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# IONIZING RADIATION AND VOLUMETRIC MAMMOGRAPHIC DENSITY

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**Abstract**

**Objectives:** Mammographic density (MD) refers to the percentage of dense tissue of an entire breast and was proposed to be used as a surrogate marker for breast cancer. High-dose ionizing radiation (IR) has been recognized as a breast cancer risk factor. The aim of our study was to investigate association between lifetime low dose ionizing radiation (LDIR) and MD. **Material and Methods: A** cross-sectional study included 467 women aged 40–60 years who underwent screening mammography in Łódź, Poland. The digital mammography examination of the breasts included both craniocaudal and mediolateral oblique views. The volumetric breast density (VBD) (%) and fibrograndular tissue volume (FG) ($cm^3$) were determined based on the analysis of mammographic image ("for processing") using Volpara Imaging Software. The exposure to IR was estimated for each individual, based on the data from interviews about diagnostic or therapeutic medical procedures performed in the area of the neck, chest, abdomen and spine, which involved X-rays and γ rays and the data about the doses derived from literature. Linear and logistic regression were fitted with VBD and FG as the outcomes and organ breast dose, effective dose and number of mammographies as the determinants, adjusted for major confounders. **Results:** The analyses showed no association between VBD or FG and the breast organ dose or the effective dose. The only significant finding observed concerned the association between the number of mammographies and the FG volume with β coefficient: 0.028 (95% CI: 0.012–0.043), and predicted mean FG volume >13.4 $cm^3$ among the women with >3 mammographies when compared to those with none. **Conclusions:** This study does not, in general, provide support for the positive association between LDIR and MD. The weak association of the FG volume with the number of mammographies warrants further verification in larger independent studies. Int J Occup Med Environ Health. 2022;35(5):635–49

**Key words:**
**breast cancer, ionizing radiation, mammography, effective dose, mammographic density, organ dose**

## INTRODUCTION

Mammographic density (MD) refers to the percentage of dense tissue of an entire breast. The basis of MD measurement is the difference in the X-ray attenuation characteristics of breast tissue composition [1,2]. Fat is radiologically lucent, so X-rays can pass through it, and it appears dark on a mammogram. As epithelial and connective tissues, including the glands, are radiologically dense, and they block X-rays more than fat tissue, they appear white on a mammogram. High-percent MD (>75%) has been found to be a strong and independent risk factor for breast cancer [3,4]. While MD decreases with older age and higher body mass index (BMI) [3,5], it also appears to be modifiable and to mediate the effects

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of certain breast cancer risk factors such as post-menopausal hormone use, tamoxifen, and some reproductive factors [6,7]. It has been also postulated that the MD may be utilized as the important factor to assess the role of environmental exposures in breast cancer risk [8].

Ionizing radiation (IR) is a form of radiation that carries sufficient energy to remove the electrons from the atomic orbital or molecules when passing through the matter. Therefore, this radiation can harm biological systems or even damage the DNA of cells, thus affecting their functioning or causing mutations. There are different types of radiation but α rays, β rays, X-rays and γ rays are the most common in naturally occurring or artificial sources. Among them, X-rays and γ rays can penetrate all human organs and tissues (unlike α and β radiation) and, therefore, can be the most hazardous for the entire body. For the same reason, i.e., the high penetrating ability, X-rays and γ rays are used in most medical imaging applications, both diagnostic and therapeutic.

Regarding the former type of radiation, it is mostly used, in particular, in traditional radiography (chest and lung examinations, mammography, etc.), computed tomography (CT) scans, and interventional fluoroscopy, while the latter in nuclear medicine procedures such as planar scintigraphy of the bone, thyroid gland or lung, single photon emission tomography (SPECT), and positron emission tomography (PET) scans. The γ rays of high energy have an ability to kill living cells and, therefore, are used in radiation therapy in order to shrink or even damage malignant tumors (brachytherapy, the γ knife, etc.)

In epidemiological research, patients and occupationally exposed medical staff are usually the target populations for studying the cancer (but also non-cancer) effects of IR on human health. The knowledge on breast cancer risk among women after exposure to IR has been derived mainly from studies of patients exposed to diagnostic or therapeutic medical radiation, and of Japanese atomic bomb survivors.

The epidemiological and clinical studies have shown that low-dose IR (LDIR) (≤100 mSv) or low-dose rate IR (LDRIR) (<6 mSv/h) exposure may lead to some pathological changes in the body [9]. The human breast is one of the most sensitive organs to IR. Exposure to the doses of IR in the range of 0.1–0.5 Sv were shown to be associated with breast cancer in females [10], and it was demonstrated that fractionated exposures are similar to single exposures of the same total dose in their ability to induce breast cancer [11]. Treatment with radiation for breast cancer (typically, a total dose of 45–60 Gy) might generate late side effects such as fibrosis and lymphaedema within the breast, with diffuse scarring, and damage to blood vessels and connective tissue [12–14].

While high-dose IR has been recognized as a breast cancer risk factor, based on the observations of the atomic bomb survivors or patients treated repeatedly with IR, virtually no previous studies had investigated the influence of IR on MD. The only 2 clinical investigations that the article authors identified, regarding breast cancer patients with adjuvant therapy, had reported no reduction in MD in the breast after radiotherapy treatment of cancer in the contralateral breast [11,15].

Whether lifetime LDIR modifies MD is largely unknown. To the best of our knowledge, only 1 previous study had investigated the association between the exposure to IR and MD, with some small increase in MD being observed [16]. This study focused on occupational exposure.

Thus, to further explore this research topic we aimed at investigating the potential role of lifetime LDIR arising in the course of medical diagnosis or treatment on the variation of MD. For this purpose we used personal medical history data from a cross-sectional study of MD in Polish women, from which we collected information about all diagnostic and therapeutic procedures in women's lives involving IR over the chest and abdomen area.

## MATERIAL AND METHODS

The cross-sectional study was described previously [17]. Briefly, women were recruited into the study at 2 mammographic screening centers in Łódź, a city in central Poland, at the time they were presenting for screening mammography. The inclusion criteria were: age 40–60 years, residency in the Łódź area, no previous diagnosis of breast cancer or previous breast augmentation surgery/implants, and not taking hormone replacement therapy (HRT) at the time of the enrollment. In Poland, the national mammography screening procedures are funded by the government for women aged 50–69 years, every 2 years. Programs (municipal) for women aged 40–49 years are also carried out, but on a minor scale and on an irregular basis. The women were enrolled in the study in 2013–2018, with 600 women, initially classified as eligible, providing their consent to participate. Out of these, for 526 women mammograms were available in the format "for processing" – as required for volumetric density calculations – of whom interviews were performed with 472 women. Five women reported using HRT during the interview and were excluded, eventually leaving 467 women for the analysis.

Since the current study was an exploratory, secondary analysis of the larger project described earlier, with practically no prior epidemiological data, no initial sample size calculations were performed.

Personal interviews were carried out at the women's homes (on average, within 1.5 month after mammography) by trained interviewers, in order to elucidate data on demographics, menstruation and menopause, a reproductive history, a history of contraceptive medications use, menopausal hormone therapy, alcohol consumption, and tobacco smoking, as well as data about any radiologic diagnostic and treatment procedures of the chest and abdomen.

Anthropometric measurements, i.e., body weight and height, as well as hip and waist circumferences, were carried out by trained nurses, on average within 1 month after mammography. The values of BMI, and the waist-to-hip ratio (WHR) (the umbilical waist circumference [cm] divided by the hip circumference) were calculated.

### Ethics statement

The study was approved by the Bioethics Committee at the Nofer Institute of Occupational Medicine (NIOM) (approval No. 2/2012 of March 13, 2012, and approval No. 3/2016 of April 1, 2016). A signed informed consent form was obtained from each study participant.

### Mammography and MD assessment

Digital mammography was performed in 2 mammographic centers, according to the standard procedure, with Mammomat Novation DR, Mammomat Fusion (Siemens Healthcare GmbH, Germany) in 1 center, and Lorad Selenia, Selenia Dimensions (Hologic Inc., USA) in the other. The examination of the breasts included both craniocaudal and mediolateral oblique views for each breast. Raw data ("for processing") generated by the digital mammography system were analyzed using Volpara Imaging Software (Volpara Health Technologies Ltd., Wellington, New Zealand), algorithm version 1.5.5.1, at the Department of Environmental Epidemiology at NIOM. Volpara applies a physics-based image model, and its principles were described by Highnam et al. [18], as an extension of the method proposed by van Engeland et al. [19].

Briefly, the algorithm determines the X-ray attenuation between the image detector and the X-ray source according to the image pixel signal. The pixel intensity corresponding to purely adipose tissue is used as a reference to which all other pixels are compared to calculate the thickness of the fibroglandular (FG) tissue that must have been present to contribute to a relatively greater X-ray attenuation than at the fatty reference point. The volumes of the adipose and FG tissues are summed across the entire breast. The volumetric breast density (VBD) calcula-

tion software takes into account the geometric effects of the radiation source position and the radiation angle with respect to both the breast and the detector. More specifically, VBD is calculated as the ratio of the FG volume to the total breast volume, and is expressed as a percentage value. The software provides 4 separate sets of mammographic measures, each based on 1 image of the standard mammography procedure: the left and right breast, each in 2 projections.

For the qualitative assessment of MD, for each women (combining her 4 views), this quantitative VBD value is mapped to 1 of 4 Volpara density grades (VDGs) based on specific thresholds (VDG a <3.5% VBD, VDG b ≥3.5% and <7.5% VBD, VDG c ≥7.5% and <15.5% VBD, and VDG d ≥15.5% VBD) so that the VDG (fifth edition) categories correlate with the density categories (a, b, c, and d) listed in the American College of Radiology Breast Imaging Reporting and Data System [20].

**Ionizing radiation exposure assessment**

The exposure to IR was estimated based on the data from interviews and the data about the doses derived from literature. Detailed information was collected about the diagnostic or therapeutic medical procedures performed in the area of the neck, chest, abdomen and spine, which involved X-rays and γ rays. In particular, the participants were asked if they had any diagnostic procedures, such as radiography, CT or scintigraphy, and how many times in the age periods specified as follow: <30 years, 30–39, 40–49, and 50–59 these had been performed. In addition, the women were asked if they had had any previous mammographies and, if so, how many. Separate questions were asked about fluoroscopic examinations and the calendar year of the examination, as well as about radiotherapy (due to hyperthyroidism, thyroid cancer, ablation, Hodgkin's disease, polycythemia or other).

The doses of IR per single examination of each procedure were determined based on the literature review. ScienceDirect and Springer databases (and also Google Scholar) were searched, with "medical examinations," "organ breast dose" and "effective dose" used as keywords; in the case of the latter 2, additionally in combination with the name of the procedure. The identified 130 scientific reports were then examined in terms of information about 1 or both types of the doses. Finally, in total, 41 articles were used for the assessment of the doses from various medical examinations, in particular planar X-ray diagnostics (e.g., a chest X-ray examination), X-ray tomographic diagnostics (e.g., CT of the thoracic spine or computed angiotomography), and scintigraphy (e.g., bone scintigraphy), fluoroscopy and mammography, which could have a significant impact on the breast doses. The list of the source references and the procedure that was applied for data selection is included in the supplemental material [21].

After collecting the data (on the organ breast doses and the effective doses) for every type of the examination, the arithmetic means were calculated to assess the doses (of each type) per each diagnostic or therapeutic procedure. These means are presented in Table 1.

The doses originating from fluoroscopy, scintigraphy (only breast doses) and radiotherapy were estimated on a case-by-case basis, taking into account the underlying indication of the diagnosis/treatment, the title of the procedure, and the irradiated body area.

The fluoroscopy was reported by 39 subjects. The doses were assigned according to a report by the Nuclear Safety Authority in Finland (STUK) [22]. Regarding scintigraphy (reported by 46 women), the doses were calculated using diagnostic reference levels (DRLs) in (MBq) for a given nuclear medicine procedure (taken from [23] and multiplied by the typical average dose per unit activity of the technetium derivatives administered (mGy/MBq) [24].The doses were then corrected for the respondent's BMI using a standard procedure.

Seven respondents reported a history of radiotherapy (3 individuals for the thyroid gland, 3 for the uterus and 1 for

Hodgkin's lymphoma). The organ breast doses coming from various radiotherapy treatments, except for the thyroid treatment, were taken from [25]. For the thyroid treatment, the relevant data were lacking and the organ breast dose was estimated using the doses presumably reaching the non-target organs (in this case, the breast) as the scattered radiation during the head and neck treatment.

The cumulated organ breast doses and the effective dose for every individual were calculated in the following manner: for each respondent, the number of examinations done of a given type was multiplied by the corresponding mean dose value, estimated based on the literature review. Then, the doses were summed over all the examination types considered in the study.

**Statistical analysis**

Arithmetic means (for continuous variables) and frequencies (for categorical variables) were calculated to describe the study population. The means and standard deviations of the breast mammographic volume ($cm^3$), FG volume ($cm^3$), and VBD (%) for the left and right breast, and their averages, were determined. The average of 4 images (2 projections per each breast) were used in statistical analyses.

To examine whether IR exposure is associated with MD over the observed range of exposures, we fitted linear (normal–error) regression models of MD. Since MD metrics and exposure metrics (the organ and effective doses) were highly skewed (the parameters of skewness equal to 2.0 and 1.7 for the fibroglandular volume and MD, respectively; and to 17.7 and 11.1 for the effective dose and the organ dose, respectively), for modeling, their values were transformed to natural logarithms, which improved the symmetry of residuals. The number of mammographies was analyzed either as continuous, or it was discretized into 3 categories (none, 1–2 and ≥3). The estimated regression coefficients β, reported in tables, relate the log of the outcome variable to the log of exposure.

**Table 1.** The mean typical values of effective dose and the organ breast dose, resulting from medical examinations, per procedure, applied in further estimations of cumulative doses per woman (based on dose assessments extracted from earlier studies [21])

| Procedure | Dose (M) | |
|---|---|---|
| | effective [mSv] | organ breast [mGy] |
| RTG | | |
| cervical spine | 0.14 | <0.01** |
| collarbone | 0.01 | 0.77 |
| lung (chest X-ray) | 0.04 | 0.14 |
| ribs | 0.32 | 4.11 |
| thoracic spine | 0.68 | 2.76 |
| lumbar spine | 1.18 | 0.85 |
| abdomen | 0.85 | 0.11 |
| pelvic | 0.73 | 0.05 |
| Computed tomography | | |
| neck | 2.75 | 0.80 |
| chest | 7.70 | 14.56 |
| spine | 6.80 | 0.45 |
| abdomen without pelvic | 10.58 | 1.70 |
| abdomen with pelvic | 11.80 | 0.72 |
| angio-CT | 23.87 | 20.00 |
| Scintigraphy* | | |
| thyroid | 1.67 | 0.13 |
| heart | 8.31 | 2.86 |
| lungs | 2.22 | 2.38 |
| liver | 4.20 | 0.03 |
| kidneys | 1.65 | 0.57 |
| bone | 3.54 | 0.25 |
| Fluoroscopy* | | |
| stomach | 9.07 | 0.18 |
| urologic | 5.92 | 0.28 |
| cardiologic | 23.90 | 2.36 |
| liver | 29.50 | 0.55 |
| lungs | 5.00 | 2.00 |
| head | 154.00 | 0.86 |
| spine | 3.21 | 0.01 |
| Mammography* | 0.29 | 3.60 |

* For these procedures, the doses were calculated using additional assumptions as described in the supplementary material [21].
** Assumed negligible.

Based on the literature review, the following variables were considered as potential confounders of the association between ionizing exposure and MD age at mammography (continuous), the menopausal status (pre- or post-menopausal), age at menopause, age of menarche (≤12,13–14, ≥15 years), previous use of sex hormones (ever, never), parity (ever, never), breastfeeding (ever, never), tobacco smoking (never, ex-, current smoker), BMI (continuous), a family history of breast cancer (yes, no).

Additionally, the variables capturing the possible variability due to specific mammographic equipment or technique, such as the mammographic center (1, 2), the mammographic X-ray system (Siemens, Hologic), and the mammographic device (apparatus) (Mammomat Novation DR, Mammomat Fusion, and LoradSelenia, Selenia Dimensions) were analyzed. The participating women were classified as post-menopausal if they reported not having their menstrual bleeding within the past 365 days; otherwise, they were classified as pre-menopausal.

The variables that had a significance level of $p < 0.15$ in the univariate linear regression models with VBD as the outcome variable were then examined in the multivariate models. Age at mammography, the menopausal status, age at menarche, BMI, tobacco smoking, a family history of breast cancer, and the mammographic device were retained in the final model, based on statistical significance ($p < 0.05$).

Crude and adjusted models were also fitted with the radiation doses expressed as categorical variables in tertiles, not restricted by linearity over the whole range of doses. Based on these models, the marginal means of MD and FG volume were estimated. Adjusted estimated means were obtained by proportionally averaging over all combinations of levels of the adjustment variables in the model. For presentation, the estimated means of the logarithmic outcome measures (breast density and fibroglandular volume) were retransformed to the original scales.

As an alternative assessment for breast density, the crude and adjusted odds ratios (ORs) for the higher breast density categories in the tertiles of exposure were calculated using a logistic regression model. For this purpose, breast density was dichotomized by taking a MD of <7.5 as a reference category vs. a MD of ≥7.5. This categorization adheres to the VDG (fifth edition; similar to BI-RADS fifth edition) breast density classification thresholds, and is equivalent to the grouping of the 2 higher density categories "c" and "d" to 1 (reference) category, vs. the other 2 ("a" and "b") treated as reference.

Stratified analyses were performed by the menopausal status and a family history of breast cancer. The likelihood ratio test was used to determine the statistical significance of the effect modification.

Six women reported a history of radiotherapy and their lifetime IR exposure was much higher comparing to the rest of the participating women. The analysis was repeated after excluding these women from the file. The results did not change substantially, and thus are not presented.

The STATA v. 15.1 (StataCorp LP) and the R software ver. 3.6 (R Core Team, 2019) were used for statistical analyses.

## RESULTS

The women's age was M±SD 54.3±3.8 years and the BMI was M±SD 27.2±4.7 kg/m$^2$ (Table 2). The majority of the participants had menarche at the age of 13–14 years (49.5%), were post-menopausal (79.0%), and were ever pregnant (93.2%), and among the parous women, 67.0% had ever breastfed. The mean age at menopause among the post-menopausal women was M±SD 50±3.8 years.

A family history of breast cancer was reported by 11.6% of the participating women, and 43.9% had ever used hormonal therapy. The average (left and right breast) FG volume equaled M±SD 61.6±31.5 cm$^3$, the total breast volume M±SD 925±471 cm$^3$, and the VBD M±SD 7.9±4.6%. Majority of women were classified into grade b

**Table 2.** The selected characteristics of the study population of 467 women aged 40–60 years, participating in mammographic screening programme in the city of Łódź, Poland

| Variable | Participants (N = 467) |
|---|---|
| Age at mammography [years] (M±SD) | 54.3±3.8 |
| BMI [kg/m$^2$] (M±SD) | 27.2±4.7 |
| Age at menarche [n (%)] | |
| ≤12 years | 133 (28.5) |
| 13–14 years | 231 (49.5) |
| ≥15 years | 96 (20.6) |
| missing data | 7 (1.5) |
| Menopausal status [n (%)] | |
| premenopausal | 98 (21.0) |
| postmenopausal | 369 (79.0) |
| Age at menopause among postmenopausal women [years] (M±SD) | 50.0±3.8 |
| Parity [n (%)] | |
| ever | 435 (93.2) |
| never | 32 (6.8) |
| Breastfeeding [n (%)] | |
| ever | 308 (67.0) |
| never | 159 (34.0) |
| Smoking [n (%)] | |
| current | 94 (20.1) |
| past | 145 (31.1) |
| never smoker | 228 (48.8) |
| Family history of breast cancer [n (%)] | |
| yes | 54 (11.6) |
| no | 413 (88.4) |
| Hormonal therapy use [n (%)] | |
| ever | 205 (43.9) |
| never | 260 (55.7) |
| missing | 2 (0.4) |
| Mammographic centre [n (%)] | |
| 1 | 267 (57.2) |
| 2 | 200 (42.8) |
| X-ray system [n (%)] | |
| Siemens Fusion | 89 (19.1) |
| Siemens Novation | 111 (23.8) |
| Hologic | 267 (57.2) |
| Mammographic device [n (%)] | |
| Mammomat Novation DR | 111 (23.8) |
| Mammomat Fusion | 89 (19.1) |
| Lorad Selenia | 138 (29.6) |
| Selenia Dimensions | 129 (27.6) |
| Fibroglandular tissue volume [cm$^3$] (M±SD) | |
| left breast | 60.7±31.2 |
| right breast | 62.6±33.4 |
| both breasts average | 61.6±31.5 |
| Breast volume [cm$^3$] (M±SD) | |
| left breast | 926.0±467.9 |
| right breast | 924.9±486.2 |
| both breasts average | 925.6±471.4 |
| Volumetric mammographic density [%] (M±SD) | |
| left breast | 7.7±4.6 |
| right breast | 8.0±4.7 |
| both breasts average | 7.9±4.6 |
| VolparaDensity Grade (VDG) [n (%)] | |
| a (<3.5%) | 38 (8.1) |
| b (≥3.5% and <7.5%) | 248 (53.1) |
| c (≥7.5% and <15.5%) | 146 (31.3) |
| d (≥15.5%) | 35 (7.5) |
| Mammographies [n (%)] | |
| 0 | 31 (6.6) |
| 1–3 | 195 (41.8) |
| >3 | 221 (47.3) |
| missing | 20 (4.3) |
| Dose (M±SD) | |
| organ breast [mGy] | 24.6±49.1 |
| total effective [mSv] | 11.7±44.3 |

(53.1%) or grade c (31.3%) in terms of VDG. Majority of women reported to have >3 (47.3%) or 1–3 (41.8%) mammographies in the past while 6.6% of women had no mammographic exam before the study.

The estimated mean lifetime IR exposure equaled M±SD 24.6±49.1 mGy for the organ breast dose, with a total

effective dose of M±SD 11.7±44.3 mSv. The 10th, 50th and 90th percentiles of estimated organ dose amounted to 4.8 mGy, 17.6 mGy and 40.6 mGy, respectively, while for the effective dose it amounted to 1.2 mSv, 4.2 mSv and 24.3 mSv.

The analyses showed no statistically significant association between the breast organ dose and or effective dose and FG or VBD (Table 3).

Negative or near-zero values of coefficients of univariate regression models (unadjusted) suggested that, on average, VBD and FG volume tended to decrease with increasing doses. These coefficients shifted towards larger values, when age and other confounders were included as explanatory variables. Adjusted model explained about 32% variability of VBD and 14% variability of FG volume, however the effect of dose in none of adjusted models reached statistical significance. Similarly, no significant associations were observed in the analysis of the lifetime doses categorized into tertiles, which takes into account potential nonlinear effects of doses in the middle ($T_2$) and upper ($T_3$) tertile, relative to the lower tertile $T_1$.

The only significant finding observed concerned the association between the number of mammographies and the FG volume with an adjusted coefficient β of 0.028 (95% CI: 0.012–0.043), when expressed as continuous, and a predicted mean FG volume greater by 13.4 $cm^3$ among the women with >3 mammographies in the past when compared to those with none (Table 4).

The logistic regression analysis showed no significant inferences between both the breast organ dose and the effective dose, or between FG and VBD. When compared to the women who reported no previous mammographies, the odds of the upper VDG (c, d) was greater than the lower grades for both groups of women who had 1–3 or >3 mammographies in the past; still, the estimates were statistically insignificant (OR = 1.36 (95% CI: 0.52–3.63) and OR = 1.40 (95% CI: 0.5–3.99), respectively) (Table 5).

The stratified analyses by the menopausal status and a family history of breast cancer did not show any significant relationship, with no statistically significant heterogeneity being observed(data not shown).

## DISCUSSION

In this study involving women aged 40–60 years undergoing screening mammography, we analyzed the association between lifetime IR resulting from medical diagnostic and therapeutic procedures, and volumetric MD or FG volume. In general, the results did not confirm the study hypothesis, and the only statistically significant finding recorded was the positive association between the greater volume of the FG tissue and the increasing number of mammographies.

To the best of our knowledge, only 1 previous epidemiological study investigated the links between exposure to IR and MD. In a population of 1476 Spanish women, the data about their current job were used, and the occupational exposures, including IR, were coded using the job exposure matrix. The study suggested an insignificant increase of the geometric mean of dense breast among 54 women with occupational exposure to IR. The exposure characterized the participants' current job, and the exposure to IR in that study was the most frequent among nurses.

In our investigation we did not analyze the doses from occupational exposure to IR. Only 15 respondents completing the questionnaire declared having a profession with a potential exposure to IR, and these were electroradiology technicians. At the workplace, they used the following diagnostic and/or therapeutic devices: an X-ray machine, a PET device, the γknife and scintigraphy. According to the NIOM dosimetry service database, the annual effective dose of healthcare workers is about 0.5 mSv. However, as electroradiology technicians are relatively well protected (lead aprons, control rooms), one can assume their doses to be far below this value. Taking further into

**Table 3.** Association between ionizing radiation: organ dose and effective dose (expressed either by continuous or categorical variables) and percent volumetric mammographic density and fibroglandular tissue volume in the population of 467 women aged 40–60 years, participating in mammographic screening programme in the city of Łódź, Poland.

| Tertile | Volumetric mammographic density [%] | | | | Fibroglandular tissue volume [$cm^3$] | | | |
|---|---|---|---|---|---|---|---|---|
| | unadjusted | | adjusted* | | unadjusted | | adjusted* | |
| | M (95% CI) | β (95% CI)** | M (95% CI) | β (95% CI)** | M (95% CI) | β (95% CI)** | M (95% CI) | β (95% CI)** |
| Organ dose | | –0.024 (–0.073–0.024) | | 0.007 (–0.038–0.052) | | –0.020 (–0.062–0.022) | | 0.023 (–0.21–0.068) |
| $T_1$[0,12.8] | 6.9 (6.2–7.6) | | 6.6 (6.0–7.3) | | 55.5 (50.5–60.9) | | 52.1 (47.5–57.2) | |
| $T_2$(12.8,23.2] | 7.2 (6.5–8.0) | | 7.2 (6.6–7.9) | | 56.4 (51.3–61.9) | | 57.4 (52.5–62.6) | |
| $T_3$(23.2,699] | 6.5 (5.8–7.2) | | 6.7 (6.1–7.4) | | 54.4 (49.5–59.7) | | 56.9 (52.1–62.3) | |
| Effective dose | | –0.025 (–0.063–(–0.013)) | | –0.010 (–0.043–0.023) | | **–0.033 (–0.066–(–0.0001))** | | –0.021 (–0.053–0.011) |
| $T_1$[0.04,2.7] | 7.1 (6.4–7.9) | | 6.8 (6.2–7.5) | | 56.5 (51.5–62.1) | | 55.3 (50.6–60.5) | |
| $T_2$(2.7,8.52] | 6.7 (6.1–7.5) | | 6.8 (6.2–7.5) | | 55.9 (50.9–61.4) | | 56.4 (51.7–61.6) | |
| $T_3$(8.52,903] | 6.7 (6.1–7.5) | | 6.9 (6.3–7.6) | | 53.8 (49.0–59.1) | | 54.5 (49.9–59.6) | |

M – predicted marginal mean.

* Adjusted for age at mammography, BMI, family breast cancer, mammographic device, age at menarche, menopausal status and smoking.

** Regression of log outcome.

Bolded are statistically significant coefficients ($p < 0.05$).

**Table 4.** Association between number of mammographies (expressed either as continuous or categorical explanatory variable) and percent volumetric mammographic density and fibroglandular tissue volume in the population of 467 women aged 40–60 years, participating in mammographic screening programme in the city of Łódź, Poland

| Variable | Volumetric breast density [%] | | | | Fibroglandular tissue volume [$cm^3$] | | | |
|---|---|---|---|---|---|---|---|---|
| | unadjusted | | adjusted* | | unadjusted | | adjusted* | |
| | β (95% CI)** | M (95% CI) | β (95% CI)** | M (95% CI) | β (95% CI)** | M (95% CI) | β (95% CI)** | M (95% CI) |
| Continuous (range 0–21) | –0.006 (–0.023–0.012) | | 0.007 (–0.009–0.023) | | 0.006 (–0.009–0.021) | | **0.028 (0.012–0.043)** | |
| 0 (ref.) mammographies | – | 7.9 (6.2–10.0) | – | 6.8 (5.5–8.5) | – | 56.3 (45.8–69.3) | – | 46.4 (37.7–57.0) |
| 1–3 mammographies | –0.146 (–0.342–(–0.050)) | 6.8 (6.2–7.5) | –0.020 (–0.190–0.150) | | –0.049 (–0.221–0.122) | 53.6 (49.4–58.2) | 0.098 (–0.066–0.263) | 51.4 (47.6–55.6) |
| >3 mammographies | –0.139 (–0.333–0.056) | 6.8 (6.2–7.5) | 0.037 (–0.145–0.218) | 6.7 (6.2–7.3) 7.0 (6.5–7.7) | –0.005 (–0.175–0.165) | 56.0 (51.9–60.6) | **0.245 (0.070–0.421)** | 59.8 (55.4–64.5) |

M – predicted marginal mean.

* Adjusted for age at mammography, BMI, family breast cancer, mammographic device, age at menarche, menopausal status and smoking.

** Regression of log outcome.

Continuous refers to regression with number of mammographies used as continuous explanatory variable; ref. denotes reference level (no mammography ever) for regression with number of mammographies represented as categorical variable with three categories (none, 1–3, >3 mammographies, respectively).

Bolded are statistically significant coefficients ($p < 0.05$).

**Table 5.** Odds ratios (OR) with their corresponding 95% confidence intervals (95% CI) for higher (c or d) versus lower (a or b) volumetric density grades in groups of women, defined by the tertiles of estimated radiation doses (organ dose to breasts and effective whole body dose) received from medical procedures, and frequency of mammographic procedures in the population of 467 women aged 40–60 years, participating in mammographic screening programme in the city of Łódź, Poland

| Exposure* | Crude OR (95% CI) | Adjusted** OR (95% CI) |
|---|---|---|
| Dose | | |
| organ dose [mGy] | | |
| $T_1$ [0,12.8] (ref.) | 1.00 | 1.00 |
| $T_2$(12.8 –23.2] | 1.04 (0.66–1.63) | 1.22 (0.7–2.14) |
| $T_3$(23.2–699] | 0.72 (0.45–1.14) | 0.88 (0.49–1.59) |
| effective dose [mSv] | | |
| $T_1$[0.04,2.7] (ref.) | 1.00 | 1.00 |
| $T_2$(2.7,8.52] | 0.81 (0.52–1.28) | 0.89 (0.53–1.52) |
| $T_3$(8.52,903] | 0.85 (0.54–1.34) | 1.02 (0.6–1.76) |
| Mammographies [n] | | |
| 0 (ref.) | 1.00 | 1.00 |
| 1–3 | 0.83 (0.39–1.80) | 1.36 (0.52–3.63) |
| >3 | 0.72 (0.34–1.55) | 1.40 (0.5–3.99) |

* Tertiles of the empirical distributions of the doses with corresponding ranges of values (right side inclusive), observed in the study.
** Adjusted for age at mammography, BMI, family breast cancer, mammographic device, age at menarche, menopausal status and smoking.

account that the tissue weighting factor for the breast is 0.12 (and assuming the uniform exposure), it was concluded that the contribution from occupational exposure was negligible in this study.

The only significant finding of our analysis, i.e., the positive association between the number of mammographies and FG volume, needs to be interpreted with caution. The organ dose received by the breast during mammography is relatively low (the 2-view mean glandular doses are as follows: a 3.72 mGy dose for digital mammography and a 4.74 mGy dose for screen-film mammography) [26], when compared to the lifetime doses from other medical imaging procedures, and it varies between examinations depending on the mammographic device and some traits of individual patients, such as breast thickness, size and density. In particular, it has been reported that a greater breast density requires more radiation for imaging. In addition, it has been observed that women with large breasts received, on average, 2.3 times more radiation comparing to those with small or average-sized breasts [27]. Thus, the number of mammographies reflects only a proxy measure of IR exposure and may be subject to some misclassification, especially among women with larger breasts. This result could be also affected by selection bias: women with more fibroglandular tissue may be inclined to perform screening mammography more frequently.

This study had a cross-sectional design, and we were able to analyze only images from a single examination. Therefore, we could not conclude about causality. Also, the reversed relationship could not be excluded either. The women who had denser breasts could have been recommended to have more frequent screening mammographies than others.

The biological mechanism underlying the possible association between LDIR and MD are poorly understand. Stromal fibrosis is a major feature of MD, and it has been documented that dense breasts have a higher level of collagen, as well as an altered expression of stromal proteins [28]. Evidence from clinical studies suggests that the increase in MD in response to the therapeutic exposure to IR (at approximate doses of 60 Gy) might be related to stromal remodeling occurring in the radiation field. Late side effects from high doses of breast irradiation due to such treatments include fibrosis and lymphedema. Fibrosis is a hardening or stiffening of the tissues as a result of a diffuse scarring. Lymphedema is caused by damage to the lymphatic vessels system. It has been suggested that also LDIR exposure can influence the breast architecture by affecting fibroblasts [29], or adipose tissue cells [30].

In our study we used 2 measures of IR: the organ dose and the effective dose. The organ dose [Gy] is a measure of

the mean energy accumulated in the organ after irradiation, divided by the organ mass. The effective dose (Sv) is a measure of energy accumulated in all specified radiosensitive organs, divided by the organ mass, and corrected for both the biological effectiveness of various radiation types, and for the radiation sensitivity of various organs and tissues. It is a measure of the whole body irradiation, and it is calculated by multiplying the absorbed dose (in grays [1 Gy]) in each irradiated organ or tissue by the radiation weighting factor, and the corresponding organ or tissue weighting factor, and then summing the doses obtained in this manner over all organs and tissues. A list of radiation and tissue weighting factors is given in the International Commission on Radiological Protection (ICRP) Publication 103 [31]. In medical exposure, the effective dose can be used for comparing the typical doses from different diagnostic procedures.

According to ICRP Publication 103 [31], the organ or tissue doses should rather be used for specific retrospective investigations of individual exposure and risks, while the effective dose is not a recommended quantity measure for this purpose, in particular, in epidemiological evaluations. Therefore, the total organ breast dose was assessed as the main exposure quantity for every individual in this study while the total effective dose was presented just for the comparison of lifetime exposures between respondents.

The strength of our study lies in the fact that it used a fully automatic and objective method for the assessment of volumetric MD. The method takes into account breast thickness, and it is expected to better reflect the amount of the FG tissue in the breast than the planar methods. The women taking HRT were not considered eligible for the study in order to avoid a strong confounding effect. Furthermore, the analysis confirmed the well-established inferences for age and BMI with breast density, which supports the validity of the study. The *post hoc* power calculations that were performed showed that this study had enough subjects to detect the difference between the means equal to $d = 0.32$ of the standard deviation in each group, with the test power of 0.8 (i.e., the probability of $\beta = 0.2$ of the study failing to detect the effect if it was really present in the population), with a significance level of $\alpha = 0.05$. This estimate translates to detectable differences of $0.32 \times 4.6\% = 1.47\%$ for the percent volumetric density, and of $0.32 \times 31.5\ cm^3 = 10.08\ cm^3$ for the fibroglandular volume, where the overall SD values (4.6% and 31.5 $cm^3$, respectively) for each outcome variable were assumed.

The conclusions of the study are only valid within the range of the radiation doses observed in the study population, and under the assumption that the linear regression model is a sufficient approximation of the influence of the radiation dose on breast density and FG volume.

A limitation of this study is that the population was not randomly selected from the general population; therefore, the study group characteristics may not reflect those in the general population of women in Łódź or in Poland. However, the strategy that was applied still allows for analyzing associations within the range of exposures observed in the study population.

Another possible source of limitations is the exposure misclassification given that we used estimated means of IR doses because the true individual radiation exposure data were not available. Similar strategy of estimation of the cumulative dose from ionizing radiation, based on the questionnaire and self – reported data, was adopted in a well-recognized European study focusing on the radiation-induced lens opacities among interventional cardiologists (EURALOC) [32]. The mean values that were used did not strictly represent the true values from different examinations for every respondent. The doses correlate with the shape of one's body, and in particular with BMI, and the automatic exposure control system adjusts the dose to the patient's size.

Moreover, the doses applied in these estimations were found mainly in quite recent papers, thus reflecting the current or most recent exposures. Unfortunately, data about exposures from distant past were not available.

A large number of respondents had examinations earlier than the data encountered in literature. It is also worth noting that older RTG devices may provide more radiation than the newest systems, so the cumulative doses might have been underestimated in this study. The next issue was the evaluation of the radiation doses from fluoroscopy, scintigraphy and radiotherapy, which are the sources of relatively high doses. Information about the type of the isotope used in scintigraphy, the radiotherapy treatment plans, and the exact procedure type in fluoroscopy was not available, thus we could only use crude approximations.

## CONCLUSIONS

This study did not find significant association between lifetime IR exposure from medical diagnostic procedures and MD among women participating in mammographic screening. The weak association of the FG volume with the number of mammographies warrants further verification in larger independent studies.

### REFERENCES


1. Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, et al. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst. 1995;87(9):670-5. https://doi.org/10.1093/jnci/87.9.670.
2. Colin C, Schott AM. Re: Breast tissue composition and susceptibility to breast cancer. J Natl Cancer Inst. 2011;103(1):77. https://doi.org/10.1093/jnci/djq464.
3. McCormack VA, dos Santos Silva, I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006;15(6): 1159-69. https://doi.org/10.1158/1055-9965.EPI-06-0034.
4. Santen RJ, Boyd NF, Chlebowski RT, Cummings S, Cuzick J, Dowsett M, et al. Critical assessment of new risk factors for breast cancer: considerations for development of an improved risk prediction model. EndocrRelat Cancer. 2007; 14(2):169-87. https://doi.org/10.1677/ERC-06-0045.
5. Burton A, Maskarinec G, Perez-Gomez B, Vachon C, Miao H, Lajous M, et al. Mammographic density and ageing: A collaborative pooled analysis of cross-sectional data from 22 countries worldwide. PLoS Med. 2017;14(6):e1002335. https://doi.org/10.1371/journal.pmed.1002335.
6. McTiernan A, Martin CF, Peck JD, Aragaki AK, Chlebowski RT, Pisano ED, et al. Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial. J Natl Cancer Inst. 2005;97(18):1366-76. https://doi.org/10.1093/jnci/dji279.
7. Vachon CM, Sellers TA, Carlson EE, Cunningham JM, Hilker CA, Smalley RL, et al. Strong evidence of a genetic determinant for mammographic density, a major risk factor for breast cancer. Cancer Res. 2007;67(17):8412-8. https://doi.org/10.1158/0008-5472.CAN-07-1076.
8. Cohn BA, Terry MB. Environmental Influences on Mammographic Breast Density in California: A Strategy to Reduce Breast Cancer Risk. Int J Environ Res Public Health. 2019;16(23) . https://doi.org/10.3390/ijerph16234731.
9. Tang FR, Loganovsky K. Low dose or low dose rate ionizing radiation-induced health effect in the human. J Environ Radioact. 2018;192:32-47. https://doi.org/10.1016/j.jenvrad.2018.05.018.
10. Land CE. Studies of cancer and radiation dose among atomic bomb survivors. The example of breast cancer. JAMA. 1995;274(5):402-7.
11. Boice JD, Jr., Preston D, Davis FG, Monson RR. Frequent chest X-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. Radiat Res. 1991; 125(2):214-22.
12. Bentzen SM. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. Nat Rev Cancer. 2006;6(9):702-13. https://doi.org/10.1038/nrc1950.

13. Robertson JM, Clarke DH, Pevzner MM, Matter RC. Breast conservation therapy. Severe breast fibrosis after radiation therapy in patients with collagen vascular disease. Cancer. 1991;68(3):502-8. https://doi.org/10.1002/1097-0142(19910801)68:3<502::aid-cncr2820680310>3.0.co;2-v.
14. Straub JM, New J, Hamilton CD, Lominska C, Shnayder Y, Thomas SM. Radiation-induced fibrosis: mechanisms and implications for therapy. J Cancer Res ClinOncol. 2015;141(11):1985-94. https://doi.org/10.1007/s00432-015-1974-6.
15. Eriksson L, He W, Eriksson M, Humphreys K, Bergh J, Hall P, et al. Adjuvant Therapy and Mammographic Density Changes in Women With Breast Cancer. JNCI Cancer Spectr. 2018;2(4):pky071. https://doi.org/10.1093/jncics/pky071.
16. Lope V, Garcia-Perez J, Perez-Gomez B, Pedraza-Flechas AM, Alguacil J, Gonzalez-Galarzo M. Occupational exposures and mammographic density in Spanish women. Occup Environ Med. 2018;75(2):124-131. https://doi.org/10.1136/oemed-2017-104580.
17. Peplonska B, Janasik B, McCormack V, Bukowska-Damska A, Kaluzny P. Cadmium and volumetric mammographic density: A cross-sectional study in Polish women. PLoS One. 2020;15(5):e0233369. https://doi.org/10.1371/journal.pone.0233369.
18. Highnam R BMJ, Yaffe MJ,Karssemeijer N, Harvey J. Robust breast composition measurement-Volpara™ in Digital Mammography – IWDM (Lecture Notes in Computer Science). Berlin, Germany: 2010.
19. van Engeland S, Snoeren PR, Huisman H, Boetes C, Karssemeijer N. Volumetric breast density estimation from full-field digital mammograms. IEEE Trans Med Imaging. 2006;25(3):273-82. https://doi.org/10.1109/TMI.2005.862741.
20. van der Waal D, den Heeten GJ, Pijnappel RM, Schuur KH, Timmers JM, Verbeek AL, et al. Comparing Visually Assessed BI-RADS Breast Density and Automated Volumetric Breast Density Software: A Cross-Sectional Study in a Breast Cancer Screening Setting. PLoS One. 2015;10(9):e0136667. https://doi.org/10.1371/journal.pone.0136667.
21. Peplonska B, Domienik-Andrzejewska J, Mirowski M, Kaluzny P. An assessment of effective and organ breast doses from different medical sources [dataset]. 2022 Mar 08, PPM Repository. Available from: https://ppm.imp.lodz.pl/info/researchdata/IMPd02d9f7331b4414a9c0d0a5c9be8f495/.
22. Rannikko S, Karila KTK, Toivonen M. Patient and population doses of x-ray diagnostics in Finland. Helsinki, Finland: Radiation and Nuclear Safety Authority, 1997
23. Husak V, Koranda P, Paskova Z, Petrova K, Prouza Z. Diagnostic reference levels (DRLs) for radiopharmaceuticals administered in nuclear medicine — four-year experience with their use: Days of Radiation Protection 2001. Conference Proceedings of the 24th Days of Radiation Protection; 2001.
24. Radiation dose to patients from radiopharmaceuticals (addendum 2 to ICRP publication 53). Ann ICRP. 1998;28(3):1-126. https://doi.org/10.1016/s0146-6453(99)00006-8.
25. Uselmann AJ, Thomadsen BR. On effective dose for radiotherapy based on doses to nontarget organs and tissues. Med Phys. 2015;42(2):977-82. https://doi.org/10.1118/1.4906190.
26. Hendrick RE, Pisano ED, Averbukh A, Moran C, Berns EA, Yaffe MJ, et al. Comparison of acquisition parameters and breast dose in digital mammography and screen-film mammography in the American College of Radiology Imaging Network digital mammographic imaging screening trial. AJR Am J Roentgenol. 2010;194(2):362-9. https://doi.org/10.2214/AJR.08.2114.
27. Miglioretti DL, Lange J, van den Broek JJ, Lee CI, van Ravesteyn NT, Ritley D, et al. Radiation-Induced Breast Cancer Incidence and Mortality From Digital Mammography Screening: A Modeling Study. Ann Intern Med. 2016;164(4):205-14. https://doi.org/10.7326/M15-1241.
28. Barcellos-Hoff MH, Medina D. New highlights on stroma-epithelial interactions in breast cancer. Breast Cancer Res. 2005;7(1):33-6. https://doi.org/10.1186/bcr972.
29. Tsai KK, Chuang EY, Little JB, Yuan ZM. Cellular mechanisms for low-dose ionizing radiation-induced perturbation of the breast tissue microenvironment. Cancer Res.

2005;65(15):6734-44. https://doi.org/10.1158/0008-5472.CAN-05-0703.

30. Maqsudur Rashid A, Ramalingam L, Al-Jawadi A, Moustaid-Moussa N, Moussa H. Low dose radiation, inflammation, cancer and chemoprevention. Int J Radiat Biol. 2019;95(4):506-15. https://doi.org/10.1080/09553002.2018.1484194.
31. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. Ann ICRP. 2007;37(2-4):1-332. https://doi.org/10.1016/j.icrp.2007.10.003.
32. Struelens L, Dabin J, Carinou E, Askounis P, Ciraj-Bjelac O, Domienik-Andrzejewska J et al. Radiation-Induced Lens Opacities among Interventional Cardiologists: Retrospective Assessment of Cumulative Eye Lens Doses. Radiat Res. 2018;189(4):399-408. https://doi.org/10.1667/RR14970.1.