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GUIDELINES

Management guidelines for BRCA positive women in South Africa and other limited resource settings

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Introduction

There has been much written and researched since the discovery of the BRCA genes in the 1990s. Mutations of BRCA1 and 2 genes are responsible for the hereditary breast and ovarian cancer syndrome (HBOC). The lifetime risk of breast cancer cumulatively in women with BRCA mutations is 60–80%, and these cancers often arise in younger women. The lifetime risk of ovarian cancer is 40–50% in BRCA1 mutation carriers, while BRCA2 positive women have a slightly reduced lifetime risk of approximately 10–30%.[1,2] This compares to the lifetime risk of breast and ovarian cancer in the general population which is 12.3% and 1.4% respectively.[3]

In a country like South Africa with such diversity and differences in access to education and healthcare, knowledge about hereditary cancer syndromes varies. Someone with a strong family history of breast and/or ovarian cancer may want to ascertain what their risks are, and find ways to manage this risk. On the other hand, where there is no or limited knowledge on HBOC, some form of guideline on screening, education and management should exist.

Screening

Screening refers to the identification of women who are at risk of carrying a BRCA mutation. There are various screening tools such as the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool and the Family History Screen (FHS-7).[4] These tools aim to determine factors contributing to increased risk, such as early age of cancer diagnosis in a first or second degree relative or a personal history, bilateral breast cancer, male family member with breast cancer, Ashkenazi Jewish descent or a personal or family history of both breast and ovarian cancer. Each of these tools has its limitations and there is no preferred or superior screening tool.[4] The aim is to identify high risk women who can then be referred to adequately trained genetic counsellors for pre- and post-test counselling. This includes BRCA test interpretation, education and discussing the implications of a positive test result.

There is limited data on BRCA in African populations. As a consequence, most of the screening and management is extrapolated from studies in developed countries.

This article aims to focus on management strategies once a woman has been confirmed to be BRCA positive.

A. Surveillance

A.1 Breast cancer: Surveillance for the prevention of breast cancer includes breast self-examination, clinical breast examination and breast imaging at regular intervals. Women identified as high risk are encouraged to do self-examination from age 18 although this practice has not been found to reduce the incidence of breast cancer.[5] It is recommended that clinical examination by a healthcare member who has experience in breast examination should commence from age 25 or 5–10 years prior to the age that a family member was diagnosed with breast cancer.[6] This practice also has not been shown to reduce cancer, but it provides some reassurance to high risk individuals and also allows them to connect with their health providers.[7]

Previously annual mammography was recommended in high risk women from the age of 25 or 5–10 years prior to a family cancer diagnosis.[8] There are concerns about exposure to ionising radiation annually from the age of 25 years. Studies that reviewed BRCA positive women who had annual mammography and the risk of radiation-induced breast cancer found that there was no net benefit of annual mammography between the ages of 25 to 29 years, however the benefit increased slightly from age 30 to 44 years.[9,10] Many studies have shown that magnetic resonance imaging (MRI) is superior to mammography in identifying cancers in high risk individuals.[11,12] MRI also had the advantage of eliminating the exposure to radiation.

Most recent guidelines (NCCM 2017) recommend annual MRI as the screening test in high risk women from age 25 until age 29.[13] Thereafter annual mammography is the test of choice. An ideal resource-rich healthcare environment should incorporate a combination of clinical examination, mammography, ultrasound and MRI. However, in a resource limited system, it is reasonable to do annual – two-yearly clinical breast examination,

mammography and ultrasound in selected cases. In view of radiation exposure, it would also be reasonable to start this practice at 30 years of age or 5–10 years prior to diagnosis of the relative.

A.2 Ovarian cancer: There is no evidence to support screening for ovarian cancer in the general population. Multimodal screening with transvaginal ultrasound and CA125, as compared to CA125 alone, detects cancer at an earlier stage but has no impact on survival.[14] This is even more controversial in high risk BRCA positive women as studies have not shown a benefit.[15,16] A more recent study found that combining CA125 4–6 monthly with a risk of malignancy algorithm [ROCA] in high risk women definitely causes a stage shift by earlier detection of cancer, however the impact on survival is still unknown.[17] Despite the lack of literature, screening with annual or semi-annual ultrasound and CA125 is still recommended in young BRCA positive women where fertility is desired, or if risk-reducing surgery is declined.

B. Chemoprevention

B.1 Breast cancer: Selective Oestrogen Receptor Modulators (SERMs) such as tamoxifen and raloxifene

It has been shown that SERMs reduce the risk of invasive breast cancer in postmenopausal women who are considered high risk for breast cancer.[18] The data on the use of these drugs in BRCA positive women is limited and often conflicting. Case controls studies of BRCA positive women who had already been diagnosed with breast cancer and were placed on tamoxifen showed a 45–60% reduction in a contralateral breast cancer. This study did not give any insight into hormone receptor status or impact on women who also had a risk-reducing bilateral oophorectomy.[19] There also seems to be some data alluding to the fact that tamoxifen only benefits BRCA2 positive women as many BRCA1 positive women may have receptor negative disease.[20]

B.2 Ovarian cancer: As with ovarian cancer in the general population, the combined oral contraceptive (COC) pill reduces the risk of ovarian cancer and this benefit increases with a longer duration of use of the COC. It has been shown that in both BRCA1 and BRCA2 carriers, the use of the COC has reduced ovarian cancer by 50%.[21] There has been conflicting data with regards to the use of the COC and risk of breast cancer. Two recent meta-analyses, however, have not shown an increase in breast cancer in high risk women.[21,22]

C. Risk-reducing surgery

All women who are BRCA carriers should be counselled on the options of risk-reducing surgery (RRS).

C.1 Prophylactic bilateral mastectomy: Bilateral mastectomy has been shown to reduce breast cancer risk by 90% in BRCA positive women.[23,24] This was confirmed by a meta-analyses which included six studies (N=2555), however this risk-reducing surgery did not decrease all-cause mortality significantly.[25] Counselling on RRS should also include information on psychosocial implications, as well as options of reconstructive surgery (either immediately or interval reconstruction) if available.

C.2 Prophylactic bilateral salpingo-oophorectomy: A meta-analyses of 10 studies has confirmed that risk reducing bilateral salpingo-oophorectomy (RRSO) in BRCA carriers reduces the risk of ovarian and fallopian tube cancer by 80%.[26] A recent observational study has highlighted differences in BRCA1 and BRCA2 carriers: it was found that with RRSO, cancers were picked up more frequently in younger women who were BRCA1 positive than BRCA2 positive. This prospective study of BRCA carriers (N-1079) found that RRSO reduced the incidence of ovarian and fallopian cancer by 85% when compared with observation over a 3-year period. In addition, it was found that RRSO reduced all-cause mortality at all ages in BRCA1 mutation carriers, however in BRCA2 carriers this benefit was only significant between the ages of 41 to 60 years of age.[27]

It is recommended that RRSO should be offered when childbearing is completed. In view of the most recent studies above, recent guidelines by the NCCN (2017) recommend that RRSO should be offered to BRCA1 carriers between the ages of 35–40 years.[13] It is reasonable to delay this in BRCA 2 carriers to age 40–45. It is important to counsel women that there is still a 1–4% risk of primary peritoneal cancer.[26]

RRSO has also been shown to reduce the risk of breast cancer by approximately 50% in BRCA1 and 2 mutation carriers in many studies, and this has been confirmed in a meta-analysis.[26,28] This is by virtue of reducing the exposure of hormones. In terms of the impact of RRSO on breast cancer reduction, there is limited data on the most appropriate age for RRSO.[13]

As the decision for RRSO is rather complex, counselling should be done by a clinician who is well informed and should discuss risk reduction of both breast and ovarian cancers as well as the impact on quality of life due to premature menopause (vasomotor effects, sexual impact, osteoporosis, as well as cardiovascular and cognitive effects).

Role of risk reducing bilateral salpingectomy [RRS] as an interim short term measure while awaiting definitive ovarian surgery

The more recent proposed theory that ovarian cancer arises from the fimbrial end of the fallopian tube as a precursor (serous tubal intra-epithelial cancer or STIC) has brought up questions on whether the fallopian tubes can be removed as risk reducing surgery in BRCA positive women where childbearing has been completed, but where ovarian function wants to be preserved for a few years before definitive surgery.

There are currently two concerns about this procedure. Firstly, the concern regarding ovarian blood supply with risk of premature menopause. Most studies have shown no difference in ovarian function at three months post-surgery, but there are no studies that look at long term data or the actual start of menopause in these women.[29]

More importantly, if women choose this option, they need to be adequately counselled that there are no guarantees that an interim cancer will not develop between the two procedures and that this procedure is currently an investigational procedure with no randomised controlled studies to support the practise.[30] However, it would not be unreasonable to offer a RRS as a measure of protection in high risk women who decline removal of the ovaries as a definitive procedure, still with the understanding that we cannot estimate risk reduction as there are no studies that give us absolute estimates.

In the South African setting, it would not be feasible in the state sector to do a 2-step procedure (RRS as an interim measure followed by oophorectomy) as it would be difficult to justify the use of limited theatre time when that time could be used for cancer surgery. However, the private sector may be able to afford this as long as the women are adequately counselled and accept the risks in view of improving quality of life with regards to delaying menopause. It is important that women understand that the standard of care recommended in BRCA positive women is risk reducing bilateral salpingo-oophorectomy.

Management post RRS

There is limited data on the management of BRCA mutation carriers after risk-reducing surgery.

1. **Management of risk after finding of STIC when performing RRSO**

RRSO requires serial sectioning of the fimbria by an experienced pathologist, as most of the serous tubal intra-epithelial carcinoma (STIC) or invasive carcinomas are found in the fallopian tubes, especially the fimbria. Despite the discovery of STIC leading to better understanding of the origin and pathology of ovarian carcinoma in BRCA positive women, there is limited data on what to do after STIC is found after RRSO. In a recent review of 407 BRCA positive women who underwent RRSO and follow-up from 1995 until 2009, 17 women (4 %) had STIC identified.[31] Ten of these women then underwent further surgical staging, of which all biopsies and specimens were negative. Three who had positive cytology received chemotherapy. Follow-up over 80 months revealed 100% survival. In view of the limited data and this study above, it can be cautiously recommended that full staging be omitted in the case of the incidental finding of STIC with RRSO. Also adjuvant chemotherapy could be omitted, especially if cytology is negative.

2. **Management of risk after RR bilateral salpingo-oophorectomy alone**

There are no studies to support screening for the 3–4% risk of primary peritoneal cancer. Women should be counselled about risk-reducing bilateral mastectomy, despite the reduction of breast cancer provided by the removal of the ovaries, as the breast cancer risk is still significantly higher than the general population.

3. **Management of risk after RR bilateral mastectomy**

There are no clear guidelines on how to manage BRCA positive women after RR bilateral mastectomy. It is prudent to do breast examination at least annually (whether or not breast reconstruction has been done). This is to detect any masses in the residual breast skin, chest wall or axilla that could be cancer. There is controversy among clinicians regarding breast imaging in this setting. There is no literature to guide management in this setting except a case report that suggests that ultrasound may be more useful.[32] Once again women should be counselled about risk-reducing bilateral oophorectomy.

4. **Management of risk after both RR mastectomy and bilateral salpingo-oophorectomy**

These women have not completely eliminated their cancer risk. Despite no clear recommendations or guidelines, annual or semi-annual clinical examination should continue. This is to detect any masses in residual breast, chest and axillary regions, as well as to investigate any abdominal symptoms as the risk of primary peritoneal cancer still exists.

Other cancer risks

It should be mentioned that though the main aim of management in a BRCA positive woman is to reduce risk of and mortality from ovarian and breast cancer, these women have also been documented to have a risk of other cancers such as melanoma and pancreatic cancers.[33]

Osteoporosis prevention

Women who have had RRSO at the approximate age of 40 years are at risk of developing osteopenia and osteoporosis.[34] Screening for osteopenia and osteoporosis with a DEXA scan should be incorporated into routine practice when following up these women.

Psychosocial support

Women who have been diagnosed with a cancer and found to be BRCA positive require extensive counselling and support. Besides their immediate cancer care, they have to deal with the impact of this diagnosis on siblings and children. Often a psychologist referral is warranted. It is also important to realise the implication of this diagnosis for women who have not been diagnosed with cancer: they are referred to as 'previvors'. The uncertainty that faces the individual with regards to cancer risk, medical choices and the impact of these treatments on quality of life is life altering. The aim should be empowerment with this knowledge, together with psychosocial support.

Conclusion

Women who have been diagnosed as BRCA positive require lifelong guidance, clinical examination and selective imaging with an emphasis placed on the prevention or reduction of breast and ovarian cancer. Risk reducing surgery significantly decreases the risk of these cancers, however there is still a small chance of cancer in the residual breast tissue as well as primary peritoneal cancer.

The private sector in South Africa is easily able to provide genetic analysis and care for these high risk women. The State sector, however, has limited funds and the main issue is the cost of the testing to confirm the BRCA status. Controversy arises when the family history is significant and the woman is unable to afford the comprehensive BRCA genetic testing. In these situations, it is reasonable to counsel the woman and her family regarding surveillance versus risk-reducing surgery and the implications and impact of this surgery on a woman. The importance of a multidisciplinary team cannot be emphasised, especially in these situations. This should include a genetic counsellor who will counsel and assess risk, as well as a breast surgeon and gynaecological oncologist. Patient autonomy and decision making should be respected, but our focus should be to provide information and to empower these women with knowledge which enables them to make these choices. South Africa is rich in diversity yet most studies on BRCA positive women have been performed in western and well-resourced countries. There is a need for further literature in our setting.

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