Target Ovarian Cancer: Position statement on family history February 2014

This position statement has been prepared to provide policy makers, journalists and clinicians with detailed information about the challenges facing women with a family history of ovarian and/or breast cancer, and lays out what Target Ovarian Cancer believes must happen in order to ensure that women at risk are correctly identified, are supported managing the risk and, should they develop the disease, able to access the most appropriate treatments. It does not form part of our health information for women, which can be found here: www.targetovariancancer.org.uk/ovariancancerinfamilies

In summary:
Target Ovarian Cancer believes that lives are being lost unnecessarily because women are missing out on vital opportunities to be identified as having an increased risk of developing ovarian cancer, on opportunities to manage the risk of developing the disease, and to receive the best treatments should they develop ovarian cancer.

Target Ovarian Cancer is calling for

- Recognition of the term Hereditary Breast and Ovarian Cancer Syndrome in national guidance and the media, to ensure women and their families are fully aware of the implications of family history, and that the risk of ovarian cancer is not underestimated.
- GPs to improve their knowledge around family history, particularly the importance of the father's side of the family.
- Genetic testing, for women diagnosed with high grade serous ovarian cancer or those with a strong family history, is accessible across the UK and includes appropriate counselling and support for women and their families. A strong family history would consist of two or more close relatives, from the same side of a family (mother or father's) with ovarian and/or breast cancer.

Target Ovarian Cancer has estimated that for a woman who is a carrier of a faulty BRCA 1 or 2 gene, which raises the risk of hereditary breast and ovarian cancer, her risk of death from ovarian cancer is more than double the risk of death from breast cancer.

In detail:

Target Ovarian Cancer believes that thousands of women who may be at risk of developing ovarian cancer because they may carry mutations in genes inherited from a parent, are missing out on vital opportunities to be identified as potentially at risk, and to be supported through the process of having that risk quantified and then managed in a way that is acceptable to them. The result is that lives are being lost unnecessarily. Currently mutations in the BRCA genes are responsible for the greatest number of hereditary cases of ovarian cancer, and also place women at a very high risk of developing breast cancer.

Lives are being lost because women, health professionals and the media are not always clear about the links between hereditary breast cancer and ovarian cancer, the fact that mutations in genes related to ovarian cancer can be passed down the father's side of the family, the symptoms of ovarian cancer, and the younger age profile of these forms of ovarian and breast cancer.

Over a thousand women each year develop ovarian cancer because they have inherited faulty genes. Being told they have ovarian cancer is hugely challenging given the poor survival rates, and is compounded by the news that other members in their family may also be at risk. It has been estimated that each woman diagnosed with a hereditary form of the disease, will have on average three close female relatives who are potentially at risk.

Testing women who are diagnosed with ovarian cancer for gene mutations may open up trials and potential new treatments for them. It will also allow other family members to seek vital help and information in a timely manner, but it is essential that women be supported with counselling through the process.

Whilst there seems a strong will amongst the clinical community to increase genetic testing there is also great uncertainty about the funding of such tests, and the capacity of the current services to cope with a large increase in demand. This threatens the drive to identify those at risk, and those who would potentially benefit from targeted treatments, leading to unnecessary and premature deaths.

What needs to change?

There needs to be concerted national action to ensure the risks associated with a family history of ovarian and/or breast cancer, are better known and understood by women and health professionals. This will ensure that more women seek advice and are appropriately referred and managed. To do this Target Ovarian Cancer propose:

- The term Hereditary Breast and Ovarian Cancer Syndrome is used within the UK in connection to familial breast and/or ovarian cancer.
- That the risks and options facing women with a strong family history of either disease are fully discussed with them. Information on the risks and symptoms of ovarian cancer should form part of this discussion, especially in the absence of a screening programme for ovarian cancer.
- That specific work is undertaken to improve GPs' knowledge about the connection between ovarian and breast cancer, and the importance of taking a father's side of the family into account when considering risk.

It is imperative that the National Institute of Health and Care Excellence commissions patient-centred guidance that covers Hereditary Breast and Ovarian Cancer Syndrome rather than focusing on one or other condition. This will ensure anyone with a strong family history of ovarian and/or breast cancer, or a health professional dealing with them, has clear and complete

information to hand on risk assessment, referrals, screening and prophylactic (preventative) surgery or chemoprevention.

In the absence of a screening programme for women at high risk of ovarian cancer due to their family history, **women should be supplied routinely with information about the symptoms of the disease.** They should be encouraged to seek help promptly if they develop symptoms (at any age) suggestive of ovarian cancer, and be offered CA125 and TVU testing without delay. This would include women who have a strong family history (two or more close relatives on the same side of the family) but have not yet been tested, or who despite a strong family history had negative results in testing for BRCA mutations.

There needs to be better evidence surrounding the capacity, feasibility and acceptability of routine testing and counselling of women with ovarian cancer for BRCA mutations. Routine testing of all women with high grade serous ovarian cancer, and those with endometrioid or clear cell epithelial ovarian cancer who have any family history for BRCA mutations, is currently permissible given the testing thresholds set in the NICE guidance on familial breast cancer[i]. Whilst it is permissible, it is not yet routine in clinical practice. This testing would allow the identification of family members at risk, and open up access to potentially important new treatments for women with BRCA mutations. However it is important to understand the issues around acceptability for women and their families, so soon after a diagnosis, in addition to managing capacity to support, test, and counsel family members to make informed choices about managing risk.

What Target Ovarian Cancer is doing:

- Target Ovarian Cancer is funding Pulse Learning to develop a continuing professional development module on family history aimed at GPs, to be launched in April 2014.
- Target Ovarian Cancer is funding a research study at the University of Cambridge (Department of Medical Genetics) into the feasibility and acceptability of routine genetic testing and counselling of women with ovarian cancer. The GTEOC Study will also look to identify other genes implicated in hereditary forms of the disease.
- Target Ovarian Cancer is calling on NICE to produce guidance on Hereditary Breast and Ovarian Cancer Syndrome.

In addition:

- Target Ovarian Cancer is developing new psychosocial materials to support women considering and undergoing testing, and those subsequently making choices about risk reduction.
- Target Ovarian Cancer will continue to challenge all media stories that fail to make adequate mention of the risks of ovarian cancer when talking about familial breast cancer.
- Target Ovarian Cancer is working with Breakthrough Breast Cancer to review information available to women with a family history of breast cancer about the risks of ovarian cancer, and vice versa.

Background information

- Approximately 15% of women diagnosed with high grade serous or endometrioid epithelial ovarian cancer carry a mutation in one or other of their BRCA genes[ii]. This is irrespective of whether they have multiple cases of the disease in their family.
- In total one in five women with ovarian cancer have an inherited predisposition to the disease[iii]. This means the majority of women who have one close family member affected, are not themselves at risk.
- Where there are two or more cases of ovarian cancer, and/or breast cancer on either their mother or their father's side of the family, women may be at increased risk of developing breast or ovarian cancer themselves, and should seek help from health professionals in quantifying that risk.
- Being supported to understand their level of risk will then help women decide whether or not to undergo genetic testing, screening (breast cancer) and/or preventative surgery or other forms of risk reduction. Whilst imminent results of a major clinical trial are awaited, there is as yet no proven benefit to screening women with a strong family history for ovarian cancer.
- Women with a close relative carrying an identified BRCA mutation can be tested for the same fault, and this can provide reassurance. In families where there are multiple cases of ovarian cancer, but no identified BRCA mutation, other family members may still be at increased risk, as our understanding of the genetic causes of familial ovarian cancer is incomplete.
- Undergoing surgical removal of ovaries and fallopian tubes is currently the most effective way of reducing the risk of developing ovarian cancer. However it does not reduce the risk to zero, and is a major procedure involving risks, and in premenopausal women induces the menopause. Therefore it is imperative the possible benefits and harms are discussed in detail with women prior to them deciding whether or not to undergo preventative surgery.
- The issue of genetic testing within families can be a major source of stress and disagreement. Women and families need support to understand the possible reactions to the testing process and results.
- The current strategy of testing women who have two or more cases of ovarian cancer or ovarian and breast cancer in their family is thought to be missing some 40% of cases of inherited faulty BRCA genes[iv]. It is not clear why this is, but may be the case in families where there are not many female relatives. This is why a strategy to test all women with high grade serous ovarian cancer could reveal more women at risk than previously.
- Mutations in the BRCA 1 or 2 gene are the most common cause of hereditary cases when there are multiple breast and ovarian cancers within a family, but they are not the only genes which can increase the risk of familial ovarian or breast cancer. Others which have been identified are Lynch syndrome (hereditary nonpolyposis colon cancer), RAD51 b and c raises the risk of ovarian cancer, and mutations in TP53 raise the risk of breast cancer.
- Knowing there is a mutation in either the BRCA1 or BRCA2 gene can help women to quantify the risk of ovarian and/or breast cancer, identify other family members who may be at risk of developing ovarian and/or breast cancer and, for those who have either ovarian and/or breast cancer, enable them to participate in clinical trials using treatments targeted at those women with these specific mutations.
- For a woman with a BRCA mutation, her greatest risk of dying comes from ovarian cancer, even though she is more likely to develop breast cancer. This is calculated using the risk of

developing breast or ovarian cancer, and the survival rates of that disease. For example, a woman has up to a 65% chance[v] of developing breast cancer, but an 85% chance of surviving five or more years[vi]. She has up to a 40% chance[vii] of developing ovarian cancer, with 43% chance of surviving five years or more[viii]. Target Ovarian Cancer estimates that a woman with a BRCA mutation has a 10% chance of dying from breast cancer (1x.65 x.15 x 100), and a 23% chance of dying due to ovarian cancer (1 x .4 x.57 x 100).

- Target Ovarian Cancer has anecdotal evidence from women, particularly those with a strong history of breast cancer in their families, that the risks of ovarian cancer are neither clearly explained, nor managed well by health professionals, resulting in women being ignorant, and often ignoring potentially important symptoms, and missed opportunities to reduce their risk of ovarian cancer.
- Data from the Target Ovarian Cancer Pathfinder Study (2012) shows that whilst most GPs (86%) know of the link between hereditary breast and ovarian cancer, just 10% of GPs are correct in knowing that the father's side of the family is as important as the mother's in terms of family history[ix].
- The NICE guidance on familial breast cancer (2013) says that genetic testing can be carried out if a woman's chance of carrying a BRCA mutation is greater than 10%. Recent studies in ovarian cancer have shown that some 15% of women with serous epithelial ovarian cancer have a mutation in either the BRCA1 or 2 gene[x].
- Having a known mutation in BRCA genes opens up the possibility to women of participating in clinical trials for as yet unlicensed targeted therapies, called PARP inhibitors. Early trials have shown promise but positive results are needed from larger trails before these treatments can be made more widely available. It is anticipated that the first license to treat women with PARP inhibitors (for relapsed platinum sensitive ovarian cancer) may be approved in 2015. This will result in a high demand for tests to determine appropriate treatment.

---

[i] www.nice.org.uk/cg164 and confirmed by Guideline Chair in person
[ii] Zhang, S., Royer R. et al (2011) Gynecologic Oncology 121 (2): 353-357
[iii] *Nature Communications* (2014; doi:10.1038/ncomms4156
[iv] Metcalfe, K. A., I. Fan et al (2009), Gynecologic Oncology 112 (1): 68-72
[v] Howlader N, Noone AM, Krapcho M, et al. (eds.). (2013) *SEER Cancer Statistics Review, 1975-2010*. Bethesda, MD: National Cancer Institute. Retrieved June 24, 2013.
[vi] http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/survival/breast-cancer-survival-statistics
[vii] Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *Journal of Clinical Oncology* 2007; 25(11):1329–1333. [PubMed Abstract]
[viii] http://www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/survival/
[ix] www.targetovariancancer.org.uk/pathfinder
[x] Zhang, S., Royer R. et al (2011) Gynecologic Oncology 121 (2): 353-357