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Breast Cancer and *BRCA1* and *BRCA2* Pathogenic Variants

Naren Basu and D. Gareth Evans

Abstract

Breast cancer remains the most common female cancer worldwide. The majority will arise spontaneously, with almost a third having a heritable component. Approximately 5–10% of all breast cancers will have a strong inherited element with pathogenic variants in the *BRCA1* and *BRCA2* amongst the most studied breast cancer genes. An overview of breast cancer is provided with references to the clinical and pathological features in *BRCA1* and *BRCA2* related cancers. The roles of PARP inhibitors and immunotherapy are discussed. The management of healthy individuals harbouring a pathogenic variant in the two genes is reviewed and future directions considered.

Keywords: *BRCA1*, *BRCA2*, breast cancer, risk reduction, mastectomy, pathogenic variant

1. Introduction

Breast cancer remains the most common cancer amongst women in the world [1]. In the UK, 25% of all female cancers originate from the breast with estimates that 1 in 7–10 will develop this disease during their lifetime [2]. In 2018, there were over 2 million new cases of breast cancer worldwide, accounting for almost 12% of all cancer [3]. In developed countries, almost 80% of breast cancers occur in post-menopausal women, predominantly in the Caucasian population.

Breast cancer represents a heterogenous disease process and an understanding of the clinical aspects is required prior to appreciating the aspects of breast cancer amongst *BRCA1/2* pathogenic variant (PV) carriers.

2. Invasive or *in-situ* (non-invasive cancer)

The vast majority of breast cancers are invasive (up to 90%) presenting via a symptomatic pathway. In contrast, *in-situ* disease tends to be more commonly identified via breast screening programmes (e.g., NHSBSP) with advances in digital mammography or incidentally. In the USA, *in situ* disease comprises almost 25% of all breast cancers, 80% of which are identified by breast screening [4].

In histopathological terms, invasive cancers will have breached the basement membrane with metastatic potential compared with the more innocuous *in-situ* disease where the disease process is contained within the basement membrane, with theoretically limited or no metastatic potential.

3. Ductal or lobular origin

The microanatomy of the breast can be considered to comprise of terminal ductal lobular unit [5, 6]. Each breast lobule is by a collecting duct terminating in the lobule. This serves as the basic functional unit of the breast. Invasive ductal carcinoma (also termed no special type carcinoma) represents the most common type of breast cancer accounting for almost 80% of cancer. Invasive lobular carcinoma is less common accounting for almost 10% of cases.

These two types of breast cancer are biologically different. Invasive lobular cancers tend to have a more spreading growth pattern, meaning that they can be more difficult to diagnose or size on routine mammograms or clinical examination. In addition, they may be resistant to neo-adjuvant chemotherapy. Invasive lobular cancers tend to be more hormone-sensitive, HER2 negative and lower grade breast cancer (see below).

4. Grade of breast cancer

This refers to the microscope assessment of the breast cancer and determining how the cells look compared with normal breast tissue [6]. This in turn will predict the biological activity of the breast cancer, with high-grade tumours considered to be faster growing with a more aggressive behaviour.

4.1 Grades in in-situ disease

Low grade—slow growing and more closely resemble normal breast tissue.

Moderate/intermediate grade—more abnormal looking compared with low grade, with a more rapid growth pattern.

High grade—cells look quite different to normal breast tissue, grow quicker with an increased chance of progressing to an invasive cancer.

4.2 Grades in invasive cancer

There are three different grades of invasive breast cancer based on an assessment of tubule formation, nuclear pleomorphism and mitotic count:

Grade 1 (well differentiated).

Grade 2 (moderately differentiated).

Grade 3 (poorly differentiated).

5. Hormone receptor status

Oestrogen receptors (ER) were first identified in 1958 (Elwood, Chicago) but an appreciation of the hormonal component of breast cancer predates this to the 1890s when George Beatson performed oophorectomy as a treatment for breast cancer in women [7]. It still remains a critical biological factor in the modern day management of breast cancer.

The oestrogen (ER) and progesterone receptors (PR) relevant to breast cancer are intracellular receptors that are activated by the hormone oestrogen (17 beta oestradiol) acting as a DNA-binding transcription factor, in particular stimulation of mammary cells.

Approximately 70–80% of breast cancers overexpress ER [8]. These hormone sensitive breast cancers may be treated with anti-hormone therapy by either selective oestrogen receptor modulators (e.g., Tamoxifen) or aromatase inhibitors.

6. HER2 receptor status

The HER2 receptor (human epidermal growth factor receptor) is a trans-membrane tyrosine kinase that is overexpressed in 15–20% of breast cancers [9]. Amplification of this oncogene is considered a marker of aggressiveness and is an important biomarker for targeted therapy. Drugs targeting the HER2 receptor (e.g., Trastuzumab, Pertuzumab) have significantly altered the clinical outcomes of otherwise poor prognosis HER2 positive breast cancers.

7. Molecular subtypes of breast cancer

Gene expression profiling has enabled molecular classification of breast cancer into intrinsic subtypes [10] that include:

1. Luminal A: hormone receptor positive (ER/PR +ve) and HER2 negative. They express low levels of the protein Ki-67, a cellular marker for proliferation. These cancers tend to be low grade, slow growing, good prognosis cancers.
2. Luminal B: hormone receptor positive (ER/PR +ve) and either HER2 positive or negative with a high level of Ki-67 expression. Faster growing and worse prognosis than luminal A cancers.
3. Triple negative breast cancer (TNBC)/basal-like: these are hormone receptor negative and HER2 negative (ER/PR/HER2 –ve). This accounts for 10–20% of all breast cancers, more commonly found in women with a *BRCA1* PV, young women and African-American women. It is a rapidly growing, poor prognosis cancer.
4. HER2-enriched: these are HER2 positive and ER/PR negative cancer (HER2 +ve, ER/PR –ve). They tend to grow faster than luminal cancers but can be treated with targeted therapies.

8. Treatments for breast cancer

The management of breast cancer is a multi-modal delivered in a multi-disciplinary setting. In brief, treatments include:

8.1 Surgery

Excision of the breast lesion and assessment of the axillary lymph node for regional metastasis. Historically this involved mastectomy with axillary clearance, which has now been refined following some seminal trial in breast cancer surgery to offering appropriate women breast conserving surgery (“lumpectomy”) and sentinel node biopsy. There are still important indications for mastectomy that would include genetic mutation status, family history, previously treated breast cancer, inflammatory breast cancer and patient choice.

8.2 Anti endocrine therapy

Hormone sensitive breast cancers are treated with anti hormonal therapy for a minimum period of 5 years that can be extended to 10–15 years based on recent

emerging data. There is an improved overall survival, reduced recurrence rate and reduction in the incidence of a contralateral breast cancer.

8.3 Radiotherapy

This is a localised, targeted therapy of high-energy X-rays that complements breast conservation surgery in almost all cases of invasive cancer, reducing local recurrence rates by almost 20–30% [11]. It may be offered following mastectomy if there is a high burden of disease.

8.4 Chemotherapy

This systemic treatment may be offered pre surgery (neo adjuvant) or post surgery (adjuvant). The choice of chemotherapy regimen is determined by number factors and may include anthracycline-taxane combinations. Perceived benefits include an improvement in survival, reduction in local recurrence and downstaging of tumour burden.

8.5 Anti HER2 treatment

HER2 targeted immunotherapy consists of monoclonal antibodies (e.g., Trastuzumab)—previously discussed.

8.6 Other treatments

PARP inhibitors: poly ADP Ribose Polymerase inhibitors are targeted therapies with increasing use in patients with a PV in the *BRCA1/2* gene. This is discussed in more detail later.

Immunotherapy: this involves stimulating the host immune system actively immunisation (use of cancer vaccine) or passive immunisation (use of tumour specific antibodies or immune modulators). Of particular growing importance is the identification of patients with TNBC overexpressing immune evasion molecules (e.g., PDL: programmed death ligand) that may offer an additional treatment modality in this poor prognosis group [12].

9. Breast cancer genetics

The majority of breast cancers arise spontaneously—with known risk factors that include oestrogen exposure, reproductive history (late first or no pregnancy) and lifestyle practices. However, a significant proportion (20–30%) of cancers will have an inherited component, with family history remaining the strongest risk factor [13]. These tend to be classed as germline PVs in contrast to somatic mutations—arising from the interactions between environment and genetics.

Approximately 5–10% of breast cancer will have a strong inherited component that can be further sub-divided [13] according to strength of penetrance:

9.1 High penetrance genes

- *BRCA1*
- *BRCA2*
- *PALB2*

- *TP53*
- *PTEN*
- *STK11*
- *CDH1*

9.2 Moderate penetrance genes

- *ATM*
- *CHEK2*
- *NF1*
- *BARD1*

9.3 Low penetrance genes

The advent of Genome wide association studies has rapidly enabled the identification of over 100 breast cancer single nucleotide polymorphisms [14] that confer a small individual increase or decrease in breast cancer risk, but appear to work in a polygenic, multiplicative pattern contributing to a more significant risk.

10. Breast cancer and the *BRCA1* gene

This tumour suppressor gene was first identified in 1990 and cloned 4 years later in the US [15]. During the next two decades a bitter commercial battle ensued regarding patenting of the genomic DNA sequence to both *BRCA1* and *BRCA2*. Ultimately, the 2013 US Supreme Court (Association of Molecular Pathology vs. Myriad Genetics) ruled that “*isolation of genes found in nature do not render them patentable*” [16].

The human *BRCA1* gene (Chromosome 17—codes for the breast cancer type 1 susceptibility protein) is involved in non error prone homologous DNA repair. The majority of PVs are frameshift resulting in a truncated protein with founder PVs in the Ashkenazi Jewish populations and Eastern European population [13].

10.1 Penetrance and lifetime risk

The inheritance pattern is autosomal dominant with birth incidence of a *BRCA1* PV estimated at 1 in 500–900, accounting for 7–10% of familial breast cancer [13].

Harbouring a *BRCA1* PV confers a lifetime risk of breast cancer of approximately 60–85% [17, 18] and up to 60% for developing ovarian cancer (usually high-grade serous carcinomas). Risk of breast cancer is inversely proportional to age—a trend not so clearly seen in ovarian cancer (i.e., not age dependant). A recent prospective cohort study of 6036 *BRCA1* PV carriers [19] identified that the breast cancer incidences per decade of age increased from 21–30 years to 31–40 years but then remained at 23.5–28.3 per 1000 person years from age 31 to 70 years. Therefore, there is a rapid increase in breast cancer incidence in early childhood that plateaus and remains constant throughout the remaining adult life.

Family history of breast cancers amongst first and second-degree relatives increased the relative risk breast cancer, a trend not seen in ovarian cancer risk in

families with ovarian cancer. *BRCA1* PVs located outside the region bounded by c.2282 to c.4071 were associated with the highest risk of developing breast cancer [19].

There is a significant risk of developing a contralateral breast cancer once diagnosed with breast cancer. Our own studies have confirmed that this risk is approximately 2–3% per year, persists for at least 30 years.

Other cancers associated with this PV 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) [13].

10.2 Pathology of *BRCA1* cancers

BRCA1 related breast cancers are heterogenous but have some important clinical features. They are most often triple negative approximately 70–80% (ER, PR, Her2 –ve) with expression of basal markers (CK5/6, CK14, SMA, P Cadherin, EGFR0). Histologically, they are similar to high-grade medullary carcinomas with pushing margins, high mitotic counts and lymphocytic infiltrate [20].

The international collaborative study (CIMBA) assessed pathological characteristics amongst 3797 *BRCA1* carriers [21] and identified that the mean age of breast cancer was 40 years. The majority of breast cancers were of the ductal, no-special type variety with the majority of cancers demonstrating a basal-triple negative phenotype (78% of tumours were ER-negative, 79% were PR-negative, 90% HER2-negative and 68% TNBC). High-grade tumours were most common, with a clear relationship between age at diagnosis and grade of breast cancer—grade decreased with increasing age.

11. Breast cancer and the *BRCA2* gene

This DNA repair gene was localised in the UK in 1994 and identified (cloned) in 1995 [22]. It is situated on Chromosome 13 at position 12.3 (13q12.3). Although the structures of the *BRCA1* and *BRCA2* gene vary from each other, there is some functional overlap. *BRCA1* associates with *BRCA2* through *PALB2*, a major binding partner of *BRCA2*. There is some data to suggest that *BRCA1* acts as an upstream regulator of *BRCA2* as *BRCA1* promotes the concentration of *PALB2* and *BRCA2* at DNA damage sites [23].

11.1 Penetrance and lifetime risk

PVs in *BRCA2* are nearly all inherited suggesting a large founder effect. This is important for practical purposes as certain populations can be tested for known PVs (e.g., single PV 999del5 accounts for almost all inherited breast and ovarian cancer in Iceland) [13].

Lifetime breast cancer risk has a wider range (40–85%) compared with *BRCA1*, and a slightly lower risk of developing ovarian cancer (20–30%) [13]. Approximately 1 in 400–800 women carry a PV (outbred population) that accounts for 10% of familial breast/ovarian cancer [14].

Several other cancers are more commonly associated with these PV: cholangiocarcinoma, melanoma, pancreatic cancer (overall RR 4.1), gastric cancer (RR 2.7) and prostate cancer (10–20% life time risk) [13]. Approximately 10% of male breast cancer is associated with *BRCA2*, a trend not seen in *BRCA1* PVs.

11.2 Pathology of *BRCA2* cancers

Breast cancer in *BRCA2* PVs carriers is a more heterogeneous group compared with *BRCA1* carriers, with more semblance to sporadic breast cancers. Pathology

shows that these breast cancers are more often ER+ve compared with controls, with some studies showing increased DCIS and lobular cancer [20].

A study of breast cancer amongst 6893 *BRCA1* and *BRCA2* PV carriers found similar proportion of ductal, no-special type cancers (approximately 80%) with a four-fold increase in lobular cancers amongst *BRCA2* carriers (8% compared with 2% in *BRCA1* patients) [21]. Overall, there were double the number of Grade 1 and 2 cancers in the *BRCA2* compared with *BRCA1*, with more Grade 3 cancers in the *BRCA1* group (77% compared with 50% in *BRCA2* carriers).

There is paucity of data regarding the pre-invasive progression pathway amongst *BRCA1/2* carriers. Whereas a DCIS associated pre-malignant pathway has been postulated in sporadic cancers, this has not been shown in *BRCA1/2* PV carriers. There is conflicting data regarding incidence of DCIS in this patient group. Some reports suggest an increased incidence of DCIS identified in risk-reducing mastectomy specimens as opposed to other studies identifying DCIS less frequently near the invasive cancer compared with sporadic tumours [24].

12. Prognosis for *BRCA* mutated breast cancer

The POSH study (Prospective Outcomes in Sporadic versus Hereditary breast cancer), designed as a prospective cohort study, assessed the outcomes of women aged 40 years or below diagnosed with an invasive breast cancer in the UK [25]. With a follow up of nearly 10 years, 12% of all patients were identified with a PV in either the *BRCA1/2* gene. Multivariate analysis identified no overall difference in survival between *BRCA* positive or *BRCA* negative patients. Amongst patients with TNBC, there was a short-term survival benefit at 2 years amongst *BRCA* carriers. The authors hypothesised that this short-lived benefit may reflect greater sensitivity of *BRCA* mutant cancer to chemotherapy and/or greater visibility of *BRCA* related cancers to the immune system [25].

Studies prior to the POSH studied inconsistent effects of *BRCA1/2* PV status on breast cancer outcomes. A meta-analysis of 66 relevant studies [26] did not identify inferior breast cancer outcomes amongst *BRCA1/2* PV carriers despite the biological differences in breast cancer type already discussed.

In addition these women have similar survival whether they are treated with breast conservation surgery or a mastectomy, despite having significant higher rates of local failure with breast conservation [27]. An international longitudinal study of 655 patients with *BRCA1/2* PVs showed no differences in overall survival, distant or regional recurrence at 20 years whether women underwent a mastectomy or breast conservation therapy with radiotherapy. Interestingly, most local recurrences are second primary breast cancers rather than failure to control the primary breast cancer [27].

12.1 Radiotherapy

The effect of radiotherapy on *BRCA1/2* associated breast cancer merits consideration. These cancers are characterised by defects in homologous recombination, resulting in inadequate repair of double stranded DNA breaks—a hallmark of PVs in the *BRCA1/2* genes. In particular, younger patients with a higher rate of cell proliferation may be more susceptible to the carcinogenic effects of radiotherapy. Studies have confirmed an increased risk of contralateral breast cancer amongst young patients with a sporadic breast cancer treated with radiotherapy suggesting an effect of low-dose scatter radiation to surround healthy tissue [28].

In patients with a *BRCA1/2* PV associated breast cancer treated with unilateral radiotherapy, hypothetically there should be an increased risk of contralateral

breast cancers particularly in the younger patient group, as the contralateral healthy breast will receive some scatter radiation. In addition, adjuvant radiotherapy to the index breast of *BRCA1/2* PV carriers should be more efficacious compared with sporadic cancer by virtue of the aberration in DNA repair. A recent Dutch study was not able to demonstrate any association between radiotherapy and contralateral breast cancer risk [29]. They observed a growing trend in their population group of *BRCA1/2* PV carriers away from breast conservation with radiotherapy towards mastectomy and contralateral mastectomy.

12.2 Chemotherapy

Healthy, normal breast tissue exposed to toxic, chemotherapeutic agents will result in DNA damage that is then partly repaired by the *BRCA1/2* DNA damage response. Different chemotherapy agents used to treat breast cancers exhibit differences in mechanism of action. Taxane-based agents work by disrupting the microtubule function whereas anthracyclines induce topoisomerase II mediated toxicity, DNA intercalation and generation of reactive oxidative species. In vitro studies have shown that platinum based chemotoxic agents have a greater sensitivity for *BRCA1* mutated cell lines which may in part be due to the disruption of DNA [30].

12.3 PARP inhibitors

This class of targeted therapy work on the principle of “synthetic lethality” [31], whereby a defect in one gene/protein results in cell survival however when synthesised with another gene/protein results in cell death.

Poly ADP Ribose Polymerase (PARP1) is an important protein that repairs single strand DNA breaks. Drugs that inhibit this protein (PARP inhibitors) result in multiple breaks in double stranded DNA that cannot be repaired, resulting in cell death. A proof of concept international study [32] showed a favourable therapeutic index for Olaparib (an orally active PARP inhibitor) amongst patients with advanced or recurrent breast cancer who harboured a *BRCA1/2* PV. The OlympiAD study, an international, randomised, Phase III trial recently reported an improved progression free survival amongst patients with metastatic breast cancer who were HER2 negative with a germline PV in either *BRCA1/2* [33]. Future directions of research will include combining PARP inhibitors with radiotherapy and platinum based agents [34].

12.4 Risk-reducing surgery

Bilateral risk-reducing mastectomy (BRRM) offers the greatest magnitude of overall risk reduction in health patients harboring a *BRCA1/2* PV 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 [35] 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.

Uptake of BRRM varies amongst women in this high-risk group. From a patient's perspective, young age and motherhood seem to be positive predictors for choosing surgery [36–38]. 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 with Poland (3%) and Israel (4%) [39, 40]. 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 three different Canadian regions, the range of uptake was from 8 to 46% [41]—suggesting that other factors are important.

Media coverage and public interest in BRRM has been heightened since 2013 when Angelina Jolie's revealed her personal experience of bilateral mastectomies based on her inheriting a pathogenic *BRCA1* PV from her late mother. The so-called "Angelina Jolie Effect" ensued with increased uptake of genetic testing and BRRM in the US and UK [42–44].

12.5 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) [45, 46], 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.

The risk reduction for breast cancer has recently been reassessed for potential selection bias [47]. This study used the same methodology previously described [45] to study a cohort of Dutch *BRCA1/2* 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 with BRRSO—women only choosing BRRSO over BRRM may have had their breast cancer risk reduction overestimated if they only chose BRRSO.

12.6 Chemoprevention

In the UK, healthy women with a *BRCA1/2* PV may consider three medications to reduce their risk:

Tamoxifen: this selective oestrogen receptor modulator (first generation) has been shown to reduce the risk in asymptomatic women by approximately 40–50% [48]. 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 [49]. Tamoxifen may be considered in pre and post menopausal women.

Raloxifene (second 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 [50]. 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 [51]. 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 with 4% in the placebo group [52].

Although there is not good quality evidence to show that endocrine therapy is not effective in *BRCA1* as 70–80% of breast cancers are triple negative and these medications only reduce ER positive cancers they may have less efficacy in *BRCA1* PV carriers.

12.7 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 [53].

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 min weekly activity, BMI < 25, <1 alcoholic drink daily) has been shown to reduce mortality in *BRCA* carriers by almost 60% [54].

The LIBRE study (Lifestyle Intervention in *BRCA1/2* PV carriers) aims to randomise healthy *BRCA1/2* PV carriers to a number of lifestyles interventions versus a control group and assess changes in physical and psychological well being [55].

13. Discussion

The worldwide burden of breast cancer poses significant challenges to health care providers. There is an increasing awareness that this heterogeneous disease requires a multi-modality approach with consideration to both prevention and treatment.

Diet and lifestyle are important modifiers in the prevention of breast cancer. Adherence to physical activity and alcohol guidelines may reduce the risk of developing breast cancer (pre and post menopausal), with weight control being more important in prevention in the post menopausal cohort [56]. Energy restriction, in particular intermittently is associated with changes in breast gene expression and systemic metabolism [57]. Future studies will need to assess the mechanism and clinical significance in breast cancer pathogenesis.

Breast cancer metabolomics is an area of growing interest. A recent study was able to determine a differential metabolic signature based on *BRCA1* functionality [58] and may provide future biomarkers.

An area of interest is establishing whether breast cancer may be considered a communicable disease. There is established causality of infection with the Human Papilloma Virus and a number of cancers namely cervical cancer and associations with penile, anal and vulvar cancer. A similar aetiology has been postulated with breast cancer with entry of the virus via the nipple areolar complex resulting in biological activity within the mammary duct epithelium resulting in breast cancer. Data from Norway [59] have identified a possible association of pre-malignant changes in the cervix and an increased risk of subsequent breast cancer. A subsequent UK study [60] has identified the presence of high-risk HPV DNA in 42% of breast cancers with viral activity confirmed in less than 20% of invasive cancers suggesting that this may be an area of on going interest in the future.

Gene therapy in cancer aims at correcting specific genetic anomalies contributing to the development of certain cancers. This can be subdivided into germline and somatic cell gene therapy and is an important treatment modality in disease processes like cystic fibrosis and blood disorders. Several *BRCA1* retroviral vectors were

assessed in Phase 2 clinical trials in ovarian cancer almost two decades ago [61] with some initial potential as a therapeutic modality. The lack of progress in viral vectors suggests that newer techniques such as gene editing may find a place.

The UK 100,000 Genome project completed recruitment in 2018. Breast cancer patients represent a significant proportion of the 85,000 patients either with a cancer or rare disease diagnosis. Whole genome sequencing has allowed rapid analysis of the entire genome in this patient subgroup and is already aiding clinicians in making therapeutic decision in breast cancer, although no new hereditary genes have yet been identified from this initiative.

14. Conclusion

Pathogenic variants in the *BRCA1* and *BRCA2* gene confer a substantial lifetime risk of developing breast cancer. These breast cancers display characteristic clinical and pathological features that are important in the clinical management of the disease.

Multiple strategies exist for healthy individuals harbouring PVs in these genes. This comprises surveillance using modern day radiology (mammography and MRI scans) and risk reducing strategies. The latter include bilateral risk-reducing mastectomy, bilateral salpingo-oophorectomy, chemoprevention and lifestyle modification.

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