women athletes with high testosterone levels. Feminists scholars have drawn attention to both the pervasiveness of testosterone with the male/masculine body, to the extent that endogenous and exogenous androgens in women become a "provocation/disruption" (Irni, 2016) or a "foreign substance" (Karkazis and Jordan-Young, 2018); and the obstinacy of committees in disregarding scientific evidence.

The third research line, "tackling oestrogen action and synthesis" led to a stellar reception of drugs (Tamoxifen and aromatase inhibitors) in clinical research and practice. This therapeutic success within HTF can be interpreted as both *scientific habitus* (as an object of study, as a problem and as therapeutic solutions), overdetermined by a clear gendered articulation that supported the persistence of the oestrogen hypothesis: that the female 'sex hormone' par excellence (oestrogen) can cause cancer and this can be controlled and prevented by agents that block its action (anti-oestrogen) or inhibit its synthesis (aromatase inhibitors). The scientific "investment" as Bourdieu puts it, whereby the:

> researchers' tendency to concentrate on those problems regarded as the most important ones (e.g. because they have been constituted as such by producers endowed with a high degree of legitimacy) is explained by the fact that a contribution or discovery relating to those questions will tend to yield greater symbolic profit. (1975: 22).

From a clinical point of view, it certainly did, as prescribing Tamoxifen is largely common sense. Although the effectiveness of the drug in reducing the risk of recurrence by about a half and mortality by about a third have been proven (EBCTCG, 2005), there is still one-third of women with ER+ tumours that will develop drug resistance and mortality, and another third of tumours that are not ER+. This is not about seeing the glass half-empty. It is more

about offering an explanation as to why the oestrogen hypothesis still dominates in the clinic despite 40 years of attempts to understand breast cancer as "a constantly evolving, moving target" (Carroll, 2016: R42).

Therefore, there are two instances where Bourdieu's field analysis can shed some light for the HTF, the first one is the one already discussed in relation to the internal and external forces operating in the field which questions its "autonomy". In this sense, the degree of legitimacy of the oestrogen hypothesis does not operate in the "internal", intrinsic world of institutions (e.g. Worcester Foundation), and scientists (Jensen, Jordan, Brodie). "In fields with weak autonomy, which are therefore deeply immersed in social relations" says Bourdieu, "external pressure" i.e. resistance from political, religious or economic forces prevails (Bourdieu, 2004: 87). The HTF, like any area of research producing highly profitable products (drugs and tests), appears as particularly exposed to heteronomy. On the one hand, the pharmaceutical industry has been an active player in the marketing of 'sex hormones' since their isolation in the 1930s. Oestrogens, in particular, have been prescribed for a range of gynaecological disorders, contraception, menopause and osteoporosis, developing a well-known history of profit-oriented performance whilst driving sex/gender specificity in disease patterns and treatment consumption (Fausto-Sterling, 2005; Krieger, *et al*, 2005; Marks, 2010; Oudshoorn 1994; Roberts, 2007; Watkins, 2007). On the other, the accumulation of capital in the HTF is, as I have argued, better understood by the interactions with the "external", social order/gender values, or to paraphrase Moi's reading of Bourdieu (1999) by conceding that gender is better understood as part of the field. This has been exemplified by "androgens in the clinic" where the mobilisation of pervasive cultural understandings of sex differences returned to the HTF an enduring struggle. This relates to the second instance of Bourdieu's field analysis, the scientific struggle for legitimacy, which he exemplified through the "conservation" or "succession" strategies, i.e. those scientists that embrace the dominant

approaches and thus secure a career of prestige through "limited innovations"; and those who attempt to transform the existing order and invest in new, challenging theories, but whose legitimacy and impact will be much restricted (Bourdieu, 1975; 1991). In the HTF, legitimation depends on the clinical context, where on the one hand, patients either improve, survive, or confirm the efficacy of new drugs and tests, and on the other, hormonal treatments need to conform with the wider models of the male and female body, therefore struggles and competition for scientific legitimacy appear to be less polarised. In this sense, while there is a clear identification of those scientists working within the dominant, legitimated area of the oestrogen hypothesis, those seeking transformation did so with a tacit acceptance of the rules of the game, intrinsic to the field. I would argue that the "alternative hypotheses" that emerged in the 1970s (i.e. research into the role of progesterone and androgens) started off not as a rupture or opposition with the older order (ER action), but by permanently questioning its many shortcomings as a single explanatory theory. Through engagement with ER, these researchers opened up innovation in areas of research which led to modest, incremental additions, but certain in the assertion that ER was no more than one of the many mechanisms. Notably, they have enjoyed moderate scientific recognition but have failed to gain legitimation in the clinic: ER assays and oncogene analysis feature in breast cancer therapeutic orientation, but both PgR and AR are still struggling to find an independent role (i.e. prognostic value and treatment). One aspect that these new hypotheses remarkably contributed was the notion of 'tumour behaviour': the consideration of ER status, as an instance in time, not a fixed trait or entity. As feminist biologist Anne Fausto-Sterling has argued, "Believing that traits are static creates methodological conundrums" (2017:65) and this has been particularly problematic in the clinical management of breast cancer − ER+ loss of status and gene mutation leading to intrinsic and acquired resistance to hormone therapies, and discordance of receptor status between primary and recurrent tumours.

The most recent research identified in the HTF, the "new perspectives on androgens", with the ongoing clinical trials with anti-androgens and SARMs point toward the AR role as a potential therapeutic target. Yet concern about virilisation is very present and recent formulations often refer to past undesirable side effects as a flaw, thus, still perpetuating the same contention. Although the social order where these latest developments and trials have emerged are embedded in a fast-changing and complex gender landscape − where gender fluidity, non-binary thinking, intersex and trans activism have broken the mould of the traditional binary system – however, caution is warranted. Whilst current scientific perspectives draw attention to the breast cancer tumour's "hormonal environment" and the "hormone receptor family" to redirect the focus outside the determinism of oestrogens, opening up (again) the possibility to decouple *sex* from *hormones*, other closely related fields such as clinical/applied medicine and the pharmaceutical/ genomics industry can still offer renewed resistance. For example, the growing body of literature, services and research centres on gender-specific medicine, which reifies sex-based difference, promotes, as Annandale and Hammarström have argued, a "vision of the biological body as binary and determinate" (2010: 583). In addition, a novel test (Oncotype DX) has recently been endorsed by international clinical guidelines for the routine management of ER+ tumours only − a gene expression testing to predict risk of recurrence and to help oncologists in deciding on whether to prescribe chemotherapy − has been positively received by health systems and specialists alike. As the oestrogen receptors enter the muddle arena of "technological expectations", the dominant position of oestrogens and its receptors in the clinic may well be unaffected.

[i] On oestrogen action: Allen and Doisy 1923 administered oestrogens to ovariectomised rats obtaining the cornification of the vagina; whilst Lacassagne 1932, observed that oestrogen injections increased the incidence of breast cancer in female and male mice.

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