# Supplemental Online Content

Breast Cancer Association Consortium. Pathology of tumors associated with pathogenic germline variants in 9 breast cancer susceptibility genes. *JAMA Oncol*. Published online January 27, 2022. doi:10.1001/jamaoncol.2021.6744

**eFigure 10.** Prevalence of PTV and MSV in breast cancer susceptibility genes by tumor grade among women aged ≤40 years at diagnosis with (A) grade 1 (B) grade 2 and (C) grade 3 breast cancer.
**eFigure 11.** Prevalence of PTV and MSV in breast cancer susceptibility genes by tumor grade among women aged 41-60 years at diagnosis with (A) grade 1 (B) grade 2 and (C) grade 3 breast cancer.
**eFigure 12.** Prevalence of PTV and MSV in breast cancer susceptibility genes by tumor grade among women aged >60 years at diagnosis with (A) grade 1 (B) grade 2 and (C) grade 3 breast cancer.
**eFigure 13.** Smoothed proportions of subtypes used in BOADICEA for PTVs in *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C* and *RAD51D.*

This supplemental material has been provided by the authors to give readers additional information about their work.

## eMethods

*Studies and inclusion criteria*

The BRIDGES study included samples from female breast cancer cases and unaffected controls, as described in Dorling et al.[1] and eTable 1. The analyses presented here are based on data from the subset of cases from population or hospital-based studies and controls that were sampled independently of family history (38 contributing studies). Only women aged between 18 and 79 years with no missing information on age were included.

Studies sampled controls from among women in the same population such that the age distribution was similar to that of the cases, without individual matching. Analyses were presented in terms of odds ratios (ORs). In the computation of cumulative risks were assumed to approximate incidence rate ratios: this is an approximation because density-based sampling was not used; however, the difference is slight because study recruitment was over a short period of time and the probability of a potential control becoming a case was small (the rare disease assumption).

Ethnicity was defined genetically using principal components analysis from the array genotype data where this was available, otherwise by self-report. For Malaysia and Singapore, we excluded admixed individuals, defined as not reaching a 50% threshold for a single ancestry (Chinese, Malay or Indian) based on genotyping. We also excluded individuals who were from a minority ancestry for that study (that is, non-east Asian individuals from the 4 Asian studies and non-European individuals from the European studies). Five countries were removed from imputation and subsequent regressions: France (missing Grade), Thailand, Belarus, and Canada (missing HER2 status), Cyprus (missing tumor size).

*Tumor Pathology Data*

Pathology information was based on histology and immunohistochemistry results from medical records, rescored whole slides or tumor microarrays, curated in BCAC database v12. Data obtained from individual study centers were centrally harmonized and checked according to a standard data dictionary. ER, PR and HER2 status was obtained mostly from medical records followed by immunohistochemistry performed on tumor tissue microarrays or whole-section tumor slides[2,3]. The cut-off was 10% for ER and PR for most studies; some USA based studies used a 1% cut-off. For HER2 scored by immunohistochemistry, in the majority of studies 0-2+ were categorized as negative and 3+ as positive in most studies. Some studies used FISH/CISH or SISH to confirm HER2 status. Most studies used the Bloom and Richardson (SBR) system for grading tumors. The variable 'Stage' was collated by studies individually but largely reflects TNM Staging. The European TNM staging (https://www.uicc.org/resources/tnm), which is very similar to the AJCC TNM staging, was used,. Some studies from the USA that used SEER staging, these were recoded as far as possible to TNM staging.

Patterns of missing in the pathology data are shown in eTables 5 and 6; pathology was more likely to be missing among younger women, but there was no correlation between missingness and genotype.

*Laboratory Methods, Variant calling and classification*

Details of library preparation and sequencing procedures are described in Dorling *et al.*[1] Library preparation was conducted using the Fluidigm Juno 192.24 system. Amplified products were combined into barcoded libraries of 768 samples, which were run on a single lane of an Illumina Hiseq4000. Samples were demultiplexed and then aligned to the reference genome (hg19) using BWA-MEM[4]. Each sample was sequenced to an average depth of 349 reads, in the target region. Depth, along with base quality, was used as part of the secondary quality control filtering. Variant calling was performed using VarDict[5]; further details of variant calling, filtering and quality control are given in Dorling *et al.*[1]

Variants were defined as PTVs if they were frameshifting insertions/deletions, stop-gain single nucleotide variants or canonical splice variants, with the exception of variants in the last exon of each gene and some canonical splice variants that may not be protein truncating. We also analyzed rare missense variants in *BRCA1*, *BRCA2* and *TP53* classified as pathogenic according to clinical guidelines. For *BRCA1* and *BRCA2* we considered variants classified as (likely) pathogenic using the ENIGMA *BRCA1/2* expert panel guidelines (https://enigmaconsortium.org/), or by clinical testing laboratory submitters to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) which largely employ adaptations of the American College of Medical Genetics (ACMG) guidelines[5]. For *TP53*, we considered a definition of (likely) pathogenic, based on ACMG guidelines[6], augmented by variants classified as (likely) pathogenic based on a published quantitative model for

*TP53* missense variant classification that utilizes a combination of bioinformatic prediction and the reported somatic:germline ratio for a given variant[1,7].

~80% of *CHEK2* PTVs were c.1100delC. *TP53* PTV and MSV carriers were considered together.

Five women carrying PTVs in both *BRCA1* and *BRCA2* and 11 women carrying PTVs in more than one 'non*BRCA1/2'* gene were excluded from these analyses. Women harbouring mutations in *BRCA1* or *BRCA2* plus a non-*BRCA* gene were included in the *BRCA1* and *BRCA2* analysis respectively, consistent with Dorling et al.[1] As numbers of such double mutations are very small compared with total numbers of *BRCA1* and *BRCA2* carriers, there was a trivial difference in the results when in sensitivity analyses these women excluded (data not shown). Specifically, 8 women carrying a *BRCA1* PTV and a PTV in a non*BRCA1/2* gene and one woman carrying a *BRCA1* PTV and TP53 MSV were included only in the *BRCA1* PTV analysis; 18 women carrying a *BRCA2* PTV and a PTV in a non*BRCA1/*2 gene and one woman carrying a *BRCA2* PTV and a *BRCA2* MSV were included only in the *BRCA2* PTV analysis. There was little difference in the results in sensitivity analyses of the association between intrinsic subtypes and *BRCA1* or *BRCA2* mutation status that excluded these women.

*Imputation using MICE and an EM-algorithm*

To evaluate heterogeneity of risk by intrinsic tumor subtypes, we used Multiple Imputation by Chained Equations (MICE) to impute missing pathology variables. ER, PR, HER2, grade, tumor size, lymph node involvement, country, age and the presence or absence of PTV or MSV in the BC genes were used to inform imputations. Missing data patterns and diagnostics for multiple imputation were inspected (data not shown). Intrinsic subtypes were constructed for each of 100 imputed datasets and results of multinomial regression for each imputed dataset pooled.

For some analyses, we also used a polytomous regression approach (TOP) which iteratively imputes pathology characteristics using an EM algorithm and has improved power for identifying heterogenous associations between risk loci and tumor subtypes.[8] When implementing TOP, we imputed only ER, PR, HER2 and Grade. Countries with missing information for >10 individuals for two or more tumor markers were excluded from the analyses.

MICE is the most widely used imputation method and provided the flexibility required to conduct all the analyses. The EM approach should converge to the maximum likelihood estimate, whereas the MICE approach relies on random resampling. As MICE is a well-established method with robust properties, and the results were very consistent where both methods were used, we used MICE as the standard approach.

*Estimating Odds ratios for association between PTV/MSV carrier status and intrinsic subtypes*

Multinomial logistic regression was used to estimate the odds ratios (ORs) associated with carrying any PTV (or pathogenic MSV) in each gene. Age interactions were evaluated by fitting an age x gene interaction term in the model. Subtype-specific age-interaction terms were meta-analyzed and Wald test p-values for the combined interaction ORs calculated.

*Calculation of cumulative risk of developing BC subtypes*

Cumulative risks for each subtype were calculated by combining age-specific ORs estimates with UK population incidence rates (2016) as baseline (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive), accounting for competing risk of not developing BC of a different subtype[9]. For these computations, the ORs were assumed to approximate the incidence rate ratios (i.e. the rare disease assumption). PTVs in *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C* and *RAD51D* were included in the absolute risk model. Age-specific ORs were derived by assuming a linear trend in the log(OR) with age for all subtypes apart from *ATM*, *BARD1*, *RAD51C*, and *RAD51D*. For *BRCA1, BRCA2*, and *PALB2* a model assuming the same age-trend in each subtype was assumed. For *CHEK2* triple-negative disease no age interaction was assumed, while for all other subtypes the model assumed the same age-trend in each subtype. Where the same age-trend was assumed, the effect size based on a (fixed-effect) meta-analysis of these subtype-specific age-interaction estimates was used. The interaction effect size was included in multinomial logistic regression as an offset term to obtain the corresponding main effects coefficients.

*Age- and gene-specific subtype proportions for BOADICEA*

For analyses carried out for inclusion of tumor subtypes in the BOADICEA risk prediction algorithm[10], the three subtypes currently considered: i) ER-positive ii) triple-negative, and iii) ER-negative but not triple-negative, were used. Age- and gene-specific subtype proportions for each tumor subtype in BOADICEA (eTable 14) were calculated by first estimating ORs for PTV carriers and the respective age-interactions for each subtype as described above. These estimates are relative to non-carriers of deleterious variants of any of the genes. Therefore, the corresponding relevant baseline subtype proportions were the proportions in non-carriers. For this, we used the non-carrier proportions in European cases in the BRIDGES analysis, to allow for possible differences in subtype proportions by ethnicity (the OR estimates were, however, from the whole dataset as there is no evidence for differences in effect size by population).

Subtype proportions were first computed in 5-year intervals, and then smoothed using Lowess, with a bandwidth of 0.2, for ER-positive, triple-negative and ER-negative non- triple-negative separately. These estimates were then further smoothed to annual proportions by assuming a linear change in proportion between the midpoint of each interval.

The proportions in each subtype were finally derived using the formula:

$$P_{sg}(t) = \frac{\lambda_{sg}(t)}{\sum_{s'} \lambda_{s'g}(t)}$$

$$= \frac{\lambda_{s0}(t) r_{sg}(t)}{\sum_{s'} \lambda_{s'0}(t)\, r_{s'g}(t)}$$

$$P_{sg}(t) = \frac{P_{s0}(t) r_{sg}(t)}{\sum_{s'} P_{s'0}(t)\, r_{s'g}(t)}$$

Where $P_{sg}(t)$ is the proportion of cases at time t in subtype s, $\lambda_{sg}(t)$ is the incidence of subtype s for gene g at time t and $r_{sg}(t)$ is the relative risk (OR) at time t, relative to gene category 0 (i.e. non-carriers).

## eTable1. Description of studies included in the analyses

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Amsterdam Breast Cancer Study | ABCS | Netherlands | Hospital-based consecutive cases; population-based controls (for iCOGS/OncoArray/BRIDGES from blood bank). | iCOGS/OncoArray/BRIDGES: Breast cancer patients diagnosed before age 50 in 1995-2011 at the Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital (NKI-AVL). | 992 | iCOGS/OncoArray/BRIDGES: Population-based cohort of women recruited through the Sanquin blood bank, all ages. | 1408 | No | Mixed | [11,12] |
| Asia Cancer Program | ACP | Thailand | Hospital-based case-control study | Cases recruited 1999-2000 and 2008-present at The National Cancer Institute (Central region), The Prince Songkla University Research Centre (South region), The HRH Princess Maha Chakri Sirindhorn Medical Centre (MSMC)-Srinakarinviroj University (Eastern region), Khon-Kaen University Cancer Centre (North-eastern region).<br>1. Women who underwent biopsy and have been pathologically diagnosed as having breast cancer.<br>2. Aged less than 71 years of age. | 601 | Controls recruited 1999-2000 and 2008-present at The National Cancer Institute (Central region), The Prince Songkla University Research Centre (South region), The HRH Princess Maha Chakri Sirindhorn Medical Centre (MSMC)-Srinakarinviroj University (Eastern region), Khon-Kaen University Cancer Centre (North-eastern region).<br>1. Women aged less than 71 years of age without cancer history of any kinds<br>2. Women who attend the out-patient clinic under the minor injuries such as cuts, broken bones.<br>3. Women who are institutionalised at the hospital with diseases | 557 | No | Mixed | None |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | not related to cancer or metabolic syndromes such as diabetes, heart diseases or conditions related to gynaecology and are well enough to give information to researchers. | | | | |
| Bavarian Breast Cancer Cases and Controls | BBCC | Germany | Hospital-based cases; population based controls | Consecutive, unselected cases with invasive breast cancer recruited at the University Breast Centre, Franconia in Northern Bavaria during 1999-2013. | 216 | Healthy women with no diagnosis of cancer aged 55 or older. Invited by a newspaper advertisement in Northern Bavaria and recruited during 1999-2013. | 157 | No | Mixed | [13,14] |
| Breast Cancer in Galway Genetic Study | BIGGS | Ireland | Hospital-based cases; population based controls | Unselected cases recruited from West of Ireland since 2001. Cases were recruited from University College Hospital Galway and surrounding hospitals | 344 | Women > 60 years with no personal history of any cancer and no family History of breast or ovarian cancer were identified from retirement groups in the West of Ireland (same catchment area as cases) during the period 2001-2008. | 21 | No | Mixed | [15-17] |
| Breast Oncology Galicia Network | BREOGAN | Spain | Population-based case-control | A population-based study conducted since 1997 in two cities in Galicia, Spain (Vigo and Santiago) covering approximately 700,000 inhabitants. The study currently includes over 1600 incident breast cancer cases diagnosed from 1997-2014 in two | 521 | Controls were frequency-matched to cases according to 5-year age group, inclusion in the universal Galician Public Health Service (SERGAS) registry database, and place of residence. They were healthy, unrelated female individuals from | 388 | No | Population-based | [17-21] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Galician hospitals with blood, tumor tissue and risk factor questionnaire. | | the same base population as cases randomly selected from SERGAS´ primary healthcare centers in the health areas of Santiago and Vigo. Recruitment began in 1997. | | | | |
| Breast Cancer Study of the University of Heidelberg | BSUCH | Germany | Hospital-based cases;healthy blood donator controls | Cases diagnosed with breast cancer/breast cancer metastasis in 2008-2011 at the University Women`s Clinic Heidelberg. | 226 | Healthy, unrelated, ethnically matched female blood donors recruited in 2007, 2009 & 2012 by German Red Cross Blood Service of Baden-Württemberg-Hessen, Institute of Transfusion Medicine & Immunology, Mannheim. | 549 | No | Mixed | [22] |
| Crete Cancer Genetics Program | CCGP | Greece | Hospital-based case-control study | Incident breast cancer cases treated between 2004 and 2013 at the University Hospital of Heraklion on Crete; all enrolled within 6 months of diagnosis. | 428 | Healthy, unrelated, ethnically matched female blood donors recruited in 2014 by the laboratory of Hemostasis at the General Hospital of Heraklion "Venizelio". | 217 | No | Mixed | Unpublished |
| CECILE Breast Cancer Study | CECILE | France | Population-based case-control study | All incident cases of breast cancer diagnosed in 2005-2007 among women <75 years of age and residing in Ille-et-Vilaine or Côte d'Or. Cases were recruited from the main cancer treatment center (Centre Eugène-Marquis in Rennes and Centre | 832 | General population control women residing in the same geographic areas frequency-matched to the cases by 5-year age groups. Controls were recruited in 2005-2007 by phone using a random digit dialing procedure and predefined numbers by | 943 | No | Population-based | [23] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Georges-François-Leclerc in Dijon) and from private or public hospitals in each area. | | socioeconomic status to control for possible selection bias. | | | | |
| Copenhagen General Population Study | CGPS | Denmark | Population-based case-control study | Consecutive, incident cases from 1 hospital with centralized care for a population of 400,000 women from 2001 to the present. | 2988 | Community controls residing in the same region as cases and with no history of breast cancer were identified from the Copenhagen General Population Study recruited 2003-2007. All controls were known to still be breast cancer-free at the end of 2007. | 4920 | No | Mixed | [24] |
| Spanish National Cancer Centre Breast Cancer Study | CNIO-BCS | Spain | Case-control study | Two groups of cases:1) 574 consecutive breast cancer patients, unselected for family history, from 3 public hospitals, 2 in Madrid and one in Oviedo, from 2000 to 2005. 2) 291 cases with at least one first degree relative also affected with breast cancer, recruited through the CNIO family cancer clinic in Madrid from 2000 to 2004. | 402 | Women attending the Menopause Research Centre between 2000 and 2004 and female members of the College of Lawyers attending a free, targeted medical check-up in 2005, all free of breast cancer and all in Madrid | 557 | Subset (N=291) | Mixed | [25] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Colombian Breast Cancer Case-Control Study | COLBCCC | Colombia | Case-control study | 1,022 unselected women diagnosed with breast cancer after January 1, 2004; enrolled between 2007 and 2012. | 370 | 1,023 healthy women attending the country-wide National Pap-Smear Screening Program in Colombia; enrolled between 2007 and 2012. Controls were matched to cases by +/- 2 years. Controls were women participating in the Colombian National Pap-Smear Screening Program (participation rate in 2005 was 77%) | 614 | No | Mixed | Unpublished |
| German Consortium for Hereditary Breast & Ovarian Cancer | GC-HBOC | Germany | Clinic-based case study and prospective cohort study | Women diagnosed with breast cancer in one of the GC-HBOC centers (Cologne, Munich, Kiel, Heidelberg, Düsseldorf, Ulm, Würzburg, Münster and Hannover). Recruitment period 1996-present. | 0 | Healthy, unrelated, ethnically and age-matched female control individuals (LIFE study, Leipzig, Germany). | 1561 | Yes | Mixed | [26-29] |
| Gene Environment Interaction and Breast Cancer in Germany | GENICA | Germany | Population-based case-control study | Incident breast cancer cases enrolled between 2000 and 2004 from the Greater Bonn area (by of the hospitals within the study region); all enrolled within 6 months of diagnosis. | 806 | Selected from population registries from 31 communities in the greater Bonn area; matched to cases in 5-year age classes between 2001 and 2004. | 891 | No | Population-based | [30,31] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Generation Scotland | GENSCOT | Scotland | Prospective family-based cohort study; nested case-control | Incident and prevalent cases of histologically-confirmed breast cancer at the time of latest updated cancer registry linkage (currently 2013). Recruitment though the General Practitioners in the areas of Glasgow, Tayside, Ayrshire, Arran and Northeast Scotland. | 384 | Two groups of controls: (1) 2:1 unrelated individuals matched to cases on age in five-years at baseline and recruitment centre; (2) first-degree female relatives with no breast cancer diagnosis at the time of selection. | 746 | No | Prospective cohort | [32] |
| Genetic Epidemiology Study of Breast Cancer by Age 50 | GESBC | Germany | Population-based study of women <50 years | All incident cases diagnosed <50 years of age in 1992-5 in two regions: Rhein-Neckar-Odenwald and Freiburg, by surveying the 38 clinics serving these regions | 498 | Selected from random lists of residents of the study regions supplied by population registries; two controls were selected for each case, matched by age and study region. Recruitment was carried out 1992-1998. | 982 | No | Population-based | [33] |
| Hannover Breast Cancer Study | HABCS | Germany | Hospital-based case-control study | Cases who received radiotherapy for breast cancer at Hannover Medical School between 1996-2003 (HaBCS I), or were diagnosed with breast cancer at a certified Breast Cancer Clinics in the Hannover region between 2012-2016 (HaBCS II), unselected for age or family history. | 819 | Anonymous female blood bank donors at Hannover Medical School, collected from 8/2005-12/2005, with known age and ethnic background. | 833 | No | Mixed | [34] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Helsinki Breast Cancer Study | HEBCS | Finland | Hospital-based case-control study, plus additional familial cases | (1) Consecutive cases (883) from the Department of Oncology, Helsinki University Central Hospital 1997-8 and 2000, (2) Consecutive cases (986) from the Department of Surgery, Helsinki University Central Hospital 2001 – 2004, (3) Familial breast cancer patients (536) from the Helsinki University Central Hospital, Departments of Oncology and Clinical Genetics (1995-) | 1240 | Healthy females from the same geographical region in Southern Finland in 2003. | 1090 | Subset (N=609) | Mixed | [35-37] |
| Hannover-Minsk Breast Cancer Study | HMBCS | Belarus | Hospital-based cases; population based controls | Ascertainment at the Byelorussian Institute for Oncology and Medical Radiology Aleksandrov N.N. in Minsk or at one of 5 regional oncology centers in Gomel, Mogilev, Grodno, Brest or Vitebsk through the years 2002-2008. | 332 | Controls from the same population aged 18-72 years. Healthy (without personally history of cancer) female probunds recruited from the same geographical regions as cases during the years 2002-2008. About 75% of controls were women invited for general medical examination at five regional gynecology clinics (in Gomel, Mogilev, Grodno, Brest or Vitebsk) and cancer-free volunteers ascertained at the Institute for Inherited Diseases in Minsk; 20% | 267 | No | Mixed | [38] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | were cancer-free female blood bank donors recruited at Republic Blood Bank, Minsk, Belarus; finally 5% of controls were healthy cancer-free relatives of some breast cancer patients. | | | | |
| Hannover-Ufa Breast Cancer Study | HUBCS | Russia | Hospital-based cases; population based controls | Consecutive Russian breast cancer patients aged 24-86 years ascertained at one of the two participating oncological centers in Bashkorstostan and Siberia through the years 2000-2008. | 224 | Population controls aged 18-84 years recruited from a population study of different populations of Russia. Healthy volunteers (without any malignancy) were selected from the same geographical regions during the years 2002-2008. | 188 | No | Mixed | [38] |
| Karolinska Breast Cancer Study | KARBAC | Sweden | Population and hospital-based cases; geographically matched controls | 1. Familial cases from Department of Clinical Genetics, Karolinska University Hospital, Stockholm. 2. Consecutive cases from Department of Oncology, Huddinge & Söder Hospital, Stockholm 1998-2000 | 287 | Blood donors of mixed gender from same geographical region. Excess material was received from all blood donors over a 3 month period in 2004 (approximately 3000) and DNA was extracted from a random sample of 1500 | 0 | Subset (N=568) | Mixed | [39,40] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Karolinska Mammography Project for Risk Prediction of Breast Cancer - Cohort Study | KARMA | Sweden | Cohort study | Inclusion of 70,877 women Oct 2010 - March 2013. 3000 women had BC at cohort entry. In all, 800 women have been diagnosed with breast cancer since study entry (Oct 2015). Approximately 250 women are diagnosed with BC annually | 2953 | Non - BC cases in the Karma Cohort | 5626 | no | Prospective cohort | Submitted |
| Kuopio Breast Cancer Project | KBCP | Finland | Population-based prospective clinical cohort | 1. Women seen at Kuopio University Hospital between 1990 and 1995 because of breast lump, mammographic abnormality, or other breast symptom who were found to have breast cancer. 2. Consecutive malignant breast cancer cases diagnosed at KUH from 2011 onwards. | 476 | Age and long-term area-of-residence matched controls selected from the National Population Register and interviewed in parallel with the cases | 70 | No | Population-based | [41,42] |
| Kathleen Cuningham Foundation Consortium for research into Familial Breast Cancer/Australian Ovarian Cancer Study | kConFab/AOCS | Australia and New Zealand | Clinic-based recruitment of familial breast cancer patients (cases); population-based case-control study of ovarian cancer (controls only) | Cases were from multiple-case breast and breast-ovarian families recruited though family cancer clinics from across Australia and New Zealand from 1998 to the present. Cases were selected for inclusion in BCAC studies if (i) family was negative for mutations in | 0 | Female controls were ascertained by the Australian Ovarian Cancer Study identified from the electoral rolls from all over Australia from 2002-2006. | 7 | Yes | Mixed | [43,44] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | BRCA1 and BRCA2 (ii) case was the index for the family, defined as youngest breast cancer affected family member. | | | | | | |
| Mammary Carcinoma Risk Factor Investigation | MARIE | Germany | Population-based case-control study | Incident cases diagnosed from 2001-2005 in the study region Hamburg in Northern Germany, and from 2002-2005 in the study region Rhein-Neckar-Karlsruhe in Southern Germany. | 2085 | 2 controls per case were randomly drawn from population registries and frequency matched by birth year and study region to the case. Controls were recruited from 2002 to 2006. | 1768 | No | Population-based | [45] |
| Cyprus Breast Cancer Case Control Study | MASTOS | Cyprus | Population-based case-control study | Women between 40-70 years of age who had a histologically confirmed diagnosis of primary breast cancer between January 1999 and December of 2005. The majority of cases were ascertained from the Bank of Cyprus Oncology Centre, which operates as a referral centre and offers treatment and follow-up for up to 90% of all breast cancer cases diagnosed in Cyprus. | 656 | Cypriot women from the general population, who were invited to participate in the National programme for breast cancer screening with the use of mammography and received a negative result. Volunteers were enrolled in the study during the same calendar period as the cases, from the 5-district mammography screening centers that operate in Cyprus. | 1091 | No | Population-based | [46] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | The rest of the patients, were recruited at the Oncology Departments of the Nicosia, Limassol, Larnaca and Paphos district hospitals. | | | | | | |
| Melbourne Collaborative Cohort Study | MCCS | Australia | Prospective cohort study: nested case-control study | Incident cases diagnosed between baseline (1990-1994) and last follow-up (2012) among the 24469 women participating in the cohort. | 793 | For each case a control was randomly selected from women from the cohort who did not develop breast cancer before the age at diagnosis of the case and matched the case on year of birth and country of birth. | 971 | No | Prospective cohort | [47] |
| Malaysian Breast Cancer Genetic Study | MYBRCA | Malaysia | Hospital-based case-control study | Breast cancer cases identified at the Breast Cancer Clinic in University Malaya Medical Centre Jan 2003-July 2014 and Subang Jaya Medical Centre Sep 2012-Sept 2014; cases are a mixture of prevalent and incident cases. Includes hospital-based and familial series. | 823 | Controls are cancer-free individuals (37-74 years) selected from women attending mammographic screening at the same hospitals. | 1090 | Yes (subset) | Mixed | [48,49] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Norwegian Breast Cancer Study | NBCS | Norway | Hospital-based case-control study | Incidence cases from three different hospitals: 1) Cases (114) mean age 64 (28-92) at Ullevål Univ. Hospital 1990-94, 2) cases (182) mean age 59 (26-75) referred to Norwegian Radium Hospital 1975-1986, 3) cases (124), mean age 56 (29-82) with stage I or II disease, in the Oslo micro-metastases study at Norwegian Radium Hospital between 1995-1998, 4) Breast cancer cases referred to the Norwegian hospitals Akershus University Hospital in Lørenskog, Ullevaal university hospital in Oslo and Rikshospitalet-Radiumhospitalet in Oslo from 2007-2010. Mean age is 63 years. Consecutive series. 5) Breast cancer cases referred to the Norwegian Radium Hospital hospitalet 2010-2013. Neoadjuvantly treated with Avastin (Bevacizumab). 6) Consecutive series of Breast cancer incidents referred to Akershus | 436 | Control subjects were healthy women, age 55-71, residing in Tromsø (440), and Bergen (109) attending the Norwegian Breast Cancer Screening Program. Healthy tissue from mammoplastic reduction surgery at a private clinic in Oslo. | 597 | No | Mixed | [50-53] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | university hospital 2004-2014. | | | | | | |
| Ontario Familial Breast Cancer Registry | OFBCR | Canada | Population-based familial case-control study | Cases diagnosed between 1 Jan 1996-31 Dec 1998 were identified from the Ontario Cancer Registry which registers >97% of all cases residing in the province at the time of diagnosis. All women with invasive breast cancer aged 20–54 years who met the | 108 | Unrelated, unaffected population controls were recruited by the Ontario Familial Breast and Colon Cancer Registries by calling randomly selected residential telephone numbers throughout the same geographical region. Eligible controls were | 415 | Subset (N=628) | Mixed | [54] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | OFBCR definition for high genetic risk (family history of specific cancers particularly breast and ovarian, early onset disease, Ashkenazi ethnicity or a diagnosis of multiple breast cancer) were asked to participate by completing risk factor questionnaires and providing a blood sample. A 25% random sample of individuals in this age category who did not meet the OFBCR definition, 35% of those aged 55–69 at high risk and 8.75% aged 55–69 at low risk were also asked to participate. Individuals diagnosed in 2001 and 2002 were also included if they met high-risk criteria. | | women with no history of breast cancer and were frequency-matched by 5-year age group to the expected age distribution of cases. | | | | |
| NCI Polish Breast Cancer Study | PBCS | Poland | Population-based case-control study | Incident cases from 2000-2003 identified through a rapid identification system in participating hospitals covering ~ 90% of all eligible cases, and cancer registries in Warsaw and Łódź covering 100% of all eligible cases. | 1564 | Randomly selected from population lists of all residents of Poland, stratified and frequency matched to cases by case city and age in 5 year categories. Recruited 2000-2003. | 1849 | No | Population-based | [55] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| The Prostate,Lung,Colorectal and Ovarian (PLCO) Cancer Screening Trial | PLCO | USA | Prospective cohort study: nested case-control | Incident cases arising in the sub-cohort of 78,232 women who gave a blood specimen in 1993-2001 are included if they were diagnosed with breast cancer. Recruitment via multiple screening centers across the US. | 1530 | Controls were women in this sub-cohort who were not diagnosed with breast cancer. Controls were matched to cases on age at randomization (4 categories) and fiscal year of randomization (2 categories). | 2221 | No | Prospective cohort | [56] |
| Predicting the Risk Of Cancer At Screening Study | PROCAS | UK | Population based study | Women diagnosed with breast cancer since joining the study of women attending the Breast Screening Programme (NHSBSP) in Greater Manchester. Recruitment period Oct 2009-May 2014. | 297 | Women attending routine NHS breast screening in Greater Manchester without a breast cancer diagnosis. Recruited during the same period as for the cases. | 1434 | No | Population-based | [57] |
| Singapore and Sweden Breast Cancer Study | SASBAC | Sweden | Population-based case-control study | Incident cases from October 1993 to March 1995 identified via the 6 regional cancer registries in Sweden, to which reporting is mandatory. | 1110 | Controls were randomly selected from the total population registry in 5-year age groups to match the expected age-frequency distribution among cases. Patients and controls were recruited from Oct 1993 through April 1995. | 1321 | No | Population-based | [58] |
| Study of Epidemiology and Risk factors in Cancer Heredity | SEARCH | UK | Population-based case-control study | 2 groups of cases identified through East Anglian Cancer Registry; 1) prevalent cases diagnosed 1991-1996 under 55 years of age at diagnosis, recruited 1996-2002; 2) incident | 12387 | Two groups of controls: (1) selected from the EPIC-Norfolk cohort study of 25,000 individuals age 45-74 recruited between 1992 and1994, based in the same geographic region | 6414 | No | Mixed | [59] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | cases diagnosed since 1996 under 70 years of age at diagnosis, recruited 1996-present. | | as cases; (2) selected from GP practices from March 2003 to present, frequency matched to cases by age and geographic region | | | | |
| Singapore Breast Cancer Cohort | SGBCC | Singapore | Hospital-based breast cancer cohort and population-based controls | Living breast cancer patients diagnosed with primary in situ or invasive breast cancer at 7 restructured hospitals in Singapore between 1980-2016. Cases are a mixture of prevalent and incident cases. | 3224 | All community-dwelling individuals who are Singaporeans or Singaporean Permanent Residents, 21 years and older. Participants were recruited between 2006 and 2010 through word-of-mouth and personal recommendations. In some cases, recruiters also sought participants through "cold-calling" or through door-to-door invitations.<br>Exclusion criteria were a medical history of cancer, acute myocardial infarction or stroke, or major psychiatric morbidity including schizophrenia, psychotic depression, and advanced Alzheimer's Disease. | 4165 | No | Hospital-based | No refs. |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Städtisches Klinikum Karlsruhe Deutsches Krebsforschungszentrum Study | SKKDKFZS | Germany | Hospital-based breast cancer cohort | Women diagnosed with primary *in situ* or invasive breast cancer at the Städtisches Klinikum Karlsruhe from March 1993 to July 2005. | 859 | No controls. | 0 | No | Patient cohort | [60] |
| IHCC-Szczecin Breast Cancer Study | SZBCS | Poland | Hospital-based case-control study | Prospectively ascertained cases of invasive breast cancer patients diagnosed at the Regional Oncology Hospital (Szczecin) in the years 2002, 2003, 2006 and 2007 or the University Hospital from 2002 to 2007 in Szczecin, West-Pomerania, Poland. Patients with pure intraductal or intralobular cancer were excluded (DCIS or LCIS) but patients with DCIS with micro-invasion were included. | 297 | Unaffected, matched to cases for year of birth, sex and region; from families with negative cancer family history; controls were part of a population-based study of the 1.3 million inhabitants of West Pomerania performed in 2003 and 2004 designed to identify familial aggregations of cancer by our centre | 189 | No | Mixed | [61-64] |

| Study | Abbreviation | Country | Study design | Case definition | Cases | Control definition | Controls | Selected familial cases | Design category | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Utah Breast Cancer Study | UBCS | USA | Mixed. (1) Pedigrees including multiple sampled breast cancer cases within 2 generations, also may include sampled, unaffected relatives; (2) hospital-based cases (from Huntsman Cancer Institute [HCI] or Intermountain Healthcare [IH]), and breast reduction controls; and (3) Population-based cases (from the Utah Cancer Registry [UCR]) and controls (from the Utah Drivers License Registry [UDLR]) | Cases recruited from late 1970s to present (on-going). Ascertainment from: (1) UCR-confirmed breast cancer cases in high-risk pedigrees; (2) invasive breast cancer cases treated or surgery performed at HCI or IH clinics; (3) prevalent, population-based UCR-confirmed breast cancer cases. | 572 | Controls also recruited from late 1970s to present (on-going) from: (1) relatives in high-risk pedigrees; (2) hospital-based cancer-free women undergoing breast reductions; (3) Population-based controls selected from the UDLR to frequency match cases by sex and birth cohort. | 270 | Some | Mixed | [65,66] |

**eTable 2: Immunohistochemistry and tumour grade - based surrogates for five intrinsic breast cancer subtypes**

| Intrinsic subtype | IHC surrogate | Abbreviation |
|---|---|---|
| Luminal A-like | ER+ and/or PR+ HER2- Grades 1 or 2 | HR+HER2-lowgrade[a] |
| Luminal B-HER2-positive like | HER-2 positive like: ER+ and/or PR+ HER2+ | HR+HER2+ |
| Luminal B-HER2-negative like | ER+ and/or PR+ HER2- Grade 3 | HR+HER2-highgrade |
| HER2 enriched | ER- PR- HER2+ | HR-HER2+ |
| TN | ER- PR- HER2- | TN |

IHC, immunohistochemistry; HR, Hormone receptor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TN, triple negative; +, positive; -, negative

[a] 'lowgrade' includes low (Grade 1) and intermediate (Grade 2) grade tumors

## eTable 3: Numbers of cases and controls, and age distributions, by country of origin

| | Controls | | | | | Cases | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Age at Interview (years) | | | | | Age at Diagnosis (years) | | | |
| Country | N | Mean | Sd | Median | IQR | N | Mean | Sd | Median | IQR |
| **Australia** | 978 | 62.0 | 8.8 | 63 | 12 | 793 | 62.2 | 9.2 | 63 | 13 |
| **Belarus**[a] | 267 | 46.4 | 13.1 | 47 | 21 | 332 | 47.4 | 12.3 | 46 | 17 |
| **Canada**[a] | 415 | 55.0 | 12.0 | 55 | 18 | 108 | 57.8 | 8.7 | 61 | 14 |
| **Colombia** | 614 | 49.7 | 10.9 | 50 | 14 | 370 | 48.7 | 11.9 | 48 | 15 |
| **Cyprus**[a] | 1091 | 55.7 | 7.0 | 56 | 10 | 656 | 51.1 | 9.0 | 51 | 13 |
| **Denmark** | 4920 | 55.5 | 12.1 | 55 | 18 | 2988 | 59.5 | 11.0 | 60 | 17 |
| **Finland** | 1160 | 41.5 | 13.3 | 42 | 23 | 1716 | 56.6 | 11.1 | 56 | 16 |
| **France**[a] | 943 | 54.6 | 11.0 | 55 | 16 | 832 | 54.2 | 10.8 | 55 | 16 |
| **Germany** | 6741 | 54.6 | 13.3 | 57 | 16 | 5509 | 58.3 | 10.6 | 60 | 15 |
| **Greece** | 217 | 57.6 | 15.1 | 62 | 19 | 428 | 55.2 | 12.0 | 55 | 19 |
| **Ireland** | 21 | 64.6 | 7.3 | 64 | 10 | 344 | 51.2 | 10.0 | 50 | 12 |
| **Malaysia** | 1090 | 56.0 | 8.5 | 56 | 13 | 823 | 52.2 | 10.6 | 52 | 15 |
| **Netherlands** | 1408 | 47.1 | 12.3 | 48 | 18 | 992 | 42.1 | 6.0 | 44 | 8 |
| **Norway** | 597 | 61.4 | 4.5 | 60 | 7 | 436 | 58.3 | 10.4 | 59 | 15 |
| **Poland** | 2038 | 55.7 | 9.9 | 55 | 16 | 1861 | 56.1 | 10.0 | 55 | 15 |
| **Russia** | 188 | 45.3 | 13.9 | 45 | 16 | 224 | 52.3 | 9.8 | 52 | 13 |
| **Singapore** | 4165 | 50.1 | 10.2 | 50 | 14 | 3224 | 53.2 | 10.1 | 53 | 14 |
| **Spain** | 945 | 51.8 | 11.8 | 53 | 17 | 923 | 55.6 | 11.0 | 56 | 16 |
| **Sweden** | 6947 | 60.8 | 8.8 | 62 | 13 | 4350 | 57.5 | 9.8 | 58 | 14 |
| **Thailand**[a] | 557 | 41.7 | 10.5 | 43 | 15 | 601 | 48.2 | 9.1 | 48 | 13 |
| **UK** | 8594 | 54.9 | 11.3 | 56 | 13 | 13068 | 54.6 | 9.0 | 55 | 13 |
| **USA** | 2491 | 61.3 | 7.7 | 61 | 9 | 2102 | 64.2 | 9.6 | 66 | 11 |
| **TOTAL** | 46387 | 55.1 | 11.9 | 56 | 16 | 42680 | 55.8 | 10.6 | 56 | 16 |

N, number of cases or controls; sd, standard deviation; IQR, interquartile range

[a] Five countries: Belarus, Canada, Cyprus, France and Thailand were excluded from imputation due to limited numbers for some pathology variables; A total of 43114 controls and 40151 cases were included

**eTable 4: Numbers of variant carriers by breast cancer susceptibility gene**

| Gene | Controls | | | Cases | | | Controls[a] | Cases[a] |
|---|---|---|---|---|---|---|---|---|
| | All ages | ≤ 50 years | > 50 years | All ages | ≤ 50 years | > 50 years | All ages | All ages |
| ***Non-carriers*** | 45,633 | 14,484 | 31,149 | 40,108 | 12,538 | 27,570 | 42,399 | 37,728 |
| ***Carriers*** | 754 | 263 | 491 | 2572 | 1232 | 1340 | 715 | 2423 |
| ***ATM PTV*** | 136 | 52 | 84 | 263 | 90 | 173 | 130 | 250 |
| ***BARD1 PTV*** | 27 | 11 | 16 | 56 | 22 | 34 | 24 | 52 |
| ***BRCA1 PTV*** | 56 | 24 | 32 | 465 | 324 | 141 | 51 | 431 |
| ***BRCA2 PTV*** | 126 | 46 | 80 | 678 | 354 | 324 | 115 | 625 |
| ***CHEK2 PTV*** | 275 | 89 | 186 | 628 | 229 | 399 | 268 | 610 |
| ***PALB2 PTV*** | 52 | 18 | 34 | 245 | 94 | 151 | 49 | 233 |
| ***RAD51C PTV*** | 26 | 8 | 18 | 43 | 11 | 32 | 26 | 42 |
| ***RAD51D PTV*** | 25 | 8 | 17 | 46 | 15 | 31 | 23 | 45 |
| ***BRCA1 MSV*** | 4 | 0 | 4 | 58 | 39 | 19 | 4 | 56 |
| ***BRCA2 MSV*** | 7 | 3 | 4 | 39 | 20 | 19 | 7 | 37 |
| ***TP53 PTV MSV*** | 20 | 4 | 16 | 51 | 34 | 17 | 18 | 42 |
| ***Total*** | 46,387 | 14,747 | 31,640 | 42,680 | 13,770 | 28,910 | 43,114 | 40,151 |

PTV, protein truncating variants; MSV, missense variants. For TP53, too few PTVs (7) were available for separate analysis and these were combined with the deleterious missense variants; PTV and MSV occurred together in one individual

[a] Numbers of cases and controls included in imputation and analyses of intrinsic subtypes (five countries: Belarus, Canada, Cyprus, France and Thailand were excluded)

## eTable 5: Cross tabulation of ER, PR, HER2 and Grade data

| | | ER-status | | | | | | PR-status | | | | | | HER2-status | | | | | | Grade | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Marker status** | **Negative** | | **Positive** | | **Unknown** | | **Negative** | | **Positive** | | **Unknown** | | **Negative** | | **Positive** | | **Unknown** | | **Grade 1** | | **Grade 2** | | **Grade 3** | | **Unknown** | |
| **ER-status** | | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| | Negative | 6607 | 100% | - | - | - | - | 5066 | 56% | 776 | 4% | 765 | 6% | 3078 | 17% | 1584 | 37% | 1945 | 11% | 254 | 4% | 1619 | 10% | 4003 | 39% | 731 | 10% |
| | Positive | - | | 26480 | | - | | 3916 | 43% | 17380 | 96% | 5184 | 40% | 15173 | 83% | 2698 | 63% | 8609 | 49% | 5576 | 85% | 12958 | 80% | 5246 | 51% | 2700 | 38% |
| | Unknown | - | | - | | 7064 | | 28 | 0% | 34 | 0% | 7002 | 54% | 132 | 1% | 26 | 1% | 6906 | 40% | 737 | 11% | 1588 | 10% | 1039 | 10% | 3700 | 52% |
| **PR-status** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Negative | 5066 | 77% | 3916 | 15% | 28 | 0% | 9010 | 100% | - | - | - | - | 4945 | 27% | 2099 | 49% | 1966 | 11% | 870 | 13% | 3015 | 19% | 4408 | 43% | 717 | 10% |
| | Positive | 776 | 12% | 17380 | 66% | 34 | 0% | - | - | 18190 | 100% | - | - | 11881 | 65% | 1904 | 44% | 4405 | 25% | 4051 | 62% | 9166 | 57% | 3634 | 35% | 1339 | 19% |
| | Unknown | 765 | 12% | 5184 | 20% | 7002 | 99% | - | - | - | - | 12951 | 100% | 1557 | 8% | 305 | 7% | 11089 | 64% | 1646 | 25% | 3984 | 25% | 2246 | 22% | 5075 | 71% |
| **HER2-status** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Negative | 3078 | 47% | 15173 | 57% | 132 | 2% | 4945 | 55% | 11881 | 65% | 1557 | 12% | 18383 | 100% | - | - | - | - | 3874 | 59% | 8824 | 55% | 4775 | 46% | 910 | 13% |
| | Positive | 1584 | 24% | 2698 | 10% | 26 | 0% | 2099 | 23% | 1904 | 10% | 305 | 2% | - | - | 4308 | 100% | - | - | 285 | 4% | 1634 | 10% | 2111 | 21% | 278 | 4% |
| | Unknown | 1945 | 29% | 8609 | 33% | 6906 | 98% | 1966 | 22% | 4405 | 24% | 11089 | 86% | - | - | - | - | 17460 | 100% | 2408 | 37% | 5707 | 35% | 3402 | 33% | 5943 | 83% |
| **Grade** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Grade 1 | 254 | 4% | 5576 | 21% | 737 | 10% | 870 | 10% | 4051 | 22% | 1646 | 13% | 3874 | 21% | 285 | 7% | 2408 | 14% | 6567 | 100% | - | - | - | - | - | - |
| | Grade 2 | 1619 | 25% | 12958 | 49% | 1588 | 22% | 3015 | 33% | 9166 | 50% | 3984 | 31% | 8824 | 48% | 1634 | 38% | 5707 | 33% | - | - | 16165 | 100% | - | - | - | - |
| | Grade 3 | 4003 | 61% | 5246 | 20% | 1039 | 15% | 4408 | 49% | 3634 | 20% | 2246 | 17% | 4775 | 26% | 2111 | 49% | 3402 | 19% | - | - | - | - | 10288 | 100% | - | - |
| | Unknown | 731 | 11% | 2700 | 10% | 3700 | 52% | 717 | 8% | 1339 | 7% | 5075 | 39% | 910 | 5% | 278 | 6% | 5943 | 34% | - | - | - | - | - | - | 7131 | 100% |

PTV, protein truncating variants; MSV, missense variants; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; N, number of cases; % of each column.
Missing as a % of the total: ER-status, 17.59%; PR-status, 32.36%; HER2-status, 43.49%; Grade, 17.76%

**eTable 6: Distribution of intrinsic tumor subtypes in women of all ages and in different age groups, by breast cancer susceptibility gene**

| | *HR+HER2-lowgrade* | | HR+HER2+ | | HR+HER2-highgrade | | HR-HER2+ | | TN | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***N*** | **Proportion** | ***N*** | **Proportion** | ***N*** | **Proportion** | ***N*** | **Proportion** | ***N*** | **Proportion** | **Total** |
| ***All ages*** | | | | | | | | | | | |
| *Non-carriers* | 2171576 | 0.576 | 459426 | 0.122 | 522590 | 0.139 | 221843 | 0.059 | 397365 | 0.105 | 3772800 |
| *BRCA1 PTV* | 6460 | 0.150 | 1258 | 0.029 | 6800 | 0.158 | 2943 | 0.068 | 25639 | 0.595 | 43100 |
| *BRCA2 PTV* | 27046 | 0.433 | 6678 | 0.107 | 15576 | 0.249 | 2196 | 0.035 | 11004 | 0.176 | 62500 |
| *ATM PTV* | 12717 | 0.509 | 2355 | 0.094 | 7886 | 0.315 | 641 | 0.026 | 1401 | 0.056 | 25000 |
| *CHEK2 PTV* | 36230 | 0.594 | 8919 | 0.146 | 9720 | 0.159 | 2944 | 0.048 | 3187 | 0.052 | 61000 |
| *PALB2 PTV* | 8739 | 0.375 | 3130 | 0.134 | 5909 | 0.254 | 1521 | 0.065 | 4001 | 0.172 | 23300 |
| *RAD51C PTV* | 1603 | 0.382 | 47 | 0.011 | 716 | 0.170 | 270 | 0.064 | 1564 | 0.372 | 4200 |
| *RAD51D PTV* | 1500 | 0.333 | 141 | 0.031 | 1458 | 0.324 | 40 | 0.009 | 1361 | 0.302 | 4500 |
| *BARD1 PTV* | 2269 | 0.436 | 88 | 0.017 | 344 | 0.066 | 394 | 0.076 | 2105 | 0.405 | 5200 |
| *BRCA1 MSV* | 1138 | 0.203 | 197 | 0.035 | 894 | 0.160 | 373 | 0.067 | 2998 | 0.535 | 5600 |
| *BRCA2 MSV* | 1327 | 0.359 | 320 | 0.086 | 1397 | 0.378 | 111 | 0.030 | 545 | 0.147 | 3700 |
| *TP53 PTV MSV* | 1217 | 0.290 | 1410 | 0.336 | 742 | 0.177 | 540 | 0.129 | 291 | 0.069 | 4200 |
| *Total* | 2271822 | | 483969 | | 574032 | | 233816 | | 451461 | | 4015100 |
| **≤40 years** | | | | | | | | | | | |
| *Non-carriers* | 100989 | 0.393 | 44491 | 0.173 | 44873 | 0.175 | 25189 | 0.098 | 41158 | 0.160 | 256700 |
| *BRCA1 PTV* | 1268 | 0.086 | 505 | 0.034 | 1846 | 0.126 | 904 | 0.061 | 10177 | 0.692 | 14700 |
| *BRCA2 PTV* | 4939 | 0.380 | 1968 | 0.151 | 2987 | 0.230 | 542 | 0.042 | 2564 | 0.197 | 13000 |
| *ATM PTV* | 623 | 0.389 | 167 | 0.104 | 698 | 0.436 | 22 | 0.014 | 90 | 0.056 | 1600 |
| *CHEK2 PTV* | 3304 | 0.501 | 1107 | 0.168 | 1368 | 0.207 | 526 | 0.080 | 295 | 0.045 | 6600 |
| *PALB2 PTV* | 733 | 0.333 | 359 | 0.163 | 595 | 0.270 | 100 | 0.045 | 413 | 0.188 | 2200 |
| *RAD51C PTV* | 25 | 0.063 | 4 | 0.010 | 43 | 0.108 | 13 | 0.033 | 315 | 0.788 | 400 |
| *RAD51D PTV* | 0 | 0.000 | 3 | 0.008 | 145 | 0.363 | 20 | 0.050 | 232 | 0.580 | 400 |
| *BARD1 PTV* | 202 | 0.404 | 26 | 0.052 | 24 | 0.048 | 27 | 0.054 | 221 | 0.442 | 500 |
| *BRCA1 MSV* | 202 | 0.144 | 43 | 0.031 | 255 | 0.182 | 6 | 0.004 | 894 | 0.639 | 1400 |
| *BRCA2 MSV* | 204 | 0.291 | 27 | 0.039 | 319 | 0.456 | 41 | 0.059 | 109 | 0.156 | 700 |
| *TP53 PTV MSV* | 251 | 0.157 | 677 | 0.423 | 76 | 0.048 | 421 | 0.263 | 175 | 0.109 | 1600 |
| *Total* | 112740 | | 49377 | | 53229 | | 27811 | | 56643 | | 299800 |

| | *HR+HER2-lowgrade* | | HR+HER2+ | | HR+HER2-highgrade | | HR-HER2+ | | TN | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***N*** | **Proportion** | ***N*** | **Proportion** | ***N*** | **Proportion** | ***N*** | **Proportion** | ***N*** | **Proportion** | **Total** |
| **41-60 years** | | | | | | | | | | | |
| *Non-carriers* | 1188674 | 0.567 | 259858 | 0.124 | 292277 | 0.139 | 129734 | 0.062 | 225757 | 0.108 | 2096300 |
| *BRCA1 PTV* | 4242 | 0.174 | 632 | 0.026 | 4266 | 0.175 | 1772 | 0.073 | 13488 | 0.553 | 24400 |
| *BRCA2 PTV* | 16129 | 0.441 | 3299 | 0.090 | 10195 | 0.279 | 990 | 0.027 | 5987 | 0.164 | 36600 |
| *ATM PTV* | 7909 | 0.531 | 1570 | 0.105 | 4167 | 0.280 | 380 | 0.026 | 874 | 0.059 | 14900 |
| *CHEK2 PTV* | 20495 | 0.584 | 5195 | 0.148 | 5870 | 0.167 | 1724 | 0.049 | 1816 | 0.052 | 35100 |
| *PALB2 PTV* | 5032 | 0.354 | 1869 | 0.132 | 3824 | 0.269 | 997 | 0.070 | 2478 | 0.175 | 14200 |
| *RAD51C PTV* | 556 | 0.253 | 27 | 0.012 | 571 | 0.260 | 146 | 0.066 | 900 | 0.409 | 2200 |
| *RAD51D PTV* | 1059 | 0.342 | 130 | 0.042 | 1022 | 0.330 | 20 | 0.006 | 869 | 0.280 | 3100 |
| *BARD1 PTV* | 1473 | 0.460 | 37 | 0.012 | 258 | 0.081 | 152 | 0.048 | 1280 | 0.400 | 3200 |
| *BRCA1 MSV* | 736 | 0.210 | 152 | 0.043 | 499 | 0.143 | 328 | 0.094 | 1785 | 0.510 | 3500 |
| *BRCA2 MSV* | 1067 | 0.410 | 264 | 0.102 | 893 | 0.343 | 46 | 0.018 | 330 | 0.127 | 2600 |
| *TP53 PTV MSV* | 819 | 0.546 | 380 | 0.253 | 266 | 0.177 | 19 | 0.013 | 16 | 0.011 | 1500 |
| *Total* | 1248191 | | 273413 | | 324108 | | 136308 | | 255580 | | 2237600 |
| **>60 years** | | | | | | | | | | | |
| *Non-carriers* | 881913 | 0.621 | 155077 | 0.109 | 185440 | 0.131 | 66920 | 0.047 | 130450 | 0.092 | 1419800 |
| *BRCA1 PTV* | 950 | 0.238 | 121 | 0.030 | 688 | 0.172 | 267 | 0.067 | 1974 | 0.494 | 4000 |
| *BRCA2 PTV* | 5978 | 0.463 | 1411 | 0.109 | 2394 | 0.186 | 664 | 0.051 | 2453 | 0.190 | 12900 |
| *ATM PTV* | 4185 | 0.492 | 618 | 0.073 | 3021 | 0.355 | 239 | 0.028 | 437 | 0.051 | 8500 |
| *CHEK2 PTV* | 12431 | 0.644 | 2617 | 0.136 | 2482 | 0.129 | 694 | 0.036 | 1076 | 0.056 | 19300 |
| *PALB2 PTV* | 2974 | 0.431 | 902 | 0.131 | 1490 | 0.216 | 424 | 0.061 | 1110 | 0.161 | 6900 |
| *RAD51C PTV* | 1022 | 0.639 | 16 | 0.010 | 102 | 0.064 | 111 | 0.069 | 349 | 0.218 | 1600 |
| *RAD51D PTV* | 441 | 0.441 | 8 | 0.008 | 291 | 0.291 | 0 | 0.000 | 260 | 0.260 | 1000 |
| *BARD1 PTV* | 594 | 0.396 | 25 | 0.017 | 62 | 0.041 | 215 | 0.143 | 604 | 0.403 | 1500 |
| *BRCA1 MSV* | 200 | 0.286 | 2 | 0.003 | 140 | 0.200 | 39 | 0.056 | 319 | 0.456 | 700 |
| *BRCA2 MSV* | 56 | 0.140 | 29 | 0.073 | 185 | 0.463 | 24 | 0.060 | 106 | 0.265 | 400 |
| *TP53 PTV MSV* | 147 | 0.134 | 353 | 0.321 | 400 | 0.364 | 100 | 0.091 | 100 | 0.091 | 1100 |
| *Total* | 910891 | | 161179 | | 196695 | | 69697 | | 139238 | | 1477700 |

PTV, protein truncating variants; MSV, missense variants, Total number over 100 imputations. The results represent the average proportion (over all 100 imputations) of all tumors of a particular subtype and age group. For some gene, subtype and age combinations data are limited, and therefore frequency is imprecise. MICE Imputation was carried out as described in the Methods and intrinsic subtypes constructed for each imputed data-set. These results are also shown in eFigures 2-5

**eTable 7: Prevalence of PTV and MSV in breast cancer susceptibility genes by intrinsic subtypes of breast cancer among women of different age groups at diagnosis**

| | *Non-Carriers* | *ATM PTV* | *BARD1 PTV* | *BRCA1 PTV* | *BRCA2 PTV* | *CHEK2 PTV* | *PALB2 PTV* | *RAD51C PTV* | *RAD51D PTV* | *BRCA1 MSV* | *BRCA2 MSV* | *TP53 PTV MSV* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **40 years** | | | | | | | | | | | | |
| HR+HER2-lowgrade | 0.8958 | 0.0055 | 0.0018 | 0.0112 | 0.0438 | 0.0293 | 0.0065 | 0.0002 | 0.0000 | 0.0018 | 0.0018 | 0.0022 |
| HR+HER2+ | 0.9010 | 0.0034 | 0.0005 | 0.0102 | 0.0399 | 0.0224 | 0.0073 | 0.0001 | 0.0001 | 0.0009 | 0.0005 | 0.0137 |
| HR+HER2-highgrade | 0.8430 | 0.0131 | 0.0005 | 0.0347 | 0.0561 | 0.0257 | 0.0112 | 0.0008 | 0.0027 | 0.0048 | 0.0060 | 0.0014 |
| HR-HER2+ | 0.9057 | 0.0008 | 0.0010 | 0.0325 | 0.0195 | 0.0189 | 0.0036 | 0.0005 | 0.0007 | 0.0002 | 0.0015 | 0.0151 |
| TN | 0.7266 | 0.0016 | 0.0039 | 0.1797 | 0.0453 | 0.0052 | 0.0073 | 0.0056 | 0.0041 | 0.0158 | 0.0019 | 0.0031 |
| **41-60 years** | | | | | | | | | | | | |
| HR+HER2-lowgrade | 0.9523 | 0.0063 | 0.0012 | 0.0034 | 0.0129 | 0.0164 | 0.0040 | 0.0004 | 0.0008 | 0.0006 | 0.0009 | 0.0007 |
| HR+HER2+ | 0.9504 | 0.0057 | 0.0001 | 0.0023 | 0.0121 | 0.0190 | 0.0068 | 0.0001 | 0.0005 | 0.0006 | 0.0010 | 0.0014 |
| HR+HER2-highgrade | 0.9018 | 0.0129 | 0.0008 | 0.0132 | 0.0315 | 0.0181 | 0.0118 | 0.0018 | 0.0032 | 0.0015 | 0.0028 | 0.0008 |
| HR-HER2+ | 0.9518 | 0.0028 | 0.0011 | 0.0130 | 0.0073 | 0.0126 | 0.0073 | 0.0011 | 0.0001 | 0.0024 | 0.0003 | 0.0001 |
| TN | 0.8833 | 0.0034 | 0.0050 | 0.0528 | 0.0234 | 0.0071 | 0.0097 | 0.0035 | 0.0034 | 0.0070 | 0.0013 | 0.0001 |
| **60 years** | | | | | | | | | | | | |
| HR+HER2-lowgrade | 0.9682 | 0.0046 | 0.0007 | 0.0010 | 0.0066 | 0.0136 | 0.0033 | 0.0011 | 0.0005 | 0.0002 | 0.0001 | 0.0002 |
| HR+HER2+ | 0.9621 | 0.0038 | 0.0002 | 0.0008 | 0.0088 | 0.0162 | 0.0056 | 0.0001 | 0.0000 | 0.0000 | 0.0002 | 0.0022 |
| HR+HER2-highgrade | 0.9428 | 0.0154 | 0.0003 | 0.0035 | 0.0122 | 0.0126 | 0.0076 | 0.0005 | 0.0015 | 0.0007 | 0.0009 | 0.0020 |
| HR-HER2+ | 0.9602 | 0.0034 | 0.0031 | 0.0038 | 0.0095 | 0.0100 | 0.0061 | 0.0016 | 0.0000 | 0.0006 | 0.0003 | 0.0014 |
| TN | 0.9369 | 0.0031 | 0.0043 | 0.0142 | 0.0176 | 0.0077 | 0.0080 | 0.0025 | 0.0019 | 0.0023 | 0.0008 | 0.0007 |

PTV, protein truncating variants; MSV, missense variants; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TN, triple-negative; OR, Odds Ratio; CI, Confidence
MICE Imputation was carried out as described in the Methods and intrinsic subtypes constructed for each imputed data-set. The histogram represents the average proportion (over all 100 imputations). For some gene, subtype and age combinations data are limited, and therefore frequency is imprecise.
These results are also shown in eFigures 7-9; numbers underlying the proportions are shown in eTable10

**eTable 8: Odds ratios for association between PTV and MSV carrier status and intrinsic subtypes refined by PR expression**

| Subtype | OR [a] | L95CI | U95CI | p-value | OR [a] | L95CI | U95CI | p-value |
|---|---|---|---|---|---|---|---|---|
| **Gene** | ***ATM PTV*** | | | | ***RAD51C PTV*** | | | |
| **HR+HER2-lowgrade** | **1.97** | **1.52** | **2.55** | **2.61E-07** | **1.17** | **0.61** | **2.25** | **0.643** |
| HR+(ER+PR+)HER2-lowgrade | 2.03 | 1.55 | 2.67 | 3.77E-07 | 1.09 | 0.53 | 2.25 | 0.813 |
| HR+(ER+PR-)HER2-lowgrade | 1.75 | 0.94 | 3.23 | 0.076 | 1.58 | 0.41 | 6.09 | 0.505 |
| HR+(ER-PR+)HER2-lowgrade | 1.56 | 0.56 | 4.41 | 0.397 | 0.01 | NA | NA | 0.798 |
| **HR+HER2+** | **1.66** | **0.93** | **2.95** | **0.085** | **0.02** | **NA** | **NA** | **0.840** |
| HR+(ER+PR+)HER2+ | 1.78 | 0.92 | 3.45 | 0.086 | 0.01 | NA | NA | 0.744 |
| HR+(ER+PR-)HER2+ | 1.56 | 0.56 | 4.41 | 0.397 | 0.01 | NA | NA | 0.798 |
| HR+(ER-PR+)HER2+ | 0.01 | NA | NA | 0.774 | 0.03 | NA | NA | 0.856 |
| **HR+HER2-highgrade** | **4.99** | **3.68** | **6.76** | **3.14E-25** | **2.01** | **0.82** | **4.93** | **0.129** |
| HR+(ER+PR+)HER2-highgrade | 5.37 | 3.83 | 7.51 | 1.16E-22 | 2.14 | 0.81 | 5.66 | 0.124 |
| HR+(ER+PR-)HER2-highgrade | 4.30 | 2.26 | 8.16 | 8.33E-06 | 0.02 | NA | NA | 0.796 |
| HR+(ER-PR+)HER2-highgrade | 2.61 | 0.65 | 10.54 | 0.177 | 6.11 | 0.86 | 43.51 | 0.071 |
| **PR-pos vs PR-neg (adjusted) [b]** | **1.16** | **0.74** | **1.81** | **0.521** | **1.16** | **0.28** | **4.73** | **0.838** |
| **Gene** | ***BARD1 PTV*** | | | | ***RAD51D PTV*** | | | |
| **HR+HER2-lowgrade** | **2.03** | **1.12** | **3.71** | **0.020** | **1.29** | **0.65** | **2.53** | **0.466** |
| HR+(ER+PR+)HER2-lowgrade | 1.99 | 1.04 | 3.81 | 0.038 | 1.09 | 0.51 | 2.33 | 0.825 |
| HR+(ER+PR-)HER2-lowgrade | 1.64 | 0.34 | 7.83 | 0.538 | 1.95 | 0.51 | 7.42 | 0.330 |
| HR+(ER-PR+)HER2-lowgrade | 0.02 | NA | NA | 0.817 | 1.74 | 0.24 | 12.97 | 0.587 |
| **HR+HER2+** | **0.07** | **NA** | **NA** | **0.873** | **0.50** | **0.07** | **3.56** | **0.486** |
| HR+(ER+PR+)HER2+ | 0.04 | NA | NA | 0.770 | 0.01 | NA | NA | 0.671 |
| HR+(ER+PR-)HER2+ | 0.02 | NA | NA | 0.817 | 1.74 | 0.24 | 12.97 | 0.587 |
| HR+(ER-PR+)HER2+ | 0.06 | NA | NA | 0.871 | 0.05 | NA | NA | 0.837 |
| **HR+HER2-highgrade** | **1.08** | **0.22** | **5.46** | **0.921** | **4.82** | **2.33** | **9.97** | **2.26E-05** |
| HR+(ER+PR+)HER2-highgrade | 0.93 | 0.14 | 6.14 | 0.943 | 4.53 | 1.97 | 10.44 | 0.0004 |
| HR+(ER+PR-)HER2-highgrade | 0.10 | NA | NA | 0.865 | 4.22 | 0.09 | 203.45 | 0.467 |
| HR+(ER-PR+)HER2-highgrade | 0.39 | NA | NA | 0.947 | 6.56 | 0.89 | 48.24 | 0.064 |
| **PR-pos vs PR-neg (adjusted)** | **1.23** | **0.30** | **5.11** | **0.777** | **0.64** | **0.23** | **1.76** | **0.385** |
| **Gene** | ***BRCA1 PTV*** | | | | ***BRCA1 MSV*** | | | |
| **HR+HER2-lowgrade** | **3.26** | **2.21** | **4.80** | **2.07E-09** | **7.15** | **2.20** | **23.31** | **0.001** |
| HR+(ER+PR+)HER2-lowgrade | 2.82 | 1.85 | 4.30 | 1.60E-06 | 5.14 | 1.38 | 19.15 | 0.015 |
| HR+(ER+PR-)HER2-lowgrade | 5.60 | 2.79 | 11.25 | 1.26E-06 | 13.87 | 2.72 | 70.80 | 0.002 |
| HR+(ER-PR+)HER2-lowgrade | 4.88 | 1.97 | 12.12 | 0.0006 | 0.27 | NA | NA | 0.910 |
| **HR+HER2+** | **2.27** | **1.16** | **4.45** | **0.017** | **4.20** | **0.53** | **33.53** | **0.176** |
| HR+(ER+PR+)HER2+ | 1.40 | 0.51 | 3.82 | 0.513 | 4.38 | 0.51 | 37.77 | 0.180 |
| HR+(ER+PR-)HER2+ | 4.88 | 1.97 | 12.12 | 0.0006 | 0.27 | NA | NA | 0.910 |
| HR+(ER-PR+)HER2+ | 0.20 | NA | NA | 0.864 | 1.49 | NA | NA | 0.970 |
| **HR+HER2-highgrade** | **13.50** | **9.16** | **19.90** | **1.76E-39** | **23.71** | **6.70** | **83.94** | **9.19E-07** |
| HR+(ER+PR+)HER2-highgrade | 8.22 | 5.01 | 13.48 | 6.92E-17 | 8.51 | 0.54 | 133.64 | 0.128 |
| HR+(ER+PR-)HER2-highgrade | 26.60 | 15.45 | 45.79 | 2.59E-32 | 47.84 | 9.90 | 231.21 | 1.50E-06 |
| HR+(ER-PR+)HER2-highgrade | 32.89 | 15.94 | 67.86 | 3.30E-21 | 99.96 | 17.24 | 579.71 | 2.83E-07 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **PR-pos vs PR-neg (adjusted)** | **0.41** | **0.27** | **0.64** | **7.05E-05** | **0.43** | **0.15** | **1.24** | **0.117** |
| **Gene** | ***BRCA2 PTV*** | | | | ***BRCA2 MSV*** | | | |
| **HR+HER2-lowgrade** | **5.05** | **4.03** | **6.33** | **4.12E-45** | **3.73** | **1.46** | **9.56** | **0.006** |
| HR+(ER+PR+)HER2-lowgrade | 4.74 | 3.74 | 6.01 | 5.13E-38 | 3.36 | 1.22 | 9.21 | 0.019 |
| HR+(ER+PR-)HER2-lowgrade | 7.27 | 5.00 | 10.56 | 2.45E-25 | 6.42 | 1.49 | 27.61 | 0.013 |
| HR+(ER-PR+)HER2-lowgrade | 4.80 | 2.43 | 9.49 | 6.48E-06 | 7.11 | 0.91 | 55.34 | 0.061 |
| **HR+HER2+** | **5.28** | **3.73** | **7.45** | **4.26E-21** | **4.02** | **0.87** | **18.59** | **0.075** |
| HR+(ER+PR+)HER2+ | 5.23 | 3.54 | 7.71 | 7.17E-17 | 2.92 | 0.38 | 22.49 | 0.304 |
| HR+(ER+PR-)HER2+ | 4.80 | 2.43 | 9.49 | 6.48E-06 | 7.11 | 0.91 | 55.34 | 0.061 |
| HR+(ER-PR+)HER2+ | 7.42 | 2.72 | 20.30 | 9.38E-05 | 0.14 | NA | NA | 0.902 |
| **HR+HER2-highgrade** | **11.53** | **8.92** | **14.90** | **7.88E-78** | **16.07** | **6.19** | **41.72** | **1.15E-08** |
| HR+(ER+PR+)HER2-highgrade | 11.00 | 8.30 | 14.59 | 2.58E-62 | 15.53 | 5.45 | 44.24 | 2.82E-07 |
| HR+(ER+PR-)HER2-highgrade | 12.49 | 8.08 | 19.31 | 6.98E-30 | 20.53 | 4.36 | 96.78 | 0.0001 |
| HR+(ER-PR+)HER2-highgrade | 14.21 | 7.26 | 27.79 | 9.23E-15 | 0.27 | NA | NA | 0.928 |
| **PR-pos vs PR-neg (adjusted)** | **0.77** | **0.58** | **1.01** | **0.0568** | **0.54** | **0.19** | **1.48** | **0.231** |
| **Gene** | ***CHEK2 PTV*** | | | | ***TP53 PTV MSV*** | | | |
| **HR+HER2-lowgrade** | **2.65** | **2.25** | **3.14** | **2.27E-30** | **1.40** | **0.62** | **3.13** | **0.417** |
| HR+(ER+PR+)HER2-lowgrade | 2.69 | 2.26 | 3.20 | 1.24E-28 | 1.28 | 0.53 | 3.11 | 0.583 |
| HR+(ER+PR-)HER2-lowgrade | 2.50 | 1.76 | 3.56 | 3.10E-07 | 2.11 | 0.41 | 10.94 | 0.375 |
| HR+(ER-PR+)HER2-lowgrade | 2.91 | 1.70 | 4.99 | 0.0001 | 7.10 | 1.61 | 31.31 | 0.010 |
| **HR+HER2+** | **3.17** | **2.36** | **4.26** | **1.78E-14** | **7.14** | **3.34** | **15.28** | **4.16E-07** |
| HR+(ER+PR+)HER2+ | 3.10 | 2.18 | 4.40 | 2.92E-10 | 7.44 | 3.24 | 17.13 | 2.35E-06 |
| HR+(ER+PR-)HER2+ | 2.91 | 1.70 | 4.99 | 0.0001 | 7.10 | 1.61 | 31.31 | 0.010 |
| HR+(ER-PR+)HER2+ | 5.80 | 2.53 | 13.30 | 3.31E-05 | 0.09 | NA | NA | 0.875 |
| **HR+HER2-highgrade** | **3.02** | **2.33** | **3.91** | **6.14E-17** | **3.40** | **1.36** | **8.46** | **0.009** |
| HR+(ER+PR+)HER2-highgrade | 3.43 | 2.59 | 4.54 | 6.21E-18 | 2.52 | 0.78 | 8.17 | 0.122 |
| HR+(ER+PR-)HER2-highgrade | 1.97 | 1.01 | 3.84 | 0.047 | 7.73 | 2.26 | 26.46 | 0.001 |
| HR+(ER-PR+)HER2-highgrade | 1.43 | 0.28 | 7.28 | 0.666 | 0.04 | NA | NA | 0.844 |
| **PR-pos vs PR-neg (adjusted)** | **1.15** | **0.87** | **1.53** | **0.331** | **0.54** | **0.24** | **1.22** | **0.141** |
| **Gene** | ***PALB2 PTV*** | | | | | | | |
| **HR+HER2-lowgrade** | **3.39** | **2.35** | **4.89** | **6.20E-11** | | | | |
| HR+(ER+PR+)HER2-lowgrade | 3.16 | 2.15 | 4.65 | 4.34E-09 | | | | |
| HR+(ER+PR-)HER2-lowgrade | 4.90 | 2.66 | 9.05 | 3.65E-07 | | | | |
| HR+(ER-PR+)HER2-lowgrade | 5.69 | 2.21 | 14.68 | 0.0003 | | | | |
| **HR+HER2+** | **5.70** | **3.35** | **9.70** | **1.37E-10** | | | | |
| HR+(ER+PR+)HER2+ | 5.48 | 3.03 | 9.93 | 2.00E-08 | | | | |
| HR+(ER+PR-)HER2+ | 5.69 | 2.21 | 14.68 | 0.0003 | | | | |
| HR+(ER-PR+)HER2+ | 6.98 | 1.11 | 43.74 | 0.038 | | | | |
| **HR+HER2-highgrade** | **9.43** | **6.24** | **14.25** | **1.53E-26** | | | | |
| HR+(ER+PR+)HER2-highgrade | 8.72 | 5.50 | 13.83 | 3.20E-20 | | | | |
| HR+(ER+PR-)HER2-highgrade | 9.21 | 4.34 | 19.56 | 7.68E-09 | | | | |
| HR+(ER-PR+)HER2-highgrade | 17.78 | 7.22 | 43.81 | 3.96E-10 | | | | |
| **PR-pos vs PR-neg (adjusted)** | **0.80** | **0.52** | **1.24** | **0.323** | | | | |

PTV, protein truncating variants; MSV, missense variants; HR, Hormone receptor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; OR, Odds Ratio; CI, Confidence Intervals

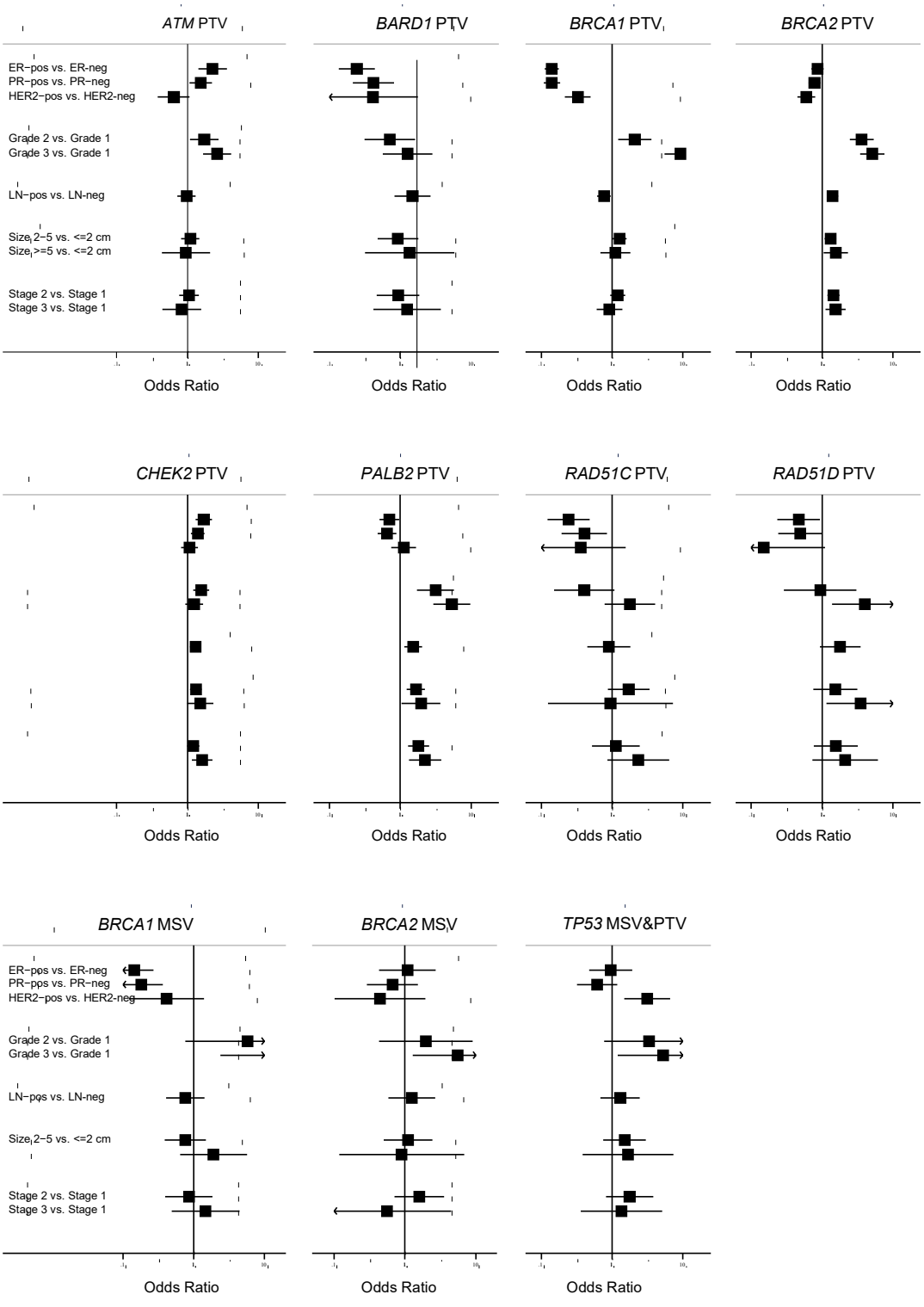
[a]OR for association with intrinsic subtype (bold) and according to ER and PR status- multinomial logistic regression with controls as baseline, adjusted for country and age [b]OR for association with PR status adjusted by intrinsic subtypes, as described in the eMethods.

## eTable 9: Odds ratios for association between PTV and MSV carrier status and intrinsic subtypes of breast cancer following imputation using an EM algorithm.

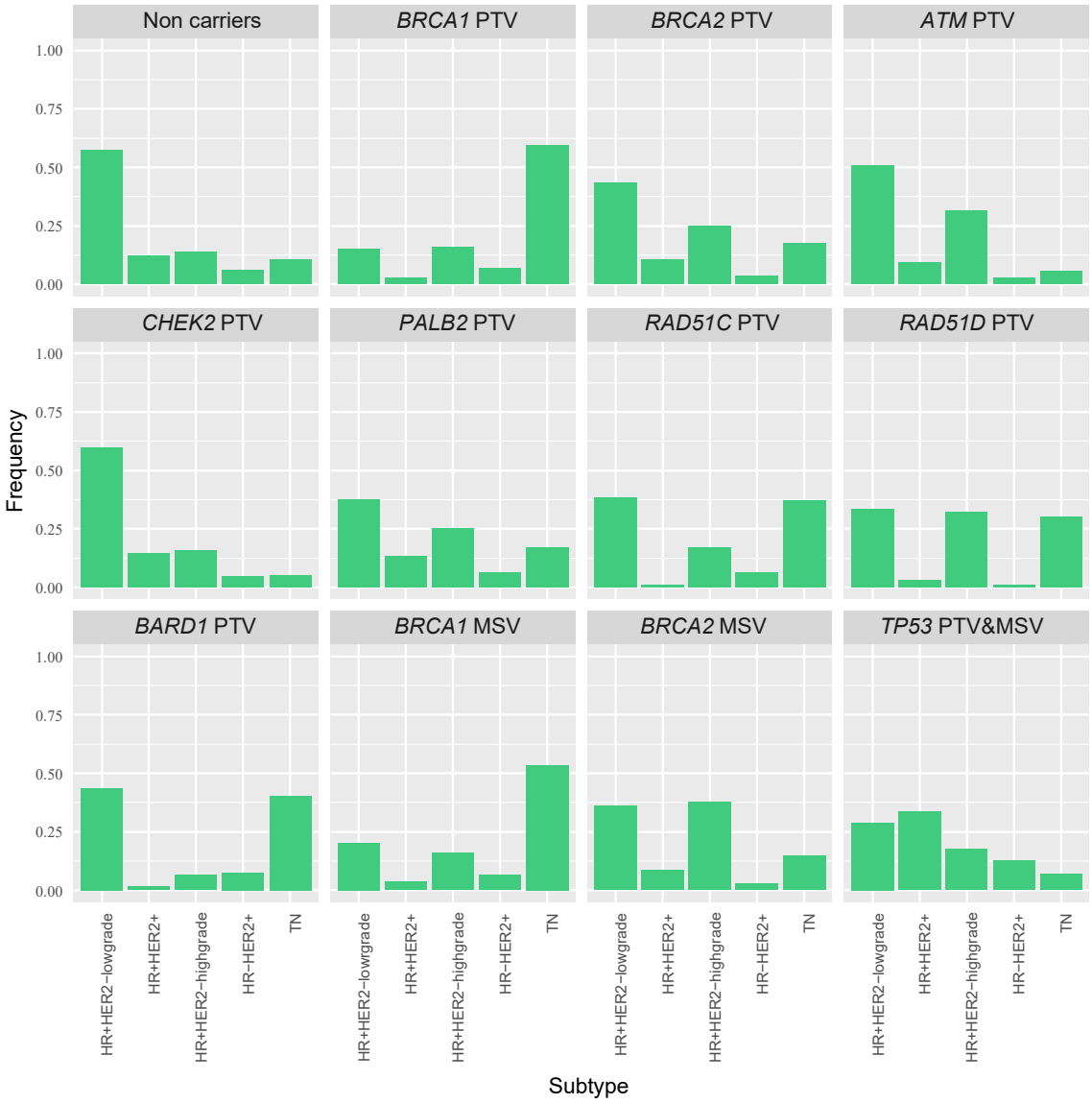
| | Intrinsic subtypes | | | |
|---|---|---|---|---|
| **Gene** | OR | L95CI | U95CI | p-value |
| *ATM PTV* | | | | |
| HR+HER2-lowgrade | 1.88 | 1.45 | 2.44 | 2.05E-06 |
| HR+HER2+ | 1.60 | 0.89 | 2.85 | 0.114 |
| HR+HER2-highgrade | 4.93 | 3.65 | 6.66 | 3.27E-25 |
| HR-HER2+ | 1.10 | 0.44 | 2.74 | 0.845 |
| TN | 0.87 | 0.42 | 1.8 | 0.704 |
| *BRCA1 PTV* | | | | |
| HR+HER2-lowgrade | 2.83 | 1.9 | 4.22 | 3.44E-07 |
| HR+HER2+ | 2.88 | 1.44 | 5.77 | 2.89E-03 |
| HR+HER2-highgrade | 12.53 | 8.46 | 18.57 | 2.01E-36 |
| HR-HER2+ | 8.51 | 4.87 | 14.89 | 5.88E-14 |
| TN | 55.4 | 40.6 | 75.61 | 2.69E-141 |
| *BRCA2 PTV* | | | | |
| HR+HER2-lowgrade | 4.70 | 3.73 | 5.9 | 6.13E-40 |
| HR+HER2+ | 6.02 | 4.28 | 8.45 | 3.62E-25 |
| HR+HER2-highgrade | 10.97 | 8.47 | 14.21 | 1.84E-73 |
| HR-HER2+ | 2.15 | 1.09 | 4.23 | 2.70E-02 |
| TN | 9.75 | 7.4 | 12.85 | 8.77E-59 |
| *CHEK2 PTV* | | | | |
| HR+HER2-lowgrade | 2.61 | 2.2 | 3.08 | 3.44E-29 |
| HR+HER2+ | 3.01 | 2.22 | 4.07 | 9.91E-13 |
| HR+HER2-highgrade | 2.93 | 2.24 | 3.83 | 4.84E-15 |
| HR-HER2+ | 2.33 | 1.51 | 3.62 | 0.0001 |
| TN | 0.94 | 0.58 | 1.53 | 0.811 |
| *PALB2 PTV* | | | | |
| HR+HER2-lowgrade | 3.04 | 2.09 | 4.42 | 5.65E-09 |
| HR+HER2+ | 5.99 | 3.57 | 10.05 | 1.22E-11 |
| HR+HER2-highgrade | 9.60 | 6.42 | 14.36 | 3.75E-28 |
| HR-HER2+ | 4.86 | 2.5 | 9.43 | 3.08E-06 |
| TN | 7.28 | 4.67 | 11.37 | 2.38E-18 |
| *BRCA1 MSV* | | | | |
| HR+HER2-lowgrade | 5.88 | 1.72 | 20.03 | 0.0046 |
| HR+HER2+ | 8.31 | 1.09 | 63.09 | 0.04 |
| HR+HER2-highgrade | 22.13 | 5.99 | 81.8 | 3.42E-06 |
| HR-HER2+ | 14.06 | 2.61 | 75.61 | 2.08E-03 |
| TN | 73.07 | 25.27 | 211.32 | 2.35E-15 |
| *TP53 MSV* | | | | |
| HR+HER2-lowgrade | 1.21 | 0.52 | 2.82 | 0.66 |
| HR+HER2+ | 7.40 | 3.49 | 15.72 | 1.87E-07 |
| HR+HER2-highgrade | 3.38 | 1.37 | 8.32 | 0.008 |
| HR-HER2+ | 5.61 | 2.01 | 15.62 | 0.001 |
| TN | 1.55 | 0.38 | 6.35 | 0.544 |

PTV, protein truncating variants; MSV, missense variants; HR, Hormone receptor; HER2, human epidermal growth factor receptor 2; TN, triple negative; OR, Odds Ratio; CI, Confidence Intervals. Polytomous logistic regression was carried out adjusting for age as a continuous variable and country, using the EM algorithm for imputation as implemented in the TOP program (Online eMethods)

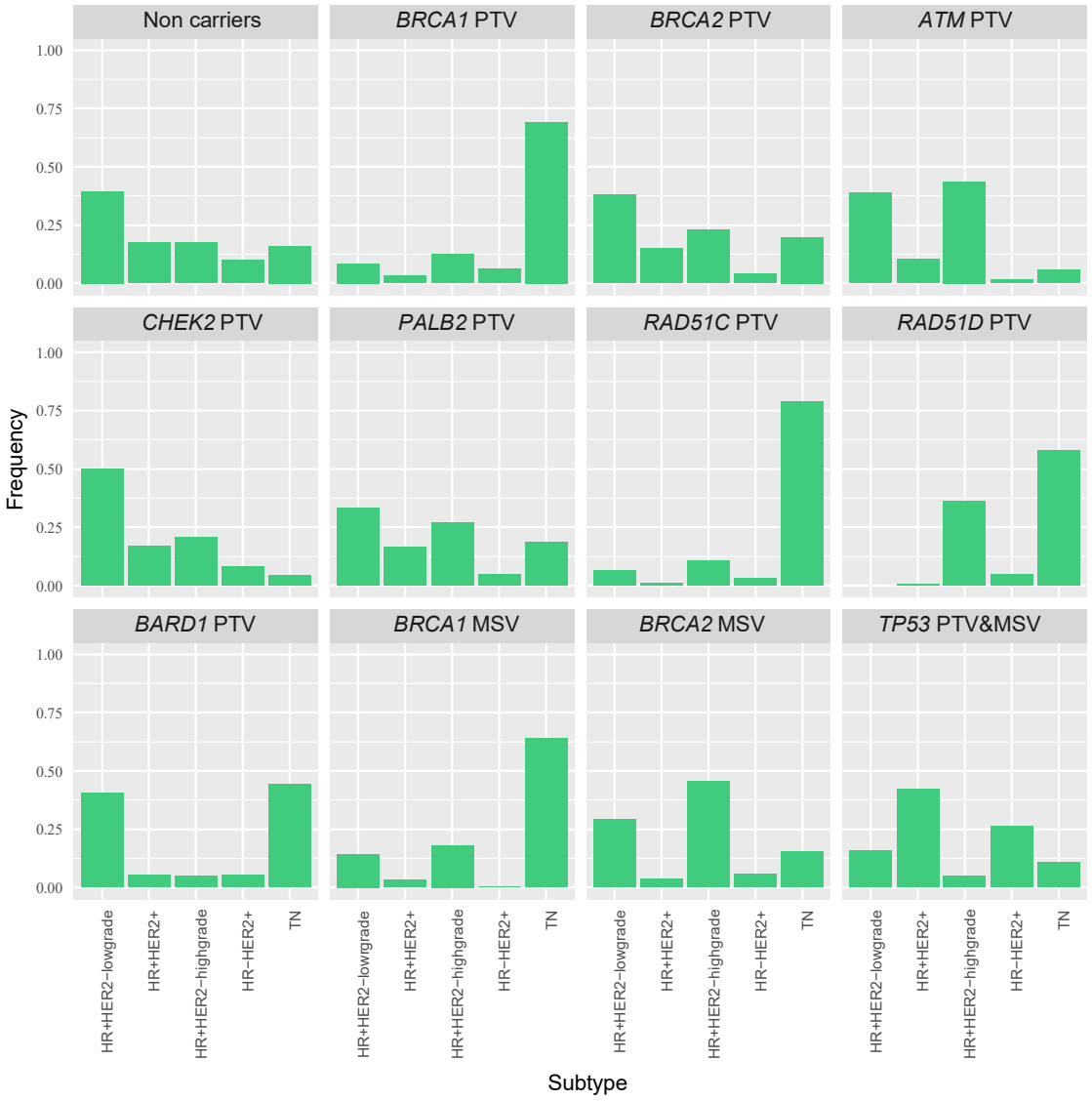
**eFigure 1. Case-only analysis of phenotypic markers and prognostic features by gene (complete case analysis)** Case-only logistic or multinomial logistic regression analyses adjusted for age at diagnosis/interview and country as described in the Methods. Odds Ratio and Confidence Intervals are shown. PTV, protein truncating variants; MSV, missense variants; ER, estrogen receptor; PR, progesterone receptor, HER2; human epidermal growth factor receptor 2; LN, lymph node.


ATM PTV
BARD1 PTV
BRCA1 PTV
BRCA2 PTV
ER−pos vs. ER-neg
PR−pos vs. PR−neg
HER2−pos vs. HER2-neg
Grade 2 vs. Grade 1
Grade 3 vs. Grade 1
LN−pos vs. LN-neg
Size 2−5 vs. <=2 cm
Size >=5 vs. <=2 cm
Stage 2 vs. Stage 1
Stage 3 vs. Stage 1
Odds Ratio
CHEK2 PTV
PALB2 PTV
RAD51C PTV
RAD51D PTV
BRCA1 MSV
BRCA2 MSV
TP53 MSV&PTV

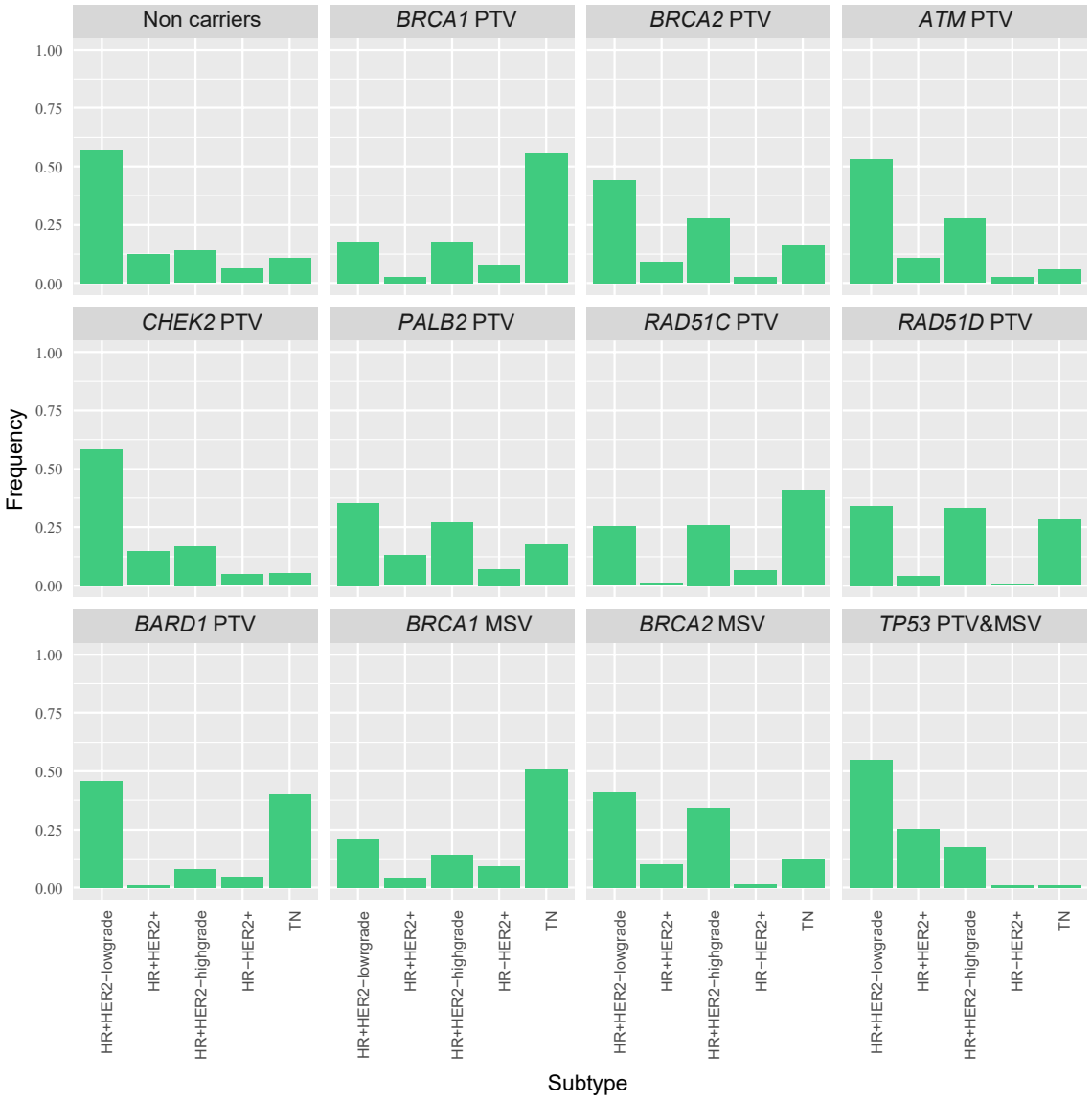
**eFigure 2. Frequency distribution of intrinsic subtypes among noncarriers and carriers of PTVs and MSVs in the 9 genes.** MICE Imputation was carried out as described in the Methods and intrinsic subtypes constructed for each imputed data-set. The histogram represents the average proportion (over all 100 imputations) of all tumors of a particular subtype. For some genes and subtypes, data are limited, and therefore frequency is imprecise. These results are also shown in eTable 10.



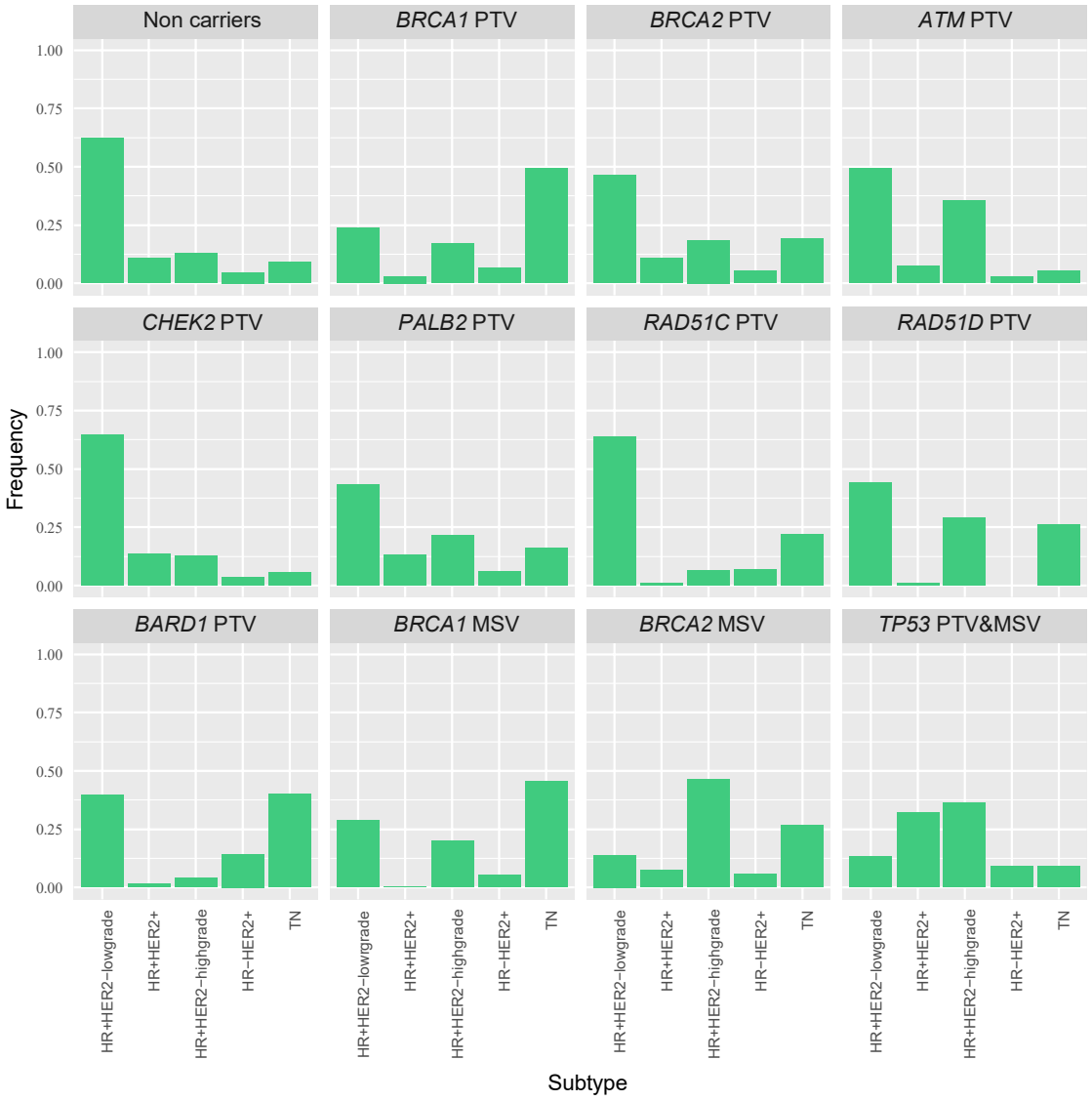
**eFigure 3. Frequency distribution of intrinsic subtypes among noncarriers and carriers of PTVs and MSVs in the 9 genes, in women aged ≤40 years.**



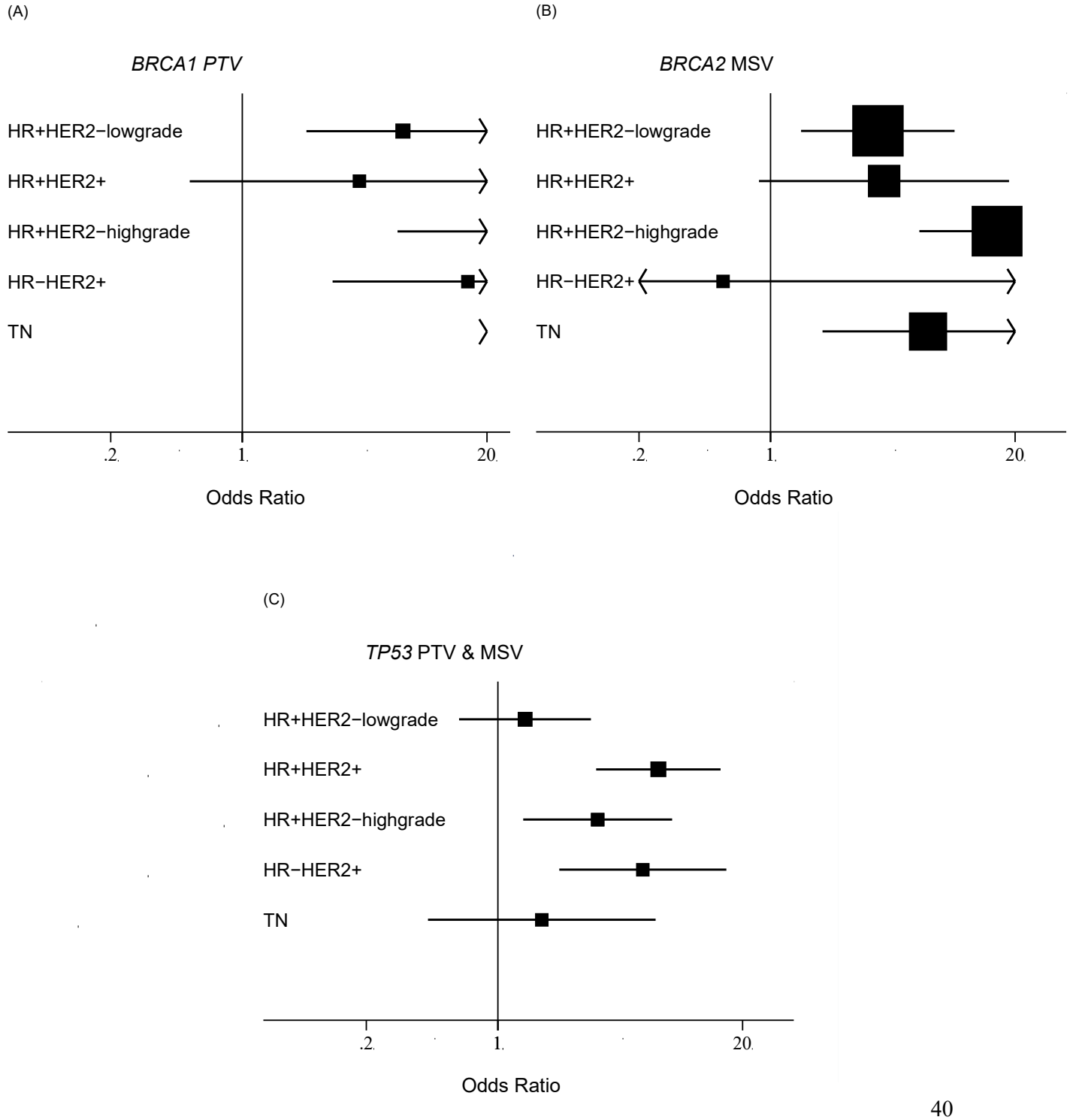
**eFigure 4. Frequency distribution of intrinsic subtypes among noncarriers and carriers of PTVs and MSVs in the 9 genes, in women aged 41-60 years.**



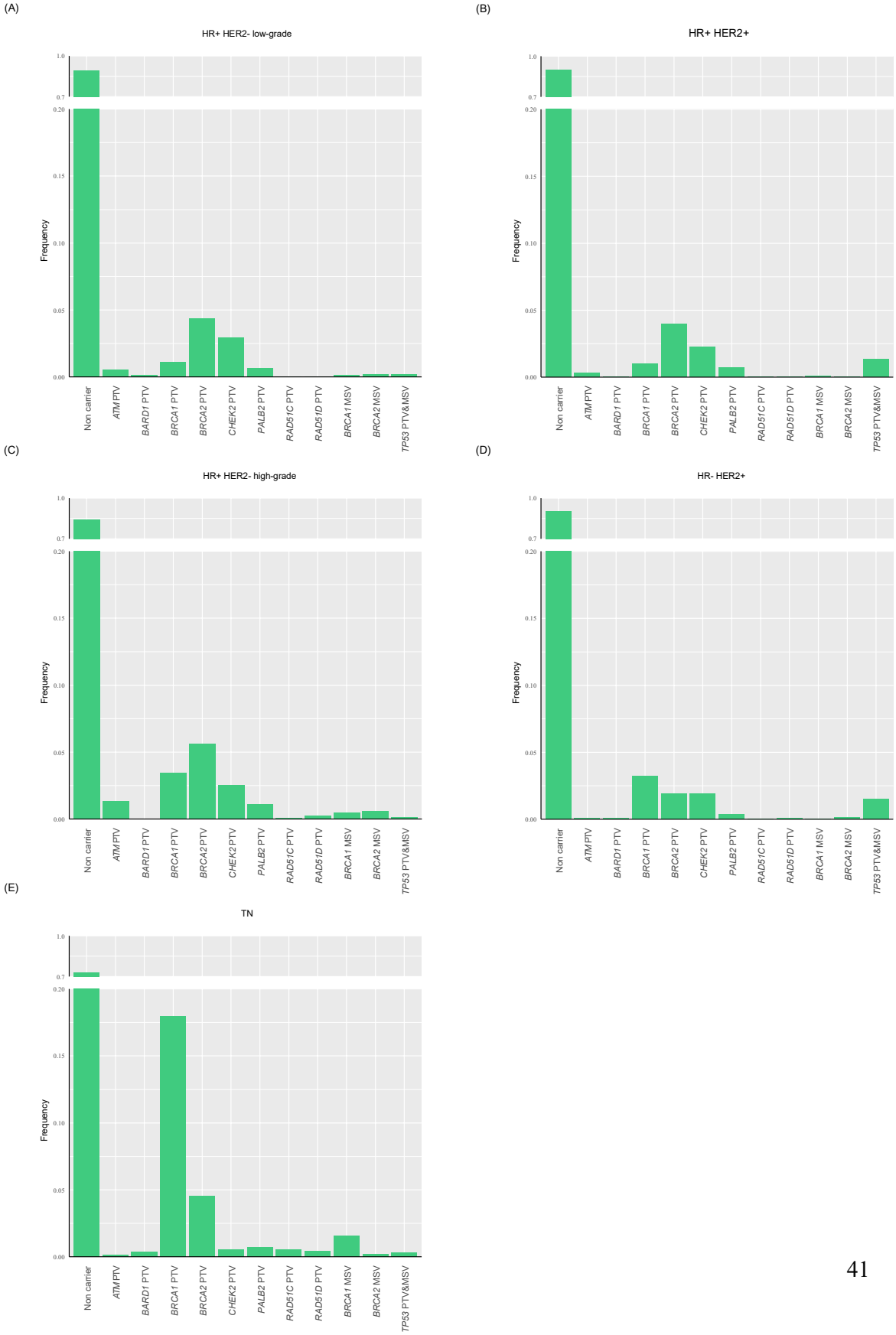
**eFigure 5. Frequency distribution of intrinsic subtypes among noncarriers and carriers of PTVs and MSVs in the 9 genes, in women aged >60 years.**



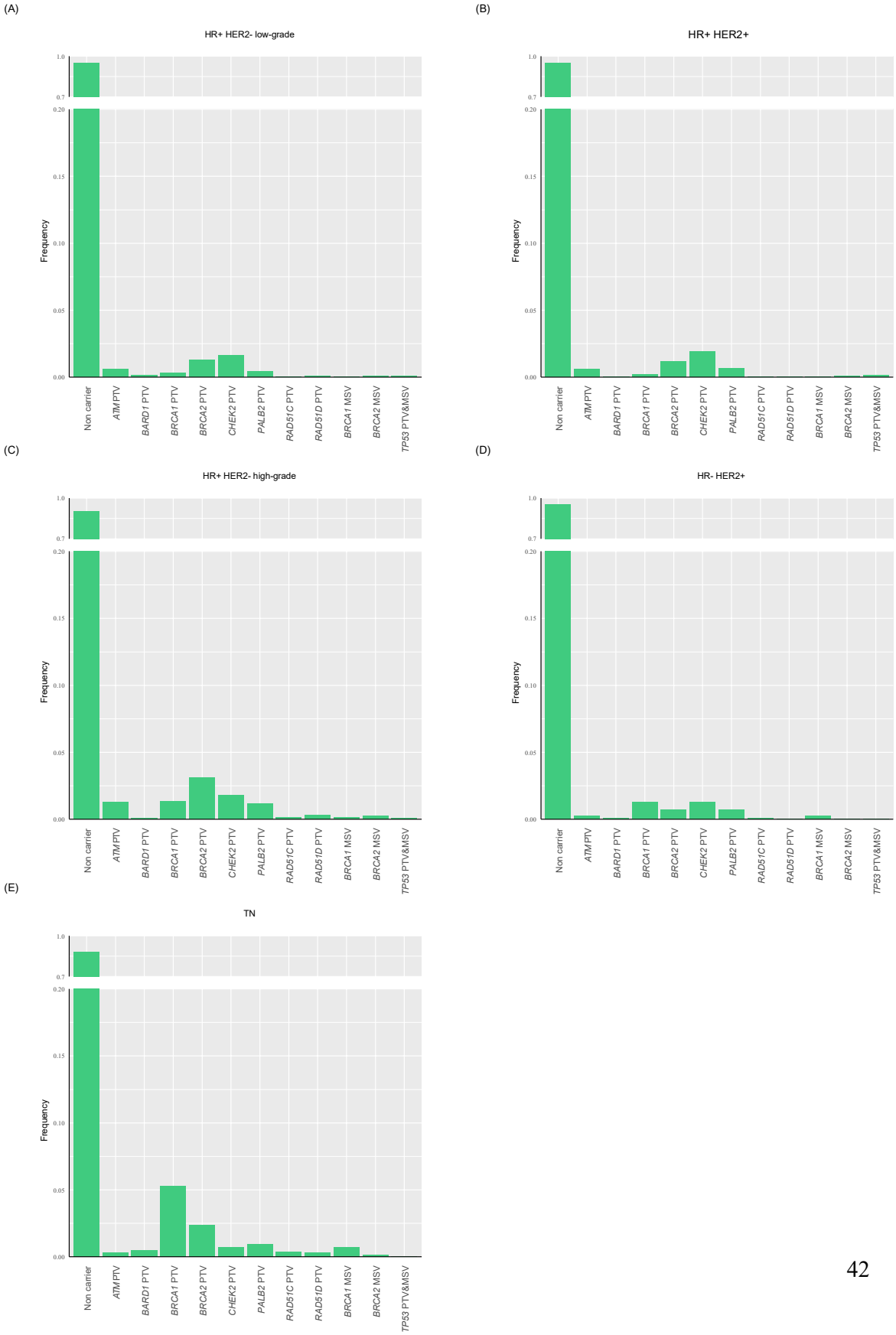
**eFigure 6. Association odds ratios for MSV carrier status in *BRCA1*, *BRCA2*, *TP53* and intrinsic subtypes of breast cancer.** MICE Imputation was carried out as described in the Methods and intrinsic subtypes constructed for each imputed data-set. Multinomial logistic regression as carried out with intrinsic subtypes as the outcome variable, adjusting by age at diagnosis/interview and country and the results of these analyses were pooled. These results are also shown in eTable 9.



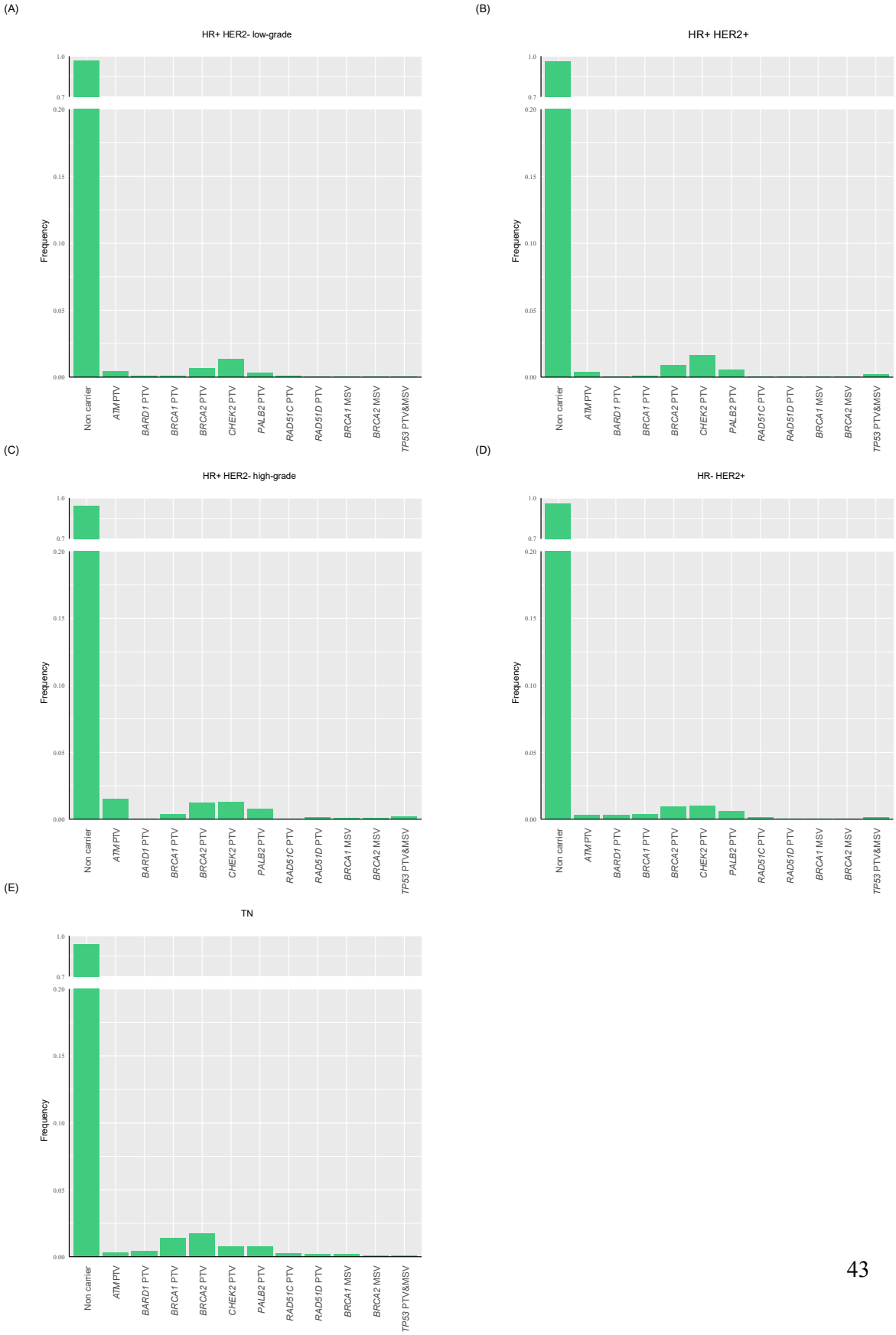
**eFigure 7. Prevalence of PTV and MSV in breast cancer susceptibility genes by intrinsic subtypes of breast cancer among women aged ≤40 at diagnosis (A) HR+ HER2- low-grade (B) HR+ HER2- (C) HR+ HER2- high-grade (D) HR- HER2+ (E) TN.**



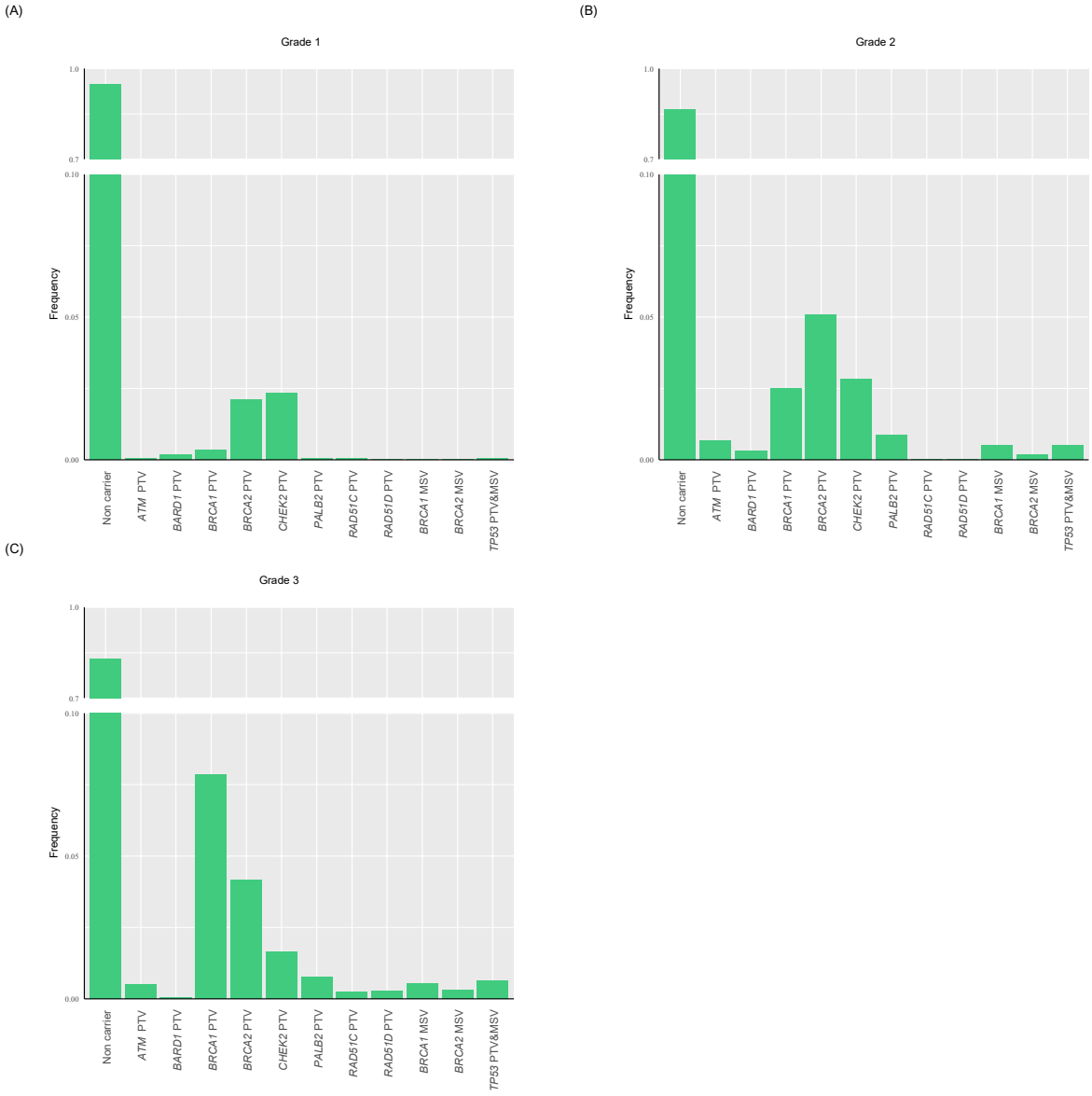
**eFigure 8. Prevalence of PTV and MSV in breast cancer susceptibility genes by intrinsic subtypes of breast cancer among women aged 41-60 at diagnosis (A) HR+ HER2- low-grade (B) HR+ HER2- (C) HR+ HER2- high-grade (D) HR- HER2+ (E) TN.**



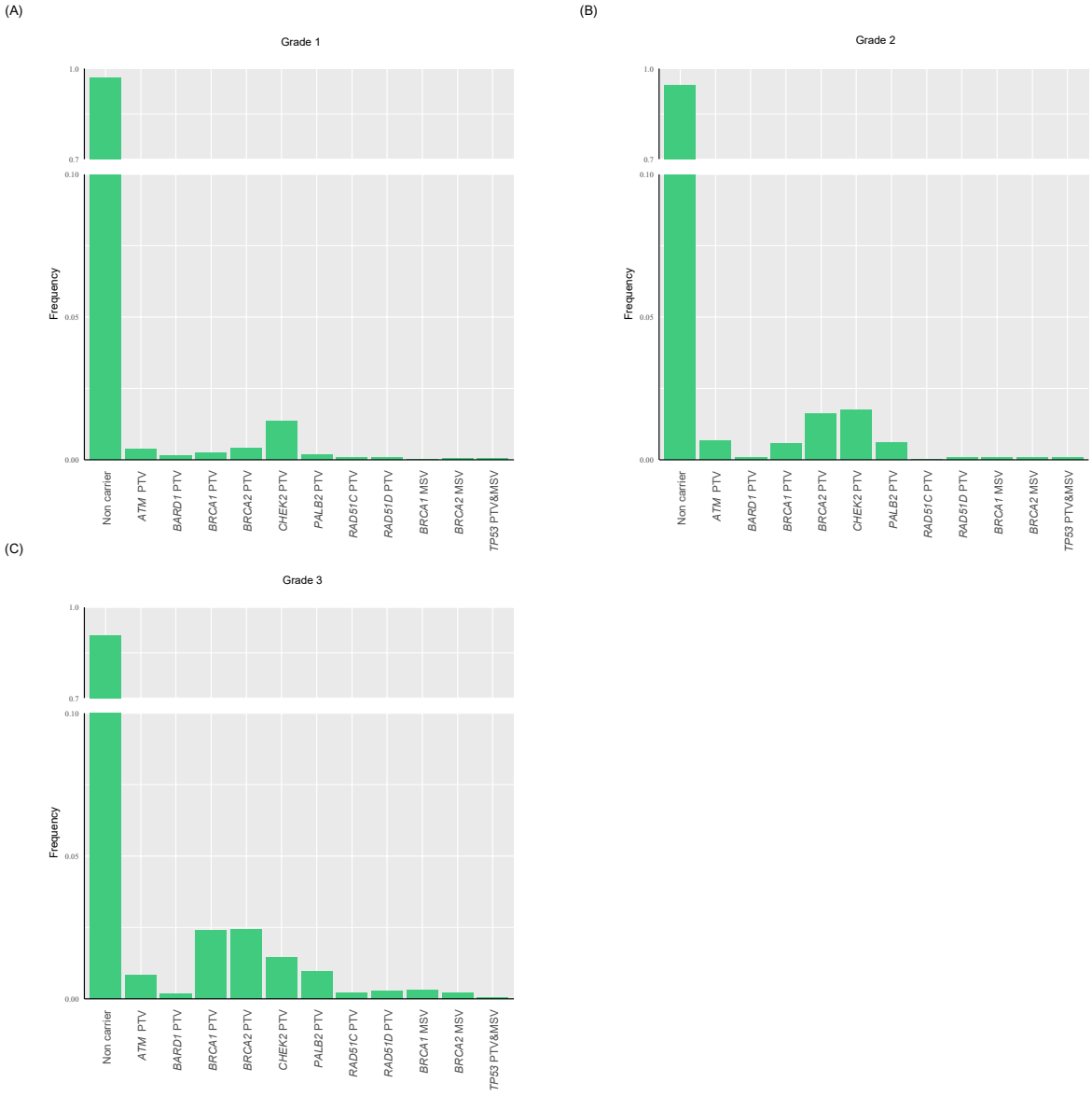
**eFigure 9. Prevalence of PTV and MSV in breast cancer susceptibility genes by intrinsic subtypes of breast cancer among women aged >60 at diagnosis (A) HR+ HER2- low-grade (B) HR+ HER2- (C) HR+ HER2- high-grade (D) HR- HER2+ (E) TN.**



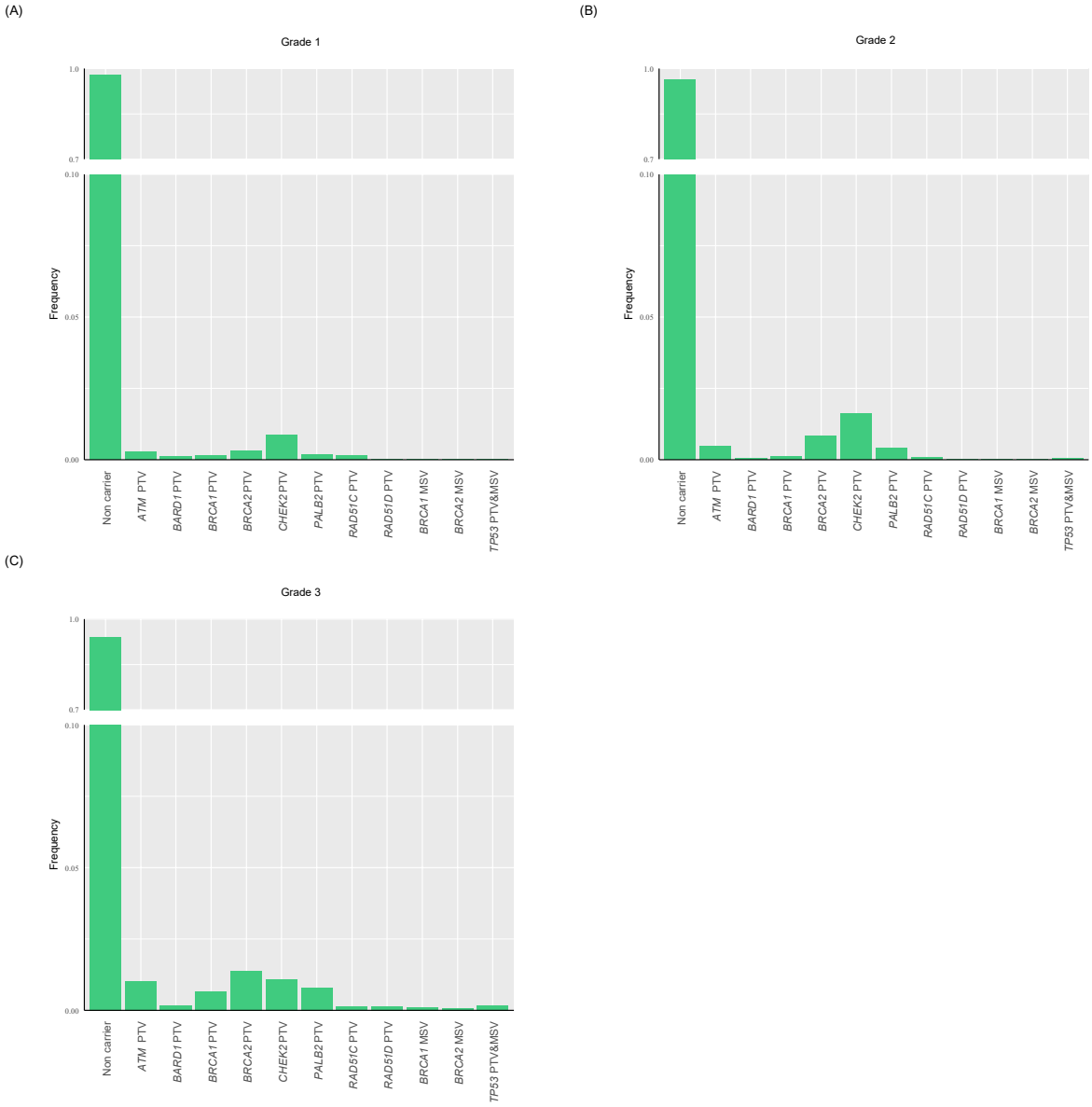
**eFigure 10. Prevalence of PTV and MSV in breast cancer susceptibility genes by tumor grade among women aged ≤40 at diagnosis (A) Grade 1 (B) Grade 2 (C) Grade 3.**



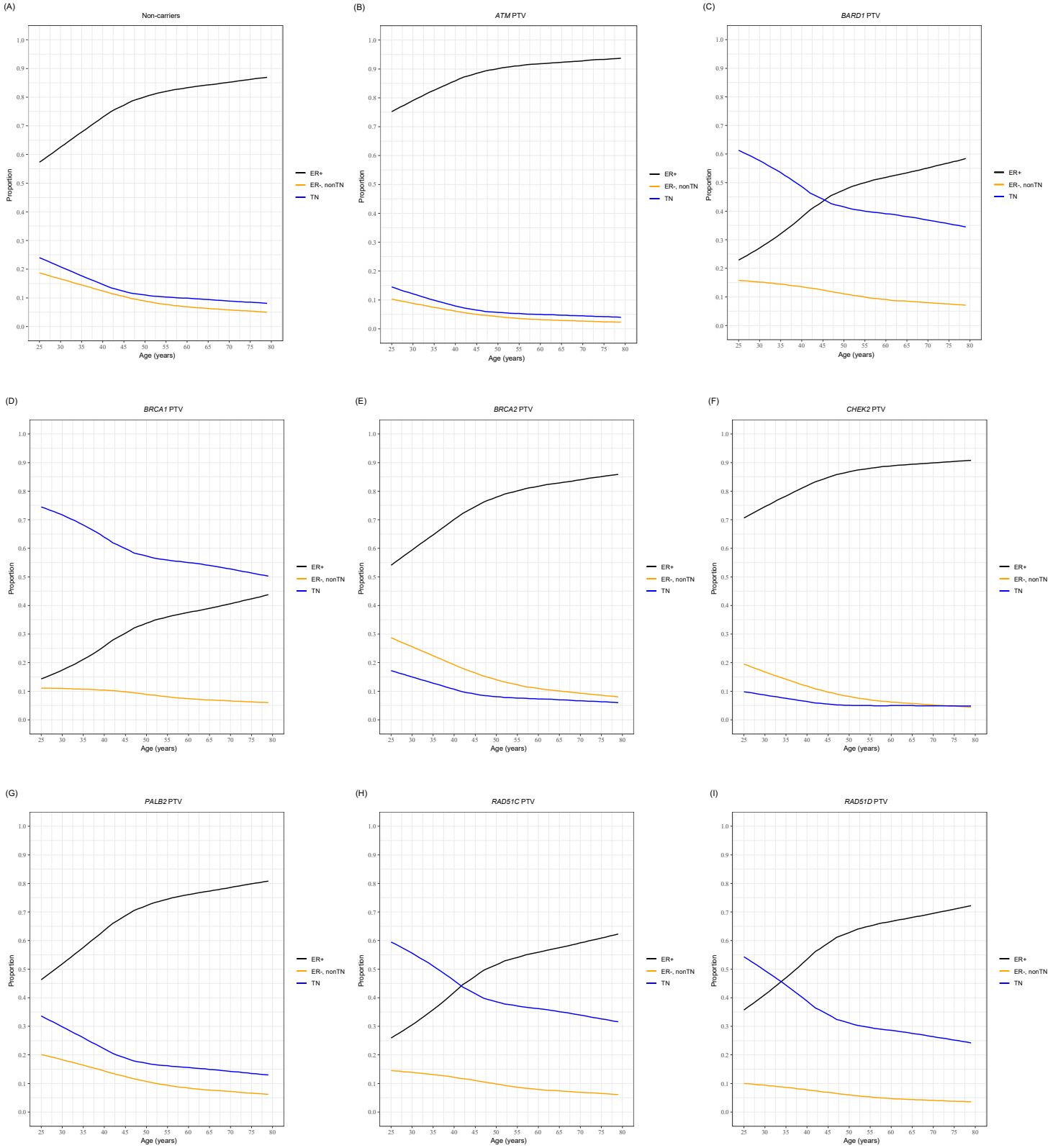
**eFigure 11. Prevalence of PTV and MSV in breast cancer susceptibility genes by tumor grade among women aged 41-60 at diagnosis (A) Grade 1 (B) Grade 2 (C) Grade 3.**



**eFigure 12. Prevalence of PTV and MSV in breast cancer susceptibility genes by tumor grade among women aged >60 at diagnosis (A) Grade 1 (B) Grade 2 (C) Grade 3.**



**eFigure 13. Smoothed proportions of subtypes used in BOADICEA for PTVs in (A) non-carriers (B) *ATM* (C) *BARD1* (D) *BRCA1* (E) *BRCA2* (F) *CHEK2* (G) *PALB2* (H) *RAD51C* and (I) *RAD51D.*** Age-specific smoothed proportions of subtypes used in BOADICEA/CanRisk were derived as described in the eMethods. These results are the same as those shown in eTable 14.



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