



Review Article

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Anti-Tumor Therapies-Cases of Breast and Prostate Cancers



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Abstract

After a circuitous detour involving numerous and varied hypotheses as to the causes of cancer, and the associated developments in chemotherapy and synergy with other modalities (surgery, radiation), and with our deeper understanding of the biology of this disease, we have now come to the conclusion that cancer is braided into our genome. A cancer cell is an astonishing perversion of the normal cell in that both rely on growth in the most basic elemental sense, viz. the division of one cell to form two daughter cells. Whilst in a normal cell, division is regulated and growth stimulated by specific complementary triggering and arresting signals, a cancer cell grows and divides frenetically without a regulating mechanism - a clonal process. Cancer is more than a clonal disease, however, it is a clonally evolving disease. When mutating, it can resist attack by a chemotherapeutic drug or by the autoimmune system; generate new cells that are increasingly adapted to survival and growth, and even speed up other mutations. The fittest cancer cells survive - the ultimate product of Darwinian selection of the fittest. I will discuss the hallmarks of cancer and the principles of cancer therapy. I will recall the long history of breast cancer from ancient times to the present, and describe the various therapeutic modalities' principles, applications, evolution and synergy (surgery, radiation, chemotherapy, bone marrow transplantation) and the complementary therapies (adjuvant, hormone replacement treatment, and palliative) and the corresponding benefits. I will also discuss past clinical trials and their conclusions (or lack thereof) and remark on current tests administered for breast and prostate cancer. I will conclude with a critique of the test guidelines issued by various national and international regulatory bodies and professional societies, providing additional evidence that so-called "population medicine" (in this case, mass screening) disregards individual variability and promotes considerably more unnecessary medical testing and procedures.

Abbreviations: aBMT: allogenic Bone Marrow Transplantation; ABMT: Autologous Bone Marrow Transplantation; ACOG: American College of Obstetricians and Gynecologists; ACP: American College of Physicians; ACR: American College of Radiology; ACS: American Cancer Society; AL: Acute Lymphoma; ALL: Acute Lymphoblastic Lymphoma; AML: Acute Myeloid Lymphoma; BBB: Blood Brain Barrier; BCDDP: Breast Cancer Detection and Demonstration Project; BPH: Benign Prostatic Hyperplasia; BRCA-1,2: BReast CAncer gene-1,2; BVP: Bleomycin, Vinblastine, (Cis)Platin; CBCSS: Canadian Breast Cancer Screening Study; CC: Cochrane Collaboration; CL: Chronic Leukemia; CMF: Cytoxan (cousin of nitrogen mustard), Methotrexate, Fluorouracil (a variant of aminopterin); c-myc: oncogene in lymphoma cells; CTFPHC: Canadian Task Force on Preventive Health Care; DES: Diethylstilbestrol; DNA: DeoxyriboNucleic Acid; DVT: Deep Venous Thrombosis; ECO: European Cancer Observatory; ED: Erectile Dysfunction; ER: Estrogen Receptor; eV: electron Volt; FDA: (U.S.) Food and Drug Administration; HGP: Human Genome Project; HIP: Health Insurance Plan; HRT: Hormone Replacement Treatment (or Therapy); KLK-3: Kallikrein-3 (gene); L: Lymphoma; LINAC: Linear Accelerator; MeV: Million electron Volts; MMM: Magnetic Resonance Mammography; MMS: Malmö (Sweden) Mammography Study; MOMP: Methotrexate, Vincristine-Oncovin, nitrogen Mustard, Prednisone; MP: Mercaptopurine; MRI: Magnetic Resonance Imaging; NCC: Nordic Cochrane Collection; NCI: (U.S.) National Cancer Institute; NHS: (U.K.) National Health Service; PEM: Positron Emission Mammography; POMP: Procarbazine Vincristine-Oncovin nitrogen Mustard Prednisone; PSA: Prostate Specific Antigen; PSTF: (U.S.) Preventive Services Task Force; RFLP: Restriction Fragment Length Polymorphism; Rb: Retinoblastoma; RSNA: Radiological Society of North America; STAMP: Solid Tumor Autologous Marrow Program; TS: TomoSynthesis; US: Ultra-Sound; VAMP: Vincristine Amethopterin Mercaptopurine Prednisone; WBC: White Blood Cells; WHI: Women's Health Initiative

Drugs Cited: Adryamicin; Amethopterin; Aminopterin (an anti-folate; a variant of methotrexate); Asparaginase; Cisplatin; Cyclophosphamide; Cytarabine; Cytoxan (cousin of nitrogen mustard); Diethylstilbestrol; Fluorouracil (an inhibitor of DNA synthesis); Mercaptopurine; Methotrexate (a variant of aminopterin); Nitrogen Mustard; Oncovin (=Vincristine); Prednisone; Premarin; Procarbazine; Statins; Tamoxifen (or ICI46474); Thioguanine; Vinblastine; Vincristine (=Oncovin)

Diseases Listed: Alport syndrome; Alzheimer's disease; Cancer (Breast; Cervical; Colon; Liver; Lobular; Lung; Prostate); Cardiovascular disease (heart disease; heart attack; stroke); Deep venous thrombosis; Diabetes; Erectile dysfunction; Hepatitis B; Hip fracture; Hodgkin's disease; Impaired hearing; Leukemia (Acute Myeloid; Chronic); Lymphomas (Acute; Acute Lymphoblastic; Burkitt's); Multiple myelomas; Myelodysplastic syndrome; Osteoporosis; Prostatitis; Retinoblastoma

Introduction

In an earlier publication [1], I have recounted the quest for cancer cures beginning some 4,000 years ago, but more particularly from the mid-19th century. I then summarized the various hypotheses formulated (blood suppuration, infectious disease, somatic mutation, two-hit) and theories advanced (viral, retro-viral, endogenous proto-oncogene) in the intervening time periods to arrive to the beginning and later developments of chemotherapy (anti-vitamins, multi-cytotoxic drugs at multi-doses, combination with surgery and radiation). After this circuitous detour, we have now come to the conclusion that cancer is stitched into our genome.

Thus, we can rid ourselves of cancer only in as much as we can rid ourselves of the processes in our physiology that depend on growth -aging, regeneration, healing, and reproduction. The best treatment remains prevention, at least the minimization of those epigenetic and ecogenetic factors that trigger the expression of cancer. Here, I would like to expand on the above concepts and dwell more at length on actual therapies. For convenience, I will limit myself to breast cancer and to a lesser extent prostate cancer.

Cancer as a Clonally Evolving Disease and Metastasis

It is helpful to recognize at the outset that a cancer cell is an astonishing perversion of the normal cell. Like it, it relies on growth in the most basic elemental sense: the division of one cell to form two daughter cells. In a normal cell, division is regulated such that growth is stimulated by specific signals and arrested by other signals. By contrast, a cancer cell grows until every visible sign of it had vanished and divides frenetically without a regulating mechanism -a clonal process. Cancer is more than a clonal disease, however, it is a clonally evolving disease. If growth occurred without evolution, cancer cells would not have the capacity to invade, survive, and metastasize. Every generation of cancer cells is partly different from its genetic parent. When mutating, it can resist attack by a chemotherapeutic drug or by the autoimmune system; it can generate new cells that are increasingly adapted to survival and growth, and it can even speed up other mutations. The fittest cancer cells survive -the ultimate product of Darwinian selection of the fittest [2].

Hallmarks of Cancer -SIERAM

Hanahan & Weinberg [3] proposed in 2000 the rules that govern the transformation of normal human cells into malignant cancers. These are:

Self-sufficiency in growth signals

Cancer cells acquire an autonomous drive to proliferate - pathological mitosis -by virtue of the activation of oncogenes such as ras (contained in a fragment of DNA present in all cells) and myc (the first engineered gene in a mouse).

Insensitivity to growth inhibitory (antigrowth) signals

Cancer cells inactivate tumor suppressor genes (such as retinoblastoma, Rb) that normally inhibit growth.

Evasion of programmed cell death (apoptosis)

Cancer cells inactivate and suppress genes and pathways that normally enable cells to die.

Limitless replicative potential (immortality)

Cancer cells activate specific gene pathways that render them immortal even after generations of growth.

Sustained angiogenesis

Cancer cells acquire the capacity to draw out their own supply of blood and blood vessels (tumor angiogenesis).

Tissue invasion and metastasis

Cancer cells acquire the capacity to migrate to other organs, invade other tissues, and colonize these organs, resulting in their spread throughout the body.

A helpful mnemonic summarizing the hallmarks of cancer is SIERAM (Signaling; Insensitivity; Evasion; Replication; Angiogenesis; and Metastasis).

Principles of Cancer Therapy

From the several studies conducted in the time period discussed earlier [4], several therapeutic principles have emerged:

Regarding cancer cells

- Cancer cells possess unique and specific vulnerabilities that render them particularly sensitive to certain chemicals that may have little impact on normal cells.
- Certain cancer cells (e.g., of the thyroid, prostate) retain a physiological "memory" of their (non-cancerous) origin.
- Attacking a cancer cell specifically begins by identifying its biological behavior, its genetic makeup, and its unique vulnerabilities.

Regarding the tumor

- Cancer is not a disorganized chromosomal chaos. It is organized chaos: Specific and identical mutations exist in particular forms of cancer.
- Cancer is not necessarily autonomous and self-perpetuating. Its growth can be sustained and propagated by hormonal function in the host. It could be fed and nurtured by our own bodies.
- Cancer is enormously heterogeneous and this heterogeneity is genetic and anatomic. Understanding that heterogeneity is of deep consequence, having led to the meticulous separation (in breast cancer) into distinct stages

and into ER (estrogen receptor)-positive and ER-negative cancers that require different treatment approaches.

d) Early stage local cancers are often inherently different from widely spread metastatic cancers even within the same form of cancer.

Regarding treatment in general

a. Cancer needs to be treated long after any visible sign of it had vanished -a principle that resulted in the first chemotherapeutic cure of cancer in adults [5].

b. To design an ideal anticancer drug, one would need to identify a specific molecular target in a cancer cell and create a chemical to attack that cancer.

c. For each particular form and stage of cancer, a particular therapy needs to be meticulously matched.

Regarding chemotherapy

A. Indiscriminate chemotherapy may not be the only strategy by which to attack cancer.

B. Chemotherapy typically kills a fixed percentage of cancer cells at any given instance no matter what their total number, this percentage being a cardinal number particular to every drug so that killing leukemia, for example, is an iterative process.

C. Toxicities notwithstanding, annihilating cancer might involve using a combination of two or more drugs, providing synergistic effects on killing. Since different drugs elicit different resistance mechanisms, and produce different toxicities in cancer cells, using drugs in concert dramatically lowers the chance of resistance and increases cell killing. Multiple drug chemotherapy has dramatically changed the prognosis of patients with previously treated stage III and stage IV cancer.

Other principles

i. The body's immune system can subvert the cancer treatment.

ii. In women with no visible tumors remaining in the body after surgery, adjuvant chemotherapy can be used to either decrease relapses of stage I and II breast cancer (using tamoxifen) or, else, to decrease relapses with localized ER (estrogen receptor)-positive breast cancer after surgery (using CMF: cytoxan+methotrexate -a variant of aminopterin+fluorouracil).

iii. Like for most other diseases, the best cancer treatment is no treatment that is the prevention of the cancer's occurrence.

iv. In breast cancer treatment, it is not so much the presence of a tumor and its size that are of concern, but rather

the tumor's potential for metastasizing, the identification of the mutations causing it, in what genes and by what mechanism(s)?

We can now turn to the study of breast cancer as an important example of therapies.

Breast Cancer

Breast cancer was mentioned in 440BC by the Greek historian Herodotus regarding Atossa -the daughter of Cyrus and queen of Persia. It was an inflammatory breast cancer (malignant cells that invaded the glands of the breast, causing a red, swollen mass). It was excised by the slave Democedes and the operation appeared to have been partly successful.

Surgery

In 1869, Joseph Lister removed a breast tumor and by the mid-1870s routinely operated on breast cancer even extending his surgery to the cancer-afflicted lymph nodes under the breast. In the mid-1890s, on the heels of his successful surgeries using various techniques to remove tumors from the stomach, colon, ovaries, and esophagus, Theodor Billroth successfully surgically removed non-metastatic breast cancers [6]. Surgery then remained the mainstay in the treatment of localized breast (and even other) localized tumors. During that time, William Stewart Halsted attacked breast cancer with relentless energy, performing increasingly meticulous and aggressive surgeries to remove tumors from the breast [7-9]. However, because of cancer recurrences around the margins of surgeries, Richard von Wolkman began removing not just the breast, but the pectoralis minor (a thin, fanlike muscle spread out under the breast) and even the pectoralis major located deeper into the breast cavity. Then, by the 1890s, Willy Meyer performed radical mastectomies, which disfigured patients and in turn led to super-radical and even ultra-radical surgery.

However, the immediate success of surgery was not a predictor of its long-term success, i.e. its ability to decrease the relapse of cancer. Obviously, that depended on the stage of the cancer. Thus, whereas a localized, early stage cancer could be eradicated with radical mastectomy, a cancer at a more advanced stage would return. This is a quandary wherein in the former case, a local mastectomy (a lumpectomy), rather than a radical mastectomy would have sufficed, in the latter case, radical mastectomy would later be followed by a return of the cancer. In other words, the ultimate survival from breast cancer, had little to do with how extensively the surgeon operated on the breast; it depended on how extensively the cancer had spread before surgery. After the discovery of X-rays (see next section), it was determined that surgery (of localized breast cancers) followed by X-radiation had synergistic properties. A similar synergism was likewise demonstrated when surgery is followed by chemotherapy (see below).

Radiation oncology

Wilhelm Roentgen [10] discovered X-rays in 1895 that could carry radiant (ionizing electromagnetic) energy through human tissues. Shortly thereafter, in 1896, Henri Becquerel discovered that certain natural materials (uranium among them) emitted their own invisible rays with properties similar to those of X-rays. Nuclear radiation was then discovered in 1902 by the husband-wife team, Pierre & Marie Curie [11] (born Sklodowska) in radium. This latter radiation had the additional property of depositing energy deep inside tissues. Unfortunately, both X-rays and nuclear radiation attack DNA or generate toxic chemicals that corrode DNA. In 1896, in a seminal clinical experiment, Emil Grubbe used an improvised X-ray tube to treat breast cancer that had relapsed after mastectomy and produced a mass in the patient's breast. The trial was not successful because X-rays could only be used to treat cancer locally, with little effect on tumors that had already metastasized. By 1905 and beyond, breast tumors were obliterated with X-rays. In 1924, Geoffrey Keynes successfully demonstrated the efficiency of X-rays and even imbedded pellets or radioactive material (dubbed brachytherapy) in treating breast cancer. He subsequently recommended a careful mixture of surgery and radiation (both at relatively small doses). George Barney Criles [12] summarized the situation thus: If the tumor is locally confined, it would be adequately treated by local surgery and radiation without the need for radical surgery; on the other hand, if the tumor had metastasized, surgery (whether local or radical) would be useless. Like Criles [12] and Keynes, Bernard Fisher concluded that radical mastectomy had no basis in biological reality and that localized tumors were to be treated by either simple mastectomy or lumpectomy-plus-radiation. Depending on the size of the tumor. In a large scale trial where 1,765 patients were randomized in three groups depending on the treatment strategy (radical mastectomy; simple mastectomy; surgery followed by radiation), Fisher found that the rates of breast cancer recurrence, relapse, death, and distant cancer metastasis were statistically identical among all three groups! As a result, nowadays, radical mastectomy is rarely, if ever, performed.

However, like for surgery, radiation medicine had two serious limitations: (a) limited use for metastatic cancers although it can be used as a control or a palliative in selected cases, but rarely curative in these circumstances and (b) it induces cancer as the very effect of X-rays killing rapidly dividing cells (DNA damage) also created cancer-causing mutations. A more discriminating therapy was needed, especially for non-localized cancers.

Following the development of the linear accelerator (in short "linac") at Stanford University, Henry Kaplan was hoping to use its highly potent energy beam of three million electron volts (MeV) in concentrated bursts to pierce through any cancer cell to death. Unfortunately, breast cancer did not lend itself to such a tool and strategy because of its propensity for occult and systemic spread.

Chemotherapy

Chemotherapy is the use of specific chemicals that heal the diseased body. It is based on the principle that a systemic disease demands a systemic cure. The requirement is to find a chemical with specific affinity for the type of cancer under treatment. Mustard gas¹ was specific to the bone marrow; it eliminated certain (but not all) cell populations and produced some fleeting remissions, unfortunately followed some time thereafter by relapses. There was an avalanche of drugs for leukemia² (cyclophosphamide, cytarabine, prednisone, asparaginase, adriamycin, guanine, vincristine, 6-mercaptopurine (6-MP), methotrexate). Toxicities notwithstanding, repeated treatments and clinical trials led to the conclusion that annihilating leukemia might involve a combination of two or more drugs. Actually, four drugs (vincristine, amethopterin, mercaptopurine, and prednisone, acronym VAMP) were retained. The difficulty remained how to best select that combination of dosages of these drugs that would eradicate the cancer³. During the VAMP trials (1961-3), it was found that the treatment eliminated leukemia but did not reach the nervous system, creating a sanctuary for cancer in the body. This was the consequence of the body's own immune system subverting cancer treatment. Thus, cure was followed by an explosive relapse in the brain.

¹Mustard gas was a First World War gas developed jointly by the dye factories and the pharmaceutical industry. It is a colorless, blistering liquid produced by reacting the solvent thiodiglycol (a dye intermediate) with boiling hydrochloric acid. It has the ability to decimate white blood cells (WBC-the so-called "Krummbhaar effect"). It could conversely be used to attack malignant WBCs such as in cancers of the lymph glands (lymphomas) and produce temporary remissions. Another chemical, 6-mercaptopurine (6-MP), produced the similar result in acute lymphoblastic lymphoma (ALL).

²Since the early 1900s, it was clear that leukemia came in different forms: (a) chronic leukemia (CL): slow increase of WBCs until choking the bone marrow and spleen; (b) acute leukemia (AL) characterized by a rapid overgrowth of WBCs with two different subtypes according to the two types of WBCs (myeloid cells and lymphoid cells): (b1) acute myeloid leukemia (AML); and (b2) acute lymphoblastic leukemia (ALL), which are immature lymphoid cells. Cancers of more mature lymphoid cells are called lymphomas (L).

³This is an optimization problem, not unlike the optimization of the radiotherapy plan in which the number of ports along which to deliver high energy radiation and the energy in such ports are optimized so as to incinerate the cancer while preserving the healthy tissues along the radiation paths [13].

The first test of intensive combination chemotherapy dubbed “MOMP” (methotrexate, vincristine also called oncovin, nitrogen mustard, prednisone) for advanced stage Hodgkin’s disease was followed by the more powerful “POMP” (that is MOMP where methotrexate was replaced by the more potent drug procarbazine). If the terror of VAMP was death by infection, that of POMP was visceral death by nausea and later sterility in men and some women. Other side effects were: peculiar infections due to the annihilation of the immune system and relapse with a second aggressive and drug resistant cancer. Thus, like for radiation therapy, chemotherapy cured cancer on the one hand but caused cancer on the other.

Further, because of the above limitations, a more stringent protocol was advocated by Donald Pinkel consisting of: (a) combinations of six, seven or even eight drugs matched together for maximum effect; (b) chemotherapy was instilled directly into the nervous system because it could not breach the blood brain barrier (BBB); (c) high doses of radiation to the brain since X-rays are not hindered or stopped by the BBB; and (d) continued chemotherapy stretching from weeks or months to two or even three years. This new protocol and its optimization achieved great success in terms of the number of remissions obtained; the stretch of time between diagnosis and relapse had reached nearly five years; and 80% of the cohorts of patients treated had been cured (as least as far as anyone could tell).

In the 1980s-1990s, Clare M King & Skolnick M [14] identified cancer-predisposing gene alterations that were quite frequently represented in the selected populations they studied, particularly the BRCA-1 gene found in up to 1% of women in these populations, making it one of the most common cancer-linked genes found in humans.

A new chemotherapeutic approach -The wiping out of cancer cluster cells

Metastasis (a curious mix of meta and stasis or “beyond stillness”) is behind the vast majority of cancer deaths when cancer cells break away from a tumor and lodge in new places. The disease becomes harder to treat. Most metastatic cancers are seeded not by single cells from the primary tumor but by clusters of diverse cancer cells that leave in a group and travel through the blood stream together. The cells in these circulating clusters communicate with one another and produce specific proteins that could be used as drug targets or biomarkers for risk of metastasis. The above conclusion was derived from experiments on mice, which showed that in the case of induced lung cancer, metastasis occurred in about 95% of the cases. Andrew Ewald further observed in petri dishes that the efficiency of metastasis formation of cancer cells aggregated into clusters is 100-fold higher than that for isolated cells, likely due to cooperation of tumor cells within clusters. The traveling clusters share molecular features and nearly all make the protein keratin-14. This suggests a new approach to therapy consisting in wiping out those cells wherever they are in the body, whether or not they are proliferating -a different approach from most standard therapies, which focus on attacking rapidly proliferating cells

but not by the circulating invasive ones that initiate secondary cancers.

Bone marrow transplantation

The chemotherapeutic equivalent of radical surgery was the procedure known as autologous bone marrow transplantation (ABMT) or autologous bone marrow transplantation (aBMT). It flourished in the 1980s as applied to leukemia and Hodgkins’ disease. The idea began with the notion that very high doses of cytotoxic drugs (5 or even 10 times the typical dose), below the toxic limit set by the bone marrow, could perhaps cure the cancer and leave it behind. The procedure consisted of the following steps: (a) obliterative chemotherapy, (b) bone marrow replacement, and (c) attack on the tumor by foreign cells. The marrow transplant could either be autologous (using the bone marrow of the patient) or allogenic (marrow from another patient). While carrying severe risks, the procedure was nonetheless applied to refractory leukemias, multiple myelomas, and Myelodysplastic syndrome -diseases known to be inherently resistant to chemotherapy. Emil Frei tested it in his ambitious trial dubbed “solid tumor autologous marrow program” (or STAMP), which built on the “success of the VAMP protocol (see above section).

STAMP was applied to metastatic breast cancer in late 1983 [15]. It produced remissions that appeared to be more durable than those obtained with conventional chemotherapy. It was subsequently expanded as an adjuvant therapy for high-risk patients with locally advanced cancer (patients with more than ten cancer-afflicted lymph nodes).

Adjuvant chemotherapy

Microscopic cancer deposits may be left behind after surgery. Rather than undertake further surgery culminating at times in radical mastectomy, Paul Carbone conjectured that chemotherapy after surgery could be used to “cleanse” the body of these residual tumors to decrease the rate of relapse from breast cancer (a treatment he dubbed as “adjuvant”). A large randomized trial of chemotherapy after breast surgery for early-stage breast cancer, sponsored by the U.S. National Cancer Institute (NCI), was conducted in Italy in 1973 by Bonadonna & Veronisi [16]. The trial (called CMF) used a combination of three drugs (cytoxan, a cousin of nitrogen mustard; methotrexate, a variant of aminopterin; and fluorouracil, an inhibitor of DNA synthesis). It showed that adjuvant chemotherapy had prevented breast cancer relapses in about one woman in every six treated women.

Adjuvant chemotherapy with tamoxifen after surgery can reduce relapse rates by nearly 50%, particularly among women above fifty years old (a group most resistant to standard chemotherapy treatment regimens and most likely to relapse with aggressive metastatic breast cancer). It should be noted that neither adjuvant therapy nor hormonal therapy (to be discussed next) obliterated cancer. Adjuvant therapy lengthened survival but many patients eventually relapsed.

Hormone replacement treatment

In 1929, Edward Doisy [17] identified the hormonal factors in the estrous cycle of females by the hormone estrogen⁴. Estrogen is the principal hormone secreted by the ovaries, and it is vital for the maintenance and growth of normal breast tissue. Doisy was able to treat cancer patients with prostate cancer using female hormones (estrogen) to stop the production of testosterone (a sort of “chemical castration”). The remissions obtained proved that hormonal manipulations could choke the growth of hormone-dependent cancers. In these situations, to produce a cancer remission, one did not need a toxic, indiscriminate cellular poison. By extension, could breast cancer be likewise starved by hormonal deprivation?

In the mid-1960s, Elwood Jensen showed that breast cancer cells are of two types, those that express high levels of estrogen receptor (ER) and those that express low levels, that is ER-positive and ER-negative tumors, respectively. Thus, variations in breast cancer cells in response to ovarian removal depend on whether the cancer cells express the ER or not. Rather than actually removing the ovaries (a procedure fraught with severe side effects, including a risk of osteoporosis), the same result could be obtained pharmacologically by employing the estrogen antagonist, tamoxifen (or ICI46474); this is tantamount to a chemical castration analogous to that of the prostate (Arthur Walpole and Dora Richardson). It remained for Dora Cole to demonstrate that a drug designed to target specific pathways in a cancer cell -not a cellular poison discovered empirically by trial and error -had successfully driven metastatic tumors into remission by showing that cancer cells that expressed the ER were highly responsive to tamoxifen while cells that lacked the ER did not respond. For the first time in the history of cancer, a drug, its target, and a cancer cell had been conjoined by a core molecular logic. Cole further reasoned that if tamoxifen could halt the progression of diffusely metastatic and aggressive stage IV cancers, might it not work even better on more localized stage II breast cancers that had spread only to the regional lymph nodes?

Hormone therapy essentially produced prolonged remissions that could stretch into years or even decades. Like adjuvant therapy, often after decades of remission, hormone-resistant cancers grew again despite the prior interventions.

Hormone replacement treatment (or therapy) (HRT) refers to any form of hormone therapy wherein the patient, in the course of medical treatment, receives hormones, either to supplement a lack of naturally occurring hormones, or to substitute other hormones for naturally occurring hormones. We are here interested solely in HRT for menopausal women.

The idea is that treatment may prevent the discomfort caused

by diminished circulating estrogen and progesterone hormones, or in the case of the surgically or prematurely menopausal women, that it may prolong life and may reduce the incidence of dementia. It involves the use of one or more of a group of medications designed to artificially boost hormone levels. The main types of hormones involved are estrogens, progesterone or progestins, and sometimes testosterone. It is often referred to as “treatment” rather than therapy.

Many studies on the effects of HRT have been conducted on rats. Overall, the results of these studies are non-conclusive and more research in this area is needed. Nonetheless, some important results can be gathered: (a) Differing brain regions may respond in a variety of ways to HRT; (b) Timing of the therapy is integral to the chances of success; and (c) How the hormones are administered, either chronically or cyclically, may make an important difference in their effectiveness.

As recently as 2005, women have had a positive and overly optimistic attitude towards HRT. Currently, however, most women do not find HRT to be an effective solution: It is initially helpful but if used for a long period of time it loses its effectiveness, and there are times when it is not only ineffective but actually detrimental to people.

In the case of menopausal women, HRT has had the following adverse effects: impaired hearing including decrease in the functionality of many regions of the ear, reduction of the effectiveness in parts of the central nervous system used for hearing, and increased chance for cardiovascular disease (particularly in the case of women caregivers who experience more acute stress in their lives). However, HRT can have beneficial effects: positive effects on the prefrontal cortex by boosting the working memory, no additional weight gain compared to women who do not use HRT, positive effects in their sex life (mainly increasing their sex drive and sexual sensitivity) that can dissipate after receiving HRT for extended periods of time ... but the effects are inconsistent across women.

For decades, HRT was widely recommended to women to reduce heart disease. However, the Women’s Health Initiative (WHI) trial (over 16,000 post-menopausal women) compared the combination (estrogen +progestin) to placebo. The findings included significant increases in breast cancer, heart disease and heart attacks, strokes, and dangerous blood clots. These findings far over-rode the alleged benefit of less colon cancer and fewer hip fractures. The results of the WHI trial were so negative that it was stopped prematurely, at 5.6 years (instead of the planned 15 years) of follow-up. New results released in 2011 continue to engender confusion, suggesting disparate outcomes with hormone replacement as a function of what age the treatment was initiated.

⁴There are two widely used versions: diethylstilbestrol (DES), a chemically synthesized estrogen, and premarin (pregnant mare urine), a natural estrogen purified from horse’s urine. The estrogen receptor (ER) is the molecule responsible for binding estrogen and relaying its signal to the cell. Estrogens could “feminize” the male body and stop the production of testosterone particularly for patients with prostate cancers (a sort of “chemical castration”).

Nonetheless, after a slowing period following the announcement of the trial's negative results, the practice continues under the guise (true perhaps for some women) that HRT (estrogen and/or progestin) palliates the unpleasant "hot flashes" post-menopausal women experience. But, this latter "benefit", even if true, is not the premise on which HRT was advocated and sold.

Of last note, a recent report in the Archives of Internal Medicine revealed that "post-menopausal women who were treated with statin drugs to lower their cholesterol had a nearly 48% increased risk of developing diabetes compared to those who were not given the drug". This is even more critical when we consider that becoming diabetic doubles the risk for Alzheimer's disease. The combination (HRT+statins) is of serious concern.

In summary:

- a. Whereas initially helpful, used for a long period of time, HRT loses its effectiveness, and there are times when it is not only ineffective but actually detrimental.
- b. In the case of menopausal women, HRT has multiple adverse effects (impaired hearing including decrease in the functionality of many regions of the ear, reduction of the effectiveness in parts of the central nervous system used for hearing, and increased chance for cardiovascular disease particularly in the case of highly stressed women). However, HRT can also have beneficial effects (boosting the working memory, no additional weight gain, positive effects in the sex life) that unfortunately can dissipate after receiving HRT for extended periods of time.
- c. Whereas significant increases in breast cancer, heart disease and heart attacks, strokes, and dangerous blood clots were found in a large and important clinical trial, HRT was discontinued for a time period but is witnessing a resurgence for alleged other benefits (palliation of hot flashes). Again, even when the surrogate end point is no longer tenable, another surrogate end point is found to justify the continued use of the therapy (a common marketing ploy).

Palliative care

Palliative care focuses on symptom relief and comfort, not on cure. It was founded by Cicely Saunders.

Benefits of breast cancer therapy

In the U.S., it has been estimated that less than 1 in 20 patients diagnosed with breast cancer and less than 1 in 10 of the total number of patients who would die of cancer had benefited from the advances in breast therapy and screening. Whether this is a "success" or a "failure" depends on the metric used for such an assessment. It can indeed dramatically vary with the gauge used.

On Cancer Prevention

For all cancers, the best treatment is prevention. In primary prevention, the disease is prevented by attacking its cause (for lung cancer; smoking cessation; for liver cancer: the hepatitis B vaccine; etc.). In secondary prevention, it is prevented by screening for its early pre-symptomatic stage (for cervical cancer: the Pap smear test; for breast cancer: mammography in its several modalities: radiography; Ultrasonography; magnetic resonance imaging-MRI)⁵.

Past Clinical Trials on Breast Cancers

Several clinical trials were conducted to ascertain whether screening a large cohort of asymptomatic women using mammography would prevent mortality from breast cancer:

- a. The Health Insurance Plan (HIP) trial [18]: 62,000 women had enrolled of whom approximately half were screened by X-ray mammography. There were 31 deaths in the screened group and 52 deaths in the control group, a modest saving of 21 recruits among 62,000. In relative numbers, this fractional reduction amounted to a saving of 40%. While 40% sounds like an astounding number, it nonetheless corresponds to a percentage of a small number. Furthermore, critics charged that the excess mortality in the controlled group was a statistical artifact, casting a pale veil on the trial.
- b. The Breast Cancer Detection and Demonstration Project (BCDDP), a demonstration not a trial (mid-1960s): 250,000 patients.
- c. The Edinburgh (Scotland) Trial: A disaster in terms of trial design.
- d. The Canadian Breast Cancer Screening Study (CBCSS), 1980 [19]. The trial faltered and its conclusions discarded.
- e. The Malmo (Sweden) Mammography Study (MMS), 1970-1988: 221,000 women. While it demonstrated the capacity of mammography to detect early cancer, particularly for women aged 50 and more, and barely discernible for younger women, it did not translate into overwhelming numbers of lives saved.

Overall, it took five decades and nine trials before any benefit could be ascribed to mammography. The reasons include:

- 1) Complexity of running early detection trials.
- 2) The mammogram is not necessarily a good tool for detecting the early presence of cancer in that its false-positive and false-negative rates are not absolute but depend on age. For women above 55, the incidence of breast cancer is sufficiently high that even a relatively poor screening tool

⁵I will not dwell here on the paths of screen testing or its pitfalls of over-diagnosis and under-diagnosis, and bias and selection.

can detect an early tumor and provide a survival benefit. For women between 40 and 55, the detection of a mass is more often than not a false-positive.

3) Small tumors may be metastatic and larger tumors are not necessarily metastatic, indicating that size is not necessarily the criterion; it is the quality of the growth rather than its quantity (its malignant potential).

By the late 1980s, the entire discipline of cancer prevention appeared to have stalled at this critical juncture (the malignant potential for metastasis of the imaged tumor). While mutagenicity is linked to carcinogenicity, it is important to know where mutations are occurring and by what mechanism(s).

The gold screen tests for breast cancer are thermography and mammography. The diagnostic tests are ultrasound (US) and magnetic resonance imaging (MRI).

Remarks on Tests Currently Administered for Certain Types of Cancer

The goal of any screening procedure is to examine a large population of patients to find that small number most likely to have a serious condition. These patients are then referred for further, usually more invasive, testing. Thus, a screening exam is not intended to be definitive, rather to have sufficient sensitivity to detect a useful proportion of cancers. The cost of higher sensitivity is a larger number of results that would be regarded as suspicious in patients without disease.

Breast cancer

Mammography for breast cancer screening for women parallels the PSA (prostate specific antigen) test in men (see below). This imaging test uses low-energy X-radiation to examine the human (female, but also male) breast. It is used both as a screening and a diagnostic test.

In mammography, the goal is the early detection of breast cancer through the detection of characteristic masses and/or micro-calcifications. Its use as a screening tool for the detection of early breast cancer in otherwise healthy women without symptoms is controversial.

Like all X-rays, mammograms use doses of ionizing radiation (albeit lower than those employed in bone radiography) to create images that are subsequently analyzed for any abnormal findings. Adjunct procedures to mammography are:

A. Ultrasound: For further evaluation of masses, including palpable masses not seen on mammograms. (Note: In a poster at the 2016 meeting of the Radiological Society of North America (RSNA), Eric Blashke and colleagues of Milwaukee Radiologists Ltd, Wauwatosa, reported that, for male breast cancers, there was no added value to incorporating ultrasound as part of the initial exam. In such patients, when

there is cancer, it shows up rather early with mammography. This conclusion was confirmed by Anja Maibaum of the Poole Hospital NHS Foundation in Bournemouth, England and Stamatia Destounis of the University of Rochester Elizabeth Wende Breast Clinic, Rochester, N.Y. However, in the rare case of a man with dense breasts, tomosynthesis (TS) or ultrasound could be used. Also, ultrasound may be more useful as a method to guide biopsy) [20].

B. Ductography (not generally used): For further evaluation of questionable findings as well as for screening and for pre-surgical evaluation in patients with known breast cancer to detect any additional lesions that might change the surgical approach, for instance from breast-conserving lumpectomy to mastectomy.

C. Magnetic resonance mammography (MRM): For greater spatial resolution of mammographic tissue imaging.

D. Positron emission mammography (PEM); and

E. New procedures, including breast tomosynthesis.

Currently recommended guidelines for having mammography screening tests for the average woman are:

I. U.S. Preventive Services Task Force (USPTF), [21-25]: Screening of women aged between 40 and 49 should not be routine but based on individual's risk factors and values (because the benefits of screenings do not outweigh the risks). Every two years between the ages of 50 and 74.

II. American Cancer Society (ACS), American College of Radiology (ACR), American Congress of Obstetricians and Gynecologists (ACOG): Annually beginning at age 40.

III. U.S. National Cancer Institute (NCI): Every one to two years for women ages 40 to 49.

IV. American College of Physicians (ACP): Individualized screening plans as opposed to wholesale biannual screening of women aged 40 to 49.

V. Canadian Task Force on Preventive Health Care (CTFPHC, 2012): Every 2-3 years between the ages of 50 and 69. It found that for women aged 50-69, screening 720 women once every 2-3 years for 11 years would prevent 1 death from breast cancer. For women age 40-49, 2100 women would need to be screened at the same frequency and period to prevent 1 death from breast cancer; and

VI. European Cancer Observatory (ECO, 2011): Every 2-3 years between the ages of 50 and 69. The reports from the above task forces note that the risks of more frequent mammograms include a small but significant increase in breast cancer induced by radiation, a risk that is greater for younger women.

On the other hand, the Cochrane Collaboration (CC, 2011) analysis of screening further concluded that: "Mammograms reduce mortality from breast cancer by an absolute amount of 0.05% or a relative amount of 15%, but also result in unnecessary surgery and anxiety such that it is not clear whether mammography screening does more good than harm and that universal screening may not be reasonable". It also states that "the best quality evidence does not demonstrate a reduction in mortality generally or a reduction in mortality from all types of cancer from screening mammography" [26-30].

In addition, the Nordic Cochrane Collection (NCC, 2012) states that "advances in diagnosis and treatment make mammography screening no longer effective today in decreasing deaths in breast cancer, and therefore no longer recommend routine screening for healthy women at any age as the risks might outweigh the benefits and warns of misleading information on the internet". Further, their analysis showed that "one in 2,000 women will have her life prolonged by 10 years of screening, however, another 10 healthy women will undergo unnecessary breast cancer treatment. Additionally, 200 women will suffer from significant psychological stress due to false positive results".

Repeated mammography starting at age 50 saves about 1.8 lives over 15 years for every 1,000 women screened. This result must be gauged against the negatives of errors in diagnosis, over-treatment and radiation exposure. Also, screening mammography does not reduce death overall, but causes significant harm by inflicting cancer scare and unnecessary surgical interventions. About 7% (more realistically, 10%-15%) of women screened with mammography will be called back (with great distress) for a diagnostic session. However, most of these recalls will result in "false positive" results. For 1,000 recalls, about 60 will have benign growths and 10 will be referred for a biopsy (of which about 3.5 will have a cancer, of which about 2 will be a low stage cancer that will be essentially cured after treatment, and 6.5 will not) [31-37].

Mammography may also produce "false negatives" (not seeing the cancer), usually around 10%-30%, due to (a) observer error, (b) cancer hidden by other dense tissue in the breast, and (c) cancer overlapping normal tissues. Furthermore, one form of breast cancer, lobular cancer, has a growth pattern that produces shadows on the mammogram which are indistinguishable from normal breast tissue. A meta-analysis review of programs in countries with organized screening found 52% over-diagnosis.

Women whose breast cancer was detected by screening mammography before the appearance of a lump or other symptoms commonly assume that the mammogram "saved their lives". In practice, the vast majority of these women received no practical benefit from the mammogram. There are five categories of cancers found by mammography [38-46]:

i. Cancers that are so easily treated that a later detection would have produced the same total cure (that is, the woman would have lived even without mammography).

ii. Cancers so aggressive that even "early" detection is too late (the woman dies despite detection by mammography).

iii. Cancers that would have receded on their own or are so slow-growing that the woman would die of other causes before the cancer produces symptoms (mammography results in over-diagnosis and over-treatment).

iv. The small number of breast cancers that are detected by screening mammography and whose treatment outcome improves as a result of earlier detection; and

v. Clinical trial data suggests that 1 woman per 1,000 healthy women screened over 10 years falls into this category. Screening mammography produces no benefit to any of the remaining 87% to 97% of women.

In summary:

a) The guidelines for screening mammography advocated by the several professional associations or/and U.S. governmental organizations are conflicting and even confusing. Would it not be helpful for patients if these entities were to agree to a uniform set of guidelines (even though these would still be "guidelines")?

b) Further, because mass screening as a tool for the detection of early breast cancer in otherwise healthy women without symptoms is controversial, shouldn't this screening be conducted on an individual basis and only in case of significant risk?

c) Still further, since the radiation sensitivity of the breast in women under age 35 is possibly greater than in older women, should it not be generally imperative that these women be screened only if there is a significant risk of cancer (such as, BRCA positive, very positive family history, palpable mass) and even in these circumstances to employ ultrasound or magnetic resonance for imaging? Also, and likewise, should screening of women aged between 40 and 49 not be routine but based on individual's risk factors and values (because the benefits of screenings do not outweigh the risks)?

d) Additionally, beyond age 50, should screening not be conducted systematically and only infrequently at appropriate time intervals to be defined?

e) Lastly, based on the important Cochrane Collaboration and the Nordic Cochrane Collection, should not routine screening be discouraged for healthy women of any age as the risks might outweigh the benefits?

Prostate cancer

The gold standard is the rectal finger test, a subjective test depending on the skill and experience of the examining physician (internist or urologist). The quantitative test is the measure of the prostatic specific antigen (PSA) blood test.

PSA is a glycoprotein enzyme encoded in humans by the kallikrein-3 (KLK3) gene⁶. It is produced in the epithelial cells of the prostate, and can be demonstrated in biopsy samples or other histological specimens using immunohistochemistry. It is present in small quantities in the serum of men with healthy prostates, but is often elevated in the presence of prostate cancer or other prostate disorders. It remains present in prostate cells after they become malignant. Individual prostate cancer cells produce less PSA than healthy cells; the raised serum levels in prostate cancer patients are due to the greatly increased number of such cells, not their individual activity. However, in most cases of prostate cancer, the cells remain positive for the antigen, which can therefore be used to identify metastasis. Also, since some high-grade prostate cancers may be entirely negative for PSA, histological analysis to identify such cases usually employs PSA in combination with other antibodies (PSAP, CD57). PSA is not a unique indicator of prostate cancer, but may also detect prostatitis (prostate inflammation) or benign prostatic hyperplasia (BPH, prostate anomalous growth).

Clinical practice guidelines for prostate cancer screening vary and are controversial due to uncertainty as to whether the benefits of screening ultimately outweigh the associated risks (see above). For those men who opt for surgical therapy (radical prostatectomy) or radiation therapy, it is difficult to interpret the relationship between PSA levels and recurrence/persistence of prostate cancer after surgical or radiation therapy. PSA levels may continue to decrease for several years after radiation therapy. The likelihood of developing recurrent prostate cancer after curative treatment is correlated to various risk factors, such as the grade of prostate cancer (Gleason score), PSA level prior to treatment, and the stage of disease prior to treatment. Low-risk cancers are the least likely to recur, but they are also the least likely to have required treatment in the first place.

The test guidelines are as set forth below:

a. The U.S. Food and Drug Administration (FDA). Every year, ritualistically, nearly thirty million men in the U.S. partake in a mass screening PSA test. The current (FDA) guideline is for all men over age fifty to have their PSA checked annually. Of these, approximately 250,000 have a “false positive” result, meaning an elevated PSA level in the absence of cancer. However, to rule out cancer, these men must further undergo excruciatingly painful biopsies that must be repeated every six months for at least the following year if the initial biopsy was negative. It is true that prostate cancer is extremely common in men, more particularly elderly men with 15% of them carrying the diagnosis. However, only 3% of men succumb to the disease. Thus, there is considerable prevalence of non-aggressive prostate cancer (a latent disease that can take a decade or more before reaching a detectable size).

b. The U.S. Preventive Services Task Force (PSTF, 2012) does not recommend PSA screening noting that: (a) PSA-based screening results in small or no reduction in prostate cancer-specific mortality; (b) It is associated with harms related to subsequent evaluation and treatments, some of which may be unnecessary; (c) “[t]he potential benefit does not outweigh the expected harms (false positives, biopsy pain, and other complications)” in patients not already diagnosed or being treated for prostate cancer”.

The test may result in (a) “over-diagnosis” and “over-treatment” because “most prostate cancer is asymptomatic for life”; (b) Treatments involve risks of complications: for every 1,000 men screened, 29 will experience erectile dysfunction, 18 will suffer urinary incontinence or impotence (erectile dysfunction, ED), 2 will have serious cardiovascular events, 1 will suffer pulmonary embolus or deep venous thrombosis (DVT), and 1 perioperative death and (c) The “potential benefit does not outweigh the expected harms”.

c. The U.S. Food and Drug Administration (FDA) has approved the PSA test for annual screening of prostate cancer in men aged 50 and older. PSA levels between 4 and 10ng/mL (nanograms per milliliter) are considered to be suspicious and consideration should be given to confirming the abnormal PSA with a repeat test. If indicated, prostate biopsy is performed to obtain tissue sample for histopathological analysis.

d. In the United Kingdom, the National Health Service (NHS, 2005) does neither mandate nor advise for PSA test, but allows patients to decide based on their doctor’s advice.

The test alone costs the U.S. the sum of \$3 billion to which must be added billions more for the biopsies, surgeries and their complications (incontinence, impotence), and radiation treatments and their complications. These figures have prompted the test inventor (Dr. Richard Adlin) to publish an op-ed in the New York Times of March 9, 2010 titled: “The Great Prostate Mistake” in which he stated that “The test’s popularity has led to a hugely expensive public health disaster” and further concluded that “The medical community must confront reality and stop the inappropriate use of PSA screening. Doing so would save billions of dollars and rescue millions of men from unnecessary, debilitating treatments”.

In summary:

- i. PSA is not a unique indicator of prostate cancer, but may also detect prostatitis (prostate inflammation) or benign prostatic hyperplasia (BPH, prostate anomalous growth).
- ii. The “guidelines” issued by the several professional and governmental organizations: The U.S. Food and Drug Administration (FDA), the U.S. Preventive Services Task

⁶PSA is a misnomer in that, though an antigen, it is not specific to the prostate as it can be found in many male and female tissues.

Force (PSTF, 2012), the United Kingdom's National Health Service (NHS, 2005), and others are confusing and even mutually contradictory.

I posit therefore whether, like in the U.K., it would not be advisable to forego the test altogether and reserve it solely to individual patients depending on their characteristics and on their doctors' advice.

The above two examples provide more evidence that so-called "population medicine" (in this case, mass screening) disregards individual variability and promotes considerably more unnecessary medical testing and procedures.

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