Is High Breast Density a Risk Factor for Breast Cancer ? Significant Points Emerging from the DMIST Study Methodological Analysis

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Abstract
High breast density (HBD) tends to be seen as a significant and independent risk factor for breast cancer. This article describes a methodological and quantitative study of the variables selected by the large DMIST study, i.e., age, hormonal status and breast density, in correlation with cancer occurrence frequency. The statistical analysis of cancer rates in every patient subgroup of a study involving more than 42,000 women in screening, shows that HBD, when isolated from other variables, does not by itself constitute a significant risk factor, compared to the number of cancers detected in each density category. The DMIST study is unique and reliable, since it performs two different mammographic explorations of each patient, independently interpreted, thus minimizing the rate of false negatives. It appears then that the notion of density as a breast cancer risk factor is probably at least questionable. Admitting that HBD is an independent risk factor has a crucial economical health care impact, through the multiplication of different imaging modalities for women with HBD. Moreover, the physiological components of such a density are not well defined in each case, and grouping all types of breast composition under the unique label of density is haphazard. Breast tissue composition should be specifically studied in relation with cancer frequency, after isolating it from other impacting factors. Its evaluation needs thorough studies on vast populations, aiming at the analysis of a clearly isolated breast density variable on equal populations for each variable value, to perform a significant analysis of variance.

Key words: breast cancer, breast density, mammographic density, risk factors

The DMIST Study: Population Subgroups and Tested Variables

In 2005, a very large prospective study in North America, involving several institutions, has been published. It is known as DMIST, standing for Digital Mammographic Imaging Screening Trial, and was conducted by ACRIN, the American College of Radiology Imaging Network. It dealt with the diagnosis performance of digital vs. analogical mammography in breast cancer screening (1). This study has been performed on 33 American and Canadian sites. 49,528 women have been tested with both technologies (digital and analogical devices). 42,117 women have been selected as having an evaluated cancer status. All of these have undergone both examinations (analogical and digital mammographies). This incontestably is, in our opinion, the major methodological asset of the study, since it is the only one among several others (analyzed in (3)) able to neutralize the inter-individual variability for each technology performance evaluation.

Three variables have been studied: Age, hormonal status and breast density. The patients' ages ranged from 47 to 69 years. Women have been dispatched in groups defined by three hormonal status values: Pre-menopause (30% of the population) if menstruations have occurred less than a month before mammographic examination, peri-menopause (10%) if they occurred at least one between one month and one year before examination, and post-menopause (60%) with an absence of menstruations for more than one year. Density was classified according to the ACR Bi-rads classification , Bi-rads 1 (10% of the population), Bi-rads 2 (43 %), Bi-rads 3 (40 %) and Bi-rads 4 (7%). The standard reference interval was one year and three months (starting with the mammographic examination), and was used to determine whether a woman was safe from cancer or not.

We have analyzed (3) the second publication by the same team, which appeared in 2008 in this journal (2), detailing the study results after dispatching the population in the different subgroups defined by the 3 variables different values. In the mentioned paper (on which we mostly rely since it is much more precise than the preceding one about categories) the four density classes have been grouped into two main categories: Group 1, named *Non Dense Breast,* representing 53% of the population and involving ACR Bi-rads 1 and 2, and Group 2, *Dense Breast,* representing 47 % of the population and involving ACR Bi-rads 3 and 4. Categories defined according to age, are the following: *Under 50* (33% of the total population), *from 50 to 64* (48%), and *65 and over* (19%). The hormonal status has been studied in the shape of two categories: The *peri and pre-menopause* together with 37% of the population, and *post-menopause* with 63%.

Quantitative Methodological Analysis of DMIST Data

Population sizes on which cancers have been detected are unequal. The provided values, either in numbers or percentages, do no allow determining for each studied variable (i.e., breast density, age and hormonal status) quantitative trends *per se*. The only way to 'neutralize' this diversity is to suggest using ratios such as 'cancers

percentages over population percentages' for each group defined by the different values of the three aforementioned variables.
For a given parameter (or variable), seen with two possible values (the best to study variation, i.e., *dense* vs. *non dense*, *under 50* vs. *over 50*, and *non-menopause* vs. *menopause*), a mean ratio of 1 plus or minus a minimal deviation indicates that the factor does not impact the number of cancers, since distribution is balanced. The more this ratio diverges from 1, the more the parameter (as such, before examining its different values) may be considered as an impacting factor.
This ratio has been computed for each value of the three parameters. Then, the mean ratio for the two categories of each parameter and the respective values of their deviations from the theoretical independence, have also been computed. The trend as an impact factor is assumed to be weak if deviation is inferior to a given threshold (the standard deviation σ of 4% considered in Gaussian distributions is here relevant, since the population number is high and patients are independent n-random variables). The more this deviation is important, the more the parameter tends to impact cancer frequency, positively for the subgroup for which the ratio is superior to the mean ratio.
Last, we have computed, for both values of each parameter, their deviation with the mean ratio. The local impact of a given parameter value is then assessed according to the importance of this deviation, especially when the parameter value ratio is higher than the mean ratio.

Emerging Topics of Interest from DMIST Contents Analysis

The Image Discriminating Ability Is Not to Be Confused with the Capability in Developing Cancers

It is important to focus on the difference between the image discriminating power and the evaluation of cancer development ability. The diagnosis performance of digital vs. analogical mammography statistical curves published in 2005 (1), have been thoroughly analyzed. The results were measured with AUC on ROC curves, meaning Area Under the Curve (for AUC) and Receiver Operating Characteristic (for ROC). Values range between 0 and 1. The closer to 1 they are, the higher the performance. Results have been provided for all detected and confirmed cancers, for patients under 50, high breast density patients, and those assigned to the 'pre or peri-menopause' category.
The conclusions were *« the overall diagnostic accuracy of digital and film mammography as a means of screening for breast cancer is similar, but digital mammography is more accurate in women under the age of 50 years, women with radiographically dense breasts, and premenopausal or perimenopausal women"*.

In the DMIST study, digital mammography is then presented as enhancing the image discriminating power for dense breasts (Bi-rads 3 and 4 categories). The digital mammography performance overpowers the analogical one by 15%. It is to be considered as a 'statistical trend' of a better discriminating power of digital mammography in this density category, and is not necessarily correlated with the observation of a higher number of cancers.

Are Breast Cancer Risk Factors Detectable on this 42,117 Women Population?

Tables 1 and 2 show the computed ratios for hormonal status (Table 1) and age (Table 2).
The population distributed in each subgroup defined by the parameter value is unequal in size between subgroups (2/3, 1/3). Numbers being high, a side effect or a bias is not to be feared (which is the case for small numbers) and rely on ratios.

Hormonal Status	Numbers of women (% of total population)	Numbers of breast cancers (% of detected cancers)	Ratio
Pre or peri menopausal	15 753 (37,41%)	99 (29,73%)	0,794
Postmenopausal	26 364 (62,59%)	234 (70,27%)	1,122

Table 1. DMIST study (2) figures: Screening detected breast cancers percentages and numbers varying according to the hormonal status variable (pre or peri-menopause, menopause). Ratios calculated as percentages of breast cancers / percentages of population.

Age	Numbers of women (% of total population)	Numbers of breast cancers (% of detected cancers)	Ratio
Under 50	14 130 (33,55%)	72 (21,62%)	0,644
Over 50	27 987 (66,45%)	261 (78,37%)	1 ,179

Table 2. DMIST study (2) figures: Screening detected breast cancers percentages and numbers varying according to the age variable (under 50, over 50). Ratios calculated as percentages of breast cancers / percentages of population.

In both cases, mean ratios differ from 1. For hormonal status, the mean ratio is 0.958. It deviates from the theoretical independence ratio by a value close to 4%, the standard '1 sigma' deviation of a Gaussian distribution (see Table 4). *A priori*, this means that the parameter by itself does not deeply impact cancer frequency. Focusing on subgroups ratios is more interesting, since it might be informative about the 'swaying from balance' origin. For age, the mean ratio equals 0.915. It deviates from the theoretical independence ratio by a value of 8.5%, equal to '2 sigma'. This begins to be significant (see Table 3).

Parameter	Mean ratio	Variation with theoretical ratio of 1 (independence)	Variation of sub-groups ratios (abs(Subgroup ratio – mean ratio))
Density*	**1**	**0**	**0,05 (5%)**
Hormonal Status	**0,958**	**0,042 (equal to 1 σ)**	**0,164 (17,1%)**
Age	**0,915**	**0,085 (equal to 2 σ)**	**0,264 (28,85%)**

Table 3. Ratios variability according to parameters: Independence (non correlation) with cancer is given with the theoretical ratio. Percentages are computed as 'abs(subgroup ratio- mean ratio))/mean ratio'.
***see Table 4.**

Density	Numbers of women (% of total population)	Numbers of breast cancers (% of detected cancers)	Ratio
Bi-rads 1 and 2	19 609 (46,56%)	164 (48,96%)	1,05
Bi-rads 3 and 4	22 508 (53,44%)	169 (50,45%)	0,95

Table 4. DMIST study (2) figures: Screening detected breast cancers percentages and numbers varying according to the density variable (not dense= Bi-rads 1 and 2, dense= Bi-rads 3 and 4). Ratios calculated as percentages of breast cancers / percentages of population.

Focusing on subgroups for both hormonal status and age leads to the following. For hormonal status, the subgroups ratios deviate from the parameter mean ratio by an absolute value of 0.167, that is 17.1% (absolute deviation value over mean ratio). The subgroup responsible for this swaying from balance is the one concerning women being in menopause (positive deviation value). It seems that cancers appear a bit more frequently in this group than in the pre or peri-menopause women. In the case of age, subgroups ratios deviate from their parameter mean ratio by 0.264, that is, 28.8%. The subgroup responsible for this deviation is the *over 50 years* group. Age is already an impacting factor (because of its deviation from independence ratio), and the present deviation is here truly significant.

Note that age and hormonal status are not independent from each other variables (hormonal status changes with age). However, they are tested here in their correlation with cancer occurrence frequency. Further observations are to be made when scrutinizing Table 5 where different values of the three parameters are conjugated and their ratios are provided.

Does Breast Density Emerge as a Cancer Risk Factor?

The ratios 'percentage of cancers over percentage of population' of Dense Breast and Non Dense Breasts show an equivalent number of cancers in both breast density categories (Table 4). For dense breasts, ratio is 1.05, and for fatty breasts it is 0.95. Mean ratio is 1, equal to the 'theoretical independence ratio', and deviation around this mean ratio is 0.05 (5%). It corresponds to the weakest deviation when compared to the respective 17.1% and 28.8% for hormonal status and age. As such, it is a weak deviation, close to '1 sigma'. So it seems that the DMIST study shows that breast density does not appear as correlated with the emergence of the observed cancers.
In favor of this assertion:

1- DMIST has a very important population, one of the largest, tending to statistically ground observations. It favors the used statistical tools. A 5% deviation is to be considered as really minimal.

2- Both density values categories are almost equal in size (population numbers): 46,56% vs. 53,44%. All women have been dispatched in both categories. If mean ratio is equal to the theoretical independence ratio, a severely unbalanced distribution in population cannot be accused to introduce a hypothetical bias.

Ratios for each subgroup, defined by each value of each parameter, are detailed in table 5. One may observe that detected cancers frequency is not systematically correlated with a high breast density, or heterogeneous breasts; at least, not significantly.
Then, when focusing on the distribution of breast density in the groups defined by the other parameter values, we have tried to check whether biases could have been introduced by specific distributions.

Hormonal status and Age	Breast Density	No of women and % of DMIST women	No of cancers and % of DMIST cancer	Ratio
Postmenopausal > 65y	Dense breasts	2507 5,95%	34 10,21%	**1,72**
Postmenopausal > 65y	Non dense breasts	5379 12,77%	62 18,62%	**1,46**
Pre- or perimenopausal 50-64y	Dense breasts	1964 4,66%	23 6,91%	**1,48**
Pre or perimenopausal 50-64y	Non dense breasts	1874 4,45%	18 5,41%	**1,22**
Postmenopausal 50-64y	Dense breasts	6716 15,95%	56 16,82%	**1,05**
Postmenopausal 50-64y	Non dense breasts	9547 22,67%	68 20,42	**0,90**
Postmenopausal <50y	Dense breasts	1107 2,6%	7 2,1%	**0,81**
Postmenopausal <50y	Non dense breasts	1108 2,6%	7 2,1%	**0,81**
Pre- or perimenopausal <50y	Dense breasts	7315 17,37%	44 13,21%	**0,76**
Pre- or perimenopausal <50y	Non dense breasts	4600 10,92%	14 4,20%	**0,39**

Table 5. DMIST Study (2) figures: Computing Ratios of detected cancers percentages over subgroup population percentage (of the total population), related with density, while age and hormonal status are coupled (dependent variables).
Missing density or menopausal classification = 643 women and 2 cancers
Elligible population = 42 760 – 643 = 42 117 women and 333 cancers

First, dense and not dense breasts are distributed all over the other categories, even in extreme age groups. This characteristic tends to show that density is not, at a first sight, dependent of age.
Moreover, women over 65 with not dense breasts have a higher detected cancer rate (1.47) than women under 50 with dense breasts (0.76): It is almost twice in value!
Of course, in extreme age values conjugated with hormonal status (over 65 and menopause vs. under 50 and no menopause), more cancers have been detected in the

dense breasts women group than in the non dense breasts women group: Respectively, 1.73 vs. 1.47, and 0.76 vs. 0.39.

However, even if, for detected cancer rates, which are differentiated by breast density, deviation is higher in extreme categories of age, this deviation is much weaker for women over 65. Difference in ratio between dense breasts women over 65 (1.73) and not dense breasts women of the same age category (1.47) is 0.26 (see Table 6). Considered as a percentage over the age category mean ratio (1.60 in the same table), results in 16.25% variation. Whereas the difference of ratios between women under 50, not menopaused, with dense breasts (0.76), and not dense breasts (0.39) goes up to 0.37, which indicates a very high percentage compared with the category mean ratio (0.575). It is equal to 64.3%! This means that if ever breast density should be correlated to cancer occurrence frequency, it is more likely to appear for women under 50 and non menopaused (which are the best cases for other parameters). These women do not generally apply for a screening campaign. Moreover, the numbers of detected cancers, in these groups, are very small when compared to the global number of cancers. There are respectively 44 and 14 (the two last lines of Table 5), a total of 58 corresponding to 17.4% of all cancers (to divide by 333, the total number of cancers). This is a 'minority' behavior, and other quantitative/qualitative tools should be used to study them.
From another point, for menopaused women groups, age between 47 and 64, this variability is null or very weak. It means that hormonal status preempts density as a factor, if ever…

Breast density could possibly be a discriminator only when other variables values are those for which the number of cancers is the lowest, i.e. the *best-case* situation (under 50, no menopause). Even in this case, the value of the mean ratio being very far from the theoretical independence ratio (0.575 compared with 1) signifies that coupling best case values introduces has a high impact (the lowest the ratio, the best it is). This ratio is by itself very weak, meaning that this subgroup population has much less developed cancers than the average tested population. It concerns 58 cases for a population of 17,000 patients, and cannot be considered as a real 'trend'. At worst, high breast density could appear as a 'potential suspect' in a very-low-risk population, but for that, a thorough and detailed study should be run, neutralizing other variables, and mostly age. Also, a particular attention should be brought to Bi-rads 4 density category, which has not been separated from Bi-rads 3 in DMIST, in order to assess whether the frequency of cancer occurrence in significantly different in both categories.

Conclusions

In our analysis of DMIST data, age appears as the most strongly correlated variable to breast cancer risk, among the three studied variables (i.e. age, hormonal status, and breast density). This goes in favor of screening campaigns recommendation, which fix the screening age at 50. It is followed by hormonal status (menopause, no menopause), knowing that age and hormonal status are dependent variables. The detected cancer rate according to breast density shows that density does not appear as a significant breast cancer risk by itself. Thanks to the double reading performed in DMIST, aiming at comparing both digital and analogical technologies in

mammography, the 42,117 women of the study have been tested twice, thus given an enhanced reliability to results. The risk of false negatives, which is the most probably associated to high breast density, is thus obviously reduced. Conclusions also appear statistically reinforced by the fact that populations manning both density broad categories are roughly comparable in numbers. It seems then that the concept of breast density, as defined by the mammographic examination, when considered as a cancer risk factor, leads to a serious controversial debate. The exact physiological components of this density are not well known, in each case: It could be translated into mammary gland tissue, fibrous support tissue, or an aqueous breast component and varies from a woman to another. Correspondences between these differences and breast cancer risk are even less known (and should be investigated before stating anything about breast cancer risk related to tissue density). Considering that mammographic density is an independent risk would have then a very high economical impact through the multiplication of imaging modalities in high breast density patients. High breast density impact evaluation needs thorough studies on vast populations, with a mandatory goal, the analysis of a clearly isolated breast density variable (not to be interwoven with other variables), on equal populations for the each variable value, in order to perform a significant analysis of variance.

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