RISK ASSESSMENT OF CONTRALATERAL BREAST CANCER IN HIGH-RISK PATIENTS & FORMULATION OF CLINICAL GUIDELINES

A thesis submitted to the University of Manchester for the degree of Doctor of Medicine in the Faculty of Medical and Human Sciences

2016

Presented By

Narendra Nath Basu

SCHOOL OF MEDICINE

Table of Contents

WORD COUNT 45940

List of Figures

List of Tables

List of Abbreviations

AI – aromatase inhibitor

ATAC –arimidex, tamoxifen alone or in combination

BRRM – bilateral risk-reducing mastectomy

BRRSO – bilateral risk-reducing salpingo oophorectomy

CBC – contralateral breast cancer

CIMBA – consortium of investigators of modifiers of *BRCA1/2*

CRRM – contralateral risk-reducing mastectomy

DCIS – ductal carcinoma in situ

ER – oestrogen receptor

GWAS – genome wide association study

HER2 – human epidermal growth factor receptor 2

HR – hazard ratio

LCIS – lobular carcinoma in situ

MDT – multi disciplinary team

MRI – magnetic resonance imaging

NICE CG164 – National Institute for Health and Care Excellence clinical guidelines on Familial Breast Cancer

NSABP – national surgical adjuvant breast and bowel project

OBRS – overall breast risk score

POSH – prospective study of outcomes in sporadic versus hereditary breast cancer

PR – progesterone receptor

RAF – risk allele frequency

RR – relative risk

RRM – risk-reducing mastectomy

SEER - Surveillance, Epidemiology and End Results

SERM – selective oestrogen receptor modulator

SNP – single nucleotide polymorphism

Abstract

Assessment of risk of contralateral breast cancer in high-risk patients and formulation of clinical guidelines

The Degree of Doctor of Medicine – University of Manchester

Narendra Nath Basu – June 2016

This thesis assesses the main risk factors contributing to contralateral breast cancer (CBC) amongst high-risk breast cancer patients with a view to formulating clinically useful guidelines. The work has focused on several keys areas; a literature review of the various factors contributing to CBC, changing trends towards increasing numbers of contralateral risk-reducing mastectomies (CRRMs), international variations amongst breast surgeons' attitudes towards risk-reducing mastectomy (RRM), attitudes towards CRRM amongst UK breast and plastic surgeons, assessment of CBC risk amongst *BRCA1/2* mutation carriers and finally the formation of the 'Manchester Guidelines for CRRM'.

Breast cancer patients harbouring mutations in high penetrance genes (i.e. *BRCA1/2, TP53, CHEK2, PALB*) have the highest risk of developing breast cancer. A positive family history also increases the risk of subsequent breast cancer, with not much evidence to support variation in risk with histological type. Risk reducing strategies include anti-endocrine treatment, risk-reducing bilateral salpingo-oophorectomy (RRBSO) and CRRM with the former likely to account for the global trend of decreasing rates of CBC.

Over the last decade, rates of CRRM have trebled in the USA – such a clear trend has not yet been confirmed in Europe. Factors driving this trend include young age at diagnosis, histological type (lobular carcinoma, lobular carcinoma in situ [LCIS] and ductal carcinoma in situ [DCIS]) and female surgeons. A direct comparison (USA v 4 European countries) found that American surgeons overall had a greater knowledge of cancer genetics and nearly all (including Dutch and British surgeons) had positive attitudes towards RRM.

A proportion of British surgeons were quoting inaccurate levels of CBC risk to their patients. Practices in the UK varied regarding CRRM – only 58% of surgeons always discussed these cases in the MDT, with less than a third ever seeking a psychological or formal genetic assessment. Surgeons primarily offered this procedure to high-risk patients (gene mutation carriers or positive family history) but felt that the main reason patients requested CRRM was to alleviate anxiety.

Studying over 1000 breast cancer patients who also had a mutation in either *BRCA1* or *BRCA2* gene revealed that the risk of CBC was approximately 2-3% per year, for at least 2 decades. Young age at first breast cancer development (<40 years) affected this risk most. The effect bilateral risk-reducing salpingo-oophorectomy (BRRSO) was initially significant in an unadjusted analysis, but when accounting for delayed entry BRRSO did not appear to affect CBC risk. The use of SNPs was not able to stratify risk of CBC further.

By considering the above, the Manchester Guidelines for CRRM have been formulated. This 5-step protocol allows clinicians to objectively assess the risk of CBC based on the evidence base and makes suggestions of a multi-disciplinary approach to managing requests for CRRM. Several breast units in the UK have already adopted these guidelines and future studies hope to validate them so that they can be used more widely.

Lay Abstract

Assessment of risk of contralateral breast cancer in high-risk patients and formulation of clinical guidelines

The Degree of Doctor of Medicine – University of Manchester
Narendra Nath Basu – June 2016

Breast cancer is the most common female cancer worldwide. Patterns of treatment in breast surgery have moved away from routine mastectomy towards breast conservation. Reports from the USA indicate that rates of mastectomies are increasing – in particular the removal of the opposite healthy breast in a women diagnosed with breast cancer – the so-called contralateral risk-reducing mastectomy (CRRM). Amongst some women diagnosed with breast cancer there has been a change in attitude whereby once "***empowerment was keeping your breast, now it is removing them***" (Hurley 2015).

Counselling women requesting CRRM is often challenging. Clinicians may be guided by their own attitudes towards risk-reducing surgery. Ultimately, they will need to weigh the multi-factorial reasons why a breast cancer patient is requesting the removal of a healthy breast against the evidence base - that supports a survival benefit in high-risk patients. To date, no formal guidelines exist to aid clinicians in processing requests for CRRM.

Guidelines should take into consideration the multiple factors that determine risk of developing cancer in the opposite breast (CBC). Assessment of CBC in the high-risk group (i.e. *BRCA1/2* carriers) is an ideal model to help formulate guidelines. The very nature of their high-risk means that disease related events following an initial diagnosis of breast cancer are expected and perhaps predictable, occurring over a shorter time frame compared to those at a general population risk. The assessment of the human genome using genome-wide association studies (GWAS) offers an additional opportunity to enable clinicians to further stratify risk with the hope that in the future women with breast cancer can be offered a personalised CBC risk score.

The overall objective of these studies is to formulate guidelines based on current evidence on how to best manage requests for CRRM. The main emphasis has been on patients who have the highest risk of developing CBC, particularly patients with a *BRCA1* or *BRCA2* mutation studied over a 30-year period in Manchester. Ultimately, breast surgeons will be faced with the task of performing these procedures. Their own attitudes to risk-reducing surgery are likely to influence the decision making process. To gauge the impact of requests for CRRM and their reaction to them, a national survey was undertaken of surgeons in England. Given that the majority of data on increasing mastectomies seems to originate from the USA, a further analysis was performed comparing attitudes to risk-reducing mastectomy (RRM) amongst American and European surgeons.

To achieve the final goal of formulating guidelines, it has been necessary to answer the following questions:

What constitutes high-risk in developing breast cancer?

What are the current trends in CRRM?

Which risk factors for CBC are described in the literature?

Attitudes to risk-reducing surgery – what do UK surgeons make of CRRM? Are there differences in attitudes towards RRM between American and European breast surgeons?

What is the risk of CBC in *BRCA1/2* mutation carriers? How long does that risk last? Are there any modifiers of that risk? Do single nucleotide polymorphisms (SNPs) in the genome of these high-risk *BRCA1/2* mutation carriers affect risk sufficiently to be able to offer these women a more 'personalised risk score'?

How should clinicians deal with breast cancer patients requesting CRRM?

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright Agreement

i. The author of this thesis (including any appendices and/or schedules to this thesis) owns certain copyright or related rights in it (the "Copyright") and he has given The University of Manchester certain rights to use such Copyright, including for administrative purposes.

ii. Copies of this thesis, either in full or in extracts and whether in hard or electronic copy, may be made only in accordance with the Copyright, Designs and Patents Act 1988 (as amended) and regulations issued under it or, where appropriate, in accordance with licensing agreements which the University has from time to time. This page must form part of any such copies made.

iii. The ownership of certain Copyright, patents, designs, trade marks and other intellectual property (the "Intellectual Property") and any reproductions of copyright works in the thesis, for example graphs and tables ("Reproductions"), which may be described in this thesis, may not be owned by the author and may be owned by third parties. Such Intellectual Property and Reproductions cannot and must not be made available for use without the prior written permission of the owner(s) of the relevant Intellectual Property and/or Reproductions.

iv. Further information on the conditions under which disclosure, publication and commercialisation of this thesis, the Copyright and any Intellectual Property and/or Reproductions described in it may take place is available in the University IP Policy (see http://documents.manchester.ac.uk/DocuInfo.aspx?DocID=487), in any relevant Thesis restriction declarations deposited in the University Library, The University Library's regulations see (http://www.manchester.ac.uk/library/aboutus/regulations) and in The University's policy on Presentation of Theses.

Alternative Format Thesis

This work, towards an MD degree is mainly by 7 published papers; this thesis has been produced, in addition, for completeness. It incorporates the essence of these publications that have been condensed or elaborated where necessary with the hope that the reviewer can appreciate the important issues that breast cancer patients and their clinicians face.

Publications arising from this thesis

1. **Basu NN**, Littlechild S, Barr L, Ross GL, Evans DG. Attitudes to contralateral risk reducing mastectomy among breast and plastic surgeons in England. *Ann R Coll Surg Engl*. 2016 Feb;98(2):121-7.

2. **Basu NN**, Ross GL, Evans DG, Barr L. The Manchester guidelines for contralateral risk-reducing mastectomy. *World J Surg Oncol*. 2015 Aug 7;13:237.

3. **Basu NN**, Ingham S, Hodson J, Lalloo F, Bulman M, Howell A, Evans DG.
Risk of contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers: a 30-year semi-prospective analysis. *Fam Cancer*. 2015 Dec;14(4):531-8.

4. **Basu NN**, Barr L, Ross GL, Evans DG. Contralateral risk-reducing mastectomy: review of risk factors and risk-reducing strategies. *Int J Surg Oncol*. 2015.

5. **Basu NN,** Barr L, Evans DG, Ross GL. Threshold for genetic testing in women with breast cancer needs to be determined. *BMJ*. 2014 Mar 6;348:g1863.

6. **Basu NN**, Evans DG, Barr L. Prophylactic mastectomy and breast cancer-reply. *Br J Hosp Med (Lond)*. 2013 Oct;74(10):595.

7. **Basu NN**, Littlechild S, Evans DG, Ross GL, Barr L. Mastectomies of healthy, contralateral breasts in patients with breast cancer. *Br J Hosp Med (Lond)*. 2013 Sep;74(9):486-7.

Presentations

International

1. **Basu NN**, Den Heijer M, van Asperen CJ, Harris H, Nippert I, Schmidtke J, Bouhnik AD, Julian-Reynier C, Beitsch PD, Tibben A, Hodson J, Evans DG. Breast surgeons' attitudes towards BRRM: A National Survey of American Surgeons. 2015 Breast Cancer Symposium – San Francisco.
   Abstract published: *J Clin Oncol* 33, 2015 (suppl 28S; abstr 25).

National

2. **Basu NN**, Ross GL, Evans DG, Barr L. A protocol for CRRM: The Manchester Guidelines. 2015
   Association of Breast Surgery Meeting – Bournemouth
   Abstract published: *Eur J Surg Oncol* 2015;41(4):s36.

3. **Basu NN**, Den Heijer M, van Asperen CJ, Harris H, Nippert I, Schmidtke J, Bouhnik AD, Julian-Reynier C, Beitsch PD, Tibben A, Evans DG. Breast surgeons attitudes towards BRRM – a comparison between the UK, the US, France and Germany. 2015
   Association of Breast Surgery Meeting - Bournemouth
   Abstract published: *Eur J Surg Oncol* 2015;41(4):s23.

4. **Basu NN**, Short J, Evans DG, Barr L. CRRM – The Manchester experience. 2014
   Association of Breast Surgery Meeting – Liverpool
   Abstract published: *Eur J Surg Oncol* 2014;40(5):618

5. **Basu NN**, Littlechild S, Evans DG, Ross GL, Barr L. CRRM- A national survey of surgeons practices and perceptions. 2013
   British Association of Surgical Oncologists Meeting – London
   Abstract published: *Eur J Surg Oncol* 2013;39(11):s64

6. **Basu NN**, O'Driscoll M, Ahmed M, Ingham S, Howell A, Lalloo F, Evans DG. Contralateral breast cancer in high-risk patients: Identification of risk factors to guide recommendations for CRRM. 2013
   Association of Breast Surgery – Manchester
   Abstract published: *Eur J Surg Oncol* 2013;39(5);520

Prizes

1. Lynn Sage / Chicago Sister Cities Award 2014. One of 14 researchers worldwide awarded funds to attend Lynn Sage Breast Cancer Symposium, Chicago, USA 2014.

2. Margaret Pritchard Memorial Prize – The Humane Research Trust Runner up (University of Manchester). 11th May 2016

Dedication

To my late father Sitesh Chandra Basu who left as my two sons Konark and Rayan arrived, I never knew the love of a father till I became one myself.

Acknowledgements

I would like to express my deepest gratitude to Professor Gareth Evans (DGE) for his support, expert guidance, understanding and encouragement throughout my study and research. Without his incredible patience, timely wisdom and counsel none of this work would be possible.

I would also like to thank James Hodson (JH) for his help with statistics as well as my co-authors on several of the publications Mr Lester Barr (LB) and Mr Gary Ross (GR).

Thanks to my other supervisors – Prof Tony Howell and Dr Brian Bigger. I am indebted to Ms Joy Stewart at the University of Manchester for all her patience over the last few years.

To my sister Anupama and mother Gitasri, I would never have been able to complete this thesis without their continuous love and encouragement.

Finally, I would like to thank my wife Riya for her unconditional love and support over many years and who has taught me "*attention is in the detail*".

The Author

Narendra Nath Basu is the Lead Consultant Oncoplastic Breast Surgeon at the Queen Elizabeth Hospital, Birmingham. He has trained in London, Manchester, Paris and Boston. During 2012-13 he was awarded the National Training Interface Group Oncoplastic Fellowship. This period was spent in Manchester where he developed an interest in contralateral breast cancer in high-risk patients.

Following his fellowship, he started his full-time consultant post at the same time registering his research at the University of Manchester. He holds the following degrees and qualifications:

BSc (Hons) – First Class. Tumour Biology. University College of London.

MBBS – Bart's and the Royal London Hospital.

MSc – Surgical Technology. St Mary's and Imperial College, London.

FRCS (General Surgery) – Royal College of Surgeons of England.

FEBS (Breast) – Fellow at the European Union of Medical Specialists.

MRCS (Eng) – Royal College of Surgeons of England.

MRCS (Ed) – Royal College of Surgeons of Edinburgh.

CHAPTER 1: Introduction

Contralateral Risk Reducing Mastectomy

Breast cancer remains the most common cancer amongst women worldwide with UK estimates that 1 in 8-10 will develop this disease during their lifetime (Harvey et al. 1999). Each year, over 50,000 new cases of breast cancer are diagnosed in the UK – globally that figure is just under 2 million. Cancer registry data suggests that there are 2 million cancer survivors in the UK, with at least 550,000 women diagnosed with breast cancer still alive (Maddams et al. 2009).

Surgery remains an obligatory component of treatment for most early breast cancers. Since the 1990s, the paradigm shift in surgical treatment has been away from mastectomy towards breast conservation. This remains the gold standard in appropriate patients in terms of oncological and aesthetic outcomes.

There are growing concerns that after an initial struggle for the acceptance of breast conservation in the 1990s, we are slowly drifting towards increasing mastectomy rates again, even of normal healthy breasts. Contralateral risk-reducing mastectomy (CRRM) is the removal of the opposite, healthy breast in patients with breast cancer. It is a contentious issue. In the USA, rates of CRRM have trebled in patients (Figure 1 and Figure 2) with both invasive and in situ disease in recent years (Tuttle et al. 2007).

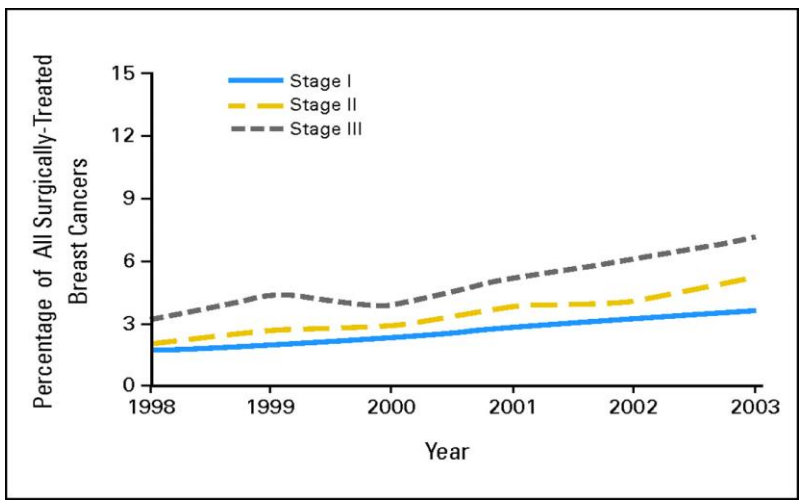


Figure 1. Trends in the proportion of all surgically treated patients who underwent CRRM by cancer stage at diagnosis. The Cochran-Armitage tests for trend for CRRM rates overall and by stage were significant (P<.001)(Tuttle et al. 2007).

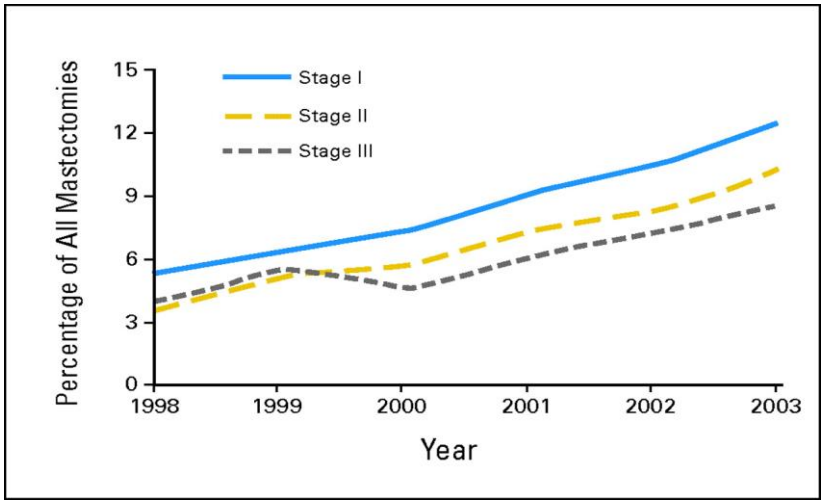


Figure 2. Trends in the proportion of all mastectomy patients who underwent CRRM by cancer stage at diagnosis. The Cochran-Armitage tests for trend for CRRM rates overall and by stage were significant (P<.001)(Tuttle et al. 2007).

This increase is somewhat surprising given that rates of contralateral breast cancer (CBC) are decreasing (Nichols et al. 2011). The use of adjuvant treatments is likely to contribute to this. Tamoxifen, aromatase inhibitors, cytotoxic chemotherapy agents and even herceptin have all been shown to reduce the incidence of CBC (Basu, Barr, et al. 2015).

When a CBC does occur, it tends to be associated with a better prognosis than the index cancer (Ciatto, Miccinesi, and Zappa 2004). Thus, the risk of death of the index cancer usually outweighs that of the CBC. Regular surveillance of breast cancer patients with modern day imaging modalities accounts for the smaller, less advanced stage presentation of a CBC. Periodic imaging of the contralateral breast allows the detection in the asymptomatic phase of most CBC which is associated with a less advanced stage (Ciatto, Miccinesi, and Zappa 2004).

Overall there is little evidence that the majority of patients choosing CRRM may have improved survival rates (Chung et al. 2012). Requests for contralateral surgery need to be considered in this light. Patients' perceptions of risk and anxiety and the trauma of recurrent disease are probably the strongest patient-

driven factors. At the time of diagnosis of an index breast cancer, most women will significantly overestimate their risk of developing CBC (Abbott et al. 2011). The fear of dying at diagnosis of the first primary cancer may distort the decision making process. The challenge for health professionals therefore is to objectively assess a woman's risk of developing a CBC, to make recommendations that are evidence based, and yet also to take into account the broader patient context.

In the UK, there is paucity of data regarding CRRM and until recently no formal guidelines for preoperative assessment and counselling. Although the National Institute for Health and Care Excellence (NICE) made a number of recommendations, predominantly for women at high risk no formal protocol for CRRM was proposed (Evans, Graham, et al. 2013). In contrast, there is a wealth of experience in the management of high-risk patients requesting Risk Reducing Mastectomy prior to any cancer diagnosis. These patients are assessed in specialised family history clinics by geneticists and psychologists prior to the evaluation for surgery. There are formalised NICE guidelines (since 2004) and accepted protocols (Lalloo et al. 2000) – none of which is currently in place for the breast cancer patient requesting a contralateral mastectomy.

Tuttle et al 2007 first reported the increasing use of CRRM. They used the US SEER database that covers approximately 25% of the US population. Over 150,000 women diagnosed with Stage 1 breast cancer were reviewed over a 6-year study period (1998-2003) (Figures 1 and 2). Rates of CRRM had gone from 1.8% (1998) to 4.5% (2003). Multivariate analysis confirmed a positive association between CRRM and young-age (6.7% of all surgically treated women who underwent CRRM were under 39 years compared to 1.3% in their 70s), lobular histology (OR 2.18) and non-Hispanic white ethnicity (OR 2.6).

The same authors (Arrington et al. 2009) performed a regional study on CRRM of 657 women with breast cancer over a 2-year period (2006-7). Independent predictors for increased CRRM rates included tumour size greater than 5cm (OR 2.9), female surgeon (OR 3.0), lobular histology (OR 3.0) and multi-centric disease (OR 2.7). Additional studies from the US have shown that the use of pre-

operative MRI, HER2 positivity and breast reconstruction are also predictors of CRRM.

A more recent study from the US reviewed almost half a million women diagnosed with breast cancer between 1998-2012 (Wong et al. 2016). The proportion of women undergoing CRRM had trebled from 3.9% in 2002 to 12.7% in 2012. During this period, almost 46% of all women undergoing CRRM underwent a reconstruction compared to reconstruction in only 16% of women undergoing a unilateral mastectomy.

Rates of DCIS are increasing (Baxter et al. 2004) and a recent report from the US showed that mastectomy rates to treat this are increasing (Rutter et al. 2015). An initial decline in mastectomy rates for DCIS from 36% (1994) to 28% (2004) has been followed by a steady increase – 33% in 2011. A different publication (Tuttle et al. 2009) confirmed a 148% overall increase in CRRM between 1998-2005 amongst those diagnosed with DCIS, with the highest increase (188%) in those undergoing a mastectomy for their diagnosed DCIS. Predictors for CRRM in the DCIS group were young age (60-69 years OR 1.97, 50-59 years OR 3.17, 40-49 years OR 4.89, 18-39 years OR 11.9), white race, recent year of diagnosis and presence of lobular carcinoma in situ.

Are we becoming victims of our own success? Modern day reconstructive options means that many women undergoing mastectomy should expect to have a good cosmetic outcome. Patients undergoing immediate breast reconstruction are more likely to choose CRRM (Ashfaq et al. 2014). A review of 102,674 breast cancer patients from SEER data confirmed found that those undergoing CRRM were 3 times more likely to undergo a reconstruction compared to those not undergoing CRRM. The authors questioned whether this trend was supported by the notion of superior symmetry and aesthetic outcomes from the reconstruction of two breasts rather than one.

Women undergoing reconstruction should be well appraised about the inherent morbidities of these complex procedures as well as the reality of revision surgery. The UK National Mastectomy Audit reported the outcomes of

mastectomy and breast reconstruction in England between 2008-9. It demonstrated complication rates for immediate reconstruction were up to 20% (Jeevan et al. 2014).

Several US studies have confirmed higher rates of complications in women choosing CRRM (Eck et al. 2014; Pinell-White, Kolegraff, and Carlson 2014; Silva et al. 2015). The largest of these (Silva et al. 2015) looked at data on over 20,000 women with breast cancer over an 8-year period (2005-13) who underwent either unilateral mastectomy with reconstruction or bilateral mastectomy (including CRRM) with reconstruction. In the bilateral mastectomy group there was a longer hospital stay, increased reoperation rate and higher wound disruption rate. Another study (Eck et al. 2014) showed that 1 in 8 women undergoing CRRM had some form of surgical morbidity (i.e. skin necrosis, haematoma, seroma) requiring reoperation in up to 50% of cases.

Surgeons' perceptions and attitudes towards risk-reducing surgery are likely to influence their practice. A European comparative study (Den Heijer et al. 2013) found that almost 100% of surgeons from the UK and the Netherlands had a positive attitude to RRM compared to French (78%) and German (66%) surgeons. In particular, those surgeons with high-volume practices and the greatest knowledge of cancer genetics had the most positive attitude towards surgery. Another study showed that although surgeons from Australia and New Zealand were aware of the objective risk factors for developing CBC, they relied on subjective factors when recommending CRRM (Musiello, Bornhammar, and Saunders 2013).

To date, attitudes towards CRRM amongst surgeons in England are unknown. Despite the rising numbers of CRRM in the US, no studies have investigated attitudes towards RRM amongst American breast surgeons and whether differences exist between the US and parts of Europe. Chapter 3 attempts to answer some of these questions.

A recent study from the Mayo Clinic evaluated the cost-effectiveness of CRRM versus routine surveillance (Zendejas et al. 2011). This included visits to the

breast clinic, radiological imaging (mammography, MRI, US), possible biopsies and subsequent treatment. They concluded that CRRM was cost-effective compared to surveillance in breast cancer patients with younger age (under 40 years) and those at high-risk (*BRCA* carriers).

The high-risk group includes those women with a known genetic mutation in the high-penetrance gene and those with a strong family history of breast and ovarian cancer in the absence of a genetic mutation. A brief overview is presented with further details (risk assessment tools, management strategies and practicalities of genetic testing) included in Appendix 1.

Familial Breast Cancer – a brief overview

The majority of breast cancers arise spontaneously. However, a significant proportion (20-30%) of cancers will have an inherited component (Newman et al. 1988). The 2013 Breast Cancer Campaign gap analysis (Eccles et al. 2013) reported significant advances in knowledge of the heritability of breast cancer from their previous report in 2007 (Figure below). The high-penetrance genes comprised 25-30% of the risk of heritable breast cancer with an increasing proportion attributable to SNPs (discussed later). The proportion of "missing heritability" has also reduced to 50% with the hope that continued efforts will see this figure diminish further in the near future.

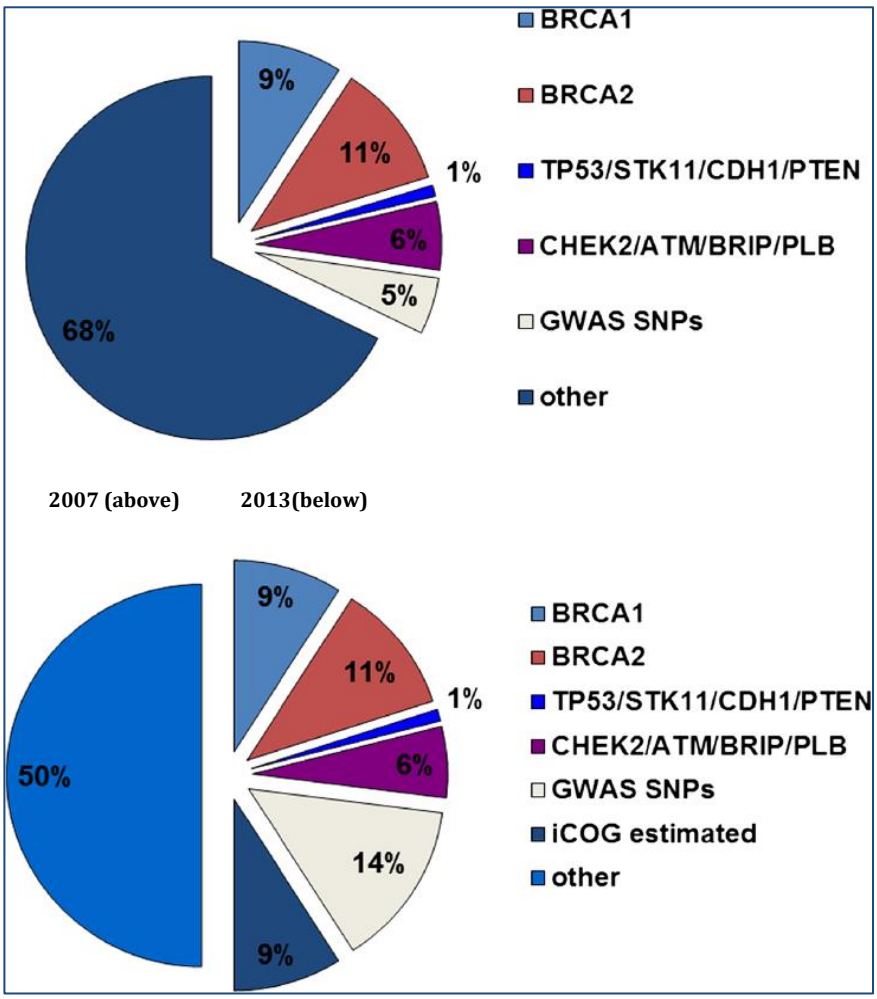


Figure 3. Familial Cancer Genetics. The proportion of the familial component of breast cancers that can be ascribed to specific genetic defects. The difference between June 2007 and 2013 shows the impact of genome-wide association studies (GWAS) that have now identified 77 common low-risk SNPs (Eccles et al. 2013).

The NICE CG164 guidelines (Evans, Graham, et al. 2013) stratified women into 3 groups based on their overall risk:

1. Near Population risk ('low')
    - Overall lifetime risk from age 20 years <17%
    - Risk between ages 40-50 years < 3%
2. Moderate Risk
    - Overall lifetime risk from age 20 years 17-30%
    - Risk between ages 40-50 years 3-8%
3. **High Risk**
    - **Overall lifetime risk from age 20 years >30%**
    - **Risk between ages 40-50 years >8%**

High-risk women harbouring a mutation in the *BRCA1* or *BRCA2* gene have a lifetime risk of up to 85% of developing breast cancer (Evans et al. 2008). Ovarian cancer is also associated with these mutations: up to 60% lifetime risk in *BRCA1* mutation carriers and up to 30% in *BRCA2* carriers (Lalloo and Evans 2012).

Relative risk of breast cancer is inversely proportional to age. Breast cancers in *BRCA1* mutation carriers are often triple negative (oestrogen receptor negative, progesterone receptor negative, HER2 receptor negative) compared to the *BRCA2* group – which tends to be a more heterogeneous group. *BRCA2* associated breast have more semblance to sporadic breast cancer – they are more often oestrogen receptor positive (ER+ve), with some studies showing increased DCIS and lobular cancers) (Da Silva and Lakhani 2010).

High Penetrance Genes:

BRCA1 – the chromosomal site of tumour suppressor gene was first identified by family linkage analysis in 1990 and cloned 4 years later in the US (Miki et al. 1994). During the next 2 decades a bitter commercial battle ensued regarding patenting of the genomic DNA sequence to both *BRCA*1 and *BRCA*2. Ultimately,

the 2013 US Supreme Court ruled that "*isolation of genes found in nature do not render them patentable*".

The human *BRCA*1 gene (Chromosome 17p - codes for the breast cancer type 1 susceptibility protein) is involved in DNA repair. The majority of mutations are frameshift resulting in a truncated protein. The inheritance pattern is autosomal dominant with birth incidence of a *BRCA*1 mutation estimated at 1 in 500- 1in 1000 (Lalloo et al. 2003), accounting for 7-10% of familial breast cancers (Lalloo and Evans 2012).

Harbouring a *BRCA*1 mutation confers a lifetime risk of breast cancer of approximately 60-85% (Evans et al. 2008; Antoniou et al. 2003) and up to 60% for developing ovarian cancer (usually high-grade serous carcinomas). Relative risk of breast cancer is inversely proportional to age. Other cancers that have been associated with a *BRCA1* gene mutation include pancreatic cancer (RR 2.26), uterine body and cervical cancer (RR 2.65, RR 3.72 respectively] and prostate cancer in the under 65s (RR 1.82) (Thompson and Easton 2002). However, none outside Breast and ovary are consistently found to be elevated (Moran et al. 2012).

BRCA1 related breast cancers are heterogenous but have some important clinical features. As mentioned they are mostly triple negative with expression of basal markers on tumour cells (CK5/6, CK14, SMA, P Cadherin, EGFR0). Histologically, they are often similar to high-grade medullary carcinomas with pushing margins, high mitotic counts and lymphocytic infiltrates (Vargas, Da Silva, and Lakhani 2010).

BRCA2 – This DNA repair gene was identified in the UK in 1994 on chromosome 13q and encodes the protein Breast Cancer 2 Susceptibility Protein (Wooster et al. 1994). Mutations in *BRCA*2 are nearly all inherited suggesting a large founder effect. This is important for practical purposes as certain populations can be tested for known mutations (e.g. a single mutation 999del5 accounts for almost all inherited breast and ovarian cancer in Iceland).

Lifetime breast cancer risk has a wider range (40-85%) compared to *BRCA1*, and a somewhat lower risk of developing ovarian cancer (30%). Approximately 1 in 600-800 women carry a mutation (outbred population) that accounts for 10% of familial breast/ovarian cancer.

Several other cancers are more commonly associated with this mutation: Cholangiocarcinoma, melanoma, pancreatic cancer (overall RR 4.1), gastric cancer (RR 2.7) and prostate cancer. Approximately 10% of Male breast cancer is associated with *BRCA*2, but is not associated with *BRCA*1 mutations.

A recent review (Bordeleau, Panchal, and Goodwin 2010) suggested that the 5-year survival of breast cancers in *BRCA1/2* mutation carriers is similar to sporadic breast cancers. In addition these women have similar survival whether they are treated with breast conservation surgery or a mastectomy (Pierce et al. 2010), despite having significantly higher rates of local failure with breast conservation. Interestingly, most local recurrences are second primary breast cancers rather than failure to control the primary breast cancer.

Once diagnosed with breast cancer, these women have a 10-year CBC risk ranging from 13-40% (Basu, Ingham, et al. 2015; Graeser et al. 2009; Metcalfe et al. 2004). Counselling these women about available treatment options and risk-reducing strategies requires an understanding of factors that modify their CBC risk. Several of these predictors have been described in the literature: early age of first breast cancer, number of affected first-degree relatives, oophorectomy and use of tamoxifen.

TP53 **–** is called the "Guardian of the Genome" is located on Chromosome 17. It is the most common known genetic mutation in human cancers. Somatic *TP53* mutations are well described and have been implicated in the multi-stage progression of several cancers (especially colon cancer). Inherited *TP53* mutations are rare, resulting in Li Fraumeni Syndrome (LFS). This is characterised by a wide spectrum of childhood and early adulthood tumours including soft tissue and bone sarcomas, brain tumours, leukaemias and adrenal cortical carcinomas.

Breast cancer remains the most common malignancy amongst these women (risk 50% by age 30 and 90% by age 60 years) (Masciari et al. 2012), with up to 7% of women with breast cancer under the age of 30 harbouring a *TP53* mutation (Evans et al. 2010).

Patients with LFS may not respond to adjuvant treatments (chemotherapy and radiotherapy) and in particular radiotherapy, where there is a potential for developing new primary malignancies (Kappel et al. 2015). Of clinical relevance is that up to 63-83% of LFS patients test positive for HER2 (Masciari et al. 2012). Clinicians may consider mutation analysis for *TP53* in very young women with breast cancer, particularly in the presence of a family history of cancer (Rath et al. 2013).

PTEN – is a tumour suppressor gene codes for the Phosphatase and Tensin Homolog protein. It is included in multigene "panel testing" and is of clinical importance. Mutation in *PTEN* confers a lifetime breast cancer risk of 67-85% (Ngeow, Sesock, and Eng 2015) but this may be an overestimate due to biased ascertainment. There is a wide spectrum of phenotypes with this anomaly with Cowden Syndrome (CS). The most commonly described include malignancies of the thyroid and endometrium and non-malignant manifestations include: hamartomas, macrocephaly, intestinal polyps and cerebellar lesions. This rare condition possibly affects 1 in 200,000 people.

PALB2 – encodes the protein (Partner and Localiser of *BRCA*2) that interacts with both *BRCA*1 and *BRCA*2 (Antoniou et al. 2014). Fanconi's anaemia is associated with biallelic germline mutation of *PALB2* and also associated with familial pancreatic cancer. It is also included in multi-gene panels and confers up to a 35% lifetime risk of breast cancer by the age of 70.

CDH1 – encodes the for the cell-adhesion protein E-cadherin, Mutation of this results in loss of cell adhesion, cancer progression and metastasis. The expression of this protein is used for practical purposes by pathologists to help differentiate lobular and ductal carcinomas (expression of the former is lost in most lobular cancers). Germline mutations of *CDH1* confer a 42% lifetime risk of

developing lobular breast cancer and up to 70% risk of developing diffuse gastric cancers. Surveillance MRI is preferred over mammography, given the latter has a low sensitivity for identifying lobular cancers (van der Post et al. 2015).

STK11 encodes the protein kinase (Serine/Threonine Kinase 11) that is associated with the autosomal dominant Peutz-Jeghers Syndrome. The hallmark of this disorder is the presence of multiple gastrointestinal hamartomatous polyps and pigmented macules but also a reported lifetime risk of breast cancer up to 54% (Apostolou and Fostira 2013).

Moderate Penetrance Genes

ATM - Ataxia-telangiectasia is an autosomal recessive condition with an estimated frequency of 1 in 40 000 to 1 in 300 000. Individuals with ataxia-telangiectasia are reported to have a 100-fold increased risk of cancer with lymphoid cancers predominating in childhood and adult onset epithelial cancers (e.g. breast). The associated lifetime risk for developing breast cancer for women carrying a single mutated allele is around 20%.

CHEK2 - Checkpoint kinase gene contributes to the same signaling pathway as *TP53* and *BRCA1*. The gene mutation is present in 1 in 200 live births Carriers of mutated *CHEK2* have been reported to have an increased risk of bilateral breast cancer and an association with colorectal cancer.

BRIP1 –(Binding partner of BRCA1) is reported to be present in 1 in 1000 live births. Previous studies had reported a 20% lifetime risk of breast cancer. However, more a recent analysis found that this mutation was not associated with a substantial increase in breast risk and as such may question their inclusion in breast cancer screening panels (Easton et al. 2016).

Low Penetrance Genes

The human genome is comprised of over 3 billion base pairs. Over the last decade significant advances have been made in studying variations in DNA sequences. Genome Wide Association Studies (GWAS) examines associations between these genetic variants called single nucleotide polymorphisms (SNPs) and disease traits.

Over 100 SNPs have been identified which may alter (increase or decrease) the risk of developing breast cancer. These are relatively common changes in nucleotides that occur with a frequency of approximately over 5%. They confer a modest risk of up to 1.05-1.35 times higher than the general population and likely work in a polygenic multiplicative manner rather than being incremental.

The use of SNPs in prime time clinical practice is anticipated and has already been included in several of the available multi-gene panels. The potential risk of clinical misinformation (Thompson et al. 2016) needs to be addressed by physicians involved in recommending these tests. Thus, the validity of risk estimates is of paramount importance as several studies have shown that SNPs may be ready for clinical use (Ingham et al. 2013).

There is considerable variation of breast cancer risk amongst those carrying a mutation in *BRCA1/BRCA*2. Age at diagnosis and cancer type of the proband case will influence this risk. The variability of this risk is highly suggestive of additional genetic (non *BRCA*1/2 alleles or genes) and non-genetic modifiers of *BRCA*1/2 (Antoniou et al. 2003). Potentially, this may enable personalised risk assessment amongst high-risk women, stratifying their risk even further – i.e. it may be possible to estimate which part of the range of lifetime risk (40-85%) an individual is likely to be affected by.

A proportion of women from families with known mutations will themselves test negative for that mutation but go on to develop breast cancer. These women are considered to be phenocopies whereby their phenotype (breast cancer)

matches the phenotype determined by genetic factors despite testing negative to a known genetic mutation. It is likely that these women are enriched by genetic modifiers that increase the penetrance of *BRCA1/2* in non-mutation carriers (Evans, Ingham, Buchan, et al. 2013). A recent study found higher rates of phenocopies in women from families with a *BRCA2* mutation. It concluded that caution should be exercised when counselling women from a family of *BRCA2* mutation carriers who tested negative for a *BRCA2* mutation as their risk of breast cancer may be higher than the population, particularly in the presence of multiple relatives with early onset breast cancer. The role of the 18 validated SNPs amongst *BRCA2* breast cancer phenocopies showed a relative risk of 1.3 which may have a clinical role in the future to help those with a negative *BRCA2* test stratify their breast cancer risk further.

Discussion

In May 2013, Angelina Jolie announced that she carried a maternally inherited pathogenic *BRCA1* mutation and had undergone BRRM with immediate implant based reconstruction (Evans et al. 2014). The aftermath – the so-called "Angelina Jolie effect" has seen a 250% increase in the number of breast referrals to the regional genetics units for gene testing and risk assessment. In Manchester, there was a similar 2.5 fold increase in uptake of BRRM 6-24 months following Ms Jolie's revelation (Evans et al. 2015). The effect this may have on the public's perceptions of CRRM remains to be seen.

The updated NICE 2013 guidelines of Familial breast cancer were published around the same time as Miss Jolie's announcement. It made a number of recommendations regarding the management of this group of women including lowering the threshold for genetic testing to a lifetime risk level of 10% (Evans, Graham, et al. 2013). The UK Genetic Testing Network has recommended mainstreaming *BRCA* testing in certain groups of women (for example triple negative breast cancers in women under the age of 40 years) so that appropriately trained breast surgeons may initiate the process of gene testing in this population group (Eccles et al. 2015).

My own studies (Chapter 3) have confirmed that attitudes to risk-reducing surgery are driven by knowledge of breast cancer genetics – and that in the setting of contralateral risk-reducing surgery, the level of knowledge amongst surgeons is suboptimal (Basu et al. 2016).

As the management of breast cancer has advanced, there have also been subtle changes to in the attitudes and conceptions of our patients. They are better informed, increasingly use the Internet, have close ties to social network sites and support groups, and will often enter a clinical consultation with firm, pre-set views in the light of this. Patients must be invited to engage in the decision-making process that must take into account their underlying psychosocial state, expectations and concerns. The multi-disciplinary team and, in particular, the breast care nurse are crucial in making these decisions.

The challenge remains to provide patients with non-biased, evidence based clinical recommendations that take into consideration objective assessment of risk. An already published literature review of the risk factors for developing contralateral breast cancer is described in the following chapter.

CHAPTER 2: Literature Review – Contralateral Breast Cancer and Risk Reducing Strategies

This literature review examines the multiple risk factors known to contribute to developing CBC. Survival data are reviewed and the contribution of the following risk factors discussed: gene mutation status, family history, histology, ER status and HER2 status. I have evaluated the different risk-reducing strategies (surgery and chemoprevention), their efficacy and cost and finally consider the patient's perspective. Chemoprevention using anti-endocrine treatment is included in the section on ER status.

Incidence of CBC

High-risk group

i) *BRCA1/2* mutation

The two most commonly studied breast cancer susceptibility genes are *BRCA1* and *BRCA2*. Mutations in these tumour suppressor genes confer an up to 85% lifetime risk of developing breast cancer (Evans et al. 2008; Ford et al. 1998; Lalloo and Evans 2012).

These women have a significant CBC risk once diagnosed with breast cancer. The risk, to age 70 years, of a CBC in *BRCA1* mutation carriers has been estimated to be above 60% (Thompson and Easton 2002) and in *BRCA2* mutation carriers slightly lower at around 50% (Ford et al. 1998). However, a recent prospective study (Mavaddat et al. 2013) has shown that these risks may be even higher at 83% and 63% respectively representing higher risks in the modern era particularly for *BRCA1* where the majority of tumours would not receive endocrine therapy.

This high-risk group of women have a CBC risk of 2-3% per year (Graeser et al. 2009; Metcalfe, Gershman, et al. 2011; Metcalfe, Lynch, et al. 2011; Metcalfe et al. 2004). Metcalfe et al 2004 studied 491 women with breast cancer, who had a

documented *BRCA1* or *BRCA2* mutation in the family. The 5-year actuarial risk of CBC was 17% and 10-year risk 30%. Other studies have shown that this risk may be variable: as high as 20% at 5-years (Pierce et al. 2000) or 42% at 12-years (Haffty et al. 2002) or as low as 10% at 5-years (Chappuis et al. 2000).

This heightened risk, particularly in women diagnosed with their primary cancer before 40 years lasts for at least 20-years. One study (Verhoog et al. 2000) found that in *BRCA1/2* carriers diagnosed with breast cancer before the age of 50 years, the 10-year risk of CBC was 40% compared to the over 50s group which was much lower at 12%.

The Metcalfe study (2004) found that additional protective factors of CBC risk included presence of a *BRCA2* mutation [vs *BRCA1* HR 0.73], tamoxifen use [HR 0.59] and oophorectomy [HR 0.44]. The protective effect of oophorectomy was most pronounced in women first diagnosed under 49 years [HR 0.24]. Graeser et al found a similar protective effect of *BRCA2* mutation status – *BRCA*1 mutation carriers had a 1.6 fold higher risk of CBC compared to B*RCA2* carriers. Metcalfe et al extended the sample size with a longer follow up period and were able to confirm the protected effect of oophorectomy (Metcalfe, Gershman, et al. 2011).

Tamoxifen has been shown to reduce rates of CBC amongst *BRCA1/2* carriers by 50% (Narod et al. 2000) in those where it was used to treat the initial breast cancer. This effect is greatest in the *BRCA2* carriers, which is expected given that tumours arising in *BRCA1* mutation carriers are mainly ER negative. In addition, this study showed that a greater proportion of CBCs were ER positive in women with previous tamoxifen use. It is likely that this is related to an antioestrogenic mechanism rather than solely by receptor-mediated oestrogen blockade. Short-term use of tamoxifen in these patients may be as effective as a conventional 5-year period of treatment (Gronwald et al. 2014).

A recent meta-analysis (Valachis, Nearchou, and Lind 2014) reviewed 23 clinical studies in the context of CBC amongst *BRCA* mutation carriers. Two factors backed by high level of evidence (Table 1 – highlighted in red) were associated

with a decreased risk of CBC: oophorectomy (RR 0.52) and increasing age greater than 50 years (RR 0.47). A reduction in CBC risk was also noted with tamoxifen use (RR 0.57) and even less so with chemotherapy (RR 0.90) from studies with moderate levels of evidence. Risk reduction by tamoxifen was most marked amongst those women who did not undergo an oophorectomy (RR 0.42 – low level of evidence).

Table 1. Summary of risk factors from multivariable analyses for contralateral breast cancer in *BRCA*-mutation carriers (Valachis, Nearchou, and Lind 2014)

Risk factors	No of studies (patients)	CBC hazard ratio (95 % CI)	Heterogeneity		Studies by quality			Consistency	Level of evidence
			I^2(%)	*p* value	High	Moderate	Low		
Age (continuous)	1 (160)	0.98 (0.95–1.02)	–	–	0	1	0		
Age >50 years old	**1 (810)**	**0.47 (0.27–0.82)**	**–**	**–**	**1**	**0**	**0**		
Age (qualitative evaluation of studies)	**3 (1386)**	**NC**	**NC**	**NC**	**0**	**1**	**2**	**Consistent[a]**	**High**
Positive ER-status	1 (810)	1.02 (0.64–1.62)	–	–	1	0	0	–	Inconclusive
Grade III	1 (810)	0.84 (0.50–1.41)	–	–	1	0	0	–	Inconclusive
Positive nodal status	1 (810)	0.76 (0.51–1.12)	–	–	1	0	0	–	Inconclusive
Tamoxifen use	5 (1492)	0.57 (0.43–0.75)	0	0.5	1	3	1	Consistent	Moderate

Risk factors	No of studies (patients)	CBC hazard ratio (95 % CI)	Heterogeneity		Studies by quality			Consistency	Level of evidence
			I^2(%)	*p* value	High	Moderate	Low		
Tamoxifen use (patients who did not undergo bilateral oophorectomy)	2 (445)	0.42 (0.27–0.63)	44	0.18	0	2	0	Consistent	Low
Tamoxifen use (patients who have undergone bilateral oophorectomy)	1 (149)	0.83 (0.24–2.89)	–	–	0	1	0	–	Inconclusive
Chemotherapy	3 (1151)	0.90 (0.66–1.22)	15	0.31	1	2	0	Consistent	Moderate
Oophorectomy	**3 (1621)**	**0.52 (0.37–0.74)**	**0**	**0.83**	**2**	**1**	**0**	**Consistent**	**High**

All 3 studies included in the qualitative evaluation have shown that the cumulative incidence of CBC decreased with increased age (lower incidence for age >50 years old in two studies (Verhoog et al. 2000; Graeser et al. 2009) and >45–54 years old in the other (Malone et al. 2010). The quality of evidence has been derived from all the five studies (including three with qualitative evaluation). All studies are considered consistent. However, no cumulative hazard ratio has been calculated due to the differences in the use of age as variable as long as the lack of multivariable analysis in the three studies with qualitative evaluation

ii) *TP53*

Inherited *TP53* mutations are rare, resulting in Li Fraumeni Syndrome (LFS). Breast cancer is the most common malignancy amongst these women (risk is 50% by age 30 and 90% by age 60 years) (Masciari et al. 2012), with up to 7% of women with breast cancer under the age of 30 harbouring a *TP53* mutation (Evans et al. 2010).

There is limited data published on CBC in *TP53* mutation carriers. Evans et al reviewed long-term outcomes of breast cancer in women aged 30 years or younger based on family history and genetic mutation status (*TP53, BRCA1, BRCA2*). The highest CBC cumulative incidence was amongst the group harbouring a *TP53* mutation. CBC rates were approximately 2-3% annually in all mutations carriers (*TP53* and *BRCA1/2*) – although only 11 *TP53* mutation carriers were included in their extended analysis. It is possible that adjuvant endocrine and anti-HER2 treatment will influence CBC risk in *TP53* mutation carriers as the majority of these patients are ER and HER2 positive (Masciari et al. 2012).

iii) *CHEK2*

The checkpoint kinase gene contributes to the same signaling pathway as *TP53* and *BRCA1*. The frequency of the gene mutation (*CHEK2* 1100delC mutation) is approximately 1% amongst of the normal Dutch population, up to 4% in unselected breast cancer patients and up to 6% in breast cancer patients with a family history of breast cancer. Carriers of mutated *CHEK2* have been reported to have a two-to three-fold increase risk of developing breast cancer (Meijers-Heijboer et al. 2002).

A Dutch study (Kriege et al. 2014) found an increased incidence of CBC [HR 3.97] amongst *CHEK2* mutation carriers compared to non-carriers with a 10-year risk of 24.1%. In addition, overall survival amongst *CHEK2* mutation carriers was worse compared to non-carriers – an effect most obvious 6 years following an initial diagnosis of breast cancer.

iv) *PALB2*

The partner and localiser of *BRCA*2 gene encodes the protein that interacts with both *BRCA*1 and *BRCA*2 (Antoniou et al. 2014). Mutation of this gene confers up to a 35% lifetime risk of breast cancer by the age of 70.

The Women's Environment, Cancer and Radiation Epidemiology Study (WECARE study) was a multi-centred, population-based, case-control study of over 50,000 women with unilateral breast cancer that included 705 women with CBC. 5 pathogenic *PALB2* mutations were identified in the study group – all of whom developed CBC (Tischkowitz et al. 2012).

v) *ATM*

Ataxia-telangiectasia is an autosomal recessive condition with an estimated lifetime risk for developing breast cancer for women carrying a single mutated allele of around 20%. The relationship between variants in the *ATM* gene and breast cancer risk is complex. Results from the WECARE Study investigated various combinations of mutations and found that this either increased or decreased CBC risk (Concannon et al. 2008).

vi) Previously treated Hodgkin's Disease

Since the 1960s, radiotherapy and chemotherapy have been used to successfully treat paediatric Hodgkin's Disease. Mantle field radiation (rarely used today) was used during this period and involved radiation to the upper body lymph node basin including the chest wall. Breast cancer is the most common secondary malignancy in Hodgkin's Disease patients treated using radiotherapy during this era (Dores et al. 2002).

A study of 398 female patients treated for Hodgkin's disease over a 17-year found that this patient group had a 37-fold increase in developing breast cancer (Basu et al. 2008). A different study found that this patient group had an almost 2% per year annual CBC risk (van Eggermond et al. 2014) – not dissimilar to women with a *BRCA1/2* mutation.

Non High-risk group

(Gao, Fisher, and Emami 2003) reviewed SEER historical data (1973-1996) to evaluate changes in trend of CBC. During this time period, 5679 (4.2%) CBCs were identified amongst 134,501 breast cancer patients. Actuarial incidence rates of CBC in this group of women at 5,10, 15 and 20 years were 3%, 6.1%, 9.1% and 12% respectively, amounting to 0.6% per annum. Multivariate analysis showed increased levels of CBC amongst those diagnosed with a medullary carcinoma [RR 1.18], women of black race [RR 1.2] and those diagnosed over the age of 55 years [1.15]. Radiotherapy was associated with a 14% increased risk of CBC after 5 years. The 5, 10, 15 and 20 actuarial rate of CBC in the radiotherapy group was 2.9%, 6.5%, 10.2% and 13.4% compared to 3.0%, 6.0%, 8.9% and 11.8% for patients without radiotherapy. 40% of CBCs occurred between 1 to 4 years following primary breast cancer, 30% between 5 and 9 years and 30% greater than 10 years. The higher rates of CBC associated with radiotherapy were also confirmed in the EORTC 10853 trial (Julien et al. 2000) and is likely to be related to internal and external scatter of radiation.

An important limitation of this historic SEER data is that it included a varied dataset including women with a positive family history of breast cancer before and after the advent of genetic testing as well as limited information on the use of systemic treatment (tamoxifen and/or chemotherapy).

A more recent follow up on the SEER database (1975-2006) (Nichols et al. 2011) confirmed that CBC rates are declining with an estimated annual percentage change of approximately -3.0%. A similar decline has been observed in parts of Europe and overall is likely to be a result of the use of anti-endocrine treatment (discussed later).

Family history

A positive family history of breast cancer increases the risk of CBC although this risk pattern is complex. (Vichapat et al. 2011) studied 8478 women with breast cancer over a 31-year period (1975-2006) and found that there was a 2.8 fold

increase in relative risk with a positive family history of breast cancer. Subgroup analysis revealed that the highest risk were those with a first and second-degree relative (RR 2.33) followed by first-degree alone (RR 1.38) and second or third degree (RR 1.13). Numerous first-degree relatives conferred an even higher risk.

The WECARE study confirmed that the risk of CBC amongst non-carriers of *BRCA1/2* mutations with a family history was highest in women diagnosed at an earlier age with their index breast cancer (<45 years), those with a young first-degree relative, particularly with bilateral disease (Reiner et al. 2013). The 10-year cumulative CBC risk stratified by age was 6.7% (50-54 years), 9.0% (40-44 years) and 14.7% (30-34 years).

A study from the Mayo Clinic (McDonnell et al. 2001) followed up 745 women with breast cancer and a positive family history who underwent a CRRM between 1960-1993. They had predicted (without CRRM) 106 CBCs in the pre-menopausal group and 50 CBCs in the post-menopausal group. CRRM had resulted in an approximate 95% reduction in relative risk as only 6 and 2 actual CBCs occurred in pre and post-menopausal women respectively.

(Rhiem et al. 2012) evaluated the risk of CBC amongst women from a high-risk family who tested negative for *BRCA1/2*. The cumulative risk of CBC at 25 years for *BRCA1* and *BRCA2* mutation carriers was 44.2% and 33.5% respectively compared to 17.2% in those who tested negative for *BRCA1/2*. They concluded that rates of CBC amongst *BRCA1/2* negative women with a strong family history were low and similar to the population with sporadic breast cancer. They acknowledged that phenocopies may have been included in their study but would only account for a small proportion of the sample 5-6% (Meijers-Heijboer et al. 2003).

Histology of index breast cancer

(Vichapat et al. 2011) reviewed 8478 women diagnosed with breast cancer at Guy's Hospital between 1975-2006. They found no significant increase in CBC amongst those with lobular breast cancer. A more recent UK study of 38,132

patients also found no increase in CBC according to the histological type of breast cancer (Langlands et al. 2016). This is an important finding given that lobular breast cancer has been shown to be an independent predictor of increased CRRM rates [OR 3.0] (Arrington et al. 2009) and possibly arises from previous studies that have shown an association of lobular cancer and CBC (Bernstein et al. 2003). Another important consideration is that mammography and ultrasound have a low sensitivity for the detection of lobular carcinoma and many centres routinely use MRI (93% sensitivity for detecting lobular cancer), which itself is an independent predictor for CRRM [OR 1.3] (Arrington et al. 2009).

High grade of primary tumours (RR 1.3 for Grade 3 cancer compared to Grade 1), increasing size (<2cm RR 1.0, 2-5cm RR 1.51, >5cm RR 1.89) and number of positive lymph nodes (Non RR 1.0, 4-9 RR 1.12, >10 RR 1.62) have all been shown to be important risk factors (Vichapat et al. 2011). Based on the findings regarding lymph node involvement, (Vichapat et al. 2011) considered whether 2 different aetiological pathways exist for CBC. The first is that the majority of CBCs occur as a de novo event – a new primary. In contrast, those that are associated with a particular aggressive phenotype (large tumour, high nodal involvement) may represent metastatic recurrences. Very few studies assessing the clonal relationship between primary breast cancer and CBC seem to support this (Shibata et al. 1996). A recent Australian study (Huang et al. 2015) was able to use DNA methylation profiling and array comparative genomic hybridization (cCGH) to determine whether a CBC was clonally related to the primary cancer which may be of use in the future in addition to standard histopathology.

The NSABP B17 trial (Fisher et al. 1999; Fisher et al. 2007; Gao, Fisher, and Emami 2003) investigated the outcomes following surgery for DCIS. 4.3% of those undergoing breast conserving surgery for DCIS developed a CBC after a follow-up period of 8 years. Overall, amongst those diagnosed with DCIS the risk of a CBC was approximately 0.6% per year with almost two-thirds of CBCs (following surgery and radiotherapy) being invasive cancer (Bijker et al. 2006; Fisher et al. 1998).

Lobular carcinoma in situ (LCIS) is a rare lesion with some controversy regarding its malignant potential and management. Rates of LCIS are increasing, a likely effect of screening. A recent report from the Memorial Sloane Kettering group (King et al. 2015) found an overall rate of cancer development of approximately 2% per year. They followed 1060 patients diagnosed with LCIS without a concurrent breast cancer for at least 8 years and found that nearly 15% of women developed breast cancer of which a quarter were in the contralateral breast. 5% of women in this study group chose bilateral mastectomies compared to 17% who chose chemoprevention (SERM or AI) to reduce their risk of developing breast cancer. (Tuttle et al. 2009) found LCIS to be a predictor of CRRM amongst those diagnosed with DCIS (OR 1.78).

HER2 status and anti-HER2 therapy

Up to 30% of breast cancers express HER2 receptor tyrosine-protein kinase (Mitri, Constantine, and O'Regan 2012). Use of the monoclonal antibody trastuzamab (Herceptin©) has been shown to improve disease free-survival (Piccart-Gebhart et al. 2005). The HERA study (Herceptin Adjuvant Trial) recently reported outcomes after a 4-year follow-up (Gianni et al. 2011). In the observation group there were 19/320 (1.1%) CBCs compared to 14/251 (0.8%) in the trastuzumab group. Although, this represents a small reduction in CBC in women treated with trastuzumab, its clinical application for risk-reduction of CBC remains debateable.

(Saltzman et al. 2012) performed a case-control study of 29,126 women using the Cancer Surveillance System (CSS) cancer registry. They were able to show that women with HER2 overexpression (ER negative /HER2 positive) and those with triple negative cancer (ER negative, PR negative, HER2 negative) had a 2.0 fold and 1.4 fold increased risk of developing CBC, respectively. Using case-control methodology the authors reviewed the association between CBC and ER/PR/Her2 status. They found that women who cancer was ER-ve / PR-ve had a 1.6 fold increased rate of developing CBC compared to those who were ER+ve/PR+ve.

Therefore, in addition to having a higher risk of recurrent disease and death, this subgroup of patients will have an elevated risk of CBC and surveillance strategies may need to be considered in monitoring this cohort.

ER status and chemoprevention

Up to 80% of breast cancers are hormone sensitive (CancerResearchUK 2015) and the majority of women will be recommended at least 5 years of anti-endocrine treatment. There are 2 major classes of drugs that are used in breast cancer: Selective Oestrogen Receptor Modulators (SERMs e.g. tamoxifen, raloxifene) and Aromatase Inhibitors (AI i.e. anastrozole, letrozole, exemestane).

The Oxford overview (EBCTCG 1998) reviewed 55 clinical trials of tamoxifen use by over 37,000 women with breast cancer. As well as improving survival, tamoxifen use in all women (including ER poor tumours) was associated with a reduction in CBC: 13% at 1 year, 26% at 2 years and 47% at 5 years. The absolute decrease in CBC was twice as large as the absolute increase in endometrial cancer.

Aromatase inhibitors are offered to post-menopausal women with hormone sensitive breast cancer. Historically, tamoxifen had been the drug of choice but several trials have shown superior results from AIs over tamoxifen in the post-menopausal breast cancer setting. (Howell et al. 2005) conducted the ATAC trial – a double-blind randomised trial, comparing 5 years of either the AI anastrozole or tamoxifen alone or the combination of both amongst 9366 post menopausal breast cancer patients. CBC incidence was substantially reduced by anastrozole compared to tamoxifen (all patients 42%, ER+ve patients 53%). The benefit of reducing CBC risk by anastrozole persisted with 10 years follow up (Cuzick et al. 2010).

The IBIS II trial recently reported no clear advantage between anastrozole or tamoxifen in preventing CBC in postmenopausal women with locally excised DCIS (Forbes et al. 2016). The MA.27 trial assessed whether a steroidal AI (exemestane) is superior to a non-steroid AI (anastrozole) amongst

postmenopausal women with breast cancer (Goss et al. 2013). Although no benefit was found in overall breast cancer outcomes fewer CBCs were noted amongst the anastrozole group (n=33) compared to the exemestane group (n=46).

Recently, (Gronwald et al. 2014) were able to confirm previous studies showing an approximately 50% reduction in CBC risk in *BRCA1/2* mutation carriers who took tamoxifen following their index breast cancer. Of interest was the similar risk-reduction of a short period of tamoxifen (<1 year) compared to longer use (>4 years). This has implications on women who have concerns over the side effect profile of long-term tamoxifen use and may rationalise the short-term use of this drug.

The overall reduction of CBC rates is largely due to anti-endocrine treatments. Nichols et al reviewed SEER data from 1975-2006. Prior to 1985, rates of CBC were stable with an estimated annual percentage change (EAPC) of 0.3%. After this period, CBC rates declined with an EAPC of -3.0% (Figure 4). From 1990 onwards, this decline in CBC was only seen amongst ER+ve and not ER-ve cancer.

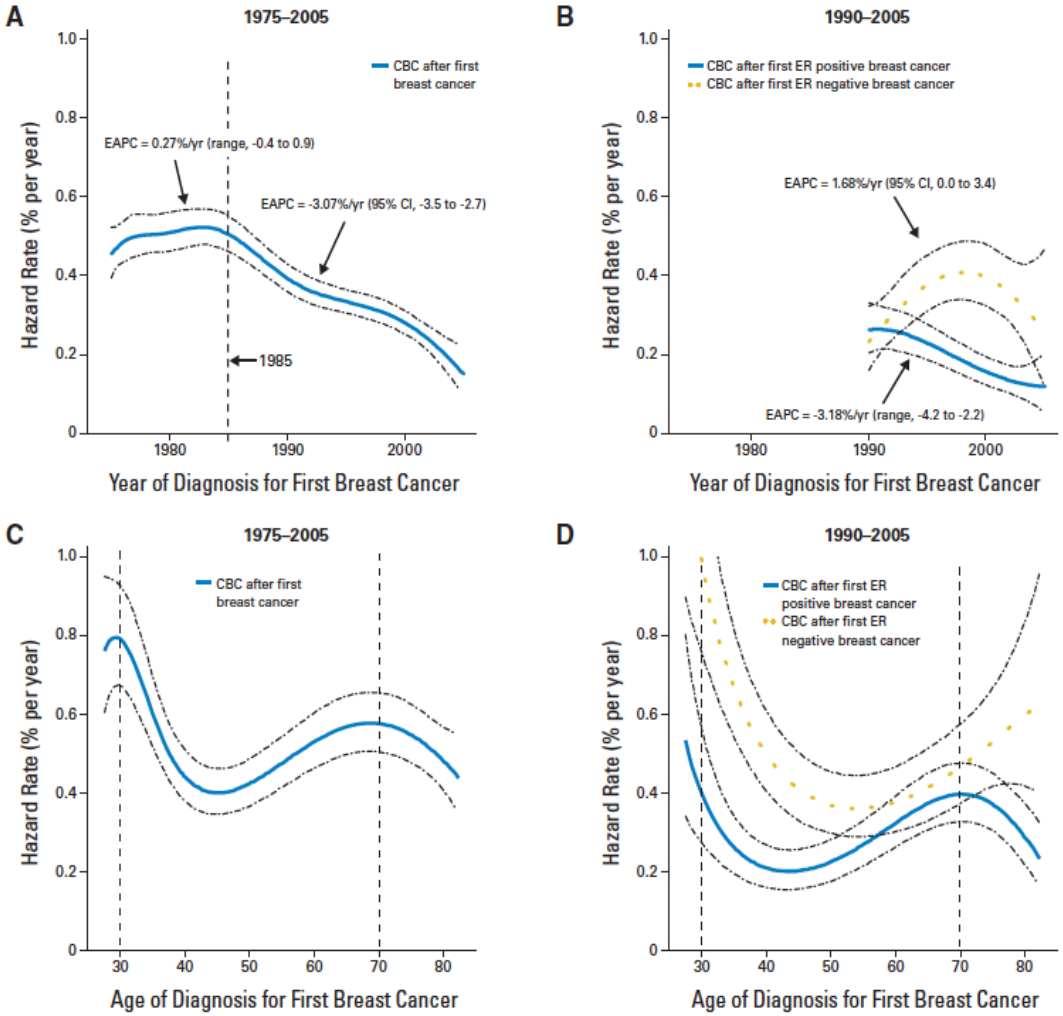


Figure 4. Annual hazard rates for CBC over time and across age from 1975 to 2005 after a breast cancer (A,C). Annual hazard rates for CBC over time and across age from 1990 to 2005 after a first ER +ve or ER –ve breast cancer (B,D). EAPC (estimated annual percentage change) is the hazard rates per year of calendar time (Nichols et al. 2011).

Chemotherapy

Cytotoxic chemotherapy agents recommended as adjuvant or neo-adjuvant treatment of primary breast cancer have been shown to reduce the risk of CBC. The Early Breast Cancer Trialists Group (EBCTG) performed a meta-analysis of 194 randomised studies reviewing the effect of systemic adjuvant treatments on breast cancer survival and recurrence (EBCTCG 2005). It showed a marginal reduction in the incidence of CBC over a 15-year follow up period, which was more definite in women under the age of 50 years.

A Swedish study (Hartman et al. 2007) reviewed 123,757 women diagnosed with breast cancer between 1970-2000. The number of synchronous cancer detected increased by 40% during the 1970s whereas the number of metachronous (CBC) decreased by 30% since 1980s. They found a dual effect of chemotherapy on CBC – it reduced the risk of developing CBC but seemed to worsen prognosis. They calculated that women developing a CBC within 5 years of their primary breast cancer diagnosis and at age less than 50 years were nearly 4 times more likely to die from breast cancer compared to women with a unilateral cancer. When a CBC occurred more than 10 years following initial diagnosis, the outcomes were similar compared to women with unilateral breast cancer.

Amongst *BRCA1/2* mutation carriers it is difficult to unravel the magnitude of CBC risk reduction of individual therapies, as often these groups of patients would have had a combination of chemotherapy, tamoxifen and oophorectomy. The WECARE group (Reding et al. 2010) confirmed that chemotherapy lowered CBC risk in non-mutation carriers (RR 0.6) and *BRCA1/2* carriers (RR 0.5) with a higher CBC risk reduction amongst *BRCA 1* carriers (*BRCA 1* RR 0.5 v *BRCA 2* RR 0.3). This is supported by several studies showing that *BRCA 1* positive tumours are more sensitive to certain chemotherapy agents (e.g. anthracyclines) and resistant to others (e.g. taxanes).

PARP (poly ADP ribose polymerase) inhibitors and their effects on triple negative and *BRCA1/2* mutation related breast cancers are the subject of much interest (Plummer 2011). Initial reports from proof-of-concept trials (Tutt et al. 2010) have confirmed their safety and efficacy, and phase III studies with an extended follow-up may determine whether these targeted therapy modalities affect contralateral breast cancer risk.

Contralateral Risk-reducing mastectomy

Survival

Survival benefit is an important consideration for any surgical intervention. A recent Cochrane review from 2010 assessed the role of RRM in preventing breast cancer (Lostumbo, Carbine, and Wallace 2010). A total of 39 studies were reviewed of which 12 looked at CRRM – none of these involved a clinical trial. Overall, CRRM was consistently associated with a reduction in the incidence of CBC with variable effects on survival. (van Sprundel et al. 2005) showed that CRRM reduced the risk of CBC by 91% in *BRCA1/2* carriers independent of BRRSO. Survival at 5 years was improved in the CRRM group (94%) compared to the observational group (77%).

However, they found that the higher mortality in the surveillance group was attributed to a higher risk of dying from ovarian cancer and the index primary cancer - after adjusting for BRRSO, the survival benefit was lost. (Herrinton et al. 2005) studied over 50,000 breast cancer patients (1979-99) and found that CRRM was associated with an improved survival [HR 0.6] compared to no CRRM over a 5-year follow-up. However, when the follow-up was longer (15 years), (Peralta et al. 2000) found no significant survival benefit. The authors of the Cochrane review concluded: "*There is insufficient evidence that CRRM improves survival and that studies that control for multiple confounding variables are needed*."

Since the Cochrane review, at least 3 studies have confirmed a survival advantage for CRRM amongst *BRCA1/2* mutation carriers confirming that this high-risk group of patients is likely derive the greatest benefit. (Evans, Ingham, Baildam, et al. 2013) reviewed 718 *BRCA1/2* mutation carriers with unilateral breast cancer over a 10-year period. The group that underwent CRRM (n=105) had a 10-year survival of 89% compared to 71% in the matched group who did not undergo CRRM (n=593). This survival benefit of CRRM remained after adjusting for RRBSO.

(Metcalfe et al. 2014) reviewed 390 women with primary breast cancer who had a pathogenic mutation in *BRCA1/2*. At 20 years the survival rate for women who underwent a CRRM was 88% compared to 66% in those who did not have a CRRM. The most significant mortality benefit from CRRM was in the second decade following initial breast cancer diagnosis. Multivariate analysis controlling for age at diagnosis and other treatment factors confirmed that CRRM was associated with a 48% reduction in death from breast cancer.

A nationwide Dutch study (Heemskerk-Gerritsen, Rookus, et al. 2015) reviewed 583 women with breast cancer with a proven *BRCA1* or *BRCA2* mutation who underwent CRRM (42%) or surveillance (58%). In the CRRM group, 4 CBC occurred compared to 64 in the surveillance group. Survival benefit was especially seen in those women at lowest risk of mortality from their primary breast cancer: first breast cancer diagnosed under the age of 40 years, lower grade tumours (Grade 1/2), not triple negative cancers and in women who did not receive adjuvant chemotherapy.

(Portschy, Kuntz, and Tuttle 2014) developed a Markov model to compare survival outcomes between CRRM and non-CRRM in non-*BRCA* patients with Stage I and II breast cancer. They estimated a less than 1% absolute 20-year survival benefit from CRRM amongst all age group and that young women (40 years and under) with ER negative disease derived the most benefit.

(Boughey et al. 2010) investigated the role of CRRM amongst women with a family history of breast cancer. They performed a case-control study of 385 patients with a previous history of breast cancer and a family history of breast cancer (parent, sibling or second-degree relative with breast cancer). Over a follow-up period of just under 20 years, 2 CBCs developed in the CRRM group compared to 31 in the non-CRRM control group. 10-years overall survival in the CRRM group was 83% compared to 74% in the non-CRRM group. The CRRM group had significantly more women with a positive family history of breast cancer and may have biased the results towards fewer CBC events in the control group. However, the authors felt that a significant reduction in the number of

CBCs in the CRRM group suggested that their observations might have been an underestimate.

Breast Reconstruction

Several studies have shown that access to immediate breast reconstruction positively affects the decision for CRRM. Recently, (Ashfaq et al. 2014) identified 102,674 patients (2004-2008) with a diagnosis of DCIS (15%) or invasive breast cancer (85%) from SEER registry data. Those undergoing mastectomy were 3 times more life to request CRRM if offered immediate reconstruction. Overall, 16% of all patients underwent CRRM with a significant proportion undergoing reconstruction (46%, $p<0.001$). Similar proportions of patients underwent implant-based reconstruction (36%) and tissue-based reconstruction (37%). There was a trend for increasing numbers of reconstructions during this time period. Caucasian women, those under the age of 45 years with a diagnosis of a node-negative lobular carcinoma or DCIS were more likely to choose reconstruction.

Women undergoing reconstruction following CRRM may be 1.5 times more likely to have a major complication requiring hospitalisation or reoperation (Miller et al. 2013) compared to unilateral mastectomy. Limited data is available comparing CRRM and reconstruction with unilateral mastectomy and reconstruction. (Crosby et al. 2011) assessed 497 patients undergoing CRRM with reconstruction and concluded that a third of patients experiencing at least one complication may not have developed a complication if they had only had a mastectomy and reconstruction of their index side.

Sentinel Lymph Node Biopsy (SLNB)

SLNB at the time of risk-reducing surgery remains controversial. A recent meta-analysis of 1251 patients (Zhou et al. 2011) showed that 1.7% (n=21) of women undergoing BRRM harboured occult invasive cancer in the mastectomy specimen. Of these 21 patients, the SLN (at the time of BRRM) was positive in only 4/21 patients and negative in the remainder (17/21). Overall, 2.8% (n=36)

of women benefited from SLNB. This included 19 cases of a positive SLNB results requiring completion axillary surgery and 17 women who had invasive disease in the mastectomy specimen but a negative SLNB, thus avoiding further axillary surgery. This is offset against the 5% lymphoedema rate (Mansel et al. 2006) associated with SLNB. (Kuwajerwala et al. 2013) retrospectively assessed 170 patients undergoing CRRM and found that of the 21.8% who had a SLNB (dual technique) at the surgeon's discretion, none had positive SLNB.

Cost

Health care economics contribute to the decision making process. Cost effectiveness with life expectancy gains is well established in the setting of bilateral RRM in women harbouring *BRCA1/2* mutations (Grann et al. 2011; Schrag et al. 2000). Few studies have looked at this in the setting of CRRM (Deshmukh et al. 2014; Roberts, Habibi, and Frick 2014; Zendejas et al. 2011). Deshmukh et al analysed matched groups, CRRM and non-CRRM, and showed that CRRM significantly increased short-term healthcare costs by $7,749. In addition, women who had a reconstruction and in particular a delayed type had significantly higher costs associated as well as those who had HER2 positive disease and received radiotherapy.

In contrast, Roberts et al found that CRRM was cost-effective in the prevention of CBC in women under the age of 50 years. From their decision tree-model, they concluded that 68,000 women under the age of 50 year would have been diagnosed with early breast cancer in 2010. If all women had undergone CRRM, savings of $19 million would have been made to avoid 3,900 contralateral breast cancers that would have developed over the next 10 years. Their CRRM group had 0.2 Quality-adjusted life years less than the non-CRRM that may have been accounted for by complications of reconstruction. They highlighted a potential greater benefit of CRRM in ER –ve disease compared to ER +ve disease, given that the latter would receive adjuvant endocrine treatment, shown to reduce CBC.

Zendejas et al used a Markov model to compare cost-effectiveness in women undergoing CRRM compared to routine surveillance (including annual mammography). They found that CRRM prior to the age of 70 years was cost-effective and in particular in those who were *BRCA*-positive.

Currently in the UK, there are no funding restrictions within the National Health Service on CRRM. Breast cancer patients can chose between delayed and immediate (performed at the same time as the therapeutic mastectomy) without financial scrutiny provided there is backing from the relevant clinicians.

Patient's Perspective

Some of the main driving forces for CRRM are patients' worry and anxiety about developing another breast cancer and having to undergo further treatment including chemotherapy. This is often the most difficult component to assess, as the psychology behind it is multi-factorial. A recent US study reported that 68.9% of patients undergoing CRRM did not have genetic or familial risk factors for CBC (Hawley et al. 2014) and that the main driving force for this was worry about recurrence. Patients over-estimate their risk of contralateral breast cancer (Abbott et al. 2011) and in doing so can compound their anxiety.

A recent study (Beesley et al. 2013) assessed the perspective from 60 consecutive patients choosing CRRM. In almost all cases, requests for CRRM were instigated by the patient and every patient unambiguously wanted CRRM. Patients responded to risk in an "all or nothing" manner and the majority did not objectively quantify this risk. The risk assessment in those that did quantify risk had little role in their decision for surgery. The authors concluded "*patients' subjective sense of vulnerability overwhelmed their appreciation of risk so that, regardless of level of risk of CBC, they found this risk intolerable and felt that only CRRM could reduce it*". This said, a rate-limiting factor will be the availability of immediate reconstruction and if this is not made possible for patients as part of their primary surgical treatment rates of CRRM are likely to be lower.

The majority of women choosing CRRM are satisfied with their decision (Tercyak et al. 2007). A study from the Mayo clinic found that 83% of women who underwent a CRRM were satisfied with their decision up to 10 years following surgery (Frost et al. 2005). However, up to a third of women felt that their satisfaction with body appearance, feelings of femininity and sexual relationship were negatively affected. Those who had a complication from their reconstruction were less likely to be satisfied overall.

Discussion

The most significant risk factors are gene mutation status and significant family history, which can result in at least a four-fold increase in CBC risk. Patients harbouring a *BRCA1/2* mutation have an approximate 2-3% annual incidence on developing CBC. In non-mutation carriers with a family history, young age at first diagnosis and a first-degree relative are particularly strong risk factors.

Tumour biology is important. The ER status is of particular importance given that approximately 80% of all breast cancers are hormone sensitive. The level of risk-reduction with anti-endocrine treatment is approximately 50% with tamoxifen and 70% with aromatase inhibitors. As predicted, women with ER negative breast cancer have an increase risk of CBC. The use of cytotoxic agents and targeted treatments (e.g. Herceptin) marginally reduces CBC, with the greatest benefit for young women having chemotherapy.

CRRM offers the greatest risk-reduction of CBC – up to 95% in women with a family history. Survival benefits are conferred on those high-risk patients with a *BRCA1/2* mutation. There are no known survival benefits in the non-high risk group.

Access to immediate breast reconstruction positively affects a woman's decision to opt for CRRM. A significant number may experience operative complications. Occult disease in the CRRM specimen occurs in less than 2% of women with no clear evidence to support sentinel lymph node biopsy.

Survival benefits and cost-effectiveness are seen in those at the highest risk of CBC (gene mutation carriers) and these patients are likely to benefit most from CRRM.

The assessment of CBC risk is multi-factorial and may be assessed in a multi-disciplinary setting. Arrington et al showed that surgeon and patient characteristics determine CRRM and include independent factors like young patient age (<40years), large tumour size (>5cm), lobular histology, positive family history, multi-centric disease and female surgeon. In addition, patients' anxiety about developing another breast cancer and going through subsequent treatment is a real entity, albeit difficult to quantify.

Table 2. Risk factors for developing CBC (estimated annual risk) (Basu, Barr, et al. 2015).

		Estimated annual risk (%)	Relative Risk-multivariate (95%CI)
PATIENT FACTORS:			
Age at first diagnosis	< 30 yrs 40-50 yrs ER+ve ER-ve	0.5-1.3 0.2-0.3 0.4-0.5	
Gene mutation	*BRCA1*	2.0-3.0	
	BRCA2	2.0-3.0	
Family History	None		1 (Reference)
	First and Second degree	0.4-1.3	2.8 (1.4-5.5)
	First degree	0.2-0.8	1.4 (0.9-2.1)
	Second or third Degree	Baseline	1.1(0.7-1.9)
TUMOUR FACTORS:			
Size	<2cm (T1) 2-5cm (T2) >5cm (T3)		1 (Reference) 1.5 (1.1-2.0) 1.9 (1.1-3.3)
LN status	None 1-3 4-9 >10		1 (Reference) 0.9 (0.6-1.2) 1.1 (0.7-1.9) 1.6 (0.8-3.1)
Histology	Ductal Lobular		1 (Reference) 1.2 (0.6-2.1)
ER status	ER Positive ER Negative		1 (Reference) 1.3 (0.9-1.9)
HER2 status	HER2 Positive HER2 Negative		1 (Reference) 1.02 (0.6-1.8)

Table 3: Risk-reduction of CBC associated with chemoprevention and surgery (Basu, Barr, et al. 2015).

		Risk reduction (95% CI)
CHEMOPREVENTION:		
Anti-endocrine	Tamoxifen in *BRCA1/2* mutation carriers Tamoxifen in non-carriers Aromatase inhibitors in non-carriers	OR 0.5 (0.3-0.9) 50% - risk reduction 70%- risk reduction
Chemotherapy	Chemo vs No Chemo	RR 0.6 (0.4-0.8)
SURGERY:		20 year survival benefit
CRRM		
CRRM in *BRCA1/2* mutation carriers		14.9%
CRRM in non-mutation carriers		<1%

CHAPTER 3: Attitudes to risk-reducing surgery

International comparative study USA and Europe

Introduction

Public awareness of high-risk breast cancer has increased in the last few years (Evans et al. 2014). As a result, individuals at increased risk are accessing appropriate services (i.e. genetics centres) to objectify that risk and consider risk-reducing strategies. BRRM confers the greatest risk-reduction in asymptomatic women at high risk of developing breast cancer (Domchek et al. 2010). For example, women with a *BRCA1/2* mutation will have an up to 85% lifetime risk of developing breast cancer (Evans et al. 2008) and can expect a risk-reduction in the magnitude of at least 90% (De Felice et al. 2015; Domchek et al. 2010; Hartmann and Lindor 2016).

Over the last decade, UK data show that the number of women undergoing these procedures has risen by almost 200% (Neuburger et al. 2013). U.S. National and state cancer databases do not record information on healthy women (Tuttle et al. 2010) making it difficult to infer similar trends in North America. This is in contrast to CRRM, where US-SEER data has shown a 150% increase in breast cancer patients over the last decade.

Uptake of BRRM varies amongst women at increased risk. From a patient perspective, young age and motherhood seem to be positive predictors for choosing surgery (Meijers-Heijboer et al. 2000). Several studies have shown international variations in uptake of BRRM with the highest rates in the UK and the Netherlands (33-50%) and the US (36%) compared to Poland (3%) and Israel (4%) (Den Heijer et al. 2013; Metcalfe et al. 2008). Differences in culture, healthcare systems and access to genetic testing are likely to contribute to these differences. However, wide variations are found within countries – for example in 3 different Canadian regions, the range of uptake was from 8-46% (Metcalfe et al. 2007) – suggesting that other factors are important.

Attitudes amongst surgeons are likely to influence uptake. Inter specialty differences exist in the US. A survey of Maryland surgeons showed that the majority of plastic surgeons (84.6%) favour BRRM compared to general surgeons (47.0%) and gynaecologists (38.3%) (Houn et al. 1995). In the setting of CRRM, female surgeons are more likely to recommend (Arrington et al. 2009) a mastectomy compared to male surgeons. A study of European countries found that high volume surgeons and those with superior knowledge of cancer genetics had more positive attitudes towards BRRM (Den Heijer et al. 2013).

Media coverage and public interest in BRRM has been heightened since Angelina Jolie's revealed her personal experience of bilateral mastectomies based on her *BRCA1* status in 2013. A recent study estimated that although 3 out of 4 Americans were aware of her surgery, less than 10% were able to use the information on Miss Jolie's risk of breast cancer relative to a woman with no mutation (Borzekowski et al. 2014). Risk communication in the context of cancer genetics is critical to ensure women can make an informed decision. Mainstreaming of *BRCA* testing is gaining popularity and in the UK (Eccles et al. 2015), breast surgeons will be initiating gene testing amongst select new breast cancer patients. As such, there is even more urgency to ensure breast surgeons communicate risk accurately and comprehensibly.

Much of the published data regarding BRRM comes from North America and Europe. There are important healthcare differences that may contribute to variations in practice. US healthcare facilities are mainly owned by private sector businesses and healthcare provided on an insurance scheme. Most insurance providers will cover *BRCA* testing and both BRRM and CRRM (not for males) and recent statutory law (Genetics Information Non-Discriminatory Act) protects an individual's health and employment insurance but not life insurance.

American breast surgeons are mainly ablative surgeons with very few offering breast reconstructive services. Reconstruction in the US is primarily conducted by plastic surgeons with a strong preference for implant based surgery

(Albornoz et al. 2013). A recent report from the US confirmed that immediate reconstruction rates had increased from 21% (1998) to 38% (2008). During that period autologous rates were unchanged, but implant rates had increased by almost 203% (Cemal et al. 2013). There was a changing pattern of mastectomies - unilateral mastectomies had decreased by 2% per year compared to increases in BRRM (12% per year) and CRRM (15% per year).

The UK's public funded National Health Service (NHS) covers the cost of appropriate genetic testing and risk-reducing surgery. The system is primarily funded by central taxation and at present will fund the majority of requests for BRRM and CRRM. Approximately 11% of the population have health insurance that will not usually cover risk-reducing procedures (LaingBuisson 2013). The last 2 decades of UK surgical practice has seen the birth of Oncoplastic Breast surgeons (Baildam 2013) who are able to offer both ablative and reconstructive surgery. The UK National Mastectomy Audit 2011 (NMBRA 2011) showed that almost 60% of immediate reconstructions were implant based (breast and or plastic surgeons) compared to free flap surgery (14% - performed by plastic surgeons) and pedicle based surgery (27% - performed by plastic and or breast surgeons).

Breast surgeons' attitudes towards RRM are likely to prejudice their practice and ultimately impact on high-risk patients access to this procedure. Given the aforementioned variations in practice, culture and healthcare systems it would be useful to examine if there is a US-Europe divide in terms of breast surgeons attitudes to RRM. An understanding of this may help one appreciate differences in practice and ultimately aid in the formulation of guidelines that may be appropriate to different health systems in different nations.

In 2009, healthcare professionals from the UK, Germany, the Netherlands and France collaborated and formed 'An International Cancer Risk Communication Study (InCRisC) questionnaire (Den Heijer et al. 2013). This postal questionnaire was aimed at breast surgeons and general practitioners. 3293 surgeons from the 4 countries were contacted and the data from 1221 (37%) of respondents analysed.

The questionnaire recorded basic demographics and level of experience and knowledge of cancer genetics examined by 2 clinical vignettes. The first scenario was regarding Louise – a healthy 35-year old women whose 32-year old sister was diagnosed with breast cancer. Respondents were asked about which family members they would take a history from. Taking a paternal history was regarded as a proxy variable to indicate knowledge in cancer genetics. The second scenario examined attitudes toward risk reducing mastectomy – Angela a 35-year old healthy woman whose 2 sisters and mother had breast cancer before the age of 50 years and had tested negative for *BRCA1/2*. Respondents were asked whether they would consider discussing BRRM with Angela despite first-degree relatives testing negative to the mutation status and also what they felt about BRRM in *BRCA1/2* carriers.

The results of this European study (Den Heijer et al. 2013) showed that breast surgeons from the UK and the Netherlands overall had a favourable attitude towards BRRM. 90% of surgeons from these two countries took a paternal history compared to Germany (72%) and France 57%). In addition, high volume breast surgeons (treating more breast patients) and thus perhaps more experience had a more favourable outlook towards risk-reducing surgery. UK and Dutch surgeons had supported BRRM in *BRCA* carriers (97 and 100% respectively) followed by France (78%) and Germany (66%). The responses regarding Angela (BRRM in non-*BRCA* high-risk individual) showed that 20% of UK surgeons would discuss BRRM compared to 9% of Dutch surgeons, 2.5% of German surgeons and 2.3% of French surgeons.

Cancer risk was most frequently communicated by German surgeons, least by Dutch surgeons with UK and French surgeons somewhere in the middle. Risk presentation format was analysed and the majority of surgeons used absolute risk numerically and framed them negatively (Nippert et al. 2014).
To my knowledge, no international comparative study has been conducted to assess variations in attitudes to BRRM and risk-communication between surgeons from the US and Europe. For this purpose, I surveyed surgeons from

the US and performed a comparative analysis with the already published data from the 4 European countries.

Methods

Permission to utilise the InCRisC questionnaire was approved by the key members of the consortium (questionnaire – Appendix 3). The questionnaire was designed previously by the members and I had no personal involvement at this stage.

I approached the American Society of Breast Surgeons (ASBS) with approximately 3152 members covering all the 50 states. The majority are active members who are general surgeons with a demonstrable interest in breast surgery and are board certified with a full license to practice surgery. The average age of members is 50 years with an even ratio of male:females (52:48). A formal application was approved to the ASBS Research Committee and questionnaires sent (February 2014) via SurveyMonkey to 2648 ASBS members. A reminder email was sent after 6 weeks.

Several factors were compared across the responses to the two questions of interest. The question relating to prophylactic mastectomy was dichotomised for the analysis by combining probably/certainly not to "no" and probably/certainly to "yes", whilst the response to the question relating to family history was already dichotomous. Categorical factors were then compared across the two response groups using Fisher's exact test. Where a significant result was found, post-hoc tests were performed, comparing the USA to the other countries, with the critical p-value Bonferroni adjusted for 4 comparisons ($p<0.0125$).

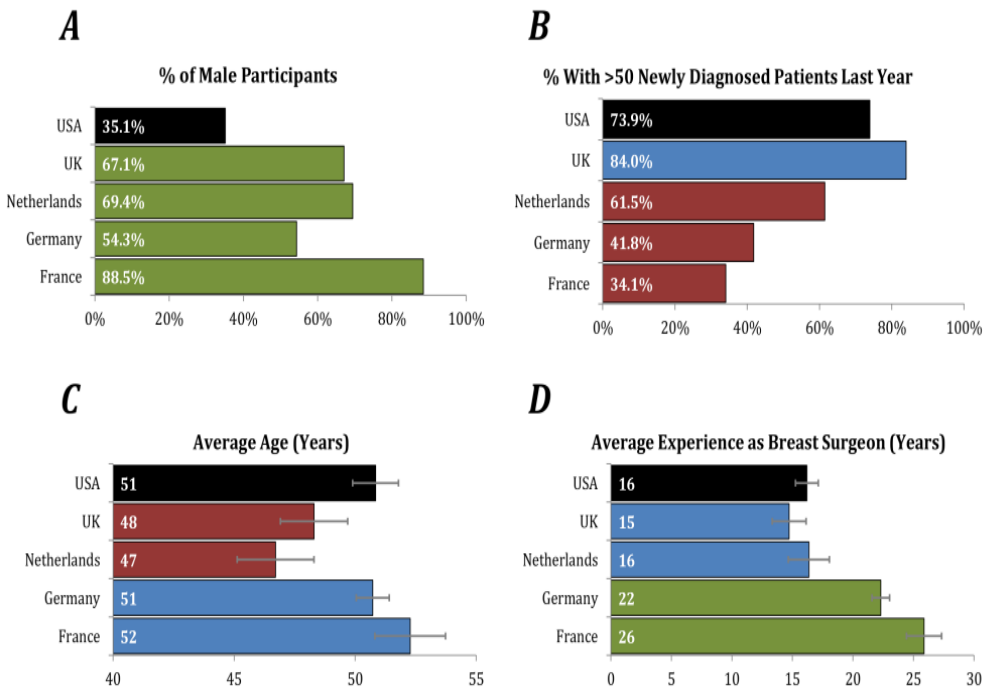
The ordinal responses to number of diagnosed patients were compared between the groups using a Kruskal-Wallis test, with a set of post-hoc Mann-Whitney tests used to compare against the USA, again using a critical p-value of 0.0125. The continuous variables were compared across the nationalities using one-way

ANOVA, with Tukey's post-hoc test used to make pairwise comparisons between groups.

Multivariable analysis was then performed using binary logistic regression models. All analyses were performed using IBM SPSS Statistics 22 (IBM Corp. Armonk, NY).

Results

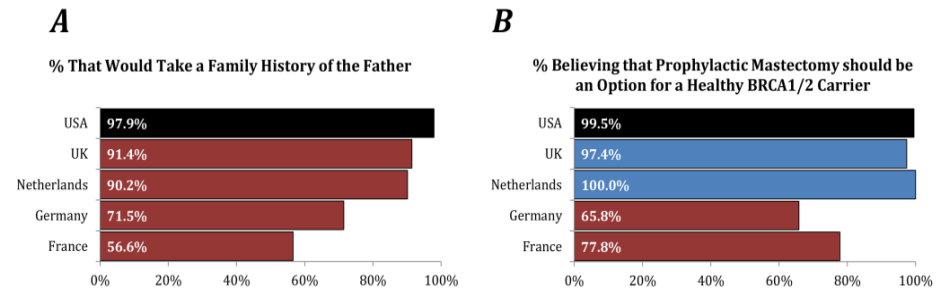
A total of 440 questionnaires were completed by American Surgeons (16.6%) compared to the 1221 questionnaires from Europeans Surgeons (37%). Comparisons of demographic factors across the five nationalities are reported in Figure 5. The USA had significantly fewer male respondents than any of the other countries (all $p<0.001$). Respondents from the USA also had significantly more newly diagnosed patients in the previous year than every other country ($p<0.001$), with the exception of the UK, which had a non-significantly higher average ($p=0.079$). Mean respondent age was similar in the USA, Germany and France (51, 51, 52 years respectively), but significantly lower in the UK (48 years, $p=0.023$) and the Netherlands (47 years, $p<0.001$). Years of experience as a breast surgeon were similar in the USA, UK and Netherlands (16, 15 and 16 years respectively), but significantly higher in Germany (22 years, $p<0.001$) and France (26 years, $p<0.001$).



Red/green bars : significantly lower / higher than the USA
Blue bars : Not significantly different to the USA
A: p-values from post-hoc Fisher exact test, with significance at p<0.0125 (Bonferroni adjustment for 4 comparisons)
B : p-values from post-hoc Mann-Whitney tests on the original 7 point ordinal scale, with significance at p<0.0125 (Bonferroni adjustment for 4 comparisons)
C/D : p-values from Tukey's, with significance at p<0.05.

Figure 5. Demographics of breast surgeons across 5 countries.

Analysis of the responses to the questions of interest is reported in Figure 6. When considering whether a family history would be taken of the father, the rate of positive responses in the USA (97.9%) was significantly higher than any of the other countries considered (all p<0.001). The proportion believing that risk-reducing mastectomy should be an option in healthy *BRCA*1/2 carriers for the USA (99.5%) was similar to the Netherlands (100.0%, p=1.000) and the UK (97.4% unadjusted p=0.045), but significantly higher than in Germany (65.8%, p<0.001) or France (77.8%, p<0.001).



Red/green bars : significantly lower / higher than the USA
Blue bars : Not significantly different to the USA
p-values from post-hoc Fisher's exact test, with significance at p<0.0125 (Bonferroni adjustment for 4 comparisons)

Figure 6. Analysis of response to 2 questions: "Would you take a family history of the father?" and "Do you believe prophylactic mastectomy should be an option for health *BRCA 1/2* carriers?"

In order to account for the significant differences in the demographics of the respondents across the countries, multivariable analyses were performed. These did not include respondent age as a factor, since it was highly correlated with the number of years of experience (Spearman's Rho = 0.834). The results of these analyses are reported in Table 4.

Table 4. Multivariable analysis – Knowledge of cancer genetics and attitudes to risk reducing surgery.

	Would take a family history of the father		Think that prophylactic mastectomy should be an option for a healthy BRCA1/2 carrier	
	Odds Ratio (95% CI)	*p-Value*	*Odds Ratio (95% CI)*	*p-Value*
Country		**<0.001***		**<0.001***
USA	-	-	-	-
France	0.05 (0.02 - 0.11)	<0.001*	0.03 (0.01 - 0.12)	<0.001*
Germany	0.08 (0.04 - 0.16)	<0.001*	0.01 (0.00 - 0.05)	<0.001*
Netherlands	0.31 (0.13 - 0.77)	0.012*	#	#
UK	0.23 (0.09 - 0.55)	0.001*	0.15 (0.03 - 0.83)	0.030*
Gender		**<0.001***		**0.042***
Female	-		-	-
Male	0.42 (0.28 - 0.63)	<0.001*	0.65 (0.43 - 0.98)	0.042*
Years as a Breast Surgeon		**0.026***		**0.052**
<10	-	-	-	-
10-14	1.72 (0.79 - 3.74)	0.171	0.64 (0.24 - 1.74)	0.383
15-19	1.18 (0.59 - 2.34)	0.638	0.63 (0.25 - 1.63)	0.343
29-24	1.06 (0.54 - 2.09)	0.861	0.38 (0.15 - 0.96)	0.041
25-29	0.66 (0.34 - 1.29)	0.220	0.89 (0.34 - 2.34)	0.814
30+	0.69 (0.36 - 1.33)	0.274	0.64 (0.25 - 1.65)	0.357
Newly Diagnosed Patients/Year		**<0.001***		**<0.001***
0-26	-	-	-	-
26-50	1.27 (0.83 - 1.96)	0.270	0.90 (0.57 - 1.41)	0.642
51-75	1.18 (0.71 - 1.96)	0.528	2.00 (1.08 - 3.71)	0.028*
76-100	1.48 (0.82 - 2.68)	0.198	2.50 (1.21 - 5.15)	0.013*
101-125	2.30 (1.11 - 4.78)	0.025*	5.28 (1.78 - 15.66)	0.003*
126-150	5.60 (1.91 - 16.41)	0.002*	2.84 (1.10 - 7.29)	0.031*
>150	5.44 (2.73 - 10.83)	<0.001*	4.69 (2.34 - 9.40)	<0.001*

Results from multivariable binary logistic regression models

#Respondents from the Netherlands were excluded, since they all responded yes, making odds ratios incalculable and the model non-convergent

Male patents were found to be significantly less likely to take a family history of the father (OR: 0.42, p<0.001). The likelihood of taking a family history of the father increased significantly with the number of new diagnoses per year, with an odds ratio of 5.44 in respondents diagnosing >150 new patients per year, compared to those with <26 new diagnoses (p<0.001). After accounting for these factors, respondents from the USA were still significantly more likely to take a family history of the father than any other country considered.

In the analysis of thoughts on risk reducing mastectomy, respondents from the Netherlands had to be excluded, since 100% believed that this should be offered to healthy *BRCA*1/2 carriers, making odds ratios incalculable, and the model non-convergent. For the remaining patients, the results were similar to the other question considered. Male surgeons were significantly less likely to agree with

the statement (OR: 0.65, p=0.042). High volume surgeons (those treating increasing numbers of newly diagnosed breast cancer patients) were associated with increasing likelihood of believing that risk reducing mastectomy should be an option for a healthy *BRCA*1/2 carrier (OR: 4.69 for >150 vs. <26 per year, p<0.001). After accounting for these confounding factors, the differences between the countries remained significant (p<0.001), with the USA significantly more likely than any other country (with the exception of the Netherlands) to think that risk reducing mastectomy should be an option for a healthy *BRCA*1/2 carrier.

Discussion

This study has shown that significant international differences exist in attitudes towards risk-reducing mastectomy. Overall, respondents from the US were similar to their counterparts in the Netherlands and the UK in terms of favouring BRRM. Similar to previously published data, French and German surgeons had the least positive attitude on this topic.

The majority of respondents from the US were female breast surgeons (64.9%) compared to the rest of Europe. In addition, females surgeons overall were more likely to take a history of the father, with significantly more US surgeons taking this history compared to the rest of Europe.

Knowledge of breast cancer genetics has previously been shown to be associated with a positive attitude towards RRM (Den Heijer et al. 2013) and this study has shown that US surgeons were amongst the most knowledgeable surgeons on this topic. Surgeons who are well informed on breast genetics are likely to appreciate the objective risks for developing breast cancer in the various risk groups and also the limitations and benefits of surveillance and risk reducing surgery respectively. In addition, this study supports the finding by Tuttle et al that female American surgeons are an independent predictor for CRRM as this group were amongst the most knowledgeable, proponents of RRM.

The main limitation of this study is that the survey of American surgeons occurred 3 years following sampling of the European surgeons. During that period, the "Angelina Jolie effect" is likely to have heightened American surgeons' awareness on this subject, although there are no studies to corroborate this. The success of questionnaire-based surveys is determined partly by the response rate. Resampling the European surgeons at the same time as the American surgeons may have resulted in a lower response rate as well as been open to recall bias as these surgeons had been previously sampled.

The response rate amongst the American Surgeons was lower than their European counterparts. Low response rates are not uncommon in these types of surveys and raising the profile of this survey in the US may have improved the response rate. In addition, the method of sampling may affect the generalizability of some of the results. The UK and US respondents were positively identified as breast surgeons by their membership to the relevant national breast associations (ABS and ASBS) whereas in France identification of breast surgeons was more difficult as they may also practice gynae-obstetrics.

Breast surgeons' personal attitudes towards RRM are likely to be based on a combination of factors: training, education, national guidelines, national practice and media. For example in France, (Julian-Reynier et al. 2011) found that French physicians have a preference for MRI screening in *BRCA1/2* mutation carriers under the age of 40 and MRI and RRBSO in the over 40's – whereas other countries prefer the surgical risk reduction options. Another example is the age of breast cancer screening. The revised American Cancer Society Guidelines (Oeffinger et al. 2015) recommend annual mammographic screening from 45-54 years with the option of mammograms from the age of 40. The NHSBSP routinely screens all women aged 50-70 with mammograms every 3 years, with the age extension allowing women from 47-73 to be screened (NHSBSP 2015). Differences in screening are an important indicator on public and political drivers for breast cancer awareness that are apparent when considering the UK and the USA.

This comparative study has shown that American breast surgeons have a heightened awareness of breast cancer genetics compared to European surgeons. They (American surgeons) have favourable attitudes to risk-reducing mastectomy, similar to surgeons from the UK and the Netherlands. The majority of respondents from the US were female surgeons compared to male surgeons in Europe. The observed differences amongst American surgeons may partly contribute to the observed trends of increasing mastectomy rates.

Attitudes to CRRM – a survey of breast and plastic surgeons in England

Introduction

The rise in CRRM in the US has already been discussed. International variations of this trend do exist. In Canada, rates of CRRM are half those observed in the US with a more modest increase over the last decade - 5% in 2007 to 7% in 2009 (Porter et al. 2014). A recent Swiss study found no significant change in CRRM rates between 1995-2009 (Guth et al. 2012). In the setting of *BRCA1/2* carriers, CRRM uptake varied from 0% in Norway, 4% in Poland, 10% in France, 28% in Canada and 49% in the USA (Metcalfe et al. 2008).

(Neuburger et al. 2013) reviewed HES (Hospital Episode Data) from England between 2002 and 2011 and found that the number of bilateral mastectomies performed in women with a diagnosis of breast cancer had increased from 521 (2002) to 931 (2009) representing an increase from 2% to 3%. It could be inferred from this data that an upward trend in CRRM rates is taking place in the UK.

My previous study highlighted important international variations amongst breast surgeons' attitudes to RRM and cancer genetics knowledge. American surgeons seemed to be most enthusiastic toward risk-reducing mastectomy. In the setting of CRRM, there is limited data on what factors surgeons evaluate when considering requests for CRRM.

(Musiello, Bornhammar, and Saunders 2013) sampled 220 Australian and New Zealand surgeons on their views regarding CRRM. No association was found between number of CRRMs performed and gender and age of surgeon. Family history and *BRCA* status were the main reasons this group of surgeons recommended CRRM. Interestingly, approximately 20% of surgeons felt that LCIS and Lobular histology were important factors to consider as well – the literature review (Chapter 2)(Basu, Barr, et al. 2015) has shown that these two factors are not associated with a significant increase in CBC risk. Musiello et al

did not assess how requests for CRRM are managed - important considerations when formulating guidelines.

In the UK, multidisciplinary teams (MDTs) draw from the expertise of various key members and are invaluable in the decision making process of this complex procedure. There is paucity of data on the actual practices of CRRM at a national level. Little is known about the decision making process (e.g. whether formal risk assessment is carried out or whether each request is assessed in a multidisciplinary setting). The 2013 NICE guidelines made a number of recommendations on preoperative assessment and counselling for risk reducing mastectomy and CRRM in high-risk patients (Evans, Graham, et al. 2013). Despite high-risk patients comprising a significant proportion of CRRMs, no agreed protocol exists for the majority of breast cancer patients who fall outside this high-risk group.

In the UK, appropriately trained oncoplastic breast and plastic surgeons perform both CRRM and unilateral or bilateral reconstructions. This is in contrast to the USA and parts of Europe, where breast surgeons would perform the mastectomy followed by reconstruction by plastic surgeons. The majority of plastic surgeons involved with the reconstructive element of CRRM work together with breast surgeons. As such, they would not necessarily be formally involved with risk assessment. An exception may be those women requiring a therapeutic mastectomy for cancer who choose immediate transverse rectus abdominis myocutaneous (TRAM)/deep inferior epigastric perforator (DIEP) flaps as their preferred reconstruction. These procedures use tissue from the abdomen that can only be used once so a delayed contralateral mastectomy and reconstruction would need to employ tissue from elsewhere or an implant. In these situations, an appreciation of risk assessment is crucial to balance the oncological issues surrounding CRRM and the desire for symmetrical reconstructions.

The principle objective of this study was to assess the practices and experiences of surgeons involved with CRRM in England. In particular, perceptions on CBC

risk and which factors surgeons concentrated on were evaluated. The role of the MDT, funding related issues and inter-specialty differences were examined.

Methods

The review of the literature (Chapter 2) helped in designing the questionnaire. The ideal questionnaire would be provide an insight around the following areas:

Surgeons' demographics – does age, gender, specialty and experience influence attitudes?

Surgeons' own levels of knowledge regarding CBC

The role if any of the MDT

Perceived reasons patients request CRRM

Surgeons' own reasons for offering CRRM

The challenge for any postal questionnaire is to make it concise yet informative so that there is a chance to get a reasonable response rate. In addition, assessment of knowledge using multiple choice question scenarios may appear didactic and unappealing to some surgeons. Therefore, knowledge was inferred from the question. For example: "*What level of CBC risk do you quote to women with breast cancer with no additional risk factors (e.g. family history, mutation status)*?" Respondents were offered a number of options including the correct answer and subsequent analyses confirmed whether surgeons are conveying accurate levels of risks to their patients.

The original questionnaire was designed by myself and sent to co-authors (DGE et al) for final comments and changes. A research application grant was successfully secured from the charitable organisation Genesis Breast Cancer Prevention (GA 13-003) to fund the stationery and postal costs for the questionnaire.

Internal validation was included in the design by collection of questionnaire data from two other breast units. The questionnaire was piloted amongst local surgeons for ease of response, validity and relevance prior to posting them out

(with a stamped addressed envelope). No reminders were sent and responses were considered over a three-month period.

A database was created that included the names of all breast and plastic surgeons working in England. The Association of Breast Surgeons (ABS) was contacted with the hope of forming a collaborative study and to gain access to their membership database. Unfortunately they did not agree to take part and the names of breast surgeons were obtained by painstakingly contacting all the 154 NHS trusts listed on the www.nhs.uk website. Information for plastic surgeons was received from the British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS). The BAPRAS members list consisted of 437 surgeons in the UK but questionnaires were sent only to those with an address in England (n=364). Consultants and non-consultant grades (staff and associate specialist doctors) were surveyed. Trainees were excluded from the study. It was accepted that not all BAPRAS members surveyed were reconstructive breast surgeons.

Statistical analysis

Statistical analysis was performed using SPSS® version 20 (IBM, New York, US). The chi-squared test and Kendall's tau-b statistic were used to evaluate any differences between surgeons.

Results

A total of 819 questionnaires were sent out. The response rate for breast surgeons was 48.3% (220/455) compared with 12.6% (46/364) for plastic surgeons. Not all respondents answered all questions. Nearly half of the surgeons sampled were between 41 and 50 years old, with less than 10% aged over 60 years across both specialties. The majority were male and of consultant grade (Fig 7).

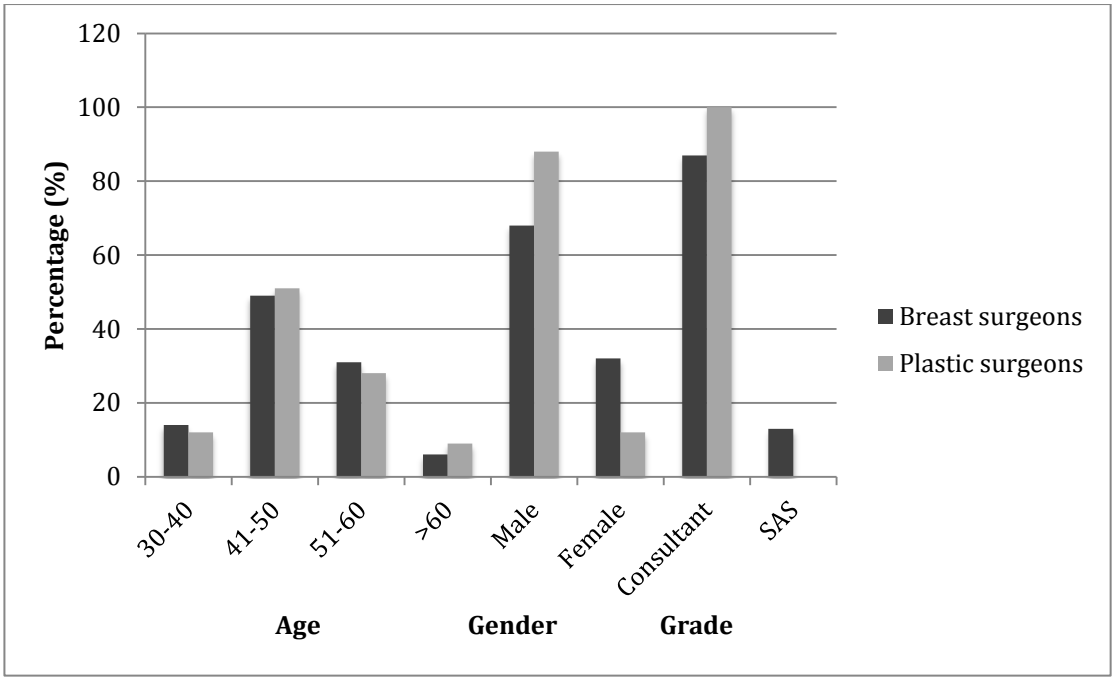


Figure 7. Demographics of respondents (Basu et al. 2016).

Number of procedures performed

Of the 220 breast surgeons, 174 (79%) had performed 1–5 CRRMs over the past year, with only 2 (1%) having performed more than 10 operations (Fig 8).

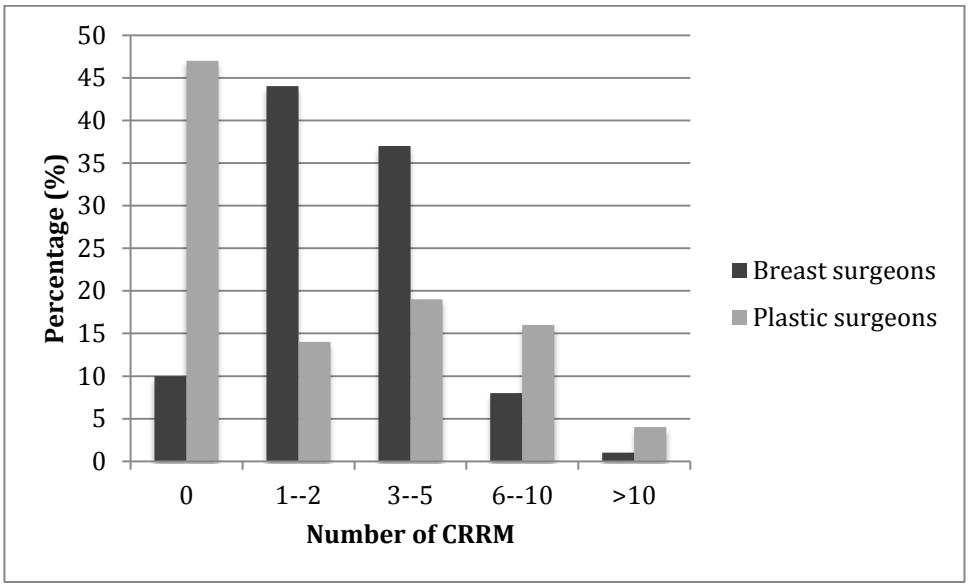


Figure 8. Number of CRRMs performed by respondents (Basu et al. 2016).

Twenty two (10%) had not performed any CRRMs. Among the 46 plastic surgeons, 14 (30%) had performed 1–5 CRRMs over the last year whereas 2 (4%) had performed more than 10. Twenty (43%) had not performed any CRRMs in the last year. Overall, breast surgeons had performed more CRRMs than plastic surgeons ($p<0.05$).

Nearly half of the respondents from both specialties (118/266, 44%) felt that requests for CRRM by patients were increasing while a third (101/266, 38%) believed there was no change. Approximately 2% (5/266) thought requests for CRRM were decreasing, with the remaining respondents unsure.

Risk assessment

Each surgeon was asked to comment about the perceived incidence of CBC. The majority felt that the incidence in their practice was unchanged. When asked what approximate risk (annual incidence) of developing CBC surgeons quoted their patients (without any additional risk factors), 11 breast surgeons (5%) reported quoting an annual incidence of 0.1%, 29 (13%) quoted 0.2–0.4%, 77 (35%) quoted 0.5–0.7%, 57 (26%) quoted 0.8–1.0% and 18 (8%) quoted >1%. Of the plastic surgeons, 1 (2%) reported quoting 0.1%, 5 (11%) quoted 0.2–0.4%, 8 (17%) quoted 0.5–0.7%, 6 (13%) quoted 0.8–1.0% and 8 (17%) quoted >1%. The combined results are displayed in Figure 9.

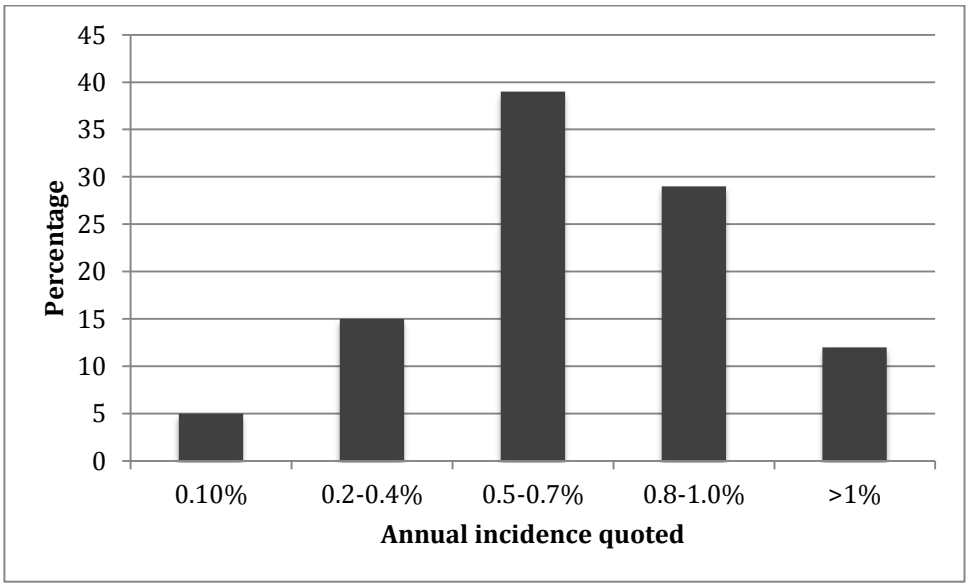


Figure 9. Quoted annual incidence of CBC by respondents (Basu et al. 2016)

Those respondents who did not choose any of the listed options stated that they do not quote a risk to their patients or that the percentage they quoted depended on the risk of the individual patient. Plastic surgeons were less likely to quote a risk to their patients than breast surgeons ($p<0.0001$).

The questionnaire asked surgeons to rank the top five reasons why patients requested CRRM. Options on the list of reasons included fear/anxiety of getting another breast cancer, young age, desire to have reconstruction match/symmetry, concern regarding family history, mistrust of surveillance, *BRCA* status, recommendation from family/ friend and 'other'. Fear/anxiety of getting another breast cancer was deemed the most important reason for requesting CRRM, followed by *BRCA* status (Fig 10). The next most common reasons were desire to have reconstruction match/symmetry, concern regarding family history and mistrust of surveillance.

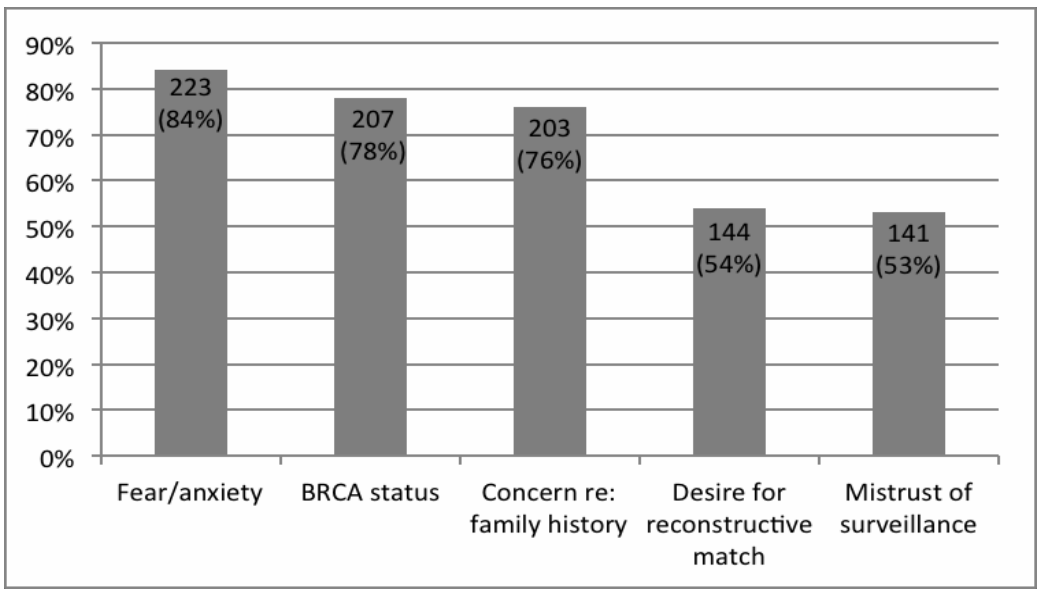


Figure 10. Top 5 reasons (as ranked by surgeons) why patients request CRRM (Basu et al. 2016)

The surgeons were also asked to rank the top five factors they felt are important in the assessment of a patient's risk for developing a CBC. Options on the list of factors included young age, histology, family history, *BRCA* status, lymph node status, grade, stage, ER/PR receptor status, HER2 positivity, multi-centric disease, breast density, obesity and premalignant disease. The majority (84%)

ranked *BRCA* status as the most important factor and family history as the second most important factor (72% of surgeons). These results are displayed in Figure 11.

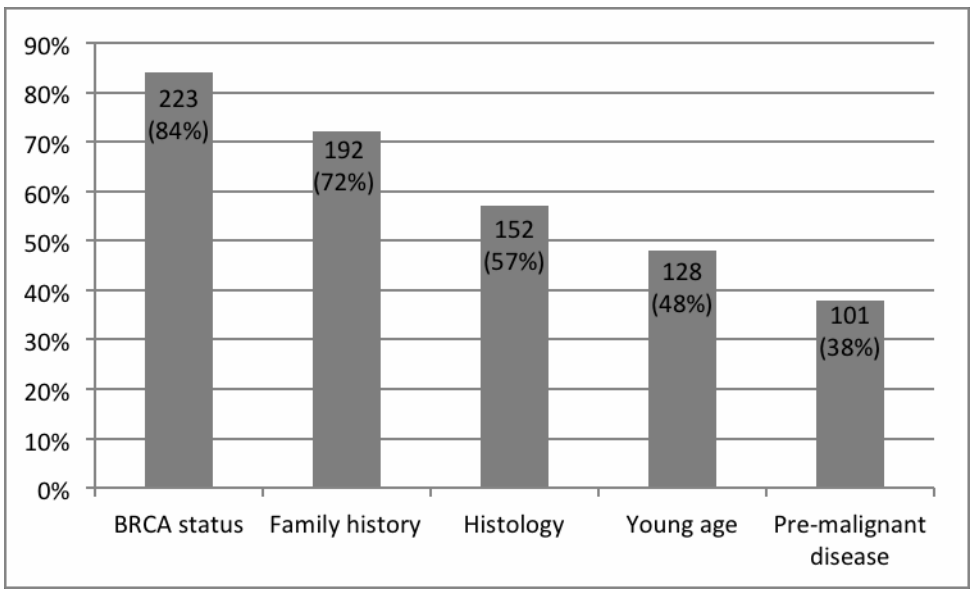


Figure 11. Top 5 reasons surgeons consider are important in the assessment of a patient's risk for developing CBC (Basu et al. 2016).

Free text from respondents covered similar themes, namely that '*the prognosis is determined by the cancer they have got, not the cancer they may never get*' and '*CRRM should only be offered to high risk patients*'. Some stated they '*dissuade* [patients] *from*', '*resist*' or are '*loath to offer*' CRRM. One surgeon commented that '*CRRM is a legitimate part of the reconstruction process*' whereas another thought the opposite: '*CRRM is performed because of increasing availability of oncoplastic procedures rather than a true clinical need.*'

Funding

The vast majority of respondents (245/266, 92%) had never been refused funding for CRRM although ten surgeons (4%) had experienced a refusal. Reasons for refusal of funding included lack of genetic testing, a greater than ten-year interval from the original cancer and refusal from private insurance stakeholders. Almost half of all those surveyed (115/266, 43%) felt that within the next three years, special applications for funding to clinical care groups would be mandatory.

Decision making/multidisciplinary team

When asked about the decision making process in their unit for CRRM, over half (58%) of the respondents said requests for CRRM are always discussed in the MDT meeting. Almost a third (29%) reported that they are sometimes discussed and 6% indicated that these cases are never discussed by the MDT.

The types of healthcare professionals involved in the decision making process for CRRM varied. Overall, a single surgeon and a breast care nurse were always involved in 67% and 75% of cases respectively while a psychologist and an oncologist were always involved in 35% and 34% of cases respectively. Geneticists were always involved in 18% of cases.

Discussion

This study has highlighted important variations in the management of women seeking CRRM. There is a wide discrepancy in the number of cases performed per surgeon across and within the two specialties surveyed. An explanation could be that it is dependent on the geography and workload of particular breast units, with tertiary centres (which have plastic surgery services and dedicated genetics services) attracting the majority of the work. It is clear from the free text answers that surgeons' views on CRRM could affect whether a woman seeking surgery can access CRRM, particularly if the decision is taken outside the MDT process.

Surgeons are often at the front line managing requests for CRRM. Consequently, the wide variation of risk quoted by surgeons is of concern. CBC risk is dependent on several factors including oestrogen receptor status, anti endocrine treatment, age of patient, and (most importantly) family history and genetics. It may be more accurate to incorporate these factors when carrying out risk assessments so that each patient receives a personal CBC risk score based on known risk factors.

It is clearly best practice to make an assessment of CBC risk in women seeking CRRM and it is possible that the calculation of risk of CBC using known objective factors may be enough in some instances to encourage a woman towards having/not having CRRM. The counselling process for the majority of breast cancer patients who are not *BRCA* mutation carriers should emphasise that the risk of relapse arises from the index cancer and as such, CRRM for these women may be of limited survival benefit.

Requests for CRRM are based on a combination of patient and surgical factors. Anxiety about a further breast cancer and mortality, wanting to avoid chemotherapy for a second time or the desire to have matching reconstructions are important considerations. It has been shown that female surgeons are more likely to recommend CRRM (Arrington et al. 2009). Surgeon related factors are also affected by country (Den Heijer et al. 2013; Metcalfe et al. 2008) with the UK among those more likely to recommend CRRM (Den Heijer et al. 2013). My study found no significant differences in respondents' age, sex or specialty grade. It had too few female respondents (n=53) to perform any subgroup analysis. However, the already discussed Arrington et al study, found that all female surgeons whose patients underwent CRRM were under the age of 50 years.

Cost effectiveness is becoming a major determinant in the medical decision making process. A clear cost benefit over routine surveillance has been shown in *BRCA* mutation carriers but this is somewhat diminished in non-mutation carriers (Zendejas et al. 2011). Surgeons feel that the criteria for CRRM funding may become more stringent in a cash stricken UK health economy. Policy makers are likely to scrutinise the survival benefit of this procedure and may restrict access, making decisions solely on CBC risk without considering the multifactorial reasons that breast cancer patients request CRRM.

A Cochrane analysis from 2010 on CRRM confirmed a reduction in incidence of CBC without a clear survival benefit in non-high risk patients (Lostumbo, Carbine, and Wallace 2010). The surgeons in my study ranked gene mutation followed by family history as the most important reasons they would

recommend CRRM. This is in keeping with published studies (Musiello, Bornhammar, and Saunders 2013).

This is the first study to assess the role of the MDT and specific health professionals in the assessment of CRRM. The responses to this questionnaire indicated that most centres in England process requests for CRRM via the MDT although this is not universal. Only a third of patients will access psychologists, which is surprising given that anxiety and psychological wellbeing are major determinants in requests for CRRM (Beesley et al. 2013).

Access to psychologists may be limited by lack of resources but is invaluable. It ensures that patients are well informed regarding alternatives to combat anxiety surrounding CRRM that may include psychological treatment (e.g. cognitive behaviour therapy or use of appropriate anxiolytic medications). The MDT process should ensure objective CBC risk and psychological assessment have taken place, and that women considering CRRM are well informed of the higher complication rates associated with this procedure (Miller et al. 2013). It is possible that requests for a delayed CRRM may circumvent the MDT process as they are not considered active cancer cases. This study has shown that surgeons and breast care nurses are the main professionals involved with the decision making process, and it may be advisable to engage the other core members where possible before making a final recommendation.

Given that rates of immediate breast reconstruction have doubled in England (Neuburger et al. 2013), there are unanswered questions from this study regarding the different types of reconstructions available and the consequences of choosing them. One respondent felt that CRRM was '*a legitimate part of the reconstruction process*', raising the concern that not all surgeons involved in CRRM use objective CBC risk in their assessment for this procedure. The desire to have reconstructions match is an important point from the patient's and surgeon's view but this needs to be weighed up against the CBC risk and the risk of surgery.

A study from 2013 assessed the patient's perspective when requesting CRRM by analysing 60 consecutive women under consideration for this procedure (Beesley et al. 2013). In almost all cases, requests for CRRM were instigated by the patient and every patient unambiguously wanted CRRM. Patients responded to risk in an 'all or nothing' manner and the majority did not quantify this risk objectively. The risk assessment for those who did quantify risk played little role in their decision for surgery. The authors concluded that '*patients' subjective sense of vulnerability overwhelmed their appreciation of risk so that, regardless of level of risk of CBC, they found this risk intolerable and felt that only CRRM could reduce it*'.

Two important factors raised by the questionnaire were objective assessment of risk of CBC and survival benefit. A third of the surgeons surveyed incorrectly quote an annual CBC risk of 0.8% or more to patients with no additional risk factors. The actual incidence for CBC in such patients is approximately 0.5% per annum whereas those with a family history or those who are *BRCA* mutation carriers themselves have an annual risk of approximately 2–3% (Basu, Ingham, et al. 2015; Metcalfe et al. 2004). Overestimation of risk in patients may intensify anxiety levels. Women should have a personalised risk assessment that takes into account the known risk factors of young age (<35 years), oestrogen receptor status, endocrine therapy use (50% reduction), family history, genetic mutation status, oophorectomy at <50 years and age of menopause. These findings are consistent with those in previous studies (Musiello, Bornhammar, and Saunders 2013), namely that surgeons use both objective and subjective factors when recommending CRRM.

Discussions on survival benefit should be tailored to the risk profile of the patient. Two studies on *BRCA1/2* patients in 2014 confirmed a survival benefit from CRRM (Evans, Ingham, Baildam, et al. 2013; Metcalfe et al. 2014). Metcalfe et al showed that at 20 years, the survival rate for those who underwent CRRM was 88% compared with 66% for those who did not, with CRRM offering a 48% reduction in death from breast cancer. In contrast, (Portschy, Kuntz, and Tuttle 2014) et al used a Markov model to compare survival between CRRM and no CRRM in patients

without *BRCA* mutation. They concluded that the absolute 20-year survival benefit from CRRM was less than 1% among all age, oestrogen receptor status and cancer stage groups.

Studies have demonstrated long-term (up to 20 years) patient satisfaction with CRRM (Boughey et al. 2015; Frost et al. 2005), with up to 92% of women stating they would choose the procedure again. Many women will be offered/choose CRRM even without any survival benefit to reduce the anxiety of developing another cancer, and these are important factors to consider during the counselling process.

It is clear that categorising patients who request CRRM according to their CBC risk is critical in the decision making process. The survival benefit in high-risk patients allows a more straightforward counselling process for CRRM. It is evident from this study that the top two reasons surgeons consider CRRM are based on genetic mutation status followed by family history. However, it is the remaining sporadic ('lower risk') breast cancer patients, among whom requests for CRRM are increasing, who need careful counselling to establish their CBC risk, psychological status and reconstructive challenges (Murphy, Milner, and O'Donoghue 2013). Surgeons in this study felt that the main reason patients request CRRM were because of fear and anxiety followed by mutation status and family history. Although there is likely to be an overlap among these reasons, it is in particular the fear and anxiety that needs to be addressed in a multidisciplinary setting.

Study limitations

There are a number of limitations for this study. A postal questionnaire must be concise to ensure that recipients will respond but the results of the survey should also be informative regarding the practices in general around CRRM. It would have been useful to assess respondents' personal experience of risk assessment (e.g. use of validated tools such as the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, the Tyrer–Cuzick model and the Manchester scoring system). Furthermore, our questionnaire did not ask

recipients to include the number of requests received for CRRM or what proportions of these procedures were carried out on high-risk patients (positive family history or *BRCA* mutation carriers). Assessment of differences between immediate and delayed CRRM as well as analysis of characteristics between respondents and non-respondents would be helpful in shaping future practice. Unfortunately, this was outside the scope of this study.

There was a poor response to the questionnaire among plastic surgeons (12.6%). Current estimates are that 30% of BAPRAS members perform oncoplastic breast surgery in the National Health Service and this may explain the low response rate. Although it was recognised that the majority of BAPRAS members would not be reconstructive breast surgeons, the questionnaire was sent to the whole membership list as it was anticipated that only those with a special interest in breast reconstruction would reply. It was not possible to determine the proportion of plastic surgical non-respondents who perform CRRM and there could be an inherent selection bias in respondents compared with non-respondents.

It may be argued that the majority of plastic surgeons are involved solely with the technicalities of breast reconstruction in CRRM and would not become involved in risk counselling. However, it is important for plastic surgeons and, in particular, breast surgeons to have some understanding of risk assessment, especially when discussing an immediate TRAM/DIEP flap for breast cancer. This study has identified that risk assessment across both specialties can be improved, with almost half of respondents overestimating the risk of CBC.

Conclusions

There is a wide variation of practices and perceptions among surgeons in England dealing with CRRM. It is likely that the number of breast cancer patients requesting this will continue to increase and surgeons need to draw from the expertise of the MDT in assessing these patients. Nationally agreed guidelines would aid surgeons and other medical professionals in counselling

this complex group of patients amidst times of increasing pressure on healthcare economics.

Chapter 4: Contralateral breast cancer in *BRCA1/2* mutation carriers

Introduction

The multiple risk factors for developing CBC have been discussed in Chapters 1 and 2. The most significant risk appears to be amongst those high-risk breast cancer patients who also harbour a pathogenic genetic mutation. The NICE guidelines stratified women further according to their lifetime risk of developing breast cancer and those with the highest risk include women with a high-penetrance gene mutation. This is discussed in detail in Chapter 1 forms the basis of my review of familial breast cancer (Appendix 1).

There are some important factors to consider regarding CBC in this high-risk group.
BRCA1 and *BRCA2* mutation carriers develop breast cancer at an earlier age than in non-mutation carriers. (Verhoog et al. 2000) suggested that age of onset of primary breast cancer affects the risk of CBC in *BRCA1* mutation carriers. However, they did not study this effect in *BRCA2* mutation carriers. Other studies have shown that most of the increased risk of CBC is in the first 10-years from primary diagnosis with risks up to 40% in that time period.

The factors associated with a reduction of CBC risk have been discussed in the Chapter 2 (Table 1)(Valachis, Nearchou, and Lind 2014). The relationship between BRRSO and breast cancer risk amongst healthy *BRCA* carriers has been investigated previously. (Domchek et al. 2010) found that BRRSO reduced the breast cancer risk by 63% and 36% amongst *BRCA1* and *BRCA 2* carriers respectively. Several other studies have confirmed this risk-reduction (Kauff et al. 2008; Rebbeck et al. 2002).

A recent study from the Netherlands has questioned whether previous studies overestimated the breast cancer risk-reduction following BRRSO in healthy *BRCA1/2* mutation carriers (Heemskerk-Gerritsen, Seynaeve, et al. 2015). This study used the same methodology previously described (Domchek et al. 2010;

Kauff et al. 2008) to study a cohort of Dutch *BRCA1/2* healthy carriers and found that following BRRSO, the incidence of breast cancer was almost halved (HR 0.36-0.62). A revised analysis taking into account the various biases (described in further detail Appendix) showed no real protective effect of BRRSO on breast cancer development (HR 1.09).

In response to the Dutch study, the original authors (Chai et al. 2015) reanalysed the benefit of RRSO on *BRCA1/2* mutation carriers in the PROSE study (Prevention and Observation of Surgical Endpoints). They excluded women with previous breast and/ovarian cancer and adjusted for 'immortal person-time bias' – factors the Dutch study suggested may have led to an overestimation of risk reduction. Their reanalyses using the Dutch methodology provided similar hazard ratios to their previous studies (*BRCA 1* HR 0.63, *BRCA 2* HR 0.40). It is not known whether a potential overestimation of the beneficial effects of BRRSO on CBC risk has been made in previous studies.

The survival benefit up to 48-63% following CRRM amongst *BRCA1* and *BRCA2* mutation carriers has already been discussed. The Dutch study (Heemskerk-Gerritsen, Rookus, et al. 2015) found that this benefit was particularly seen in mutation carriers diagnosed with their first breast cancer before 40 years, those with non-triple negative breast cancer and those not undergoing adjuvant chemotherapy.

In the UK, the "Angelina Jolie" effect (Evans et al. 2014) has seen a 2.5 fold increase in appropriate referrals to the genetics clinics with a doubling in the demand for gene testing. As such, this study is timely to assess risk factors in this group of patients and also assess what role oophorectomy may have on CBC risk in light of the recent Dutch publication.

SNP (Single Nucleotide Polymorphisms)

There is considerable variation of breast cancer risk amongst those carrying a mutation in *BRCA1/BRCA*2. Age at diagnosis and cancer type of the proband case will influence this risk. The variability of this risk is highly suggestive of additional genetic (non *BRCA*1/2 alleles or genes) and non-genetic modifiers of *BRCA*1/2 (Antoniou et al. 2003). Potentially, this may enable personalised risk assessment amongst high-risk women, stratifying their risk even further – i.e. it may be possible to estimate which part of the range of lifetime risk (40-85%) an individual is likely to be affected by.

Through large scale GWAS, common SNPs associated with breast cancer risk in the general population have been studied and in particular modifiers of risk in *BRCA1/2* mutation carriers (Antoniou et al. 2010). Antoniou et al found direct associations between SNPs and breast cancer risk amongst BRCA1/2 carriers - 9 such SNPs (*TOX3, FGFR2, MAP3K, LSP1*, 2q35, *SLC4A7*, 1p11.2, 5p12, 6q25.1 loci) have been shown to increase the risk of developing breast cancer in *BRCA2* carriers from as much as 42% to 96%.

(Ingham et al. 2013) et al used 18 validated SNPs associated with breast cancer risk in the general population (*CASP8, TOX3, MAP3K, 2q, cdkn2a, 10q22, COX11, notch, 11q13, 10q21, SLC4A&, 6q25.1, 8q24, RAD51L1, LSP1, 5p12* and *10q*) to test whether they could be used predict breast cancer incidence amongst *BRCA1/2* mutation carriers. Amongst 462 *BRCA1* mutation carriers 58% developed breast cancer during the follow-up period compared to 280 cancers (62%) in the 445 *BRCA2* mutation carriers. They showed a strong relationship between the SNP profile and the age at which breast cancer develops amongst *BRCA2* but not *BRCA1* carriers. The figure (Figure 12) shows a significant difference in age at the development of breast cancer between the risk groups (overall breast risk score split into quintiles –discussed in further detail in the methods section). They concluded: "*it may now be appropriate to use these SNPs to help women with BRCA2 make maximally informed decisions about their management options*".

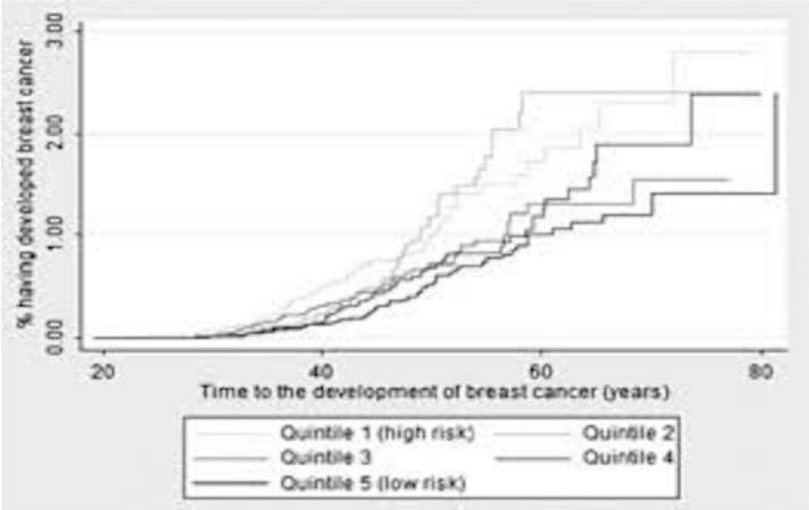


Figure 12: **Cumulative hazard of developing breast cancer in 445 *BRCA2* mutation carriers by risk group (overall breast cancer risk score split into quintiles) (Ingham et al. 2013)**

I present data from one of the largest studies performed on contralateral breast cancer risk in *BRCA1* and *BRCA2* mutation carriers. This cross-sectional study combined prospective and retrospective data. Factors assessed included whether the rate of occurrence of contralateral breast cancer is affected by time from first diagnosis, age at diagnosis of first breast cancer and early menopause. The effect of oophorectomy has been addressed in view of recent concerns regarding magnitude of breast cancer risk-reduction. The role of validated susceptibility SNPs in risk assessment for CBC in *BRCA1* and *BRCA2* was evaluated for the first time.

Methods

Study population

The Genetic Medicine Department, St Mary's Hospital, Manchester is one of the largest specialist units in the UK. Families from the Northwest region with a history of breast and ovarian cancer are referred and assessed here. A prospective database has been maintained recording details of individuals and their family members who are referred for genetic testing and subsequently found to carry a pathogenic mutation in the either *BRCA1* or *BRCA2* gene.

Patient data were collected from the Regional Genetics Service and the Family History Clinic at the Genesis Breast Cancer Prevention Centre in Manchester. Inclusion criteria for the study were: presence of a pathogenic mutation in *BRCA1* or *BRCA2* in women diagnosed with breast cancer after 1974 and before March 2015. I excluded women with bilateral breast cancer prior to genetic testing, those who developed ovarian cancer and those who underwent risk-reducing mastectomy prior to development of a CBC.

Data regarding age at first breast cancer diagnosis, CBC diagnosis, date of last follow-up, age at menopause and risk-reducing oophorectomy status were obtained from medical notes, pathology reports and from the North West Cancer Intelligence Service Database (NWCIS). I had no role in the collection of this data.
Date of last follow-up was until date of death or last contact with the service. All cases were checked against the NWCIS database in May 2011 to assess CBC status and whether they were still alive.

BRCA1/2 testing was performed following written consent over a twenty-year period based on strength of family history in particular young age at diagnosis and ovarian cancer. Breast cancer patients without any family history could access genetic testing via on-going research studies. Overall, the observation period for data collection was in excess of thirty-years.

The earliest recorded first breast cancer diagnosis was January 1974 (*BRCA1*) and March 1974 (*BRCA2*) –and the latest recorded date of follow-up for any case was March 2015.

Ethics Statement

This research was performed in accordance with the Declaration of Helsinki. Ethics approval was sought prior to my involvement with the study following review by the NHS Health Research Authority, National Health Research Ethics Committee North West, Greater Manchester Central (Barlow House, 4 Minshull Street, Manchester, M1 3DZ).

Data Collection

Patients gene tested prior to developing their first cancer were considered to have been tested on the date of the cancer for the analysis. Where oophorectomy occurred before the first cancer, patients were considered to be in the oophorectomy group from the start of follow up. For the menopausal age, patients were treated to be pre-menopausal initially. At the point that menopause occurred, they moved into either the <45 or 45+ group, depending on their age at the time. The exact menopausal age was not available for patients aged over 45, hence patients were moved into the late menopause group at the time that they turned 45.

DNA Testing

Women attending clinic provided blood samples. Consent was obtained following pre-test genetic counselling by approved counsellors. DNA Sanger and multiplex ligation-dependant probe amplification (MLPA) analysis was used to identify women with pathogenic mutations of the *BRCA1* or *BRCA2* genes. Relatives of those identified with a mutation were then offered targeted screening by predictive testing for the family specific genetic mutation.

SNP Methods

Numerous breast cancer susceptibility loci have been identified. I used the 18 SNPs previously used by Ingham et al 2013 ((*CASP8, TOX3, MAP3K, 2q, cdkn2a, 10q22, COX11, notch, 11q13, 10q21, SLC4A&, 6q25.1, 8q24, RAD51L1, LSP1, 5p12* and *10q*), shown to be associated with breast cancer risk in the general population. *BRCA1/2* mutation carriers were typed for these SNPs adhering to the Consortium of Investigators of modifiers of *BRCA1/2* (CIMBA) genotyping quality control criteria (Antoniou et al. 2010).

To calculate an overall breast cancer risk SNP score (OBRS), I used published per SNP odds ratios and risk allele frequencies (RAF) (Turnbull et al. 2010) to generate odds ratios for the three SNP genotypes (no risk alleles, 1 risk allele, 2 risk alleles). Appendix 3 is the published SNP odds ratios and RAF (Turnbull et

al. 2010). For example, at locus *FGFR2*, the SNP with the strongest risk association (rs2981579) has an OR of 1.43 and RAF 0.42. The odds ratios for each genotype were then multiplied together to obtain each woman's OBRS. This was the same methodology used by (Ingham et al. 2013).

Statistical Analysis

Initially, the times to CBC in each group were estimated using Kaplan-Meier curves, with the period of follow up from the date of the initial cancer diagnosis to CBC, with patients censored at death or loss to follow up. Comparisons were then made across factors using log-rank tests. Statistical guidance was gratefully received from one of the co-authors of the published manuscript (JH).

The Kaplan-Meier analysis had two major shortcomings. The first was that it did not account for the fact that only those patients who were alive and free from CBC at the time of genetic testing could be included in the analysis. The second issue was that two of the factors considered (oophorectomy and menopause) could occur at any time during the follow up. This meant that patients changed groups during follow up (e.g. moving from the "no" to "yes" oophorectomy group). It also gave the potential for immortal time bias where, in order to receive an oophorectomy or develop menopause during the follow up, patients needed to remain alive and free from CBC for a sufficient time.

In order to account for these two shortcomings, an adjusted Kaplan-Meier analysis was performed with guidance from a statistician (JH). In this, patients were left-censored, hence they entered the study at the time that they received their genetic testing, rather than the time of their first diagnosis of breast cancer. In addition to this, for the oophorectomy and age at menopause, patients were treated as being in the "no" or "pre-menopausal" groups initially, before moving to the appropriate group at the time that oophorectomy/menopause occurred. Where applicable, the results of both of these approaches are reported, in order to highlight how accounting for the two biases influenced the results
In order to produce hazard ratios, and to perform multivariable analysis, the data were also analysed using a delayed entry cox regression approach, using

the Complex Samples package in IBM SPSS Statistics 22 (IBM Corp. Armonk, NY). This accounted for the biases discussed above by using delayed entry, so that patients entered the study at the time of their genetic test, and by treating oophorectomy and menopause as time dependent covariates, with patients moving between groups over the course of their follow up. Univariable models were first produced for each factor in turn, followed by a multivariable model considering all factors simultaneously.

Missing data were excluded on a per-analysis basis, and $p<0.05$ was deemed to be indicative of statistical significance throughout.

Results

After applying the exclusion criteria, data were available for 1,011 patients, of whom 506 had *BRCA1*, and 505 *BRCA2* confirmed mutations. The mean age at the first breast cancer was significantly (t-test $p<0.001$) higher in *BRCA2* (46.1 years, SD=10.4) than in *BRCA2* (42.3 years, SD=9.7). The median follow up from the first breast cancer was 7.8 years (range 0–37.0), with CBC occurring in 20.0% (202/1,011) patients in the study. The cumulative risk of CBC at 20 years was 45.7% (Table 5), which is equivalent to 2.3% per year.

Table 5: Cumulative risk of CBC in *BRCA1, BRCA2* mutation carriers

	Years since initial breast cancer diagnosis		
	5yrs	**10yrs**	**20yrs**
BRCA1 mutation carriers	10.4%	25.7%	44.4%
BRCA2 mutation carriers	6.8%	19.5%	48.1%
Overall	***8.6%***	***22.3%***	***45.7%***

Quoted values are from the adjusted Kaplan-Meier models, which account for delayed entry.

The analysis was then performed using a delayed entry cox regression model with time dependent covariates, in order to account for immortal time bias, and the delayed entry of patients into the study (Table 6).

Table 6 – Results from adjusted Kaplan-Meiers, and univariable and multivariable delayed entry Cox regression models

Factor	BC2 Rates at 20 Years†	Univariable Models			Multivariable Model		
		N	*Hazard Ratio (95% CI)*	*p-Value*	*N*	*Hazard Ratio (95% CI)*	*p-Value*
Gene				**0.551**			**0.836**
BRCA1	44.4%	388	-		224	-	
BRCA2	48.1%	394	0.89 (0.57 - 1.35)		226	1.05 (0.65 - 1.72)	
Age at Menopause#				**0.131**			**0.384**
<45	39.8%	117	-		95	-	
45+	45.0%	477	1.01 (0.56 - 1.83)		272	1.56 (0.79 - 3.09)	
Pre-Menopause	46.9%	188	1.69 (0.86 - 3.31)		83	0.99 (0.40 - 2.41)	
Oophorectomy#				**0.532**			**0.333**
No	47.5%	637	-		330	-	
Yes	39.2%	145	0.83 (0.46 - 1.50)		120	0.72 (0.36 - 1.41)	
Age at BC1				**0.017***			**0.044***
<40	55.4%	273	-		146	-	
40-49	41.1%	296	0.64 (0.40 - 1.03)		177	0.50 (0.25 - 0.97)	
50+	36.4%	213	0.43 (0.23 - 0.81)		127	0.36 (0.15 - 0.84)	
SNP Score Quintile				**0.543**			**0.529**
1	41.7%	96	-		96	-	
2	46.1%	88	1.33 (0.61 - 2.91)		88	1.48 (0.70 - 3.29)	
3	49.9%	93	1.62 (0.76 - 3.45)		93	1.59 (0.75 - 3.36)	
4	63.8%	83	1.78 (0.85 - 3.74)		83	1.94 (0.89 - 4.20)	
5	37.6%	90	1.13 (0.51 - 2.51)		90	1.25 (0.58 - 2.71)	

#*Treated as a time-dependent covariate*

†*From adjusted Kaplan-Meier models, accounting for delayed entry and time dependence of stated covariates *Significant at p<0.05*

This analysis was based on the 782 patients whose genetic tests were performed prior to developing CBC, as the excluded patients did not fit into the delayed entry framework. Univariable analyses detected no evidence of significant relationships between CBC and *BRCA* type (p=0.551), age at menopause (p=0.131), oophorectomy (p=0.532) or the SNP score quintile (p=0.543). Age at the first cancer was significant (p=0.017), with increasing age associated with a reduced risk of CBC (20 year rate 55.4% for <40 years vs. 36.4% for 50+ years). Dividing the patients into the two *BRCA* groups found that this difference was most pronounced in *BRCA1* patients (Figure 13). A multivariable analysis was also performed for the 450 patients with complete data for all of the variables considered, which returned similar results.

As a validation of the results, the analysis I also performed using a standard Kaplan-Meier approach. This included the data of all patients, regardless of the time of their genetic testing, and did not account for the effects of delayed entry or immortal time bias. This gave broadly similar results, with the age at first breast cancer being significant (p=0.003), and the majority of the other factors remaining non-significant. The only exception was oophorectomy, which was highly significant in this analysis (p<0.001, Figure 14). Figure 14a shows the associated Kaplan-Meier plot, whilst Figure 14b shows the adjusted Kaplan-Meier plot, which accounts for delayed entry and immortal time bias (as in table 4). As can be seen, accounting for these biases has a large impact on the conclusions of the analysis, which gives a rationale for the analytical approach.

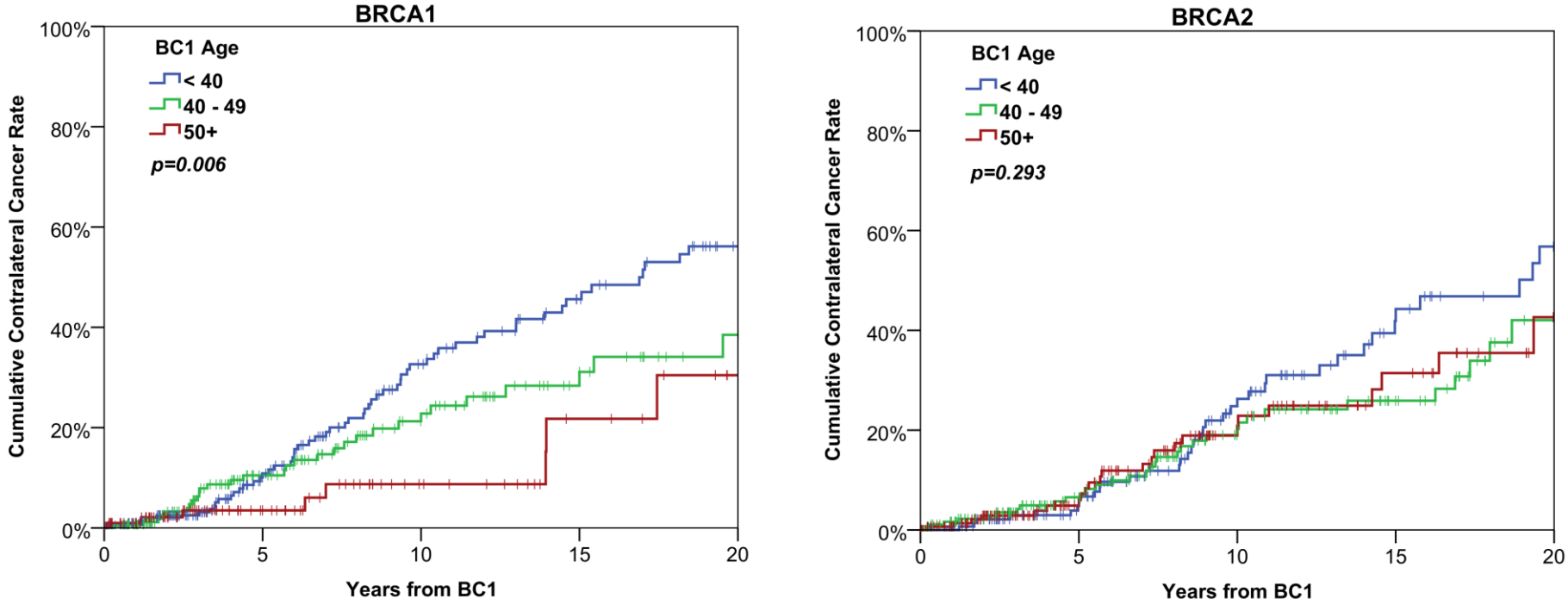


Figure 13: Standard Kaplan-Meier plots of the risk of contralateral breast cancer (*BRCA1 and* 2) showing the effect of age of first breast cancer diagnosis (<40 years, 40-49 years, >50 years).

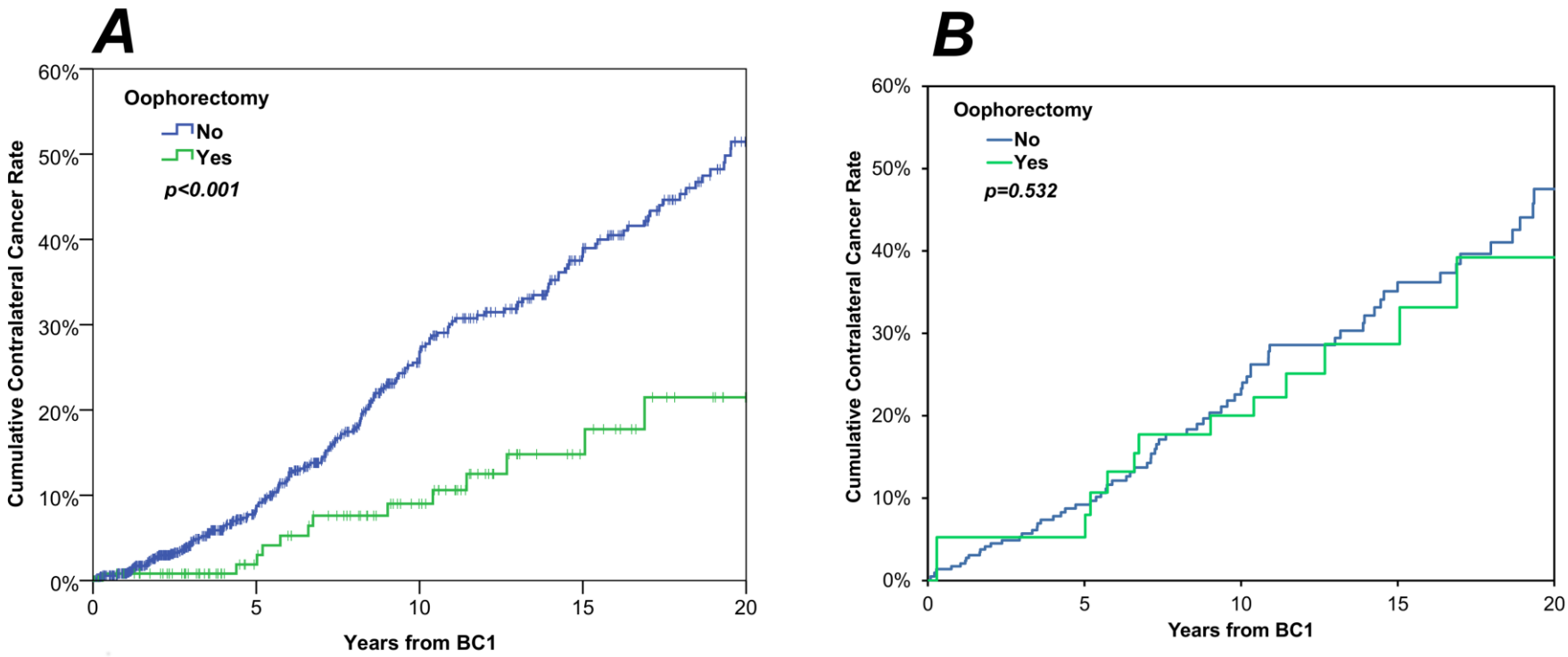


Figure 14: Risk of contralateral breast cancer according to risk-reducing oophorectomy. Figure 2a is a standard Kaplan-Meier plot, with p-value from a log-rank test. Figure 2b is an adjusted Kaplan-Meier plot, which accounts for the delayed entry of patients, and the time dependence of oophorectomy, with patients moving into the oophorectomy group at the time that the surgery was performed. The p-value is from a univariable delayed entry cox regression model.

SNP Results

I assessed the relationship between time to development of contralateral breast cancer between the various risk groups (OBRS split into quintiles). No significant differences were found in any of the SNP quintile groups (p=0.543). In addition, a subgroup analysis was performed, considering the effect of SNP within each *BRCA* type. Separate univariable models were produced for each *BRCA* type with SNP quintile as a factor. SNP was not found to be a significant predictor of CBC in either *BRCA1* (p=0.289) or *BRCA2* (p=0.594), with hazard ratios for the upper, relative to the lower quartiles of SNP of 0.43 (95% CI: 0.12 – 1.64) and 2.31 (95% CI: 0.74 – 7.23) respectively.

Discussion

This data indicates that the risk of CBC following an initial breast cancer diagnosis in *BRCA1* and *BRCA2* mutation carriers is relatively constant at 2-3% per year, persisting for at least 20 years.

My findings differ somewhat from other published data. (Metcalfe et al. 2004) reported CBC rates of approximately 40% at 10 years – almost twice the rate shown by this data. Their study included affected family members, with not all cases being proven mutation carriers. (Graeser et al. 2009) reported the cumulative CBC risk at 25 years to be 47.4%, similar to the 2.3% per year rate that I have reported. The mean age at first breast cancer was slightly higher in this cohort (44.2 years) compared to Metcalfe (42.1 years)[9] and Graeser (43.4 years). Whether this accounts for the differences in cumulative CBC risk is not known.

Previous studies have reported a higher rate of CBC amongst *BRCA1* carriers with the Graeser study showing a 1.6 fold increase in this group. In my study, *BRCA1* carriers had an approximately 3% higher cumulative rate of CBC at 5 and 10-years (albeit not significant), and which diminished by 20 years.

Initial breast cancer diagnosis prior to the age of 40 years was a significant risk factor in the cohort as a whole. This is similar to the findings of 2 previous studies that looked at women younger than 50 years (Metcalfe et al. 2004) and *BRCA1* only carriers (Verhoog et al. 2000) respectively. When considering the *BRCA* subgroups, I found that the association between age and CBC was only significant in *BRCA1*, which was consistent with other findings (Graeser et al. 2009). Young age at first breast cancer was the only risk factor that maintained any significance in the multivariable analysis.

(Domchek et al. 2010) performed a multi-centre prospective study assessing the role of risk-reducing mastectomy and BRRSO in patients with *BRCA1/2* mutations. In keeping with my study, they found that BRRSO in women with a prior diagnosis of breast cancer was not associated with a reduction in risk of a contralateral breast cancer (the role of BRRSO in healthy *BRCA1/2* mutation carriers has been previously discussed). Their findings may be explained by differences in adjuvant treatment as well as risk-reducing oophorectomy being performed close to age 50 years.

In contrast, other studies have found a protective effect of BRRSO (Metcalfe et al. 2004; Pierce et al. 2006). In this study, I attempted to overcome two major types of bias, namely immortal time bias and delayed entry bias. Prior to using the delayed entry cox regression model and time dependent covariates, the effect of BRRSO on CBC was significant ($p<0.001$) with a hazard ratio of 0.35, (95% CI 0.20 – 0.61). This significance was not maintained after accounting for the two sources of bias ($p=0.532$, HR 0.83, 95% CI 0.46 – 1.50). These findings are similar to the recent Dutch (previously discussed) study assessing breast cancer risk after BRRSO in *BRCA* healthy mutation carriers (Heemskerk-Gerritsen, Seynaeve, et al. 2015).

The Manchester group (Evans, Ingham, Baildam, et al. 2013) recently reported a survival advantage of CRRM in *BRCA1* and *BRCA2* carriers that appears to act independently of BRRSO. Overall uptake of CRRM was 14% over a 25-year period – however the rates are increasing rapidly with the passage of time - 10% (1985-2001) to 22% (2001-2010). SEER data indicate a 150% increase in the rates

of CRRM that includes mutation carriers and non-*BRCA1/2* high family risk patients (Basu, Barr, et al. 2015). The German group (Rhiem et al. 2012) found that the risk of CBC for *BRCA1/2* negative families is low and similar to that in women with sporadic breast cancer, confirming my finding that CBC risk is dependant on mutation status and age of onset of first breast cancer.

During the extended observation period in this study, there have been inevitable changes in practice – one of the main being a global decrease in the incidence of CBC (Nichols et al. 2011). I have accounted for some of the other potential confounding factors, particularly the omission of oestrogen receptor status. The role of tamoxifen was not assessed, as non-standard reporting of oestrogen receptor status prior to 1995 would have precluded nearly half the subjects. A recent report (Phillips et al. 2013) confirmed that tamoxifen use reduces the risk of contralateral breast cancer in *BRCA1* and *BRCA2* carriers. This study assessed women with ER negative first breast cancer who received tamoxifen postulating that there may be an oestrogen-responsive occult phase. This may have implications for mutation carriers with breast cancer considering chemoprevention, particularly if they have not had premenopausal risk-reducing oophorectomy.

I accept that during this period, major refinements in high-quality imaging as well as increased use of MRI that may have identified more CBC during surveillance. In addition, wider availability of genetic testing and heightened patient awareness are difficult factors to account for in my study.

SNP

This is the first time that the feasibility of SNP testing in risk assessment for CBC has been studied. Ingham et al had previously reported that SNP testing could be used further to differentiate breast cancer risks in *BRCA2* carriers. However, I found no significant predictive ability in stratifying CBC risk. The use of the delayed entry model precluded analysis of almost half of all the mutation

carriers and may account for the non-significant findings. I also used weightings based on the general population of breast cancer that were less likely to be predictive for *BRCA1* which predominantly has ER negative cancers, This is evidenced by a reverse trend in prediction compared to *BRCA2* as previously shown for unilateral breast cancer occurrence (Ingham et al. 2013). It is hoped that continued international collaborations (Chenevix-Trench et al. 2007) will unravel further SNPs that may be assessed to guide high-risk women and offer individualised risk assessment.

My study has important implications for the management of women with mutations in *BRCA1 or BRCA2*. Following a first breast cancer diagnosis the risk of a CBC remains raised for at least 25 years. This data may help women, especially those diagnosed with their first breast cancer before the age of 40 years to make an informed decision regarding the benefits of CRRM.

The rationale for considering BRRSO in *BRCA1/2* mutation carriers who have been diagnosed with breast cancer is multi-factorial. The counselling process should discuss the reduction in risk of developing ovarian cancer as well as the potential modification of risk of breast cancer recurrence and CBC. Caution should be exercised when evaluating the magnitude of contralateral breast cancer risk-reduction.

The increasing accuracy of the breast cancer risks associated with an individual's *BRCA* mutation status will hopefully allow clinicians to provide more personalised management options in the future than presently offered.

Chapter 5: "The Manchester Guidelines" – for CRRM

Introduction

There is a wealth of literature on the appropriate management of women requesting bilateral risk-reducing mastectomy (BRRM) because of family history or known genetic mutation (Lostumbo, Carbine, and Wallace 2010). Existing guidelines on BRRM include the updated 2013 NICE Guidelines on Familial Breast Cancer in the UK (Evans, Graham, et al. 2013). Protocols exist for the counseling process for these women before embarking on the surgery, with the Manchester guidelines for BRRM being amongst the first (Lalloo et al. 2000). However, no such protocols or guidelines are in place for women requesting CRRM after a diagnosis of cancer.

Reasons for requesting this procedure are complex and Chapter 3 has shown a variable practice amongst breast and plastic surgeons in England. The proposed protocol is based on the literature review of risk factors for CBC (Chapter 2)(Basu, Barr, et al. 2015), my study of CBC amongst *BRCA1/2* mutation carriers (Chapter 4)(Basu, Ingham, et al. 2015) and the results of the survey of surgeons' attitudes to risk-reducing surgery (Chapter 3)(Basu et al. 2016). The co-authors of the already published "Manchester Guidelines" (Basu, Ross, et al. 2015) all contributed to the construction of these guidelines and the preparation of the manuscript (DGE, GR and LB).

Methods:

Assessment of the patient requesting CRRM.

These guidelines have been formulated to aid clinicians dealing with requests for CRRM. Where possible, a level of evidence has been assigned from the designations set by the Centre of Evidence Based Medicine. There are several steps in the process of preoperative assessment and counseling that are clinically important before an informed consent to CRRM can be given. These can be summarised as follows:

Step 1: Taking a history

Step 2: Calculating the risk of contralateral breast cancer

Step 3: Cooling off period whenever possible

Step 4: MDT discussion

Step 5: Patient consent

Step 1: Taking a history

The first element of history taking is to determine the reasons behind a patient's request to discuss CRRM. For the majority of women the decision to request contralateral surgery is based on factors other than inherited genetic risk (Beesley et al. 2013). Women with breast cancer may have complex, multi-factorial reasons for requesting CRRM, and so the history should typically begin with open-ended questions to let the patient discuss her reasoning, objectives, hopes and fears. Objective assessment of this is challenging, with only a few reports in the literature (Beesley et al. 2013).

Table 7 lists the main reasons patients request CRRM (Han et al. 2011) and is verified by my own study of clinical practice in England (Basu et al. 2016). Patients list fear of a second diagnosis, fear of chemotherapy and anxiety about their children's future as the main drivers, followed by gene mutation status and family history – whereas surgeons rank gene mutation and family history as the main reasons to offer CRRM (Basu et al. 2016).

Table 7. Reasons patients request CRRM (Basu, Ross, et al. 2015)

Reasons patients request CRRM
Gene Mutation
Family History
Fear / anxiety - second breast cancer - long term survival
Avoid chemotherapy
Symmetry of reconstruction
Mistrust of surveillance
Offered TRAM/DIEP – a "once only" option

The breast cancer patient requesting CRRM is different to the patient considering BRRM. Although the latter may have experience of a family member's breast cancer journey, they would not have had the personal experience of breast cancer, and their reasons for choosing risk-reducing mastectomy may vary significantly (Beesley et al. 2013; Meiser et al. 2000; Stefanek, Hartmann, and Nelson 2001). Fear of developing another breast cancer is a frequently expressed concern, but not necessarily related to whether or not this would influence life expectancy. For some women fear of having repeated chemotherapy is their main concern. For others, it is mistrust of annual mammographic surveillance particularly if their first breast cancer was mammographically occult, or if they have had a stressful 'recall' following a surveillance mammogram. Greater confidence in good outcomes following breast reconstruction may prompt a discussion of whether better symmetry might be obtained by bilateral rather than unilateral mastectomy, a factor that may also explain the 'Angelina Jolie' effect of increased interest in BRRM (Evans et al. 2015). For women whose primary motive is better long-term survival, a simple explanation that CRRM will not achieve this in those who do not carry a gene mutation may stop the discussion going further. However women may have strongly held motivations for CRRM quite independent of any effect on survival chances and these need to be understood and recorded.

The clinical history also needs to assess the index breast cancer and highlight any potential poor prognostic indicators. It may be useful to objectively assess this risk using one of several validated predictive tools readily available. In addition, any co-morbidities should be identified that would influence further surgery and in particular reconstructive surgery. In Step 5 of the process a more detailed discussion is required of their expectations around breast reconstruction including a discussion of the risks and benefits of the reconstructive options in their case.

Step 2: Calculating the risk of contralateral breast cancer

Women being considered for CRRM should have an objective assessment made of their risk of developing CBC, as well as an explanation of whether CRRM would or would not influence survival prospects. It is well documented that many women overestimate both their personal risk of CBC and the survival benefit of CRRM. At the same time, they underestimate the adverse effects of the additional surgery (Katz and Morrow 2013; Rosenberg et al. 2013). My own study has shown that surgeons may be counseling women based on inaccurate interpretation of CBC risk (Basu et al. 2016). A significant proportion of breast cancer patients will undergo CRRM despite knowing there is no survival advantage amongst non-mutation carriers (Rosenberg et al. 2013).

CBC risk is multi-factorial as seen in Chapter 2. It is important to calculate an individualised lifetime risk of CBC to stratify patients into different risk-groups, prior to consent for CRRM. This will facilitate the counseling process and provide a useful standard so that practices throughout can be audited.

Table 8. Summary of risk factors for CBC and levels of evidence
(Basu, Ross, et al. 2015)

Family history - <45 years with first degree relative (RR 2.5) • <55 years with first degree relative (RR 1.5) • first degree relative with bilateral disease (RR 3.5) Level II Evidence (Reiner et al. 2013)
Gene mutation status – *BRCA1/2* mutation (RR4) Level II Evidence (Basu, Ingham, et al. 2015; Evans, Ingham, Baildam, et al. 2013; Metcalfe et al. 2004)
Chest Radiotherapy for Hodgkin Lymphoma – rate of CBC unknown
Young age at diagnosis - <30 years 0.5-1.3% annual CBC rate Level II Evidence (Nichols et al. 2011)
ER status - ER positive (reference point RR 1) • ER negative (RR 1.3) Level II Evidence
Anti-endocrine treatment (risk reduction) Tamoxifen 50% Aromatase inhibitor 70% Level I Evidence (Cuzick et al. 2010)
DCIS – 0.6% annual CBC risk of DCIS and/or invasive carcinoma (RR 1.0) Level II evidence (Tuttle et al. 2009)
Lobular histology combined with family history (RR2.0)
Oophorectomy under 40 years (risk reduction) (RR0.5)

The risk of CBC in patients with known *BRCA* gene mutations is approximately 2-3% per annum (Basu, Ingham, et al. 2015), and likely higher in *TP53* mutation carriers (Evans et al. 2010). The baseline risk of CBC in patients with no family history is approximately 0.5% per annum (Lizarraga et al. 2013). The use of anti

endocrine treatment is associated with a 50-70% risk-reduction, with a greater reduction in risk from aromatase inhibitors (Cuzick et al. 2010). These baseline risks can be modified by certain factors listed in the Table 14. Patients diagnosed with unilateral breast cancer requesting CRRM and who have a strong family history should ideally have formal assessment of risk and genetic testing carried out by a clinical geneticist. In other cases a useful objective assessment of risk of CBC can be calculated as follows.

Life expectancy at birth for women varies within the UK (range 78.5 years – Glasgow to Purbeck 86.6 year) (ONS 2012) and I have used 80 years as the average life expectancy. Thus, to obtain the number of years of CBC risk one can simply use the following calculation:

80years – patients age (years) = Number of years of CBC risk.

The quoted annual incidence of CBC at 0.5% per year can be used as a guide to the background risk for CBC in women diagnosed with breast cancer. To obtain a lifetime risk based on this one can use the following calculation (this assumes good life expectancy from the ipsilateral primary and typically would only apply to stage 1 cancers):

Number of years of CBC risk x 0.5% = Life-time risk of CBC

Once this value has been calculated, one can modify the risk based on patient's personal risk profile as follows:

ER positive disease and on anti-endocrine treatment – Multiply by 0.5 (50% risk reduction)

Gene carriers – Multiply by 4 (2% annual incidence of CBC)

Oophorectomy under 40 years (surgical, chemotherapy induced or natural) – Multiply by 0.5 (50% reduction)

Family history – Multiply by 2

NOTE: Where numerous factors are being considered the multiplicative interaction of factors is not known. For those patients with a known genetic mutation and a family history, consider modifying risk based on gene mutations (i.e. multiply by 4) only. Anti-endocrine treatment in those who have had oophorectomy under the age of 40 years, consider risk-reduction by one factor (i.e. multiply by 0.5) as there is no data to my knowledge on whether the relationship is additive.

The quoted baseline annual incidence of CBC of 0.5% per annum is reduced in ER positive tumours by 50% after 5 years of adjuvant tamoxifen, but even more by an aromatase inhibitor.

Unilateral ductal carcinoma in situ (DCIS) is associated with an increased risk of developing a contralateral invasive cancer or DCIS. This annual risk is estimated at 0.6% and may be used in the above formula.

These calculations are of course only a guide, but they are useful to stratify risk into clinically relevant risk categories such as the following:

Low Risk	<10% remaining life-time risk of CBC
Above Average Risk	10-20% remaining life-time risk of CBC
Moderate Risk	20-30% remaining life-time risk of CBC
High Risk	>30% remaining life-time risk of CBC

The use of risk categories has proved invaluable in the context of BRRM, and there are several validated tools now to calculate breast cancer risk based on family history and lifestyle factors for women without a cancer diagnosis (Evans and Lalloo 2010)(i.e. Manchester Score, Tyrer-Cuzick, BOADICEA). At present, there are no validated tools to calculate CBC risk in the context of CRRM.

Step 3: Cooling off period whenever possible

The decision making process around BRRM is characterised by several months of pre- and post-test counseling. In contrast, women who request CRRM may do so within a few hours or days from their diagnosis of breast cancer. Nationally defined targets for prompt treatment following a diagnosis of breast cancer may impact on the shared decision making process by limiting the time available for careful consideration of the pros and cons of CRRM.

For the majority of patients it is probably in their best clinical interest to defer any decision about CRRM until after their primary cancer treatment has been completed. This "cooling off period" minimises the risk that they make a decision for CRRM as a knee-jerk reaction at a time when they are emotionally vulnerable. There are exceptions to this recommendation however. These include the patient with a known genetic mutation (e.g. *BRCA1/2* mutation) who may have made a decision many months or years previously to undergo bilateral mastectomies for therapeutic and risk-reducing reasons in the event of a cancer being diagnosed. Non-mutation carriers in the high-risk group defined in Step 2, such as those with a significant family history or previous mantle radiotherapy, may also decide on CRRM as part of their primary treatment on diagnosis of a unilateral cancer, and again may not benefit from a cooling off period.

Overall, the majority of women are satisfied with their decision of CRRM up to a decade following surgery (Frost et al. 2005). However, it is not known whether timing of this decision impacts on the level of satisfaction. Where feasible, this step allows women to carefully consider the various options available to them in a non-time constrained manner. However, this is not always possible as the need to treat the affected side and possible reconstructive options will influence the decision making process and the speed at which happens.

Patients considering an immediate TRAM/DIEP reconstruction for their primary therapeutic mastectomy are also an important possible exception and are discussed further in step 5.

Step 4: MDT discussion

Given the complexity of the decision making process, **all** women considering CRRM should be assessed in a multi-disciplinary setting – surprisingly this is not universally practised in the UK (Basu et al. 2016). The core members of the team should include breast care nurse, breast surgeon, oncologist, radiologist and pathologist and where possible an oncoplastic-reconstructive surgeon familiar with the various reconstructive options including free TRAM/DIEP. For patients with a family history, discussion with a clinical geneticist of their risk of CBC and the possibility of genetic testing should be offered during the patients cooling off period Often the breast care nurse will have developed a close relationship with the patient and is the patient's advocate at the MDT meeting. She should have the option of requesting additional psychology assessment if she feels necessary but we would not regard this as mandatory. The patients reasons for requesting CRRM should be discussed at the MDT in the light of her objective risk of CBC, influence on survival chances, risks and benefits of the additional surgery, and the alternative options around surveillance and imaging. Additionally, it is useful to review the imaging, as some women may be particular challenging in offering radiological surveillance on the contralateral side.

The main benefit of a multi-disciplinary approach is that requests for CRRM can be scrutinized across various specialties and facilitate shared decision-decision making. A recent report showed that introduction of this approach resulted in almost a third of requests for CRRM being declined, mainly due to a low risk of CBC in light of a high risk of systemic relapse (Leff et al. 2015). There is good evidence across various specialties supporting this form of collaborative working (Patkar et al. 2011). This approach enables the MDT process to consider each request for CRRM on an individual basis prior to making a consensus led decision with the option of patient led appeal for extenuating circumstances.

Step 5: Patient consent

Each of the steps described above is part of the consent process, commencing with a clear discussion of the benefits that the patient hopes to achieve with CRRM, and a clear explanation of the objective risk of CBC and whether or not any survival advantage can be achieved. Particularly for the non-gene carrier where no survival advantage exists, the conclusion that CRRM is appropriate and has the support of the MDT meeting should be recorded in the clinical notes. The next step is to explore the various reconstruction options available to the patient if that is what she wishes, combined with a clear explanation of the limitations of such surgery, its risks and complications. Unrealistic expectations of a perfect outcome and no postoperative complications should be addressed if present. The final step is the signing of a formal Consent Form, on which there is only sufficient space for the recording of a brief summary of the risks and benefits; all of these prior discussions should be recorded within the clinical notes prior to the actual signing of the form.

A particularly challenging situation is the patient who requests CRRM at the same time as her therapeutic mastectomy as part of her primary treatment. This puts the surgeon under time pressure to go through a complex consent process. For patients in the high-risk group defined in Step 2 the situation may be fairly straightforward as often the patient will have had considered bilateral mastectomy as her preferred option long before the actual diagnosis. For patients undergoing primary neo-adjuvant systemic therapy the situation is also more straightforward, because a period of several months of "cooling off" between those first discussions and the final decision to proceed gives the surgeon and his/her MDT time to complete the above steps. For the patient requiring a therapeutic mastectomy as her first treatment, and who chooses an immediate TRAM/DIEP flap as her preferred reconstruction, the decision has to be made within a few days, as otherwise the option of bilateral symmetrical reconstruction is lost forever. In these circumstances there may be no time to proceed to a formal genetic assessment or to offer a cooling off period. The opportunity for CRRM should probably not be denied to the patient in those circumstances, as long as the risks and benefits are clearly explained and approved by the MDT, and recorded in the clinical notes.

Currently there is not enough provision in the UK for every MDT to have an oncoplastic surgeon who can offer free TRAM/DIEP reconstruction as a core member. Many MDTs in the UK have to refer outwith to an extended MDT member (usually a plastic surgeon) which causes time delays and lengthens the decision making process for patients and anxiety levels. Ideally all MDT's should include an oncoplastic surgeon familiar with the various reconstructive options.

Women who are deemed not suitable for CRRM are currently offered annual mammography surveillance for 5 years or up to the age of 50 years – whichever is longer.

Discussion

The management of breast cancer patients requesting CRRM is complex and best undertaken in a multi-disciplinary setting. Several challenges exist for clinicians in this setting. The first is their inability to calculate accurately the individualized risk of CBC for each patient given the numerous risk factors already described. I have suggested a potential framework, but development of a validated algorithm remains a high priority in research in this area of study. The other challenge remains managing the expectations of women for whom CRRM offers no survival advantage and who form the vast majority of women requesting CRRM.

This protocol serves as a tool for clinicians involved in this complex shared decision making process with their patients. The simple risk calculation that I have described is based on a published systematic review of known risk factors, and provides a clinically useful method of assigning patients to a variety of risk categories. It is hoped that this risk calculation will aid both patients and clinicians to jointly come to a decision regarding CRRM following a clear explanation of the objective risks of CBC and the potential benefits, risks and limitations of CRRM. I acknowledge that it is not possible to be prescriptive in terms of who should be allowed or refused CRRM.

The main limitations of this protocol are that recommendations are based on a systematic review of known risk factors that have not been assessed in a clinical setting. As such, the estimates of contralateral breast cancer risk need to be used with caution when multiple factors are being considered given that there is a limited evidence base to assess if these interactions are multiplicative. This formula has been designed to act as a guide rather than a precise tool for the objective assessment of risk. Efforts are underway to validate this protocol in a large retrospective study. However, to my knowledge there are no established guidelines to aid the clinician objectively assess requests for CRRM. As such this protocol is the first to attempt to address this important issue. I hope that in the interim, these guidelines and the steps described within them help in reaching a shared decision. This will ensure each request for CRRM is judged based on its own merits.

Chapter 6: Summary and Future Work

The number of woman being diagnosed with breast cancer continues to increase and remains the most common cancer amongst women worldwide. Breast cancer survivorship is a growing healthcare issue as these women often have complex needs including concerns about developing a CBC. This may be in the context of a woman newly diagnosed with breast cancer or even several years following initial diagnosis.

As rates of mastectomies continue to increase clinicians must consider potential drivers of this change in trend. This is most apparent in the setting of CRRM and Chapter 1 has highlighted this. Most of the observed increase originates from the USA where at least 5 predictive factors for CRRMs has been consistently reported:

Young age
Lobular histology – carcinoma and in situ disease
Use of MRI
Recent year of diagnosis
DCIS

Chapter 2 reviewed the various risk factors for developing CBC and the most significant risk factor was the presence of a mutation in one of the high-penetrance genes. Mutations of the *BRCA1/2* are amongst the most studied in this setting and my study (Chapter 4) is in line with the rest of literature showing that breast cancer patients with a *BRCA1/2* mutation have a lifetime risk of CBC in the magnitude of 2-3% per annum. My study showed that this risk is most significant in women whose first breast cancer was diagnosed before the age of 40.

A survival benefit from CRRM has been shown amongst *BRCA1/2* carriers, particularly those diagnosed with their primary breast cancer before 40 years (Heemskerk-Gerritsen, Rookus, et al. 2015). Given that this patient group (under 40s) has the highest risk for developing a CBC it would be logical that the

guidelines for CRRM identify this group at particular risk and deriving the greatest survival benefit.

Histology of the primary breast cancer was reviewed in Chapter 2. Overall there is insufficient data to support the previous notions that lobular carcinomas are associated with a higher incidence of CBC. Therefore, the association between increasing numbers of CRRMs and lobular cancer histology may be based on misinterpretation of the evidence base or additional factors such as the low sensitivity of standard modalities (clinical examination, mammography, ultrasound) when diagnosing lobular cancers.

Current indications for breast MRI in the USA are listed below (ACR 2014):

Lesion characterisation
Neoadjuvant chemotherapy
Infiltrating lobular carcinoma
Infiltrating ductal carcinoma
Axillary adenopathy, primary unknown
Postoperative tissue reconstruction
Silicone and non-silicone breast augmentation
Lesion characterisation
Contralateral breast examination in patients with breast malignancy
Post lumpectomy for residual disease
Surveillance of high-risk patients
Recurrence of breast cancer

These guidelines for MRI cite infiltrating lobular carcinoma and examination of the contralateral breast in breast cancer patients as common indications for MRI use in the USA. A recent meta-analysis of 22 studies (Brennan et al. 2009; Houssami et al. 2008) found that use of MRI in newly diagnosed breast cancer patients resulted in nearly 1 in 10 women being recalled for an abnormality which resulted in a diagnosis of breast cancer in about half the cases (4% incremental cancer detection rate). Some of the same authors (Houssami et al. 2014) performed another meta-analysis and found that preoperative MRI use did not improve survival by identifying local or distant recurrences. As such, best practice would deem judicious use of MRI and counselling women of the high sensitivity but reduced specificity associated with this imaging modality.

In 2013, there were approximately 7300 new cases of DCIS diagnosed in the UK – making up almost 15% of all newly diagnosed breast cancer (CancerResearchUK 2015). The prognosis of DCIS is very good – 98% of women are alive at 10 years (Fisher et al. 1999). It is surprising that a 150% increase in CRRM rates has been seen in this good prognosis group, where CRRM is unlikely to have any beneficial impact on survival.

There is a 0.6% annual incidence of CBC following treated DCIS (NSABP B17 – Chapter 2), with 2 out of 3 contralateral breast cancer being invasive disease.

DCIS is often regarded as a "fallout" from the breast screening programmes – the UK age standardised incidence of DCIS has risen form 3.6/100,000 in 1988 to 16.2/100,000 (Francis et al. 2015). It now forms 20% of screen detected neoplastic lesions and as such is an important consideration. My personal experience is that the emotional impact of a screen detected breast cancer is often more severe compared to a symptomatic breast cancer. In those diagnosed with DCIS where a mastectomy is considered, a paradox exists (Kennedy 2006) – women are reassured about DCIS being pre-invasive and non-life threatening yet they are recommended extensive surgery (mastectomy). This particular group may need additional psychosocial support as lessons learnt from the US show that many are undergoing CRRM.

The proposed Manchester Guidelines (Chapter 5) takes into consideration 5 important factors:

- Life expectancy
- Oestrogen receptor status
- Presence of genetic mutation
- Family history
- Oophorectomy status

The guidelines have used 80 years as the expected life expectancy of women diagnosed with Stage 1 breast cancer. Multiple factors will affect life expectancy including existing co-morbidities, adjuvant treatments, geography, and socioeconomic status to name a few. For the purpose of a simple, clinically

useful tool none of these additional factors have been addressed. Therefore it is important that these guidelines and the suggested algorithm are used with caution.

The effect of anti-endocrine treatment on CBC has been evaluated (Chapter 2). There is over 3 decades of experience with various anti-oestrogen agents and it is likely that this is the single most important factor for declining rates of CBC. It is also apparent that aromatase inhibitors confer a larger magnitude of CBC risk reduction compared to SERMs and is commonly the first line choice in post-menopausal women. Given that the majority of breast cancers are hormone receptor positive, I have included this as part of the algorithm in risk calculation. It may be argued that the suggested multiplication of CBC risk by 0.5 in women with ER positive cancers taking anti-oestrogens may be underestimating the risk reduction in those women taking aromatase inhibitors and that multiplication by a factor of 0.6 would be more accurate. I have included the former due to its ease in calculations.

Chapter 4 reviewed the CBC risk in over 1000 women diagnosed with breast cancer over a 30-year period. To my knowledge, this is the largest study to date with the longest follow-up period. The main finding was that women with a *BRCA1/2* mutation had a CBC risk of 2-3% per year for at least 20 years and is in keeping with other published studies. The proposed risk calculator has used the lower value (2%) and suggested multiplying the risk by a factor of 4. It is hoped that future work may be able to provide a more accurate CBC risk for *BRCA1/2* mutation carriers – my own work using SNPs was unable to stratify this risk further.

The inclusion of family history in the algorithm is based on yet unpublished data from Manchester. I used a multiplication factor of 2, as this data seems to suggest an approximate 1% per annum CBC risk amongst those breast cancer patients from the family history clinic who did not harbour a pathogenic genetic mutation. This value is not dissimilar from the literature (Chapter 2) and it is hoped that further evaluation of the Manchester Family History data will be able to support this.

The effect of oophorectomy on CBC risk is complex. My own study found no significant impact of this amongst *BRCA1/2* carriers. In addition, there is limited data in the literature regarding the effect of oophorectomy on CBC risk amongst non-*BRCA1/2* mutation carriers. The potential pitfalls of bias has already been discussed (Chapter 1 and Appendix) and my own study (Chapter 4) was able to clearly show the significance of RRBSO on CBC risk reduction was reduced when accounting for delayed entry of patients.

Despite this, I have suggested a 50% reduction of risk by oophorectomy under the age of 40 years (surgical, natural or chemotherapy induced) in CBC calculation. Much of this is based on the risk reduction estimates from studies on *BRCA1/2* mutation carriers (Domchek et al. 2010; Kauff et al. 2008). In addition, a large population-based data linkage study of 21,067 premenopausal breast cancer patients (Obermair et al. 2014) found that RRBSO reduced breast cancer specific mortality (HR 0.43). Overall, it would seem reasonable to include oophorectomy as a modifier of CBC risk.

The main limitation of the proposed guidelines is that the proposed algorithm is not validated. It is evidence based but lacks the ability to assess whether the numerous factors have a multiplicative relationship. Therefore, a validation study is required to test the algorithm.

A prospective study designed to include the relevant risk factors identified in Chapter 2 may take several decades of follow up to firstly identify CBCs and secondly to evaluate the potential interactions of the risk factors already described.

An alternative is to consider using the Manchester Guidelines in an already established prospective study. The POSH study (Prospective Study of outcomes in Sporadic versus Hereditary breast cancer) recruited over 3000 women aged 18-40 years diagnosed with breast cancer between 2000-2008 (Eccles et al. 2007). This study would be ideal to consider validation studies of these guidelines as these women diagnosed with breast cancer (18-40 year olds) would perhaps

have the longest and most intense follow up to allow us to study the various proposed risk factors.

A recent study (Maishman et al. 2015) evaluated how well one of the available online prognostic tools (PREDICT) performed in estimating survival in women recruited to the POSH study. PREDICT provided accurate long-term (8 and 10 year) survival estimates for these young breast cancer patients. However, at 5-year follow-up, PREDICT both overestimated and underestimated survival in ER positive and ER negative disease respectively.

Collaborative efforts are underway with the Southampton group to evaluate the proposed algorithm amongst the POSH study group with a view to providing some validated data that can be incorporated into an on-line risk calculator in the future.

A recent UK study (Saha and Leff 2016) is the first to report on the clinical application of the Manchester Guidelines. The authors studied 226 women seeking RRM who were discussed at the Mid Essex RRM MDT. They used the algorithm (Chapter 5) to calculate CBC risk in 103 women with breast cancer and would offer surgery if the lifetime risk was >30%. They found a 65% concordance rate of MDT decisions (approval for surgery) in women where the Manchester guidelines predicted an overall lifetime risk in excess of 30%. Using this cut off they could consider declining almost a third of requests for CRRM. This study also used prognostic information from PREDICT to act as a surrogate marker of disease prognosis and found similar results when using this and the Manchester Guidelines.

Chapter 3 evaluated attitudes amongst surgeons towards risk-reducing surgery. UK breast and plastic surgeons need to be better informed as to objective risk estimates for developing CBC. Up to a third of surgeons from both specialties quote higher risks of CBC than the accepted 0.5% per annum. Therefore, surgeons need to concentrate their efforts on ensuring that they are able to provide evidence-based recommendations that is clearly lacking in a proportion of the respondents.

Surgeons consistently rate gene-mutation status and family history as the main risk factors to be considered for CRRM. The literature review has confirmed that these two factors are the most significant factors to be considered. Over 50% of UK surgeons consider histology as an important factor to consider for CRRM. Although, the questionnaire did not specify the histological variants, Australian and US data indicates that lobular carcinoma and lobular carcinoma in situ are predictors for CRRM. An opportunity exists to appraise the surgical fraternity regarding the lack of evidence to suggest that this group of patients are at significant increased risk of CBC.

It is of concern that breast units in the UK do not routinely discuss requests for CRRM in their MDTs. As such, recommendations for this procedure are subject to the various biases that surgeons have ("*I loathe to offer this*" or "*this is a justified part of breast reconstruction")* who are sometimes themselves ill informed about objective risk levels. Utilisation of the Manchester Guidelines has already been shown to scrutinise requests for CRRM in an Essex breast unit and has resulted in almost a third of requests being rejected for lack of objective risk.

Standardising practice throughout the UK could reduce the so-called "post-code lottery" that exists with CRRM. There are unverified reports regarding patients desperate for this procedure "shopping around" various breast units until their request is approved. Best practice should include some consistency on recommendations throughout the country. It may be argued that it is a failing of the counselling process if some of these understandably anxious breast cancer patients are approaching other centres for CRRM.

Anecdotal reports suggest that certain commissioning groups throughout the country may start to restrict breast cancer patients accessing symmetrisation or revisional reconstructive process – deemed "Procedures of limited clinical value" (RCS 2011). Several UK surgeons felt that in the future funding may be an issue particularly where there was no known survival benefit associated with request for CRRM. In the future, some of the health economics studies reviewed

in Chapter 2 may form the basis of UK commissioning groups vetoing funding for CRRMs.

The comparative study (US-Europe) has shown that UK and Dutch surgeons are more similar to American surgeons compared to French and German surgeons. Surgeons from the US had a greater knowledge of cancer genetics compared to the rest of Europe and were more proactive in some of their risk communication methods. In addition, the majority of respondents were female American surgeons compared to all four nations from Europe where the majority of respondents were male surgeons. A combination of both these factors may in part account for a cultural trend amongst American surgeons whereby they respond more favourably to requests of CRRM.

It is likely that the biology of breast cancer is similar in the USA and Europe. Therefore, the excess in numbers of CRRMs performed in the US is likely in part to be patient driven as well as surgeon driven. In 1987, Nancy Regan chose to have a mastectomy despite recommendations for breast conservation for a 7mm tumour – the 3 months following this saw breast conservation rates drop by 25% in the US (Nattinger JAMA 1998). A recent report from Michigan (Sabel and Cin 2016) reviewed the media coverage following American celebrities disclosing their breast cancer diagnosis. They found that US media had a bias towards the reporting of bilateral mastectomy (45%) for the treatment of breast cancer compared to unilateral mastectomy (26%). Whether these women had additional risk factors is unknown, but it is likely that these celebrities have affected mastectomy rates in the same way that the "Angelina Jolie effect" has impacted on genetic referrals. The authors concluded that: "*women today are choosing double mastectomy based on inaccurate information about the risks and benefits. And because they are coming to their surgeon with their mind made up, there's less opportunity for surgeons to educate*".

Since the publication of the Manchester Guidelines for CRRM, several UK breast units have adopted these guidelines (South Manchester, Birmingham, Wolverhampton, Worcester, Mid Essex Units). CRRM remains a contentious issue the body of work presented in this thesis has already made an impact on

clinical practice. It is hoped that future work will attempt to validate these guidelines and ultimately include the algorithm as part of the available on-line prognostic tools. This will ensure that clinicians deliver and patients receive evidence-based recommendations on CBC.

References:

1. Abbott, A., N. Rueth, S. Pappas-Varco, K. Kuntz, E. Kerr, and T. Tuttle. 2011. 'Perceptions of contralateral breast cancer: an overestimation of risk', *Ann Surg Oncol*, 18: 3129-36.
2. ACR. 2014. 'American College of Radiology guidelines for Magnetic Resonance Imaging (MRI) of the breast.
3. Albornoz, C. R., P. B. Bach, B. J. Mehrara, J. J. Disa, A. L. Pusic, C. M. McCarthy, P. G. Cordeiro, and E. Matros. 2013. 'A paradigm shift in U.S. Breast reconstruction: increasing implant rates', *Plast Reconstr Surg*, 131: 15-23.
4. Antoniou, A. C., J. Beesley, L. McGuffog, O. M. Sinilnikova, S. Healey, S. L. Neuhausen, Y. C. Ding, T. R. Rebbeck, J. N. Weitzel, H. T. Lynch, C. Isaacs, P. A. Ganz, G. Tomlinson, O. I. Olopade, F. J. Couch, X. Wang, N. M. Lindor, V. S. Pankratz, P. Radice, S. Manoukian, B. Peissel, D. Zaffaroni, M. Barile, A. Viel, A. Allavena, V. Dall'Olio, P. Peterlongo, C. I. Szabo, M. Zikan, K. Claes, B. Poppe, L. Foretova, P. L. Mai, M. H. Greene, G. Rennert, F. Lejbkowicz, G. Glendon, H. Ozcelik, I. L. Andrulis, M. Thomassen, A. M. Gerdes, L. Sunde, D. Cruger, U. Birk Jensen, M. Caligo, E. Friedman, B. Kaufman, Y. Laitman, R. Milgrom, M. Dubrovsky, S. Cohen, A. Borg, H. Jernstrom, A. Lindblom, J. Rantala, M. Stenmark-Askmalm, B. Melin, K. Nathanson, S. Domchek, A. Jakubowska, J. Lubinski, T. Huzarski, A. Osorio, A. Lasa, M. Duran, M. I. Tejada, J. Godino, J. Benitez, U. Hamann, M. Kriege, N. Hoogerbrugge, R. B. van der Luijt, C. J. van Asperen, P. Devilee, E. J. Meijers-Heijboer, M. J. Blok, C. M. Aalfs, F. Hogervorst, M. Rookus, M. Cook, C. Oliver, D. Frost, D. Conroy, D. G. Evans, F. Lalloo, G. Pichert, R. Davidson, T. Cole, J. Cook, J. Paterson, S. Hodgson, P. J. Morrison, M. E. Porteous, L. Walker, M. J. Kennedy, H. Dorkins, S. Peock, A. K. Godwin, D. Stoppa-Lyonnet, A. de Pauw, S. Mazoyer, V. Bonadona, C. Lasset, H. Dreyfus, D. Leroux, A. Hardouin, P. Berthet, L. Faivre, C. Loustalot, T. Noguchi, H. Sobol, E. Rouleau, C. Nogues, M. Frenay, L. Venat-Bouvet, J. L. Hopper, M. B. Daly, M. B. Terry, E. M. John, S. S. Buys, Y. Yassin, A. Miron, D. Goldgar, C. F. Singer, A. C. Dressler, D. Gschwantler-Kaulich, G. Pfeiler, T. V. Hansen, L. Jonson, B. A. Agnarsson, T. Kirchhoff, K. Offit, V. Devlin, A. Dutra-Clarke, M. Piedmonte, G. C. Rodriguez, K. Wakeley, J. F. Boggess, J. Basil, P. E. Schwartz, S. V. Blank, A. E. Toland, M. Montagna, C. Casella, E. Imyanitov, L. Tihomirova, I. Blanco, C. Lazaro, S. J. Ramus, L. Sucheston, B. Y. Karlan, J. Gross, R. Schmutzler, B. Wappenschmidt, C. Engel, A. Meindl, M. Lochmann, N. Arnold, S. Heidemann, R. Varon-Mateeva, D. Niederacher, C. Sutter, H. Deissler, D. Gadzicki, S. Preisler-Adams, K. Kast, I. Schonbuchner, T. Caldes, M. de la Hoya, K. Aittomaki, H. Nevanlinna, J. Simard, A. B. Spurdle, H. Holland, X. Chen, R. Platte, G. Chenevix-Trench, and D. F. Easton. 2010. 'Common breast cancer susceptibility alleles and the risk of breast cancer for BRCA1 and BRCA2 mutation carriers: implications for risk prediction', *Cancer Res*, 70: 9742-54.

5. Antoniou, A. C., S. Casadei, T. Heikkinen, D. Barrowdale, K. Pylkas, J. Roberts, A. Lee, D. Subramanian, K. De Leeneer, F. Fostira, E. Tomiak, S. L. Neuhausen, Z. L. Teo, S. Khan, K. Aittomaki, J. S. Moilanen, C. Turnbull, S. Seal, A. Mannermaa, A. Kallioniemi, G. J. Lindeman, S. S. Buys, I. L. Andrulis, P. Radice, C. Tondini, S. Manoukian, A. E. Toland, P. Miron, J. N. Weitzel, S. M. Domchek, B. Poppe, K. B. Claes, D. Yannoukakos, P. Concannon, J. L. Bernstein, P. A. James, D. F. Easton, D. E. Goldgar, J. L. Hopper, N. Rahman, P. Peterlongo, H. Nevanlinna, M. C. King, F. J. Couch, M. C. Southey, R. Winqvist, W. D. Foulkes, and M. Tischkowitz. 2014. 'Breast-cancer risk in families with mutations in PALB2', *N Engl J Med*, 371: 497-506.
6. Antoniou, A., P. D. Pharoah, S. Narod, H. A. Risch, J. E. Eyfjord, J. L. Hopper, N. Loman, H. Olsson, O. Johannsson, A. Borg, B. Pasini, P. Radice, S. Manoukian, D. M. Eccles, N. Tang, E. Olah, H. Anton-Culver, E. Warner, J. Lubinski, J. Gronwald, B. Gorski, H. Tulinius, S. Thorlacius, H. Eerola, H. Nevanlinna, K. Syrjakoski, O. P. Kallioniemi, D. Thompson, C. Evans, J. Peto, F. Lalloo, D. G. Evans, and D. F. Easton. 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: 1117-30.
7. Apostolou, P., and F. Fostira. 2013. 'Hereditary breast cancer: the era of new susceptibility genes', *Biomed Res Int*, 2013: 747318.
8. Arrington, A. K., S. L. Jarosek, B. A. Virnig, E. B. Habermann, and T. M. Tuttle. 2009. 'Patient and surgeon characteristics associated with increased use of contralateral prophylactic mastectomy in patients with breast cancer', *Ann Surg Oncol*, 16: 2697-704.
9. Ashfaq, A., L. J. McGhan, B. A. Pockaj, R. J. Gray, S. P. Bagaria, S. A. McLaughlin, W. J. Casey, 3rd, A. M. Rebecca, P. Kreymerman, and N. Wasif. 2014. 'Impact of breast reconstruction on the decision to undergo contralateral prophylactic mastectomy', *Ann Surg Oncol*, 21: 2934-40.
10. Baildam, A. D. 2013. 'Oncoplastic surgery - Standard of care', *EJC Suppl*, 11: 266-7.
11. Basu, N. N., L. Barr, G. L. Ross, and D. G. Evans. 2015. 'Contralateral risk-reducing mastectomy: review of risk factors and risk-reducing strategies', *Int J Surg Oncol*, 2015: 901046.
12. Basu, N. N., S. Ingham, J. Hodson, F. Lalloo, M. Bulman, A. Howell, and D. G. Evans. 2015. 'Risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a 30-year semi-prospective analysis', *Fam Cancer*, 14: 531-8.
13. Basu, N. N., S. Littlechild, L. Barr, G. L. Ross, and D. G. Evans. 2016. 'Attitudes to contralateral risk reducing mastectomy among breast and plastic surgeons in England', *Ann R Coll Surg Engl*, 98: 121-7.
14. Basu, N. N., G. L. Ross, D. G. Evans, and L. Barr. 2015. 'The Manchester guidelines for contralateral risk-reducing mastectomy', *World J Surg Oncol*, 13: 237.
15. Basu, S. K., C. Schwartz, S. G. Fisher, M. M. Hudson, N. Tarbell, A. Muhs, K. J. Marcus, N. Mendenhall, P. Mauch, L. E. Kun, and L. S. Constine.

2008. 'Unilateral and bilateral breast cancer in women surviving pediatric Hodgkin's disease', *Int J Radiat Oncol Biol Phys*, 72: 34-40.
16. Baxter, N. N., B. A. Virnig, S. B. Durham, and T. M. Tuttle. 2004. 'Trends in the treatment of ductal carcinoma in situ of the breast', *J Natl Cancer Inst*, 96: 443-8.
17. Beesley, H., C. Holcombe, S. L. Brown, and P. Salmon. 2013. 'Risk, worry and cosmesis in decision-making for contralateral risk-reducing mastectomy: analysis of 60 consecutive cases in a specialist breast unit', *Breast*, 22: 179-84.
18. Beggs, A. D., and M. P. Dilworth. 2015. 'Surgery in the era of the 'omics revolution', *Br J Surg*, 102: e29-40.
19. Bernstein, J. L., R. H. Lapinski, S. S. Thakore, J. T. Doucette, and W. D. Thompson. 2003. 'The descriptive epidemiology of second primary breast cancer', *Epidemiology*, 14: 552-8.
20. Bijker, N., P. Meijnen, J. L. Peterse, J. Bogaerts, I. Van Hoorebeeck, J. P. Julien, M. Gennaro, P. Rouanet, A. Avril, I. S. Fentiman, H. Bartelink, and E. J. Rutgers. 2006. 'Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853--a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group', *J Clin Oncol*, 24: 3381-7.
21. Bordeleau, L., S. Panchal, and P. Goodwin. 2010. 'Prognosis of BRCA-associated breast cancer: a summary of evidence', *Breast Cancer Res Treat*, 119: 13-24.
22. Borzekowski, D. L., Y. Guan, K. C. Smith, L. H. Erby, and D. L. Roter. 2014. 'The Angelina effect: immediate reach, grasp, and impact of going public', *Genet Med*, 16: 516-21.
23. Boughey, J. C., T. L. Hoskin, A. C. Degnim, T. A. Sellers, J. L. Johnson, M. J. Kasner, L. C. Hartmann, and M. H. Frost. 2010. 'Contralateral prophylactic mastectomy is associated with a survival advantage in high-risk women with a personal history of breast cancer', *Ann Surg Oncol*, 17: 2702-9.
24. Boughey, J. C., T. L. Hoskin, L. C. Hartmann, J. L. Johnson, S. R. Jacobson, A. C. Degnim, and M. H. Frost. 2015. 'Impact of reconstruction and reoperation on long-term patient-reported satisfaction after contralateral prophylactic mastectomy', *Ann Surg Oncol*, 22: 401-8.
25. Brennan, M. E., N. Houssami, S. Lord, P. Macaskill, L. Irwig, J. M. Dixon, R. M. Warren, and S. Ciatto. 2009. 'Magnetic resonance imaging screening of the contralateral breast in women with newly diagnosed breast cancer: systematic review and meta-analysis of incremental cancer detection and impact on surgical management', *J Clin Oncol*, 27: 5640-9.
26. Cemal, Y., C. R. Albornoz, J. J. Disa, C. M. McCarthy, B. J. Mehrara, A. L. Pusic, P. G. Cordeiro, and E. Matros. 2013. 'A paradigm shift in U.S. breast reconstruction: Part 2. The influence of changing mastectomy patterns on reconstructive rate and method', *Plast Reconstr Surg*, 131: 320e-6e.

27. Chai, X., S. Domchek, N. Kauff, T. Rebbeck, and J. Chen. 2015. 'RE: Breast Cancer Risk After Salpingo-Oophorectomy in Healthy BRCA1/2 Mutation Carriers: Revisiting the Evidence for Risk Reduction', *J Natl Cancer Inst*, 107.
28. Chappuis, P. O., L. Kapusta, L. R. Begin, N. Wong, J. S. Brunet, S. A. Narod, J. Slingerland, and W. D. Foulkes. 2000. 'Germline BRCA1/2 mutations and p27(Kip1) protein levels independently predict outcome after breast cancer', *J Clin Oncol*, 18: 4045-52.
29. Chenevix-Trench, G., R. L. Milne, A. C. Antoniou, F. J. Couch, D. F. Easton, and D. E. Goldgar. 2007. 'An international initiative to identify genetic modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: the Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (CIMBA)', *Breast Cancer Res*, 9: 104.
30. Chung, A., K. Huynh, C. Lawrence, M. S. Sim, and A. Giuliano. 2012. 'Comparison of patient characteristics and outcomes of contralateral prophylactic mastectomy and unilateral total mastectomy in breast cancer patients', *Ann Surg Oncol*, 19: 2600-6.
31. Ciatto, S, G Miccinesi, and M Zappa. 2004. 'Prognostic impact of the early detection of metachronous contralateral breast cancer', *Eur J Cancer*, 40: 1496-501.
32. Cloud, A. J., A. Thai, Y. Liao, and M. B. Terry. 2015. 'The impact of cancer prevention guideline adherence on overall mortality in a high-risk cohort of women from the New York site of the Breast Cancer Family Registry', *Breast Cancer Res Treat*, 149: 537-46.
33. Concannon, P., R. W. Haile, A. L. Borresen-Dale, B. S. Rosenstein, R. A. Gatti, S. N. Teraoka, T. A. Diep, L. Jansen, D. P. Atencio, B. Langholz, M. Capanu, X. Liang, C. B. Begg, D. C. Thomas, L. Bernstein, J. H. Olsen, K. E. Malone, C. F. Lynch, H. Anton-Culver, J. L. Bernstein, Cancer Women's Environment, and Group Radiation Epidemiology Study Collaborative. 2008. 'Variants in the ATM gene associated with a reduced risk of contralateral breast cancer', *Cancer Res*, 68: 6486-91.
34. Crosby, M. A., P. B. Garvey, J. C. Selber, D. M. Adelman, J. M. Sacks, M. T. Villa, H. Y. Lin, S. J. Park, and D. P. Baumann. 2011. 'Reconstructive outcomes in patients undergoing contralateral prophylactic mastectomy', *Plast Reconstr Surg*, 128: 1025-33.
35. Cuzick, J., I. Sestak, M. Baum, A. Buzdar, A. Howell, M. Dowsett, J. F. Forbes, and Atac Latte investigators. 2010. 'Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial', *Lancet Oncol*, 11: 1135-41.
36. Cuzick, J., I. Sestak, J. F. Forbes, M. Dowsett, J. Knox, S. Cawthorn, C. Saunders, N. Roche, R. E. Mansel, G. von Minckwitz, B. Bonanni, T. Palva, and A. Howell. 2014. 'Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial', *Lancet*, 383: 1041-8.
37. Da Silva, L., and S. R. Lakhani. 2010. 'Pathology of hereditary breast cancer', *Mod Pathol*, 23 Suppl 2: S46-51.
38. De Felice, F., C. Marchetti, A. Musella, I. Palaia, G. Perniola, D. Musio, L. Muzii, V. Tombolini, and P. Benedetti Panici. 2015. 'Bilateral risk-

reduction mastectomy in BRCA1 and BRCA2 mutation carriers: a meta-analysis', *Ann Surg Oncol*, 22: 2876-80.

39. Den Heijer, M., C. J. van Asperen, H. Harris, I. Nippert, J. Schmidtke, A. D. Bouhnik, C. Julian-Reynier, D. G. Evans, and A. Tibben. 2013. 'International variation in physicians' attitudes towards prophylactic mastectomy - comparison between France, Germany, the Netherlands and the United Kingdom', *Eur J Cancer*, 49: 2798-805.
40. Deshmukh, A. A., S. B. Cantor, M. A. Crosby, W. Dong, Y. Shen, I. Bedrosian, S. K. Peterson, P. A. Parker, and A. M. Brewster. 2014. 'Cost of contralateral prophylactic mastectomy', *Ann Surg Oncol*, 21: 2823-30.
41. Domchek, S. M., T. M. Friebel, C. F. Singer, D. G. Evans, H. T. Lynch, C. Isaacs, J. E. Garber, S. L. Neuhausen, E. Matloff, R. Eeles, G. Pichert, L. Van t'veer, N. Tung, J. N. Weitzel, F. J. Couch, W. S. Rubinstein, P. A. Ganz, M. B. Daly, O. I. Olopade, G. Tomlinson, J. Schildkraut, J. L. Blum, and T. R. Rebbeck. 2010. 'Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality', *JAMA*, 304: 967-75.
42. Dores, G. M., C. Metayer, R. E. Curtis, C. F. Lynch, E. A. Clarke, B. Glimelius, H. Storm, E. Pukkala, F. E. van Leeuwen, E. J. Holowaty, M. Andersson, T. Wiklund, T. Joensuu, M. B. van't Veer, M. Stovall, M. Gospodarowicz, and L. B. Travis. 2002. 'Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years', *J Clin Oncol*, 20: 3484-94.
43. Easton, D. F., F. Lesueur, B. Decker, K. Michailidou, J. Li, J. Allen, C. Luccarini, K. A. Pooley, M. Shah, M. K. Bolla, Q. Wang, J. Dennis, J. Ahmad, E. R. Thompson, F. Damiola, M. Pertesi, C. Voegele, N. Mebirouk, N. Robinot, G. Durand, N. Forey, R. N. Luben, S. Ahmed, K. Aittomaki, H. Anton-Culver, V. Arndt, Group Australian Ovarian Cancer Study, C. Baynes, M. W. Beckman, J. Benitez, D. Van Den Berg, W. J. Blot, N. V. Bogdanova, S. E. Bojesen, H. Brenner, J. Chang-Claude, K. S. Chia, J. Y. Choi, D. M. Conroy, A. Cox, S. S. Cross, K. Czene, H. Darabi, P. Devilee, M. Eriksson, P. A. Fasching, J. Figueroa, H. Flyger, F. Fostira, M. Garcia-Closas, G. G. Giles, G. Glendon, A. Gonzalez-Neira, P. Guenel, C. A. Haiman, P. Hall, S. N. Hart, M. Hartman, M. J. Hooning, C. N. Hsiung, H. Ito, A. Jakubowska, P. A. James, E. M. John, N. Johnson, M. Jones, M. Kabisch, D. Kang, Investigators kConFab, V. M. Kosma, V. Kristensen, D. Lambrechts, N. Li, Investigators Lifepool, A. Lindblom, J. Long, A. Lophatananon, J. Lubinski, A. Mannermaa, S. Manoukian, S. Margolin, K. Matsuo, A. Meindl, G. Mitchell, K. Muir, Nbcs Investigators, I. Nevelsteen, A. van den Ouweland, P. Peterlongo, S. Y. Phuah, K. Pylkas, S. M. Rowley, S. Sangrajrang, R. K. Schmutzler, C. Y. Shen, X. O. Shu, M. C. Southey, H. Surowy, A. Swerdlow, S. H. Teo, R. A. Tollenaar, I. Tomlinson, D. Torres, T. Truong, C. Vachon, S. Verhoef, M. Wong-Brown, W. Zheng, Y. Zheng, H. Nevanlinna, R. J. Scott, I. L. Andrulis, A. H. Wu, J. L. Hopper, F. J. Couch, R. Winqvist, B. Burwinkel, E. J. Sawyer, M. K. Schmidt, A. Rudolph, T. Dork, H. Brauch, U. Hamann, S. L. Neuhausen, R. L. Milne, O. Fletcher, P. D. Pharoah, I. G. Campbell, A. M. Dunning, F. Le Calvez-Kelm, D. E. Goldgar, S. V.

Tavtigian, and G. Chenevix-Trench. 2016. 'No evidence that protein truncating variants in BRIP1 are associated with breast cancer risk: implications for gene panel testing', *J Med Genet*, 53: 298-309.

44. EBCTCG. 1998. 'Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group', *Lancet*, 351: 1451-67.
45. Early Breast Cancer Trialists' Collaborative Group (EBCTG). 2005. 'Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials', *Lancet*, 365: 1687-717.
46. Eccles, B. K., E. Copson, T. Maishman, J. E. Abraham, and D. M. Eccles. 2015. 'Understanding of BRCA VUS genetic results by breast cancer specialists', *BMC Cancer*, 15: 936.
47. Eccles, D., S. Gerty, P. Simmonds, V. Hammond, S. Ennis, D. G. Altman, and Posh steering group. 2007. 'Prospective study of Outcomes in Sporadic versus Hereditary breast cancer (POSH): study protocol', *BMC Cancer*, 7: 160.
48. Eccles, S. A., E. O. Aboagye, S. Ali, A. S. Anderson, J. Armes, F. Berditchevski, J. P. Blaydes, K. Brennan, N. J. Brown, H. E. Bryant, N. J. Bundred, J. M. Burchell, A. M. Campbell, J. S. Carroll, R. B. Clarke, C. E. Coles, G. J. Cook, A. Cox, N. J. Curtin, L. V. Dekker, S. Silva Idos, S. W. Duffy, D. F. Easton, D. M. Eccles, D. R. Edwards, J. Edwards, D. Evans, D. F. Fenlon, J. M. Flanagan, C. Foster, W. M. Gallagher, M. Garcia-Closas, J. M. Gee, A. J. Gescher, V. Goh, A. M. Groves, A. J. Harvey, M. Harvie, B. T. Hennessy, S. Hiscox, I. Holen, S. J. Howell, A. Howell, G. Hubbard, N. Hulbert-Williams, M. S. Hunter, B. Jasani, L. J. Jones, T. J. Key, C. C. Kirwan, A. Kong, I. H. Kunkler, S. P. Langdon, M. O. Leach, D. J. Mann, J. F. Marshall, L. Martin, S. G. Martin, J. E. Macdougall, D. W. Miles, W. R. Miller, J. R. Morris, S. M. Moss, P. Mullan, R. Natrajan, J. P. O'Connor, R. O'Connor, C. Palmieri, P. D. Pharoah, E. A. Rakha, E. Reed, S. P. Robinson, E. Sahai, J. M. Saxton, P. Schmid, M. J. Smalley, V. Speirs, R. Stein, J. Stingl, C. H. Streuli, A. N. Tutt, G. Velikova, R. A. Walker, C. J. Watson, K. J. Williams, L. S. Young, and A. M. Thompson. 2013. 'Critical research gaps and translational priorities for the successful prevention and treatment of breast cancer', *Breast Cancer Res*, 15: R92.
49. Eck, D. L., G. Perdikis, B. Rawal, S. Bagaria, and S. A. McLaughlin. 2014. 'Incremental risk associated with contralateral prophylactic mastectomy and the effect on adjuvant therapy', *Ann Surg Oncol*, 21: 3297-303.
50. Evans, D. G., J. Barwell, D. M. Eccles, A. Collins, L. Izatt, C. Jacobs, A. Donaldson, A. F. Brady, A. Cuthbert, R. Harrison, S. Thomas, A. Howell, Z. Miedzybrodzka, and A. Murray. 2014. 'The Angelina Jolie effect: how high celebrity profile can have a major impact on provision of cancer related services', *Breast Cancer Res*, 16: 442.
51. Evans, D. G., J. Graham, S. O'Connell, S. Arnold, and D. Fitzsimmons. 2013. 'Familial breast cancer: summary of updated NICE guidance', *BMJ*, 346: f3829.

52. Evans, D. G., and A. Howell. 2015. 'Can the breast screening appointment be used to provide risk assessment and prevention advice?', *Breast Cancer Res*, 17: 84.
53. Evans, D. G., S. L. Ingham, A. Baildam, G. L. Ross, F. Lalloo, I. Buchan, and A. Howell. 2013. 'Contralateral mastectomy improves survival in women with BRCA1/2-associated breast cancer', *Breast Cancer Res Treat*, 140: 135-42.
54. Evans, D. G., S. L. Ingham, I. Buchan, E. R. Woodward, H. Byers, A. Howell, E. R. Maher, W. G. Newman, and F. Lalloo. 2013. 'Increased rate of phenocopies in all age groups in BRCA1/BRCA2 mutation kindred, but increased prospective breast cancer risk is confined to BRCA2 mutation carriers', *Cancer Epidemiol Biomarkers Prev*, 22: 2269-76.
55. Evans, D. G., A. Moran, R. Hartley, J. Dawson, B. Bulman, F. Knox, A. Howell, and F. Lalloo. 2010. 'Long-term outcomes of breast cancer in women aged 30 years or younger, based on family history, pathology and BRCA1/BRCA2/TP53 status', *Br J Cancer*, 102: 1091-8.
56. Evans, D. G., A. Shenton, E. Woodward, F. Lalloo, A. Howell, and E. R. Maher. 2008. 'Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family', *BMC Cancer*, 8: 155.
57. Evans, D. G., J. Wisely, T. Clancy, F. Lalloo, M. Wilson, R. Johnson, J. Duncan, L. Barr, A. Gandhi, and A. Howell. 2015. 'Longer term effects of the Angelina Jolie effect: increased risk-reducing mastectomy rates in BRCA carriers and other high-risk women', *Breast Cancer Res*, 17: 143.
58. Evans, G. R., and F. Lalloo. 2010. 'Development of a scoring system to screen for BRCA1/2 mutations', *Methods Mol Biol*, 653: 237-47.
59. FH01. 2010. 'Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study', *Lancet Oncol*, 11: 1127-34.
60. Fisher, B., J. Dignam, N. Wolmark, E. Mamounas, J. Costantino, W. Poller, E. R. Fisher, D. L. Wickerham, M. Deutsch, R. Margolese, N. Dimitrov, and M. Kavanah. 1998. 'Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17', *J Clin Oncol*, 16: 441-52.
61. Fisher, E. R., J. Dignam, E. Tan-Chiu, J. Costantino, B. Fisher, S. Paik, and N. Wolmark. 1999. 'Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17: intraductal carcinoma', *Cancer*, 86: 429-38.
62. Fisher, E. R., S. R. Land, R. S. Saad, B. Fisher, D. L. Wickerham, M. Wang, J. P. Costantino, and N. Wolmark. 2007. 'Pathologic variables predictive of breast events in patients with ductal carcinoma in situ', *Am J Clin Pathol*, 128: 86-91.
63. Forbes, J. F., I. Sestak, A. Howell, B. Bonanni, N. Bundred, C. Levy, G. von Minckwitz, W. Eiermann, P. Neven, M. Stierer, C. Holcombe, R. E.

Coleman, L. Jones, I. Ellis, J. Cuzick, and Ibis-Ii investigators. 2016. 'Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial', *Lancet*, 387: 866-73.

64. Ford, D., D. F. Easton, M. Stratton, S. Narod, D. Goldgar, P. Devilee, D. T. Bishop, B. Weber, G. Lenoir, J. Chang-Claude, H. Sobol, M. D. Teare, J. Struewing, A. Arason, S. Scherneck, J. Peto, T. R. Rebbeck, P. Tonin, S. Neuhausen, R. Barkardottir, J. Eyfjord, H. Lynch, B. A. Ponder, S. A. Gayther, M. Zelada-Hedman, and et al. 1998. 'Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium', *Am J Hum Genet*, 62: 676-89.
65. Francis, A., J. Thomas, L. Fallowfield, M. Wallis, J. M. Bartlett, C. Brookes, T. Roberts, S. Pirrie, C. Gaunt, J. Young, L. Billingham, D. Dodwell, A. Hanby, S. E. Pinder, A. Evans, M. Reed, V. Jenkins, L. Matthews, M. Wilcox, P. Fairbrother, S. Bowden, and D. Rea. 2015. 'Addressing overtreatment of screen detected DCIS; the LORIS trial', *Eur J Cancer*, 51: 2296-303.
66. Frost, M. H., J. M. Slezak, N. V. Tran, C. I. Williams, J. L. Johnson, J. E. Woods, P. M. Petty, J. H. Donohue, C. S. Grant, J. A. Sloan, T. A. Sellers, and L. C. Hartmann. 2005. 'Satisfaction after contralateral prophylactic mastectomy: the significance of mastectomy type, reconstructive complications, and body appearance', *J Clin Oncol*, 23: 7849-56.
67. Gao, X., S. G. Fisher, and B. Emami. 2003. 'Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: a population-based study', *Int J Radiat Oncol Biol Phys*, 56: 1038-45.
68. Gianni, L., U. Dafni, R. D. Gelber, E. Azambuja, S. Muehlbauer, A. Goldhirsch, M. Untch, I. Smith, J. Baselga, C. Jackisch, D. Cameron, M. Mano, J. L. Pedrini, A. Veronesi, C. Mendiola, A. Pluzanska, V. Semiglazov, E. Vrdoljak, M. J. Eckart, Z. Shen, G. Skiadopoulos, M. Procter, K. I. Pritchard, M. J. Piccart-Gebhart, and R. Bell. 2011. 'Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial', *Lancet Oncol*, 12: 236-44.
69. Goss, P. E., J. N. Ingle, J. E. Ales-Martinez, A. M. Cheung, R. T. Chlebowski, J. Wactawski-Wende, A. McTiernan, J. Robbins, K. C. Johnson, L. W. Martin, E. Winquist, G. E. Sarto, J. E. Garber, C. J. Fabian, P. Pujol, E. Maunsell, P. Farmer, K. A. Gelmon, D. Tu, H. Richardson, and Ncic Ctg Map Study Investigators. 2011. 'Exemestane for breast-cancer prevention in postmenopausal women', *N Engl J Med*, 364: 2381-91.
70. Goss, P. E., J. N. Ingle, K. I. Pritchard, M. J. Ellis, G. W. Sledge, G. T. Budd, M. Rabaglio, R. H. Ansari, D. B. Johnson, R. Tozer, D. P. D'Souza, H. Chalchal, S. Spadafora, V. Stearns, E. A. Perez, P. E. Liedke, I. Lang, C. Elliott, K. A. Gelmon, J. A. Chapman, and L. E. Shepherd. 2013. 'Exemestane versus anastrozole in postmenopausal women with

early breast cancer: NCIC CTG MA.27--a randomized controlled phase III trial', *J Clin Oncol*, 31: 1398-404.

71. Graeser, M. K., C. Engel, K. Rhiem, D. Gadzicki, U. Bick, K. Kast, U. G. Froster, B. Schlehe, A. Bechtold, N. Arnold, S. Preisler-Adams, C. Nestle-Kraemling, M. Zaino, M. Loeffler, M. Kiechle, A. Meindl, D. Varga, and R. K. Schmutzler. 2009. 'Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers', *J Clin Oncol*, 27: 5887-92.
72. Grann, V. R., P. R. Patel, J. S. Jacobson, E. Warner, D. F. Heitjan, M. Ashby-Thompson, D. L. Hershman, and A. I. Neugut. 2011. 'Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers', *Breast Cancer Res Treat*, 125: 837-47.
73. Gronwald, J., A. Robidoux, C. Kim-Sing, N. Tung, H. T. Lynch, W. D. Foulkes, S. Manoukian, P. Ainsworth, S. L. Neuhausen, R. Demsky, A. Eisen, C. F. Singer, H. Saal, L. Senter, C. Eng, J. Weitzel, P. Moller, D. M. Gilchrist, O. Olopade, O. Ginsburg, P. Sun, T. Huzarski, J. Lubinski, and S. A. Narod. 2014. 'Duration of tamoxifen use and the risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers', *Breast Cancer Res Treat*, 146: 421-7.
74. Guth, U., M. E. Myrick, C. T. Viehl, W. P. Weber, A. M. Lardi, and S. M. Schmid. 2012. 'Increasing rates of contralateral prophylactic mastectomy - a trend made in USA?', *Eur J Surg Oncol*, 38: 296-301.
75. Haffty, B. G., E. Harrold, A. J. Khan, P. Pathare, T. E. Smith, B. C. Turner, P. M. Glazer, B. Ward, D. Carter, E. Matloff, A. E. Bale, and M. Alvarez-Franco. 2002. 'Outcome of conservatively managed early-onset breast cancer by BRCA1/2 status', *Lancet*, 359: 1471-7.
76. Han, E., N. Johnson, M. Glissmeyer, T. Wagie, B. Carey, T. DelaMelena, and J. Nelson. 2011. 'Increasing incidence of bilateral mastectomies: the patient perspective', *Am J Surg*, 201: 615-8.
77. Hartman, M., K. Czene, M. Reilly, J. Adolfsson, J. Bergh, H. O. Adami, P. W. Dickman, and P. Hall. 2007. 'Incidence and prognosis of synchronous and metachronous bilateral breast cancer', *J Clin Oncol*, 25: 4210-6.
78. Hartmann, L. C., and N. M. Lindor. 2016. 'The Role of Risk-Reducing Surgery in Hereditary Breast and Ovarian Cancer', *N Engl J Med*, 374: 454-68.
79. Harvey, J., Clark, G., Osborne, C., and D.C. Allred. 'Estrogen receptor status by immunohistochemistry is superior to ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer', *J Clin Oncol*, 17(5):1474-81.
80. Hawley, S. T., R. Jagsi, M. Morrow, N. K. Janz, A. Hamilton, J. J. Graff, and S. J. Katz. 2014. 'Social and Clinical Determinants of Contralateral Prophylactic Mastectomy', *JAMA Surg*.
81. Heemskerk-Gerritsen, B. A., M. A. Rookus, C. M. Aalfs, M. G. Ausems, J. M. Collee, L. Jansen, C. M. Kets, K. B. Keymeulen, L. B. Koppert, H. E. Meijers-Heijboer, T. M. Mooij, R. A. Tollenaar, H. F. Vasen, M. J. Hooning, and C. Seynaeve. 2015. 'Improved overall survival after contralateral risk-reducing mastectomy in BRCA1/2 mutation

carriers with a history of unilateral breast cancer: a prospective analysis', *Int J Cancer*, 136: 668-77.

82. Heemskerk-Gerritsen, B. A., C. Seynaeve, C. J. van Asperen, M. G. Ausems, J. M. Collee, H. C. van Doorn, E. B. Gomez Garcia, C. M. Kets, F. E. van Leeuwen, H. E. Meijers-Heijboer, M. J. Mourits, T. A. van Os, H. F. Vasen, S. Verhoef, M. A. Rookus, and M. J. Hooning. 2015. 'Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction', *J Natl Cancer Inst*, 107.
83. Herrinton, L. J., W. E. Barlow, O. Yu, A. M. Geiger, J. G. Elmore, M. B. Barton, E. L. Harris, S. Rolnick, R. Pardee, G. Husson, A. Macedo, and S. W. Fletcher. 2005. 'Efficacy of prophylactic mastectomy in women with unilateral breast cancer: a cancer research network project', *J Clin Oncol*, 23: 4275-86.
84. Houn, F., K. J. Helzlsouer, N. B. Friedman, and M. E. Stefanek. 1995. 'The practice of prophylactic mastectomy: a survey of Maryland surgeons', *Am J Public Health*, 85: 801-5.
85. Houssami, N., S. Ciatto, P. Macaskill, S. J. Lord, R. M. Warren, J. M. Dixon, and L. Irwig. 2008. 'Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer', *J Clin Oncol*, 26: 3248-58.
86. Houssami, N., R. Turner, P. Macaskill, L. W. Turnbull, D. R. McCready, T. M. Tuttle, N. Vapiwala, and L. J. Solin. 2014. 'An individual person data meta-analysis of preoperative magnetic resonance imaging and breast cancer recurrence', *J Clin Oncol*, 32: 392-401.
87. Howell, A., A. S. Anderson, R. B. Clarke, S. W. Duffy, D. G. Evans, M. Garcia-Closas, A. J. Gescher, T. J. Key, J. M. Saxton, and M. N. Harvie. 2014. 'Risk determination and prevention of breast cancer', *Breast Cancer Res*, 16: 446.
88. Howell, A., J. Cuzick, M. Baum, A. Buzdar, M. Dowsett, J. F. Forbes, G. Hoctin-Boes, J. Houghton, G. Y. Locker, J. S. Tobias, and Atac Trialists' Group. 2005. 'Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer', *Lancet*, 365: 60-2.
89. Huang, K. T., T. Mikeska, J. Li, E. A. Takano, E. K. Millar, P. H. Graham, S. E. Boyle, I. G. Campbell, T. P. Speed, A. Dobrovic, and S. B. Fox. 2015. 'Assessment of DNA methylation profiling and copy number variation as indications of clonal relationship in ipsilateral and contralateral breast cancers to distinguish recurrent breast cancer from a second primary tumour', *BMC Cancer*, 15: 669.
90. Hurley. 2015. 'Why more women are ignoring their doctors and getting double mastectomies'.
91. Ingham, S. L., J. Warwick, H. Byers, F. Lalloo, W. G. Newman, and D. G. Evans. 2013. 'Is multiple SNP testing in BRCA2 and BRCA1 female carriers ready for use in clinical practice? Results from a large Genetic Centre in the UK', *Clin Genet*, 84: 37-42.
92. Jeevan, R., D. A. Cromwell, J. P. Browne, C. M. Caddy, J. Pereira, C. Sheppard, K. Greenaway, and J. H. van der Meulen. 2014. 'Findings of

a national comparative audit of mastectomy and breast reconstruction surgery in England', *J Plast Reconstr Aesthet Surg*, 67: 1333-44.

93. Julian-Reynier, C., J. Mancini, E. Mouret-Fourme, M. Gauthier-Villars, V. Bonadona, P. Berthet, J. P. Fricker, O. Caron, E. Luporsi, and C. Nogues. 2011. 'Cancer risk management strategies and perceptions of unaffected women 5 years after predictive genetic testing for BRCA1/2 mutations', *Eur J Hum Genet*, 19: 500-6.
94. Julien, J. P., N. Bijker, I. S. Fentiman, J. L. Peterse, V. Delledonne, P. Rouanet, A. Avril, R. Sylvester, F. Mignolet, H. Bartelink, and J. A. Van Dongen. 2000. 'Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group', *Lancet*, 355: 528-33.
95. Kappel, S., E. Janschek, B. Wolf, M. Rudas, B. Teleky, R. Jakesz, and D. Kandioler. 2015. 'TP53 germline mutation may affect response to anticancer treatments: analysis of an intensively treated Li-Fraumeni family', *Breast Cancer Res Treat*, 151: 671-8.
96. Katz, S. J., and M. Morrow. 2013. 'Contralateral prophylactic mastectomy for breast cancer: addressing peace of mind', *JAMA*, 310: 793-4.
97. Kauff, N. D., S. M. Domchek, T. M. Friebel, M. E. Robson, J. Lee, J. E. Garber, C. Isaacs, D. G. Evans, H. Lynch, R. A. Eeles, S. L. Neuhausen, M. B. Daly, E. Matloff, J. L. Blum, P. Sabbatini, R. R. Barakat, C. Hudis, L. Norton, K. Offit, and T. R. Rebbeck. 2008. 'Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study', *J Clin Oncol*, 26: 1331-7.
98. Kennedy. 2006. ''I haven't had breast cancer but I've had a mastectomy anyway': do women with ductal carcinoma in situ have appearance concerns?', *Breast Cancer Res*, 8: 41.
99. King, T. A., M. Pilewskie, S. Muhsen, S. Patil, S. K. Mautner, A. Park, S. Oskar, E. Guerini-Rocco, C. Boafo, J. C. Gooch, M. De Brot, J. S. Reis-Filho, M. Morrogh, V. P. Andrade, R. A. Sakr, and M. Morrow. 2015. 'Lobular Carcinoma in Situ: A 29-Year Longitudinal Experience Evaluating Clinicopathologic Features and Breast Cancer Risk', *J Clin Oncol*, 33: 3945-52.
100. Kriege, M., C. T. Brekelmans, C. Boetes, P. E. Besnard, H. M. Zonderland, I. M. Obdeijn, R. A. Manoliu, T. Kok, H. Peterse, M. M. Tilanus-Linthorst, S. H. Muller, S. Meijer, J. C. Oosterwijk, L. V. Beex, R. A. Tollenaar, H. J. de Koning, E. J. Rutgers, J. G. Klijn, and Group Magnetic Resonance Imaging Screening Study. 2004. 'Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition', *N Engl J Med*, 351: 427-37.
101. Kriege, M., A. Hollestelle, A. Jager, P. E. Huijts, E. M. Berns, A. M. Sieuwerts, M. E. Meijer-van Gelder, J. M. Collee, P. Devilee, M. J. Hooning, J. W. Martens, and C. Seynaeve. 2014. 'Survival and contralateral breast cancer in CHEK2 1100delC breast cancer

patients: impact of adjuvant chemotherapy', *Br J Cancer*, 111: 1004-13.
102. Kuwajerwala, N. K., N. S. Dekhne, P. A. Pentiak, D. Fend, R. E. Callahan, M. Amine, V. Lucia, and J. Swartz. 2013. 'Sentinel lymph node biopsy in contralateral prophylactic mastectomy: are we overtreating? Experience at a tertiary care hospital', *Clin Breast Cancer*, 13: 287-91.
103. LaingBuisson. 2013. 'Laing's healthcare market review 2012/13. London: LaingBuisson.'.
104. Lalloo, F., A. Baildam, A. Brain, P. Hopwood, D. G. Evans, and A. Howell. 2000. 'A protocol for preventative mastectomy in women with an increased lifetime risk of breast cancer', *Eur J Surg Oncol*, 26: 711-3.
105. Lalloo, F., and D. G. Evans. 2012. 'Familial breast cancer', *Clin Genet*, 82: 105-14.
106. Lalloo, F., J. Varley, D. Ellis, A. Moran, L. O'Dair, P. Pharoah, D. G. Evans, and Group Early Onset Breast Cancer Study. 2003. 'Prediction of pathogenic mutations in patients with early-onset breast cancer by family history', *Lancet*, 361: 1101-2.
107. Langlands, F., J. White, O. Kearins, S. Cheung, R. Burns, K. Horgan, N. Sharma, and D. Dodwell. 2016. 'Contralateral breast cancer: incidence according to ductal or lobular phenotype of the primary', *Clin Radiol*, 71: 159-63.
108. Leach, M. O., C. R. Boggis, A. K. Dixon, D. F. Easton, R. A. Eeles, D. G. Evans, F. J. Gilbert, I. Griebsch, R. J. Hoff, P. Kessar, S. R. Lakhani, S. M. Moss, A. Nerurkar, A. R. Padhani, L. J. Pointon, D. Thompson, R. M. Warren, and Maribs study group. 2005. 'Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS)', *Lancet*, 365: 1769-78.
109. Leff, D. R., C. Ho, H. Thomas, R. Daniels, L. Side, F. Lambert, J. Knight, M. Griffiths, M. Banwell, J. Aitken, G. Clayton, S. Dua, A. Shaw, S. Smith, and V. Ramakrishnan. 2015. 'A multidisciplinary team approach minimises prophylactic mastectomy rates', *Eur J Surg Oncol*.
110. Lizarraga, I. M., S. L. Sugg, R. J. Weigel, and C. E. Scott-Conner. 2013. 'Review of risk factors for the development of contralateral breast cancer', *Am J Surg*, 206: 704-8.
111. Lostumbo, L., N. E. Carbine, and J. Wallace. 2010. 'Prophylactic mastectomy for the prevention of breast cancer', *Cochrane Database Syst Rev*: CD002748.
112. Maddams, J., D. Brewster, A. Gavin, J. Steward, J. Elliott, M. Utley, and H. Moller. 2009. 'Cancer prevalence in the United Kingdom: estimates for 2008', *Br J Cancer*, 101: 541-7.
113. Maishman, T., E. Copson, L. Stanton, S. Gerty, E. Dicks, L. Durcan, G. C. Wishart, P. Pharoah, Posh Steering Group, and D. Eccles. 2015. 'An evaluation of the prognostic model PREDICT using the POSH cohort of women aged 40 years at breast cancer diagnosis', *Br J Cancer*, 112: 983-91.
114. Malone, K. E., C. B. Begg, R. W. Haile, A. Borg, P. Concannon, L. Tellhed, S. Xue, S. Teraoka, L. Bernstein, M. Capanu, A. S. Reiner, E. R. Riedel, D.

C. Thomas, L. Mellemkjaer, C. F. Lynch, J. D. Boice, Jr., H. Anton-Culver, and J. L. Bernstein. 2010. 'Population-based study of the risk of second primary contralateral breast cancer associated with carrying a mutation in BRCA1 or BRCA2', *J Clin Oncol*, 28: 2404-10.

115. Mansel, R. E., L. Fallowfield, M. Kissin, A. Goyal, R. G. Newcombe, J. M. Dixon, C. Yiangou, K. Horgan, N. Bundred, I. Monypenny, D. England, M. Sibbering, T. I. Abdullah, L. Barr, U. Chetty, D. H. Sinnett, A. Fleissig, D. Clarke, and P. J. Ell. 2006. 'Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial', *J Natl Cancer Inst*, 98: 599-609.
116. Masciari, S., D. A. Dillon, M. Rath, M. Robson, J. N. Weitzel, J. Balmana, S. B. Gruber, J. M. Ford, D. Euhus, A. Lebensohn, M. Telli, S. M. Pochebit, G. Lypas, and J. E. Garber. 2012. 'Breast cancer phenotype in women with TP53 germline mutations: a Li-Fraumeni syndrome consortium effort', *Breast Cancer Res Treat*, 133: 1125-30.
117. Mavaddat, N., S. Peock, D. Frost, S. Ellis, R. Platte, E. Fineberg, D. G. Evans, L. Izatt, R. A. Eeles, J. Adlard, R. Davidson, D. Eccles, T. Cole, J. Cook, C. Brewer, M. Tischkowitz, F. Douglas, S. Hodgson, L. Walker, M. E. Porteous, P. J. Morrison, L. E. Side, M. J. Kennedy, C. Houghton, A. Donaldson, M. T. Rogers, H. Dorkins, Z. Miedzybrodzka, H. Gregory, J. Eason, J. Barwell, E. McCann, A. Murray, A. C. Antoniou, and D. F. Easton. 2013. 'Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE', *J Natl Cancer Inst*, 105: 812-22.
118. McDonnell, S. K., D. J. Schaid, J. L. Myers, C. S. Grant, J. H. Donohue, J. E. Woods, M. H. Frost, J. L. Johnson, D. L. Sitta, J. M. Slezak, T. B. Crotty, R. B. Jenkins, T. A. Sellers, and L. C. Hartmann. 2001. 'Efficacy of contralateral prophylactic mastectomy in women with a personal and family history of breast cancer', *J Clin Oncol*, 19: 3938-43.
119. Meijers-Heijboer, E. J., L. C. Verhoog, C. T. Brekelmans, C. Seynaeve, M. M. Tilanus-Linthorst, A. Wagner, L. Dukel, P. Devilee, A. M. van den Ouweland, A. N. van Geel, and J. G. Klijn. 2000. 'Presymptomatic DNA testing and prophylactic surgery in families with a BRCA1 or BRCA2 mutation', *Lancet*, 355: 2015-20.
120. Meijers-Heijboer, H., C. T. Brekelmans, M. Menke-Pluymers, C. Seynaeve, A. Baalbergen, C. Burger, E. Crepin, A. W. van den Ouweland, B. van Geel, and J. G. Klijn. 2003. 'Use of genetic testing and prophylactic mastectomy and oophorectomy in women with breast or ovarian cancer from families with a BRCA1 or BRCA2 mutation', *J Clin Oncol*, 21: 1675-81.
121. Meijers-Heijboer, H., A. van den Ouweland, J. Klijn, M. Wasielewski, A. de Snoo, R. Oldenburg, A. Hollestelle, M. Houben, E. Crepin, M. van Veghel-Plandsoen, F. Elstrodt, C. van Duijn, C. Bartels, C. Meijers, M. Schutte, L. McGuffog, D. Thompson, D. Easton, N. Sodha, S. Seal, R. Barfoot, J. Mangion, J. Chang-Claude, D. Eccles, R. Eeles, D. G. Evans, R. Houlston, V. Murday, S. Narod, T. Peretz, J. Peto, C. Phelan, H. X. Zhang, C. Szabo, P. Devilee, D. Goldgar, P. A. Futreal, K. L. Nathanson, B. Weber, N. Rahman, M. R. Stratton, and C. HEK2-Breast Cancer Consortium. 2002. 'Low-penetrance susceptibility to breast cancer

due to CHEK2(*)1100delC in noncarriers of BRCA1 or BRCA2 mutations', *Nat Genet*, 31: 55-9.

122. Meiser, B., P. Butow, M. Friedlander, V. Schnieden, M. Gattas, J. Kirk, G. Suthers, E. Haan, and K. Tucker. 2000. 'Intention to undergo prophylactic bilateral mastectomy in women at increased risk of developing hereditary breast cancer', *J Clin Oncol*, 18: 2250-7.
123. Metcalfe, K. A., D. Birenbaum-Carmeli, J. Lubinski, J. Gronwald, H. Lynch, P. Moller, P. Ghadirian, W. D. Foulkes, J. Klijn, E. Friedman, C. Kim-Sing, P. Ainsworth, B. Rosen, S. Domchek, T. Wagner, N. Tung, S. Manoukian, F. Couch, P. Sun, S. A. Narod, and Group Hereditary Breast Cancer Clinical Study. 2008. 'International variation in rates of uptake of preventive options in BRCA1 and BRCA2 mutation carriers', *Int J Cancer*, 122: 2017-22.
124. Metcalfe, K. A., P. Ghadirian, B. Rosen, W. Foulkes, C. Kim-Sing, A. Eisen, P. Ainsworth, D. Horsman, C. Maugard, D. Provencher, A. Robideaux, D. Gilchrist, A. Chudley, E. G. Lemire, S. Armel, A. Finch, P. Sun, and S. A. Narod. 2007. 'Variation in rates of uptake of preventive options by Canadian women carrying the BRCA1 or BRCA2 genetic mutation', *Open Med*, 1: e92-8.
125. Metcalfe, K., S. Gershman, P. Ghadirian, H. T. Lynch, C. Snyder, N. Tung, C. Kim-Sing, A. Eisen, W. D. Foulkes, B. Rosen, P. Sun, and S. A. Narod. 2014. 'Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis', *BMJ*, 348: g226.
126. Metcalfe, K., S. Gershman, H. T. Lynch, P. Ghadirian, N. Tung, C. Kim-Sing, O. I. Olopade, S. Domchek, J. McLennan, A. Eisen, W. D. Foulkes, B. Rosen, P. Sun, and S. A. Narod. 2011. 'Predictors of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers', *Br J Cancer*, 104: 1384-92.
127. Metcalfe, K., H. T. Lynch, P. Ghadirian, N. Tung, C. Kim-Sing, O. I. Olopade, S. Domchek, A. Eisen, W. D. Foulkes, B. Rosen, D. Vesprini, P. Sun, and S. A. Narod. 2011. 'Risk of ipsilateral breast cancer in BRCA1 and BRCA2 mutation carriers', *Breast Cancer Res Treat*, 127: 287-96.
128. Metcalfe, K., H. T. Lynch, P. Ghadirian, N. Tung, I. Olivotto, E. Warner, O. I. Olopade, A. Eisen, B. Weber, J. McLennan, P. Sun, W. D. Foulkes, and S. A. Narod. 2004. 'Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers', *J Clin Oncol*, 22: 2328-35.
129. Miki, Y., J. Swensen, D. Shattuck-Eidens, P. A. Futreal, K. Harshman, S. Tavtigian, Q. Liu, C. Cochran, L. M. Bennett, W. Ding, and et al. 1994. 'A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1', *Science*, 266: 66-71.
130. Miller, M. E., T. Czechura, B. Martz, M. E. Hall, C. Pesce, N. Jaskowiak, D. J. Winchester, and K. Yao. 2013. 'Operative risks associated with contralateral prophylactic mastectomy: a single institution experience', *Ann Surg Oncol*, 20: 4113-20.
131. Mitri, Z., T. Constantine, and R. O'Regan. 2012. 'The HER2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advances in Therapy', *Chemother Res Pract*, 2012: 743193.

132. Moran, A., C. O'Hara, S. Khan, L. Shack, E. Woodward, E. R. Maher, F. Lalloo, and D. G. Evans. 2012. 'Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations', *Fam Cancer*, 11: 235-42.
133. Murphy, J. A., T. D. Milner, and J. M. O'Donoghue. 2013. 'Contralateral risk-reducing mastectomy in sporadic breast cancer', *Lancet Oncol*, 14: e262-9.
134. Musiello, T., E. Bornhammar, and C. Saunders. 2013. 'Breast surgeons' perceptions and attitudes towards contralateral prophylactic mastectomy', *ANZ J Surg*, 83: 527-32.
135. Narod, S. A., J. S. Brunet, P. Ghadirian, M. Robson, K. Heimdal, S. L. Neuhausen, D. Stoppa-Lyonnet, C. Lerman, B. Pasini, P. de los Rios, B. Weber, and H. Lynch. 2000. 'Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group', *Lancet*, 356: 1876-81.
136. Neuburger, J., F. Macneill, R. Jeevan, J. H. van der Meulen, and D. A. Cromwell. 2013. 'Trends in the use of bilateral mastectomy in England from 2002 to 2011: retrospective analysis of hospital episode statistics', *BMJ Open*, 3.
137. Newman, B., M. A. Austin, M. Lee, and M. C. King. 1988. 'Inheritance of human breast cancer: evidence for autosomal dominant transmission in high-risk families', *Proc Natl Acad Sci U S A*, 85: 3044-8.
138. Ngeow, J., K. Sesock, and C. Eng. 2015. 'Breast cancer risk and clinical implications for germline PTEN mutation carriers', *Breast Cancer Res Treat*.
139. NHSBSP. 2015.
140. Nichols, H. B., A. Berrington de Gonzalez, J. V. Lacey, Jr., P. S. Rosenberg, and W. F. Anderson. 2011. 'Declining incidence of contralateral breast cancer in the United States from 1975 to 2006', *J Clin Oncol*, 29: 1564-9.
141. Nippert, I., C. Julian-Reynier, H. Harris, G. Evans, C. J. van Asperen, A. Tibben, and J. Schmidtke. 2014. 'Cancer risk communication, predictive testing and management in France, Germany, the Netherlands and the UK: general practitioners' and breast surgeons' current practice and preferred practice responsibilities', *J Community Genet*, 5: 69-79.
142. NMBRA. 2011.
143. Obermair, A., D. R. Youlden, P. D. Baade, and M. Janda. 2014. 'The impact of risk-reducing hysterectomy and bilateral salpingo-oophorectomy on survival in patients with a history of breast cancer--a population-based data linkage study', *Int J Cancer*, 134: 2211-22.
144. Oeffinger, K. C., E. T. Fontham, R. Etzioni, A. Herzig, J. S. Michaelson, Y. C. Shih, L. C. Walter, T. R. Church, C. R. Flowers, S. J. LaMonte, A. M. Wolf, C. DeSantis, J. Lortet-Tieulent, K. Andrews, D. Manassaram-Baptiste, D. Saslow, R. A. Smith, O. W. Brawley, R. Wender, and Society American Cancer. 2015. 'Breast Cancer Screening for Women at Average Risk: 2015 Guideline Update From the American Cancer Society', *JAMA*, 314: 1599-614.

145. ONS. 2012.
146. Parkin, D. M., L. Boyd, and L. C. Walker. 2011. '16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010', *Br J Cancer*, 105 Suppl 2: S77-81.
147. Patkar, V., D. Acosta, T. Davidson, A. Jones, J. Fox, and M. Keshtgar. 2011. 'Cancer multidisciplinary team meetings: evidence, challenges, and the role of clinical decision support technology', *Int J Breast Cancer*, 2011: 831605.
148. Peralta, E. A., J. D. Ellenhorn, L. D. Wagman, A. Dagis, J. S. Andersen, and D. Z. Chu. 2000. 'Contralateral prophylactic mastectomy improves the outcome of selected patients undergoing mastectomy for breast cancer', *Am J Surg*, 180: 439-45.
149. Phillips, K. A., R. L. Milne, M. A. Rookus, M. B. Daly, A. C. Antoniou, S. Peock, D. Frost, D. F. Easton, S. Ellis, M. L. Friedlander, S. S. Buys, N. Andrieu, C. Nogues, D. Stoppa-Lyonnet, V. Bonadona, P. Pujol, S. A. McLachlan, E. M. John, M. J. Hooning, C. Seynaeve, R. A. Tollenaar, D. E. Goldgar, M. B. Terry, T. Caldes, P. C. Weideman, I. L. Andrulis, C. F. Singer, K. Birch, J. Simard, M. C. Southey, H. L. Olsson, A. Jakubowska, E. Olah, A. M. Gerdes, L. Foretova, and J. L. Hopper. 2013. 'Tamoxifen and risk of contralateral breast cancer for BRCA1 and BRCA2 mutation carriers', *J Clin Oncol*, 31: 3091-9.
150. Piccart-Gebhart, M. J., M. Procter, B. Leyland-Jones, A. Goldhirsch, M. Untch, I. Smith, L. Gianni, J. Baselga, R. Bell, C. Jackisch, D. Cameron, M. Dowsett, C. H. Barrios, G. Steger, C. S. Huang, M. Andersson, M. Inbar, M. Lichinitser, I. Lang, U. Nitz, H. Iwata, C. Thomssen, C. Lohrisch, T. M. Suter, J. Ruschoff, T. Suto, V. Greatorex, C. Ward, C. Straehle, E. McFadden, M. S. Dolci, and R. D. Gelber. 2005. 'Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer', *N Engl J Med*, 353: 1659-72.
151. Pierce, L. J., A. M. Levin, T. R. Rebbeck, M. A. Ben-David, E. Friedman, L. J. Solin, E. E. Harris, D. K. Gaffney, B. G. Haffty, L. A. Dawson, S. A. Narod, I. A. Olivotto, A. Eisen, T. J. Whelan, O. I. Olopade, C. Isaacs, S. D. Merajver, J. S. Wong, J. E. Garber, and B. L. Weber. 2006. 'Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer', *J Clin Oncol*, 24: 2437-43.
152. Pierce, L. J., K. A. Phillips, K. A. Griffith, S. Buys, D. K. Gaffney, M. S. Moran, B. G. Haffty, M. Ben-David, B. Kaufman, J. E. Garber, S. D. Merajver, J. Balmana, A. Meirovitz, and S. M. Domchek. 2010. 'Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy', *Breast Cancer Res Treat*, 121: 389-98.
153. Pierce, L. J., M. Strawderman, S. A. Narod, I. Oliviotto, A. Eisen, L. Dawson, D. Gaffney, L. J. Solin, A. Nixon, J. Garber, C. Berg, C. Isaacs, R. Heimann, O. I. Olopade, B. Haffty, and B. L. Weber. 2000. 'Effect of radiotherapy after breast-conserving treatment in women with breast cancer and germline BRCA1/2 mutations', *J Clin Oncol*, 18: 3360-9.

154. Pinell-White, X. A., K. Kolegraff, and G. W. Carlson. 2014. 'Predictors of contralateral prophylactic mastectomy and the impact on breast reconstruction', *Ann Plast Surg*, 72: S153-7.
155. Plummer, R. 2011. 'Poly(ADP-ribose) polymerase inhibition: a new direction for BRCA and triple-negative breast cancer?', *Breast Cancer Res*, 13: 218.
156. Porter, G., B. Wagar, H. Bryant, M. Hewitt, E. Wai, K. Dabbs, A. McFarlane, and R. Rahal. 2014. 'Rates of breast cancer surgery in Canada from 2007/08 to 2009/10: retrospective cohort study', *CMAJ Open*, 2: E102-8.
157. Portschy, P. R., K. M. Kuntz, and T. M. Tuttle. 2014. 'Survival outcomes after contralateral prophylactic mastectomy: a decision analysis', *J Natl Cancer Inst*, 106.
158. Rath, M. G., S. Masciari, R. Gelman, A. Miron, P. Miron, K. Foley, A. L. Richardson, I. E. Krop, S. J. Verselis, D. A. Dillon, and J. E. Garber. 2013. 'Prevalence of germline TP53 mutations in HER2+ breast cancer patients', *Breast Cancer Res Treat*, 139: 193-8.
159. RCS. 2011. 'Procedures of limited clincal value'.
160. Rebbeck, T. R., H. T. Lynch, S. L. Neuhausen, S. A. Narod, L. Van't Veer, J. E. Garber, G. Evans, C. Isaacs, M. B. Daly, E. Matloff, O. I. Olopade, B. L. Weber, Prevention, and Group Observation of Surgical End Points Study. 2002. 'Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations', *N Engl J Med*, 346: 1616-22.
161. Reding, K. W., J. L. Bernstein, B. M. Langholz, L. Bernstein, R. W. Haile, C. B. Begg, C. F. Lynch, P. Concannon, A. Borg, S. N. Teraoka, T. Torngren, A. Diep, S. Xue, L. Bertelsen, X. Liang, A. S. Reiner, M. Capanu, K. E. Malone, and Wecare Collaborative Study Group. 2010. 'Adjuvant systemic therapy for breast cancer in BRCA1/BRCA2 mutation carriers in a population-based study of risk of contralateral breast cancer', *Breast Cancer Res Treat*, 123: 491-8.
162. Reiner, A. S., E. M. John, J. D. Brooks, C. F. Lynch, L. Bernstein, L. Mellemkjaer, K. E. Malone, J. A. Knight, M. Capanu, S. N. Teraoka, P. Concannon, X. Liang, J. C. Figueiredo, S. A. Smith, M. Stovall, M. C. Pike, R. W. Haile, D. C. Thomas, C. B. Begg, and J. L. Bernstein. 2013. 'Risk of asynchronous contralateral breast cancer in noncarriers of BRCA1 and BRCA2 mutations with a family history of breast cancer: a report from the Women's Environmental Cancer and Radiation Epidemiology Study', *J Clin Oncol*, 31: 433-9.
163. Rhiem, K., C. Engel, M. Graeser, S. Zachariae, K. Kast, M. Kiechle, N. Ditsch, W. Janni, C. Mundhenke, M. Golatta, D. Varga, S. Preisler-Adams, T. Heinrich, U. Bick, D. Gadzicki, S. Briest, A. Meindl, and R. K. Schmutzler. 2012. 'The risk of contralateral breast cancer in patients from BRCA1/2 negative high risk families as compared to patients from BRCA1 or BRCA2 positive families: a retrospective cohort study', *Breast Cancer Res*, 14: R156.
164. Roberts, A., M. Habibi, and K. D. Frick. 2014. 'Cost-effectiveness of contralateral prophylactic mastectomy for prevention of contralateral breast cancer', *Ann Surg Oncol*, 21: 2209-17.

165. Rosenberg, S. M., M. S. Tracy, M. E. Meyer, K. Sepucha, S. Gelber, J. Hirshfield-Bartek, S. Troyan, M. Morrow, L. Schapira, S. E. Come, E. P. Winer, and A. H. Partridge. 2013. 'Perceptions, knowledge, and satisfaction with contralateral prophylactic mastectomy among young women with breast cancer: a cross-sectional survey', *Ann Intern Med*, 159: 373-81.
166. Rutter, C. E., H. S. Park, B. K. Killelea, and S. B. Evans. 2015. 'Growing Use of Mastectomy for Ductal Carcinoma-In Situ of the Breast Among Young Women in the United States', *Ann Surg Oncol*, 22: 2378-86.
167. Sabel, M. S., and S. D. Cin. 2016. 'Trends in Media Reports of Celebrities' Breast Cancer Treatment Decisions', *Ann Surg Oncol*.
168. Saha, and D. R. Leff. 2016. 'Improving decision-making in contralateral mastectomy requests: Comparison between contralateral risk estimates and retrospective MDT decisions', *Eur J Surg Oncol*, 42: S56.
169. Saltzman, B. S., K. E. Malone, J. A. McDougall, J. R. Daling, and C. I. Li. 2012. 'Estrogen receptor, progesterone receptor, and HER2-neu expression in first primary breast cancers and risk of second primary contralateral breast cancer', *Breast Cancer Res Treat*, 135: 849-55.
170. Schrag, D., K. M. Kuntz, J. E. Garber, and J. C. Weeks. 2000. 'Life expectancy gains from cancer prevention strategies for women with breast cancer and BRCA1 or BRCA2 mutations', *JAMA*, 283: 617-24.
171. Shibata, A., Y. C. Tsai, M. F. Press, B. E. Henderson, P. A. Jones, and R. K. Ross. 1996. 'Clonal analysis of bilateral breast cancer', *Clin Cancer Res*, 2: 743-8.
172. Silva, A. K., B. Lapin, K. A. Yao, D. H. Song, and M. Sisco. 2015. 'The Effect of Contralateral Prophylactic Mastectomy on Perioperative Complications in Women Undergoing Immediate Breast Reconstruction: A NSQIP Analysis', *Ann Surg Oncol*, 22: 3474-80.
173. Slade, I., D. Riddell, C. Turnbull, H. Hanson, N. Rahman, and M. C. G. programme. 2015. 'Development of cancer genetic services in the UK: A national consultation', *Genome Med*, 7: 18.
174. Stefanek, M., L. Hartmann, and W. Nelson. 2001. 'Risk-reduction mastectomy: clinical issues and research needs', *J Natl Cancer Inst*, 93: 1297-306.
175. Taylor, R., and K. Taguchi. 2005. 'Tamoxifen for breast cancer chemoprevention: low uptake by high-risk women after evaluation of a breast lump', *Ann Fam Med*, 3: 242-7.
176. Tercyak, K. P., B. N. Peshkin, B. M. Brogan, T. DeMarco, M. F. Pennanen, S. C. Willey, C. M. Magnant, S. Rogers, C. Isaacs, and M. D. Schwartz. 2007. 'Quality of life after contralateral prophylactic mastectomy in newly diagnosed high-risk breast cancer patients who underwent BRCA1/2 gene testing', *J Clin Oncol*, 25: 285-91.
177. Thompson, D., and D. F. Easton. 2002. 'Cancer Incidence in BRCA1 mutation carriers', *J Natl Cancer Inst*, 94: 1358-65.
178. Thompson, E. R., S. M. Rowley, N. Li, S. McInerny, L. Devereux, M. W. Wong-Brown, A. H. Trainer, G. Mitchell, R. J. Scott, P. A. James, and I. G. Campbell. 2016. 'Panel Testing for Familial Breast Cancer: Calibrating

the Tension Between Research and Clinical Care', *J Clin Oncol*, 34: 1455-9.
179. Tischkowitz, M., M. Capanu, N. Sabbaghian, L. Li, X. Liang, M. P. Vallee, S. V. Tavtigian, P. Concannon, W. D. Foulkes, L. Bernstein, Wecare Study Collaborative Group, J. L. Bernstein, and C. B. Begg. 2012. 'Rare germline mutations in PALB2 and breast cancer risk: a population-based study', *Hum Mutat*, 33: 674-80.
180. Turnbull, C., S. Ahmed, J. Morrison, D. Pernet, A. Renwick, M. Maranian, S. Seal, M. Ghoussaini, S. Hines, C. S. Healey, D. Hughes, M. Warren-Perry, W. Tapper, D. Eccles, D. G. Evans, M. Hooning, M. Schutte, A. van den Ouweland, R. Houlston, G. Ross, C. Langford, P. D. Pharoah, M. R. Stratton, A. M. Dunning, N. Rahman, and D. F. Easton. 2010. 'Genome-wide association study identifies five new breast cancer susceptibility loci', *Nat Genet*, 42: 504-7.
181. Tutt, A., M. Robson, J. E. Garber, S. M. Domchek, M. W. Audeh, J. N. Weitzel, M. Friedlander, B. Arun, N. Loman, R. K. Schmutzler, A. Wardley, G. Mitchell, H. Earl, M. Wickens, and J. Carmichael. 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: 235-44.
182. Tuttle, T. M., A. Abbott, A. Arrington, and N. Rueth. 2010. 'The increasing use of prophylactic mastectomy in the prevention of breast cancer', *Curr Oncol Rep*, 12: 16-21.
183. Tuttle, T. M., E. B. Habermann, E. H. Grund, T. J. Morris, and B. A. Virnig. 2007. 'Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment', *J Clin Oncol*, 25: 5203-9.
184. Tuttle, T. M., S. Jarosek, E. B. Habermann, A. Arrington, A. Abraham, T. J. Morris, and B. A. Virnig. 2009. 'Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ', *J Clin Oncol*, 27: 1362-7.
185. Valachis, A., A. D. Nearchou, and P. Lind. 2014. 'Surgical management of breast cancer in BRCA-mutation carriers: a systematic review and meta-analysis', *Breast Cancer Res Treat*, 144: 443-55.
186. van der Post, R. S., I. P. Vogelaar, F. Carneiro, P. Guilford, D. Huntsman, N. Hoogerbrugge, C. Caldas, K. E. Schreiber, R. H. Hardwick, M. G. Ausems, L. Bardram, P. R. Benusiglio, T. M. Bisseling, V. Blair, E. Bleiker, A. Boussioutas, A. Cats, D. Coit, L. DeGregorio, J. Figueiredo, J. M. Ford, E. Heijkoop, R. Hermens, B. Humar, P. Kaurah, G. Keller, J. Lai, M. J. Ligtenberg, M. O'Donovan, C. Oliveira, H. Pinheiro, K. Ragunath, E. Rasenberg, S. Richardson, F. Roviello, H. Schackert, R. Seruca, A. Taylor, A. Ter Huurne, M. Tischkowitz, S. T. Joe, B. van Dijck, N. C. van Grieken, R. van Hillegersberg, J. W. van Sandick, R. Vehof, J. H. van Krieken, and R. C. Fitzgerald. 2015. 'Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers', *J Med Genet*, 52: 361-74.
187. van Eggermond, A. M., M. Schaapveld, P. J. Lugtenburg, A. D. Krol, J. P. de Boer, J. M. Zijlstra, J. M. Raemaekers, L. C. Kremer, J. M. Roesink, M. W. Louwman, B. M. Aleman, and F. E. van Leeuwen. 2014. 'Risk of

multiple primary malignancies following treatment of Hodgkin lymphoma', *Blood*, 124: 319-27; quiz 466.
188. van Sprundel, T. C., M. K. Schmidt, M. A. Rookus, R. Brohet, C. J. van Asperen, E. J. Rutgers, L. J. Van't Veer, and R. A. Tollenaar. 2005. 'Risk reduction of contralateral breast cancer and survival after contralateral prophylactic mastectomy in BRCA1 or BRCA2 mutation carriers', *Br J Cancer*, 93: 287-92.
189. Vargas, A. C., L. Da Silva, and S. R. Lakhani. 2010. 'The contribution of breast cancer pathology to statistical models to predict mutation risk in BRCA carriers', *Fam Cancer*, 9: 545-53.
190. Verhoog, L. C., C. T. Brekelmans, C. Seynaeve, E. J. Meijers-Heijboer, and J. G. Klijn. 2000. 'Contralateral breast cancer risk is influenced by the age at onset in BRCA1-associated breast cancer', *Br J Cancer*, 83: 384-6.
191. Vichapat, V., C. Gillett, I. S. Fentiman, A. Tutt, L. Holmberg, and M. Luchtenborg. 2011. 'Risk factors for metachronous contralateral breast cancer suggest two aetiological pathways', *Eur J Cancer*, 47: 1919-27.
192. Vogel, V. G., J. P. Costantino, D. L. Wickerham, W. M. Cronin, R. S. Cecchini, J. N. Atkins, T. B. Bevers, L. Fehrenbacher, E. R. Pajon, Jr., J. L. Wade, 3rd, A. Robidoux, R. G. Margolese, J. James, S. M. Lippman, C. D. Runowicz, P. A. Ganz, S. E. Reis, W. McCaskill-Stevens, L. G. Ford, V. C. Jordan, N. Wolmark, Breast National Surgical Adjuvant, and Project Bowel. 2006. 'Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial', *JAMA*, 295: 2727-41.
193. Wong, S. M., R. A. Freedman, Y. Sagara, F. Aydogan, W. T. Barry, and M. Golshan. 2016. 'Growing Use of Contralateral Prophylactic Mastectomy Despite no Improvement in Long-term Survival for Invasive Breast Cancer', *Ann Surg*.
194. Wooster, R., S. L. Neuhausen, J. Mangion, Y. Quirk, D. Ford, N. Collins, K. Nguyen, S. Seal, T. Tran, D. Averill, and et al. 1994. 'Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13', *Science*, 265: 2088-90.
195. Zendejas, B., J. P. Moriarty, J. O'Byrne, A. C. Degnim, D. R. Farley, and J. C. Boughey. 2011. 'Cost-effectiveness of contralateral prophylactic mastectomy versus routine surveillance in patients with unilateral breast cancer', *J Clin Oncol*, 29: 2993-3000.
196. Zhou, W. B., X. A. Liu, J. C. Dai, and S. Wang. 2011. 'Meta-analysis of sentinel lymph node biopsy at the time of prophylactic mastectomy of the breast', *Can J Surg*, 54: 300-6.

Appendix 1

Familial Breast Cancer

Breast cancer remains the most common cancer amongst women in the world with UK estimates that 1 in 8-10 will develop this disease during their lifetime. The majority of breast cancers arise spontaneously. However, a significant proportion (20-30%) of cancers will have an inherited component (Newman et al. 1988).

Over the last 3 years, there has been a 250% increase in the number of breast referrals to the regional genetics units for gene testing and assessment (Evans et al. 2014). Some of this may be fuelled by the so-called "Angelina Jolie effect" – a term coined following this international celebrity's revelation of her *BRCA1* mutation status and decision to undergo bilateral risk reducing mastectomy in 2013. However some aspects of risk-reducing surgery pre-date this phenomenon. For example in the US, over the last decade rates of contralateral risk-reducing mastectomy have trebled (Wong et al. 2016).

Surgeons are often in the frontline managing women concerned with their family history. Whether this is in the context of a newly or previously diagnosed breast cancer or an asymptomatic individual concerned about her family history, surgeons need to be familiar with breast cancer genetics.

The NICE 2013 guidelines of Familial breast cancer made a number of recommendations regarding the management of this group of women including lowering the threshold for genetic testing to a lifetime risk level of 10% (Evans, Graham, et al. 2013). The UK Genetic Testing Network has recommended mainstreaming *BRCA* testing in certain groups of women (for example triple negative breast cancers in women under the age of 40 years) so that appropriately trained breast surgeons may initiate the process of gene testing in this population group (Eccles et al. 2015).

My own studies (Chapter 3) have confirmed that attitudes to risk-reducing surgery are driven by knowledge of breast cancer genetics – and that in the setting of contralateral risk-reducing surgery, the level of knowledge amongst surgeons is suboptimal (Basu et al. 2016).
An overview of Familial Breast cancer is presented with particular emphasis on the various penetrance genes, risk assessment tools, management strategies and practicalities of gene testing are discussed.

High Penetrance Genes:

BRCA1 – the chromosomal site of tumour suppressor gene was first identified by family linkage analysis in 1990 and cloned 4 years later in the USA (Miki et al. 1994). During the next 2 decades a bitter commercial battle ensued regarding patenting of the genomic DNA sequence to both *BRCA*1 and *BRCA*2. Ultimately, the 2013 US Supreme Court ruled that "*isolation of genes found in nature do not render them patentable*".

The human *BRCA*1 gene (Chromosome 17p - codes for the breast cancer type 1 susceptibility protein) is involved in DNA repair. The majority of mutations are frameshift resulting in a truncated protein. The inheritance pattern is autosomal dominant with birth incidence of a *BRCA*1 mutation estimated at 1 in 500- 1in 1000 (Lalloo et al. 2003), accounting for 7-10% of familial breast cancers (Lalloo and Evans 2012).

Harbouring a *BRCA*1 mutation confers a lifetime risk of breast cancer of approximately 60-85% (Evans et al. 2008; Antoniou et al. 2003) and up to 60% for developing ovarian cancer (usually high-grade serous carcinomas). Relative risk of breast cancer is inversely proportional to age. Other cancers that have been associated with a *BRCA1* gene mutation include pancreatic cancer (RR 2.26], uterine body and cervical cancer (RR 2.65, RR 3.72 respectively] and prostate cancer in the under 65s [1.82] (Thompson and Easton 2002). However, none outside Breast and ovary are consistently found to be elevated (Moran et al. 2012).

BRCA1 related breast cancers are heterogenous but have some important clinical features. They are mostly triple negative (Oestrogen receptor -ve, Progesterone Receptor -ve, HER2 receptor -ve) with expression of basal markers on tumour cells (CK5/6, CK14, SMA, P Cadherin, EGFR0). Histologically, they are often similar to high-grade medullary carcinomas with pushing margins, high mitotic counts and lymphocytic infiltrates (Vargas, Da Silva, and Lakhani 2010).

BRCA2 – This DNA repair gene was identified in the UK in 1994 on chromosome 13q and encodes the protein Breast Cancer 2 Susceptibility Protein (Wooster et al. 1994). Mutations in *BRCA*2 are nearly all inherited suggesting a large founder effect. This is important for practical purposes as certain populations can be tested for known mutations (e.g. a single mutation 999del5 accounts for almost all inherited breast and ovarian cancer in Iceland).

Lifetime breast cancer risk has a wider range (40-85%) compared to *BRCA1*, and a somewhat lower risk of developing ovarian cancer (30%). Approximately 1 in 600-800 women carry a mutation (outbred population) that accounts for 10% of familial breast/ovarian cancer.

Several other cancers are more commonly associated with this mutation:
Cholangiocarcinoma, melanoma, pancreatic cancer (overall RR 4.1], gastric cancer [RR 2.7] and prostate cancer. Approximately 10% of Male breast cancer is associated with *BRCA*2, but is not associated with *BRCA*1 mutations.

Breast cancers in *BRCA*2 mutation carriers are a more heterogenous group compared to *BRCA*1 carriers, with more semblance to sporadic breast cancers and thus more often ER+ve compared to controls; some studies showing increased DCIS and lobular cancers.

A recent review (Bordeleau, Panchal, and Goodwin 2010) suggested that the 5-year survival of breast cancers in *BRCA1/2* mutation carriers is similar to sporadic breast cancers. In addition these women have similar survival whether they are treated with breast conservation surgery or a mastectomy (Pierce et al. 2010), despite having significantly higher rates of local failure with breast

conservation. Interestingly, most local recurrences are second primary breast cancers rather than failure to control the primary breast cancer.

The 2013 Breast Cancer Campaign gap analysis (Eccles et al. 2013) reported significant advances in knowledge of the heritability of breast cancer from the previous report in 2007 (Figure below). The high-penetrance genes comprised 25-30% of the risk of heritable breast cancer with an increasing proportion attributable to SNPs (discussed later). The proportion of "missing heritability" has also reduced to 50% with the hope that continued efforts will see this figure diminish further in the near future.

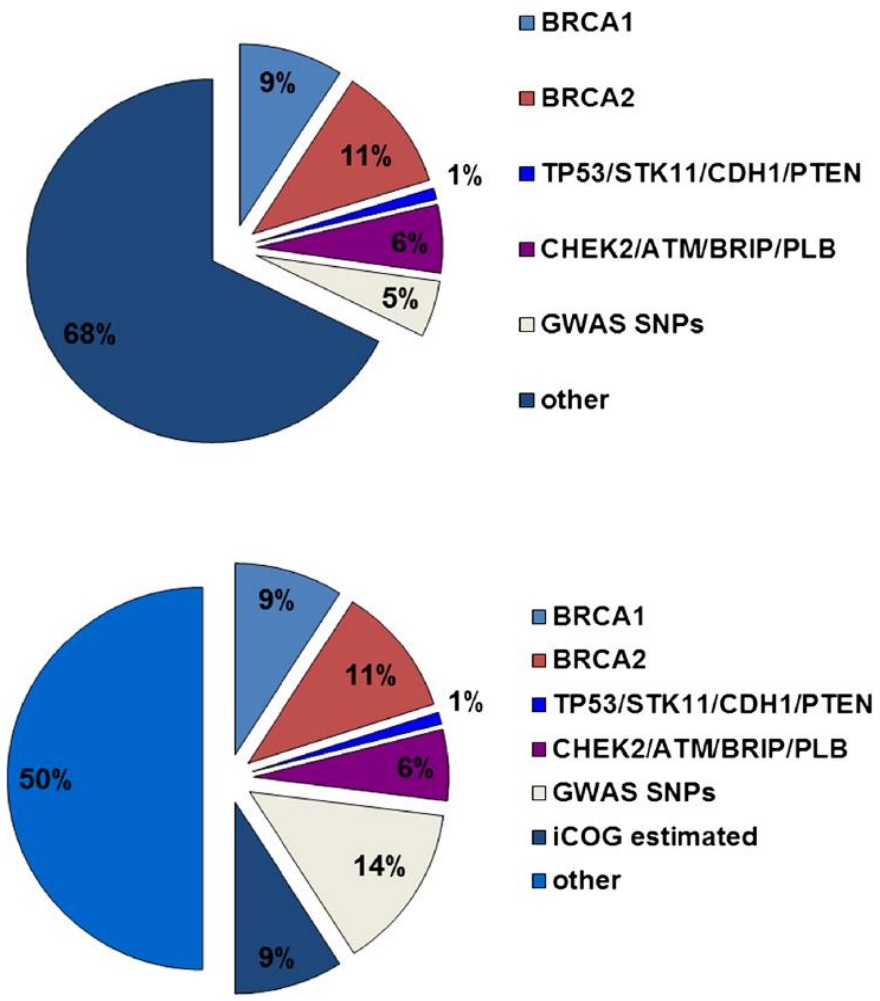


Figure 3. Familial Cancer Genetics. The proportion of the familial component of breast cancers that can be ascribed to specific genetic defects. The difference between June 2007 (above) and 2013 (below) shows the impact of genome-wide association studies (GWAS) that have now identified 77 common low-risk SNPs (Eccles et al. 2013).

TP53 – is called the "Guardian of the Genome" and is located on Chromosome 17. It is the most common known genetic mutation in human cancers. Somatic *TP53* mutations are well described and have been implicated in the multi-stage progression of several cancers (especially colon cancer). Inherited *TP53* mutations are rare, resulting in Li Fraumeni Syndrome (LFS). This is characterised by a wide spectrum of childhood and early adulthood tumours including soft tissue and bone sarcomas, brain tumours, leukaemias and adrenal cortical carcinomas.

Breast cancer is the most common malignancy amongst these women (risk is 50% by age 30 and 90% by age 60 years) (Masciari et al. 2012), with up to 7% of women with breast cancer under the age of 30 harbouring a *TP53* mutation (Evans et al. 2010). Patients with LFS may not respond to adjuvant treatments (chemotherapy and radiotherapy) and in particular radiotherapy, where there is a potential for developing new primary malignancies (Kappel et al. 2015). Of clinical relevance is that up to 63-83% of LFS patients test positive for HER2 (Masciari et al. 2012). Clinicians may consider mutations analysis for *TP53* in very young women with breast cancer, particularly in the presence of a family history of cancer (Rath et al. 2013).

PTEN – is a tumour suppressor gene that codes for the Phosphatase and Tensin Homolog protein. It is included in multigene "panel testing" and is of clinical importance. Mutation in *PTEN* confers a lifetime breast cancer risk of 67-85% (Ngeow, Sesock, and Eng 2015) but this may be an overestimate due to biased ascertainment. There is a wide spectrum of phenotypes with this anomaly with Cowden Syndrome (CS). The most commonly described include malignancies of the thyroid and endometrium and non-malignant manifestations include: hamartomas, macrocephaly, intestinal polyps and cerebellar lesions. This rare condition possibly affects 1 in 200,000 people.

PALB2 – encodes the protein (Partner and Localiser of *BRCA*2) that interacts with both *BRCA*1 and *BRCA*2 (Antoniou et al. 2014). Fanconi's anaemia is associated with biallelic germline mutation of *PALB2* and it is associated with

familial pancreatic cancer. It is also included in multi-gene panels and confers up to a 35% lifetime risk of breast cancer by the age of 70.

CDH1 – encodes the for the cell-adhesion protein E-cadherin. Mutation of this results in loss of cell adhesion, cancer progression and metastasis. The expression of this protein is used for practical purposes by pathologists to help differentiate lobular and ductal carcinomas (expression of the former is lost in most lobular cancers). Germline mutations of *CDH1* confer a 42% lifetime risk of developing lobular breast cancer and up to 70% risk of developing diffuse gastric cancers. Surveillance MRI is preferred over mammography, given the latter has a low sensitivity for identifying lobular cancers (van der Post et al. 2015).

STK11 encodes the protein kinase (Serine/Threonine Kinase 11) that is associated with the autosomal dominant Peutz-Jeghers Syndrome. The hallmark of this disorder is the presence of multiple gastrointestinal hamartomatous polyps and pigmented macules but also a reported lifetime risk of breast cancer up to 54% (Apostolou and Fostira 2013).

Moderate Penetrance Genes

ATM - Ataxia-telangiectasia is an autosomal recessive condition with an estimated frequency of 1 in 40 000 to 1 in 300 000. Individuals with ataxia-telangiectasia are reported to have a 100-fold increased risk of cancer with lymphoid cancers predominating in childhood and epithelial cancers (e.g. Breast) predominating in adults. The associated lifetime risk for developing breast cancer for women carrying a single mutated allele is around 20%.

CHEK2 (Checkpoint kinase gene) contributes to the same signaling pathway as *TP53* and *BRCA1*. The gene mutation is present in 1 in 200 live births Carriers of mutated *CHEK2* have been reported to have an increased risk of bilateral breast cancer and an association with colorectal cancer.

BRIP1 –(Binding partner of BRCA1) is reported to be present in 1 in 1000 live births. Previous studies had reported a 20% lifetime risk of breast cancer. However, more a recent analysis found that this mutation was not associated with a substantial increase in breast risk and as such may question their inclusion in breast cancer screening panels (Easton et al. 2016).

Low Penetrance Genes

The human genome is comprised of over 3 billion base pairs. Over the last decade significant advances have been made in studying variations in DNA sequences. Genome Wide Association Studies (GWAS) examines associations between these genetic variants called single nucleotide polymorphisms (SNPs) and disease traits.

Over 100 SNPs have been identified which may alter (increase or decrease) the risk of developing breast cancer. These are relatively common changes in nucleotides that occur with a frequency of approximately over 5%. They confer a modest risk of up to 1.05-1.35 times higher than the general population and likely work in a polygenic multiplicative manner rather than being incremental.

Prime time clinical use of SNPs is anticipated and they have been included in several of the available multigene panels. The potential risk of clinical misinformation (Thompson et al. 2016) needs to be addressed by physicians involved in recommending these tests. Thus, the validity of risk estimates is of paramount importance.

There is considerable variation of breast cancer risk amongst those carrying a mutation in *BRCA1/BRCA*2. Age at diagnosis and cancer type of the proband case will influence this risk. The variability of this risk is highly suggestive of additional genetic (non *BRCA*1/2 alleles or genes) and non-genetic modifiers of *BRCA*1/2 (Antoniou et al. 2003). Potentially, this may enable personalised risk assessment amongst high-risk women, stratifying their risk even further – i.e. it

may be possible to estimate which part of the range of lifetime risk (40-85%) an individual is likely to be affected by.

Through large scale GWAS, common SNPs associated with breast cancer risk in the general population have been studied and in particular modifiers of risk in *BRCA1/2* mutation carriers (Antoniou et al. 2010). One study showed that 7 of the 9 risk associated SNPs in *BRCA2* carriers could increase the risk of these individuals from 42% to 96% risk of developing breast cancer by the age of 80 years. A subsequent study was able to show that 18 of the validated breast cancer SNPs may be used to differentiate breast cancer risk in *BRCA2* carriers (Ingham et al. 2013) but not *BRCA1* carriers concluding "*it may now be appropriate to use these SNPs to help women with BRCA2 make maximally informed decisions about their management options*".

A proportion of women from families with known mutations will themselves test negative for that mutation but go on to develop breast cancer. These women are considered to be phenocopies whereby their phenotype (breast cancer) matches the phenotype determined by genetic factors despite testing negative to a known genetic mutation. It is likely that these women are enriched by genetic modifiers that increase the penetrance of *BRCA1/2* in non-mutation carriers (Evans, Ingham, Buchan, et al. 2013). A recent study found higher rates of phenocopies in women from families with a *BRCA2* mutation and concluded that caution should be exercised when counselling women from a family of *BRCA2* mutation carriers who tested negative for a *BRCA2* mutation as their risk of breast cancer may be higher than the population, particularly in the presence of multiple relatives with early onset breast cancer. The role of the 18 validated SNPs amongst *BRCA2* breast cancer phenocopies showed a relative risk of 1.3 which may have a clinical role in the future to help those with a negative BRCA2 test stratify their breast cancer risk further.

The 100,000 Genomes Project (2012-17)(Beggs and Dilworth 2015) has gained much publicity and aims to sequence genomes from approximately 70,000 individuals in the UK – a proportion of which will be breast cancer patients. Although this project is primarily concerned with somatic mutations, there is

scope to examine breast cancer in those with germline mutations (e.g. *BRCA* carriers who develop breast cancer).

Gene Testing

Next generation sequencing (NGS) has transformed gene testing from the era of Sanger-based sequencing. This technology allows testing to be performed more quickly and cost-effectively, invaluable in the clinical setting.
Testing is usually performed by or in conjunction with the genetics services and 2 different scenarios need to be considered:

1. Predictive Testing – testing of an unaffected individual. This requires that a family member (usually with cancer) have a known mutation. Where an individual has multiple members of the family with breast and ovarian cancer or a very high probability of carrying a *BRCA*1/2 mutation, it may be possible to offer genetic testing without ascertainment of a mutation in the family. In the UK, the threshold for genetic test was reduced from a 20% probability of detecting a *BRCA*1/2 to 10% (NICE 2013), in line with other developed countries.
2. Mainstreaming Cancer Genetics (MCG) – involves routine genetic testing as part of a new cancer diagnosis. Harbouring a genetic mutation in newly diagnosed breast and ovarian cancer patients may influence treatment options including surgery (e.g. bilateral mastectomy / bilateral salpingo-oophorectomy) and systemic strategies (e.g. PARP inhibitors). At present, many specialist genetics units in the UK do not have the capacity to deal with the increased numbers of gene testing. MCG offers an opportunity to provide newly diagnosed cancer patients (certain criteria) with genetic testing as part of their routine cancer pathway thereby reducing waiting times and allowing important oncological decisions to be made (Slade et al. 2015).

Interpreting a *BRCA*1/2 Gene Test Result:

There are three possible outcomes following testing:

1. Positive – pathogenic variant has been confirmed

2. Negative –('true negative') the known mutation identified in a relative has not been identified
3. Variants of Uncertain Clinical Significance (VUS) – Upton 20% of *BRCA*1/2 testing may result in VUS, further reduced in well-characterised ethnic populations. There are no agreed international standards for *BRCA* test reporting or classification, and misinterpretation of a VUS result may cause significant harm to patients and their family members.

   Efforts are underway to standardize the interpretation of VUS (Eccles et al. 2015) and it remains best practice to ensure that both a positive and VUS result prompts a referral to the genetics services.

Risk Assessment

In the clinical setting, risk assessment begins with a full history and an accurate three-generation pedigree. Maternal and paternal factors are equally important, something that some clinicians overlook (Nippert et al. 2014). Of particular importance are the number of family members with associated cancers, age at which relatives developed relevant cancers (the younger the more significant) and bilateral breast cancer.

A number of risk calculation tools are available to help clinicians counsel individuals about their risk of developing breast cancer or their probability of detecting a mutation in the *BRCA*1/2 gene. Computerized and manual tools exist and the accuracy of risk prediction improved by the inclusion of information on tumour pathology.

GAIL MODEL – predicts risk of developing over the subsequent 5 years. It utilizes 7 key risk factors, several of which are non-genetic (e.g. previous breast biopsy and race/ethnicity). A major limitation of the Gail model is that it only includes first-degree relatives and may underestimate risk by 50%.

CLAUS MODEL – does not utilize any non-hereditary risk factors and is poorly

concordant with the Gail Model. It was based on risks of women in the US with breast cancer in the 1980s, thus underestimating breast cancer risk now when a higher incidence exists.

BRCAPRO – this statistical model also allows risk calculation of the probability of carrying a *BRCA1*/2 mutation based on a family history or breast and ovarian cancer. It does not include any non-hereditary factors, which may limit its accuracy.

TYRER-CUZICK MODEL - combines genetic and non-genetic risk factors (i.e. hormonal risk factors, benign breast disease – ADH) and in several studies performed the best in breast cancer risk estimation.

BOADICEA MODEL (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) – is a polygenic risk model, developed using segregation analysis. It has been endorsed by NICE (CG 164).

MANCHESTER MODEL – is simple clinical tool to enable calculation of risk of carrying *BRCA*1/2 mutation. It is particularly useful in *BRCA*1 calculations and allocates a score for each affected individual in a family. The various scores from the maternal or paternal lineage are summed up and if they exceed a given threshold (usually represent 10-20% likelihood of carrying a mutation), a genetic test may be recommended. This has also been endorsed by NICE (CG 164).

Management of Familial Breast Cancer Patients

The two main considerations when considering this patient group - whether surveillance of their risk is preferred or whether some form of risk-reducing strategy is appropriate. Those patients choosing the former should understand that their overall risk of developing breast cancer is not altered – however, they are screened at an asymptomatic stage with the hope that this translates to early detection with a favourable outcome.

Recommendations will depend very much on the level of risk. The NICE CG 164 guidelines stratifies women into 3 groups based on their overall risk:

Near Populations risk ('low')

- Overall lifetime risk from age 20 years <17%
- Risk between ages 40-50 years < 3%

Moderate Risk

- Overall lifetime risk from age 20 years 17-30%
- Risk between ages 40-50 years 3-8%

High Risk

- Overall lifetime risk from age 20 years >30%
- Risk between ages 40-50 years >8%

High risk patients include those harbouring a mutation in one of the high penetrance genes mentioned above (i.e. *BRCA1/2, PT53, PTEN, CDH11, PALB2, STK11*) as well as those whose test negative for a genetic mutation but the strength of the family history is such that their overall lifetime risk is greater than 30%. It is likely the latter group of individuals harbour an as yet unidentified genetic mutation.

Surveillance

Mammography

In the UK, all women from the ages of 50-70 years are invited to have screening mammograms every 3 years, with the age extension trial extending this to 47-73 years. Given that 80% of breast cancers occur in women over the age of 50 years, the rationale for screening this group is ultimately to reduce mortality by early diagnosis, although much controversy exists regarding over diagnosis. It is possible that almost a third of women attending routine 3 yearly screening may benefit from more regular mammograms by virtue of other quantifiable risk factors (i.e. family history, lifestyle, breast density of mammogram and genetic factors analysed

from saliva) and allow women to have a more personalised risk score (Evans and Howell 2015).

The FH01 study assessed asymptomatic women at intermediate risk of developing breast cancer (according to family history). It confirmed that annual mammograms from the age of 40-49 in this group could detect significantly smaller tumours, fewer node positive cancers and ultimately a lower 10-year mortality rate compared to those who did not receive any screening (FH01 2010).

Current NICE guidelines follow on from this and recommend annual mammograms to women at high and intermediate risk of breast cancer in a secondary care setting, starting at 40 years of age (annual mammograms high risk 40-59 years, intermediate risk 40-49) (Evans, Graham, et al. 2013).

MRI

Several studies have shown that MRI has a greater sensitivity compared to mammography to detect breast cancer in susceptible patients(Kriege et al. 2004; Leach et al. 2005). Dense breast tissue in younger women limits the role of mammography as a sole modality. Combining contrast enhanced MRI with mammography can detect 70-100% of lesions in the high-risk group. One pitfall is the detection of DCIS (more common in *BRCA2* carriers) where MRI has reduced sensitivity. The current NICE CG 164 recommend high-risk patients to undergo annual MRI from the age of 30 years, with those carrying a *TP53* mutation starting at the age of 20 years.

Bilateral risk reducing mastectomy (BRRM)

BRRM offers the greatest magnitude of overall risk reduction in those at increased risk of breast cancer by removing in excess of 90% of the breast tissue. A recent Cochrane review showed that BRRM reduces the risk of developing breast cancer by 85-100 (Lostumbo, Carbine, and Wallace 2010) in high-risk patients. It also showed that BRRM reduced the risk of dying

from breast cancer by 81-100% in high-risk patients and 100% in the moderate risk group. Overwhelmingly, the majority of patients are satisfied with their decision several years following surgery. The few who do regret this decision are more likely to have been recommended surgery by their physician.

In the UK, rates of BRRM have trebled over the last decade (Neuburger et al. 2013). There are multiple factors contributing to this: increased availability of immediate reconstruction, public awareness and lowering of threshold for genetic testing. In May 2013, Angelina Jolie revealed she harboured the *BRCA*1 mutation and had undergone BRRM with immediate reconstruction. Since then, referrals to regional genetic units in the UK and number of BRRMs performed (Manchester) have increased 2.5 fold (Evans et al. 2014; Evans et al. 2015) confirming that public awareness is a critical driver to this observed trend.

Bilateral Risk-Reducing Salpingo Oophorectomy (BRRSO)

Women choosing this procedure will reduce their risk of developing ovarian by almost 90%. In addition, there appears to be a reduction in their subsequent risk of developing breast cancer (premenopausal women) (Domchek et al. 2010; Rebbeck et al. 2002), with several previous studies showing a risk-reduction of almost 50%. Unlike breast cancer, surveillance for ovarian cancer is limited to measurements of tumour markers (CA125) and transvaginal ultra-sound – both of which may lack sensitivity. As such, uptake of BRRSO is high (up to 75%).

BRRSO renders women post menopausal (surgical menopause) with additional risks to the cardiovascular and skeletal system. In addition, most women are recommended to have completed their family prior to considering this surgery. The climacteric symptoms following this procedure can be debilitating and many women will consider use of HRT to combat these symptoms. Use of HRT itself may increase the risk of developing breast cancer in these women already deemed at high-risk.

However, short-term use of HRT does not seem to negate the protective effect of BRRSO on breast cancer risk. The lowest risk of breast cancer seems to be with the use of oestrogen only HRT which is only offered to those who have had a hysterectomy and may need to be considered in addition to the BRRSO.

The risk reduction for breast cancer has recently been scrutinized (Heemskerk-Gerritsen, Seynaeve, et al. 2015). This Dutch study questioned whether original studies may have been subjected to 3 types of selection bias described below:

Cancer-induced testing bias – in healthy women, genetic testing usually precedes risk-reducing surgery. However, some women who do not undergo risk-reducing surgery have their genetic mutation detected due to their cancer diagnosis. Some healthy women at risk may not undergo testing or risk reducing surgery and would not be selected. Cancer-induced testing bias refers to the variation in genetic testing of cancer patients compared to healthy at-risk patients that may overestimate cancer risk reduction (Ref Klaren Rookus JNCI 2003).
Immortal person time bias – by design, death or study outcome cannot occur during follow up period
Informative censoring – participants are lost to follow up due to reasons related to the study

This study used the same methodology previously described (Domchek et al. 2010) to study a cohort of Dutch *BRCA 1/2* healthy carriers and found that following BRRSO, the incidence of breast cancer was almost halved (Hazard Ratio 0.36-0.62). A revised analysis taking into account the various biases described above showed no real protective effect of BRRSO on breast cancer development (Hazard Ratio 1.09). This has important clinical implications when considering the variations of uptake of BRRM compared to BRRSO – women only choosing BRRSO over BRRM may have had their breast cancer risk reduction overestimated if they only chose BRRSO.

Several studies have shown similar risk reduction in contralateral breast cancer development in *BRCA1/2* carriers undergoing BRRSO (HR 0.44)(Metcalfe et al. 2004)– however whether these studies overestimated the risk reduction for contralateral breast cancer needs to be addressed.

Chemoprevention

In the UK, women at increased risk of developing breast cancer may consider three medications to reduce their risk:

Tamoxifen – this selective oestrogen receptor modulator (1st generation) has been shown to reduce the risk in asymptomatic women by approximately 40-50% (IBIS 1, NSABP Breast Cancer Prophylaxis Trial)((Howell et al. 2014). In women with breast cancer, tamoxifen has a similar risk reduction in developing CBC. The side-effect profile (hot flushes, increased incidence of endometrial cancer, thromboembolic phenomenon) is an important consideration as less than 15% of women will choose this and remain compliant (Taylor and Taguchi 2005). Tamoxifen may be considered in pre and post menopausal women.

Raloxifene (2nd generation SERM), used in the prevention and treatment of osteoporosis has a much better side effect profile with no increase in endometrial cancers but increases thromboembolic risk similar to tamoxifen. Risk reduction was inferior to tamoxifen over an extended follow (Vogel et al. 2006). Raloxifene is considered in the post-menopausal setting only.

Aromatase Inhibitor – Exemestane has been shown to offer 65% relative risk reduction in post-menopausal women at increased risk with a minimal side-effect profile (Goss et al. 2011). The IBIS II trial (International Breast Cancer Intervention Studies) randomised post-menopausal women with an increased risk of breast cancer to anastrozole or placebo. At 5 years follow-up, 2% of women taking Anastrozole had developed breast cancer compared to 4% in the placebo group (Cuzick et al. 2014).

Lifestyle

Worldwide, the number of oestrogen receptor positive breast cancers is increasing with a reverse pattern seen with oestrogen negative cancer. In developed countries, hormone sensitive breast cancer is particularly amenable to lifestyle prevention – with recent studies suggesting that modification of lifestyle measure may prevent up to 30% of breast cancers (Parkin, Boyd, and Walker 2011).

Amongst *BRCA* carriers, smoking, increased weight and reduced physical activity further increases the risk of breast cancer. These lifestyle measures need to commence in adolescence and adherence to this (150 minutes weekly activity, BMI < 25, <1 alcoholic drink daily) has been shown to reduce mortality in *BRCA* carriers by almost 60% (Cloud et al. 2015).

Appendix 2

Questionnaire sent to UK surgeons (CRRM)

Mr Naren Basu
National Oncoplastic Fellow
Dept. of Breast Surgery
Wythenshawe Hospital
Southmoor Road
Manchester
M23 9LT

E-mail: naren.basu@uhsm.nhs.uk

National Survey on Surgeon's Perspective on Contralateral Risk Reducing Mastectomy (CRRM)

Dear

Contralateral risk reducing mastectomy, removal of the opposite healthy breast in women with breast cancer, is a contentious issue. Data from the USA suggests that rates of CRRM have almost trebled in the last decade.

In the UK, there are no guidelines for when to perform this procedure and no consensus amongst surgeons as to indications for this procedure. This study aims to assess the perceptions of breast surgeons on this topic so that future decisions on CRRM can be made more objectively.

We would be grateful for a few minutes of your time to complete the questionnaire and kindly return it in the self-addressed envelope provided.

Once again, many thanks for your help.

Kind regards,

Mr Naren Basu - National Oncoplastic Fellow
Mr Lester Barr - Consultant Surgeon and Chairman of Genesis Breast Cancer Prevention
Professor Gareth Evans - Professor of Medical Genetics and Chairman NICE Familial Breast Cancer Group
Mr Gary Ross - Consultant Plastic Surgeon and BAPRAS Breast Lead

Please tick the appropriate box or fill in the details

1. Your details - Age 30-40 ☐ 41-50 ☐ 51-60 ☐ >60 ☐

- Male ☐ Female ☐

Speciality: - Breast Surgeon ☐ Plastic Surgeon ☐

Grade: - Consultant ☐ SAS Grade ☐

2. Trends in CRRM

A) Approximate number of CRRM performed in the last 12 months:

0 ☐ 1-2 ☐ 3-5 ☐ 6-10 ☐ >10 ☐

B) Requests for CRRM by patients in your practice are:
Increasing ☐
Decreasing ☐
No change ☐
Unsure ☐

C) In your practice, the incidence of contralateral breast cancer is:
☐ Increasing
☐ Decreasing
☐ Unchanged
☐ Not sure

D) In your practice, survival in patients who develop contralateral breast cancer is: ☐ Reduced ☐ Unchanged ☐ Not sure

E) What approximate risk (annual incidence %) of developing contralateral breast cancer do you quote to your patients without any additional risk factors:
☐ 0.1% ☐ 0.2-0.4% ☐ 0.5-0.7% ☐ 0.8-1% ☐ >1%

3. Funding:

A) Have you ever been refused funding for CRRM? ☐ Yes ☐ No
If YES, please elaborate in comments Section 5.

B) In the next 3 years, I expect we will have to apply to the PCT/CCG or equivalent for funding:
☐ Agree ☐ Disagree

4. Decision making:

A) In your unit, which professionals are involved in the decision making process for CRRM:

Single Surgeon Always ☐ Sometimes ☐ Never ☐
Second Surgeon Always ☐ Sometimes ☐ Never ☐
Breast Care Nurse Always ☐ Sometimes ☐ Never ☐
Oncologist Always ☐ Sometimes ☐ Never ☐
Psychologist Always ☐ Sometimes ☐ Never ☐

Geneticist Always ☐ Sometimes ☐ Never ☐

B) Requests of CRRM are discussed in the multi-disciplinary meeting:

Always ☐
Sometimes ☐
Never ☐

C) Please rank from the list below the top 5 reasons patients request CRRM in your experience (1- most important, 5 – least important):

☐ Fear/anxiety of getting another breast cancer
☐ Young age
☐ Desire to have reconstruction match / symmetry
☐ Concern regarding family history
☐ Mistrust of surveillance
☐ BRCA status
☐ Recommendation from family/friend
☐ OTHER – Please specify

D) Please rank from the list below the top 5 factors you feel are important in the assessment of the patient's risk for developing contralateral breast cancer (1 – most important, 5 – least important)

☐ Young age
☐ Histology (e.g. lobular)
☐ Family history
☐ BRCA status
☐ Lymph node status
☐ Grade
☐ Stage
☐ ER / PR negativity
☐ HER2 positivity
☐ Multi-centric disease
☐ Breast density
☐ Obesity
☐ Pre-malignant disease e.g. LCIS

5. Comments:

Please include any comments in the space below:

Appendix 3.

Published risk allele frequencies (Turnbull et al. 2010)

Associations in the current study at previously known breast cancer loci

	Strongest association in current study				Published association				Association for published SNP in current study			
Locus	**Most signifcant SNP**	**Alleles[a]**	**Per-allele OR (95% CI)[b]**	***P***	**Published SNP**	**Alleles[a]**	**(r^2)[c]**	**Published OR**	**Best tag in GWAS (r^2)[d]**	**Alleles[a]**	**Per-allele OR (95% CI)[b]**	***P***
FGFR2	rs2981579	G/A (0.42)	1.43 (1.35–1.53)	3.6×10^{-31}	rs2981582[e]	G/A (0.38)	1.0	1.26 (1.22–1.29)[1]	rs2981579 ($r^2 = 1.0$)	G/A (0.42)	1.43 (1.35–1.53)	3.6×10^{-31}
TOX3	rs3803662	G/A (0.26)	1.30 (1.22–1.39)	3.2×10^{-15}	rs3803662	G/A (0.25)	1.0	1.19 (1.15–1.23)[1]	rs3803662	G/A (0.26)	1.30 (1.22–1.39)	3.2×10^{-15}

	Strongest association in current study				Published association				Association for published SNP in current study			
Locus	**Most signifcant SNP**	**Alleles[a]**	**Per-allele OR (95% CI)[b]**	***P***	**Published SNP**	**Alleles[a]**	**(r^2)[c]**	**Published OR**	**Best tag in GWAS (r^2)[d]**	**Alleles[a]**	**Per-allele OR (95% CI)[b]**	***P***
MAP3K1	rs889312	A/C (0.28)	1.22 (1.14–1.30)	4.6×10^{-9}	rs889312	A/C (0.38)	1.0	1.12 (1.08–1.16)[1]	rs889312	A/C (0.28)	1.22 (1.14–1.30)	4.6×10^{-9}
8q24	rs1562430	C/T (0.58)	1.17 (1.10–1.25)	5.8×10^{-7}	rs13281615	A/G (0.40)	0.42	1.08 (1.05–1.12)[1]	rs13281615	A/G (0.41)	1.14 (1.07–1.21)	2.2×10^{-5}
2q35	rs13387042	G/A (0.49)	1.21 (1.14–1.29)	2.0×10^{-10}	rs13387042	G/A (0.49)	1.0	1.12 (1.09–1.15)[10]	rs13387042	G/A (0.49)	1.21 (1.14–1.29)	2.0×10^{-10}
LSP1	rs909116	C/T (0.53)	1.17 (1.10–1.24)	7.3×10^{-7}	rs3817198	T/C (0.30)	0.23	1.07 (1.04–1.11)[1]	rs3817198	T/C (0.33)	1.12 (1.05–1.19)	0.0006

	Strongest association in current study				Published association				Association for published SNP in current study			
Locus	**Most signifcant SNP**	**Alleles[a]**	**Per-allele OR (95% CI)[b]**	***P***	**Published SNP**	**Alleles[a]**	**(r^2)[c]**	**Published OR**	**Best tag in GWAS (r^2)[d]**	**Alleles[a]**	**Per-allele OR (95% CI)[b]**	***P***
5pl2	rs9790879	T/C (0.40)	1.10 (1.03–1.17)	0.0032	rs10941679	(A/G) (0.25)	0.48	1.19 (1.11–1.28)[4]	rs7716600 (r^2 = 0.75)	C/A (0.22)	1.11 (1.04–1.19)	0.0034
6q25.1	rs3757318	G/A (0.07)	1.30 (1.17–1.46)	2.9×10^{-6}	rs2046210	G/A (0.34)	0.088	1.15[f] (1.03–1.28)[7]	rs6900157 (r^2 = 0.96)	T/C (0.35)	1.15 (1.08–1.22)	1.8×10^{-5}
SLC4A7	rs4973768	C/T (0.47)	1.16 (1.10–1.24)	5.8×10^{-7}	rs4973768	C/T (0.46)	1.0	1.11 (1.08–1.13)[5]	Rs4973768	C/T (0.47)	1.16 (1.10–1.24)	5.8×10^{-7}
COX11	rs1156287	A/G (0.29)	0.91 (0.85–0.97)	0.0058	rs6504950	G/A (0.27)	0.91	0.95 (0.92–0.97)[5]	rs7222197 (r^2 = 1.0)	G/A (0.28)	0.92 (0.86–0.99)	0.021

	Strongest association in current study				Published association				Association for published SNP in current study			
Locus	**Most signifcant SNP**	**Alleles[a]**	**Per-allele OR (95% CI)[b]**	***P***	**Published SNP**	**Alleles[a]**	**(r^2)[c]**	**Published OR**	**Best tag in GWAS (r^2)[d]**	**Alleles[a]**	**Per-allele OR (95% CI)[b]**	***P***
RAD51L1	rs8009944	C/A (0.75)	0.88 (0.82–0.95)	0.0004	rs999737	C/T (0.24)	0.13	0.94 (0.88–0.99)[6]	rs999737	C/T (0.25)	0.89 (0.83–0.95)	0.0009
lpll.2	rs11249433	A/G (0.42)	1.08 (1.02–1.15)	0.010	rs11249433	A/G (0.39)	1.0	1.16 (1.09–1.24)[6]	rs11249433	A/G (0.42)	1.08 (1.02–1.15)	0.010
CASP8	rs10931936	T/C (0.74)	0.88 (0.82–0.94)	0.00015	rs1045485	G/C (0.13)	0.083	0.88 (0.84–0.92)[8]	rs17468277 (r^2 = 1.0)	C/T (0.13)	0.93 (0.85–1.02)	0.14

[a]Allele (frequency of the second listed allele).

[b]Per-allele OR for the second listed allele, relative to the first. In each case the second listed allele was that which correlated with the second-listed published allele.

[c] r^2 between the published SNP and most significant SNP in this study based on HapMap CEU.

[d] r^2 between the published SNP and the best tagSNP in this study based on HapMap CEU.

[e] Note that fine-mapping and functional analyses suggest that the strongest association for breast cancer is with rs2981578[25]. It is correlated with rs2981579 and rs2981582 at $r^2 = 0.85$.

No more strongly correlated tag for rs2981578 was typed in the GWAS.

[f] Estimated OR in Europeans. Estimated OR in Chinese was 1.36

Appendix 4

InCRisC Questionnaire

Appendix 5

List of published manuscripts