

# On Mammography and Hormone Replacement Therapy



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Received: November 30, 2017; Published: December 12, 2017

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## Introduction

About 250 years ago, French philosopher Francois-Marie Arouet Voltaire, wrote:

*"Doctors prescribe medicine of which they know little,  
to cure diseases of which they know less,  
in human beings, of which they know nothing".*

Has this state of affairs changed very much since then? I believe so. However, many would argue "hardly", aside from new technological advances and certain heroic surgical procedures. Our model continues to be population-based (also known as "mass medicalization") rather than patient-centric. Further, notwithstanding the current dogma on "evidence-based" medicine, meaning that the health care provided is based on solid scientific evidence of utility, a large proportion of tests and prescriptions used frequently have little or no such supportive evidence. Another flaw of today's "evidence-based" medicine is what has been termed "eminence-based" medicine wherein experts make recommendations or "guidelines" for a large proportion of decisions for which no or minimal data exists. These guidelines have a pronounced impact, as they are believed to represent the standard of care, even though they are based on opinion with a paucity of facts. Actually, even the prestigious U.S. Institute of Medicine concluded that *"any valid evidence supports 'well below half' of the practice of medicine (!)"*. Examples abound such as, statins and statin combinations, prostate specific antigen tests, mammography, hormone replacement therapy, etc., I will discuss here mammography and hormone replacement therapy, which are of particular importance in women's healthcare.

## Mammography

Mammography for breast cancer screening for women parallels the prostate specific antigen (PSA) test in men. 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. 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. 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 (lower than those employed in bone radiography) to create images that are subsequently analyzed for any abnormal findings.

### A. Adjunct procedures to mammography are:

- Ultrasound: For further evaluation of masses, including palpable masses not seen on mammograms;
- Ductography (not generally used): For further evaluation of questionable findings as well as for screening 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;
- Magnetic resonance mammography: For greater spatial resolution of mammographic tissue imaging;
- Positron emission mammography; and
- New procedures, including breast tomosynthesis.

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

- U.S. Preventive Services Task Force (2009): 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;
- American Cancer Society, American College of Radiology, American Congress of Obstetricians and Gynecologists: Annually beginning at age 40;

- c. National Cancer Institute: Every one to two years for women ages 40 to 49;
- d. American College of Physicians: Individualized screening plans as opposed to wholesale biannual screening of women aged 40 to 49;
- e. Canadian Task Force on Preventive Health Care (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
- f. European Cancer Observatory (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 (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"*. In addition, the Nordic Cochrane Collection (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). Mammography may also produce "false negatives" (not seeing the cancer), usually around 10%-30%, and 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 four categories of cancers found by mammography:

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

### C. In summary

The guidelines for screening mammography advocated by the several professional associations or/and 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")? 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? Still further, since the radiation sensitivity of the breast in women under age 35 is 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)? Additionally, beyond age 50, should screening not be conducted systematically and only infrequently at appropriate time intervals to be defined? 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? The above provides more evidence that population medicine (in this case, mass screening) disregards individual variability and promotes considerably more unnecessary medical testing and procedures.

## Conclusion

- a. Since the guidelines for screening mammography advocated by the several professional associations or/and governmental organizations are conflicting and even confusing, this screening should be conducted on an individual basis and only in case of significant risk.
- b. Since the radiation sensitivity of the breast in women under age 35 is possibly greater than in older women, it would 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 the screening should employ ultrasound or magnetic resonance for imaging.
- c. 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).
- d. Beyond age 50, screening should not be conducted systematically but only infrequently at appropriate time intervals to be defined.
- e. Based on the important Cochrane Collaboration and the Nordic Cochrane Collection, routine screening should be discouraged for healthy women of any age as the risks might outweigh the benefits. Whereas much more could be said about the mammography test, I would now like to proceed to the example of hormone replacement therapy.

## Hormone Replacement Therapy

Hormone replacement therapy (HRT) refers to any form of hormone therapy wherein, in the course of medical treatment, the patient 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:

- a. Impaired hearing including decrease in the functionality of many regions of the ear;
- b. Reduction of the effectiveness in parts of the central nervous system used for hearing, and
- c. 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:

- a. Positive effects on the prefrontal cortex by boosting the working memory,
- b. No additional weight gain compared to women who do not use HRT, and
- c. 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.

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.*

### Summary

Whereas initially helpful, HRT loses its effectiveness when used for a long period of time, and there are times when it is not only ineffective but actually detrimental. 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, it can also have beneficial effects (boosting the working memory, no additional weight gain, and positive effects in the sex life) that unfortunately can dissipate after receiving HRT for extended periods of time. 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 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). What then is the key to the change in this population medicine paradigm? It resides in the 6 rights: “right” doctor, “right” screen test, “right” patient, “right” drug, “right dose”, and “right” cost. This should be tackled and hopefully implemented.



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DOI: [10.32474/IGWHC.2017.01.000101](https://doi.org/10.32474/IGWHC.2017.01.000101)



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