

## **Trends in *BRCA* testing and socioeconomic deprivation**

**Short running title:** Trends in *BRCA* testing and deprivation

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## **ABSTRACT**

*BRCA* testing received much publicity following Angelina Jolie's editorial 'My Medical Choice' in May 2013 and updated NICE clinical guidance (CG164) in June 2013. We assessed the effect of these two concurrent events on *BRCA* testing in one UK catchment area and relate this to socioeconomic deprivation. A database of 1393 patients who received *BRCA* testing was collated. This included individuals with breast/ovarian cancer, and those unaffected by cancer, where a relative has a  $\geq 10\%$  probability of carrying a *BRCA* variant which affects function. A segmented regression was conducted to estimate changes in testing. To examine the relative distribution of testing by deprivation, the deprivation status of patients who received testing was examined.

Between April 2010-March 2017, testing increased 11-fold and there was an 84% increase (P=0.006) in BRCA1/2 testing in the month following both publications. In the pre-publication period, there was no statistically significant difference in testing between advantaged and disadvantaged areas (OR 1.21 95% CI 0.99-1.48; P=0.06). In the post-publication period helped by a larger sample size, the difference was statistically significant (OR 1.18 95% CI 1.08-1.29; P=0.0002) and of a similar magnitude to the pre-publication period. Testing increased following Jolie's editorial and NICE guidance update. However further research is needed to examine differences in testing by deprivation group which adjusts for confounders.

**Key Words:** Hereditary Breast Ovarian cancer; Equity; Uptake

## **INTRODUCTION**

Breast cancer (BC) is the most commonly diagnosed cancer in women in the United Kingdom (UK) with an approximate lifetime risk of 12-13%<sup>1,2</sup>. Ovarian cancer (OC) has a lifetime risk of 1.4-2.5%.<sup>1,3</sup> Breast cancer affects men with a much lower lifetime risk of <1%.<sup>4</sup> Although the susceptibility factors are unclear in the majority of patients with breast and ovarian cancer, some of these cancers are caused by germline variants which affect function in *BRCA1* or *BRCA2*, with variation in the relative contribution of *BRCA1* and *BRCA2*.

It has been estimated that germline variants in *BRCA* which affect function exist in 0.2-0.3% of the overall general population, in 5-10% of patients with BC,<sup>5</sup> in 5-13% of patients with OC,<sup>3</sup> and in 0.4-1.2% of patients with prostate cancer (PC).<sup>6</sup> *BRCA* germline variants have also been found to be associated with cancers of the pancreas, stomach, skin, colon and others.<sup>7</sup> Identification of patients with *BRCA* variants is important as the presence of such germline variants affects treatment, follow-up and cancer prevention.<sup>8</sup> Further, risk-reducing lifestyle modifications, medications and procedures may be indicated, for example, bilateral

mastectomy and/or salpingo-oophorectomy.<sup>9,10</sup> Studies have found *BRCA* testing to be clinically effective and cost-effective, particularly in individuals with a family history of hereditary breast and breast and ovarian cancer (HBOC). Indeed, a recent modelling study found that implementation of *BRCA* testing across the general female population aged 30 years and older would be cost-effective.<sup>11</sup>

On 14 May 2013, the celebrity Angelina Jolie raised public awareness of *BRCA* testing globally following her widely publicized *New York Times* editorial ‘My Medical Choice.’<sup>12</sup> The editorial described Jolie’s experience, why she decided to undergo *BRCA* testing and why she opted to undergo risk-reducing procedures (a preventative double mastectomy) because of her *BRCA* status.<sup>13–15</sup> About the same time, on 25 June 2013, the National Institute for Health and Care Excellence (NICE) published its updated guidance for Familial Breast Cancer Testing [CG164].<sup>16</sup> NICE recommended that testing should be conducted in patients with ovarian or breast cancer, or in their relatives, where the probability of combined *BRCA1* or *BRCA2* variants which affect function is  $\geq 10\%$ .<sup>16</sup> At the same time, there was considerable publicity about the potential use of chemoprevention using tamoxifen or raloxifene.<sup>14</sup>

The extent to which Jolie’s editorial and NICE CG164 led to changes in uptake rates of *BRCA* testing in terms of equity of access has not been previously explored in the UK.<sup>16</sup> Disparities in cancer survival by deprivation groups persist for most types of cancer and also across geographical settings.<sup>17–19</sup> The NHS atlas of variation (2013) reported that North West England has one of the lowest rates of *BRCA* genetic testing.<sup>20</sup> However, in 2016/17, the lowest rate reported by UK Genetic Test Network (UKGTN) was in Yorkshire and Humber Commissioning Region (23.4 per 100,000) and the highest was in the South East Commissioning Hub (71.1 per 100,000).<sup>21</sup> To explore disparities within the North West region, the aim of this study was to analyse trends in uptake rates following Jolie’s editorial and NICE

CG164 and relate this to equity of access to *BRCA* testing. This study followed Standards for Reporting Implementation Studies (STaRI) guidelines for transparent and accurate reporting of implementation studies.<sup>22</sup>

## **METHODS**

### **Study population and data sources**

Research was conducted using retrospective, routinely collected hospital data from the Merseyside and Cheshire Regional Genetic Service (RGS) hosted by Liverpool Women's NHS Foundation Trust. The RGS is responsible for care in Merseyside and Cheshire (with the exception of boundary areas) serving a catchment area of approximately 2.4 million people. We identified women aged  $\geq 18$  years old from April 2010 and March 2017 who received *BRCA* testing.

For the purposes of this research, *BRCA* testing refers to DNA sequencing analysis of both *BRCA1* and *BRCA2* genes and comparing that analysis to reference sequence. Testing also included multiplex ligation-dependent probe amplification (MLPA) dosage analysis to exclude the presence of whole deletion or duplication. The method of sequence analysis has changed over the timeframe of the study from bi-directional fluorescent sequencing in 2010 to long range polymerase chain reaction (PCR) and next generation sequencing on Illumina MiSeq (minimum 100x coverage) using an in-house variant calling bioinformatic pipeline with sanger confirmation of variants called or areas of the gene with less than 100x coverage.

The NICE guideline for CG164 updated previous guidance on familial breast cancer, published in 2004 and 2006.<sup>23,24</sup> *BRCA* testing was expanded to individuals affected with a relevant cancer (except those with Ashkenazi Jewish ancestry) if the probability of combined *BRCA1* and *BRCA2* variants which affect function was 10% or more (CG164 1.5.13). In addition,

*BRCA* testing expanded to individuals unaffected by cancer if their combined *BRCA1* and *BRCA2* functional variant probability was  $\geq 10\%$  and an affected relative was unavailable for testing (CG164, 1.5.12).<sup>25</sup> Specifically, this paper does not include predictive *BRCA* gene testing which describes the use of a *BRCA* test in an asymptomatic person to predict future risk of disease where a variant within a *BRCA* gene is already known within the family and the patient's DNA is tested for that variant alone (CG164, 1.3.6).<sup>16,26</sup> This will be the subject of a separate paper.

Baseline characteristics of patients who received *BRCA* testing and also the study setting population were collected. Patients aged <18 years old were excluded from the dataset as per ethics requirements. In addition, 5.7% (80/1393) of patients were registered at an address outside of England and were therefore excluded from the dataset as information on their respective Index of Multiple Deprivation (IMD) based on their Lower Layer Super Output Area (LSOA) was not available.

Socioeconomic deprivation is intrinsically linked to health, and it is widely acknowledged that with many diseases, the incidence is higher in more deprived populations.<sup>27</sup> These inequalities are due to complex structural factors including differential exposure to risk factors like stress and pollution, protective factors like education and good housing, and lifestyle risk factors like smoking, alcohol and unhealthy diet.<sup>28</sup> Supplementary Figure 1(a) illustrates the pattern of deprivation within each area, taken from the Index of Multiple Deprivation for 2015 and (b) illustrates the incidence of new cases for all cancers for 2011-2015 within Merseyside and Cheshire. The population is diverse in terms of social deprivation, including some of the most deprived and least deprived areas in England.

## **Time periods of interest**

Our defined time point of interest was the combination of the New York Times editorial by Angelina Jolie on 14 May 2013 and the release of NICE CG164 guidance on 25 June 2013.<sup>12,16</sup> These combined publications provided information and guidance on the use of *BRCA* testing for the diagnosis and treatment specifically for breast and ovarian cancers and risk assessment of family members. In this study we compare ‘pre-publication’ with ‘post-publication’ as both the Jolie editorial and the NICE guidance were published within weeks of each other in 2013. Consequently, their effects could not be separated.

## **Measures**

We summarize baseline characteristics of patients who received *BRCA* testing which included gender, age, type of cancer, variant status and IMD. Monthly trends in the proportion of patients who received testing were measured over time. Subsequently, we analyzed equity of access to *BRCA* testing by deprivation group, classified by the IMD pre and post-publication.

Based on postcode of residence, each patient who received *BRCA* testing was assigned to a LSOA and this was mapped to an IMD quintile calculated across the whole of England using this measure. LSOAs are the smallest geographical units for which IMD scores are available. From the 2011 Census, there were 32844 LSOAs used in the 2015 Indices of Deprivation in England.<sup>29</sup> Each LSOA contains a small cluster of postcodes with comparable characteristics and have a mean population of approximately 1500 people. LSOAs are not necessarily homogenous in terms of sociodemographics, although often border natural geographical features like roads and rail lines.<sup>29</sup>

For all the recipients of *BRCA* testing at Merseyside and Cheshire RGS, their LSOA were mapped to an IMD quintile from the 2015 Indices of Deprivation in England.<sup>29</sup> The comparator group, described as ‘the catchment population’ included all LSOAs which were located within

local authority (LA) districts in Merseyside and Cheshire. As such, the LSOA Mid-Year Population Estimates for Mid-2016 from within the LA districts (including Cheshire East, Cheshire West and Chester, Halton, Knowsley, Liverpool, Sefton, St. Helens, Warrington and Wirral) were mapped to IMD quintiles and the population for each IMD quintile was calculated for the catchment population.<sup>30</sup>

The IMD score combines seven indicators (income, employment, health deprivation and disability, education, skills and training, barriers to housing and services, crime, and living environment), into a single deprivation index. We defined equity of access based on the philosophy of the NHS in the UK as having an objective of providing equal health care access for equal health care need.<sup>31</sup>

### **Statistical analysis**

The crude rate of *BRCA* testing was presented as it was assumed that individual-level variables remained relatively stable over the study period.<sup>32</sup> The data was adjusted to assess monthly trends in testing from April 2010 to March 2017 per 100,000 population for the catchment area of Merseyside and Cheshire RGS. Analyses were based on 37 monthly pre-publication data points (Apr 2010–Apr 2013) and 45 monthly post-publication data points (July 2013–Mar 2017). An interrupted time series (ITS) analysis was performed to estimate the overall publication impact (intervention effect) by predicting what would have been observed post-publication (or counterfactual rates) had pre-publication levels and/or trends continued uninterrupted and comparing this with what was modelled using observed post-publication data. The endpoint of the observed post-publication period (March 2017) was used to calculate the average difference over the post-publication time points on the aggregated time-series to estimate two parameters of interest associated with both publications: change in subsequent



level of testing and change in subsequent trend prior to the publications, the level of change in testing following the publications and following through the remainder of the study period.<sup>33,34</sup>

ITS, known as segmented regression analysis, is a strong quasi-experimental alternative when randomized design is not feasible and has the causal hypothesis that observations after treatment have a different level (or slope) from those before the intervention (or in this case the intervention is the two publications). The regression model was specified as following:  $\hat{Y}_t = \beta_0 + \beta_1 * time_t + \beta_2 * intervention_t + \beta_3 * post\_intervention_t + e_t$ . Here  $\hat{Y}_t$  is the incidence of *BRCA* testing at time point  $t$ .  $\beta_0$  estimates the baseline level of the outcome just before the beginning of the time series.  $\beta_1$  estimates the pre-intervention trend,  $\beta_2$  the change in the level between the time point immediately before vs. after the lag period and  $\beta_3$  the change in trend occurring immediately after the lag period. The final model specification was derived using a backward-stepwise approach ( $P < 0.1$ ) to remove non-significant regression terms in order to maximize statistical power. A generalized least squares (GLS) model with autoregressive moving average (ARMA 6,0) process was fitted and Durbin-Watson statistics indicated no significant autocorrelation. Finally, the likelihood ratio test and residual plot indicated that the model was correctly specified. The absolute and relative effect of the publications was calculated and the 95% confidence intervals (CI) for coefficients were calculated by the bootstrapping method. Statistical and economic analysis was conducted using R (version 3.42) and RStudio 1.1.383.<sup>35</sup>

To address the secondary aim of this study, the IMD score for each member of the catchment population was defined as that of their respective LSOA for the purposes of analysis. Deprivation scores were divided into national quintiles for the catchment population. Odds ratios and associated confidence intervals were calculated for the quintiles in a binary logistic regression analysis.

## RESULTS

Between April 2010 and March 2017, 1394 *BRCA* tests were undertaken, of whom 170 (12.2%) were identified with a *BRCA* variant which is known to affect function. Patient baseline characteristics are described in Table 1. Female patients comprised 96.2% of the study population and the mean age at the time of the *BRCA* test was 53.4 years (SD 13.0; range 16-93 years). Of the total study population, 58.5% had breast cancer, 23.2% had ovarian cancer, 2.4% had BOC, 3.0% had another type of cancer and 12.8% were personally unaffected by cancer but their probability of carrying *BRCA* variants which affect function was 10% or more and an affected relative was unavailable for testing. The likelihood that patients were identified with a known functional variant was significantly lower by 36% in the post-publication period (11.1%; 129/1157) compared with the pre-publication period (17.4%; 41/236;  $P=0.008$ ).

At the beginning of the period of observation, there were an estimated 0.14 *BRCA* tests received per 100,000 population per month and a per month increase of 0.01 *BRCA* tests received per 100,000 population ( $P=0.085$ ) over the period March 2010 and April 2013 (Table 2). Based on our segmented regression analysis, testing increased by 0.30 per 100,000 (95% CI 0.09-0.51) following the combined publications, which was approximately an 84.3% increase ( $P=0.006$ ), followed by a 0.01 per 100,000 population (95% CI 0.01-0.02) ( $P=0.002$ ) increased trend in testing per month.

At the end of the post-publication observation period (45 months follow-up), it was estimated that testing had increased from 0.62 to 1.52 per 100,000 population. This translated to an approximate 145% (95% CI 30.4-295.7%) increase in testing, or an absolute increase in testing of 0.89 per 100,000 population (95% CI 0.04-1.13). Therefore, between April 2010 and March 2017, testing rates increased approximately 11-fold from 0.14 to 1.52 tests per 100,000 population per month. The trend in incidence of *BRCA* testing is illustrated in Figure 2.

Supplementary Figure 2 illustrates the standardised change in uptake of *BRCA* testing pre and post-publication by IMD quintile (1=most deprived to 5=least deprived). While pre-publication testing was limited, the number of *BRCA* tests increased more than four-fold per year across all quintiles post-publication. However, there were large disparities in uptake across the different geographical areas (Figure 2).

Social deprivation data was collected for all LSOAs within the catchment area of Merseyside and Cheshire. The catchment area deprivation scores were divided into population-matched quintiles, with proportions of *BRCA* tests received calculated for each. A chi-squared test assessed whether the observed frequencies of *BRCA* testing by IMD quintiles matched the expected frequencies. We found that *BRCA* testing by IMD quintile differed significantly from the expected proportion of *BRCA* testing given the catchment population distribution ( $P=0.04$ ), shown in Figure 3.

In Table 3, odds ratios were calculated for each quintile relative to the incidence within the most deprived group (first quintile). In the pre-publication period, there was no statistically significant difference in testing between the advantaged and disadvantaged areas (OR 1.21 95% CI 0.99-1.48,  $P=0.06$ ). During the post-publication period, testing was significantly higher as deprivation reduced (OR 1.18 95% CI 1.08-1.29,  $P<0.001$ ), but this was helped by the higher sample size in the post-publication period.

An assessment of testing by quintile found that pre-publication, the odds of receiving *BRCA* testing were higher in the fourth quintile compared to the first (OR 1.45 95% CI 1.00-2.11,  $P<0.05$ ). Post-publication, the odds of receiving testing were higher in the third and fourth quintile, compared to the first quintile (OR 1.24 95% CI 1.04-1.48,  $P<0.05$ ) and (OR 1.48 95% CI 1.09-1.54,  $P<0.05$ ). However, as part of sensitivity analysis, we found that pre-publication, a significant increase in odds of *BRCA* testing were not found when comparing the fifth quintile

to the two most deprived quintiles (first and second combined). Likewise, post-publication, the odds of testing in the least deprived quintile compared to the two most deprived quintiles were not found to differ significantly.

## **DISCUSSION**

This study found that the implementation of NICE clinical guidelines in combination with celebrity endorsement yielded an estimated 145% increase in *BRCA* testing. While NICE clinical guidelines are recommendations ‘as an option’, delayed implementation at a local level may have limited patient access for some.

Whilst it was anticipated that both the publication of NICE CG164 and Jolie’s editorial were the main contributors to increased *BRCA* testing, it is of course possible that there were other contributors. As advancements in genomic technologies continue and become more widespread, a ‘mainstreaming model’ has been introduced where *BRCA* testing is now offered as part of routine gynae-oncology care pathway and such streamlining may have also contributed to increased testing.<sup>36</sup> This mainstreaming model involved up-skilling oncology specialists (through online, face-to-face learning packages and written algorithms) to consent, order, interpret and deliver results for genetic testing.<sup>37,38</sup>

Increased testing may also be the result of advances in effective treatment options that are tailored to *BRCA* variants, such as olaparib, a poly ADP-ribose polymerase (PARP) inhibitor which has been proven to prolong progression-free survival in *BRCA* positive breast and ovarian cancers.<sup>39,40</sup> In essence, increased treatment options may have encouraged clinicians to offer testing due to an improved risk-benefit profile. Further, as direct-to-consumer (DTC) *BRCA* tests have become widely available, it is possible that marketing campaigns and confirmatory testing due to the use of DTC tests may have increased demand.

Whilst it was anticipated that both the publication of CG164 and Jolie's editorial were the main contributors to increased *BRCA* testing, the extent to which these contributors may have impacted testing in different socioeconomic groups based on their differential awareness and demand is uncertain. Clearly, there are also confounding factors, such as differences in cancer incidence in different socioeconomic groups, which also need to be considered. A recent qualitative study by Wright et al. (2018) found that some patients felt regretful and angry when *BRCA* testing was offered to them as many had already been diagnosed with cancer and that the timing of the test was illogical. While some patients had heard of *BRCA* testing, they believed that they were ineligible based on beliefs shaped by recent media discussions as no members of their family had breast cancer.<sup>41</sup>

The identification of *BRCA* variants in ovarian cancer patients may have significant financial implications as olaparib has a UK list price of £3950 per pack per month.<sup>42</sup> As such, implementation studies are needed to examine care delivery to ensure access is based on actual health care need.

An important study limitation was that the rate of *BRCA* testing was unadjusted. Therefore, the comparison between rates of *BRCA* testing pre- and post-publication of CG164 and Jolie's editorial may have been confounded by changes in individual-level variables such as age, sex and other factors which impact the clinical need for *BRCA* testing. While this study found that socioeconomic deprivation may be associated with lower rates of *BRCA* testing, multiple factors may have contributed to this. However, multivariate analysis was not possible in this study due to a lack of comparative data available for the catchment population. The significance of the results of this study are nevertheless interesting and with clinical relevance as post-publication the observed rate of *BRCA* testing was found to be higher in the least deprived population compared to the most deprived population.

Other studies in the USA have found that rates of referrals for *BRCA* testing in patients with a diagnosis of OC and BC differed by race and insurance status.<sup>43,44</sup> In addition, a survey found that ethnic minority BC patients were less willing to undergo molecular testing.<sup>45</sup> Another study for genetic testing for Long QT syndrome (LQTS) found that those who were anxious or depressed were more likely to perceive barriers to communicating genetic information to family members.<sup>46</sup> Meanwhile, a preference elicitation study found that the valuation of genetic testing for colorectal cancer also varied by income and employment status of the patient.<sup>47</sup>

In cystic fibrosis (CF), implementation of CF newborn screening programs across the US remains suboptimal in nonwhite populations due to poor characterization of CFTR gene variants in diverse ethnic groups.<sup>48</sup> Similarly, high-risk *APOL1* genotypes increase the risk of kidney disease by seven-fold, and they are more common in individuals of African descent. However, the mechanisms by which *APOL1* genotypes increase the risk of kidney disease remains poorly understood, and thus treatments that specifically target individuals with high-risk genotypes have been slow to develop.<sup>49</sup> Therefore, potential disparities in genetic testing may not only depend on socioeconomic status, but also on differing clinician and patient preferences, poor characterization of genetic variants and insufficient mechanisms to manage vulnerable patient populations.<sup>20,43,44,49,50</sup> Thus, as with *BRCA* testing, the prevalence of disease in different population groups is an important factor to consider when analyzing disparities. Consequently, novel approaches including the analyses of patient level data, preference elicitation studies and qualitative research are needed to understand more about health care implementation.

There remains a paucity of evidence to inform how different modalities of implementation of *BRCA* testing could be used to target vulnerable populations within the UK. Although one survey found that following celebrity endorsement from Angelina Jolie, there was increased

awareness of health challenges, more purposeful communication efforts may better assist public understanding given the complexity of the information.<sup>51</sup> A survey found that the increased presence of HBOC in the media since Jolie's disclosure led to greater awareness from people from different social backgrounds.<sup>13</sup> However another study found that increased awareness of testing is not always associated with improved understanding about the implications of testing.<sup>51</sup>

An economic study in the USA found that while *BRCA* testing increased following publication of Jolie's editorial, the proportion of patients which consumed additional health care resources declined.<sup>52</sup> Our study found that there was reduced likelihood that patients were identified with a variant which affects function in the post-publication period. Therefore, these findings highlight the importance of ensuring potential surges in health seeking do not result in unnecessary resource use that may not benefit patients at low risk. Although, in our study it was not possible to examine whether *BRCA* testing was guideline concordant due to a lack of personal and family history of cancer data.

While this research has identified interesting findings relating to the impact of Jolie's editorial and NICE guidelines and also differences in *BRCA* testing, the overall findings are subject to some limitations. All models are imprecise, despite the fact that Autoregressive Integrated Moving Average (ARIMA) models inherently account for autocorrelation, non-stationarity, and seasonality. However, estimates of the overall effect on rates of *BRCA* testing involved extrapolation which is inevitably associated with uncertainty. Furthermore, the regression method chosen assumed a linear trend over time and although it assumed larger standard errors in the post-publication period. The main threat to validity in interrupted time series analyses relate to time-varying confounding, such as co-interventions, possible changes in treatment coding, or changes in the population under study.<sup>53</sup> Another problem with such analyses is that

interventions may be implemented at different rates and inconsistently and therefore, there remains uncertainty in the overall impact of both publications.

An additional study limitation was that in designing the analysis, it was not feasible to add a non-equivalent no-treatment control group. It is not obvious why there would be variation in the provision of health services as both the Merseyside and Cheshire Regional Genetic Service (RGS) are regional, cover the same geographical footprint and both work to standard testing protocols. However, we have only accessed data from one RGS, which is the sole provider for genetic testing within the region, and thus, any patient accessing testing through another provider is not included. Those patients living near the boundary of the region may have attended the adjacent RGS or some patients may have accessed private testing. Another limitation relates to the sensitivity of IMD quintiles matched to each LSOA. Moreover, within each LSOA there may be significant variation in terms of deprivation and this is an important consideration when interpreting the results. Additionally, recorded *BRCA* data might be subject to recording or adjudication errors, and the reliability of the coding of *BRCA* tests might have changed over time. However, there was no evidence of changes in treatment coding or significant changes in the underlying study population.

## **CONCLUSIONS**

This study shows that clinical guidelines and celebrity endorsements may have had a significant impact on health service use in terms of the rate of *BRCA* testing. However, while such publications and publicity may increase awareness and uptake, the proportion of patients identified with having a *BRCA* variant which affects function decreased. This highlights the importance of ensuring that potential surges in health seeking do not translate to inappropriate resource use that may not benefit patients at low risk and that may result in a significant cost burden to the taxpayer. The NHS in the UK has the philosophy of offering ‘a comprehensive



service, available to all' irrespective of ability to pay.<sup>31</sup> As such, additional studies that control for confounders are needed to establish whether access to *BRCA* testing is based on actual health care need.

Supplementary information is available at the European Journal of Human Genetics website.

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## **TABLES**

**Table 1 Baseline study population demographics**

**Table 2 Temporal trends in receipt of *BRCA* testing from 2010 to 2017 (per 100,000 population)**

**Table 3 Comparative odds ratios (95% CI) for each population-matched IMD quintile**

## **FIGURES**

**Figure 1** Standardized incidence of *BRCA* testing per 100,000 population. The red dots indicate the observed uptake per month. The red line represents the trend line pre and post-publication of Jolie's editorial and NICE CG164. The blue dashed line represents the extrapolated pre-publication regression line. \*Post-publication is the period which followed the New York Times Editorial 'My Medical Choice' by Angelina Jolie and update to NICE CG164

**Figure 2 Map of Merseyside and Cheshire illustrating receipt of *BRCA* testing: (a) Pre-Publication and (b) Post-Publication**

**Figure 3 Distribution of cancer *BRCA* testing Pre and Post-Publication**