BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years

L Robertson1,2,8, H Hanson1,3,8, S Seal1, M Warren-Perry1, D Hughes1, I Howell1, C Turnbull1, R Houlston1, S Shanley2, S Butler2, DG Evans4, G Ross5, D Eccles6, A Tutt7, N Rahman*,1,2 and TNT Trial TMG, BCSC (UK)*

1Division of Genetics and Epidemiology, Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey SM2 5NG, UK; 2Department of Cancer Genetics, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton SM2 5PT, UK; 3Sw Thames Regional Genetics Service, St George’s University of London, St George’s Hospital, Tooting, London SW17 0RE, UK; 4Department of Genetic Medicine, St Mary’s Hospital, Manchester Academic Health Science Centre, Manchester M13 9WL, UK; 5Breast Cancer Unit, Royal Marsden NHS Foundation Trust, London SW3 6JJ, UK; 6Human Cancer Sciences Division, Faculty of Medicine, University of Southampton, Southampton University Hospitals NHS Trust, Southampton SO16 6YD, UK; 7Breakthrough Breast Cancer Research Unit, King’s College, London SE1 9RT, UK

Keywords: triple-negative; BRCA1; breast cancer; genetic testing

BACKGROUND: Triple-negative (TN) tumours are the predominant breast cancer subtype in BRCA1 mutation carriers. Recently, it was proposed that all individuals below 50 years of age with TN breast cancer should be offered BRCA testing. We have evaluated the BRCA1 mutation frequency and the implications for clinical practice of undertaking genetic testing in women with TN breast cancer.

METHODS: We undertook BRCA1 mutation analysis in 308 individuals with TN breast cancer, 159 individuals from unselected series of breast cancer and 149 individuals from series ascertained on the basis of young age and/or family history.

RESULTS: BRCA1 mutations were present in 45 out of 308 individuals. Individuals with TN cancer <50 years had >10% likelihood of carrying a BRCA1 mutation in both the unselected (11 out of 58, 19%) and selected (26 out of 111, 23%) series. However, over a third would not have been offered testing using existing criteria. We estimate that testing all individuals with TN breast cancer <50 years would generate an extra 1200 tests annually in England.

CONCLUSION: Women with TN breast cancer diagnosed below 50 years have >10% likelihood of carrying a BRCA1 mutation and are therefore eligible for testing in most centres. However, implementation may place short-term logistical and financial burdens on genetic services.

British Journal of Cancer (2012) 106, 1234–1238. doi:10.1038/bjc.2012.31 www.bjcancer.com

© 2012 Cancer Research UK

Keywords: triple-negative; BRCA1; breast cancer; genetic testing

Triple-negative (TN) breast cancer describes a subgroup of tumours that lack expression of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2) (Foulkes et al., 2010). Overall, TN cancers account for about 15% of all breast cancers, but occur more frequently in younger women and are the predominant cancer subtype in individuals with a germline BRCA1 mutation (Bauer et al., 2007; Atchley et al., 2008; Blows et al., 2010; Foulkes et al., 2010).

The identification of a BRCA mutation has profound consequences for clinical management; impacting on the likelihood of developing contralateral breast cancer and/or ovarian cancer and increasingly having implications for optimal therapy (Antoniou et al., 2003; Fong et al., 2009; Tutt et al., 2010; Nathanson and Domchek, 2011). Due to financial and logistical constraints, BRCA testing is currently rationed in most countries. In the US and much of Europe, BRCA testing is typically undertaken if the likelihood of detecting a mutation is >10% (American Society of Clinical Oncology, 2003; Gadzicki et al., 2011). In the UK, the National Institute for Health and Clinical Excellence (NICE) recommended that testing should minimally be offered if the likelihood of detecting a mutation is >20%, though many UK centres also offer testing if the likelihood is between 10–20%, (McIntosh et al., 2004; NICE, 2006). Several different methods to determine which cases are eligible for testing are utilised in clinical practice, most of which require specialised knowledge and/or software (Antoniou et al., 2008).

The recognition of the strong association of the TN phenotype and BRCA1 mutations has led to efforts for establishing the frequency of BRCA1 mutations in individuals with TN breast cancer. To date, several small studies have evaluated this in both unselected series and case series selected on the basis of family history and/or age (Table 1). Additionally, it was recently proposed that BRCA testing all women with TN cancers diagnosed below 50 years would be cost-effective with respect to overall health spending at a national level (Kwon et al., 2010), based on an estimated mutation prevalence of 10–25%. However, this study did not address the practical and cost implications for the local services that undertake testing.
In this study, we have undertaken BRCA1 analysis in 308 individuals with TN breast cancer; the largest study to date. We have used the data to further evaluate the mutation frequency and to consider the practical ramifications of undertaking BRCA testing in individuals with TN breast cancer.

**MATERIALS AND METHODS**

**Cases**

We included 308 TN breast cancers from UK. Oestrogen receptor, PR and HER2 status were confirmed either in a histopathology report and/or a clinician’s referral letter. When not explicitly stated, ER and PR status were scored as negative when there was absent expression (equivalent to a Quickscore of 0 out of 8). Human epidermal growth factor receptor was regarded as negative when scored as 0 or 1 – for HER2 by immunohistochemistry and/or when there was non-amplification of HER2 by fluorescent in situ hybridisation.

The cases were either from case series unselected with respect to genetic susceptibility (the unselected series n = 159) or from case series that were specifically ascertained because of young age at diagnosis and/or a family history of breast cancer (the selected series n = 149). The unselected series came from either the ongoing TNT trial ISRCTN97330959 (Kilburn, 2008), a UK-wide randomised phase III trial of carboplatin compared with docetaxel for patients with metastatic or recurrent locally advanced TN breast cancer (n = 81); or the Marsden sample series, which was a collection of samples from breast cancer patients attending the oncology clinics at the Marsden Hospital (n = 78). The selected series came from either the Familial Breast Cancer Study (n = 90), from referrals to our regional genetics department (n = 25) or from the Prospective study of Outcomes in Sporadic versus Hereditary breast cancer (POSH, n = 34). The latter was a UK-wide study that recruited individuals with invasive breast cancer aged <40 years (Eccles et al, 2007). None of the cases have been included in any other published study on TN breast cancer. The study was undertaken as part of our research into the genetic causes of breast cancer, which has been approved by the London Multicentre Research Ethics Committee (MREC/01/2/18).

**BRCA1 analysis**

BRCA1 mutation analysis, including multiplex ligation-dependent probe amplification (MLPA) analysis for large deletions/duplications, was performed in DNA from all cases. This was either performed through a clinical BRCA test by the local centre, or was undertaken by ourselves by sequencing genomic DNA through the 24 coding exons and intron–exon boundaries of BRCA1 and undertaking MLPA using probe mix P002. All mutations were confirmed by separate bi-directional sequencing in a second sample. All copy number changes were confirmed in a fresh aliquot of DNA with a different probe mix (P087). The mutation nomenclature is in accordance with HGVS convention with numbering starting at the first A of the ATG initiation site, using U14680.1 as the reference sequence.

**Assessment of eligibility for clinical BRCA testing**

Currently, in UK there is variability in the threshold used for BRCA testing; in the South West Thames Regional Genetics and Royal Marsden Cancer Genetics services we use a threshold of 10% and primarily use the Manchester score to assess this (Evans et al, 2005). Family history information was available for 271 individuals. We calculated the Manchester score, and designated those with a score ≥15, as eligible for clinical testing (Supplementary Tables 1 and 2). Of note, this classification does not necessarily mean that these cases actually had clinical BRCA testing; for many, this information was not known and in some cases we were aware that testing had not occurred. The classification denotes whether the patient would have been eligible for testing by genetics departments operating a 10% mutation detection threshold.

**Age-specific TN breast cancer incidence**

National breast cancer figures in England are not subclassified by receptor status. Therefore, to estimate the annual age-specific incidence of TN breast cancer in England we used the national figures for age-specific breast cancer incidence published by the Office for National Statistics for England (Office for National Statistics, 2006) and data from a study of 10159 cases of breast cancer subtype by immunohistochemistry (Blows et al, 2010). This allowed us to estimate the annual age-specific incidence of TN breast cancer in England.

**RESULTS**

**BRCA1 mutation frequency**

The full results of all 308 cases are given in Supplementary Table 1. Overall, there were 45 BRCA1 mutations in the 308 individuals (14.6%). This included 15 (9.4%) BRCA1 mutations in 159 individuals in the unselected series, and 30 (20.1%) BRCA1 mutations in 149 individuals in the selected series (Table 2). There was a strong age-effect with marked decrease in mutation frequency in individuals aged over 50 years in both the unselected and selected series (Table 2). If one considers just individuals with sporadic TN breast cancer, that is, those without a first or second degree relative with breast or ovarian cancer, 8 out of 103 (8%) had a BRCA1 mutation, and all were under 50 years of age.

**Eligibility for clinical BRCA testing**

Family history data was available in 271 individuals, which included 122 out of 159 individuals in the unselected series and

---

**Table 1** Studies with over 50 cases that have evaluated BRCA1 mutation prevalence in TN cancers

| Number of cases | BRCA1 mutations (%) | Unselected/selected | Selection criteria                                                                 | Reference         |
|-----------------|---------------------|---------------------|-------------------------------------------------------------------------------------|-------------------|
| 144             | 20 (14)             | Unselected          | Bilateral and/or family history of breast cancer.                                   | Collins et al (2009) |
| 96              | 9 (9)               | Selected            | Seen in Genetic clinics and underwent BRCA testing.                                 | Zhang et al (2011)  |
| 93              | 32 (34)             | Selected            | Ashkenazi Jewish heritage. Tested for founder mutations.                            | Gonzalez-Angulo et al (2011) |
| 77              | 12 (16)             | Unselected          | TN < 41 years                                                                       | Comen et al (2011)  |
| 64              | 19 (30)             | Selected            | TN < 40 years and did not qualify for testing according to ASCO guidelines          | Evans et al (2011)  |
| 63              | 8 (13)              | Selected and unselected | TN < 41 years                                                                      | Evans et al (2011)  |
| 54              | 5 (9)               | Selected            | TN < 40 years                                                                       | Evans et al (2011)  |

Abbreviation: TN = Triple-negative.
Table 2 Summary of BRCA1 mutations in 308 TN breast cancer cases

|                | Unselected series BRCA1 mut/all (%) | Selected series BRCA1 mut/all (%) | Total BRCA1 mut/all (%) |
|----------------|------------------------------------|----------------------------------|-------------------------|
| All            | 15/159 (9)                         | 30/149 (20)                      | 45/308 (15)             |
| <50 years      | 11/58 (19)                         | 26/111 (23)                      | 37/169 (22)             |
| ≥50 years      | 4/101 (4)                          | 4/38 (11)                        | 8/139 (6)               |

Abbreviation: TN = Triple-negative.

Table 3 Eligibility for clinical BRCA testing by age and mutation status

|                | Unselected series MS ≥ 15/all (%) | Selected series MS ≥ 15/all (%) | Total MS ≥ 15/all (%) |
|----------------|-----------------------------------|---------------------------------|-----------------------|
| All            | 20/120 (16)                       | 65/149 (43)                     | 85/271 (31)           |
| <40 Years      | 5/16 (31)                         | 28/78 (39)                      | 33/94 (35)            |
| <50 Years      | 10/43 (23)                        | 45/111 (40)                     | 55/154 (36)           |
| BRCA1 mutations| 7/12 (58)                         | 20/30 (67)                      | 27/42 (64)            |
| BRCA1 mut. <40 years | 2/3 (67)                      | 8/15 (53)                      | 10/18 (55)            |
| BRCA1 mut. ≥50 years | 5/8 (63)                       | 17/26 (65)                     | 22/34 (65)            |

Abbreviation: MS = Manchester score.

Table 4 Age-specific incidence of TN breast cancer and impact on BRCA testing

| Age       | Total cases in England | Proportion that are TNβ (%) | TN cases per year | Proportion not eligible for BRCA testing per year, if all TN tested | Additional BRCA tests per year, if all TN tested |
|-----------|------------------------|-----------------------------|-------------------|---------------------------------------------------------------------|-----------------------------------------------|
| <40 Years | 1765                   | 29                          | 512               | 69                                                                  | 353                                           |
| <50 Years | 7384                   | 21                          | 1551              | 77                                                                  | 1194                                          |
| ≥60 Years | 16156                  | 17                          | 2747              | 79                                                                  | 2170                                          |
| All       | 38004                  | 16                          | 6081              | 84                                                                  | 5108                                          |

Abbreviation: TN = Triple-negative. *Office for National Statistics (2006). Extrapolated from the data in Blows et al (2010).

Impact of using age-specific testing threshold on BRCA testing

To estimate the number of BRCA tests that would be undertaken in TN cases, if age-specific criteria were employed, we used the cancer registration statistics from the Office for National Statistics for England (Office for National Statistics, 2006), together with the estimates of the proportion of breast cancers that are TN by age (Blows et al, 2010). These suggest that ~6000 women with TN breast cancer are diagnosed each year in England, of which ~500 are <40 years of age and ~1500 are <50 years of age (Table 4). If one assumes that the data from the unselected series are broadly representative of the proportion of these cases that would not currently be eligible for clinical BRCA testing, 69% (11 out of 16) of TN <40 years, 77% (33 out of 43) <50 years, 79% (72 out of 91) <60 years and (84%) (102 out of 122) of all TN cases would not be eligible for clinical BRCA testing (percentages reflect the number of individuals not eligible for testing/total number of individuals in that age group for whom eligibility status was known, see Supplementary Table 1). If all individuals with TN breast cancer diagnosed before 50 years of age were tested, these data suggest that an additional ~1200 BRCA tests would be performed per year in England.

DISCUSSION

We have undertaken the largest analysis of BRCA1 in TN breast cancer to date, and showed that the frequency of BRCA1 mutations in unselected individuals with TN breast cancer is ~10%, increasing to ~19% of individuals diagnosed below 50 years. The latter is similar to the frequency of BRCA1 mutations (23%) in individuals diagnosed before 50 years that were selected for inclusion because of a family history of breast cancer and/or young age at diagnosis. Our study included samples from four different sources and more precise figures would be obtainable from larger, prospective studies. Nevertheless, our results are similar to those previously reported and we believe that they are likely to be broadly accurate (refs in Table 1).

We estimated the proportion of individuals included in this study that would currently qualify for a clinical BRCA test. Our analysis suggests that over a third of the BRCA1 mutation-positive individuals we identified would not have been eligible for clinical genetic testing in departments that use a 10% mutation detection threshold calculated without consideration of histological parameters.

Taken together, these data strongly indicate that histological parameters should be included in deciding which individuals should be offered BRCA testing. There have been efforts to incorporate histological parameters into existing BRCA-testing selection systems, such as BOADICEA and the Manchester system, (Evans et al, 2009; Mavaddat et al, 2010). Additionally, studies to define testing criteria in individuals that are not eligible for testing using current systems (e.g., individuals with TN breast cancer but without a family history) have been undertaken (Young et al, 2009; Evans et al, 2011). We believe a drawback to these approaches is that complex evaluation by specialist practitioners is typically required for most cases, but is unnecessary in the sizeable proportion eligible for testing on the basis of age alone.

A simpler approach, which would be readily comprehensible by clinicians and patients, would be to define a BRCA testing eligibility criteria for women with TN breast cancer based on age. Only individuals above the age threshold would require the more detailed, specialist review incorporating family history and scoring algorithms to decide whether they were eligible for BRCA testing.

Our data suggests that diagnosis of TN cancer below 50 years would be a suitable age threshold for BRCA testing. It is also consistent with recent simulation data, suggesting that this testing threshold would be a cost-effective strategy and would result in substantial reduction in subsequent breast and ovarian cancer in mutation-positive women (Kwon et al, 2010). However, implementation of routine BRCA testing in all TN breast cancers diagnosed before 50 years would increase the logistical and financial burdens on genetic departments. We estimate that it would lead to ~1200 extra tests in England each year, which may be challenging for some departments to immediately implement with current resources and procedures. However, new sequencing technologies are leading us into an era of fast, affordable gene testing. Together with procedural reorganisation to allow BRCA testing in affected individuals to be undertaken though oncology services (with support from genetics as required), this should enable genetic services to introduce BRCA testing to women with TN breast cancer diagnosed below 50 years of age, within the next few years.
ACKNOWLEDGEMENTS

We thank all the individuals that participated in this study and the physicians, nurses and genetics counsellors who referred patients and provided samples. We thank E Ebbs for assistance in running the ABI sequencers. We thank D Dudakia, J Bull and A Zachariou for assistance with recruitment, D Pernet and A Elliott for database management and A Strydom for assistance with the manuscript. The full list of Breast Cancer Susceptibility Collaboration (UK) and the TNT Trial Management Group is provided in the Supplementary Information. This work was funded by Cancer Research UK (C8620/A8372 and C8620/A8857), US Military Acquisition (ACQ) Activity, Era of Hope Award (W81XWH-05-1-204) and the Institute of Cancer Research. The TNT trial is jointly supported by CRUK and Breakthrough Breast Cancer (CRUK/07/012). We acknowledge NHS funding to the Royal Marsden/Institute of Cancer Research National Institute for Health Research Specialist Cancer Biomedical Research Centre and from the Department of Health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy’s & St Thomas’ NHS Foundation Trust in partnership with King’s College London and King’s College Hospital NHS Foundation Trust and the Experimental Cancer Medicine Centre Initiative which is jointly funded by Cancer Research UK, the National Institute for Health Research, Welsh Assembly Government, HSC R&D Office for Northern Ireland and Chief Scientist Office, Scotland.

Supplementary Information accompanies the paper on British Journal of Cancer website (http://www.nature.com/bjc)

REFERENCES

American Society of Clinical Oncology (2003) American Society of Clinical Oncology Policy Statement Update: Genetic Testing for Cancer Susceptibility. J Clin Oncol 21: 2397–2406
Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski S, Tulininis H, Thorlacius S, Eerola H, Nevanlinna H, Syrrı̀kakis K, Kallioniemi OP, Thompson D, Evans C, Peto J, Laloo F; Evans DG, Easton DF (2003) Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 72: 1117–1130
Antoniou AC, Hardy R, Walker L, Evans DG, Shenton A, Eeles R, Shaylor S, Pichert G, Isatt L, Rose S, Douglas F, Eccles D, Morrison PJ, Scott J, Zimmern RL, Easton DF, Pharoah PDP (2008) Predicting the likelihood of carrying a BRCA1 or BRCA2 mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester screening system using data from UK genetics clinics. J Med Genet 45: 425–431
Atchley DP, Albarracin CT, Lopez A, Valero V, Amos CI, Gonzalez-Angulo AM, Hortobagyi GN, Arun BK (2008) Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. J Clin Oncol 26: 4282–4288
Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V (2007) Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer 109: 1721–1728
Blows FM, Driver KE, Schmidt MK, Broeks A, van Leeuwen FE, Wesseling J, Cheang MC, Gelmon K, Nielsen TO, Blomqvist C, Heikkilä P, Heikkinen T, Nevanlinna H, Akslen LA, Begn LR, Foulkes WD, Jones JL, Eastern DF, Garcia-Closas M, Caldas C, Pharoah PD, Huntsman D (2010) Subtyping of breast cancer by imaging histochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10 159 cases from 12 studies. Plos Med 7: e1000279
Collins LC, Martyniak A, Kandil MJ, Studler ZK, Mascari S, Miron A, Richardson AL, Schnitt SJ, Garber JE (2009) Basal cytokeratin and epidermal growth factor receptor expression are not predictive of BRCA1 mutation status in women with triple-negative breast cancers. J Genet Genomics 36: 11–134
Eccles D, Gerty S, Simmonds P, Hammond V, Ennis S, Altman DG, P OSH steering group (2007) Prospective study of Outcomes in Sporadic versus Hereditary breast cancer (POSH) study protocol. BMC Cancer 7: 160
Evans DG, Howell A, Ward D, Laloo F, Jones JL, Eccles DM (2011) Prevalence of BRCA1 and BRCA2 mutations in triple negative breast cancer. J Med Genet 48: 521–527
Evans DG, Laloo F, Cramer A, Jones EA, Knox F, Amir E, Howell A (2009) Addition of pathology and biomarker information significantly improves the performance of the Manchester scoring system for BRCA1 and BRCA2 testing. J Med Genet 46: 811–817
Evans DG, Laloo F, Wallace A, Rahman N (2005) Update on the Manchester Scoring System for BRCA1 and BRCA2 testing. J Med Genet 42: e39
Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, Mortimer P, Swisland H, Lau A, O’Connor MJ, Ashworth A, Carmichael J, Kaye SB, Schellens JH, de Bonis JS (2009) Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 361: 1133–1143
Foulkes WD, Smith IE, Reis-Filho JS (2010) Triple-negative breast cancer. N Engl J Med 363: 1938–1948
Gadzikiewicz D, Evans DG, Harris H, Julian-Reynier C, Nippert I, Schmidtke J, Tibben A, van Asperen CJ, Schlepperger B (2011) Genetic testing for familial/hereditary breast cancer—comparison of guidelines and recommendations from the UK, France, the Netherlands and Germany. J Comm Genet 2: 53–69
Gonzalez-Angulo AM, Timms KM, Liu S, Chen H, Litton JK, Potter J, Lynch J, Stemple-Hale K, Hennessey BT, Arun BK, Hortobagyi GN, Do KA, Mills GB, Meric-Bernstam F (2011) Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res 17: 1082–1089
Kibburn LS, TNT Trial Management Group (2008) ‘Triple negative’ breast cancer: a new area for phase III breast cancer clinical trials. Clin Oncol (R Coll Radiol) 20: 35–39
Kwon JS, Gutierrez-Barrera AM, Young D, Sun CC, Daniels MS, Lu KH, Arun B (2010) Expanding the criteria for BRCA mutation testing in breast cancer survivors. J Clin Oncol 28: 4214–4220
Mavaddat N, Rebbeck TR, Lakhani SR, Easton DF, Antoniou AC (2010) Incorporating tumour pathology information into breast cancer risk prediction algorithms. Breast Cancer Res 12: R28
McIntosh A, Shaw C, Evans G, Turnbull N, Bahar N, Barclay M, Easton D, Emery J, Gray J, Halpin J, Hopwood P, McKay J, Sheppard C, Sibbering M, Watson W, Wailoo A, Hutchinson A (2004) Clinical guidelines and evidence review for the classification and care of women at risk of familial breast cancer. In NICE Clinical Guideline 14 National Collaborating Centre for Primary Care/University of Sheffield: London NICE (2006) Familial breast cancer: The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care. In NICE Clinical Guideline 41 (Partial Update of Clinical Guideline 14). http://www.nice.org.uk/nicemedia/live/10994/30244/30244.pdf
Nathanson KL, Domchek SM (2011) Therapeutic approaches for women predisposed to breast cancer. Ann Rev Med 62: 295–306
Office for National Statistics (2006) Cancer Statistics Registrations, England (Series M81), No. 37. London http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations-england-series-m81/no–37–2006/index.html
Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, Friedlander M, Arun B, Loman N, Schmutzler RK, Wardley A, Mitchell G,
Earl H, Wickens M, Carmichael J (2010) Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. *Lancet* 376: 235–244
Young SR, Pilarski RT, Donenberg T, Shapiro C, Hammond LS, Miller J, Brooks KA, Cohen S, Tenenholz B, Desai D, Zandvakili I, Royer R, Li S, Narod SA (2009) The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. *BMC Cancer* 9: 86
Zhang J, Pei R, Pang Z, Ouyang T, Li J, Wang T, Fan Z, Fan T, Lin B, Xie Y (2011) Prevalence and characterization of BRCA1 and BRCA2 germline mutations in Chinese women with familial breast cancer. *Breast Cancer Res Treat*; e-pub ahead of print 26 May 2011; doi:10.1007/s10549-011-1596-x

This work is published under the standard license to publish agreement. After 12 months the work will become freely available and the license terms will switch to a Creative Commons Attribution-NonCommercial-Share Alike 3.0 Unported License.