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The TESTBREAST journey: Revisiting the importance of early detection by frequent screening of women at high risk of breast cancer

Layla Andour[1] | Sophie C. Hagenaars[1] | Kiki Vangangelt[1] | Janneke Aalberts[1] | Valerie Rebattu[1] | Dorien M. A. Berends van der Meer[1] | Elma Meershoek-Klein Kranenbarg[1] | Katja N. Gaarenstroom[2] | Christi J. van Asperen[3] | Rob A. E. M. Tollenaar[1] | Wilma E. Mesker[1] | on behalf of the TESTBREAST study team

[1]Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands

[2]Department of Obstetrics and Gynecology, Leiden University Medical Center, Leiden, The Netherlands

[3]Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands

Correspondence
Wilma E. Mesker, Department of Surgery, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands.
Email: w.e.mesker@lumc.nl

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Abstract

Women with an inherited pathogenic variant (PV) in a breast cancer (BC) susceptibility gene, or familial predisposition (FP) have an increased risk to develop BC. There is a need for improvement of screening methods due to interval cancers and radiation exposure. The aim of the TESTBREAST study is to develop a blood test suitable for early diagnosis. Here, the clinical composition of participants is provided. From 2010 to 2022, 1108 women were included in the TESTBREAST study, with currently 750 participants suitable for serum analysis.

The median follow-up was 7 years [1–14]. Of the 1108 participants, 70% ($n = 728$) had a PV. BC was diagnosed in 16.5% ($n = 124$), mainly stage I-II (68.5%), and mostly BRCA1 ($n = 47$, 47%) and BRCA2 ($n = 29$, 29%) carriers. Invasive cancer was diagnosed in 100 cases: 76% ($n = 76$) had a PV with a median age of 49 [26–68] at diagnosis, whereas 24% ($n = 24$) had a FP, with a median age of 51 years [25–65]. The general population (the Netherlands) is aged 61 years on average at diagnosis. Triple negative breast cancer (TNBC) occurred in 51% ($n = 39$) of the TESTBREAST women with a PV, whereas this was 11% in the general population. Within the TESTBREAST cohort, BRCA carriers were younger at diagnosis and often had the aggressive TNBC

Abbreviations: BC, Breast Cancer; BCSP, Breast Cancer Screening Program; DCIS, Ductal Carcinoma in Situ; ER, Estrogen Receptor; FMS, Federation of Medical Specialists, the Netherlands; FP, Familial Predisposition; GP, General Practitioner; HER2, Human Epidermal Growth Factor Receptor 2; IKNL, Dutch National Cancer registry; LCIS, Lobular Carcinoma in Situ; LTR, Lifetime Risk; MRI, Magnetic Resonance Imaging; NCCN, National Comprehensive Cancer Network; NICE, National Institute of Health and Care Excellence; NST, No Special Type; PR, Progesterone Receptor; PV, Pathogenic Variant; QOL, Quality of Life; RRGS, Risk Reducing Gynecologic Surgery; RRM, Risk Reducing Mastectomy; RRO, Risk-Reducing Oophorectomy; RRS, Risk-Reducing Salpingectomy; RRSO, Risk-Reducing Salpingo-Oophorectomy; TESTBREAST, Trial Early Serum Test Breast; TNBC, Triple Negative Breast Cancer; UK, United Kingdom; US, United States; UV, Unclassified Variant.

J. Aalberts, T. M. A. Berends-van der Meer, S. C. Hagenaars, L. Andour, W.E. Mesker, R. A. E. M Tollenaar, W. M. Meershoek-Klein Kranenbarg, K. N. Gaarenstroom, C. M. R. Haekens, K. B. M. I. Keymeulen, J. Remmelzwaal, M. Piek-den Hartog, E. J. T. Rutgers, C. Drukker, C. Lemstra, A. Prozee, J. de Vries, A. Stam, C. Bandel, I. Meijer, A. E. Dassen, S. Makineli, E. E. van Oers-Hazelzet, A. J. Witkamp, K. E. Schenk, W. van der Eijk, M. B. E. Menke-Pluijmers, J. de Droog-Laane, B. A. Kortmann.

Rob A. E. M. Tollenaar and Wilma E. Mesker shared last authorship.

subtype. Improvement of current screening methods for early detection is especially important for this group of high-risk women to reduce interval cancers, exposure to radiation, and to improve survival.

KEYWORDS
breast cancer, germline mutation, hereditary breast and ovarian cancer, high-risk, screening

What's New?

Women who are at high risk of breast cancer (BC), either because of a BRCA1/2 mutation or family history, require more aggressive screening. Here, the authors report on the clinical characteristics of the high-risk women who developed BC during the TESTBREAST study. Of the 1108 participants, 124 (16.5%) developed breast cancer. Their median age at diagnosis was younger than in the general population, and they were more likely to have triple-negative BC, which is more aggressive and difficult to treat. The findings suggest that earlier and more frequent screening is advisable in the high-risk population.

1 | INTRODUCTION

Around 5%–10% of all breast cancer (BC) cases are associated with a positive family history.[1] Conventional screening programs focus on women with an average risk of BC, which affects one out of seven women in the Netherlands.[2] Many international guidelines differ in recommendations regarding the screening of the general population, but overall the advice is to offer screening to women aged 40–74 years (50–75 years in the Netherlands), with screening mainly consisting of mammography and Magnetic Resonance Imaging (MRI).[3] However, women with an increased risk of developing breast cancer, also called high-risk women here, need intensified screening.

Increased risk may be due to a familial predisposition (FP) or because of a pathogenic variant (PV) in one of the BC susceptibility genes.[1] In these high-risk women, 25% is attributable to an identified susceptibility gene, such as BRCA1/2. Carriers of such genes have a lifetime risk (LTR) up to 85% to develop BC.[4] Another high-risk gene is PALB2, which has a LTR of around 50%.[5] Carriers of moderate risk genes, such as CHEK2 (LTR 20%–30%),[5] account for approximately 2%–3% of the population of high-risk women. This means that in the majority of these high-risk women, the exact cause of their elevated risk remains unclear.[1,4]

BC screening among high-risk women starts earlier and is performed more frequently, compared to the nationwide screening program. In the Netherlands, screening outside population screening is offered according to the Dutch guideline for breast cancer (FMS),[6] which is roughly comparable to other international guidelines, such as the National Comprehensive Cancer Network (NCCN) in the United States (US)[7] and the National Institute of Health and Care Excellence (NICE) in the United Kingdom (UK).[8]

The adapted program for high-risk women differs for each risk classification. An overview of the screening strategies per risk classification is provided in Figure S1.[6] In general, high-risk women who are carriers of a PV of BRCA1/2 undergo BC screening, including a yearly physical examination, MRI, and a mammography initiated at 30 years (BRCA2) or even 25 years (BRCA1) old. For other high-risk women, the exact frequency and diagnostic methods depend on their risk classification.[6] The NCCN guidelines advise annual screening via mammography from the age of 30 and annual MRI at the minimum age of 25 years, depending on the age at diagnosis of the youngest family member with BC.[7] According to the NICE guidelines, annual mammography should be performed between 30 and 39 years in BRCA1 and BRCA2 carriers, and annual MRI in women aged 30–49 years.[8] In a previous meta-analysis regarding women at high risk, mammography showed a sensitivity of 32% and specificity of 95%, and for the MRI, this was 77% and 86%, respectively.[9,10] These data urge the need for further improvement of early detection of BC.

In addition to earlier initiation of screening and more frequent diagnostic testing, the schedule of surveillance can be quite a burden for these high-risk women, especially since screening is started at such a young age.[6] With the current screening methods, BC screening with mammography and MRI is postponed in case of pregnancy or lactation, which is not optimal. Additionally, the risk of interval cancers makes the need for optimization of screening both more important and demanding.[11]

In 2010, the Trial Early Serum Test BREAST cancer (TESTBREAST) study was initiated with the aim to improve the current screening program and early detection of BC in women at high risk of BC. A detailed description of the study method was published previously, along with lessons learned regarding study logistics and sample processing.[12] The intention of this study is to develop a blood test containing a panel of proteins—with high specificity for breast cancer—that is suitable for detecting longitudinal changes in an individual. Ideally, this blood test will be incorporated in the current screening program to aid in the early detection of breast cancer by identifying even subtle changes in protein levels.

Results from the first serum analysis have already been reported: during surveillance, we evaluated changes in a series of protein levels measured via a blood test in a longitudinal setting.[13] In this current article, we evaluated the inclusion process, sample collection, and the

clinical characteristics of patients who have developed BC in the decade of the TESTBREAST study and compared this with data from the national breast cancer registry for sporadic cases.

2 | METHOD

2.1 | Study design

The TESTBREAST study was initiated in 2010 as a prospective, multicenter, cohort study in the Netherlands. Patients were enrolled between June 2010 and June 2022 (Table S1). Women with a high risk of BC due to their family history or due to a PV of a susceptibility gene, who underwent breast surveillance in the hospital, were included. A blood sample was obtained during their visits at the outpatient clinics for breast surveillance.

Considering the inclusion of patients has been closed, a retrospective assessment was performed between December 2023 and February 2024 to determine if all included patients had met the eligibility criteria and to assess the up-to-date incidence of breast cancer in the study cohort.

2.2 | Inclusion and exclusion criteria

Women between the age of 25 to 75 years at high risk of breast cancer (here: high-risk women) were included in the TESTBREAST study, after referral by clinical genetic services. There, they received genetic counselling and risk estimation. Each woman received screening advice based on her individual risk classification to follow a specific screening schedule in the outpatient clinic. A high risk was defined as having a LTR of ≥20% to develop BC, due to either a germline PV mutation or based on a family history with BC (familial predisposition, without a known gene mutation). Based on the PV and/or affected family members, the classification ranges from moderate (LTR >20% and <30%) to strong risk (LTR >30%).[6] Exclusion criteria comprised a history of BC or other malignancies, other than basal cell carcinoma. Moreover, participants who returned to the general practitioner (GP) or the national BC screening program (BCSP), or women who underwent risk-reducing surgery of their breasts (risk-reducing/prophylactic mastectomy) prior to having completed a 5-year follow-up period in this study, were also excluded. Cases/patients were defined as high-risk participants who did develop breast cancer—either invasive or in situ (ductal carcinoma in situ (DCIS) and/or lobular carcinoma in situ (LCIS))—at some point during their follow-up. A complete follow-up was defined as ≥5 years to allow sufficient time to monitor whether a woman developed BC.

2.3 | Blood sample collection

During regular screening appointments at the outpatient clinic for hereditary BC, women with a PV or FP were asked to have blood samples drawn as part of the TESTBREAST study.[13] Depending on the screening schedule of the institute, this occurred once every half year or on a yearly basis, and in some cases even up to four times a year when women volunteered to donate blood more frequently in the study. From August 2022 on, enrollment of new participants was discontinued based on the powered sample size calculation beforehand. Collection of samples from included patients continues up to 5-year follow-up. The most recent update in sample collection occurred in March 2024. If participants develop a carcinoma, collection of sampling is discontinued.

2.4 | Subtypes of invasive cancer

Tumor subtypes were defined based on hormone status and human epidermal growth factor receptor 2 (HER2)-status, but not on Ki-67 since this was not known for all patients. Here, the luminal A-like subtype was characterized by positive estrogen (ER) and/or progesterone (PR) and negative HER2 status. The luminal B-like subtype was defined as ER and/or PR positive and HER2 positive BC. HER2-enriched breast cancer included patients with negative ER/PR expression but with a HER2-positive tumor. Finally, patients with triple negative BC (TNBC) had a tumor with negative ER, PR, and HER2 expression.

2.5 | Clinical composition

We describe the clinical composition of our high-risk TESTBREAST cohort and place it into perspective with women diagnosed with sporadic BC, based on data from literature and the Dutch national cancer registration (IKNL, Netherlands Comprehensive Cancer Organization).[2] Data from IKNL was derived from online, publicly available data on their website, which mainly included documentation from 2023. Since not all data were generally accessible from IKNL, results were complemented with data from previous literature.

3 | RESULTS

Over the years, a total of 1193 participants were enrolled across nine participating centers (Table S1). Finally, after meeting the eligibility criteria, 1108 women were included in the presented analyses (Figure S2). Clinical data of these 1108 participants were used to examine the number of women that carry a PV of one of the BC susceptibility genes, and to gain insight into the number of women who have undergone risk-reducing surgery. Ultimately, after extraction of women who returned to the GP, who underwent a risk-reducing mastectomy (RRM) before complete follow-up (≥5 years) or were lost to follow-up, a total number of 750 participants (Figure S3) remained. This remaining group of 750 high-risk women was analyzed for their BC diagnoses (cases/patients in the TESTBREAST cohort).

Data of these 750 TESTBREAST participants, including cases and women currently in the follow-up (who have not yet developed BC,

TABLE 1 Characteristics of participants in the TESTBREAST study.

Characteristics	All eligible women $n = 1108$ (100%)	Suitable for analysis $n = 750$ (100%)
Median age [distribution]	51 [26–81]	51 [27–81]
Age groups		
<50 years	512 (46.2%)	354 (47.2%)
50–74 years	590 (53.2%)	393 (52.4%)
≥75 years	6 (0.5%)	3 (0.4%)
Reason high risk		
Familial predisposition	364 (32.9%)	222 (29.6%)
Non-pathogenic BRCA1 UV (still familial risk)	3 (0.3%)	1 (0.1%)
Non-pathogenic BRCA2 UV (still familial risk)	4 (0.4%)	2 (0.3%)
Susceptibility gene in family, patient not tested	16 (1.4%)	10 (1.3%)
Of which UV in family	6 (0.5%)	4 (0.5%)
Carrier susceptibility gene	728 (65.7%)	518 (69.1%)
Gene carriers		
BRCA1	337 (30.4%)	222 (29.6%)
Of which BRCA1 UV (possible still pathogenic)	1 (0.1%)	1 (0.1%)
BRCA2	335 (30.2%)	254 (33.9%)
Of which BRCA2 UV (possible still pathogenic)	3 (0.3%)	2 (0.3%)
PALB2	9 (0.8%)	7 (0.9%)
ATM	5 (0.5%)	4 (0.5%)
CHEK2	28 (2.5%)	22 (2.9%)
NF1	5 (0.5%)	4 (0.5%)
BRCA1 and BRCA2	2 (0.2%)	2 (0.3%)
PTEN	7 (0.6%)	3 (0.4%)
Development of cancer		
No carcinoma	687 (62%)	626 (83.5%)
Invasive carcinoma	102 (9.2%)	100 (13.3%)
DCIS	15 (1.4%)	15 (2%)
LCIS	2 (0.2%)	2 (0.3%)
DCIS and LCIS	2 (0.2%)	2 (0.3%)
Prophylactic mastectomy and benign histology	133 (12.0%)	N/A
Prophylactic mastectomy and DCIS histology	3 (0.3%)	3 (0.4%)
Prophylactic mastectomy and LCIS histology	2 (0.2%)	2 (0.3%)
Unknown, last visit no carcinoma	150 (13.5%)	N/A
Unknown, has another primary tumor	13 (1.2%)	N/A
Risk-reducing/prophylactic gynecologic operation	488 (44.0%)	349 (46.5%)
Previous surgery on breast		
Excision and benign histology	24 (2.2%)	19 (2.5%)
Breast reduction	38 (3.4%)	27 (3.6%)
Status		
Alive	906 (81.8%)	730 (97.3%)
Dead	14 (1.3%)	5 (0.7%)
Censored before 5 year	188 (17%)	15 (2%)
Serum samples		
Available	1024 (92.5%)	691 (92.1%)
One sample	282 (25.5%)	172 (22.9%)
Two samples	212 (19.1%)	140 (18.7%)

TABLE 1 (Continued)

Characteristics	All eligible women $n = 1108$ (100%)	Suitable for analysis $n = 750$ (100%)
Three or more samples	530 (47.8%)	379 (50.5%)
Missing/no samples	84 (7.6%)	59 (7.9%)
Median amount of serum samples	Median 3 [1–26]	Median 3 [1–23]

Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; UV, unclassified variant.

$n = 626$, Table S2), were assessed to compare their clinical characteristics to BC patients from the national registry. A detailed overview of our entire cohort is described in Table 1. The median follow-up time, during which clinical data were registered and samples were collected, was 7 years [range 1–14]. Since the start of the study, 14 out of the enrolled 1108 (1.3%) women have passed away (Table 1). Out of these 14 women, 9 (64.3%) had another primary malignancy, such as an ovarian carcinoma ($n = 5$, 35.7%). Out of the five remaining participants, three had developed breast cancer (21.4%), with metastasis confirmed in two women. Finally, in the last two women, the cause of death was unknown (14.3%).

4 | CHARACTERISTICS OF PARTICIPANTS

Most women ($n = 728$, 65.7%) in the TESTBREAST cohort of 1108 participants were proven carriers of a PV variant (Table 1 and Figure S4), compared to a lower number of women ($n = 380$, 34.3%) with an FP. Concordantly, we also found more gene carriers in the group of patients with BC, of which both invasive and in situ ($n = 124$, Table S3). Most of the gene carriers in our cohort ($n = 750$) are carriers of BRCA1 ($n = 222$, 29.6%) and BRCA2 ($n = 254$, 33.9%).

4.1 | Risk-reducing surgery

During the course of the study, 138 of the 1108 (12.5%) eligible women underwent an RRM. Out of those with a BRCA1/2 mutation ($n = 672$), 130 (19.4%) women underwent an RRM. This consisted of 76 of 337 (22.6%) BRCA1 and 54 of 335 (16.1%) BRCA2 carriers. Almost half of the women in our cohort (488 out of 1108, 44.0%) also had either a risk-reducing salpingo-oophorectomy (RRSO), a risk-reducing salpingectomy (RRS) with a delayed oophorectomy (RRO), or solely an RRS and not yet an RRO performed. Women who underwent an RRS with or without a delayed RRO participated in the TUBA- or TUBA-WISP II study.[14]

The group of women who underwent risk-reducing gynecologic surgery (RRGS) consisted mostly of BRCA carriers (91%). Of the BRCA1 carriers, 227 (67.4%) underwent an RRGS at a median age of 40 [25–69] years, and 221 (66.0%) of the BRCA2 carriers at 43 [29–74] years. Of the 138 women who had undergone an RRM, four developed another malignancy during their follow-up. Among the remaining 134 women, 89 (66.4%) had also undergone an RRGS.

5 | CARCINOMA: INVASIVE AND IN SITU

In the cohort of 750 women, the incidence of BC in February 2024 was 16.5% ($n = 124$), consisting of 100 patients with an invasive carcinoma (Table S3) and 24 patients with an in situ (DCIS and LCIS) carcinoma (Table S4). Characteristics of the (first) primary tumor are described in Table S3; additional data in case of a bilateral or multifocal tumor can be found in Table S5.

Of the 124 cases, five (4.0%) women had an in-situ carcinoma detected after an RRM. Among the 488 women who had undergone an RRGS, 68 (13.9%) women developed BC. Of these women, 38 (55.9%) were BRCA1 and 26 (38.2%) BRCA2 carriers.

5.1 | Tumor stage

In the TESTBREAST cohort, the stage was unknown in eight of the cases. Most patients were diagnosed with an early stage I BC (53.4%, Figure 1A and Table S6), whereas in sporadic cancer patients from the national registry, the initial detection was more evenly spread between stages I and II (40% and 35%, respectively, Figure 1B). The occurrence of late stage IV was lower in the TESTBREAST cohort (1.7%), compared to the sporadic cases in the national registry (5%).

5.2 | Subtypes: invasive carcinoma

In the TESTBREAST cohort, most of the patients had a tumor with a luminal A (49.0%) or TNBC (44.8%) subtype (Figure 2A/B). This contrasts with the sporadic cases of BC in the national registry, where 85% of the patients had a hormone receptor positive carcinoma, predominantly the luminal A subtype (77%). In 11% of the sporadic cases, the subtype was TNBC. In four of the TESTBREAST cases, the tumor subtype was unknown.

Of the 43 TNBC patients in the TESTBREAST cohort (Table S7), 33 (76.7%) were BRCA1 carriers, six (14%) BRCA2 carriers, and four (9.3%) had an FP. A total of seven (16.3%) of the TNBC patients had a grade 2 tumor, whereas 33 (76.7%) had a grade 3 tumor. Finally, most of the TNBC patients had a stage I ($n = 27$, 65.9%) or stage II tumor ($n = 10$, 24.4%). Only a small number of patients had a stage III ($n = 3$, 7.3%) or stage IV (n = 1, 2.4%) carcinoma. The stage was unknown in two of the TNBC cases.

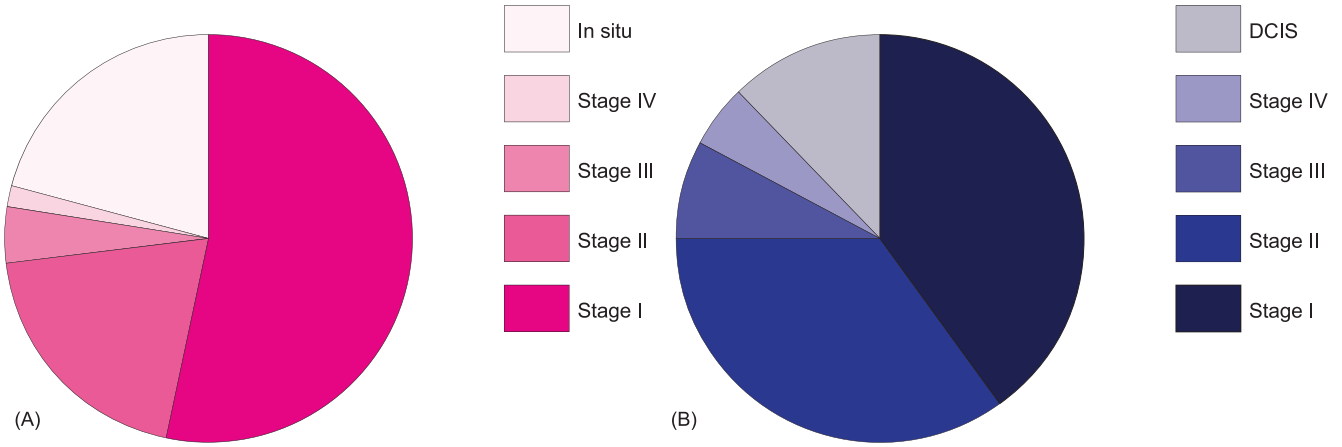

FIGURE 1 (A) Tumor stage among TESTBREAST participants diagnosed with breast cancer ($n = 124$); stage I (53.4%), stage II (19.8%), stage III (4.3%), stage IV (1.7%), in situ (DCIS and LCIS: 20.7%). (B) stage among patients of the national registry; stage I (40%), stage II (35%), stage III (8%), stage IV (5%), DCIS (12%).

5.3 | Familial predisposition versus proven genetic mutation

Within the TESTBREAST cohort, patients with a PV and those with an FP were separately analyzed to assess potential clinical differences regarding their risk. The distribution of breast cancer subtypes in patients with an FP (Figure 2C) resembles that of the national registry with sporadic cases, compared to patients with a PV (Figure 2D). In the group with a PV, patients with a BRCA1 and BRCA2 mutation were also separately analyzed (Figure 2E/F): in the TESTBREAST cohort, patients with a BRCA1 mutation ($n = 47$) more often had the TNBC subtype (75.0%), whereas BRCA2 carriers with breast cancer ($n = 29$) more frequently had the luminal A subtype (71.4%). The subtype was unknown in three cases with a BRCA1 PV and in one case with a BRCA2 PV.

6 | AGE

6.1 | Breast cancer diagnosis

The median age at diagnosis of BC of the TESTBREAST patients was 49 years [26–68]. Of those patients, women with an FP were generally older (median 52 years [40–64]), compared to women with a PV (median 48 years [26–68]). TESTBREAST patients were generally younger at the time of diagnosis, compared to the average age of the sporadic cases from the national registry (61 years).[15]

6.2 | Age and tumor stage

In the TESTBREAST cohort, 54.8% ($n = 34$) of the patients with a stage I tumor ($n = 62$) were aged 50–74 years at diagnosis, and this was 71% in cases from the national registry (Tables S8/S9 and Figure S5). In stage III patients in the TESTBREAST cohort ($n = 5$), 80% ($n = 4$) were younger than 50 years, in comparison to 24% of the stage III patients in the national registry (sporadic BC, Figure S6).

6.3 | Age, subtype and cause of high risk

In the TESTBREAST cohort, 48 (48.0%) women with invasive BC were aged 50–74 years, and 52 women (52.0%) were aged <50 years when they developed BC. The subtype of the tumor was unknown in two cases aged <50 years and in two women aged 50–74 years. Patients aged 50–74 years more often had a tumor of the luminal A subtype ($n = 29$, 30.2%), whereas the group of women aged <50 years more often had the TNBC subtype ($n = 29$, 30.2%). In the group of 48 women aged 50–74 years, 34 (70.8%) of the women had a PV. Of the 52 women aged <50 years, 42 (80.8%) had a PV.

7 | DISCUSSION

The goal of the TESTBREAST study is to improve current screening for BC, especially for women at high risk, using a blood test for early detection. In this article, we provide an overview of the characteristics among the Dutch national, multicenter TESTBREAST population, consisting of women with an inherited or familial increased risk of BC, compared to sporadic cases from the Dutch national cancer registry.

7.1 | Pathogenic variant and familial predisposition

In our TESTBREAST cohort, 65.7% of the women had a PV of one of the BC susceptibility genes, most of whom were BRCA1 (30.4%) and BRCA2 (30.2%) carriers. In previous literature, it was described that most of the familial BC cases do not have an identified cause, and around 30% is explicable due to a PV in one of the susceptibility genes.[4] Since our cohort consists of relatively more gene carriers

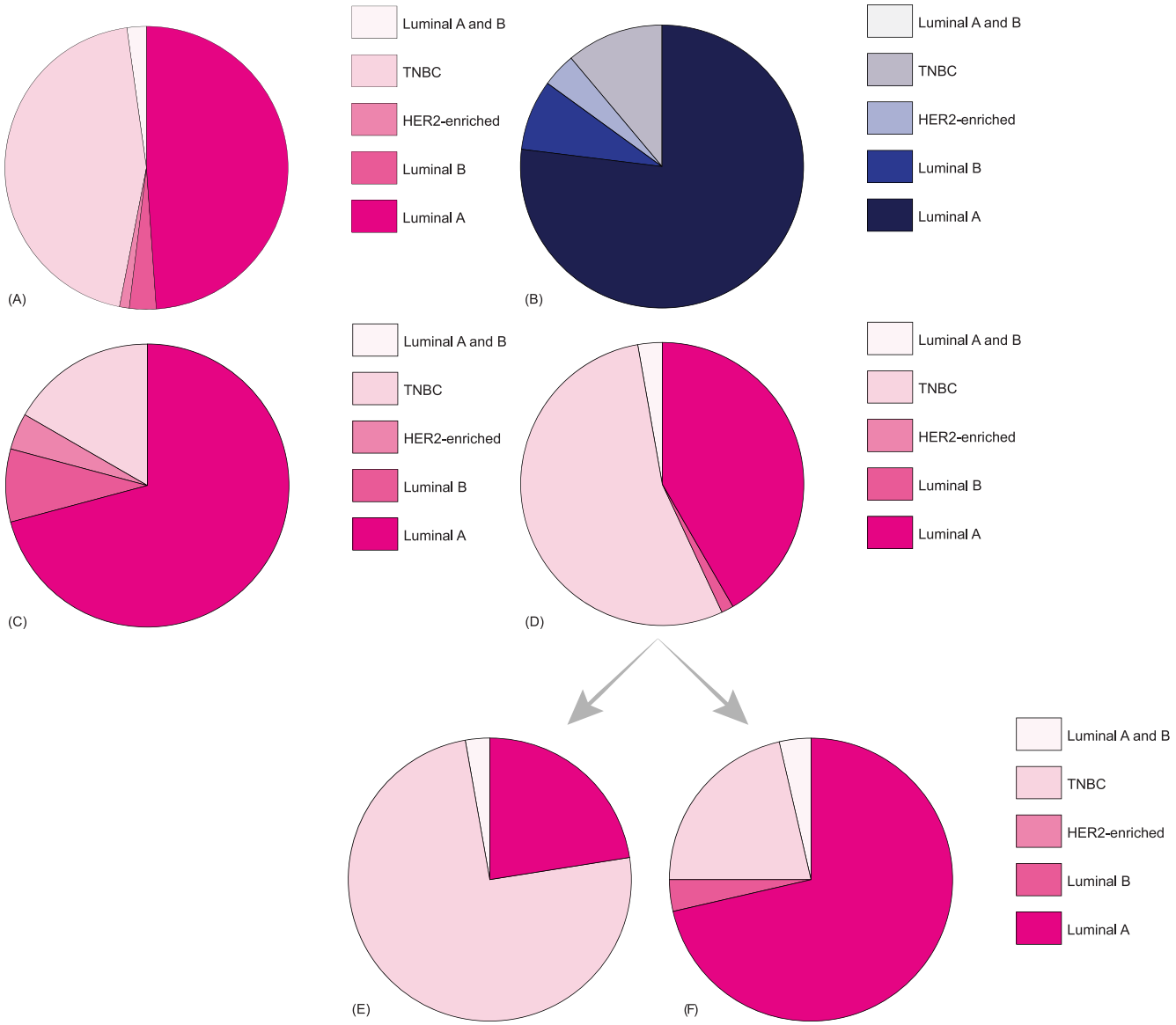

FIGURE 2 (A) Breast cancer subtypes in the entire TESTBREAST cohort ($n = 100$); luminal A (49.0%), luminal B (3.1%), HER2-enriched (1.0%), TNBC (44.8%), luminal A and B (2.1%). (B) subtypes in the national registry; luminal A (77%), luminal B (8%), HER2-enriched (4%), TNBC (11%). (C) subtypes in TESTBREAST patients with familial predisposition ($n = 24$); luminal A (70.8%), luminal B (8.3%), HER2-enriched (4.2%), TNBC (16.7%), luminal A and B (0%). (D) subtypes in TESTBREAST patients with proven genetic risk ($n = 76$); luminal A (41.7%), luminal B (1.4%), HER2-enriched (0%), TNBC (54.2%), luminal A and B (2.8%). (E) Breast cancer subtypes in TESTBREAST patients with a BRCA1 mutation ($n = 47$); luminal A (22.7%), luminal B (0%), HER2-enriched (0%), TNBC (75.0%), Luminal A and B (2.7%). (F) subtypes in TESTBREAST patients with a BRCA2 mutation ($n = 29$); luminal A (71.4%), luminal B (3.6%), HER2-enriched (0%), TNBC (21.4%), Luminal A and B (3.6%).

compared to this previous article on women with an increased risk of BC,[4] the composition of the characteristics of the TESTBREAST cohort might have a different representation. The relatively high number of women with a PV might be due to the relatively high incidence of genetic mutations in the Dutch population, which is thought to be the result of inheritance of the mutation from common ancestors (founder mutation) and a relatively isolated population up until after the Second World War.[16,17] Peelen et al. even described a specific mutation in the BRCA1 gene that had never been documented outside the Netherlands.[17] Other countries with a relatively high frequency of mutations are Iceland and Poland, which is also thought to be due to founder mutations and geographic isolation.[18] It might also be attributed to a certain selection bias, since only women who underwent screening in the outpatient clinic were included and not those screened via the GP.

7.2 | Risk-reducing surgery

A total of 138 of the 1108 women in the TESTBREAST cohort underwent an RRM and 488 an RRGS. In our cohort, 22.6% of the BRCA1 and 16.1% of the BRCA2 carriers had undergone an RRM. Other

studies that included BRCA1 ($n = 139$) and BRCA2 ($n = 483$) carriers showed an incidence of, respectively, 54.7% and 21.7% of preventive operations among these women.[19,20]

Around 44.0% of the 1108 women had undergone an RRGS: this consisted of 227 women of the 337 (67.4%) BRCA1 carriers, and 221 of the 335 (66.0%) BRCA2 carriers. BRCA1 carriers had undergone this procedure at a median age of 40 years, and the BRCA2 carriers at 43 years. This is in line with the Dutch guideline, which advises an RRSO around the age 35–40 in BRCA1 carriers and 40–45 in BRCA2 carriers.[21] A previous longitudinal cohort study of Kotsopoulos et al. in 872 BRCA1 patients (mean follow-up 7.6 years) estimated that around 65% of the BRCA1 carriers will have a risk-reducing gynecologic operation in their life.[22]

The high number of risk-reducing surgeries in our cohort emphasizes the impact that being at high risk of breast and ovarian cancer has on the quality of life (QOL). A study by Parker et al. found that women who underwent an RRM had a worse QOL compared to women who did not have this operation.[23] An RRSO at the recommended age between 35 and 40 years (BRCA1) and 40–45 years (BRCA2) leads to early surgically induced menopause.[24] This may result in psychological, emotional, sexual, and physical complaints,[25] which are also possible explanations for a lower QOL score.[26]

Two important factors that play a role in the decision-making process of undergoing an RRM are possible cultural differences and the effect of media. For example, the Angelina Jolie effect has been mentioned in the literature, which resulted in an increase in RRM and more genetic testing after 2013 in the United States, after her announcement that she underwent this operation.[27] Furthermore, earlier research found that French women were less inclined to favor an RRM, compared to women from the United Kingdom (UK).[28] The attitude of a physician towards an RRM might also influence this decision: den Heijer et al. found that physicians in the Netherlands and UK more often had a positive outlook on an RRM, in comparison to GPs and breast surgeons in France and Germany.[29]

Since our population consisted of Dutch women, these factors might explain the relatively high risk-reducing operations in our cohort, in relation to other studies which include women of other nationalities.

7.3 | Development of breast cancer

A total of 124 out of the 750 women in the TESTBREAST cohort developed BC, of whom 100 were invasive and 24 in situ. This corresponds to an incidence of 16.5% after a median follow-up of 7 years since the enrollment of participants. Depending on the PV they carry, these women have an LTR of up to 50% (PALB2) and even 85% (BRCA1/2) to develop BC.[4,30]

Out of these 124 patients, five (4%) had an in-situ carcinoma that was found after an RRM. In a study of Khurana et al., which included 45 high-risk women, one woman had DCIS (2.2%) and one had an invasive carcinoma (2.2%) after an RRM.[31]

Of the TESTBREAST participants, 13.9% of the women who had undergone an RRGS developed BC (invasive or in situ), of whom 94.1% were BRCA1/2 carriers. Even though previous studies suggested that an RRSO might also influence the risk of developing BC,[32] a recent prospective study of Stuursma et al. in women with a PV of BRCA1/2 concluded that an RRSO did not affect the incidence of BC.[33] Other studies also did not find (strong) evidence that an RRSO decreases the risk of developing breast cancer in BRCA1/2 carriers.[34,35] In our cohort, an RRGS also did not appear to have a protective effect against developing BC, as the incidence across the entire cohort (16.5%) was similar among women who had undergone an RRGS (13.9%).

7.4 | Characteristics of patients

The median age at diagnosis of the TESTBREAST cohort was 49 years: women with a PV had a median age of 48 years, and women with an FP 52 years. Women at high risk of BC were generally younger, compared to sporadic cases in the Netherlands (average 61 years) and the US (median 60 [52–67]).[36] Our data underlines the importance of early and frequent screening: most of the TESTBREAST patients with invasive BC had stage I cancer (50%), which is correlated with better survival.[37] Of all cases in the TESTBREAST cohort, 43% had the TNBC subtype, of which mostly grade 3 (76.7%), stage I (62.8%) and stage II (23.3%) tumors. In a study of Plasilova et al., most of the 38,628 TNBC patients had a grade 3 tumor ($n = 29,353$, 79.8%), which is in line with our findings. They subsequently found that other patients often had a grade 2 tumor ($n = 2996$, 24.2%), and a smaller number had a grade 1 tumor ($n = 888$, 2.4%), which was also in unison with our data.[38] Another study of Yeh et al. in 190 TNBC patients found mainly stage I ($n = 101$, 53%) and stage II ($n = 55$, 29%) BC.[39] Stage III ($n = 33$, 17%) was less frequently observed and only one patient had stage IV ($n = 1$, 1%) BC. Again, this generally aligned with results from our cohort.

We found that characteristics of TESTBREAST patients with a FP were more similar to cases from the national registry, compared to the TESTBREAST women with a PV. We also found that the tumors of BRCA2 carriers resembled the sporadic cases more, compared to BRCA1 carriers. In our cohort, the TNBC subtype was most frequent in patients with a BRCA1 mutation (75.0%), whereas this was the luminal A subtype in BRCA2 carriers (71.4%). Mavaddat et al. included 4325 BRCA1 and 2568 BRCA2 patients, and found TNBC in 68% of the BRCA1 carriers and in 16% of the BRCA2 carriers.[40] Overall, BRCA1 patients more often have TNBC, whereas BC in BRCA2 patients more often behaves like the sporadic cases (luminal subtypes). As such, characteristics of patients in the TESTBREAST cohort were consistent with previously reported findings on BRCA1/2 carriers.[1,40]

8 | CHALLENGES

8.1 | Risk classification

One of the challenges in the TESTBREAST study involved the group of women that returned to the GP or the national screening program,

based on their risk classification. In some cases, this resulted in an incomplete 5-year follow-up, which was part of our study criteria for analysis of the serum samples. The different risk classifications also presented challenges in characterizing our study participants. At this moment, women with an FP are classified as moderate (20–30%) or high risk (>30%), mainly depending on which family members and how many of them are affected. Over the years, the definition of the risk classification has changed, along with the knowledge on the unclassified variants of the BRCA genes, which makes it a dynamic process. A tool that can help decide the risk and therefore the fitting surveillance for an individual is the CanRisk Tool, which is developed specifically for breast and ovarian cancer.[41] It also takes personal lifestyle and clinical features into consideration to aid in risk prediction. Assessing the risk for each person separately, instead of for several family members at once, has the preference since it offers a more individual program.[41,42]

8.2 | Radiation

There is still room for improvement regarding sensitivity/specificity of current diagnostic tools. The primary screening method is mammography, which has the risk of exposure to radiation. A previous study showed that BRCA1/2 carriers who are exposed to radiation before the age of 30 have an increased risk to develop BC.[43] Miglioretti et al. estimated the incidence of BC related to radiation during screening, based on a model-based approach.[44] The findings indicated that annual screening in women aged 40–74 (based on a work-up of 100.000 women, 35 screening moments per woman) resulted in the induction of 125 BC cases related, whereas this would be 68 in case of biennial screening in this age group.

Therefore, alternating, for example, between a mammography 1 year and a blood test the other year could help to reduce the risk of radiation-induced BC. Especially carriers of BRCA2, CHD1, and PALB2 mutations are at risk, due to the early start of screening: in the case of a BRCA2 mutation, additional mammography to MRI is advised from the age of 30, which amounts to approximately 46 mammography's and 35 MRIs in the surveillance period between 25 and 70 years, compared to 13 mammography's women in the national screening program undergo in their life (Figure S1).

Current guidelines advise screening with not only MRI, but also mammography to avoid missing DCIS cases, which are often only visible as microcalcifications on a mammography. Starting at a later age could result in a radiation reduction. However, in BRCA2 patients, DCIS occurs more often, and there still seems to be an additional value of the mammography in BRCA2 patients, especially in those younger than 40 years.[6,45] If a blood test could replace the diagnostics instead, the exposure to radiation could be (further) reduced. First results of serum analysis in longitudinally acquired serum samples of three women with BC and three without (30 samples over time) showed unique patterns of protein clustering in each woman.[13] Further analysis is still needed and ongoing to determine if a blood test is suitable for monitoring purposes.

8.3 | Interval cancer

Another concern is the occurrence of interval cancer. Buist et al. included women aged >40 years with invasive BC, diagnosed within 2 years after the index mammogram (last mammogram before the detection of cancer) and before the next screening.[46] According to their findings, interval cancer occurred especially in younger women aged 40–49 years.[46] In their cohort of 576 patients, 73 women aged 40–49 years developed cancer ($n = 38$ interval cancer, 52.1%), whereas this was 503 in women aged ≥50 years ($n = 124$ interval cancer, 24.7%). There was an association between younger age, high breast density, and quick tumor growth related to interval cancers. Independent of age, there was an association between menopausal status and high breast density and the occurrence of an interval cancer. Menopausal status was more strongly correlated with interval cancer compared to (young) age: 52.1% of the young women had an interval cancer, whereas this was 64% in the premenopausal group. Factors related to interval cancers in the premenopausal group were similar to those in younger women. Other studies also supported the association between high breast density and interval cancer.[47,48] Exact numbers of the incidence of interval cancer in our TESTBREAST cohort are not clear, as specific dates of imaging are not recorded in the study, but the relatively young age and more aggressive tumors of women in the TESTBREAST cohort make them more susceptible to develop interval cancer, according to these data.

8.4 | Quality of screening

Finally, a further concern is the quality of the screenings program that is currently under pressure in the Netherlands. According to the Healthcare and Youth Inspectorate report (2024) the workload is heavy; there is insufficient emphasis on improvement of the program, and efforts to make screening more accessible to all target groups are lacking.[49] This, again, accentuates the need for improvement of current screening, not only for high-risk women but also for women in the general population.

9 | CONCLUSION

The TESTBREAST study cohort mainly consists of proven carriers of one of the two most common susceptibility genes (BRCA1/2). The data reported from this study underline the importance of early and more frequent screening in a high-risk population: in contrast to data from the national registry, which includes sporadic cases, the TESTBREAST patients were generally younger and more frequently had the more aggressive TNBC subtype, which especially affected the BRCA1 carriers. However, most of the invasive breast cancer patients in the TESTBREAST cohort had stage I cancer, which is associated with better survival. Furthermore, the occurrence of late stage IV cancer was lower in our cohort compared to the women in the national registry. Altogether, these data accentuate the need for an optimally functioning screening method—possibly in the form of a less invasive

blood test—since early detection is especially important for this young patient group.

AUTHOR CONTRIBUTIONS

Layla Andour: Conceptualization; investigation; methodology; writing – review and editing; visualization; writing – original draft; formal analysis. **Sophie C. Hagenaars:** Writing – review and editing. **Kiki Vangangelt:** Writing – review and editing. **Janneke Aalberts:** Writing – review and editing. **Valerie Rebattu:** Project administration; writing – review and editing. **Dorien M. A. Berends van der Meer:** Project administration; writing – review and editing. **Elma Meershoek-Klein Kranenbarg:** Writing – review and editing; project administration. **Katja N. Gaarenstroom:** Writing – review and editing. **Christi J. van Asperen:** Writing – review and editing; conceptualization. **Rob A. E. M. Tollenaar:** Writing – review and editing; supervision. **Wilma E. Mesker:** Writing – review and editing; conceptualization; funding acquisition; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The TESTBREAST study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of the Leiden University Medical Center (NL59318.058.16) in agreement with Dutch law for medical research involving human subjects. Informed consent was obtained from all patients.

ORCID

Layla Andour https://orcid.org/0000-0002-0073-9601
Sophie C. Hagenaars https://orcid.org/0000-0002-9121-1975

REFERENCES

1. Larsen MJ, Thomassen M, Gerdes AM, Kruse TA. Hereditary breast cancer: clinical, pathological and molecular characteristics. *Breast Cancer (Auckl)*. 2014;8:145-155.
2. IKNL. Netherlands Comprehensive Cancer Organisation (NKR). 2024 https://iknl.nl/borstkankercijfers
3. Ren W, Chen M, Qiao Y, Zhao F. Global guidelines for breast cancer screening: a systematic review. *Breast*. 2022;64:85-99.
4. Shiovitz S, Korde LA. Genetics of breast cancer: a topic in evolution. *Ann Oncol*. 2015;26(7):1291-1299.
5. Lowry KP, Geuzinge HA, Stout NK, et al. Breast cancer screening strategies for women with ATM, CHEK2, and PALB2 pathogenic variants: a comparative modeling analysis. *JAMA Oncol*. 2022;8(4):587-596.
6. FMS. Borstkanker: Screening (Breast cancer—Screening): Federatie Medisch Specialisten. https://richtlijnendatabase.nl/richtlijn/borstkanker/screening/screeningsmiddelen/mammografie.html
7. NCCN. National Comprehensive Cancer Network (NCCN): Clinical Practice Guidelines in Oncology, Breast Cancer Screening and Diagnosis. https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf
8. NICE. National Institute for Health and Care Excellence (NICE). Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. https://www.nice.org.uk/guidance/cg164/resources/familial-breast-cancer-classification-care-and-managing-breast-cancer-and-related-risks-in-people-with-a-family-history-of-breast-cancer-pdf-35109691767493
9. Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. *Ann Intern Med*. 2008;148(9):671-679.
10. Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med*. 2004;351(5):427-437. doi:10.1056/NEJMoa031759
11. Carmichael H, Matsen C, Freer P, et al. Breast cancer screening of pregnant and breastfeeding women with BRCA mutations. *Breast Cancer Res Treat*. 2017;162(2):225-230.
12. Patuleia SIS, Hagenaars SC, Moelans CB, et al. Lessons learned from setting up a prospective, longitudinal, multicenter study with women at high risk for breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2021;30(3):441-449. doi:10.1158/1055-9965.EPI-20-0770
13. Hagenaars SC, Dekker LJM, Ravesteijn B, et al. Longitudinal serum protein analysis of women with a high risk of developing breast cancer reveals large interpatient versus small Intrapatient variations: first results from the TESTBREAST study. *Int J Mol Sci*. 2022;23(20):12399.
14. Steenbeek MP, van Bommel MHD, int Hout J, et al. TUBectomy with delayed oophorectomy as an alternative to risk-reducing salpingo-oophorectomy in high-risk women to assess the safety of prevention: the TUBA-WISP II study protocol. *Int J Gynecol Cancer*. 2023;33(6):982-987. doi:10.1136/ijgc-2023-004377
15. RIVM (Dutch National Institute for Public Health and the Environment). Breast cancer in the Netherlands. https://www.rivm.nl/en/breast-cancer-screening-programme/breast-cancer-in-netherlands
16. Balmaña J, Díez O, Rubio IT, Cardoso F. BRCA in breast cancer: ESMO clinical practice guidelines. *Ann Oncol*. 2011;22:20-22.
17. Peelen T, van Vliet M, Petrij-Bosch A, et al. A high proportion of novel mutations in BRCA1 with strong founder effects among Dutch and Belgian hereditary breast and ovarian cancer families. *Am J Hum Genet*. 1997;60(5):1041-1049.
18. Metcalfe KA, Narod SA. Breast cancer prevention in women with a BRCA1 or BRCA2 mutation. *Open Med*. 2007;1(3):e184-90.
19. Meijers-Heijboer H, van Geel B, Putten WL, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med*. 2001;345(3):159-164. doi:10.1056/NEJM200107193450301
20. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE study group. *J Clin Oncol*. 2004;22(6):1055-1062. doi:10.1200/JCO.2004.04.188
21. FMS. Erfelijk en Familiair Ovariumcarcinoom (Hereditary and Familial Ovarian cancer): Federatie Medisch Specialisten. https://richtlijnendatabase.nl/richtlijn/erfelijk_en_familiair_ovariumcarcinoom/erfelijk_en_familiair_ovariumcarcinoom_algemeen.html

22. Kotsopoulos J, Gronwald J, Karlan BY, et al. Hormone replacement therapy after oophorectomy and breast cancer risk among BRCA1 mutation carriers. *JAMA Oncol*. 2018;4(8):1059-1065.
23. Parker PA, Peterson SK, Shen Y, et al. Prospective study of psychosocial outcomes of having contralateral prophylactic mastectomy among women with nonhereditary breast cancer. *J Clin Oncol*. 2018;36(25):2630-2638.
24. Terra L, Hooning MJ, Heemskerk-Gerritsen BAM, et al. Long-term morbidity and health after early menopause due to oophorectomy in women at increased risk of ovarian cancer: protocol for a Nationwide cross-sectional study with prospective follow-up (HARMOny study). *JMIR Res Protoc*. 2021;10(1):e24414.
25. Alves-Nogueira AC, Melo D, Carona C, Figueiredo-Dias M. The psychosocial impact of the decision to undergo risk-reducing Salpingo-oophorectomy surgery in BRCA mutation carriers and the role of physician-patient communication. *Curr Oncol*. 2023;30(2):2429-2440.
26. Philp L, Alimena S, Ferris W, et al. Patient reported outcomes after risk-reducing surgery in patients at increased risk of ovarian cancer. *Gynecol Oncol*. 2022;164(2):421-427.
27. Basu NN, Hodson J, Chatterjee S, et al. The Angelina Jolie effect: contralateral risk-reducing mastectomy trends in patients at increased risk of breast cancer. *Sci Rep*. 2021;11(1):2847.
28. Julian-Reynier CM, Bouchard LJ, Evans DG, et al. Women's attitudes toward preventive strategies for hereditary breast or ovarian carcinoma differ from one country to another: differences among English, French, and Canadian women. *Cancer*. 2001;92(4):959-968. doi:10.1002/1097-0142(20010815)92:4
29. den Heijer M, van Asperen CJ, Harris H, et al. International variation in physicians' attitudes towards prophylactic mastectomy: comparison between France, Germany, The Netherlands and the United Kingdom. *Eur J Cancer*. 2013;49(13):2798-2805.
30. Dorling L, Carvalho S, Allen J, et al. Breast cancer risk genes - association analysis in more than 113,000 women. *N Engl J Med*. 2021;384(5):428-439. doi:10.1056/NEJMoa1913948
31. Khurana KK, Loosmann A, Numann PJ, Khan SA. Prophylactic mastectomy: pathologic findings in high-risk patients. *Arch Pathol Lab Med*. 2000;124(3):378-381.
32. Choi YH, Terry MB, Daly MB, et al. Association of Risk-Reducing Salpingo-Oophorectomy with Breast Cancer Risk in women with BRCA1 and BRCA2 pathogenic variants. *JAMA Oncol*. 2021;7(4):585-592. doi:10.1001/jamaoncol.2020.7995
33. Stuursma A, van der Vegt B, Jansen L, Berger LPV, Mourits MJE, de Bock GH. The effect of risk-reducing Salpingo-oophorectomy on breast cancer incidence and histopathological features in women with a BRCA1 or BRCA2 germline pathogenic variant. *Cancers (Basel)*. 2023;15(7):2095.
34. Mavaddat N, Antoniou AC, Mooij TM, et al. Risk-reducing salpingo-oophorectomy, natural menopause, and breast cancer risk: an international prospective cohort of BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res*. 2020;22(1):8. doi:10.1186/s13058-020-1247-4
35. Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ, et al. Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. *J Natl Cancer Inst*. 2015;107(5):33.
36. Hendrick RE, Monticciolo DL, Biggs KW, Malak SF. Age distributions of breast cancer diagnosis and mortality by race and ethnicity in US women. *Cancer*. 2021;127(23):4384-4392.
37. S S, B R, S S, MAT-L M. Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173 797 patients. *BMJ*. 2015;351:h4901. doi:10.1136/bmj.h4901
38. Plasilova ML, Hayse B, Killelea BK, Horowitz NR, Chagpar AB, Lannin DR. Features of triple-negative breast cancer: analysis of 38,813 cases from the national cancer database. *Medicine (Baltimore)*. 2016;95(35):e4614.
39. Yeh J, Chun J, Schwartz S, et al. Clinical characteristics in patients with triple negative breast cancer. *Int J Breast Cancer*. 2017;2017:1796145.
40. Mavaddat N, Barrowdale D, Andrulis IL, et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the consortium of investigators of modifiers of BRCA1/2 (CIMBA). *Cancer Epidemiol Biomarkers Prev*. 2012;21(1):134-147. doi:10.1158/1055-9965.EPI-11-0775
41. Carver T, Hartley S, Lee A, et al. CanRisk tool-a web Interface for the prediction of breast and ovarian cancer risk and the likelihood of carrying genetic pathogenic variants. *Cancer Epidemiol Biomarkers Prev*. 2021;30(3):469-473.
42. Tüchler A, De Pauw A, Ernst C, et al. Clinical implications of incorporating genetic and non-genetic risk factors in CanRisk-based breast cancer risk prediction. *Breast*. 2024;73:103615.
43. Pijpe A, Andrieu N, Easton DF, et al. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK). *BMJ*. 2012;345:e5660.
44. Miglioretti DL, Lange J, van den Broek JJ, et al. Radiation-induced breast cancer incidence and mortality from digital mammography screening: a modeling study. *Ann Intern Med*. 2016;164(4):205-214.
45. Phi XA, Saadatmand S, De Bock GH, et al. Contribution of mammography to MRI screening in BRCA mutation carriers by BRCA status and age: individual patient data meta-analysis. *Br J Cancer*. 2016;114(6):631-637.
46. Buist DSM, Porter PL, Lehman C, Taplin SH, White E. Factors contributing to mammography failure in women aged 40–49 years. *JNCI: Journal of the National Cancer Institute*. 2004;96(19):1432-1440.
47. Mandelson MT, Oestreicher N, Porter PL, et al. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst*. 2000;92(13):1081-1087.
48. Gilliland FD, Joste N, Stauber PM, et al. Biologic characteristics of interval and screen-detected breast cancers. *J Natl Cancer Inst*. 2000;92(9):743-749. doi:10.1093/jnci/92.9.743
49. IGJ. Quality of breast cancer screening sufficient, but under pressure (Health and Youth Care Inspectorate; Inspectie Gezondheidszorg en Jeugd [IGJ]). https://www.igj.nl/publicaties/rapporten/2024/07/16/kwaliteit-uitvoering-bevolkingsonderzoek-borstkanker-voldoende-maar-onder-druk.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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