Original Study

Intensive Imaging Surveillance of Survivors of Breast Cancer May Increase Risk of Radiation-induced Malignancy

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Abstract

Non-recommended imaging is commonly indicated in surveillance of early breast cancer survivors, despite guidelines recommending against. Five theoretic imaging surveillance models were used to estimate imaging radiation-induced malignancy risks. Our models suggest that non-recommended imaging may increase imaging radiation-induced malignancy risks and should be avoided during early breast cancer surveillance.

Background: Current clinical guidelines recommend mammography as the only imaging method for surveillance in asymptomatic survivors of early breast cancer (EBC). However, non-recommended tests are commonly used. We estimated the imaging radiation-induced malignancies (IRIM) risks in survivors of EBC undergoing different imaging surveillance models. **Materials and Methods:** We built 5 theoretical models of imaging surveillance, from annual mammography only (model 1) to increasingly imaging-intensive approaches, including computed tomography (CT) scan, positron emission tomography-CT, bone scan, and multigated acquisition scan (models 2 through 5). Using the National Cancer Institute's Radiation Risk Assessment Tool, we compared the excess lifetime attributable cancer risk (LAR) for hypothetical survivors of EBC starting surveillance at the ages of 30, 60, or 75 years and ending at 81 years. **Results:** For all age groups analyzed, there is a statistically significant increase in LAR when comparing model 1 with more intensive models. As an example, in a patient beginning surveillance at the age of 60 years, there is a 28.5-fold increase in the IRIM risk when comparing mammography only versus a schedule with mammography plus CT scan of chest-abdomen and bone scan. We found no differences when comparing models 2 through 5. LAR is higher when surveillance starts at a younger age, although the age effect was only statistically significant in model 1. **Conclusion:** Non-recommended imaging during EBC surveillance can be associated with a significant increase in LAR. In addition to the lack of survival benefit, additional tests may have significant IRIM risks and should be avoided.

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Introduction

Breast cancer (BC) is the most frequently diagnosed cancer globally and is the leading cause of cancer-related deaths in women.[1] Improvements in early diagnosis and adjuvant therapy have decreased mortality rates.[2] As the number of survivors of BC increases, interest in surveillance after curative treatment has also increased. As of 2014, it is estimated that more than 3 million survivors of BC live in the United States, and the majority of these are survivors of early BC (EBC) that will enter into a prolonged survivorship phase in which surveillance to diagnose recurrence and to identify a second BC is performed.[3,4] There is consensus that mammography is the only imaging method with evidence-based demonstrated efficacy for surveillance in asymptomatic survivors of EBC (allowing to efficiently detect local recurrence and second BC), and clinical guidelines recommend against the use of other imaging modalities different from mammography.[1,5-9]

Despite the available evidence and recommendations, non-recommended imaging tests are commonly used in clinical practice.[10-15] There are many possible explanations for non-adherence to surveillance guidelines. These include the belief

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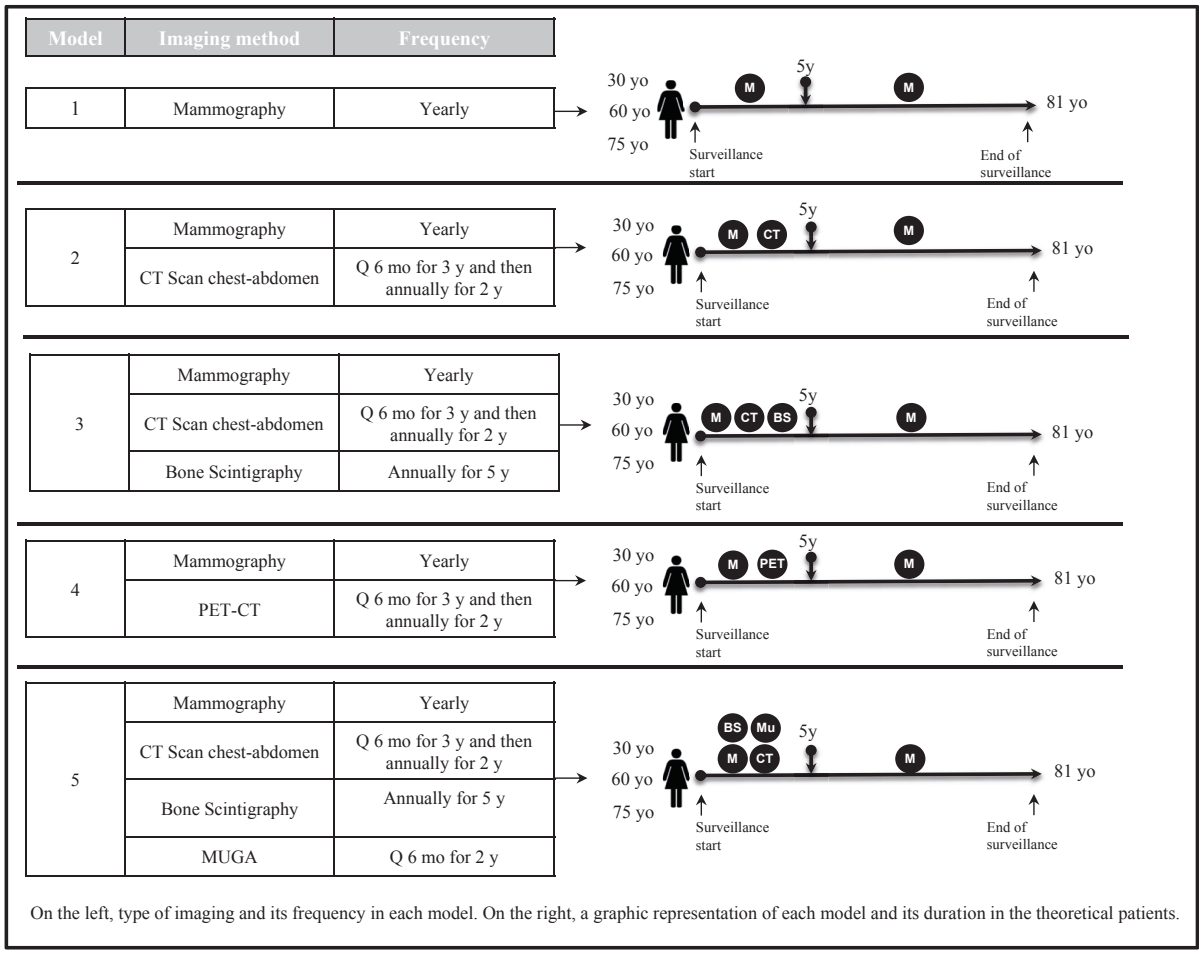
Figure 1 Description of Surveillance Models



On the left, type of imaging and its frequency in each model. On the right, a graphic representation of each model and its duration in the theoretical patients.

Abbreviations: BS = bone scintigraphy; CT = computed tomography; M = mammography; MU, MUGA = multigated acquisition; PET = positron emission tomography; Q = every; yo = years old.

among patients and physicians that an intensive imaging approach would lead to an earlier diagnosis of recurrence and improved outcomes, concerns over liability risks of not performing additional imaging studies, and perceived inconsistency about the scientific evidence and recommendations against intensive imaging surveillance.[14-16] One additional possible explanation may be the assumption that imaging is not associated with harm and/or the possible benefits of imaging outweigh any risk. This assumption may reflect the paucity of studies assessing the risks associated with imaging during BC surveillance, because most published studies have focused on its benefits, financial burden, and false-positive results.

Previously, we reported the risk of imaging radiation-induced malignancies (IRIM) for participants in BC clinical trials.[17] Herein, we estimate the IRIM risk in patients curatively treated for EBC undergoing a spectrum of surveillance strategies with varying imaging intensity.

Materials and Methods

Surveillance Models

To assess the cumulative effective radiation dose and risk of IRIM with several imaging surveillance strategies, we built 5 theoretical models of imaging surveillance that can be applied to survivors of BC. These models range from annual mammography to very imaging-intensive approaches. Imaging procedures and their frequency for each model are reported in Figure 1.

Cumulative Effective Radiation Dose and IRIM Calculation

For each surveillance model, we calculated the cumulative effective radiation dose and the risk of IRIM for hypothetical patients starting surveillance at the ages of 30, 60, or 75 years and ending it at 81 years old (womens' life expectancy at birth in the United States).[18] The cumulative lifetime effective radiation dose was based on the average effective dose for each applicable imaging test as reported in Table 1.

To assess the risk of IRIM, we calculated the excess lifetime attributable cancer risk (LAR) for each model and age at surveillance start, using the National Cancer Institute's Radiation Risk Assessment Tool (RadRAT version 3.7.1; National Cancer Institute, Bethesda, MD).[23] LAR is a summary statistic calculating the probability of cancer attributable to radiation in an exposed member

Table 1 Effective Radiation Doses Among Procedures in Survivors of Breast Cancer

Imaging Procedure	Effective Dose, mSv[19-22]	
	Average Effective Dose	Range Reported in Published Data
Mammography	0.4	0.1-0.6
Chest CT scan	7.0	4.0-18.0
Abdomen CT scan	8.0	3.5-25.0
Whole body bone scintigraphy	6.3	6.0-7.0
PET-CT scan	22.0	13.0-31.0
MUGA scan	10.0	8.0-12.0

Abbreviations: CT = computed tomography; mSv = millisieverts; MUGA = multigated acquisition; PET = positron emission tomography.

of a population. LAR is calculated using the survival function for a population unexposed to radiation and is based on the assumption of a linear non-threshold (LNT) relationship between exposure to radiation and risk of cancer, as detailed in the Biological Effects of Ionizing Radiation VII Report.[24] RadRAT was used as recommended by the developers.[23,25] LAR is expressed as mean number of cases per 100,000 individuals at risk (with a 90% uncertainty range). In our study, LAR would represent the number of IRIM per 100,000 survivors of BC under surveillance. For instance, in case of a mean LAR of 1000, this would mean that 1% of patients surveilled would develop an IRIM.

RadRAT demographic inputs for each model were female gender and year of birth (calculated as year 2016 minus 30, 60, or 75, depending on the age at surveillance start). Each imaging study performed during the applicable surveillance model was recorded as a single exposure event, considering all organs as acutely exposed. The absorbed dose of each imaging procedure was entered in milligrays after converting the average effective dose reported in Table 1 and applying radiation and tissue weighting factor of 1. LAR is expressed as the chances in 100,000 with a 90% uncertainty range. When comparing LAR between models, differences were considered significant if their corresponding uncertainty ranges did not overlap.

Results

Cumulative lifetime effective radiation dose and LAR for each model and age at surveillance start are shown in Table 2.

As expected, lifetime cumulative effective dose increases as more intensive approaches are performed. Considering an age at surveillance start of 60 years, the increase in the mean lifetime cumulative effective dose in models 2 through 5 compared with model 1 (yearly mammogram) is 15.3-, 19.0-, 22.0-, and 23.8-fold, respectively. Also, within the same surveillance model, the lifetime cumulative effective dose is higher when surveillance starts at a younger age. For example in model 3, the dose is 12% higher when surveillance starts at 30 years compared with surveillance starting at 75 years (171.9 vs. 153.9 mSv).

Similarly, the mean LAR significantly increases when more intensive strategies are used instead of annual mammography only (model 1). For all ages analyzed, there is a statistically significant difference in LAR when comparing model 1 with any of the more intensive models, but we have found no significant differences when comparing models 2 through 5. In case surveillance starts at the age

Table 2 Lifetime Cumulative Effective Dose and Lifetime Attributtable Cancer Risk for Each Model

Surveillance Approach				Lifetime Cumulative Effective Dose, mSv	Mean Lifetime Attributed Cancer Risk, /100,000
Model	Imaging Method	Frequency	Age at Surveillance Start		(90% Uncertainty Range)
1	Mammography	Yearly	30	20.4	158.0 (86.9-242.0)
			60	8.4	37.2 (21.4-60.3)
			75	2.4	6.2 (3.3-10.4)
2	Mammography	Yearly	30	140.4	1790.0 (1060.0-2690.0)
	Chest-abdomen CT scan	Every 6 months × 3 years, then yearly × 2 years	60	128.4	857.0 (503.0-1350.0)
			75	122.4	356.0 (211.0-552.0)
3	Mammography	Yearly	30	171.9	2190.0 (1280.0-3530.0)
	Chest-abdomen CT scan	Every 6 months × 3 years, then yearly × 2 years	60	159.9	1060.0 (603.0-1640.0)
	Bone scintigraphy	Yearly × 5 years	75	153.9	444.0 (253.0-733.0)
4	Mammography	Yearly	30	196.4	2690.0 (1650.0-4010.0)
	PET-CT	Every 6 months × 3 years, then yearly × 2 years	60	184.4	1310.0 (802.0-1990.0)
			75	178.4	544.0 (322.0-834.0)
5	Mammography	Yearly	30	211.9	2700.0 (1580.0-4180.0)
	Chest-abdomen CT scan	Every 6 months × 3 years, then yearly × 2 years	60		
	Bone scintigraphy	Yearly × 5 years	75	199.9	1330.0 (792.0-2080.0)
	MUGA scan	Every 6 months × 2 years		193.9	567.0 (334.0-910.0)

Abbreviations: CT = computed tomography; mSV = millisieverts; MUGA = multigated acquisition; PET = positron emission tomography.

Figure 2 Mean LAR per Model and Age Group

Abbreviation: LAR = lifetime attributable cancer risk.

of 60 years, the increase in LAR in models 2 through 5 compared with model 1 is 23.0-, 28.5-, 35.5-, and 35.8-fold, respectively (Figure 2).

When comparing LAR within the same model according to age at surveillance start, we have found a significant LAR increase with an earlier start of surveillance only in model 1. In the rest of the models, LAR increases with start at younger age, but this is not statistically significant (Figure 2).

Model 5 is identical to model 3 but with the addition of multigated acquisition (MUGA) scan, as it may be indicated in case a patient receives cardiotoxic drugs during (neo) adjuvant therapy. MUGA increases LAR in approximately 25% compared with LAR in model 3, but this is not significant.

Discussion

The American Society of Clinical Oncology, the American Cancer Society, the European Society of Medical Oncology, the National Comprehensive Cancer Network, the UK National Institute for Health and Clinical Excellence, and the American College of Radiology have released well-established clinical guidelines that provide recommendations for the surveillance after EBC curative treatment.[1,5-9] All recommend against the use of imaging procedures other than yearly mammogram during surveillance of asymptomatic survivors of BC. These recommendations are based on observational mammography studies in the surveillance setting as well as randomized clinical trials and a Cochrane systematic review.[19-22,26-29] These have consistently concluded that follow-up based on physical examination and yearly mammography alone are as effective as more intensive approaches in terms of timeliness of recurrence detection, overall survival, and quality of life. It should be noted that the randomized trials conducted in Italy that showed no benefit from additional imaging have not used the imaging modalities currently available. Results from a Japanese randomized trial that is close to complete enrollment, and that compares mammography with intensive surveillance including modern imaging techniques, are awaited and may potentially modify the current recommendations in case the study shows an overall survival benefit for intensive surveillance.[30]

Women with risk factors that increase their lifetime risk for second BC (eg, in case of BRCA 1/2 mutations) may warrant evaluation with other breast imaging techniques and are not the focus of our study.[9] As well, patients with symptoms or signs of BC relapse definitely warrant additional imaging to diagnose the local, regional, or distant recurrence and are not the focus of our study either.

Despite the available evidence and guidelines recommending against the use of advanced imaging, as well as of tumor markers, hematology, and blood chemistry during surveillance, these are still commonly used in clinical practice.[10-15] Therefore, low adherence to clinical guidelines seems to be a key problem during EBC survivorship care. Smith et al have reported that, out of a population of 152 survivors of EBC, in only 75% of the cases were the recommendations from guidelines followed by performing annual mammography.[31] Panageas et al showed in a Surveillence, Epidemiology, and End Results-Medicare population, 40% of women with stage I to II BC had at least one advanced imaging examination performed, and 30% had computed tomography (CT) scans, whereas Parmar et al showed that 27% underwent CT scans.[14,32] Other authors have shown variable rates of nonadherence to imaging recommendations during surveillance that range from 10% (only within the first 18 months of follow-up)[33] up to 50%.[31,34] Although some of these imaging tests may be performed to evaluate specific signs or symptoms, some studies have shown that the majority of them are done for non-recommended surveillance.[11,35]

Multiple studies consistently demonstrating lack of adherence to surveillance guidelines raises the question of what drives noncompliance. Several factors concerning health care providers (HCPs) and patients can explain this observation.[14-16]

First, despite the lack of evidence favoring this approach, HCPs sometimes tailor the imaging surveillance intensity to the patient and tumor characteristics, and in patients with higher risk of relapse, additional imaging is sometimes indicated. Also, HCPs may have difficulty convincing patients that counterintuitively, an early diagnosis of recurrence does not render a survival benefit, as suggested by current evidence.[15] It may be less time-consuming to order a scan than to counsel and reassure patients about the lack of benefit from intensive imaging surveillance. Additionally, Han et al have shown that up to 65% of primary care physicians and up to 61% of oncologists perceive current recommendations against intensive imaging surveillance as ambiguous.[15] This could be partly explained by differences among guidelines. For example, Merkow et al showed that, among BC guidelines, CT scans were recommended against in 2, discussed without a clear recommendation in 1, and not addressed in 3 out of a total of 6 guidelines.[36] It is also known that a medico-legal defensive approach by HCPs can contribute to the noncompliance with recommendations.[34] Finally, the likelihood of using advanced imaging techniques could be related to ownership of corresponding imaging equipment by physicians that order those tests.[37]

Among patients, frequent testing to prove that cancer has not recurred can be reassuring, and patients may prefer a more intensive approach.[38] With the increase in availability of medical information, patients' demand for additional tests has increased and may influence HCP's decisions on surveillance strategies.[34] In a German study that surveyed 801 survivors of BC, between one-third and one-half of surveyed patients requested non-recommended procedures (laboratory and imaging) during surveillance.[39] In a cross-sectional survey of women treated for primary BC and free of signs and symptoms of relapse, 81.6% preferred additional investigations such as x-ray and blood tests during their follow-up period.[40]

There are several potential consequences associated with the lack of adherence to surveillance guidelines. First, the costs of performing non-recommended tests and from the evaluation of false-positive results add an additional value of $260 to $630 million to the annual cost for BC survivorship care in the United States, compared with a strategy that follows recommendations in guidelines.[9] Lyman et al showed that the surveillance costs for patients undergoing advanced imaging were 1.6 higher than the average cost during the surveillance period ($29,998 vs. $18,403).[41] False-positive results can also trigger additional testing, and this can increase not only costs, but also radiation exposure, risks, and patient anxiety.[42]

Performing surveillance tests can be perceived by survivors of cancer as an existential threat. Patients can experience anxiety, fear, and worry associated with performing the exams and expecting the imaging results. This is related to their fear of cancer relapsing and potential procedures and treatments if a relapse is confirmed.[43] For example, a German survey of survivors of BC regarding surveillance practices showed that close to 10% of patients surveyed felt that intensive approach increased their sense of fear.[39] Considering the lack of proven survival benefit of these additional tests (other than annual mammography), these types of psychological distress are avoidable.

Another consequence of performing non-recommended surveillance tests is radiation-associated risks from imaging; these have not previously been systematically studied. The lack of knowledge by HCPs of the risks derived from imaging tests may contribute to non-recommended scanning.

We analyzed the risk of IRIM during EBC surveillance, and our results suggest that the number of second cancer cases will be significantly increased from the exposure to radiation owing to non-recommended imaging tests, and this increment in LAR is clinically relevant at any age. For example, patients undergoing CT scans and bone scintigraphy during the first 5 years of surveillance (a relatively common practice during EBC survivorship care) have a risk of IRIM that is almost 29 times higher than the risk in patients undergoing mammography only (model 3 vs. 1, start at surveillance age 60 years). This would imply that, of 100,000 patients who would start their surveillance at an age of 60 years, 37.2 cases of IRIM would be expected among those undergoing only annual mammography. In contrast, 1060 cases of IRIM could be expected out of 100,000 starting their surveillance at 60 years of age, when CT scans and bone scintigraphy are performed on top of annual mammography (as detailed in model 3). Additionally, for patients requiring left ventricular ejection fraction assessment (eg, in case of treatment with cardiotoxic agents), MUGA scan contributes to an increment in LAR.

Our findings are consistent with published studies using different methodology and/or in different settings. Previously, we have shown that patients undergoing an imaging-intensive surveillance approach in the context of BC clinical trials in the adjuvant setting may have a significant risk of IRIM.[17] Also, Chien et al showed, in a population-based study, that patients with curatively treated non-Hodgkin lymphoma receiving more than 8 CT scans during surveillance had a greater risk for developing second primary malignancies (hazard ratio, 2.25; $P < .001$) than those with 8 scans or less.[44]

Our results should be put into the appropriate context. First, definitive evidence linking diagnostic imaging with cancer development in adults is lacking. Radiation-induced malignancies are infrequent events, and no definitive epidemiologic data clearly relating imaging radiation with IRIM is available. Epidemiologic studies including thousands or even millions of subjects followed over long periods of time would be needed to demonstrate a significant risk related to exposure to low-dose radiation.[45] Because of this, radiation-induced malignancy risk estimates in patients undergoing medical imaging comes mainly from extrapolation of atomic bomb survivors' data. Data from Japanese atomic bomb survivors shows that exposures above 100 mSv have proven increased malignancy risk.[46] On the contrary, there is no epidemiologic data supporting increased risks at doses below 10 mSv (dose level in most single-imaging procedures). Meanwhile, controversy exists to establish a definitive risk at doses between 10 and 100 mSv.[47] We have shown that with the exception of model 1, patients undergoing surveillance with any other model receive a cumulative effective dose exceeding 100 mSv, regardless of the age at surveillance start.

To our knowledge, this the first study quantitatively assessing the risk of IRIM owing to imaging tests performed during surveillance in survivors of BC. Our work is not without limitations. First, LAR was estimated using RadRAT, which is based on the LNT model. Although the validity of the LNT model when estimating imaging

risks has been questioned, no alternative model is as widely accepted, and RadRAT estimates are the most widely adopted and consistent with current standards.[48,49]

Also, we assumed that each imaging procedure produced a uniform whole-body radiation dose, ignoring organ-specific radiosensitivity and variability in the dose received by different organs and within the same organ; this leads to an IRIM risk overestimation. Lastly, it is not possible to directly attribute any individual malignancy to imaging radiation as genetic and environmental predispositions, chemotherapy, and radiotherapy can contribute to second malignancy risks, in many cases in a greater magnitude than imaging radiation.

Reaching a definitive and incontestable conclusion about the relationship between imaging procedures and radiation-induced malignancies would require large-scale epidemiologic studies with prolonged follow-up; these do not appear feasible. In the absence of this definitive evidence, LNT model-based approaches such as the one in our study provide valuable information about the risks of non-recommended imaging during EBC surveillance, and contribute to the decision-making process in survivorship care.

Randomized trials, a systematic review, and several well-established guidelines recommend against the use of imaging tests beyond annual mammography during surveillance of asymptomatic survivors of EBC. Additional and intensive imaging is nonetheless common in clinical practice. Although this may have several explanations, we believe the lack of data on the risk of IRIM contributes to noncompliance. We have shown that imaging tests, in addition to mammography, can be associated with a significant increase in LAR when used in surveillance in survivors of EBC. Therefore, unless new evidence arises indicating that these tests may have a significant benefit in BC outcomes, they should not be performed in asymptomatic patients, and recommendations in clinical guidelines must be followed. In addition to the lack of survival benefit, non-recommended imaging adds unnecessary costs, leads to anxiety and false positives, and, as we have shown, may carry substantial risks of IRIM.

Clinical Practice Points

- Mammography is the only imaging method with evidence-based demonstrated efficacy for surveillance in asymptomatic EBC survivors. Clinical guidelines recommend against the use of other imaging modalities different from mammography. Despite this, imaging tests are commonly used in clinical practice.
- We built 5 theoretical models of imaging surveillance to estimate the IRIM risks in patients curatively treated for EBC undergoing a spectrum of surveillance strategies with varying imaging intensity; from annual mammography to imaging-intensive approaches.
- For each model, we calculated the cumulative effective radiation dose and the risk of IRIM using the National Cancer Institute's Radiation Risk Assessment Tool for hypothetical patients starting surveillance at the ages of 30, 60, or 75, and ending it at 81 years old. To assess the risk of IRIM, we calculated the excess LAR for each model and age at surveillance start.
- Lifetime cumulative effective dose and mean LAR significantly increased when imaging-intensive strategies are used instead of annual mammography only. For all ages analyzed, there is a statistically significant difference in LAR when comparing mammography only with any of the more intensive models. As an example, in a patient beginning surveillance at the age of 60, there is a 28.5-fold increase in the IRIM risk when comparing mammography only versus a schedule with mammography plus CT scan of chest-abdomen and bone scan.
- Despite study limitations, our models suggest that non-recommended imaging may increase IRIM risks and should be avoided during EBC surveillance.

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Disclosure

The authors have stated that they have no conflicts of interest.

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