Cardiovascular Mortality Associated with Mammographic Screening

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Mortalidade Cardiovascular Associada ao Rastreamento Mamográfico

Mortalidad Cardiovascular Asociada al Cribado Mamográfico

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Abstract

Introduction: Cardiovascular harms of mammographic screening have not been the subject of study or concern, including in the cardio-oncology area of. The result is an important gap in literature despite the evidence of great magnitude of overdiagnosis and overtreatment in screening and its association with increased cardiovascular mortality. **Objective:** Present and discuss the main evidence regarding the causes of increased cardiovascular mortality associated with screening. **Method:** Systematic searches were performed in the literature through four search strategies in two databases (MEDLINE and LILACS), to identify the causes of increased cardiovascular mortality potentially associated with overdiagnosis and overtreatment. For each one of the search strategies, it was used the classification of the *Oxford Centre for Evidence-Based Medicine* to assign the level of evidence of the results. **Results:** Two major groups of causes of increased cardiovascular mortality were identified: the first linked directly to the diagnosis of breast cancer; and the second to the treatment of breast cancer, including surgery and adjuvant radiotherapy. The increase of cardiovascular mortality included several subgroups of causes such as acute myocardial infarction, pulmonary thromboembolism, heart failure, arrhythmias, heart valve disease and stroke. **Conclusion:** There are consistent evidence about cardiovascular mortality associated with breast cancer diagnosis and treatment in conditions clinically compatible with screening. It is also likely to be one of the most important causes of mortality related to screening, especially those associated with overtreatment with adjuvant radiotherapy.

Key words: Breast Neoplasms/diagnosis; Cardiovascular Diseases/mortality; Mass Screening; Mammography; Radiotherapy, Adjuvant.

Resumo

Introdução: Os danos cardiovasculares do rastreamento mamográfico não têm sido objeto de estudo ou preocupações, inclusive na área de cardio-oncologia. O resultado é uma importante lacuna na literatura a despeito de evidências da grande magnitude do sobrediagnóstico e do sobretratamento no rastreamento e sua ligação com aumento da mortalidade cardiovascular. **Objetivo:** Apresentar e discutir as principais evidências a respeito das causas de aumento de mortalidade cardiovascular associadas ao rastreamento. **Método:** Foram realizadas buscas sistemáticas na literatura, por meio de quatro estratégias de busca em duas bases de dados (MEDLINE e LILACS), para identificar as causas de aumento de mortalidade cardiovascular potencialmente associadas ao sobrediagnóstico e ao sobretratamento. Para cada uma das estratégias de busca, os resultados tiveram seu nível de evidência atribuídos de acordo com a classificação do *Oxford Centre for Evidence-Based Medicine*. **Resultados:** Dois grandes grupos de causas de aumento da mortalidade cardiovascular foram identificados: o primeiro ligado diretamente ao diagnóstico de câncer de mama; e o segundo ao tratamento do câncer de mama, incluindo cirurgia e radioterapia adjuvante. O aumento de mortalidade cardiovascular incluiu diversos subgrupos de causas, tais como infarto agudo do miocárdio, tromboembolismo pulmonar, insuficiência cardíaca, arritmias, doença orovalvar e acidente vascular encefálico. **Conclusão:** Existem evidências consistentes sobre mortalidade cardiovascular associada ao diagnóstico e ao tratamento do câncer de mama em situações clinicamente compatíveis com o rastreamento. É provável também que essa seja uma das causas mais importantes da mortalidade relacionada ao rastreamento, em especial aquelas associadas ao sobretratamento com radioterapia adjuvante.

Palavras-chave: Neoplasias da Mama/diagnóstico; Doenças Cardiovasculares/mortalidade; Programas de Rastreamento; Mamografia; Radioterapia Adjuvante.

Resumen

Introducción: El daño cardiovascular causado por el cribado mamográfico no ha sido objeto de estudio ni de preocupación, incluso en el área de la cardio-oncología. El resultado es una brecha importante en la literatura a pesar de la evidencia de la gran magnitud del sobrediagnóstico y el sobretratamiento en cribado. y su asociación con el aumento de la mortalidad cardiovascular. **Objetivo:** Presentar y discutir los principales pruebas en las causas del aumento de la mortalidad cardiovascular asociados con la tamización. **Método:** Se realizaron búsquedas sistemáticas en la literatura a través de cuatro estrategias de búsqueda en dos bases de datos (MEDLINE y LILACS), para identificar las causas del aumento de la mortalidad cardiovascular potencialmente asociadas con el sobrediagnóstico y el sobretratamiento. Para cada una de las estrategias de búsqueda, a los resultados se les asignó su nivel de evidencia de acuerdo con la clasificación del Oxford Centre for Evidence-Based Medicine. **Resultados:** Se identificaron dos grupos principales de causas de aumento de la mortalidad cardiovascular: el primero relacionado directamente con el diagnóstico de cáncer de mama; y el segundo para el tratamiento del cáncer de mama, incluida la cirugía y la radioterapia adyuvante. El aumento de la mortalidad cardiovascular incluyó varios subgrupos de causas como infarto agudo de miocardio, tromboembolismo pulmonar, insuficiencia cardíaca, arritmias, enfermedad orovalvar y accidente cerebrovascular. **Conclusión:** Existe evidencia consistente de mortalidad cardiovascular asociada con el diagnóstico y tratamiento del cáncer de mama en condiciones clínicamente compatibles con la tamización. También es probable que sea una de las causas más importantes de mortalidad relacionada con la tamización, especialmente aquellas asociadas con el sobretratamiento con radioterapia adyuvante.

Palabras clave: Neoplasias de la Mama/diagnóstico; Enfermedades Cardiovasculares/mortalidad; Tamizaje Masivo; Mamografía; Radioterapia Ayuvante.

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INTRODUCTION

It is known that breast cancer mammographic screening increases the diagnosis of breast cancer that would never manifest clinically (overdiagnosis)[1-3] and that this increase of diagnosed cases leads to unnecessary oncologic treatment (overtreatment)[4]. This expansion of the treatment is counterintuitive as much as it was expected that, with screening, morbidity would be reduced. However, the fact is that cases of overdiagnosis never evolved to more advanced staging, even without treatment. Overtreatment induced by mammographic screening is already proven for adjuvant radiotherapy and surgery (conservative and mastectomy)[4].

Nonetheless, the mammographic screening associated harms are rarely included in primary studies, reviews or clinical guidelines. Overall, even the most common harms of screening as false-positive results and overdiagnosis are not considered[1]. Furthermore, it is necessary to understand that overdiagnosis and overtreatment are surrogate outcomes and very little attention was given to the study of harms produced by these two conditions[2]. Particularly, the causes of cardiovascular mortality increase with mammographic screening has not been the object of study or concern, including in cardio-oncology. The result is an important gap in the international scientific literature despite the evidences about the relevant magnitude of overdiagnosis[3] and overtreatment[4]. Had the cardiovascular harms been considered, it is possible, according to some estimates that the screening-associated mortality surpassed even the benefit of mortality reduction by breast cancer because of overdiagnosis and overtreatment[5], showing the importance of delving into the theme.

OBJECTIVE

The present review has the objective to present and discuss the main available evidences about the causes of cardiovascular mortality increase associated to the diagnosis and treatment of breast cancer in situations clinically compatible with overdiagnosis and overtreatment resulting from mammographic screening.

METHOD

Based in the systematic review of the literature on harms and benefits of mammographic screening previously conducted by the authors whose methods are described in details in other publications[1,2], the situations involving breast cancer diagnosis and treatment that could be considered as a consequence of mammographic screening were defined. This systematic review evidenced yet the potential cardiovascular harms associated to overdiagnosis and overtreatment that were not directly investigated in mammographic screening clinical trials[2].

For the present article, therefore, new systematic searches were conducted in the literature to produce a review about the causes of potential increase of cardiovascular mortality associated to the overdiagnosis or unnecessary treatment as result of mammographic screening. As the overdiagnosis and overtreatment are counterfactual, it is not possible to study directly these cases being necessary to identify which clinical situations would be compatible with them. This occurs because individually it is impossible to determine accurately who indeed was overdiagnosed or unnecessarily treated. In these situations, the increase of cardiovascular mortality is more relevant because there is no counterpart of benefits of the mammographic screening to reduce breast cancer mortality as, by definition, it is diagnosis and treatment of a cancer that would not evolve clinically even undetected[1]. The long survival of cases of overdiagnosis turn them susceptible as well to long-term harms of the oncologic therapy.

The clinically conditions considered compatible with screening were the following: diagnosis of ductal carcinoma *in situ* (DCIS) or invasive breast cancer in initial/localized-stage; surgery (including conservative and mastectomy) or adjuvant radiotherapy for treatment of DCIS or invasive breast cancer in initial/localized-stage. The lack of conclusive literature evidence[2,4] about its association with mammographic screening, the possibilities of overtreatment with hormone therapy, chemotherapy and trastuzumab were not included in the searches or eligibility criteria to select articles in the current review, being addressed only in the discussion of this article for the sake of completeness of the approach to the theme. As the cardiovascular harms of overdiagnosis of breast cancer, it is important to emphasize that the complications resulting from breast cancer were not addressed as well, which not even exist clinically in the cases of overdiagnosis, but of the iatrogenic impacts of the diagnostic investigation and the diagnostic *per se*.

The research question was defined by the acrostic PICO, the clinical condition studied was the diagnosis and treatment of localized breast cancer (*in situ* or invasive), compatible with cases identified through mammographic screening (population/intervention), compared to the absence of screening (and consequent absence of diagnosis and treatment), with cardiovascular mortality as outcome. Thus, it was attempted to identify the causes of the cardiovascular mortality increase. The search was conducted in the bases MEDLINE and LILACS. For each cause of identified cardiovascular death, it were verified

the list of references retrieved in MEDLINE in the specific searches for that cause. In LILACS, the strategy of search utilized was: breast [Words of the title] and cancer [Words of the title] and cardiovascular [Words of the summary]. In MEDLINE, the searches involved the three strategies of search described below:

Search about cardiovascular harms of overtreatment with surgery:

(((breast[tiab] OR mamar*[tiab]) AND (tumor[tiab] OR tumors[tiab] OR cancer[tiab] OR neoplasm*[tiab] OR carcinoma[tiab] OR "Breast Neoplasms"[Majr] OR "Breast Neoplasms"[Mh]) AND ("breast cancer surgery" OR mastectomy OR lumpectomy) AND ("mortality rates" OR "post-surgical complication*" OR "post-surgical mortality" OR "cardiovascular death" OR "cardiovascular mortality" OR "In-hospital case-fatality rates" OR "cardiac death")) AND ("1990/01/01"[PDat]: "2019/08/31"[PDat]))

Searches about cardiovascular harms of overtreatment with radiotherapy:

((((((systematic review[ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR (systematic review[tiab] AND review[pt]) OR consensus development conference[pt] OR practice guideline[pt] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR drug class reviews[ti]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline[pt] OR pmcbook)) OR (systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri*[tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[tiab] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication[tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) AND ((clinical[tiab] AND trial[tiab]) OR clinical trial*[mh] OR clinical trial[pt] OR random*[tiab] OR random*[tw] OR random allocation[mh] OR "randomized controlled trial"[pt] OR "controlled clinical trial"[pt]) AND (breast[tiab] OR mamar*[tiab]) AND (tumor[tiab] OR tumors[tiab] OR cancer[tiab] OR neoplasm*[tiab] OR carcinoma[tiab] OR "Breast Neoplasms"[Majr] OR "Breast Neoplasms"[Mh] OR DCIS OR "Ductal Carcinoma in situ") AND (cardiovascular[tiab] OR heart[tiab] OR cardiac[tiab]) AND (Radiotherapy OR "Radiation Therapy")))) AND ("1990/01/01"[PDat] : "2019/08/31"[PDat]))

Search about cardiovascular harms of overdiagnosis:

("cardiovascular death" OR "cardiovascular mortality" OR "cardiac death") AND ("cancer diagnosis" OR overdiagnosis) AND ("1990/01/01"[PDat]: "2019/05/31"[PDat])

The search strategies did not consider any idiom restriction. Because this is a fairly studied theme in the literature, it was also required for the selection of the references about cardiovascular harms of the adjuvant radiotherapy that the study design would have to be randomized or systematic review of randomized clinical trials.

The parameter to identify the highest level of available evidence was the classification of the Oxford Centre for Evidence-Based Medicine[6]. The classification has five levels, level 1, the best evidence and level 5, the worst, in addition to a specific classification for questions of research about health harms[6]. The focus was to review the cardiovascular mortality (total or in subgroups) because it is a hard endpoint of great relevance for public health and whose gauging is more objective.

RESULTS

Evidences exist about the two great groups of cardiovascular mortality increase: one, connected directly to the breast cancer diagnosis itself and another to the breast cancer treatment. The subdivision of this last category resulted in the several therapeutic modalities utilized in the oncologic treatment of localized breast cancer cases, including adjuvant radiotherapy and surgery.

In the first group, there are the cardiovascular deaths associated directly to the diagnosis of breast cancer. In that search, 52 articles from MEDLINE were retrieved, three of them for full reading, and two selected at the end of the process[7,8]. Of the studies selected for full reading, one was excluded for not presenting harms directly associated

to diagnosis/overdiagnosis of breast cancer[9]. Both studies selected are population-based cohorts classified as level 3 of evidence. References about breast biopsy-related deaths were not encountered.

From MEDLINE, 83 articles on mortality due breast surgery were retrieved, by either surgical mortality or long-term complications, four of them selected for full reading and only one selected per the eligibility criteria[10]. For articles selected for full reading, there was one exclusion for failing to present results of cardiovascular complications of the surgical treatment[11]. The study selected addresses a case-series, classified as level 4 of evidence.

The search at MEDLINE for adjuvant radiotherapy-associated cardiovascular mortality retrieved 43 articles, four of which were kept for full reading and only one of them selected according to the eligibility criteria[12]. Of the studies kept for full reading, one was excluded because it was a systematic review including only observational studies[13], and two were excluded for not specifying the stage of the analyzed breast cancer cases[14,15]. The study selected was a meta-analysis of randomized clinical trials of localized cancer treatment classified as level 1 of evidence.

LILACs searches resulted in 36 references, none of them selected pursuant to the defined eligibility criteria.

DISCUSSION

To the best of our knowledge, the current review is the first of the world literature to address all possible causes of increase of cardiovascular mortality associated to breast cancer screening. It is known that breast cancer surviving women have higher cardiovascular mortality than the population in general[16]. However, these studies deal with cancer survival without considering that, actually, a great part of these represents overdiagnosis resulting from mammographic screening[5]. Furthermore, studies about cardiovascular mortality increase after the diagnosis of breast cancer are considered limited and none of them was specifically focused to clinical conditions associated to breast cancer screening or attempted to find the several causes of this increase in a comprehensive manner. It will be discussed separately below the results of each one of the causes of cardiovascular mortality increase potentially associated to mammographic screening.

Cardiovascular mortality directly associated to overdiagnosis

A cohort study with 74,977 women in Sweden selected for the current review addressed the main evidences of increase of cardiovascular death risk soon after the diagnosis of breast cancer[7]. The estimate of this increase considered the time of the breast cancer diagnosis measured in weeks with the objective of separating the effect of the diagnosis from the possible consequences of the treatment[7]. In this study, the risk of cardiovascular death (ICD 10: I00-I99) in the first weeks after the diagnosis was higher than in the subsequent weeks[7]. The relative risk (RR) for overall mortality in the first week was 1.8 (CI 95%: 1.2-2.4) in the multivariate model with adjusted risk for possible confounding factors as age, marital status, socioeconomic level and education, remaining significantly elevated during one month[7].

Confirmed still the higher relative risk of cardiovascular death after diagnosis in those patients that did not have preexisting psychiatric diseases, which also occurred with the increase of suicide risk after breast cancer diagnosis[7]. Stratified analysis per group of cardiovascular causes showed significant statistical increase of risk of cardiovascular death for all the cardiovascular subgroups studied until four weeks after the diagnosis of cancer. These subgroups were acute myocardial infarction, "embolism or thrombosis", stroke (ischemic or hemorrhagic) and "other heart diseases"[7].

Beyond doubt, the less known of the cardiovascular harms identified in the current review is the increase of cardiovascular mortality soon after breast cancer diagnosis. The most accepted explanation for this phenomenon would be that the diagnosis of cancer, due to its stigma of lethal disease and cause of suffering, would function as a "stressful life event", which is associated to several unfavorable cardiovascular outcomes[8]. Animal model results have proved that the acute psychological stress is related to the onset of myocardial ischemia, arrhythmogenesis, platelet aggregation, endothelial dysfunction, increase of the blood viscosity by hemoconcentration, increase of the systemic blood pressure and vessel constriction[17].

Innumerous trials have associated severe acute psychological stress with the triggering of myocardial acute infarction and cardiac sudden death. These studies describe these triggering factors, among them stressful life events such as cancer diagnosis, occurrence of natural disasters, military attacks and relatives decease, further to others related to occupational and financial life[17-21]. For instance, the *Women's Health Initiative* – a postmenopausal women cohort – identified statistically significant association of several stressful life events with increase of coronary arterial disease and stroke incidence, regardless of sociodemographic factors and depressive symptoms[22].

Another highly lethal cardiovascular condition, acute aortic dissection, can also be triggered by psychological stress. In a series of 175 consecutive cases in a US reference hospital, the onset of the acute aortic dissection was associated with psychological stress, including

cancer diagnosis, in 40% of the cases[14]. The probable physiopathological explanation for this association would be the acute increase of systemic arterial pressure with stress, which would exceed the traction limit of the aortic tissue[23].

Another possible cause would be cardiomyopathy of Takotsubo also called stress-induced myocardiopathy; it is a lesser known cause of severe heart failure. It mimics the diagnosis of acute myocardial infarction, representing 2% of the final diagnosis of the cases initially attended with acute coronary syndrome[24]. Takotsubo myocardiopathy presents episodes of psychological stress as a precipitating factor in about 30% of cases, being more common in women and, like breast cancer, affects predominantly postmenopausal women[24].

The conclusion is that there is biologic plausibility for the association of several cardiovascular diagnosis with the increase of the cardiovascular mortality observed soon after the diagnosis of breast cancer such as acute myocardial infarction, brain stroke, cardiac sudden death, thromboembolism, acute aorta dissection and Takotsubo myocardiopathy. The hypothetical alternative explanation for cardiovascular mortality soon after cancer diagnosis would be the possibility of complications from biopsies, but without support of the literature[25,26].

Cardiovascular mortality connected to overtreatment with surgery

The mortality and even the incidence of acute cardiovascular outcomes because of mastectomy and conservative surgeries appear to be modest as the literature shows, although it is necessary to notice that this is a barely studied subject. In a USA multicenter grand case-series selected in the present review, the occurrence of postoperative stroke was 0.1% in the group submitted either to mastectomy or in the group submitted to conservative surgeries, however, without any deaths noticed in the latter[10]. This same study revealed that the incidence of myocardial acute infarction in until 30 days post-mastectomy was 0.06%, the same percent for cardiac sudden death[10]. Takotsubo myocardiopathy is also described as a rare postoperative complication of breast cancer conservative surgery[27].

Cardiovascular mortality connected to overtreatment with radiotherapy

Breast cancer radiotherapy increases the risk of several cardiovascular diseases as well, like ischemic cardiac disease, cardiomyopathy, pericarditis and actinic heart valve disease [28,12]. The irradiation of the left breast provokes a sharper increase of this risk[29]. Women submitted to right breast cancer irradiation, for that reason, are included as control group of studies evaluating the cardiac harms of radiotherapy. A recent systematic review of observational studies evidenced a statistically significant increase of 23% of the cardiovascular mortality in these cases when compared to cases when the right breast was irradiated[13]. Another meta-analysis with data of randomized and observational clinical trials with patients treated with radiotherapy presented 38% higher risk of cardiac mortality (CI 95%: 1.18 – 1.62) compared to patients not submitted to radiotherapy, an absolute increase of 125.5 cardiac deaths per 100 thousand person-years[30].

Another meta-analysis of clinical trials showed that the relative risks of death by coronary arterial diseases, non-ischemic heart failure, arrhythmia, pulmonary thromboembolism (PTE) and heart valve disease of the group treated with adjuvant radiotherapy were respectively 1.31, 1.94, 2.14, 2.10 and 1.97, all of them with statistical significance [21]. The risk of severe coronary events (defined as myocardial acute infarction, coronary revascularization or death by ischemic heart disease) increases linearly with the dose of irradiation and apparently does not have a lower safety limit for which no risk increase would exist[12,31]. There is evidence that the increased risk of cardiovascular complications is greater in women treated before the age of 50, both for ischemic heart disease, for heart valve disease and for heart failure[29]. Nonetheless, the data of meta-analysis of adjuvant radiotherapy clinical trials are inconclusive on that matter[12].

The causal relation between radiotherapy and death increase by PTE is not well understood. PTE is a known cause of mortality in patients with cancer in general and its incidence is four to six-fold greater in these patients than in the general population[32]. Further to the increase of thrombosis by cancer itself, oncologic therapy increases even more the risk of PTE. This is well established for surgery, chemotherapy and hormone therapy but it is barely known in radiotherapy[32]. A meta-analysis of clinical trials of adjuvant radiotherapy for breast cancer revealed increase of mortality by PTE in these patients (RR of 1.94)[33]. The possible physiopathological mechanism would be cellular destruction and promotion of prothrombotic inflammatory processes by ionizing radiation[32].

The evolution of radiotherapy techniques in the last decades led to a drop of the dose in the heart (6.3 to 4.4 Gy) and in the lung (9.6 to 5.7 Gy) when the mean doses in the current decade are compared to the doses of the classical clinical trials of adjuvant radiotherapy for breast cancer[12]. The effects of this reduction of the dose over the long-term risks are not yet well known[12]. The irradiation of the left anterior descending artery – because of its vulnerable anatomic location and its importance for the irrigation of the anterior, septal and lateral left

ventricle wall – is one of the main issues that still needs to be overcome[34].

The new technique of deep inspiration with suspension of the respiration can reduce the dose of the radiation to the heart either in radiotherapy of moderate intensity or volumetric modulated arch therapy[35]. Other alternative radiotherapy techniques as partial irradiation of the breast could reduce even more these risks in the future, but still remain experimental[36].

The post-treatment time interval where adjuvant radiotherapy harms start to appear and its duration are yet not a consensus in the literature. The model proposed by Baum[5] considered that the increase of the risk of acute myocardial infarction and lung cancer starts soon after radiotherapy and lasts for 30 years [5]. In a meta-analysis of clinical trials of adjuvant radiotherapy for breast cancer, the mortality for other causes than breast cancer (including cardiovascular, lung cancer and esophageal cancer) was statistically higher in the group treated with radiotherapy in the periods from five to 14 years after the treatment and in the period of 15 years or more[33].

In a populational-base case-control study, the increment started five years after radiotherapy and continued for at least 20 years[31]. It suggested yet that women with impalpable tumors discovered with the screening would have higher increase of risk of coronary event than those with larger tumors (RR respectively of 20.4% and 6.9%), although the difference between the two groups has no statistical significance[31].

A meta-analysis with 45 clinical trials revealed that the mortality by cardiovascular diseases (excluding cerebrovascular disease and PTE) after adjuvant radiotherapy for breast cancer appears to increase soon after the first quinquennial post treatment (RR of 1.40) persisting until more than 15 years after the therapy (RR of 1.42)[12]. Although the relative risk is similar in these two cases, the absolute risk is higher in older women because of the higher baseline risk of death from cardiovascular disease[12].

The data of the *Surveillance, Epidemiology and End Results*, reveal that the mortality by cardiovascular disease increases in the first five years after treatment (RR of 1.19) and continues until more than 20 years (RR of 1.90), increasing with time, at least for the cohorts treated in the decade of 1970 and beginning of 1980[37].

Regarding long-term harms of radiotherapy – especially in more than 15 years after treatment – it is probable that there is a cohort effect also since women with more time of follow up are also those who were treated with older techniques and higher dose of radiation. The increase of the death risk by all causes, except breast cancer, is seen yet in the cohorts treated more recently, although with less intensity than those treated in the decade of 1970[12]. The effects on cardiovascular mortality in the first five years (RR of 1.40) are of the same magnitude of the produced in 15 years or more[12]. This upholds the higher impact of mortality in the first years after the treatment, even with the cohort effect tending to increase the risk in groups with more time of follow up. Still, this is a controversial matter with favorable and contrary studies to this early risk increase[29,31].

The present discussion deals with adjuvant radiotherapy associated to the mammographic screening. As conservative therapy is more common in this context than mastectomy, it is natural that adjuvant radiotherapy stands out. It is also necessary to understand that the scenarios analyzed here address the overtreatment, where the risks of radiotherapy are not offset by its benefits in reducing the mortality by breast cancer. Considering breast cancer cases detected by imaging but with clinical significance in women with 50 years or more, the absolute benefit of adjuvant radiotherapy after conservative surgery to reduce the mortality by breast cancer would be around 2% to 5%[12], in addition to ensuring oncologic results similar to mastectomy, but with better esthetic result and reduction of surgical complications.

As the mortality increase by coronary arterial disease and lung cancer are the overtreatment major associated risks with radiotherapy, an elevated baseline risk for these two diseases can lead even to a larger number of deaths. The most important case is smoking because it increases either the risk of lung cancer and coronary arterial disease to the extent where adjuvant radiotherapy risks overpass the benefits in women with high tobacco burden, even considering the cases where there was no unnecessary treatment (overtreatment)[12]. It is also a risk factor for PTE and esophageal cancer. For high burden tobacco addiction, the treatment with adjuvant radiotherapy would increase the absolute risk of incidence of lung cancer in 4.4% and death by heart diseases in 1.2%. The smoking cessation would lessen this absolute risk and, even, in case it occurred already in the beginning of the radiotherapy, it would be able to diminish these risks of the treatment, since its effects would begin mainly ten years after the cessation, when the risks of cardiovascular mortality are higher by adjuvant radiotherapy[12].

The clinical trial PRIME II evaluated another perspective of reduction of overtreatment with radiotherapy, which compares the conservative surgery with and without adjuvant radiotherapy in women with breast cancer with good prognosis. However, in this study, there was a small benefit in the diminishing of local recurrence with radiotherapy, perpetuating the controversy over which would be the best conduct, considering the available prognostic factors[38].

Overtreatment with hormone therapy

In the last decades, hormone therapy has established itself in clinical practice as part of adjuvant therapy for breast cancer[39], based in the results of clinical trials that demonstrated reduction of mortality with the use of adjuvant tamoxifen for five years[33].

Due to its routine use in the treatment of localized tumors and, particularly, those with a good prognosis with hormone receptors, it is very likely that there is overtreatment with hormonal therapy in clinical practice. Nevertheless, a meta-analysis of randomized clinical trials of mammographic screening[4] failed to prove this increase, which most likely is associated to the date these trials were made. For the majority of randomized clinical trials, there are no information about treatment with hormone therapy. The two trials with information about this theme present only a percent of use of 17% and 2%[4].

Assuming there was overtreatment with hormone therapy, it implies the presence of associated risks with the use of tamoxifen such as increase of incidence of thromboembolism and uterine cancer. The reduced effect of tamoxifen in the incidence of coronary arterial disease[26] on its turn, would offset these risks. It is estimated that the relation between risks and benefits of the aromatase inhibitors are also balanced, not changing the overall mortality[26,40].

Overtreatment with chemotherapy

The Brazilian guideline for breast cancer treatment, in cases of low risk localized invasive cancers, with good prognosis and more compatible with potential overdiagnosis, the classic chemotherapy protocol (cyclophosphamide , methotrexate and -fluorouracil - CMF is still recommended), though anthracyclines (adriamycin/doxorubicin) are also considered as an option in individualized cases[41]. For the cases with intermediate or high risk, in general, the protocol contains anthracycline[41].

Considering the curative interaction of these therapies, the relatively long survival time and the possibility of overtreatment, it is essential to know the toxicity of the chemotherapy schemas utilized in this context and its effects in average and long term. The number of deaths by acute toxicity during treatment with CMF in breast invasive ductal carcinoma is of three in one thousand (0.3%)[26]. The protocols including anthracyclines present high toxicity than CMF and augment the risk of heart failure in the long term[29,42]. In less than 1% of the cases, these protocols may generate serious cardiac complications as cardiomyopathy and congestive heart failure[43,44]. The anthracyclines-associated cardiotoxicity grows exponentially with the dose and can be irreversible [44]. The incidence of congestive heart failure reaches 5% of the cases when the cumulative dose of doxorubicin achieves 400 mg/m^2. The risk of cardiotoxicity is higher in elder women, hypertensive, with preexisting coronary arterial disease or with previous history of mediastinal radiotherapy[44].

The existence of overtreatment with chemotherapy connected to the mammographic screening is still not well established in the literature[4,26]. On the other hand, the reduction of the treatment with chemotherapy – a possible benefit of the screening – does not present as well a proper scientific proof[4,26]. Because of the limited effect of mammographic screening in the reduction of advanced cases of breast cancer, the drop of cases treated with chemotherapy should be, at the most, modest and restricted to women older than 50 years, having in mind that the screening of younger women does not diminish the advanced presentation of the disease[45,46].

It appears to exist a recent trend in US to decrease the use of chemotherapy from 26.6% (CI 95%: 23.0%-30.7%) to 14.1% (CI 95%: 12%-16.3%) in patients with invasive breast cancer with positive estrogen receptor, negative HER2 and without invasion of lymph nodes or with micrometastasis[47]. This drop, if maintained, diminishes the possibility of overtreatment with chemotherapy.

Overall, the intention here is not to affirm that there is no overtreatment with chemotherapy. It is acknowledged only that there isn't an established connection in the literature between mammographic screening and increase of treatment with chemotherapy[4], that is, there is no conclusive evidence of mammographic screening-induced overtreatment with chemotherapy. Similar situation occurs with the evidence about hormone therapy and targeted therapy with trastuzumab.

Overtreatment with trastuzumab

The use of target-therapy with the monoclonal antibody trastuzumab disseminated in the clinical practice since the end of the 2010 decade for the subgroup of women with HER2 positive breast cancer and started to represent a therapeutic alternative either for initial or metastatic breast cancer cases.

Cardiotoxicity is the major risk associated to this therapy. Though it is generally reversible with the discontinuation of the treatment with trastuzumab, some cases may evolve to severe heart failure and death. In a prospective and multicenter series of 81 cases of initial breast cancer treated with trastuzumab in Brazil, 46% presented ejection fraction of the left ventricle lower than 50% or drop of more than 10% of the ejection fraction pre-treatment and one case evolved to death because of cardiotoxicity[48]. There is also report of Takotsubo

myocardiopathy after therapy with trastuzumab and pertuzumab[49].

As the target therapy with trastuzumab was not used then when mammographic screening clinical trials were performed, there are no conclusive evidences of the existence of overtreatment with trastuzumab or its reduction with the practice of screening. Therefore, it is not possible to affirm that the risks associated to the use of trastuzumab are augmented or reduced in women who were screened with mammography.

Limitations

The present study adopted the approach of critical review of the literature whose focus lies in the conceptual contributions of each item of the literature included. Like other reviews of this nature, its product is practically a yet unexplored hypothesis in the literature[50], binding the increase of the cardiovascular mortality associated to breast cancer diagnosis and treatment to overdiagnosis and overtreatment resulting from mammographic screening. The present review contains all the elements of the so-called integrative review[51]. Although there are several aspects typical of systematic review of the literature, such as research question, search strategies and eligibility criteria to select the articles, others were omitted as search of gray literature, blind selection of titles-abstracts by more than one reviewer and meta-analysis. These choices occurred also because of the impossibility of studying directly the cases of overdiagnosis and overtreatment due to its counterfactual nature and the necessity of conducting several reviews over each one of the harms identified. Furthermore, it was not appropriate to conduct meta-analysis, since for two of the search strategies performed, the amount of studies selected was very small and for adjuvant radiotherapy, it was encountered a systematic review with meta-analysis already completed, so the option was for a narrative presentation of the results of the studies. Therefore, similar to other studies classified as critical reviews, the current review intends to pursue a new interpretation for the existing data[50]. In that line, it was attempted to interpret and correlate the findings presented *vis-à-vis* the body of evidences about harms of the mammographic screening.

CONCLUSION

Although the literature on mammographic screening is extensive, the cardiovascular harms associated to this practice have been repeatedly ignored. Consistent evidences exist about the increase of cardiovascular mortality associated to the breast cancer diagnosis and treatment in clinical situations compatible with the overdiagnosis and overtreatment resulting from screening. It is probable as well that the increase of cardiovascular mortality is one of the most important harms of mammographic screening, in special the harms resulting from adjuvant radiotherapy. Despite relatively rare, the cardiovascular harms addressed herein are being discussed within the context of overdiagnosis and consequent overtreatment where, by definition, benefits to offset the harms do not exist. The present review did not have as objective to compare quantitatively the cardiovascular harms with the benefit of mammographic screening to reduce breast cancer mortality, because in the literature there are no studies that have quantified comprehensively this excess of mortality and estimated the balance between harms and benefits. This is a theme yet open that needs to be further explored.

CONTRIBUTIONS

Arn Migowski conceived the study, reviewed the literature, contributed for the interpretation of the results, participated of the wording and review of the manuscript. Paulo Nadanovsky and Cid Manso de Mello Vianna contributed for the interpretation of the results and critical review of the article. All the authors read and approved the final version of the manuscript, ensuring its accuracy and integrity.

DECLARATION OF CONFLICT OF INTERESTS

There are no conflicts of interest to declare.

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