Research Square

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Breast Cancer Incidence by Age at Finding of Mammographic Abnormality in Women Participating in French Organized Screening Campaigns.

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Abstract

Purpose: Using reduced samples, statistical modelling was already predicted the occurrence of Breast-cancer or its prognosis from previous radiological findings. This study aims to predict breast-cancer risk by mammographic abnormalities finding age in the French breast-cancer screening campaign.

Methods: The study involved 261,083 women aged 50-74 living in French Departments (Ain, Doubs, Haute-Saône, Jura, Territoire-de-Belfort, Yonne). These women had at least two screening mammograms between Jan-1999 and Dec-2017 of which the first was classified as “normal/benign”. The incidence of mammographic-abnormality (*microcalcification, spiculated-mass, obscured-mass, architectural-distortion, asymmetric-density)* and the incidence of breast-cancer after abnormality detection were estimated abnormalities finding age, using an actuarial life-table method. Breast-cancer risk was predicted in a Cox multivariate model.

Results: The incidence of mammographic-abnormality was 95.4[94.9; 95.9]/1000 person-years. Breast-cancer (6,326 cases) incidence was 3.3[3.0; 3.1]/1000 person-years. That incidence was 5 times higher in women who showed a speculated-mass vs. those who did not (6.9[6.4; 7.4] vs. 1.3[1.2; 1.3]). Whatever the abnormality, the incidence of cancer was higher when it was present in only one breast. Depending on the spiculated-mass finding age, the risk increased by at least 40% between the age groups 55-59years (1.4[1.0; 1.8]) and ≥70years (2.4[1.9; 3.3]).

Conclusion: The study showed the increased risk of cancer with the abnormalities finding age and the low risk related to the presence of the same mammographic-abnormality in both breasts compared to the isolated mammographic-abnormality in one of the breasts. This should alert radiologists to the relevance of certain diagnostic procedures in the management of a bilateral mammographic abnormality.

Introduction

Breast cancer (B-cancer) is the world’s most common and severe cancer in women: it would be responsible for 11.6% of cancers and 6.6% of deaths from cancer in women [1]. As other European countries, France has been offering a national organized B-cancer screening program (BCSP) since 2004 [2, 3]. The BCSP targets women aged 50-74 years old with no other risk factor than age and offer them a clinical breast examination and a mammography screening by a licensed radiologist once every two years [2, 4]. All mammograms considered as normal or benign in a first reading seance are submitted to a second reading whether or not an immediate diagnostic assessment has been carried out[3].

To distinguish between a benign and malign breast lesions, the radiologists use the Breast Imaging Reporting System and Data System (BIRADS) classification [5]. The radiological findings that support this classification are indicative of certain forms or locations of B-cancer [6-11]. Breast microcalcifications are present in about 30% of all malignant breast lesions, in over half of the malignant infraclinical breast lesions, and lead to depict 85-95% of all cases of ductal carcinoma in situ in screening campaigns [10]. The positive predictive value of malignancy varies according to the mass contour [6]. Although there are several other risk factors [7, 12, 13], it is established that B-cancer can occur without apparent mammographic finding, especially in the case of radiologically dense breasts[14].

Statistical modelling was already predicted the occurrence of B-cancer or its prognosis from previous radiological findings. A few studies converged towards a positive association between the risk score calculated on previous mammograms and image-detected B-cancer at screening mammograms [15-18]. In addition to the reduced sample size, these studies did not describe the B-cancer risk according to the finding age of each radiological abnormality.

To optimize the interpretation of these mammographic abnormalities in the daily practice of radiologists, the contribution of artificial intelligence and deep-learning is increasingly emphasized [19-23]. Certainly, if there is one field of medicine in which artificial intelligence will offer many advances, it is of course, the fields of prevention and screening [24]. However, despite the significant contribution of these new technologies, the conventional reading of mammograms by radiologists is still essential [19, 25]. In addition to the discussion on their ethical and legal aspects [26], there is no algorithm that has beyond doubt been

proven to outperform double reporting by two certified breast radiologists [19]. To develop other more efficient algorithms, large databases are required [21, 22].

Pending the availability of such algorithms, the present study intends to alert radiologists by predicting B-cancer risk by mammographic abnormalities finding age.

Methods

Study context

The study consisted of a follow-up of 261,083 women, aged 50 to 74 years, living in six French Departments (Ain, Doubs, Haute-Saône, Jura, Territoire-de-Belfort, Yonne). These women have at least two screening mammograms between 1999/01/01 and 2017/12/31 of which the first was considered as “normal/benign”.

The study excluded women with less than two participations in the BCSP (90,274 out of 351,357). Were also excluded women with diagnosis of B-cancer at their first participation (3,417 out of 9,743 women who had at least one cancer during the study period). In fact, in these six Departments, women are still able to participate in the BCSP after a diagnosis of B-cancer during a previous campaign.

The mammographic abnormalities studied were: microcalcifications, spiculated-mass, obscured-mass, architectural-distortion and asymmetric-density. The definitions of these mammographic abnormalities are standardized in the BCSP. However, the study retained the description of microcalcification only if an immediate (or deferred) diagnostic workup confirmed the presence of microcalcification. The incidence of each mammographic abnormality has been described, subsequently, the B-cancer incidence has been described according to each mammographic abnormality finding age.

BCSP organization

In the six departments, BCSP management structures (BCSP-structure) were in charge, the organization of screening campaigns in accordance with BCSP specifications [3, 5]. Before each campaign, a list of women was established and updated according to information from Health Insurance Plans. These women were invited by regular mail at their 50th birthday (first invitation) and then every two years after a negative mammogram (subsequent invitation) until the age of 74 years. The letter of invitation allows each woman to have a mammogram (two frontal and two oblique external incidences) in one of the radiological centers approved by the BCSP.

In each radiological center, the first reading of a mammogram was performed on a hard copy or a screen display. The radiologist first reader had also to collect sociodemographic, clinical, and radiological information on a standardized form. Using the printed films, the second reading, or even a third consensual or expert reading, was carried out in the BCSP-structure.

Data collection

The data analysed were extracted from the databases of the BCSP-structure. These databases were regularly enriched with sociodemographic, diagnostic, and follow-up data provided by radiologists, pathologists, oncologists, surgeons, gynecologists, general practitioners, health insurance plan, or medico-administrative databases.

The study distinguished the follow-up of the left breast from that of the right breast. The end date of follow-up (end-date) was the date of the last mammogram. Women aged <73 years were considered “lost to follow-up” whenever the date of the last mammogram was before 2015 because they could have had another mammogram before age 74. The end of follow-up criterion was the diagnosis of a B-cancer lesion.

Regarding B-cancer diagnosis, the study adopted the C50 code of the 10th version of the WHO International Classification of Diseases (ICD-10) [27] : i) ductal carcinoma in situ, lobular carcinoma in situ, and nipple Paget's disease were classified as "adenocarcinoma in situ" (TIS); ii) infiltrating/invasive ductal or lobular carcinomas were classified as "infiltrating

adenocarcinoma" (ADK-I); and, iii) all other malignant tumors (papillary, tubular, mucinous, medullary, etc.) were classified as "rare form". Were considered first reading cancers (Cancer-R1), when the diagnostic process was started after a positive first mammographic reading (ACR in 0,3,4,5). Were considered second reading cancers (Cancer-R2), when the diagnostic process was started after a positive mammographic second reading (ACR in 0,3,4,5) following a negative first reading (ACR in 1,2). Interval breast cancers were those detected in the interim between regular screening examinations.

Campaign dynamics

For the analysis of the incidence of each mammographic abnormality, the follow-up started date was the date of the first screening mammogram. For each breast, this follow-up was censored at the abnormality finding date or at the study end-date if absence of abnormality.

In the B-cancer incidence analysis, the follow-up started date was the date of the first screening mammogram and this follow-up was censored at the end-date in the absence of B-cancer or at the date of the mammogram that triggered a B-cancer diagnostic procedure (date of B-cancer occurrencein the examined breast. In case of interval B-cancer, the follow-up was censored at the date of interval B-cancer diagnosis. The follow-up was censored at the end-date in all other cases, e.g., loss to follow-up, relocation, refusal to participate in BCSP, age >74 years, or death from causes other than B-cancer.

Factors studied

The factors were: i) the age at finding of each abnormality (in five categories: 50-54, 55-59, 60-64, 65-69, and 70-74 years); ii) the presence of each abnormality in the contralateral breast if it’s present in the examined breast (in five categories: absence of the abnormality in the examined breast "NA", absence of the abnormality in the contralateral breast while it’s present in the examined breast "Absent", presence of abnormality in the contralateral breast before its presence in the examined breast "Anterior", presence of abnormality in both breasts at the same date "Same_date", presence of abnormality in the contralateral breast after its presence in the examined breast "Posterior"); iii) the initial concomitance (associated abnormalities seen immediately on the same date) or posterior concomitance (abnormalities in successive association over time) of ≥2 mammographic abnormalities in the examined breast (no abnormality "NA", an isolated abnormality "1-isolated", two abnormalities in initial association "2-initial", two abnormalities in posterior association "2-posterior", ≥3 abnormalities in initial association "3-initial", ≥3 abnormalities in posterior association "3-posterior"); and iv) the abnormalities occurrence's order(Spiculated-mas first, Microcalcification first, Obscured-mass first, Asymmetric-density first, Architectural-distortion first, ≥2 abnormalities appeared first); v) use of hormone replacement therapy (Yes, No, Uncertain); vi) breast density (Types I to IV).

Statistical analysis

Student's t test was used to compare the age-groups (censored follow-up vs. others).

All cumulative incidences (mammographic abnormality or B-cancer) were estimated by the actuarial life-table method. Their 95% confidence-intervals were estimated by the Greenwood method.

In incidence analysis (each mammographic abnormality), the women contributed to the calculation of person-times starting from the date of first mammogram until the date of abnormality finding in the examined breast or until the end-date. Similarly, in the B-cancer incidence analysis, women contributed to the calculation of person-times starting from the date of first mammogram until the date of cancer occurrence in the examined breast or, in the absence of cancer, until the end-date. The cumulative incidences were described and compared between groups using the log-rank test or the CI comparison.

The B-cancer risk analysis according to the age at finding of each mammographic abnormality was carried out by estimating the adjusted relative risk (RRa) using a multivariate Cox model. Only women who had at least one of the five mammographic abnormalities, were included in this analysis. The cox-model included all covariates regardless of their p-values in univariate analysis. Because of their multiple collinearities, the five variables relative to the presence of an abnormality in the contralateral breast were introduced into the final model in three modalities (Absent, Present ("Anterior"+"Same_date"+"Posterior") and NA).

The parameters of the model were estimated by the maximum likelihood method. All analyses were performed using STATA software version 13 (College Station, Texas, USA). The threshold of statistical significance was 5%.

Results

The study included 261,083 women whose mean age (±standard deviation) at first mammogram was 57.3±6.6 years. Of these, 40,208 (15,4%) had a censored follow-up before 74 years of age because of death (132), loss to follow-up (38,194), relocation (411), or refusal to participate in the BCSP (1,471). At baseline, women censured for refusal of participation or death were significantly older than the others (59.2±5,8 years vs. 57.3±6.6 years, p<0.0001 and 58.7±5.7 years vs. 57.3±6.6 years, p<0.0001, respectively) but women censored for relocation or loss to follow-up were significantly younger (55.8±5.0 years vs. 57.3±6.6 years, p<0.0001 and 56.3±5.0 years vs. 57.3±6.6 years, p<0.0001, respectively).

Incidence of mammographic abnormalities

On average, women had 4.1±1.7 mammograms; some had 8(656 women) or 9(2 women) mammograms. The mean delay between two consecutive mammograms was 2.5±0.9 years. At least one of the five mammographic abnormalities was observed in 122,343 women (46.9%) at an average age of 60.0±6.8 years. The average duration of follow-up was 4.9 years. The overall incidence of mammographic abnormality (any abnormality, any breast) was estimated at 95.4/1000 person-years (p-y) [IC: 94.9; 95.9]. Regarding breast laterality, 87,592 women had at least one abnormality in the left breast vs. 85,158 women with at least one abnormality in the right breast (estimated incidence 59.2/1000 p-y [58.8; 59.5] vs. 56.9/1000 p-y [56.6; 57.3]).

The mean age at first finding of a mammographic abnormality was 60.3±6.7 years (range: 51-74 years). The mean follow-up (time-at-risk) before this finding ranged from 6.1 years (obscured-mass) to 7.2 years (spiculated-mass) with no difference between right and left breasts (***Table-1***). Regardless of laterality, the incidence of microcalcifications increased whereas the incidence of obscured-mass decreased with breast density.

In the left-breast, the first abnormality found at a mean age of 60.3±6.8 years, was microcalcification (8.6% of cases) or spiculated-mass (7.7%), or obscured-mass (60.5%), or asymmetric-density (4.9%), or architectural-distortion (7.1%), or a combination of at least two abnormalities (11.2%). In the right-breast, the mean age at the finding of the first abnormality was 60.2±6.7 years and the proportions of the abnormalities cited above were respectively: 9.2%, 7.7%, 60.1 %, 5.1%, 8.1%, and 9.8%. In the left-breast, this first abnormality was detected in 40.8% of cases at the 1st mammogram (M1), 24.3% at M2, 14.8% at M3, and 20.1% at M4 or later. In the right breast, these percentages were respectively: 40.5, 24.4, 15.0, and 20.2 at M4 or later.

Incidence of breast cancer

In the 261,083 participants followed for 7.4 years on average, at least one B-cancer was found in 6,326 women (3,137 left breast, 2,802 right breast, 257 bilateral, 130 unspecified location), which represents an incidence of 3.3/1000 p-y [3.0; 3,1]. The cancers were ADK-I (63.8%), TIS (10.5%), “rare form”(2.7%) or unspecified (23.0%). These cancers were cancer-R1(84.5%), cancer-R2(4.5%) or interval-cancers (11.0%). 88.4% of the 130 cancers whose laterality (left/right) was not specified, were interval-cancers.

The mean age at diagnosis of B-cancer was 63.8±6.3 years, and 20.5% of cancers were diagnosed in women with none of the five mammographic abnormalities. Among 2,414 cases of the 5,028 cases associated with at least one of the five mammographic abnormalities, the abnormality (single in 64.4% of cases) was seen on the mammography that initiated the B-cancer diagnostic procedure.

B-cancer cumulative-incidence was significantly lower in women with no mammographic abnormality than in those with at least one abnormality (Left-Breast: 0.6[0.6; 0.7] vs. 3.6[3.5; 3.7], Right-Breast: 0.6[0.5; 0.6] vs. 3.3[3.2; 3.4]). The incidence of B-cancer was 5 times higher in women with than without spiculated-mass (Left-Breast: 7.7[7.2; 8.2] vs. 1.4[1.3; 1.5]; Right-Breast: 6.9[6.4; 7.4] vs. 1.3[1.2; 1.3]) (***Table-2***).

Although the confidence-intervals are overlapped a few times, the Log-rank test concludes that there is a significant difference regardless of the explanatory variable (***Table-3***). The incidence of B-cancer increased significantly ($p<0.0001$) with the finding age of spiculated-mass (Left-Breast: 50-54 years: 4.2[3.3; 5.2]; ≥70 years: 13.0[11.2; 15.2]) or with the finding age of microcalcification (Left-Breast: 50-54 years: 5.8[5.1; 6.7]; ≥70 years: 12.2[10.4; 14.4]). Whatever the abnormality, the incidence of B-cancer was higher when the abnormality was present only in the examined breast (absent in the contralateral breast) (***Table-3***).

The incidence was constant between the second and eighth mammograms. Women with spiculated mass diagnosed before any other abnormality had a higher incidence between M2 and M7 than other women (***Figure 1***). Similarly, women with an association (initial or posterior) of at least three of the five abnormalities had higher incidence rates between M2 and M7 (***Figure-2***).

Compared to 50-54 years, the B-cancer risk was 1.7 times higher when the architectural distortion finding age was 65-69years (RR_a: 1.4[1.0; 2.0], p=0.03) (***Table-4***). According to the spiculated-mass finding age, the B-cancer risk increased by at least 40% between the age groups 55-59 years (Left- Breast: 1.4[1.0; 1.8]; Right- Breast: 1.9[0.9; 1.4]) and ≥70years (Left-Breast: 2.4 [1.9; 3.3]; Right-Breast: 2.0 [1.5; 2.7]).

Discussion

This study, which involved, on average, a series of four mammograms per woman, showed a high incidence of B-cancer based on five radiological abnormalities. The B-cancer risk increased with the finding age of spiculated-mass and microcalcification. Whatever the abnormality, the B-cancer risk was higher when the abnormality was present only in the examined breast. The study made it possible to estimate the mean delays: i) D1 between first mammogram and the finding of radiological abnormality; ii) D2 between first mammogram and the B-cancer diagnosis; iii) D3 between the finding of radiological abnormality and B-cancer diagnosis. When the mammographic finding was a spiculated-mass, an asymmetric-density, or an architectural-distortion, D3 was shorter than the usual two-year delay between two mammograms in the BCSP. This converges with the recommendation to perform other mammograms between two campaigns in case of mammographic finding classified ACR3.

Although the observed delay between two consecutive mammograms was greater than two years (the delay recommended by the BCSP [2-4]), this study showed that having a normal mammogram does not reduce the B-cancer risk during the next mammogram. Actually, this stability between the second and the seventh mammograms is consistent with trends in the stability of incidence already described in France [28] and Spain [29].

The link between aging and B-cancer and the link between B-cancer and each mammographic abnormality has been already described [6] [10] [11, 13] [9] [30]. In view of these previous data, it should be recognized that the increased risk of B-cancer with the spiculated-mass finding age (observed here) is comparable to a synergy between two risk factors (age and spiculated-mass). In addition, the lower risk associated with radiological abnormalities in both breasts on the same date in comparison with an isolated abnormality in one breast is poorly documented, especially in a screening context. This should alert radiologists to the relevance of certain diagnostic procedures in the presence of a bilateral radiological finding, especially since this study showed that there is more localization of cancer in the left breast compared to the right breast. This lower risk would explain the low proportion of bilateral cancers seen in this study. Moreover, it has been shown that there is no apparent increase in the risk of developing a contralateral B-cancer according to the histology of primary cancer [31, 32]. A quantitative analysis of homolateral views of mammograms would provide useful information regarding B-cancer risk over the short term [16-18]. In France, since post-diagnostic follow-up is usually carried out outside the BCSP, this study cannot predict on the evolution of the radiological abnormality in the contralateral breast after B-cancer diagnosis.

The absence of radiological abnormality was related to the histopathological characteristics of the tumor modulated by patient's specific factors. Thus, a small-size tumor, the absence of microcalcifications (often linked with tumor necrosis), or a

minimal or absent stroma reaction do not facilitate lesion detection, especially in a radiologically dense breast [14]. In this study, any risk of B-cancer was not found related to breast density.

By increasing breast density, hormone replacement therapy (HRT) is associated with an increased risk of disagreement between mammogram readers, especially regarding breast for mass [33]. HRT is also associated with B-cancer [29]. In France, the risk of B-cancer differs according to the type of estrogen-progesterone combination [34]. In this study, women with HRT (vs. others) had a lower incidence of microcalcifications, a higher incidence of asymmetry, a higher incidence of B-cancer but same order risk of B-cancer.

In France, B-cancer's detection rate was stable since 2004 [35]; it was estimated at 7/1000 p-y in women participating in a biennial BCSP campaign. In the current controversy over the usefulness of BCSP [36-38], the high incidence showed in this study, highlights the benefit the BCSP and the need to strengthen the follow-up after the finding of a radiological abnormality. In terms of B-cancer morbidity estimation, the present results agree with other incidence studies [12, 29, 39].

Limitations

The incidence rates found here may be underestimated because of incomplete data due to censoring before age of 74 for loss to follow-up or relocation while the results of last mammograms were classified ACR 3, 4 or 5.

Based on mammographic reading reports, this study cannot establish, with certainty, the link between a radiological abnormality seen during a mammogram and a similar abnormality seen during a subsequent mammogram.

The lack of interconnection between departmental databases does not make it possible to know the antecedents of women who have relocated one or more times between the age of 50-74 years. Women excluded because having only one participation in BCSP probably have a history of BCSP campaigns participation in other departments.

Conclusion

The study highlights a stable incidence of B-cancer between successive mammograms, an increased risk of B-cancer with the finding age of spiculated-mass and microcalcification. The reduced delay between the mammographic findings date and the B-cancer diagnosis date would justify a specific follow-up protocol after the finding of certain mammographic findings, in particular spiculated-mass. The low risk related to the presence of the same mammographic abnormality in both breasts compared to the presence of the isolated mammographic abnormality in one of the breasts. In this period when the quality of the program remains compromised because of overdiagnostics and other diagnostic explorations deemed unnecessary by BCSP critics, these results should alert radiologists to the relevance of certain diagnostic procedures in the management of a bilateral mammographic abnormality.

Declarations

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All authors declare no financial or other relationships or activities that could appear to have influenced the submitted study.

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Conflict of interest

The authors have declared no conflicts of interest.

Availability of data and material

To have access to the study data, the request must be made in accordance with the French regulations in force at the time of the request.

Code availability

To access the data analysis code, request must be made to the corresponding author.

Authors' contributions

The study was conceived and designed by AK and CB. The data was acquired and collated by CB, RR, SC and analyzed by AK and CB. The study was drafted and revised critically by all authors (AK, CB, RR, SC, CRM and NS) and NS was the study's guarantor. All authors gave final approval of the version to be published and have contributed to the study. No ethical approval required.

Ethics approval

The data were anonymized before analysis. The BCSPs' databases are agreed by the French "Commission Nationale de l'Informatique et des Libertés (CNIL) [40]. At the time of the study, in accordance with the French current legislation, a study that did not change the usual management of patients did not require the opinion of an ethics committee.

Consent to participate

Not applicable

Consent for publication

Not applicable

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Tables

Table 1: Cumulative incidence of radiographic findings in mammography according to the characteristics of women at baseline.

characteristics at baseline	Microcalcification		Spiculated mass		Obscured mass		Asymmetric density		Architectural distortion	
	Case(T*)	C-In [CI 95%]	Case(T*)	C-In [CI 95%]	Case(T*)	C-In [CI 95%]	Case(T*)	C-In [CI 95%]	Case(T*)	C-In [CI 95%]
Left breast										
Overall (n=260,825) †	15,257 (7.1)	8.2 [8.1 ; 8.3]	12,016 (7.2)	6.4 [6.3 ; 6.5]	65,505 (6.1)	41.1 [40.8; 41.4]	6,365 (7.3)	3.3 [3.2 ; 3.4]	9,681 (7.2)	5.2 [5.1 ; 5.3]
Age (year) 1st mammogram										
50-54 (n=125,261)	7,037 (7.0)	8.1 [7.9 ; 8.3]	5,659 (7.1)	6.4 [6.2 ; 6.6]	29,424 (6.1)	38.8 [38.3 ; 39.2]	3,423 (7.2)	3.8 [3.7 ; 4.0]	4,322 (7.0)	4.9 [4.8 ; 5.1]
55-59 (n=51,186)	3,482 (8.6)	7.8 [7.5 ; 8.0]	2,882 (8.9)	6.3 [6.1 ; 6.6]	14,914 (7.3)	39.7 [39.1 ; 40.3]	1,367 (9.1)	2.9 [2.8 ; 3.1]	2,286 (8.9)	5.0 [4.8 ; 5.3]
60-64 (n=40,727)	2,645 (8.2)	8.0 [7.7 ; 8.3]	2,129 (8.3)	6.3 [6.1 ; 6.6]	11,650 (6.8)	41.9 [41.1 ; 42.7]	1,032 (8.4)	3.0 [2.8 ; 3.2]	1,674 (8.2)	5.0 [4.7 ; 5.2]
65-69 (n=29,311)	1,556 (5.6)	9.5 [9.0 ; 9.9]	992 (5.7)	5.9 [5.8 ; 6.3]	6,858 (4.9)	47.8 [46.7 ; 49.0]	450 (5.8)	2.7 [2.4 ; 2.9]	1,058 (5.7)	6.4 [6.0 ; 6.8]
≥70 (n=14,340)	537 (2.9)	13.0 [12.0 ; 14.2]	354 (2.9)	8.5 [7.7 ; 9.4]	2,659 (2.6)	71.4 [68.8 ; 74.2]	93 (2.9)	2.2 [1.8 ; 2.7]	341 (2.9)	8.2 [7.4 ; 9.1]
Breast Density 1st mammogram										
Type I (n=35,040)	888 (7.2)	3.5 [3.3 ; 3.7]	1,147 (7.2)	4.5 [4.3 ; 4.8]	8,764 (6.1)	41.1 [40.3 ; 42.0]	582 (7.3)	2.3 [2.1 ; 2.5]	942 (7.2)	3.7 [3.5 ; 4.0]
Type II (n=161,222)	8,479 (7.1)	7.4 [7.3 ; 7.6]	7,412 (7.1)	6.4 [6.3 ; 6.6]	41,122 (6.0)	42.5 [42.1 ; 42.9]	4,057 (7.2)	3.5 [3.4 ; 3.6]	6,096 (7.1)	5.3 [5.2 ; 5.5]
Type III (n=58,524)	5,192 (7.2)	12.3 [12.0 ; 12.7]	3,156 (7.5)	7.2 [7.0 ; 7.5]	14,377 (6.4)	38.7 [38.0 ; 39.3]	1,613 (7.6)	3.6 [3.5 ; 3.8]	2,463 (7.4)	5.7 [5.4 ; 5.9]
Type IV (n=6,039)	698 (7.2)	16.1 [14.9 ; 17.3]	301 (7.7)	6.5 [5.8 ; 7.3]	1,242 (6.8)	30.3 [28.6 ; 32.0]	113 (7.8)	2.4 [2.0 ; 2.9]	180 (7.7)	3.9 [3.3 ; 4.5]
HRT 1st mammogram										
No/U(n=227,089)	12,711 (6.9)	8.1 [7.9 ; 8.2]	9,977 (7.0)	6.2 [6.1 ; 6.4]	55,875(6.0)	41.2 [40.9	5,503 (7.1)	3.4 [3.3 ; 3.5]	8,100 (7.0)	5.1 [5.0 ; 5.2]

						; 41.6]				
Yes (n=33,740)	2,546 (8.3)	9.0 [8.7 ; 9.4]	2,039 (8.5)	7.1 [6.8 ; 7.4]	9,630(7.1)	40.4 [39.6 ; 41.3]	862 (8.7)	2.9 [2.7 ; 3.1]	1,581 (8.5)	5.5 [5.3 ; 5.8]
Right breast										
Overall (n= *260,854)* ††	15,040 (7.1)	8.1 [8.0 ; 8.2]	11,449 (7.2)	6.1 [6.0 ; 6.2]	62,932 (6.2)	39.2 [38.9; 39.5]	6,309 (7.3)	3.3 [3.2 ; 3.4]	9,332 (7.2)	5.0 [4.9 ; 5.1]
Age (year) 1st mammogram										

Table 2: Breast cancer Cumulative incidence according to the presence of mammographic abnormalities.

Mammographic abnormalities	Cumulative Incidence							
	Left breast				Right breast			
	Nb of women (T*)	P-Y	Case	C-In[CI 95%]	Nb of women (T*)	P-Y	Case	C-In[CI 95%]
Overall	260,825 (7.6) †	1,953,560.6	3,394	1.7 [1.7 ; 1.8]	260,854 (7.5) ††	1,953,706.4	3,059	1.6 [1.5 ; 1.6]
Mammographic abnormalities								
No abnormality	173,233 (7.1)	1,229,252.5	785	0.6 [0.6 ; 0.7]	175,696 (7.1)	1,249,074.8	731	0.6 [0.5 ; 0.6]
≥1 abnormality	87,592 (8.3)	724,308.1	2,609	3.6 [3.5 ; 3.7]	85,158 (8.3)	704,631.6	2,328	3.3 [3.2 ; 3.4]
Microcalcification								
No	245,568 (7.4)	1,826,457.0	2,417	1.3 [1.3 ; 1.4]	245,814 (7.4)	1,827,982.0	2,185	1.2 [1.1 ; 1.2]
Yes	15,257 (8.3)	127,103.6	977	7.7 [7.2 ; 8.2]	15,040 (8.4)	125,724.5	874	7.0 [6.5 ; 7.4]
Spiculated mass								
No	248,809(7.4)	1,848,301.9	2,587	1.4 [1.3 ; 1.5]	249,405 (7.4)	1,853,980.0	2,370	1.3 [1.2 ; 1.3]
Yes	12,016 (8.9)	105,258.7	807	7.7 [7.2 ; 8.2]	11,449 (8.7)	99,726.5	689	6.9 [6.4 ; 7.4]
Obscured mass								
No	195,320 (7.2)	1,407691.3	1,959	1.4 [1.3 ; 1.5]	197,922(7.2)	1,429,130.8	1,794	1.3 [1.2 ; 1.3]
Yes	65,505 (8.3)	545,869.3	1,435	2.6 [2.5 ; 2.8]	62,932 (8.3)	524,575.7	1,265	2.4 [2.3 ; 2.5]
Asymmetric density								
No	254,460 (7.5)	1,900756.4	2,983	1.6 [1.5 ; 1.6]	254,545 (7.5)	1,901,211.3	2,715	1.4 [1.4 ; 1.5]
Yes	6,365 (8.3)	52,804.2	411	7.8 [7.1 ; 8.6]	6,309 (8.3)	52,495.1	344	6.6 [5.9 ; 7.3]
Architectural distortion								
No	251,144 (7.4)	1,869595.7	3,034	1.6 [1.6 ; 1.7]	251,522 (7.5)	1,872,887.6	2,671	1.4 [1.4 ; 1.5]
Yes	9,681 (8.7)	83,964.9	360	4.3 [3.9 ; 4.8]	9,332 (8.7)	80,818.9	388	4.8 [4.3 ;

5.3]

T* Average time at risk (in year) – † 258 women did not have the left breast – †† 229 women did not have the right breast – C-In [CI 95%]: cumulative incidence per 1000 person-year [95% confidence interval] – Nb: Number – P-Y: Person-year.

Table 3: Cumulative incidence by type of cancer's localization (left/right), according to the characteristics of the radiological abnormalities and the characteristics of the women.

Characteristics	Left-Breast cancer's Cumulative Incidence			Right-Breast cancer's Cumulative Incidence		
	Nb of women	Case	C-In [CI 95%]	Nb of women	Case	C-In [CI 95%]
Overall	*260,825*†	3,394	1.7 [1.7 ; 1.8]	*260,854*††	3,059	1.6 [1.5 ; 1.6]
Finding age(year): Microcalcification			*			*
*A*bsent	245,568	2,417	1.3 [1.3 ; 1.4]	245,814	2,185	1.2 [1.1 ; 1.2]
50-54	4,328	190	5.8 [5.1 ; 6.7]	4,241	157	4.9 [4.2 ; 5.7]
55-59	3,544	214	6.7 [5.9 ; 7.7]	3,469	181	5.8 [5.0 ; 6.7]
60-64	3,178	253	8.4 [7.4 ; 9.5]	3,175	214	7.2 [6.3 ; 8.2]
65-69	2,458	174	8.4 [7.2 ; 9.7]	2,458	177	8.5 [7.3 ; 9.8]
≥70	1,749	146	12.2 [10.4 ; 14.4]	1,697	145	12.5 [10.6 ; 14.7]
Contralateral presence if a Microcalcification seen			*			*
Absent	5,631	650	14.3 [13.2 ; 15.4]	5,414	554	12.5 [11.5 ; 13.6]
Anterior	287	17	6.2 [3.9 ; 10.0]	286	27	10.1 [6.9 ; 14.7]
Same date	9,053	295	3.9 [3.5 ; 4.3]	9,053	285	3.7 [3.3 ; 4.2]
Posterior	286	15	5.6 [3.4 ; 9.3]	287	8	2.9 [1.5 ; 5.9]
Finding age(year): Spiculated mass			*			*
*A*bsent	248,809	2,587	1.4 [1.3 ; 1.5]	249,405	2370	1.3 [1.2 ; 1.3]
50-54	2,593	78	4.2 [3.3 ; 5.2]	2,438	74	4.4 [3.5 ; 5.5]
55-59	2,813	151	6.0 [5.1 ; 7.1]	2,687	118	4.9 [4.1 ; 5.9]
60-64	2,738	199	7.3 [6.3 ; 8.3]	2,669	181	6.8 [5.8 ; 7.8]
65-69	2,278	215	10.0 [8.8 ; 11.4]	2,195	180	8.7 [7.5 ; 10.1]
≥70	1,594	164	13.0 [11.2 ; 15.2]	1,460	136	11.8 [10.0 ; 14.0]
Contralateral presence if a Spiculated mass seen			*			*
Absent	8,581	753	10.1 [9.4 ; 10.9]	8,014	642	9.3 [8.6 ; 10.1]
Anterior	336	12	3.6 [2.0 ; 6.3]	348	10	2.8 [1.5 ; 5.2]
Same date	2,751	36	1.5 [1.1 ; 2.1]	2,751	32	1.3 [0.9 ; 1.9]
Posterior	348	6	1.7 [0.8 ; 3.8]	336	5	1.5 [0.6 ; 3.6]
Finding age(year): Obscured mass			*			*
Absent	195,320	1,959	1.4 [1.3 ; 1.5]	197,922	1,794	1.3 [1.2 ; 1.3]
50-54	18,256	291	2.2 [1.9 ; 2.4]	17,553	236	1.8 [1.6 ; 2.1]

55-59	15,534	345	2.4 [2.2 ; 2.7]	14,874	298	2.2 [2.0 ; 2.5]
60-64	14,120	373	2.7 [2.5 ; 3.0]	13,709	336	2.5 [2.3 ; 2.8]
65-69	10,552	274	3.1 [2.7 ; 3.5]	10,030	253	3.0 [2.7 ; 3.4]
≥70	7,043	152	3.4 [2.9 ; 4.0]	6,766	142	3.3 [2.8 ; 3.9]
Contralateral presence if an Obscured-mass seen			*			*
Absent	32,813	891	3.4 [3.1 ; 3.6]	30,240	760	3.1 [2.9 ; 3.3]
Anterior	5,521	117	2.3 [1.9 ; 2.7]	5,750	140	2.6 [2.2 ; 3.0]
Same date	21,421	351	2.0 [1.8 ; 2.2]	21,421	313	1.8 [1.6 ; 2.0]
Posterior	5,750	76	1.4 [1.1 ; 1.8]	5,521	52	1.0 [0.8 ; 1.3]
Finding age(year): Asymmetric density			*			*
*A*bsent	254,460	2,983	1.6 [1.5 ; 1.6]	254,545	2,715	1.4 [1.4 ; 1.5]
50-54	1,482	54	6.8 [5.2 ; 8.9]	1,409	40	5.5 [4.0 ; 7.4]
55-59	1,415	79	6.7 [5.4 ; 8.4]	1,422	84	7.1 [5.8 ; 8.8]
60-64	1,444	106	7.4 [6.2 ; 9.0]	1,486	85	5.8 [4.7 ; 7.2]
65-69	1,201	93	7.9 [6.5 ; 9.7]	1,219	79	6.6 [5.3 ; 8.2]
≥70	823	79	11.2 [9.0 ; 13.9]	773	56	8.3 [6.4 ; 10.8]
Contralateral presence if an asymmetry seen			*			*
Absent	5,262	405	9.3 [8.4 ; 10.3]	5,206	333	7.7 [6.9 ; 8.6]
Anterior	162	2	1.4 [0.4 ; 5.6]	190	0	0
Same date	751	4	0.7 [0.2 ; 1.7]	751	9	1.5 [0.8 ; 2.8]
Posterior	190	0	0	162	2	1.4 [0.4 ; 5.6]
Finding age(year): Architectural distortion			*			*
*A*bsent	251,144	3,034	1.6 [1.6 ; 1.7]	251,522	2,671	1.4 [1.4 ; 1.5]
50-54	2,646	60	2.8 [2.2 ; 3.6]	2,517	76	3.8 [3.1 ; 4.8]
55-59	2,415	71	3.1 [2.5 ; 3.9]	2,329	72	3.3 [2.6 ; 4.1]
60-64	2,090	98	4.8 [3.9 ; 5.8]	2,045	84	4.2 [3.4 ; 5.2]
65-69	1,561	70	5.2 [4.1 ; 6.6]	1,5	96	7.5 [6.1 ; 9.2]
≥70	969	61	10.1 [7.9 ; 13.0]	941	60	10.2 [7.9 ; 13.1]
Contralateral presence if a distortion seen			*			*
Absent	7,043	328	5.4 [4.8 ; 6.0]	6,694	358	6.2 [5.6 ; 6.9]
Anterior	246	10	4.1 [2.2 ; 7.7]	258	5	2.0 [0.8 ; 4.7]
Same date	2,134	20	1.1 [0.7 ; 1.7]	2,134	23	1.3 [0.9 ; 1.9]
Posterior	258	2	0.8 [0.2 ; 3.1]	246	2	0.8 [0.2 ; 3.3]

Abnormalities's concomitance			*			*
No Abnormality	173,233	785	0.6 [0.6 ; 0.7]	175,696	731	0.6 [0.5 ; 0.6]
1-isolated	69,116	1,517	2.7 [2.6 ; 2.8]	67,823	1,358	2.5 [2.3 ; 2.6]
2-initial	6,702	397	7.4 [6.7 ; 8.1]	6,294	340	6.7 [6.0 ; 7.4]
2-posterior	9,222	444	5.1 [4.7 ; 5.6]	8,685	416	5.1 [4.7 ; 5.7]
3-initial	413	67	20.3 [16.0 ; 25.8]	397	49	15.4 [11.7 ; 20.4]
3-posterior	2,139	184	8.8 [7.6 ; 10.2]	1,959	165	8.6 [7.4 ; 10.0]
Abnormalities occurrence's order			*			*
Spiculated-mass first	6,725	348	6.1 [5.5 ; 6.8]	6,576	288	5.2 [4.6 ; 5.8]
Obscured-mass first	53,019	856	2.0 [1.8 ; 2.1]	51,183	776	1.8 [1.7 ; 2.0]
Microcalcification first	7,569	394	6.4 [5.8 ; 7.1]	7,815	350	5.5 [4.9 ; 6.1]
Architectural distortion first	7,087	179	2.9 [2.5 ; 3.4]	6,916	208	3.5 [3.0 ; 4.0]
Asymmetric density first	4,328	247	7.1 [6.3 ; 8.1]	4,305	208	6.0 [5.3 ; 6.9]
≥2 abnormalities first	8,864	585	7.9 [7.3 ; 8.6]	8,363	498	7.2 [6.6 ; 7.8]
Hormone Replacement Therapy			*			*
No/Unspecified	227,085	2,785	1.7 [1.6 ; 1.7]	227,111	2,545	1.5 [1.5 ; 1.6]
Yes	33,740	609	2.0 [1.9 ; 2.2]	33,743	514	1.7 [1.6 ; 1.9]
Breast density			*			*
D-I	35,040	322	1.2 [1.1 ; 1.4]	35,046	267	1.0 [0.9 ; 1.2]
D-II	161,222	2,059	1.7 [1.7 ; 1.8]	161,248	1,876	1.6 [1.5 ; 1.6]
D-III	58,524	926	2.0 [1.9 ; 2.2]	58,52	827	1.8 [1.7 ; 2.0]
D-IV	6,039	87	1.8 [1.5 ; 2.2]	6,040	89	1.9 [1.5 ; 2.3]

* Pr>chi2<0.0001(Log-rank test) – † 258 did not have the left breast – †† 229 did not have the right breast – C-In [CI 95%]: cumulative incidence/1000P-Y [95% confidence interval] – Nb: Number.

Figures

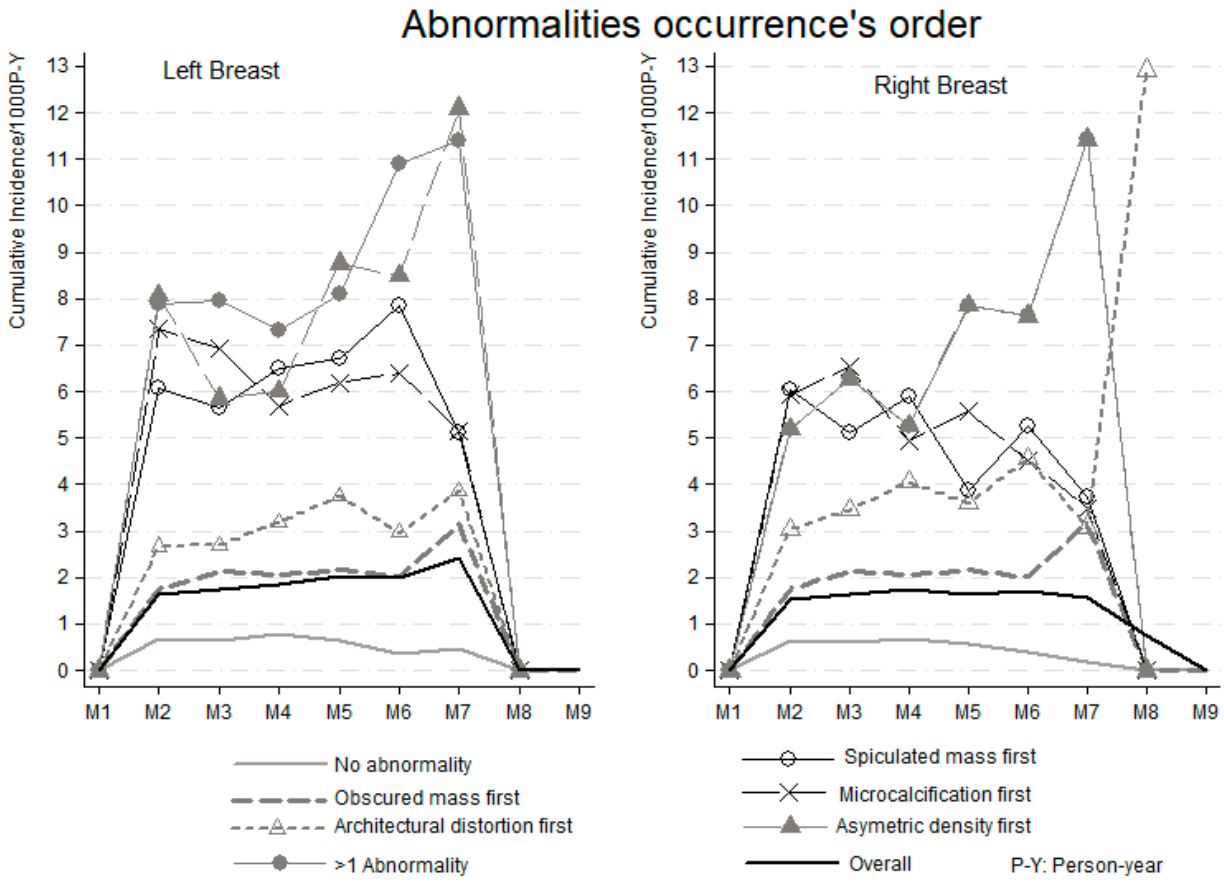

Figure 1

Evolution of the cumulative incidence according to the order of occurrence of the radiological abnormalities in the left and right breast and according by the screening mammogram (M) rank. No abnormality (no abnormality in the breast concerned); >1 abnormality (Several abnormalities first occurred on the same date); Overall (Sample Cumulative Incidence).

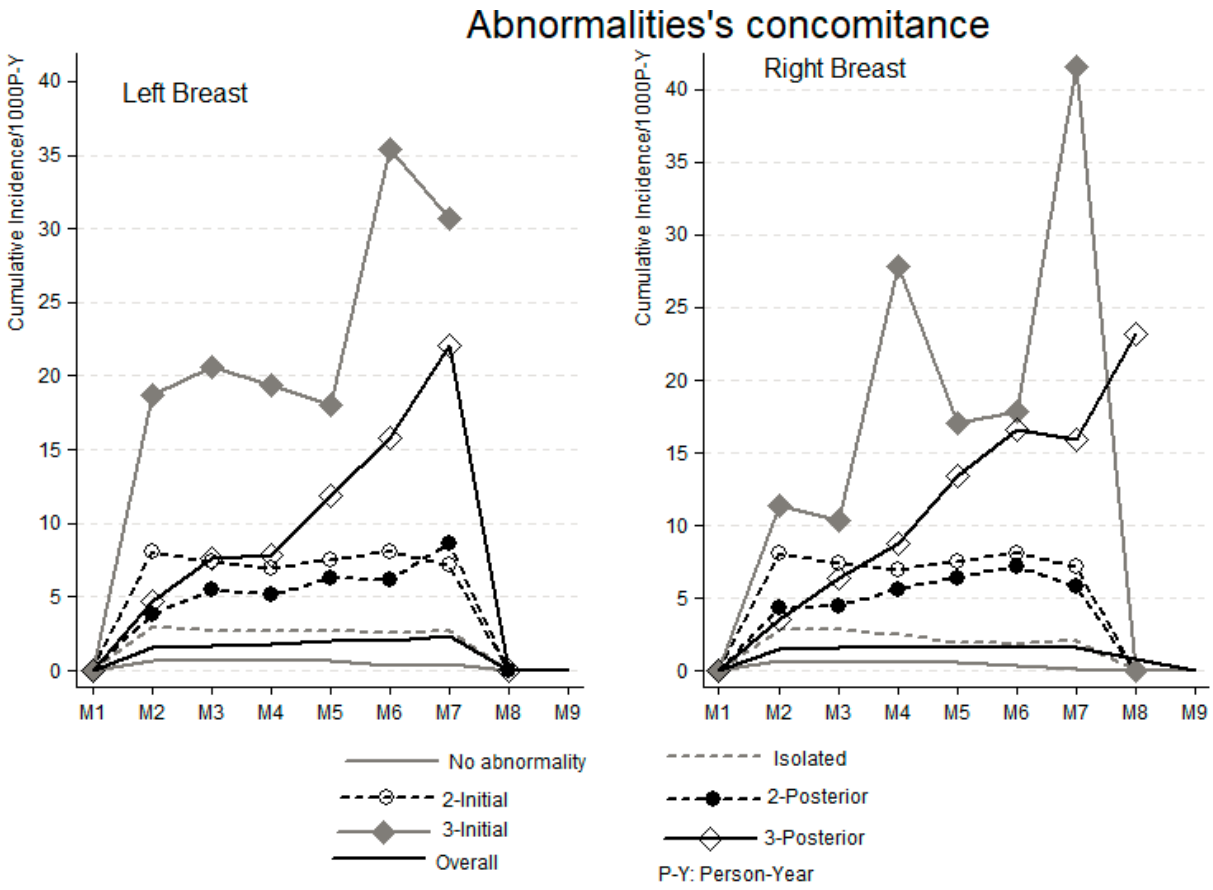

Figure 2

Evolution of cumulative incidence according to the concomitance of radiological abnormalities in the left and right breasts and according to the rank of the screening mammogram (M). No abnormality (if no abnormality in the breast concerned); 1-isolated (1 isolated sign); 2-Initial (2 abnormalities in initial association); 2-posterior (2 abnormalities in posterior association); 3-Initial (≥3 abnormalities in initial association); 3-posterior (≥3 abnormalities in posterior association); Overall (Sample Cumulative Incidence).