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Are the biopositive effects of X-rays the only benefits of repetitive mammograms?☆

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Summary Breast cancer mortality rates fell between 1990 and 2000. When something positive occurs in medicine attempts are usually made to explain the observation or claim the credit. In this case, credit has been given to improvements in standard treatments and to increased use of mammography, each said to have made a contribution. Published data on the results of clinical trials utilising high-dose radiation or chemotherapy do not support this position. Improvements in breast cancer mortality are more likely to be the result of the biopositive effects of the low-dose radiation delivered during mammography, based on lower death rates from breast cancer in women subjected to repetitive mammographic screening, albeit with no significant change in all-cause death rates. This is supported by a study in which breast cancer rates were lowered by diagnostic X-rays of the chest.

Introduction

Peto et al. [1] noted that the breast cancer mortality rate between 1990 and 2000 in women 50–69 years old dropped by 30% in the UK and 25% in the USA, and attributed this to improvements in the many types of treatment interventions, each responsible on its own for only a moderate reduction. The early portion (from 1990 to 1993) of the rate decrease was described by Bailar and Gornik [2], who also noted the then recent "substantial increase in the use of mammography among women over 50". The implication was that increased use of mammography was contributing to a reduction in the breast cancer mortality rate somehow, but without significant reductions in all-cause mortality, as shown below. Our hypothesis is that the biopositive effects of X-rays are the only benefits of repetitive mammograms and not the treatments performed on women with positive mammograms.

Lower breast cancer death rates are associated with mammograms

It is still widely believed that mammographic screening for breast cancer leads to higher survival rates although this conclusion is not supported by actual data. While a review of a Swedish mammographic screening programme showed that those screened had a $RR = 0.99$ (ns) for breast cancer

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death, the Two County Council study found a $RR = 0.72$ [3].

In an update to a Cochrane review on this topic, it was reported that the all-cause mortality after 13 years of follow-up of three clinical trials of medium quality was *unchanged* ($RR = 1.00$). The two best-quality trials failed even to find a significant effect on death from breast cancer ($RR = 0.97$) [4]. Lower quality trials usually cited to justify screening showed $RR = 0.75$ for breast cancer mortality, but showed $RR = 1.06$ for all-cause mortality, meaning that even these lower-quality trials did not support annual mammography for life extension. The common problem with these trials was poor randomisation between the control and treatment groups. An additional bias surfaced: it was found that when researchers were uncertain about the cause of death, they were more likely to ascribe it to breast cancer if the woman had been in the control group than if she had been in the treatment group [5].

The directors of some of the trials objected to this negative evaluation, so they re-evaluated the Swedish trials with the result that, after 16 years of follow-up, the all-cause mortality was *still* unchanged ($RR = 0.98$)! The breast cancer deaths were lower ($RR = 0.79$), but the only significant effect was in women $\geq$55 years old [6].

Common failure to distinguish between lowered breast cancer death rates and unchanged all-cause death rates in women diagnosed with breast cancer has led to misinterpretation of the results of screening and treatments and, consequently, resources are wasted on treatments that do not extend life or its quality.

Oncologists may be misled, for example, by *a recent* oncology text in which the results of nine large mammography trials are given as lowering breast cancer deaths for all ages (mean $RR = 0.80$ for mammography), but without presentation *of all-cause* mortality [7].

Gynecologists may be misled, for example, by a *recent* gynecology text, in which the supposed benefits from mammographic screening, reductions in breast cancer mortality of up to 25% are given ($RR = 0.75$), because *all-cause* mortality is *not* given [8].

Possible causes of lower breast cancer death rates

Surgery

For at least the past quarter-century the treatment of breast cancer by surgery has been applied at about the same rate, certainly in the UK and USA. While a 1969 study showed that fewer radical mastectomies were performed in the UK than in the USA [9], a 25-year follow-up of a randomized trial found no significant difference in disease-free survival time between radical (Halsted) and total mastectomy in women with either positive or negative lymph nodes [10]. Earlier evidence had shown that radical, total and segmental mastectomy gave the same all-cause death rates [11]. Because of the steady rate of surgery as the primary treatment during the last 30 years in the UK and USA, it is unlikely to be responsible for the recent drop in breast cancer death rates regardless of how radical a procedure is performed. Despite the shift in recent years to less extensive surgical procedures, this change has not altered all-cause death rates, and could hardly have lowered breast cancer death rates, thus surgery is not really a "variable" in the time period of concern.

High-dose radiation

The cumulative doses of X-ray or gamma radiation delivered to treat breast cancer are usually in the range of about 4500–5000 cGy. This total amount of radiation is given in doses of about 200 rads per day. Treatments are given five days a week for 5–6 weeks [12]. The addition of high-dose radiation to total mastectomy did not significantly change the cancer free survival times in the 25 years follow-up of the randomized trial cited above [10]. In the Early Breast Cancer Trialists' Collaborative Group's comprehensive overview of all available adjuvant radiotherapy trials for breast cancer started between 1961 and 1990, the absolute survival gain was 1%, and the absolute reduction in breast cancer deaths was 4%. The recent Danish Breast Cancer Cooperative Group trial seemed to show a reduction in breast cancer deaths of 8% [13]. These small reductions cannot explain the larger reductions in breast cancer death rates given above.

Chemotherapy

Because of the extreme side-effects of the typical cytotoxic drugs, no truly double-blind placebo-controlled trials have actually taken place for the adjuvant chemotherapy of breast cancer, and never will be because of the ethical dilemma of providing placebos with similar side-effects to those of the drugs [14]. This is in addition to lead-time bias, stage migration, publication bias and selection bias common to drug trials. In addition, there was a near cessation of placebo-controlled

trials in 1980. The most influential trial, from the National Cancer Institute of Milan, Italy, reported impressive results from node-positive women to cyclophosphamide + methotrexate + 5-fluorouracil (CMF) after 1 year; but after 9 years, as reported in 1984, there was only a 12% improvement in relapse-free survival, and this only in premenopausal women, not in the much greater number of postmenopausal ones. However, the Guy's-Manchester and West Midlands Trials showed no significant benefit even in premenopausal women [15].

The Early Breast Cancer Trialists' Collaborative Group's meta-analysis of all the trials begun before 1985 showed cancer-free survival advantages of about 6% absolute after 10 years follow-up, with no overall survival advantage [16]. Newer chemotherapeutic regimens have improved an end-point called "time to progression" by only a few weeks despite some impressive figures for "relative risk reduction" [17]. According to a review from the National Cancer Institute (US): "... among patients with newly diagnosed stage 1 breast cancer, for whom 5 years overall survival is greater than 90%, a 2- or 3-drug chemotherapy regimen lasting 4–6 months, with its adverse effects, offers an absolute survival benefit of just 1 to 2%" [18].

Chemoprevention

In their report on the Royal Marsden Hospital trial, Powles et al. [19] showed that there was no effect of tamoxifen on breast cancer incidence in healthy women followed for 6 years. This was confirmed by the study by Veronesi et al. [20] of 4 years duration, but not by the Breast Cancer Prevention Trial (BCPT) of the US NCI of 3 years on average of treatment. However, the absolute reduction of breast cancer incidence in the BCPT was from 1.2% to 0.6%, and it must be mentioned that side-effects nullified even this result so far as indicating any overall treatment value [21]. A more favourable review of this trial seemed to suffer from inadequate randomisation and arbitrary alteration of data for the control group [22].

Low-dose radiation from diagnostic X-rays

Using the data in an updated review of the 5 Swedish mammography studies, in which the $RR = 0.79$ for breast cancer mortality [6], we calculated the cumulative radiation dose for each individual study based on the number of examinations (2–7), the number of views (1,2), the attendance rate and the X-ray dose per mammogram in that era of about 2 cGy [23]. The mean value was 12 cGy of cumulative dose.

The Canadian fluoroscopy study involved 31,710 Canadian women being examined and treated for tuberculosis with X-ray doses to the chest beginning between 1930 and 1952, and followed for up to 50 years. The results from all provinces except Nova Scotia, for which too few low-dose data points were taken, are shown in Fig. 1. These are age-adjusted, since first exposure at ages 10–14 was considered to be four times as damaging as exposure over age 35. The data chosen were breast cancer incidence (after 10-years from the first X-ray exposure of the patient) per million person years of exposure. The *RR* of breast cancer at 10–19 cGy cumulative exposure was 0.66 compared with controls; the *RR* was 0.85 at 20–29 cGy; and it was not significantly higher at 30–69 cGy [24]. This interpretation of the study has been faulted because two similar studies failed to show the beneficial effect of low-dose X-rays; however, one of the studies used 2–98 cGy as the lowest

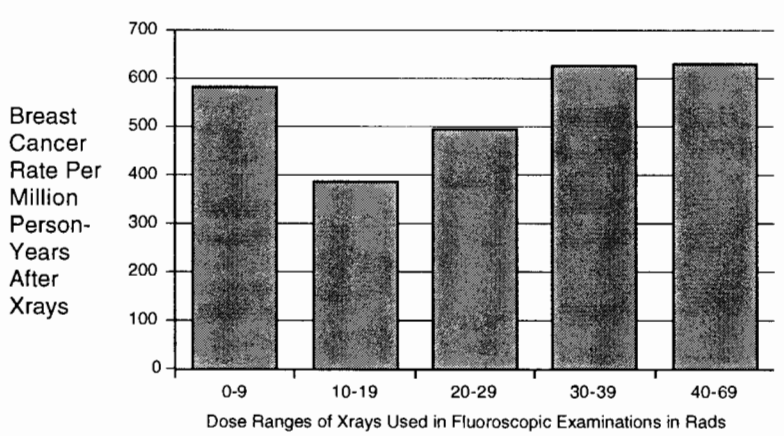

Figure 1 Breast cancer rates vs. cumulative X-ray doses. Adjusted for age of first X-ray exposure. Based on tabular data from [24].

cumulative treatment dose, showing no increase in breast cancer in this group [25]; and the other study had no data below 60 cGy [26].

From the Canadian fluoroscopy study in Fig. 1 it can be seen that the *RR* = 0.66 for breast cancer at the closest cumulative dose range (10–19 rads) to the 12 cGy received by women in the Swedish trials. Even if the Swedish women continued to receive mammograms at the same rate until (or after) the end of the study, and doubled their cumulative doses to 24 rads, their *RR* would be 0.85 for breast cancer based on the Canadian fluoroscopy study. These *RR*s match what is expected from the likely doses of X-rays (0.80), and are not likely to have resulted from conventional treatments.

Other organs also have lower cancer rates as a biopositive effect of low-dose radiation. For example, for half of all US counties, representing 90% of the US population, lung cancer rates decrease by about 35% as the mean radon level in homes (by county) increases from 18–110 Bq/m^3, and by 25% at 110–220 Bq/m^3 [27]. Similar smaller studies in England and France confirm these findings [28].

Theories of how low-dose radiation produces health benefits are well-developed [29]. Irradiated cells initiate protective responses within a few hours, including radical detoxification, DNA repair, cell removal by stimulated immune response, and apoptosis. These responses are also used to repair endogenous DNA and other metabolic damage as well [30,31]. Radiation damage caused by a low initial dose induces a DNA repair mechanism that allows efficient repair of a large number of breaks from a high later dose. This has been investigated by biochemical experimenters in great detail [32]. Radiation hormesis, therefore, is a moderate overcompensation to a disruption in homeostasis caused by the radiation; it is a stimulus to the repair mechanisms that cope with non-radiation damage as well, so that the overall effect is a health benefit [33]. Acute doses of 1–50 cGy are beneficial, and 10 cGy/year appears to be the optimum hormetic dose [31], but there is considerable individual variation. These doses refer especially to external whole-body low-LET radiation.

Conclusions

"Since the benefit achieved (by mammograms) is marginal, the harm caused is substantial, and the costs incurred are enormous, we suggest that public funding for breast cancer screening in any age group is not justifiable" was the conclusion of Wright and Mueller [34]. We agree because superior detection methods for breast cancer have been available, specifically the Anti-Malignin Antibody in Serum (AMAS) test [35]. PET scans can reveal early lymph node involvement [36]. Given these alternatives, it would be wise to abandon mammographic screening of healthy women by overcoming the financial and emotional attachments to the procedure.

While mortality from breast cancer fell in women aged 50–69 between 1990 and 2000, attempts to attribute this decline to improvements in standard treatments and earlier diagnosis with mammography are not supported by the literature. Lower breast cancer mortality is more likely to be the result of the well-documented biopositive effects of low-dose irradiation by X-rays (radiation hormesis) according to the evidence presented in support of our hypothesis. We invite epidemiologists to refine the relationship between cumulative diagnostic radiation and breast cancer death rate. More consideration should be given to providing optimal, rather than minimal, radiation doses for everyone [37].

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References

[1] Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20–69 years. Lancet 2000;355:1822.

[2] Bailar III JC, Gornik HL. Cancer undefeated. N Engl J Med 1997;336:1569–74.

[3] Sjonell G, Stahle L. Mammographic screening does not reduce breast cancer mortality. Lakartidningen 1999;96(8): 908–13.

[4] Olsen O, Gøtzsche PC. Cochrane review on screening for breast cancer with mammography. Lancet 2001;358: 1340–2.

[5] Gøtzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? Lancet 2000;355:129–34.

[6] Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist ER. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet 2002;359(9310):909–19.

[7] Rimer BK, Schildkraut J, Hiatt RA. In: DeVita Jr VT, Hellman S, Rosenberg SA, editors. Cancer screening in cancer principles and practice of oncology. Philadelphia, PA: Lippincott Williams & Wilkins; 2001. p. 627–32.

[8] Mishell DR Jr, Stenchever MA, Droegemueller W, Herbst AL. Comprehensive gynecology. St. Louis, MO: Mosby; 1997. p. 366–72.

[9] Leopold E. A darker ribbon. Boston, MA: Beacon Press; 1999,. p. 208.
[10] Fisher B, Jeong J-H, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by radiation. N Engl J Med 2002;347(8):567–75.
[11] Lerner BH. The breast cancer wars. New York: Oxford University Press; 2001. p. 34, 178–179, 226–227, 256–257.
[12] Arizona Cancer Center, Tucson, AZ, USA. 2003. Available from: www.azcc.arizona.edu/prevent/Breast-cancer07.htm.
[13] Kurtz JM. Radiotherapy for early breast cancer: was a comprehensive overview of trials needed? Lancet 2000;355:1739–40.
[14] Desbiens NA. In randomized controlled trials, should subjects in both placebo and drug groups be expected to guess that they are taking drug 50% of the time? Med Hypotheses 2002;59(3):227–32.
[15] Moss RW. Questioning chemotherapy. Brooklyn, NY: Equinox Press; 2000,. p. 84–89.
[16] Schipper H, Dick JAM. Does consensus help in breast cancer? Lancet 1994;344:836.
[17] Nabholtz J-M, Reese D, Lindsay M-A, Riva A. Evidence for the use of chemotherapy in breast cancer. Int J Clin Oncol 2002;7:254–64.
[18] Agrawal M, Emanuel EJ. Ethics of phase 1 oncology studies. Reexamining the arguments and data. J Am Med Assoc 2003;290(8):1075–82.
[19] Powles T, Eeles R, Ashley S, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. Lancet 1998;352:98–101.
[20] Pritchard KI. Is tamoxifen effective in prevention of breast cancer? Lancet 1998;352:80–1.
[21] Lee JR, Zava D, Hopkins V. What your doctor may not tell you about breast cancer. New York, NY: Warner Books; 2002. p. 183–190.
[22] Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst 1999;91(21):1829–46.
[23] Gofman JW, O'Connor E. X-rays: health effects of common exams. San Franciso, CA: Sierra Club Books; 1985.
[24] Miller AB, Howe GR, Sherman GJ, et al. Mortality from breast cancer after irradiation during fluoroscopic examinations in patients being treated for tuberculosis. N Engl J Med 1989;321(19):1285–9.
[25] Boice Jr JD, Monson RR. Breast cancer in women after repeated fluoroscopy of the chest. J Natl Cancer Inst 1977;59(3):823–32.
[26] Shore RE, Hildreth N, Woodard E, Dvoretsky P, Hempelmann L, Pasternack B. Breast cancer among women given X-ray therapy for acute post-partum mastitis. J Natl Cancer Inst 1986;77:689–96.
[27] Cohen BL. Lung cancer rate vs. mean radon level in US counties of various characteristics. Health Phys 1997;72(1):114–9.
[28] Cohen BL. Test of the linear-no threshold theory of radiation carcinogenesis for inhaled radon decay products. Health Phys 1995;68(2):157–74.
[29] Parsons PA. Radiation hormesis: an ecological and energetic perspective. Med Hypotheses 2001;57(3):277–9.
[30] Feinendegen LE, Pollycove M. Biologic responses to low doses of ionizing radiation: detriment versus hormesis: part 1. Dose responses of cells and tissues. J Nuclear Med 2001;42(7):17N–27N.
[31] Luckey TD. Radiation hormesis. Boca Raton, FL: CRC Press; 1991. p. 5, 228–230.
[32] Wolff S. Is radiation all bad? The search for adaptation. Radiat Res 1992;131:117–23.
[33] Cuttler JM. Low-dose irradiation therapy to cure gas gangrene infections. Washington, DC: American Nuclear Society Winter Meeting; 2002. p. 17–21.
[34] Wright CJ, Mueller CB. Screening mammography and public health policy: the need for perspective. Lancet 1995; 346:29–32.
[35] Thornthwaite JT. Anti-malignin antibody in serum and other tumour marker determinations in breast cancer. Cancer Lett 2000;148:39–48;
Thornthwaite JT. Oncolab, Inc., Boston, MA, USA. 2003. Available from: www.amascancertest.com.
[36] Einstein Industries Inc., San Diego, CA, USA, PET Scan InfoCenter. 2003. Available from: www.petscaninfocenter.com.
[37] Luckey TD. Nurture with ionizing radiation: a provocative hypothesis. Nutrition Cancer 1999;34(1):1–11.