Breast Cancer Research and Treatment (2019) 173:727–733
https://doi.org/10.1007/s10549-018-5039-9

EPIDEMIOLOGY

The intron 3 16 bp duplication polymorphism of p53 (rs17878362) is not associated with increased risk of developing triple-negative breast cancer

Brianna C. Morten[1,2] · Simon Chiu[3] · Christopher Oldmeadow[3,4] · Jan Lubinski[5] · Rodney J. Scott[1,2,6] · Kelly A. Avery-Kiejda[1,2]

Received: 11 July 2018 / Accepted: 2 November 2018 / Published online: 14 November 2018

Abstract

Purpose Very little is known about the genetic risk factors associated with triple-negative breast cancer (TNBC), an aggressive clinical subtype characterised by the absence of ER, PR and HER2. p53, the tumour suppressor gene, is essential for maintaining genomic stability in response to cellular stress. In breast cancer, the mutation rates of *TP53* vary depending on the subtype, such that ER-negative tumours have a high rate, and in ER-positive tumours they are less common. Previous studies have implicated the intronic polymorphism in *TP53* (rs17878362; or PIN3) with an increased risk of developing breast cancer, although little has been discerned on its prevalence in different subtypes. In this study, we investigated the prevalence of the PIN3 genotype in the blood of cohorts with ER-positive and the ER-negative subtype TNBC, and assessed its association with outcome.

Methods We genotyped 656 TNBC and 648 ER-positive breast cancer patients, along with 436 controls, and compared the prevalence of polymorphism rs17878362 in these cohorts.

Results We found there to be no differences in the prevalence of the PIN3 genotype between the ER-positive and TNBC cohorts. Furthermore, no statistically significant difference was observed in the outcome of patients in either cohort with respect to their PIN3 genotype.

Conclusions Taken together, our results do not support an association of the PIN3 genotype with increased breast cancer risk, either in ER-positive or ER-negative patients.

Keywords p53 · rs17878362 · Breast cancer · Risk factor · TNBC

Introduction

Breast cancer is the most common cancer in women worldwide, and it is responsible for the second-highest number of cancer-related mortalities [1]. It is a highly heterogeneous

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10549-018-5039-9) contains supplementary material, which is available to authorised users.

✉ Kelly A. Avery-Kiejda
Kelly.Kiejda@newcastle.edu.au

[1] Centre for Information Based Medicine, Hunter Medical Research Institute, New Lambton Heights, NSW, Australia

[2] Priority Research Centre for Cancer Research, Innovation and Translation, School of Biomedical Sciences and Pharmacy, Faculty of Health and Medicine, The University of Newcastle, Callaghan, NSW, Australia

[3] CREDITSS—Clinical Research Design, Information Technology and Statistical Support Unit, Hunter Medical Research Institute, New Lambton Heights, NSW, Australia

[4] School of Medicine and Public Health, The University of Newcastle, Callaghan, NSW, Australia

[5] Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland

[6] Pathology North, John Hunter Hospital, Newcastle, NSW, Australia

disease that can be classified into a number of different subtypes, based on the expression of key hormone receptors for estrogen (ER), progesterone (PR) and human epidermal growth factor (HER2) [2]. Two-thirds of breast cancers are diagnosed as ER-positive and have a favourable prognosis, while a smaller proportion (10–20%) of breast cancers lack expression of the hormone receptors ER, PR and HER2, and are known as triple-negative breast cancer (TNBC) [3]. This particularly aggressive subtype has an increased likelihood of the development of distant metastasis and death within 5 years of diagnosis [4]. There is very little known about the genetic risk factors associated with the development of TNBC and the ability to estimate the risk of developing this aggressive breast cancer subtype may improve breast cancer outcomes.

The tumour suppressor gene *TP53* is an important transcription factor that is crucial for the response to DNA damage and maintenance of genomic stability. It is activated by a variety of cellular stressors that allow it to induce its tumour suppressive functions including cell cycle arrest, senescence, DNA repair or apoptosis [5]. Its importance as a key regulator of genetic integrity is highlighted by its germline mutation in Li-Fraumeni Syndrome (LFS), an inherited familial predisposition to a wide variety of cancers, particularly breast cancer, and its high mutation rate in human cancers [6]. In breast cancer, the somatic mutation rate of *TP53* is variable in distinct breast cancer subtypes [7]. *TP53* mutations are rare in ER-positive breast cancers (12% and 29% in luminal A and B, respectively), but are common in ER-negative tumours (HER2-enriched 72% and basal-like 80%) [8].

In addition to mutations, numerous polymorphisms have been identified in the coding and noncoding regions of *TP53*, some of which are associated with cancer risk and that can alter the function of p53. Namely, the single-nucleotide polymorphism (SNP) at residue 72 in exon 4 (R72P; rs1042522) has been shown that R72 greatly induces p53-dependent apoptosis *in vitro*, compared to the P72 variant [9]. The most well-characterised noncoding polymorphism is a 16 bp duplication (−5′ACCTGGAGGGCT GGGG3′; A1 = one copy; A2 = two copies) in intron 3 of the *TP53* gene (polymorphism in intron 3, PIN3; rs17878362) [10]. There is some suggestion that PIN3 may be useful as a prognostic indicator in breast cancer. In a study on breast cancer tissues, Hrstka et al. found an association between the A2 allele and lymph node positivity, suggesting that the A2 allele is associated with a more aggressive breast cancer phenotype [11]. In contrast, our own studies have shown that patients whose tumours possessed the A2/A2 allele had significantly better disease-free survival [12].

Meta-analyses investigating rs17878362 in the germline have identified an increased risk of developing breast cancer in carriers of the A2 allele [13–16]. However, there are inconsistencies between studies based on different geographical locations and ethnic groups, or associations between familial or sporadic breast cancer [17, 18]. Hormone receptor status may also account for some of the differences, but this has not been investigated.

Despite the discrepancies between analyses of rs17878362 and breast cancer risk, it is not known if the polymorphism can alter the risk of developing ER-negative breast cancer and, in particular, TNBC, which has the highest rate of *TP53* mutations amongst the breast cancer subtypes. The aim of this study was to determine the association of the rs17878362 polymorphism with the risk of developing TNBC compared to ER-positive breast cancers.

Materials and methods

Study cohort

DNA was extracted from the blood of 361 TNBC patients and 648 ER-positive breast cancers supplied by the Australian Breast Cancer Tissue Bank (Darcy Rd, Westmead, New South Wales, Australia). In addition, DNA was also extracted from the blood of 295 TNBC patients and was provided by the Department of Genetics and Pathology, Pomeranian Medical University (Szczecin, Poland). This study was approved by the local institutional ethics review committee for participation in this study. Additional 436 control samples were also included using DNA extracted from the blood of participants with no known history of breast cancer, recruited from 2004 to 2005 for the Hunter Community Study. This study complies with the 1964 Helsinki Declaration with ethical approval from the Hunter New England Human Research Ethics Committee (Approval number: 09/05/20/5.01). All patients have consented to their blood and clinical information being used in this study.

Genotyping of rs17878362

The 16 bp duplication in intron 3 of *TP53* (PIN3; rs17878362) was genotyped using the PCR-based fragment length polymorphism method, as previously described [19]. The primers were designed to target the 16 bp duplication in intron 3 of TP53, as previously described [19]. Briefly, 50 ng of genomic DNA was amplified using 2X SYBR green PCR master mix (Applied Biosystems), 5 µM forward and reverse primers targeting rs17878362, and nuclease-free water to a total volume of 11 µl. Amplification was performed using a 7500 real-time PCR system (Applied Biosystems), using the cycle conditions of 95 °C for 10 min for 1 cycle, and 95 °C for 15 s and 56 °C for 60 s for 40 cycles. Following amplification, the fragmented DNA was separated by electrophoresis on a 4% agarose gel and visualised by UV light following GelGreen staining (Gene Target Solutions, NSW,

Australia). The allele homozygous for no duplication (A1/A1) depicted a 119 bp fragment, heterozygous for the duplication (A1/A2) showed a 119 bp fragment and a 135 bp fragment, and the allele homozygous for the duplication (A2/A2) depicted a 135 bp fragment only (Online Resource 1, Supplementary Fig. 1).

Sequencing of TP53 fragment

To confirm genotyping results, the fragmented DNA from 10% of the genotyped cases and controls was sequenced by dideoxy sequencing as previously described [20].

Statistical analysis

Power calculations were assessed using Quanto (Version 1.2.4, May 2009, University of Southern California Biostats, USA). We calculated that with our 436 controls and 656 TNBC cases, we would have 80% power at $p=0.05$ to detect a 3% difference between the groups, assuming a type 1 error rate of 0.05 ($\alpha=0.05$) and a type II error rate of 0.2 ($1-\beta=0.8$) with a minor allele frequency of 6.5%. Therefore, our study has enough statistical power to determine differences in risk greater than 3%, and provide statistically significant results with increased risk defined as an odds ratio (OR) > 2. Hardy–Weinberg Equilibrium was calculated in the control groups using a goodness of fit χ^2 test. The genotype frequencies in these populations fit the Hardy–Weinberg Equilibrium (Online Resource 1, Supplementary Table 1). All statistical analyses were performed as previously described [19]. Briefly, the genotype frequencies of the PIN3 polymorphism were compared in cases and controls using Chi-squared (χ^2) analysis and ORs and 95% confidence intervals (CI) were calculated using unconditional logistic regression and multinomial regression for "by cancer type" outcomes. Population subsets and age-adjusted regression models were assessed as a sensitivity analysis; there was no change to crude genetic effect. *T* tests were used to determine the differences in the age at diagnosis of the different breast cancer subtypes by their genotype. Kaplan–Meier plots and Cox proportional hazards models were used to assess the differences in breast cancer-specific hazards. The time period used to assess survival was defined as the time between a patient's first breast cancer event and death or follow-up. Survival time was censored at 10-year follow-up. Fine and Gray's competing risk models were used to assess cancer-specific survival, and the significance levels of all tests were set at $p<0.05$ (two-sided) and corrected for multiple comparisons using the Bonferroni method.

Results

Prevalence of the PIN3 genotype in the germline of ER-positive and triple-negative breast cancer

All TNBC and ER-positive breast cancer cases ($n=656$ and 648, respectively) and controls ($n=436$) were analysed for their PIN3 (rs17878362) genotype: A1/A1 (0/0; no duplication), A1/A2 (0/16; heterozygous for the duplication) and A2/A2 (16/16; the duplication is present). The clinical characteristics of the participants used in this study, including age at diagnosis, tumour grade, breast cancer subtype, outcome and their PIN3 genotypes, are shown in Tables 1 and 2. The TNBC patient cohort consisted of two populations, one sourced from the Australian Breast Cancer Tissue Bank (ABCTB) and a Polish cohort. In all cases, the mean and median age was assessed and compared between the cases and controls (Tables 1, 2).

Table 1 shows that there was a significant difference in age between the cases and controls (mean age Controls = 68.49, TNBC = 57.58, ER-positive = 58.90; $p<0.0001$). Within the cases, there were significantly more high-grade tumours (87% of TNBCs were GA or Grade 3, whereas 66% of ER-positive were grade 3, $p<0.0001$) and deaths (9.6% of cases in TNBC versus 3.9% in ER-positive cases, $p<0.0001$), in TNBC patients, when compared to those that were ER-positive (Table 1). There was no significant difference in the PIN3 genotype between ER-positive and TNBC cases or controls (Table 1). Additionally, no significant differences were observed between the Australian and Polish TNBC cohorts (Online Resource 1, Supplementary Table 2).

Table 2 shows a summary crossed by genotype, and no significant differences were observed.

Association of the PIN3 genotype with breast cancer risk

To test for an association of the PIN3 genotype with ER-positive and triple-negative breast cancer subtypes, a logistic regression analysis was performed using an additive model of allelic distribution. While there was a trend for decreasing risk with the addition of alleles in ER-positive disease (OR 0.921; 95% CI 0.716–1.184), and a small increase in risk (OR 1.041; 95% CI 0.814–1.331) with the addition of alleles in TNBC cases, these differences were not significant ($p=0.5548$, Table 3). Logistic regression analysis confirmed that there was no population bias (Online Resource 1, Supplementary Table 3).

Table 1 Comparison of clinical information between different breast cancer subtypes and controls

Variable	Control ($n=436$)	TNBC ($n=656$)	ER+ ($n=648$)	Total ($N=1740$)	p value
Age					
Mean (SD)	68.49 (7.36)	57.58 (12.87)	58.90 (13.15)	60.80 (12.66)	< 0.0001
Median (min, max)	69 (55, 86)	58 (26, 90)	59 (25, 95)	61 (25, 95)	
Death					
Alive		593 (90%)	623 (96%)	1216 (93%)	< 0.0001
Dead		63 (9.6%)	25 (3.9%)	88 (6.7%)	
Missing	436	0	0	0	
Genotype					
0/0	325 (75%)	488 (74%)	498 (77%)	1311 (75%)	0.6956
0/16	104 (24%)	152 (23%)	137 (21%)	393 (23%)	
16/16	7 (1.6%)	16 (2.4%)	13 (2.0%)	36 (2.1%)	
Missing	0	0	0	0	
Tumour grade					
Control	436 (100.0%)			436 (25%)	< 0.0001
G1		2 (0.3%)	51 (7.9%)	53 (3.1%)	
G2		84 (13%)	172 (27%)	256 (15%)	
G3		436 (68%)	425 (66%)	861 (50%)	
GA		122 (19%)		122 (7.1%)	
Missing	0	12	0	12	

ABCTB Australian Breast Cancer Tissue Bank, *TNBC* triple-negative breast cancer, *ER+* ER-positive, *G1-3* Grade, *GA* Grade alternative

Association of the PIN3 genotype with breast cancer survival

Next, survival analysis was performed to determine if the addition of PIN3 was indicative of worse disease-free survival in ER-positive or TNBC patients. The two genotypes that were identified were 0/0 and the combination of one allele or more (0/16 or 16/16). Kaplan–Meier survival plots demonstrated no significant difference in survival outcomes of patients with ER-positive, TNBC or a combination of the two breast cancer subtypes and the PIN3 genotype (Fig. 1). The hazard ratios are shown in Table 4.

Discussion

Breast cancer is a heterogeneous disease that consists of a number of different pathological subtypes. These different subtypes can be classified as being either ER-positive (Luminal subtypes) or ER-negative (TNBC, basal, HER2+). ER-positive breast cancers have a favourable outcome due to the effectiveness of targeted therapies such as Tamoxifen, while the ER-negative breast cancer, TNBC, is an aggressive subtype with poor prognosis. As such, understanding the mechanisms which drive the development of particular subtypes of breast cancer is crucial to improving survival outcomes.

Meta-analyses have previously shown that the 16/16 genotype is significantly associated with an increased risk of developing breast cancer. He et al. (2011) showed an increase in breast cancer risk using either a dominant (OR 1.14, 95% CI 1.02–1.27, p 0.017), recessive (OR 1.61, 95% CI 1.21–2.25, $p=0.001$) or additive model (OR 1.66, 95% CI 1.24–2.21, $p=0.001$,) in 3,700 cases compared to 3,332 controls [14]. This was confirmed by Wu et al. (2013) who summarised 19 studies. They found better stratification using large sample sizes (> 500 subjects, dominant model: OR 1.52, 95% CI 1.11–2.08; recessive model: OR 1.49, 95% CI 1.10–2.03), and significant differences were identified using a dominant model (OR 1.21, 95% CI 1.03–1.41, $p=0.001$) but not a recessive model (OR 1.28, 95% CI 0.87–1.89) in their meta-analyses [15]. Sagne et al. (2013) found a slight, but significant increased breast cancer risk in heterozygotes (OR 1.18, 95%, CI 1.02–1.37, $p<0.01$), with no altered breast cancer risk in homozygotes (OR 1.41, 95% CI 0.97–2.06) [13]. Furthermore, these meta-analyses showed that the OR was dependent on ethnicity, tending to be lower in populations of European origin, and no differences were observed based on the familial or sporadic origin of the disease [13–15].

In contrast, we did not find an association between the PIN3 genotype and either ER-positive breast cancers or

Table 2 Association of PIN3 genotypes with breast cancer subtype risk

Variable	Genotype				
	0/0 ($n=1311$)	0/16 ($n=393$)	16/16 ($n=36$)	Total ($N=1740$)	p value
Age					
Mean (SD)	60.81 (12.67)	61.04 (12.68)	58.03 (12.04)	60.80 (12.66)	0.3943
Median (min, max)	61 (26, 95)	62 (25, 90)	59 (32, 79)	61 (25, 95)	
Cohort					
Polish	220 (17%)	65 (17%)	10 (28%)	295 (17%)	0.2153
Australian	1091 (83%)	328 (83%)	26 (72%)	1445 (83%)	
Missing	0	0	0	0	
Cancer type					
Control	325 (25%)	104 (26%)	7 (19%)	436 (25%)	0.6956
ER+	498 (38%)	137 (35%)	13 (36%)	648 (37%)	
TNBC	488 (37%)	152 (39%)	16 (44%)	656 (38%)	
Missing	0	0	0	0	
Data source					
ABCTB TNBC	268 (20%)	87 (22%)	6 (17%)	361 (21%)	0.5606
Control	325 (25%)	104 (26%)	7 (19%)	436 (25%)	
ABCTB ER+	498 (38%)	137 (35%)	13 (36%)	648 (37%)	
Polish TNBC	220 (17%)	65 (17%)	10 (28%)	295 (17%)	
Missing	0	0	0	0	
Death					
Alive	917 (93%)	271 (94%)	28 (97%)	1216 (93%)	0.6964
Dead	69 (7.0%)	18 (6.2%)	1 (3.4%)	88 (6.7%)	
Missing	325	104	7	436	
Tumour grade					
Control	325 (25%)	104 (27%)	7 (19%)	436 (25%)	0.4691
G1	44 (3.4%)	9 (2.3%)		53 (3.1%)	
G2	193 (15%)	55 (14%)	8 (22%)	256 (15%)	
G3	652 (50%)	193 (49%)	16 (44%)	861 (50%)	
GA	87 (6.7%)	30 (7.7%)	5 (14%)	122 (7.1%)	
Missing	10	2	0	12	

ABCTB Australian Breast Cancer Tissue Bank, *TNBC* triple-negative breast cancer, *ER+* ER-positive, *G1-3* Grade, *GA* Grade alternative

Table 3 Logistic regression with an additive model in all breast cancers, ER-positive or TNBC cases

Model	Outcome	Odds ratio estimate	Odds ratio		Type 3 Test		
			Lower 95% confidence limit for odds ratio	Upper 95% confidence limit for odds ratio	Wald Chi-square	P value	R^2
Cancer	Any Cancer	0.981	0.786	1.225	0.0286	0.8658	0.0001
Cancer type	ER+	0.921	0.716	1.184	1.1784	0.5548	0.0001
	TNBC	1.041	0.814	1.331			

ER+ ER-positive, *TNBC* triple-negative breast cancer

p value: based on an additive assumption model relative to the 0/0 genotype

TNBC. Furthermore, there was no significant association of the 16/16 genotype with breast cancer, regardless of ER expression. In our analyses, we used an additive model of allelic distribution, which was used in previous meta-analyses and is not likely to be the cause of the lack of association found in this study. A major confounding factor affecting the PIN3 polymorphism distribution is the geographical origin of the cohort and ethnicity. We

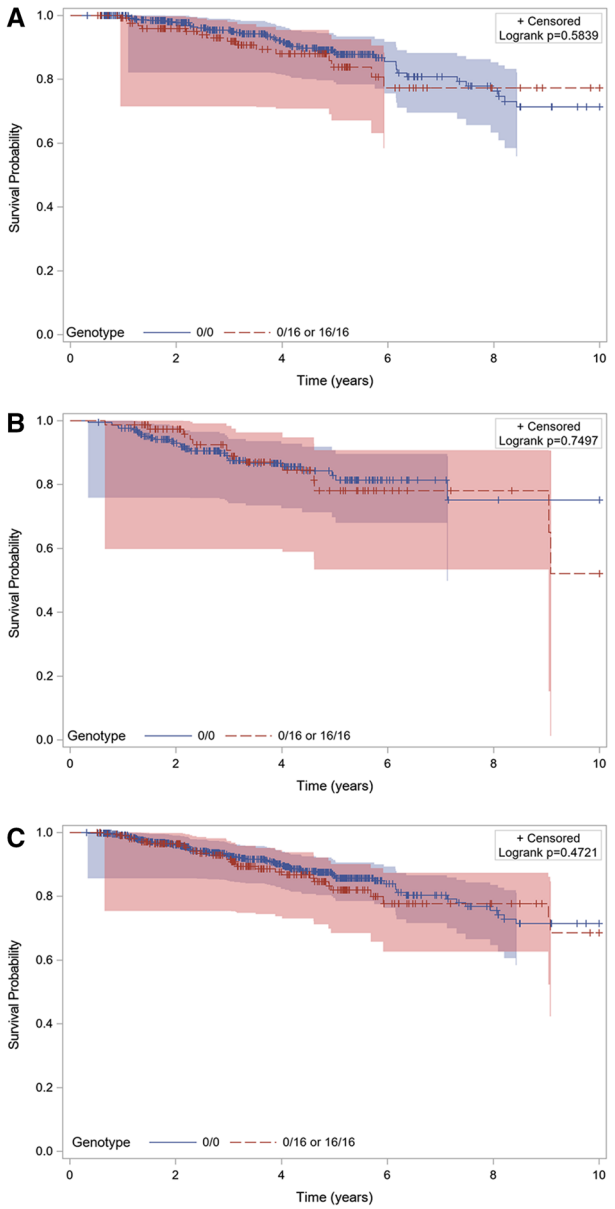

Fig. 1 Kaplan–Meier plot of overall survival in different breast cancer subtypes between the two genotype categories (0/0 and 0/16 or 16/16). **a** ER-positive cohort ($n=648$), **b** TNBC Australian cohort ($n=361$), **c** combined breast tumour cohorts (Australian cohorts only; $n=1009$)

were unable to ascertain sufficient ethnic information for our breast cancer cohorts, and as such this could not be accounted for during analysis, and may provide one reason for the discrepancy between our results and others. Additionally, our study may have been underpowered to observe the small albeit significant effects that have been seen in larger meta-analyses [13–15].

Hrstka et al. [11] reported an association between PIN3 in tumour tissues and lymph node positivity ($p=0.0193$, χ^2 test), suggesting that it may be implicated in tumour progression or survival. Our previous studies have suggested an association of somatic PIN3 genotypes with better breast cancer outcomes [OR 5.590; 95% CI 0.9656–8.217, $p=0.0586$ (Log-rank), $p=0.0427$ (Gehan-Breslow)] [12]. However, in the current study, we did not observe any differences in risk between the genotypic frequencies and the more aggressive TNBC, and no association between allelic frequencies with overall survival. This is supported by other reports that also showed no association between the PIN3 genotypic frequencies and different breast cancer clinical features [21]. This may be in part to these studies investigating the frequency of the polymorphism in tumour DNA, not the genomic DNA from whole blood.

Taken together, our results do not support an association of the PIN3 genotype with increased breast cancer risk, either in ER-positive or ER-negative patients. This suggests that the addition of the polymorphic allele may be an acquired change during tumour progression, but that it may not be a necessary determinant of tumour development. Further studies in larger cohorts are required to confirm these results.

Table 4 Cox Proportional model of the effects between genotypes

Model[a]	Label	95% Confidence Interval			
		Hazard ratio	Lower	Upper	*P* value
Combined	Genotype 0/16 or 16/16	1.119	0.725	1.725	0.6118
TNBC	Genotype 0/16 or 16/16	1.081	0.559	2.088	0.8174
ER+	Genotype 0/16 or 16/16	1.158	0.651	2.060	0.6180

P value: compared to patients with 0/0 genotype

TNBC triple-negative breast cancer, *ER+* ER-positive

[a]All models adjusted for age, combined model adjusted for breast cancer cohorts

Acknowledgements The authors would like to thank the Australian Breast Cancer Tissue Bank (ABCTB) for providing the DNA extracted from the blood of breast cancer patients.

Funding This study was funded by the Hunter Medical Research Institute Bloomfield Group Foundation Grants (HMRI 13-02 (KAK), HMRI 12-08 (KAK)); the National Breast Cancer Foundation Collaborative Breast Cancer Research Program Grant (RJS); the Hunter Cancer Research Alliance; the Australian Postgraduate Award (BCM) and the Hunter Medical Research Institute MM Sawyer Scholarship (HMRI 11-39) (to BCM). The funding source had no role in study design; the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of all institutional and/or national research committees, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136(5):E359–E386. https://doi.org/10.1002/ijc.29210
2. Carey L, Winer E, Viale G, Cameron D, Gianni L (2010) Triple-negative breast cancer: disease entity or title of convenience? Nat Rev Clin Oncol 7(12):683–692. https://doi.org/10.1038/nrclinonc.2010.154
3. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, Lickley LA, Rawlinson E, Sun P, Narod SA (2007) Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 13(15 Pt 1):4429–4434. https://doi.org/10.1158/1078-0432.CCR-06-3045
4. Podo F, Buydens LM, Degani H, Hilhorst R, Klipp E, Gribbestad IS, Van Huffel S, van Laarhoven HW, Luts J, Monleon D, Postma GJ, Schneiderhan-Marra N, Santoro F, Wouters H, Russnes HG, Sorlie T, Tagliabue E, Borresen-Dale AL, Consortium F (2010) Triple-negative breast cancer: present challenges and new perspectives. Mol Oncol 4(3):209–229. https://doi.org/10.1016/j.molonc.2010.04.006
5. Aubrey BJ, Strasser A, Kelly GL (2016) Tumor-Suppressor Functions of the TP53 Pathway. Cold Spring Harb Perspect Med 6 (5). https://doi.org/10.1101/cshperspect.a026062
6. Olivier M, Hollstein M, Hainaut P (2010) TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol 2(1):a001008. https://doi.org/10.1101/cshperspect.a001008
7. Olivier M, Langerod A, Carrieri P, Bergh J, Klaar S, Eyfjord J, Theillet C, Rodriguez C, Lidereau R, Bieche I, Varley J, Bignon Y, Uhrhammer N, Winqvist R, Jukkola-Vuorinen A, Niederacher D, Kato S, Ishioka C, Hainaut P, Borresen-Dale AL (2006) The clinical value of somatic TP53 gene mutations in 1,794 patients with breast cancer. Clin Cancer Res 12(4):1157–1167. https://doi.org/10.1158/1078-0432.CCR-05-1029
8. Cancer Genome Atlas N (2012) Comprehensive molecular portraits of human breast tumours. Nature 490(7418):61–70. https://doi.org/10.1038/nature11412
9. Dumont P, Leu JIJ, Della Pietra AC, George DL, Murphy M (2003) The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. Nat Genet 33(3):357–365. https://doi.org/10.1038/ng1093
10. Lazar V, Hazard F, Bertin F, Janin N, Bellet D, Bressac B (1993) Simple sequence repeat polymorphism within the p53 gene. Oncogene 8(6):1703–1705
11. Hrstka R, Beranek M, Klocova K, Nenutil R, Vojtesek B (2009) Intronic polymorphisms in TP53 indicate lymph node metastasis in breast cancer. Oncol Rep 22(5):1205–1211
12. Morten BC, Wong-Brown MW, Scott RJ, Avery-Kiejda KA (2016) The presence of the intron 3 16 bp duplication polymorphism of p53 (rs17878362) in breast cancer is associated with a low Delta40p53:p53 ratio and better outcome. Carcinogenesis 37(1):81–86. https://doi.org/10.1093/carcin/bgv164
13. Sagne C, Marcel V, Amadou A, Hainaut P, Olivier M, Hall J (2013) A meta-analysis of cancer risk associated with the TP53 intron 3 duplication polymorphism (rs17878362): geographic and tumor-specific effects. Cell Death Dis 4(2):e492. https://doi.org/10.1038/cddis.2013.24
14. He X-F, Su J, Zhang Y, Huang X, Liu Y, Ding D-P, Wang W, Arparkorn K (2011) Association between the p53 polymorphisms and breast cancer risk: meta-analysis based on case–control study. Breast Cancer Res Treat 130(2):517–529. https://doi.org/10.1007/s10549-011-1583-2
15. Wu D, Zhang Z, Chu H, Xu M, Xue Y, Zhu H, Zhang Z (2013) Intron 3 Sixteen Base Pairs Duplication Polymorphism of P53 Contributes to Breast Cancer Susceptibility: Evidence from Meta-Analysis. PLOS ONE 8(4):e61662. https://doi.org/10.1371/journal.pone.0061662
16. Costa S, Pinto D, Pereira D, Rodrigues H, Cameselle-Teijeiro J, Medeiros R, Schmitt F (2008) Importance of TP53 codon 72 and intron 3 duplication 16 bp polymorphisms in prediction of susceptibility on breast cancer. BMC Cancer 8(1):32. https://doi.org/10.1186/1471-2407-8-32
17. De Vecchi G, Verderio P, Pizzamiglio S, Manoukian S, Bernard L, Pensotti V, Volorio S, Ravagnani F, Radice P, Peterlongo P (2008) The p53 Arg72Pro and Ins16bp polymorphisms and their haplotypes are not associated with breast cancer risk in BRCA-mutation negative familial cases. Cancer Detect Prev 32(2):140–143. https://doi.org/10.1016/j.cdp.2008.06.003
18. Wang-Gohrke S, Becher H, Kreienberg R, Runnebaum IB, Chang-Claude J (2002) Intron 3 16 bp duplication polymorphism of p53 is associated with an increased risk for breast cancer by the age of 50 years. Pharmacogenetics 12(3):269–272
19. Ashton KA, Proietto A, Otton G, Symonds I, McEvoy M, Attia J, Gilbert M, Hamann U, Scott RJ (2009) Polymorphisms in TP53 and MDM2 combined are associated with high grade endometrial cancer. Gynecol Oncol 113(1):109–114. https://doi.org/10.1016/j.ygyno.2008.12.036
20. Avery-Kiejda KA, Morten B, Wong-Brown MW, Mathe A, Scott RJ (2014) The relative mRNA expression of p53 isoforms in breast cancer is associated with clinical features and outcome. Carcinogenesis 35(3):586–596. https://doi.org/10.1093/carcin/bgt411
21. Rodrigues MS, Machado CA, Pagnoncelli D, Avvad E, Paixao JC, Gallo CV (2011) TP53 and XRCC1 polymorphisms and breast cancer prognosis: a case-case study. Clinics (Sao Paulo) 66(6):1097–1100