Breast Cancer Induced by X-Ray Mammography Screening? A Review Based on Recent Understanding of Low-Dose Radiobiology

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Abstract

Screening mammography offers the possibility of discovering malignant diseases at an early stage, which is consequently treated early, thereby reducing the mortality rate. However, ionizing radiation as used in low-dose X-ray mammography may be associated with a risk of radiation-induced carcinogenesis. In the context of the harmful effects of ionizing radiation, this article reviewed novel radiobiological data and provided a simulation of the relative incidence of radiation-induced breast cancer due to screening against a background baseline incidence in a population of 100,000 individuals. The use of modern digital mammographic technology was assumed, giving rise to a glandular dose of 2.5 mGy from a 2-view per breast image. Assuming no latency time, this led to a ratio of induced incidence rate over baseline incidence rate of about 1.6‰ for biennial screening in women aged 50–74 years, although it cannot be excluded that the dose and dose rate effectiveness factor values relying on new radiobiological insights may lower this number to about 0.7‰. This carcinogenic risk is considered small in relation to the potential beneficial effects of screening, especially as latency time was not taken into consideration. However, individuals who are known to be carriers of risk-increasing genetic variations and/or have an inherited disposition of breast cancer should avoid ionizing radiation as much as possible and should be referred to ultrasound or magnetic resonance imaging. In addition, a significant, but difficult to quantify, risk of cancer is present for individuals who suffer from hypersusceptibility to ionizing radiation.

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Introduction

Cancer of the breast is the most common malignancy in women worldwide [1]. A study in 187 countries on mortality and incidence for the period 1980–2010 revealed that the global incidence increased from an estimated number of 641,000 in 1980 to 1,643,000 cases in 2010, an annual rate of increase of 3.1% [1]. Within Eu-

E.K.J. Pauwels would like to dedicate this article to Dr. Ad Tates, friend and scientist, who taught him the basics of radiobiology in the early seventies and who contributed considerably to his understanding of the positive and negative effects of ionizing radiation in medicine.

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rope, the incidence rate increases from south to north and from east to west [2], and in the USA the highest rate of female breast cancer mortality is found in the northeast (relative risk around 1.3 in the all-race category) [3].

Among the etiological factors, a great deal of attention has been paid to cancer genomics, and these studies had identified a number of gene variations that increase the risk of breast cancer; it was estimated that 5–10% of all breast cancer cases are due to familial autosomal dominant effects [4]. Genome-wide association studies have identified at least 20 susceptibility genes that harbor intermediate- or high-risk mutations in breast cancer [5, 6], and undoubtedly more will follow [7]. Among these are carcinogenic mutations in either BRCA1 or BRCA2 genes, and female carriers of these high-penetrance variations have an 80% lifetime risk of developing breast cancer [8]. Apart from genetic susceptibility, other factors are related to an increased risk of breast cancer: ethnicity, age of menarche, parity, obesity, diabetes, lifestyle, socioeconomic status, environment and particularly radiation have all been associated with breast cancer risk [9, 10]. Hence, increased breast cancer has been demonstrated in young women who underwent frequent and/or lengthy (fluoroscopic) X-ray examinations for tuberculosis [11, 12], spinal disorders [13] or treatment by radiotherapy as in Hodgkin's disease [14]. A comparison between a cohort of young Japanese women, less than 10 years of age when they were exposed to ionizing radiation from the atomic bomb explosion in Hiroshima, and Canadian cohorts who underwent moderate-dose irradiation of the chest for various diseases revealed that these young people were likely to develop breast cancer at a later age [15, 16]. This difference disappeared at the ages of 30–40 years, whereas the risk increased again at older ages. A review [17] comprising 11 retrospective studies and 3 case-control studies revealed that the risk of breast cancer increased at 8 years following chest irradiation and continued to increase at longer follow-up periods in comparison with age-controlled women in the general population. These and other studies [18, 19] raised the question of how far screening of breast cancer in the general population adds to the incidence of breast cancer due to ionizing radiation used in X-ray mammography. This is a relevant question as screening programs are intensified, and public information has contributed to awareness of this disease.

The aim of this paper was to approach the risk of screening X-ray mammography in a broad medical scientific context, elucidate recent X-ray-related radiobiological insights and summarize recent preclinical data rele-

vant to the risk of radiation-induced breast cancer. Furthermore, although only models exist, we provided fresh data on the incidence of possible malignant transformation due to screening. Accordingly, this review consisted of three parts: the first part summarized the present knowledge regarding the assessment of radiobiological effects, including cellular damage and responses due to ionizing radiation. Indeed, it is most likely that radiation has an adverse carcinogenic effect on cells due to mutations in tumor suppressor genes. The second part highlighted in vitro and ex vivo X-ray studies regarding the risk of malignant transformation of mammary cells. The third part dealt with breast cancer induction as a response to screening X-ray mammography and provided a risk estimate of breast cancer induction. This estimate was based on available data from the scientific literature, the Biological Effects of Ionizing Radiation (BEIR VII) 2006 report, the International Committee on Radiation Protection (ICRP) 2007 report [20] and a previously published excess risk model [19]. This allowed us to provide an approximate incidence value of radiation-induced cancers by screening mammography and to relate this to the baseline incidence of breast cancer in women. Against this particular background this article will contribute to the ongoing discussions on the radiation safety of breast cancer screening with X-ray mammography.

The gray (Gy), measured in joules per kilogram, is of relevance for this paper and is the measurement unit for the total energy absorbed by the irradiated tissue. The mean glandular dose by mammographic screening amounts to 2.5 mGy, using technologically advanced digital mammographic X-ray imaging [21]. For the extrapolation from high to low doses and from high to low dose rates, the dose and dose rate effectiveness factor (DDREF) was introduced to take into account that the risk seems smaller at low doses and low dose rates. A DDREF of 1.5 means that the risk is 1.5 times lower. X-ray mammography is considered a low-dose and low-dose-rate examination.

A Survey of Radiation Damage and Cellular Responses

The carcinogenic effects of ionizing radiation are well documented and have been the subject of numerous papers [22–25]. In short, epidemiological data from the atomic bomb survivors in Japan provided data on doses above 50–100 mGy. Furthermore, these papers provided ample evidence that an excess cancer risk is linearly re-

lated to the effective dose. Below this dose level there is no robust epidemiological data available that allow for a conclusive estimate [26]. Nevertheless, international bodies like BEIR have endorsed a linear nonthreshold model [27]. This principle translates into the rule that any ionizing radiation requires protection since there is no safe dose. In this context it should be noted that low-dose radiation may induce a beneficial effect (also called hormesis), mostly demonstrated in experimental in vitro studies [28]. In recent papers, however, Tang and Loke [29] and Perez et al. [30] discuss this effect and advocated that translation of such biopositive effects to the human organism should be made with caution.

The literature suggests that misrepaired DNA damage, particularly DNA double-strand break (DSB), can cause cell transformation (including carcinogenesis) [31]. This does not mean that one single transformed cell is going to develop as a cancer, but there is no cancer without transformed and instable cells. Hence, to investigate the fate of DSB or of any DNA damage that can lead to the formation of DSB is critical. The initial DNA damage results from the physical energy microdepositions and subsequent radical oxygen species that attack DNA molecules: e.g., 40 DSBs are created on average by 1 Gy of ionizing radiation. The DNA damage response system is an intracellular defense system, in general terms consisting of numerous proteins functioning as sensors, mediators, transducers and effectors, which are able to repair the damage or induce cell death by mitotic death, senescence or apoptosis (programmed cell death) [32]. What makes the difference between individuals is not only the capability to recognize the existence of the DNA damage and to repair it appropriately or not, but also the capability to favor the DNA damage repair pathway that would lead to the lowest yield of misrepaired DNA damage. For example, in the particular case of DSB, there are at least two major principles for repairing DSB: the end-joining that consists in ligating the two broken ends; the recombination that consists in cutting some DNA sequences and thereafter inserting them in the breaks induced by radiation. While the defect in DNA end-joining is associated with cellular death and radiosensitivity, the lack of control of recombination (hyperrecombination) likely causes genomic instability and cellular transformation [33].

Szumiel and Foray [34] indicated that many specific proteins are involved and are essential to carry out the necessary steps for efficient and error-free DSB repair. For example, one specific protein in this category is ataxia telangiectasia mutated kinase (ATM), which is mainly localized in the cytoplasm as a dimeric and inactive form.

The ATM kinase phosphorylates a number of protein substrates that hold specific SQ/TQ domains and are involved in the DSB recognition and repair, cell cycle arrest and cellular death steps through a hierarchical and orderly cascade. There are numerous ATM substrates including BRCA1, BRCA2 and p53, all involved in the radiation response [35]. Following exposure to ionizing radiation, the ATM protein molecules become monomeric and diffuse to the nucleus where they trigger the phosphorylation of the H2AX histone variant at serine 139 (γ-H2AX) which reflects the recognition of DSB managed by the end-joining pathway. In parallel, the ATM kinase activity in the nucleus contributes to inhibit the activity of certain nucleases like MRE11, which prevents hyperrecombination [36, 37].

The absence or the delay of the ATM nucleoshuttling, i.e. translocation of ATM from the cytoplasm to the nucleus, has been observed in many diseases, especially neurodegenerative diseases, e.g. Huntington disease, as a result of trapping ATM in the cytoplasm due to its interaction with abnormal proteins, e.g. huntingtin [37]. The ATM nucleoshuttling can be restored by statins, which stimulate DNA repair. These observations open a new field of investigations of the DNA damage response system and especially the dynamics of DNA damage signaling and repair related to the kinetics of the ATM nucleoshuttling. This will provide new insights regarding the mechanisms of individual radiosensitivity and genomic instability [34, 38].

Biological Assays for the Assessment of Radiation Exposure

In the field of radiation protection, two major validated and standardized techniques are commonly used, and their principles are mentioned briefly below: the micronucleus assay [39] and the γ-H2AX assay [40]. Micronuclei are fragments of unrepaired DSBs. They are generally acentric and are not segregated with other chromosomes during mitosis. In consequence, a micronucleus is expulsed from the nucleus and after some cycles from the cell. Within the framework of this article, it is noteworthy that the micronucleus frequency is not a significant biomarker for the prediction of breast cancer risk or susceptibility [41], although it has been recognized that increased frequencies of micronuclei are linked to the presence of (pre)neoplastic lesions [42].

Another assay of chromosomal damage is based upon the assessment of the nuclear foci formed by the H2AX phosphorylation at the site of DSBs easily quantified by immunofluorescence [43, 44]. In addition to the γ-H2AX

immunofluorescence, the phosphorylation of γ-H2AX can also be quantified by Western blot or by ELISA assays, but these techniques do not provide any information of the spatial distribution of foci in the nucleus [45].

Radiobiological Responses following Radiation at Low Doses

At low radiation doses, below 50–100 mGy, specific mechanisms that do not occur at higher doses have been observed. This phenomenon, the so-called low-dose hypersensitivity in normal persons, has been observed initially by Joiner and Denekamp [46]. A recent extensive review by Martin et al. [47] provided a comprehensive overview of the experimental data detailing the incidence, mechanism and significance of low-dose hypersensitivity to radiation, featuring excess of cell death. This is considered a specific way of suppressing precancerous phenomena in cells in which a complete and efficient repair process has failed. In the present paper, low-dose hypersusceptibility refers to an excessive individual probability to undergo a harmful effect by low-dose radiation, whereas low-dose hyper(radio)sensitivity refers to a general effect in which cells die from excessive sensitivity to low doses (<0.5 Gy) of ionizing radiation [48].

Thus, low-dose radiation may result in carcinogenic DNA damage and may as well elicit a number of damaging control mechanisms to remove neoplastically transformed cells as well. Special caution, though, needs to be given to hyperradiosusceptibility to low-dose radiation in some individuals.

In vitro and ex vivo Studies of Breast Cancer Risk

The possibility of DNA misrepair due to ionizing radiation is widely believed to be one of the main causes of neoplasia [49–51]. Therefore, radiation exposure of the female breast by routine mammography screening may contribute to the increased incidence of breast cancer in the population. Indeed, radiation-induced cellular alterations of mammary epithelial cells have been the subject of various studies, and this paragraph will summarize recent key findings from in vitro and ex vivo experiments.

Slonina et al. [48] made clear that at low radiation doses <0.4 Gy, fibroblasts and keratinocytes can be hypersensitive to radiation. Their data suggested that this uncommon low-dose chromosomal hypersensitivity may be a characteristic of an individual patient. This 'proof of principle' convinced Colin et al. [52] to study the effect of irradiation with a mammograph used routinely for patients

on breast epithelial cells obtained from biopsy samples. The cells came from two groups of patients: low-risk individuals with no family history of breast cancer and individuals with a lifetime risk equal or higher than 20% attested by a geneticist. The cells were irradiated in a way to mimic the mean glandular dose, i.e. a repeated dose of 2 mGy separated by 3 min to simulate a 2-view mammography, and a single dose of 4 mGy to serve as a control. DSBs were assessed by means of γ-H2AX and micronucleus assays. With regard to this damage, the results indicated that 10 min after irradiation, the dose effect was significantly higher in high- than in low-risk patients (p = 0.006 at 2 + 2 mGy). At 24 h after irradiation, the dose effect was also higher in high- than in low-risk individuals but lacked significance (p = 0.12). The micronucleus assays as for unrepaired low- and high-risk cells did not show a significant difference, which was attributed to the difficulty in scoring. On the other hand, the γ-H2AX data demonstrated radiation effects exacerbated in high-risk cases. As emphasized by the researchers, their study had focused on unrepaired DSBs induced by mammography. Although these breaks, when misrepaired, could lead to genomic instability and radiation-induced cancer, their study only highlighted the generation of DNA damage. Thus, the paper of Colin et al. [52] focusing on radio-induced DNA damage in nontumoral breast epithelial cells demonstrated the existence of individual variations linked with the familial history of breast cancer.

Hernández et al. [53] also investigated the deleterious effects of mammographic screening using normal young and older age human epithelial cells from mammary specimens. Both the young and the aged cells were irradiated under a mammographic device, and the formation of γ-H2AX foci was examined to estimate DSB induction and disappearance over time following radiation exposure. The interval between 2 shots was under 30 s, and the analysis was carried out 120 min after radiation exposure. This study revealed that aged cells had a diminished capacity to cope with mammography-induced DNA damage. It was shown that only 2 shots (10 mGy per shot, a dose equivalent to 2-view screens based on a total glandular dose of 4.5 mGy) were sufficient to generate an increased amount of damage in the aged cells, but not in their young counterparts (p < 0.05). The main conclusion from these experiments was that aged cells revealed accumulation of irreparable DSBs and/or telomere erosion, a deleterious effect not observed in young cells. Furthermore, temporal analysis showed that this low-dose X-ray exposure led to delayed disappearance of DSBs in the aged versus the young cells. These results are in agree-

ment with the increased carcinogenic risk of radiation exposure observed at older ages in epidemiological studies [54].

Thus, DSBs followed by the phosphorylation of the histone H2AX give rise to the recruitment of DNA repair molecules, and the generated foci are well suited to visualize radiation damage in biological targets. An interesting result of the use of this biomarker is the fact that aged epithelial breast cells are more sensitive to low-dose ionizing radiation than younger ones. Moreover, this assay is particularly useful in assessing the effect of ionizing radiation in high-risk individuals, even at low doses as used in X-ray digital mammography.

An Estimation of Induced Breast Cancer due to Low-Dose Radiation Exposure

For relatively low doses below 50–100 mGy, recent experimental data suggested [55–57] that the dose-response curve concaves upward at least partly because of 'nontargeted effects'. This effect made BEIR VII use a DDREF that should be used to decrease risk estimations at low doses and dose rates in comparison to high doses and dose rates as well as for radiation protection standards. For breast cancer risk associated with screening mammography, a DDREF of 1.5 was used by De Gelder et al. [19], although BEIR VII mentions a 95% credible interval between 1 and 3 [58]. This led us to estimate the induced cancer risk on the basis of a previously published study by De Gelder et al. [19], who calculated the risk and explored the relative incidence of radiation-induced breast cancer due to screening against the background of baseline incidence of breast cancer in a population.

For our estimations of incidence rates, we used the following starting points:
- Biennial screening at the age of 50–74
- Use of full-field digital mammography
- Glandular dose of 2.5 mGy for 2-view examination
- DDREF corrections in the range of 1–3, highlighting 1, 1.5 and 2
- Estimation in a population of 100,000 women, aged 0–100
- 100% rate of screening participation
- No latency period
- Numbers valid for 2012

Incidence rates rather than mortality rates were estimated, as the latter is subject to continuously changing treatment regimens and consequent survival rates. Age-standardized incidence rates for breast cancer per 100,000 women, aged 0–100, per country in 2012 were published by Ferlay [59]. For our estimates, the average of 10 European countries that have the highest incidence rates were used: Belgium, Denmark, France, the Netherlands, the UK, Ireland, Germany, Italy, Finland and Switzerland, in that sequence, varying from 111.2 to 83.1 breast cancer cases per 1,000 women. This allowed us to estimate a baseline incidence per 100,000 women aged 0–100 (without screening) of 9,625 for the year 2012. Furthermore, we adjusted the numbers provided by De Gelder et al. [19], who calculated an induced incidence per 100,000 women, aged 0–100, based on a glandular dose of 1.3 mGy (1 view) and a DDREF of 1.5. Instead, a radiation dose of 2.5 mGy per 2 views per gland was used, leading to a ratio-induced incidence rate over baseline incidence rate of about 1.6‰. Apart from the DDREF value of 1.5, BEIR VII mentions a 95% credible interval of 1–3, whereas the ICRP 2007 mentions a value of 2. DDREF values between 1 and 2 have the highest probability [48], and these numbers lead to a ratio-induced incidence rate over baseline incidence rate of 2.2‰ (for a DDREF = 1.0) and 1.1‰ (for a DDREF = 2.0). A DDREF of 3, which has a low probability, would result in a ratio-induced incidence rate over baseline incidence rate of around 0.7‰.

How Does This Relate to Newer Radiobiological Insights?

The DDREF value may be affected by newer radiobiological insights [59], and it has been suggested that the current DDREF value of 1.5 is too small and could even be as high as 4, relying on animal experimental data and radiation-induced cellular processes. Thus, it may well be that there is a need to reevaluate DDREF values starting from 'significant radiobiological data suggesting nonlinear effects at low and very low dose, implying that health effects may be significantly less at low dose rates than risk factors currently used' (partially cited in Preston [58]). This would imply that mutations and chromosomal aberrations observed at low dose ranges up to about 100 mSv would need further scientific clarification regarding the degree of a cancer response. As yet, as long as there are no convincing data indicating otherwise, advisory bodies such as BEIR and ICRP retain values ranging from 1 to 2 in order to maintain stability in the radiation protective system [60].

In connection with what has been stated above, data from Preston [58] indicated as well that DDREF could be less in a small number of breast cancer patients. In such patients, the risk is higher at low doses and low dose rates than at higher doses and dose rates, which may, at least,

be partly due to the hypersensitivity phenomenon. For instance, a DDREF of 0.5 would result in a ratio-induced incidence rate over baseline incidence rate of about 4.4‰.

Implications

One important technological improvement with regard to mammography for screening regimens is the use of digital imaging. In a Norwegian screening program, a randomized trial of women aged 49–69 years out of a total of 24,000 women indicated that digital mammography resulted in a significantly higher cancer detection rate (p = 0.07) and specificity (p = 0.005) than did screen film mammography [61]. This is an important outcome as the higher accuracy comes with a lower radiation dose. In this context, various aspects of digital imaging in relation to diagnostic radiation are mentioned.

First, in view of individual patient care, it is of the utmost relevance to offer the best available technology. This avoids falsely reassuring imaging results as well as a positive screening resulting in a recall for further assessment. Apart from the great psychological consequences and the psychosocial harm [62, 63], there is the accumulated risk associated with additional X-ray mammography [64].

Second, our estimates are based upon the radiation dose for digital mammography, which leads to a reduction of the induced incidence rate of 22% [65] versus screen film mammography.

Third, among the population that undergoes the screening by mammography, there are those who (without knowing) suffer from some degree of germline mutations. For these mutation carriers, a lower radiation dose would undoubtedly diminish the risk of radiation-induced breast cancer. In this respect, Colin and Foray [66] recommended 1 single view mammography for screening. Nevertheless, although mammography is the mainstay of screening, carriers of genetic mutations that increase the lifetime risk of breast cancer as well as those with a family history of breast cancer should be referred to magnetic resonance (MRI) and/or ultrasound imaging as part of the screening process to limit exposure to ionizing radiation ('personalized screening') [67], even if an increase in false-positive findings had been reported [68, 69]. The same is true for women who underwent therapeutic irradiation of the chest for childhood, adolescent or young adult cancer. These women have a substantially elevated risk for breast cancer [17, 70]. In this category of patients, various articles and published guidelines recommended initial breast screening with both MRI and mammography and using

MRI in follow-up studies [71, 72], whereas ultrasound is an option for high-risk women who cannot undergo MRI [73]. In this respect, it should be noted that noncontrast 1- to 1.5-tesla MRI breast imaging has a sensitivity of approximately 90%, but a specificity of 75% [74], whereas in high-risk women these numbers are 77 and 39%, respectively [75]. These data illustrate that MRI as such cannot be used for screening purposes.

Fourth, the lower radiation dose involved in digital mammography has a favorable but difficult to quantify impact on the occurrence of tumor induction in comparison to analog mammography for the same number of views. This is related to the fact that breast density has been advocated as a risk factor of breast cancer, but it is still not clear if breast density by itself is a true risk factor [76] or if breast density – which occurs mostly in young women – implies an increase in the mammographic dose to obtain a good image, thereby increasing the cancer risk due to a higher exposure to ionizing radiation. It is worth recalling that breast cancer screening should not start before the age of 50 years of age.

Fifth, the study by Colin et al. [52] confirmed that apart from DSBs directly caused by ionizing radiation, biological systems also suffer from delayed genomic instability. This implies that ionizing radiation induces at least two mechanically different types of genomic instability leading to cancer predisposition: one that is a direct consequence of radiation and another that follows an error-prone recombination repair pathway, called the hyperrecombination process (known as the 'LANI effect' by Colin et al. [52]). The latter is generally encountered in genetic syndromes associated with higher cancer risk, such as BRCA mutations. This additional genomic instability can be even more prominent than the direct effect induced by ionizing radiation and illustrates that the physical dose alone is not sufficient to predict the biological effects of ionizing radiation [77]. Clinically, this phenomenon is linked to an increased risk of X-ray mammography-induced breast cancer in mutation-positive women, resulting in an increased mortality of about 1.5–2.5‰ for annual screening [78].

Sixth, in the particular case of mammography, a repeated dose effect must be taken into account: during the short interval needed to change the photographic cassette, no DSBs had been observed by Colin et al. [52]. Hence, chromatin is still decondensed when the second X-ray view is taken, giving rise to numerous and severe DSBs. This finding implied that individuals hypersensitive to radiation could suffer from additional effects that favor genomic instability.

Finally, against the background of this paper, it must be mentioned that the radiation dose is part of a trade-off with regard to image quality. Although a very low dose sounds attractive, it may provide insufficient image quality to make a reliable diagnosis. On the other hand, a higher radiation dose may lead to more distinct image features and a more confident diagnosis. Thus, a balance between these two considerations is important and in this respect computer-assisted image enhancement can offer improvements with regard to signal-to-noise ratio and contrast [79].

Conclusion

This article reviewed the breast cancer risk induced by patient exposure from screening X-ray mammography. Considering the growing volume of breast cancer screenings, the carcinogenic effect of ionizing radiation and the risk of induced malignancy have become a topic of scientific debate. In this context, we estimated the incidence rate of radiation-induced breast cancer due to screening against the background of the baseline incidence of this malignancy. Consequently, we began from the use of modern digital imaging equipment and used numerical radiobiological values that have recently been reported. Our calculations provided fresh values of cancer induction. For women who have no family history of breast cancer and/or do not carry detrimental gene variations, we calculated an average ratio of induced incidence rate over baseline incidence rate for breast tumors of about 1.6‰ in Western Europe, although a ratio-induced incidence rate over baseline incidence rate as low as 0.7‰ could be excluded. This may serve as an indication for a risk/benefit ratio and could enable the individual to make a more informed decision to undergo the screening procedure. However, the risk of mammography screening in women who have an abnormal DNA damage response and checkpoint control may be much higher than actually thought. As a result, it would be very desirable to identify those women with a high family risk of breast cancer who are really at risk by a functional testing of the DNA damage response system and checkpoint control. For these women, specific screening of breast cancer would then be carried out with a careful use of mammography, while other women would not need mammography screening as early.

Disclosure Statement

There is no conflict of interest.

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