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International Consortium on Mammographic Density: Methodology and population diversity captured across 22 countries

Valerie A. McCormacka
International Agency for Research on Cancer

Anya Burton
International Agency for Research on Cancer

Isabel dos-Santos-Silva
London School of Hygiene and Tropical Medicine

John H. Hipwell
University College London

Caroline Dickens
University of the Witwatersrand

See next page for additional authors

Authors
Valerie A. McCormacka, Anya Burton, Isabel dos-Santos-Silva, John H. Hipwell, Caroline Dickens, Dorria Salem, Rasha Kama, Mikael Hartman, Charmaine Pei Ling Lee, Kee-Seng Chia, Vahit Ozmen, Mustafa Erkin Aribal, Anath Arzee Flugelman, Martín Lajous, Ruy Lopez-Riduara, Megan Rice, Isabelle Romieu, Giske Ursin, Samera Qureshi, Huiyan Ma, Eunjung Lee, Carla H. van Gils, Johanna O.P. Wanders, Sudhir Vinayak, Rose Ndumia, Steve Allen, Sarah Vinnicombe, Sue Moss, Jong Won Lee, Jisun Kim, Ana Pereira, Maria Luisa Garmendia, Reza Sirous, Mehri Sirous, Beata Peplonska, Agnieszka Bukowska, Rulla M. Tamimi, Kimberly Bertrand, Chisato Nagata, Ava Kwong, Celine Vachon, Christopher Scott, Beatriz Perez-Gomez, Marina Pollan, Gertraud Maskarinec, Graham Giles, John Hopper, Jennifer Stone, Nadia Rajaram, Soo-Hwang Teo, Shivaani Mariapun, Martin J. Yaffe, Joachim Schüz, Anna M. Chiarelli, Linda Linton, and Norman F. Boyd

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International Consortium on Mammographic Density: Methodology and Population Diversity captured across 22 Countries

A full list of authors and affiliations appears at the end of the article.

Abstract

Mammographic density (MD) is a quantitative trait, measurable in all women, and is among the strongest markers of breast cancer risk. The population-based epidemiology of MD has revealed genetic, lifestyle and societal/environmental determinants, but studies have largely been conducted in women with similar westernized lifestyles living in countries with high breast cancer incidence rates. To benefit from the heterogeneity in risk factors and their combinations worldwide, we created an International Consortium on Mammographic Density (ICMD) to pool individual-level epidemiological and MD data from general population studies worldwide. ICMD aims to characterize determinants of MD more precisely, and to evaluate whether they are consistent across populations worldwide. We included 11755 women, from 27 studies in 22 countries, on whom individual-level risk factor data were pooled and original mammographic images were re-read for ICMD by a core team to obtain standardized comparable MD data. In the present article, we present (i) the rationale for this consortium; (ii) characteristics of the studies and women included; and (iii) study methodology to obtain comparable MD data from original re-read films. We also highlight the risk factor heterogeneity captured by such an effort and, thus, the unique insight the pooled study promises to offer through wider exposure ranges, different confounding structures and enhanced power for sub-group analyses.

1. Introduction

Since Wolfe's first studies linking mammographic parenchymal patterns to breast cancer (BC) risk in 1976, breast density – typically measured on a mammogram as mammographic density (MD) – is now recognized as one of the strongest risk factors for this malignancy [1-3]. Several features of MD make its population-level research feasible and particularly informative. MD is a continuous trait, quantifiable and, in theory, measurable in virtually all

Corresponding author: V. McCormack, Section of Environment and Radiation, IARC, Lyon, FRANCE. 69008. mccormackv@iarc.fr. Tel +33 4 72 73 85 66.

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women who are eligible to receive a mammogram. High MD is associated with a large population attributable fraction for BC in high-risk countries [4]. Several observations suggest that MD is on a causal pathway for BC, including that tumours arise within localised areas of dense tissue [5], MD and BC have a partially shared genetic basis [6] and the effects of several risk BC factors have concordant effects on MD, and some may be mediated through MD [7,8]. An understanding of population-level MD distributions and determinants may inform the aetiology of this common cancer in women worldwide.

Over the last 3 decades, important determinants of MD have been revealed, including genetic factors [9] and lifestyle and societal/environmental influences such as reproductive factors, alcohol intake, smoking and measures of growth and body size [7,10-14]. Acquisition of this knowledge benefitted greatly from the availability of mammograms in organized BC screening programmes, but consequently the populations most studied to date have had lifestyles typical of high income countries (e.g. low parity, late age at first birth, relative young age at menarche and tall stature). Studying MD in populations with more diverse lifestyles, as can be found across countries and ethnic groups, might be more informative. This approach has already been taken in an international study of women in the US, Norway, Hawaii and Japan [15], and in multi-ethnic studies [16-20]. We extended this concept by establishing an International Consortium of MD (ICMD) studies that is enriched by the inclusion of ethnic groups and countries which span the lowest to the highest BC incidence rates worldwide.

An international study of MD will shed light on the MD range at a given age, whether MD reflects an inherent feature of breast biology in all women, and the effect of a broader range of lifestyles not observable in a single population – e.g., after many pregnancies and years of breast feeding. The objectives of ICMD are thus to establish a resource platform of individual-level risk factor and standardized comparable MD data from ethnically and internationally diverse populations and use this resource to investigate the determinants of MD worldwide, whether they are consistent across countries, women and menopausal status, and whether differences in population-level MD distributions reflect differences in population-level BC incidence rates.

2. Methods

Study and sample selection

The International Consortium of Mammographic Density (ICMD) is co-ordinated by the International Agency for Research on Cancer (IARC). In ICMD, we pooled individual-level MD and epidemiologic data from studies of breast cancer-free women worldwide. ICMD eligibility criteria were first applied at the study-level and then at the individual-level, as follows. Eligible studies were those of women who underwent mammography for the purpose of screening, had retrievable mammographic images in electronic format and individual-level risk factor information. Studies conducted in mammography settings that were exclusively for symptomatic disease or for women with a personal or family history of breast cancer were excluded. From within eligible studies, an individual woman was eligible for inclusion if she was 35 years or over at the time of mammography, if at least one of her mammograms was available and if, at the minimum, she had information for the calculation

or estimation of age, parity and body mass index (BMI) at mammography. Women with a personal history of breast cancer were excluded.

Studies conducted in populations with diverse BC incidence rates were targeted and invited to participate in ICMD. To achieve such diversity, we included studies across all continents and multi-ethnic studies, given known geographic and ethnicity-associated variations in BC incidence rates [21]. Studies were identified through existing research networks, through consultation with collaborators in Asia, Africa and South America, and finally through internet-searches of screening programmes in areas of the world that were not already represented. In total, 27 studies contributed to ICMD, some of which included multiple ethnic groups, thus ICMD includes 40 study- and ethnicity-specific groups, hereafter referred to as “population groups”. Each ICMD participating study gained local ethics approval and the overall consortium was approved by the IARC ethics committee (IEC 12-34).

Determinants of MD will initially be investigated separately in pre and post-menopausal women in each population group to examine whether associations hold across women worldwide and across major reproductive-defined periods in women's lives. To enable these investigations, we aimed to include an equal number of women (n=200), randomly selected from each stratum defined by population group and menopausal status. This sample size of 200 was calculated in order to estimate these stratum-specific mean percent MDs within 1% at a 95% confidence level, assuming a stratum-specific standard deviation of 7% (for which n=180). An additional 20 subjects (∼10% extra) was added to account for potential later exclusions (e.g. missing data, image quality poor). When selecting from organized screening program databases, we restricted ICMD inclusion to women screened within a recent time frame (dates are provided in Table 1).

Mammographic image: types and transfers

So as not to exclude informative populations, there was no restriction on the type of mammographic image included, i.e. we included digitized screen-film (analogue) images and digital images from both full-field digital mammography (FFDM) and computed radiography (CR, an analogue system converted to digital with laser scanner-read plates). For digital images, both “raw” (original format) and “processed” (“for presentation”) formats were included. The latter is an image manipulated by manufacturer-specific algorithms to aid diagnosis. For processed images, we extracted the processing software version.

Images were anonymized prior to transfer to IARC via a secure FTP. For the most part, anonymization was carried out using *NiftyView* [22], a cross platform graphical user interface provided to collaborators to remove embedded image labels and personal information from DICOM tags.

Mammographic Density Measurement

Area-based methods of MD measurement involve partitioning the total breast area into the dense area, which represents radio-dense fibro-glandular tissue, and the remaining non-

dense, which reflects radiolucent adipose tissue. An example of this method is provided in Figure 1. PMD is then calculated as 100 × dense area/total breast area. A non-trivial challenge in ICMD was to obtain comparable MD measurements across studies, given that the images types differed substantially. This task was complicated by the lack of a true gold-7 standard measurement method for MD [23], and whilst existing automated methods are time-efficient and are predictive of BC risk [24], none could be applied to all of the ICMD image types. We thus decided, *a priori*, to measure MD using the interactive thresholding method Cumulus (Dr Martin Yaffe, Sunnybrook Health Sciences Centre, Toronto), which can be applied to all DICOM images. Cumulus-measured MD has consistently shown strong associations with BC risk [25]. Cumulus version 6 was applied, which performs automatic breast edge delimitation, whilst the user delimits other non-breast areas manually and sets the greyscale level to dichotomize dense from non-dense greyscale levels (Figure 1). We did not choose a categorical classification of MD as it would have less statistical power in analysing this quantitative trait. To aid reading, 8-bit digitized images were converted to 16-bit prior to reading and raw digital images were inverse log transformed.

MD reading protocol

Whilst Cumulus-based MD readings tend to have high repeatability for a given reader, readings are reader-specific [26] thus to achieve comparability of MD readings across studies we conducted centralized readings by a small team of experienced readers (VM, NB, IS) using a protocol designed to ensure no association between study and reader. Studies with the same image type (digitized analogue, processed digital or raw digital) were grouped (3 to 7 studies per group) and within each group, images were randomly allocated to batches of approximately 90 (plus repeats, see following section), which were then divided evenly between readers. One image per woman was read and readers were blinded to all personal and study information. View, but not laterality, affects measured MD [27], thus if multiple views were available, we preferentially read the more widely available left medio-lateral oblique (MLO), right-MLO, left cranio-caudal (CC) then right-CC.

Within-reader measurement errors in MD were assessed by re-reading 3 randomly selected images within each reading batch, and between-reader differences by re-reading 5 randomly selected images from each batch by the other 2 readers. Additionally two batches (at the start and towards the end) were read by all 3 readers. A total of 13575 readings were completed over an 8 month period across 146 reading batches. The only exception to this is the Canadian images which could not be transferred internationally, so they were read by a single reader. During the MD assessment process, readers noted features that may impact on the MD measurement.

Absolute breast and dense areas in number of pixels were converted to cm^2 using the pixel size information, which was extracted from DICOM tags or obtained from collaborators (Suppl. Table 1). For one study (US-USC), this information was not available for 78 of 444 images, so these images will be included in PMD but not absolute area-based analyses.

Risk factor data and its harmonization

Minimal risk factor data required for inclusion were age, height, weight and parity. The first three variables were inclusion criteria as age and BMI (calculated as weight/height^2 in kg/m^2) are both strongly inversely related to MD, yet positively associated with postmenopausal BC risk, thus the pertinent BC risk factor is percent MD (PMD) or dense area for a woman's age and BMI [28]. The timing of height and weight ascertainment, ideally, but not always, at the time of mammography, was obtained. In addition to these variables, we requested woman-level information on reason for mammography, ethnicity, age at menarche, age at first birth, age at last birth, breast feeding durations, use of exogenous hormones (i.e. oral contraceptives and hormone therapy), age at menopause, reason for menopause, personal cancer history, personal history of breast problems, family history of breast cancer, tobacco and alcohol consumption and indicators of socioeconomic status. We requested each variable in its original, most basic format and their definitions.

To date, the key variables from study-specific datasets have been merged into a single harmonized core dataset. Where definitions of a variable varied between studies (for example parity could be defined as the total number of children, number of live births, number of full term births,) the definitions were also imported. Continuous variables were converted to a common unit of measurement. Some studies collected continuous variables in categories (for example, age at first birth). The categorical variable was imported into the main dataset as a separate variable and the estimated median of that category pooled with the continuous data from other studies. For Figure 4 the categories of age at first birth and age at menarche were derived from the continuous variable in the main study dataset, therefore for some studies this was the median of the category; study-level definitions for age at first birth and parity are shown in Supplemental Table 2.). Whilst the original random selection of women from each menopausal group was based on study-specific definitions of menopause, those definitions were also individually obtained and will be presented in future menopause-focussed investigations.

Data were checked for consistency and implausible values checked. For the core data, adult heights less than 1.0 m or over 2.1 m, or with a BMI less than 12 kg/m^2 or greater than 80 kg/m^2, were excluded. As the available data on complex lifestyle variables such as contraceptive use, hormone therapy, smoking and alcohol use, varied substantially between studies, to begin with, these data were pooled into the core dataset into simplified variables stating if the participant is a current, past, ever or never user. For future analyses focusing on these variables, more complex data will be re-extracted from the original datasets, and their definitions and distributions presented at that point.

3. Results and Discussion

Studies included: countries and screening settings

ICMD includes 11755 women from 27 studies across 22 countries. The countries and their BC incidence rates are provided in Figure 2. All world regions are included, as are countries with 4-fold differences in BC incidence rates, e.g. from ~25/100,000 in India and Iran, to over 90 in the UK and US. The consortium includes less or never-studied countries in terms

of MD, notably South Africa, Kenya, Turkey, Iran and India. Most studies were in a restricted geographical region of the country, as indicated in Table 1. The table also provides further details of study populations. Hereafter, studies will primarily be referred to by their country name, with the exception of the multiple studies in the UK and US. Multiple ethnic groups were included in the studies from Israel (Jewish and Arab), the UK (White, Black, and Asian women), the US (White, Black, Asian and Native Hawaiian), Singapore and Malaysia (Malay, Chinese and Indian) and Australia (by country of birth; Australia, Greece and Italy).

Amongst the studies included, mammograms were taken in various settings. Over half (54%) of ICMD women were screened in organized screening programs (i.e., invitation to screening was sent to all women in a defined population) or in the US where screening coverage rates are similar to those of organised screening programs. The 13 studies were in Israel, The Netherlands, Norway, Spain, Canada, Australia, Japan, the US and all but one of the UK studies. For some of these studies risk factors data had been collected as part of larger cohorts (US Multiethnic Cohort study, the US Nurses' Health Study (NHS) and NHS II, the Melbourne Collaborative Cohort Study) or ICMD women were controls in case-control studies.

For 20% of ICMD women, screening was opportunistic, e.g. the woman self-presented at a screening facility, without an invitation. The ICMD contributions from Egypt, Iran, People's Republic of Korea, Malaysia and China Hong Kong came from such settings. For example, in the Women's Health Outreach Program in Egypt, women self-present at stationary and mobile mammography units throughout the country and risk factor data were routinely collected at presentation [29].

Eight percent of women (3 studies) came from general health research studies, in which mammograms were conducted for the purposes of the study e.g. mothers in the Chilean Cohort Study of Breast Cancer Risk (DERCAM study), the Mexican Teachers' Cohort and a study of nurses in Poland. A further three ICMD studies (10% of ICMD women) were feasibility studies or trials of mammography. These were a UK screening trial of annual mammography ages 39-48 years (UK-Age Trial), the Bahcesehir Breast Cancer Screening Project and the Singapore Breast Screening Project.

A challenge in ICMD was to find low-risk settings in which women representative of the general population had or were undergoing mammographic screening. The remaining 8% of ICMD women, from 3 studies, were from such settings. Mammography was part of *ad hoc* community outreach trials e.g., one-off screening initiatives, where, with the addition of an interviewer-administered questionnaire at mammography, relevant data were or would be available. The settings were as follows: in India, free mammography was provided to women in a rural community during March 2008; in Nairobi, Kenya, the Aga Khan Hospital provides low-cost mammography during breast cancer awareness month (October 2013) and during visits thereafter until December 2013 women were invited to complete the questionnaire; and in South Africa, when the Pink Drive's mobile mammography van was providing free community screening in Soweto in 2014, women were invited to take part in an interviewer-administered two-page questionnaire.

Mammographic images

A summary of image types included is provided in Table 2 (and study-specific details in Suppl. Table 1). In all, 51.1% of images were digitized screen-film images and the remaining images were digital images, of which 9.0% were captured on CR and 91.0% on FFDM systems. Machines used in multiple studies include models of the GE Senograph, Hologic Lorad Selenia and Siemens Mammomat (Table 2 and Suppl. Table 1). Of the digital images, 91.3% were in processed formats and 8.7% were in the original 'raw' format.

The vast majority (94.5%) of images were considered of acceptable quality, whilst only 2.3% were considered suboptimal (due to low resolution, image errors or artefacts) and were excluded (Table 2). The main issues with the few remaining images were poor skin visibility and truncation of the breast. Where the skin was not visible (1.6% of images), only the dense area could be estimated and not total breast area or PMD. Where the skin was 'barely visible' (0.3% of images) estimates of dense area, total area and PMD were included in the main analyses, but will be excluded in sensitivity analyses. This mainly occurred in digitised analogue films, perhaps due to a suboptimal optical range of the digitizer. Truncated images (0.9%) were often due to the breast being too large for the plate used. For these images, if multiple images were taken, they were viewed simultaneously and the image encompassing the greater proportion of the breast was read using an estimated enlarged breast area to account for the area off the film.

The overall PMD distributions across women in ICMD are shown in Figure 3A, illustrating the PMD range from 0 to 80%. Within-reader SDs were much smaller than between-woman SDs (Figure 3B), thus each reader had an intra-class correlation over 90%. By design, between-study differences will not be due to reader differences, however the reader-specific distributions had different degrees of right skewness (skewness parameters by reader are 0.42, 0.81 and 1.02), thus transformations were needed before linear regression (i.e. normal-errors) modelling of PMD or of dense-area could be performed. To achieve this, we first corrected for batch-drift across each reader's readings by fitting a quadratic association of PMD on batch order and predicting batch-corrected PMD as PMD in the absence of batch drift as per PMD readings for the batch range where drift was absent. Thereafter, square-root transformations were taken of dense area, breast area and PMD, to achieve normally distributed outcomes for normal-errors regression models. This transformation has been frequently used for area-based MD measures [30]; square-root dense area represents the radius of a circle defining the dense area, or the length of the side of a square with dense area.

Risk factors: Lifestyle heterogeneity captured

Risk factor information was typically collected by questionnaire at or around mammography, with the exception of five studies (table 1), for which explanatory data were collected at least 2 years before or several years after mammography. Menopausal status was ascertained at the individual level in all but one study. Height and weight were measured in 18 of the 27 studies and self-reported by women in the remaining studies. Anthropometrics were measured in two-thirds of studies and self-reported in the remaining; in most studies they were recorded at the time of mammography (Table 1). The remaining

key variables (age at first birth, age at first menstruation and parity) were self-reported in all studies.

Median age at mammography was 52 years (90% range 39-66 years) across studies; there were over 2000 women in each age interval: 35-44, 45-49, 50-54, 55-59 and 60+ years. Most studies span this age range, with the exception of Chile and the UK-Age Trial, which by their original study design only included younger populations and studies set in screening programs with older recommended screening ages. The wide age range will enable finer analyses by age and menopausal status than previously possible.

A flavour of the immense heterogeneity of lifestyles captured in ICMD is shown in Figure 4. For each risk factor, population groups were ranked according to the breast cancer risk for that factor. Notably, when the top and bottom ranked groups are compared, for every risk factor, there were ranges present in one group that do not exist in another. For example, only 28 (13%) of the 216 women from Hong Kong had a BMI greater than 25 kg/m^2, whereas only 34 (7%) out of 494 women from Egypt had a BMI below 25 kg/m^2 (Figure 4A). The stature of women also varied from a mean height of 150.3 cm (SD 5.9) in India to 166.6 cm (SD 5.6) in Norway.

The reproductive factors shown in figures 4B-4D are, for the most part, as expected, with profiles associated with higher BC risk being more prevalent in higher income countries – including earlier menarche, later age at first birth and lower parity – and the reverse was seen in transitional countries. However, on closer examination, the risk factor combinations in ICMD displayed more complexity, which can be illustrated by comparing women from South Africa, Iran and Israel (Arab sub-group). All three groups had amongst the highest mean BMIs (Fig. 4A), consistent with the high obesity prevalence in those transitional or post-transitional countries [31-33]. These three groups of women also had a relatively young age at first birth, with approximately 70% having had their first child by 23 years of age (Fig. 4B) - a percentage nearly double that in ICMD groups from Europe and the US. However, these 3 groups differed considerably in terms of age at menarche and parity – the Israel Arab group of women had a mean age at menarche (12.8 years), i.e., over 2 years earlier than their South Africa counterparts (14.9 years). This large difference in means is comparable to the size of the secular trends in menarche that occurred over nearly 80 years in the UK or US [34,35]. Parity also differed between these groups; whereas the parity of South African women is relatively low (median 2-3), 30% of Iranian and 60% of Israeli Arab women in ICMD had at least 6 births. These differences are consistent with the timing of the fertility transitions, which, although rapid, occurred much later in Iran than in South Africa [36,37]. The ICMD pooled data also included many women with very high parity (over 700 women with 6 or more births), which will enable an examination of the effect of repeated pregnancies on breast composition.

Such heterogeneity is present in several other risk factors, including breastfeeding, alcohol intake and smoking habits and will greatly enable the assessment of their influence associations with MD.

Challenges and limitations

A large-scale pooling project such as ICMD, whilst statistically powerful, is not without considerable challenges and limitations. First, concerning the representativeness of included women, the diversity of screening settings (none of which have complete population coverage) will impact on who the ICMD study sample represents - be it the general population in the relevant geographical area or a more restricted subset of this population. For analyses of the determinants of MD, the generalisability of the MD distribution itself to that of a larger study population is not of primary concern, rather it is whether risk factor-MD associations observed in ICMD are generalizable to the general population. In this respect, ICMD study samples that originate from specific occupations (e.g. the NHS and the Polish study) or from more affluent or more educated sectors of the population can contribute valuably and validly. However, for the investigation of whether population-level MD distributions reflect population-level differences in breast cancer incidence rates, findings will only be valid if the comparisons of the same underlying populations are made. For this component, it should be emphasized that breast cancer incidence rates are not estimated from a follow-up of women in ICMD, rather they will be obtained from external population-level estimates from cancer registries covering the same or similar catchment population. In many settings, screening attendees are more likely to be of higher socioeconomic status/educational level and would thus have higher BC incidence rates. Such biases are likely to affect studies to greater or lesser degrees depending on the screening features, e.g. cost involved, extent of catchment population, how women are invited or how screening is advertised. In particular, the study samples from short-term once-off screening in Kenya and from opportunistic screening programs may have an over-representation of more educated women who had to pay for the transport to reach the hospital and the fees, albeit reduced, for mammography. The community-level free screening in Soweto, South Africa, may have a higher proportion of women with previous breast problems, a family history of disease or symptomatic disease.

Second, a further challenge is to create meaningful harmonized risk factor data. Their harmonized data may lose precision by collapsing data into simplified variables, but analyses will also be conducted on smaller subsets with exposures pooled in finer detail. Socioeconomic data do not have the same discriminatory ability or meanings in different settings, so within-study categories will be the basis of this exposure.

Finally, the greatest challenge in ICMD is to achieve comparable MD data. Whilst the reading protocol should remove reader-effects, image types vary between studies, and a whole study's MD readings may be shifted up or down according to the particular system's processing algorithm and the reader's interpretation of the threshold cut-point in images displayed in raw or in processed formats. Indeed, systematic differences in dense area, breast area and in PMD are known to arise from the type of image, e.g. due to processing or differential compression [38]. The likely influence on MD needs to be considered as films from most studies were of a single image type and could thus act as a strong confounder. Further, analogue films originated predominantly from high-risk populations where screening occurred in earlier years, as long as 30 years ago, whereas recent films from lower-risk populations were more likely to be digital. Two analytical approaches will be

taken in an attempt to overcome the potential influence of processing algorithms on MD: (i) analyses will first be conducted at the study-level and study-specific effects combined using meta-analytic approaches, so that there is no variation in image type within each analysis and thus no confounding by image type; (ii) for analyses of the full ICMD dataset within the same statistical model, MD values (PMD and dense area) will first be corrected for the influence of the image type and processing algorithm. The calibration correction factors will be derived from sets of paired digital images that have been stored in both raw and processed images (from 2 FFDM and 1 CR system). These results will be presented in a separate article.

Summary

ICMD has assembled a rich international resource of individual-level epidemiologic and MD information allowing the study of the epidemiology of MD. The risk factor heterogeneity captured is extensive and will help elucidate influences on the natural history of the breast's fibro-glandular composition. Population shifts in MD distributions are relevant for population strategies of disease prevention and require the understanding of the determinants of population means, for which ICMD will provide a valuable contribution.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Valerie A. McCormack[1], Anya Burton[1], Isabel dos-Santos-Silva[2], John H. Hipwell[3], Caroline Dickens[4], Dorria Salem[5], Rasha Kamal[6], Mikael Hartman[7], Charmaine Pei Ling Lee[7,8], Kee-Seng Chia[8], Vahit Ozmen[9], Mustafa Erkin Aribal[9], Anath Arzee Flugelman[10], Martín Lajous[11,12], Ruy Lopez-Riduara[12], Megan Rice[13], Isabelle Romieu[14], Giske Ursin[15,16,17], Samera Qureshi[18], Huiyan Ma[19], Eunjung Lee[17], Carla H. van Gils[20], Johanna O.P. Wanders[20], Sudhir Vinayak[21], Rose Ndumia[21], Steve Allen[22], Sarah Vinnicombe[23], Sue Moss[24], Jong Won Lee[25], Jisun Kim[25], Ana Pereira[26], Maria Luisa Garmendia[26], Reza Sirous[27], Mehri Sirous[27], Beata Peplonska[28], Agnieszka Bukowska[28], Rulla M. Tamimi[13], Kimberly Bertrand[29], Chisato Nagata[30], Ava Kwong[31], Celine Vachon[32], Christopher Scott[32], Beatriz Perez-Gomez[33], Marina Pollan[33], Gertraud Maskarinec[34], Graham Giles[35,36], John Hopper[36], Jennifer Stone[37], Nadia Rajaram[38], Soo-Hwang Teo[38,39], Shivaani Mariapun[38], Martin J. Yaffe[40], Joachim Schüz[1], Anna Chiarelli[41], Linda Linton[42], and Norman F. Boyd[42]

Affiliations

[1]Section of Environment and Radiation, International Agency for Research on Cancer, Lyon, France [2]Dept. of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK [3]Centre for Medical Image Computing, University College London, UK [4]University of the Witwatersrand, South Africa [5]Cairo University, Egypt [6]Woman Imaging Unit, Radiodiagnosis Department, Kasr El Aini, Cairo University Hospitals, Cairo, Egypt [7]Saw Swee Hock School of

Public Health, National University of Singapore, Singapore [8]NUS Graduate School for Integrative Sciences and Engineering, National University of Singapore, Singapore [9]Istanbul University, Turkey [10]National Cancer Control Center, Israel [11]Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, USA [12]Center for Research on Population Health, Instituto Nacional de Salud Pública, Mexico, Mexico City, Mexico [13]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, USA [14]Section of Nutrition and Metabolism, International Agency for Research on Cancer, Lyon, France [15]Cancer Registry of Norway, Oslo, Norway [16]Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway [17]Department of Preventive Medicine, University of Southern California, Los Angeles, California, USA [18]Norwegian Center for Minority Health Research (NAKMI), Oslo, Norway [19]Department of Population Sciences, Beckman Research Institute, City of Hope, Duarte, USA [20]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands [21]Aga Khan University Hospital, Nairobi, Kenya [22]Department of Imaging, Royal Marsden NHS Foundation Trust, London, UK [23]Division of Imaging & Technology, Ninewells Hospital Medical School, Dundee, UK [24]Wolfson Institute of Preventive Medicine, Queen Mary University of London, UK [25]Asan Medical Center, Seoul, Republic of Korea [26]Institute of Nutrition and Food Technology, University of Chile, Chile [27]Isfahan University of Medical Sciences, Isfahan, Iran [28]Nofer Institute of Occupational Medicine, Łódź, Poland [29]Slone Epidemiology Center, Boston University, Boston, MA, USA [30]Gifu University, Gifu, Japan [31]Division of Breast Surgery, The University of Hong Kong Faculty of Medicine, Hong Kong, People's Republic of China [32]Dept. Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA [33]Cancer Epidemiology Unit, Instituto de Salud Carlos III and CIBERESP, Madrid, Spain [34]University of Hawaii Cancer Center, Honolulu, Hawaii, USA [35]Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, Australia [36]School of Population and Global Health, The University of Melbourne, Australia [37]Centre for Genetic Origins of Health and Disease, University of Western Australia, Australia [38]Cancer Research Malaysia, Breast Cancer Research Unit, University Malay Cancer Research Institute, Kuala Lumpur, Malaysia [39]Cancer Research Malaysia, Subang Jaya, Malaysia [40]Medical Biophysics, University of Toronto, Canada [41]Ontario Breast Screening Programme, Toronto, Canada [42]Princess Margaret Cancer Centre, Toronto, Canada

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Highlights

- The International Consortium on Mammographic Density (ICMD) is a pooling study of individual-level epidemiologic data and re-read mammographic density information.
- The rationale and methods of ICMD are described.
- 11755 women, from 27 studies in 22 countries are included.
- The immense heterogeneity in breast cancer risk factors are highlighted.

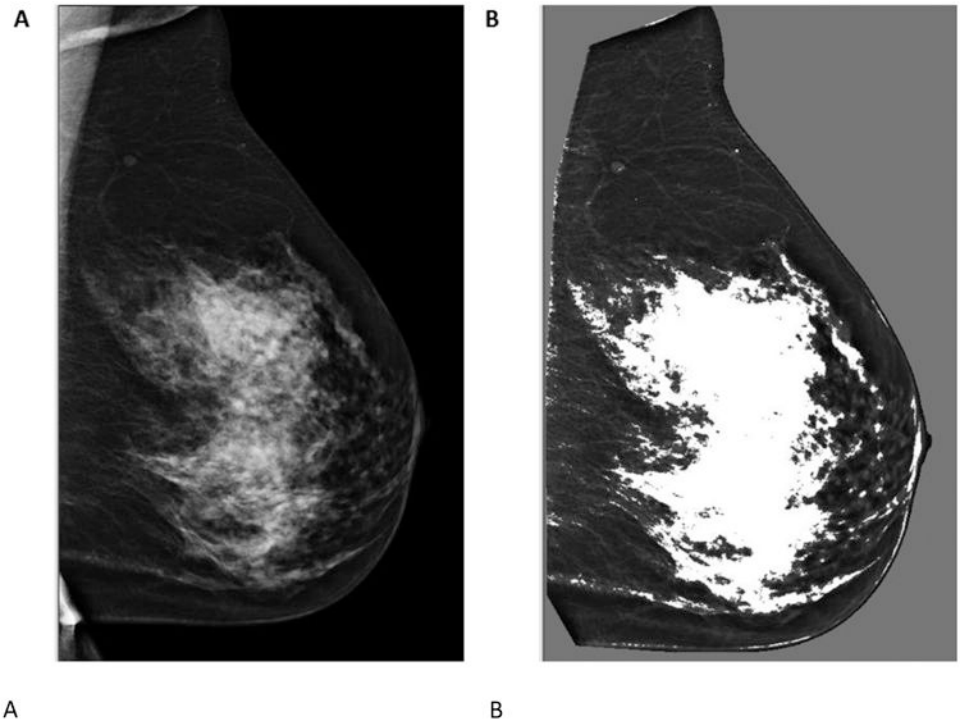

Figure 1. Cumulus-based mammographic density reading

(A) Example from of a FFDM Hologic image as it is first read into Cumulus and (B) after Cumulus-version 6 auto-delimits the skin edge and then the user delimits the pectoral muscle and selects a threshold to dichotomize the greyscale levels into dense and non-dense levels. This 70 μm pixel image was read as: breast area =5155276 pixels = 252.6cm^2, dense area = 1375976 pixels = 67.4 cm^2, thus percent mammographic density (PMD) is 26.7%.

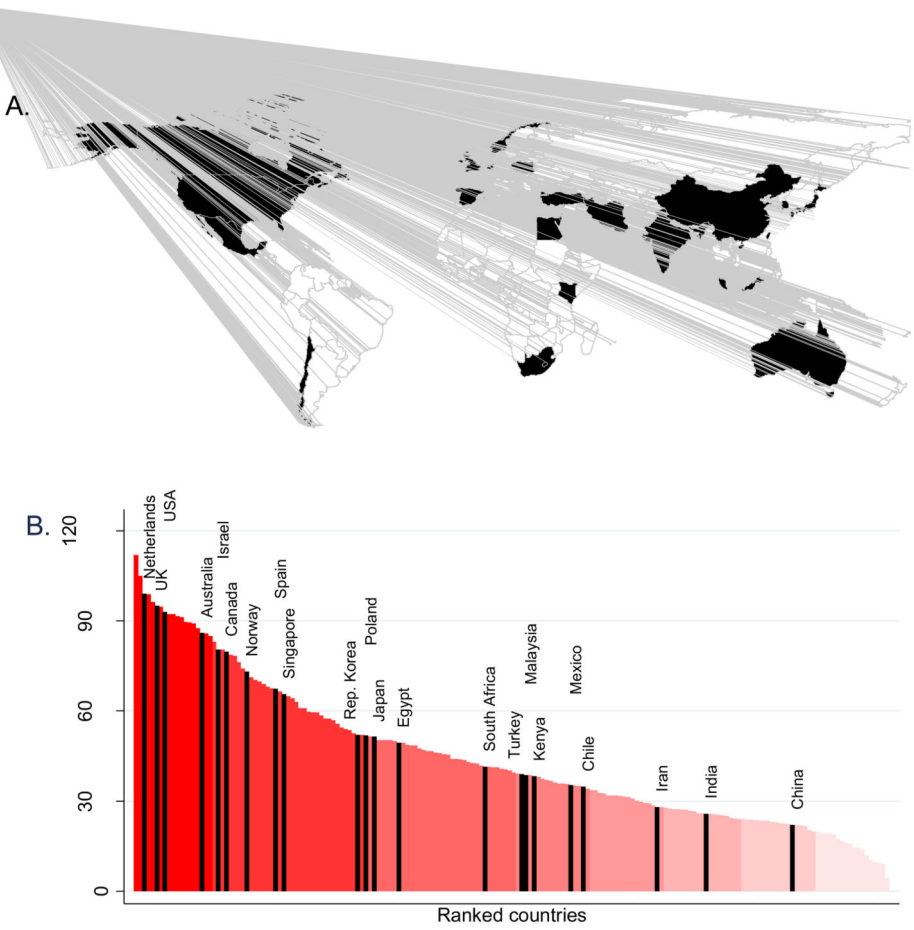

Figure 2.

(A) 22 countries participating in ICMD and (B) Ranking of participating countries by their age-standardized breast cancer incidence rate in 2012 (from IARC GLOBOCAN 2012 [56])

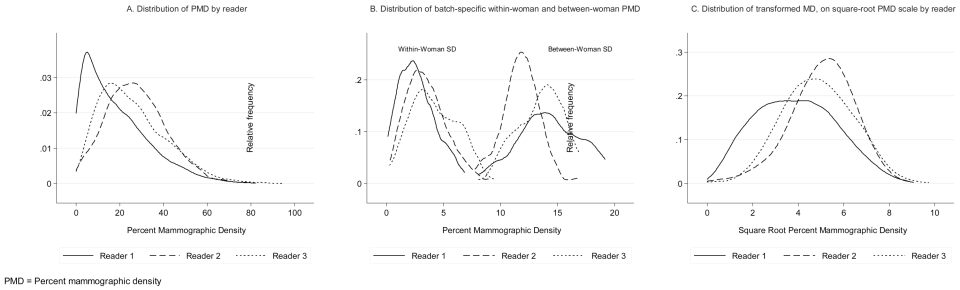

Figure 3.

Density readings across ICMD: (A) Original percent mammographic density (PMD) readings, by reader (B) Distribution of within and between-woman standard deviation (SD) of PMD across reading batches, for each reader. (C) Distribution of square root PMD by reader

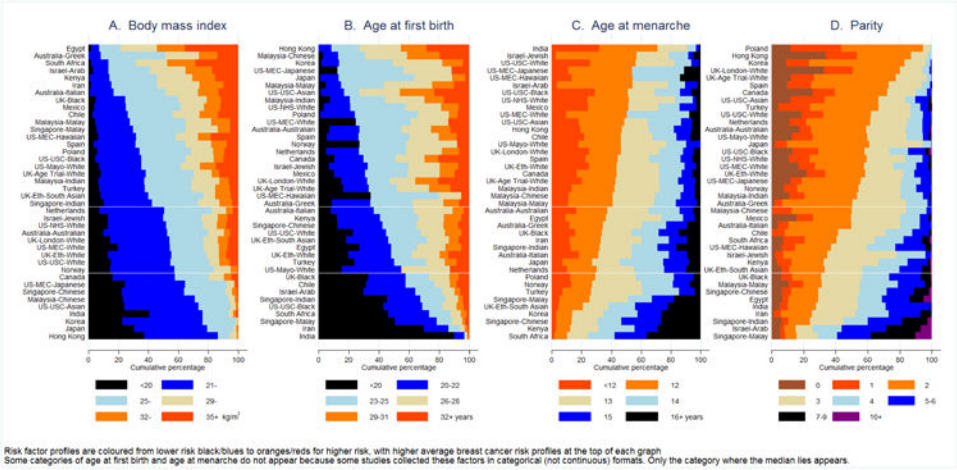

Figure 4. Bar charts of the distribution of (A) BMI, (B) age at menarche, (C) age at first birth and (D) parity across the study and ethnic groups included in ICMD

Table 1

Characteristics of the 27 studies included in ICMD

Country, Location, Study Name, (Ref.)	Study name, mammography location and setting, years of mammography, stratified sample (if applicable)	Mammography details			Anthropometry*, Timing of anthropometry (median years before mammogram)	Ethnic groups
		Mammography setting: a. Organized screening (13studies) b. Opportunistic (5) c. Research Study (3) d. Mammography trial e. Ad-hoc community (3)	No. women	Age (range, years)		
Australia, Victoria State [39]	Subset of Melbourne Collaborative Cohort Study screened in BreastScreen Victoria, 1991-2006	a. Organized sx with invitation	719	40-70	M, 2.7	(i) Australia-born, (ii) Greek-born, (iii) Italian-born
Canada, Ontario province	Ontario Breast Screening Program and Princess Margaret Cancer Center (PMCC), 2000-03	a. Organized sx with invitation and c. Research study (PMCC)	379	40-85	S, 1.5	White
Chile, Santiago city [40]	Chilean Cohort Study of Breast Cancer Risk (DERCAM study): Mothers of Growth and Obesity Chilean Cohort Study, Santiago, 2011-2013	c. Research study	193	35-53	M, 0.9	Chilean/Mestizo
China, Hong Kong [41]	Hong Kong Sanatorium and Hospital and the University of Hong Kong, Hong Kong, 2013-14	b. Opportunistic (self-selection)	216	35-72	M, 0.0	Hong Kong Chinese
Egypt, nationwide [29]	Women's Health Outreach Program, 4 fixed in hospitals and 4 mobile units operating across Egypt, 2012-13	b. Opportunistic sx, walk-in (no invitation) in community	494	42-70	M, 0.0	Egyptian
India, single rural setting	One-off community screen in rural setting near Hyderabad, Kims Ushalakshmi Centre for Breast Diseases, 2008	e. Ad-hoc: one-off community sx (free), self-presentation	186	35-70	M, 0.0	Indian
Iran, Isfahan city	Attendees of Screening at Isfahan University of Medical Sciences, Isfahan, 2013	b. Opportunistic (self-selection)	400	35-70	M, 0.0	Persian
Israel, nationwide [42]	Israel National Breast Screening Program, 2011-12	a. Organized sx with invitation	781	35-76	M, 0.0	(i) Jewish, (ii) Arab
Japan, Gifu city [43]	Attendees of population-based BC screening program, Gifu city, 2001-2	a. Organized sx with invitation	390	36-70	S, 0.0	Japanese
Kenya, Nairobi city	Aga Khan Hospital, Nairobi, low cost mammography during	e. Ad-hoc: Self-presentation during 3 months of low-cost sx	352	35-79	M, 0.0	Black Kenyan

Country, Location, Study Name, (Ref.)	Study name, mammography location and setting, years of mammography, stratified sample (if applicable)	Mammography details			Anthropometry*, Timing of anthropometry (median years before mammogram)	Ethnic groups
		Mammography setting: a. Organized screening (13studies) b. Opportunistic (5) c. Research Study (3) d. Mammography trial e. Ad-hoc community (3)	No. women	Age (range, years)		
	and after breast cancer awareness and after breast cancer awareness and after breast cancer awareness	month, Oct-Dec 2013 month, Oct-Dec 2013 month, Oct-Dec 2013				
Republic of Korea, Seoul city	ASAN Medical Center, Seoul, Republic of Korea, 2007-14	b. Opportunistic (self-selection)	389	35-81	M, 0.0	Korean
Malaysia, Greater Kuala Lumpur [30]	MyMammo study, volunteers for opportunistic screening in suburban area of Greater Kuala Lumpur, 2011-14	b. Opportunistic (self-selection)	867	38-74	M (77 %), S (23%), 0.0	(i) Chinese, (ii) Malay, (iii) Indian
Mexico, Jalisco state [44]	Mexican Teachers' Cohort Study (EsMaestras), baseline mammogram from the Jalisco study site, 2007	c. Research study	400	36-69	M (93%), S (7%), 0.9	Mexican/Mestizo
Netherlands, Utrecht area [45]	Prospect-EPIC, Utrecht vicinity, Netherlands, 1993-97	a. Organized sx with invitation	386	49-69	M, 0.0	White
Norway, nationwide [46]	Norwegian Breast Cancer Screening Program, 2004, nationally representative sample	a. Organized sx with invitation	200	50-69	S, 0.0	White
Poland, Lodz city [47]	Breast Cancer Risk Factors in Nurses, Cross-sectional study of nurses and midwives, Łódź, Poland, 2008-10	c. Research study (84% response rate)	398	40-61	M, -0.1	White
Singapore, nationwide [48]	Singapore Breast Cancer Screening Project, 1993-1997	d. Organized sx with invitation (trial participants)	599	49-66	M, 0.0	(i) Chinese, (ii) Malay, (iii) Indian
South Africa, Soweto, Gauteng province	PinkDrive Community Screening, mobile mammography van in Soweto, Gauteng, 2013	e. Ad-hoc: One-off community screening (self-selection)	406	35-81	M, 0.0	Black South African
Spain, multiple locations [49]	Determinants of Mammographic Density, cross-sectional study in 7 screening centres, 2007-2008	a. Organized sx with invitation	799	45-66	M, 0.0	White
Turkey, Istanbul [50]	Bahcesehir Mammographic Screening Project, 2010-11	d. Mammography study: feasibility study	398	39-56	M, 0.0	Turkish
UK-Ethnicity, London [19]	NHS Central and East London Breast Screening Program, 1992-2004	a. Organized sx with invitation	582	48-65	S, -2.4 (i.e. after)	(i) White, (ii) South Asian, (iii) Black

Country, Location, Study Name, (Ref.)	Study name, mammography location and setting, years of mammography, stratified sample (if applicable)	Mammography details			Anthropometry*, Timing of anthropometry (median years before mammogram)	Ethnic groups
		Mammography setting: **a. Organized screening (13studies)** **b. Opportunistic (5)** **c. Research Study (3)** **d. Mammography trial** **e. Ad-hoc community (3)**	**No. women**	**Age (range, years)**		
UK–Age Trial, England and Wales [51**]**	Age Trial, NHS screening centres across England and Wales, 1992-2004, annual screening at ages 39-48	d. Study invitation to trial of organized sx at young ages	166	39-48	S, -9.7 (i.e. after)	White
UK, London [24**]**	Controls from Royal Marsden Hospital and NHS Central and East London Breast Screening Program case-control study, controls from CELBSS, invitation to all women at ages 47+, 2010-12	a. Organized sx with invitation	269	45-70	S, 0.0	91% White, 9% Black
US-MEC Hawaii, Hawaii [52**]**	Controls from a nested case-control study within the Hawaii component of the Multiethnic Cohort study, 1986-2003 (mammograms), but study recruitment during 1993-6	a. Organized/routine sx without invitation (majority)	543	37-70	S, ∼5.0	(i) Japanese (ii) Native (iii) White- Hawaiian
US-Mayo, 3 midwest states [53**]**	Mayo Mammography Health Study Cohort, screenees at Mayo Clinic from Minnesota, Iowa and Wisconsin states, 2003-06	a. Organized/routine sx without invitation	399	35-69	M, 0.0	US White
US – NHS, multiple [54,55**]**	Nurses' Health Study and Nurses' Health Study II, subset who agreed to mammogram access, 1987-2009	a. Organized/routine sx without invitation	400	35-70	S, 1.0	US White
US-USC, California state [20**]**	2 Uni. Southern California breast cancer case-control studies. (i) Asian-American women and (ii) Women's Contraceptive and Reproductive Experiences (CARE) study 1990-98	a. Organized/routine sx without invitation	444	35-64	S, 3.7	(i) Asian, (ii) White (iii) African-American
TOTAL	*27 studies*		*11755*			

Abbreviations: M=measured; S=self-reported; sx = screening.

Total numbers of women are prior to exclusions.

Table 2

Image characteristics

Mammographic Feature	Detail	No. studies*	No. women (Column %)
Laterality†	Left	21	10051 (88.5%)
	Right	0	1304 (11.5%)
	Mixture within study	6	
View	MLO	16	6484 (55.2%)
	CC	12	5271 (44.8%)
Machine and processing type	Digitized Analogue††	14	6007 (51.1%)
	CR Digital - raw	0	0 (0.0%)
	CR Digital – processed	2	516 (4.4%)
	FFDM – raw	2	500 (4.3%)
	FFDM - processed ‡ Kodak Lumisys 85	11 5	4732 (40.3%) 1912 (31.8%)
Digitizer (analogue images only)	Array 2905 HD	5	2465 (41.0%)
	Lumiscan, Lumisys	1	386 (6.4%)
	Astra2400S, UMAX	1	400 (6.7%)
	MammoAdvantage	1	400 (6.7%)
	Cobrascan/omnimedia	1	444 (7.4%)
DICOM pixel size (μm)	< 80	14	5244 (44.6%)
	80-109	10	3262 (27.7%)
	110-139	0	0 (0.0%)
	140-249	6	1877 (16.0%)
	250+	3	935 (8.0%)
	Unknown	1	58 (0.5%) - Will be excluded from area-based analyses
Image quality for Cumulus MD reading	Acceptable	N/A	11106 (94.5%)
	Skin barely visible		39 (0.3%)
	Other quality issues		36 (0.3%)
	Skin not visible		192 (1.6%)
	Image truncated		108 (0.9%)
	Too poor - EXCLUDE		272 (2.3%)

Abbreviations: CR = computed radiography; FFDM = full-field digital mammography; MD = mammographic density; MLO = mediolateral oblique (mammography view); CC = cranio-caudal (mammographic view);

*Some studies contributed a mixture of images types and/or views

†Unknown for 1 study (400 women)

††Includes 390 images that were printed CR mammograms (Senographe DMR Fuji FCR AC-3CS) and were subsequently digitized (digitizer Kodak Lumisys 85)

‡Type of digital mammography systems and processing algorithm: Fujifilm; Hologic Lorad Selenia; GE Senograph DS / 2000D /Essential; Philips Mammodiagnost DR; Agfa DX-M; Siemens Mammomat Inspiration/Novation DR; Medi-Future Brestige