

## Counterpoint: Angelina's choice-or the choice of anyone else in her place

This is the counterpoint to the article with the title “Angelina’s choice” written by Goel<sup>[1]</sup> and published in the October 2013 issue of South Asian Journal of Cancer. Several thousands of women have undergone prophylactic bilateral mastectomy (PBM) till date. It is nothing new. It has been done for more than 20 years. So why has the topic been raised now? Just because a global celebrity is involved and made her choice public, does it give everyone the right to criticize her? Let us remember that one man’s poison is another man’s food. For one person removing both breasts in anticipation may be like killing oneself early. But do all women think like that? Are all women alike? For Angelina, at least, that was not the case.

Long ago, I read a book about straight and crooked thinking. Sometimes the question betrays the true feeling, intention, or bias of the person. For instance if a stray dog is called a “mongrel,” we already understand that the person is averse to stray dogs and consider them as of mixed breed and not worthy. The same has been the case in the framing of the questions by Goel. Hence, I have taken the liberty of rewording the same questions to make them neutral. I have also taken the privilege of moving the last question to the beginning. With that proviso, let us look at the medical evidence regarding Angelina’s choice and whether it is the best way to fulfill her stated goals.

1. Is preventive (bilateral or contralateral) mastectomy a safe procedure? Can it be universally recommended? Can it be uniformly performed? Is it the only alternative after discovering an aberrant gene?

Yes, preventive (bilateral or contralateral) mastectomy is a safe procedure. It has been performed for more than 20 years and thousands of women have undergone it without major safety issue.<sup>[2]</sup>

No, it cannot be universally recommended. The procedure is a surgical option to be discussed on case to case basis for individuals who are at high risk for the development of breast cancer (BC) (5%-10% risk) and pertains to women with the following characteristics:<sup>[3,4]</sup>

- (a) BRCA1 or BRCA2 mutation carriers (main indication for bilateral prophylactic mastectomy)
- (b) Li-Fraumeni syndrome with BC
- (c) Cancer in one breast and a family history of BC
- (d) Radiation therapy to the chest before the age of 30

- (e) Presence of lobular carcinoma *in situ*.

Some consider that women having dense breasts or breasts with diffuse microcalcification could also benefit from prophylactic mastectomy, as the screening for BC is difficult in such people.

Yes, it can be uniformly performed at most oncology centers. Mastectomy is a relatively simple procedure that does not require opening of any body cavity (like thorax or abdomen).

No, it is not the only alternative for women who have genes that confer high risk of malignancy. Other options are as follows:

- (a) Intensified BC screening for high-risk women may detect cancer at an early, treatable stage
- (b) Lifestyle changes in weight, diet, exercise, avoidance of smoking, limiting alcohol may reduce the risk to some degree
- (c) Certain medications that block the effect of estrogen (e.g., tamoxifen, exemestane) can reduce the risk by about 50%.<sup>[5]</sup>

Specifically in one study, women who were BRCA1 (383) and BRCA2 (454) mutation carriers and diagnosed with unilateral BC (UBC) were given tamoxifen to prevent BC in the opposite breast. A total of 520 contralateral BCs (CBCs) occurred over 20,104 person-years of observation. Tamoxifen use reduced the risk of CBC by 58% in BRCA1 and 48% in BRCA2 mutated patients.<sup>[6]</sup>

It has also to be kept in mind that this benefit is not without side effects. Use of tamoxifen is also associated with increased risk of endometrial cancer.

- (d) Prophylactic salpingo-oophorectomy reduces estrogen levels and the risk of both ovarian and BC – with the reduction in BC risk being about 50% in high risk women.<sup>[7]</sup>
2. For Angelina (and other women like her) is bilateral mastectomy the best currently known option for a cancer free life? Does it give her the best chance of longevity?

Recent studies show that prophylactic mastectomy offers a woman the greatest risk reduction, giving her the lowest risk of developing BC in the future. Undergoing a preventive mastectomy does not guarantee that BC will not develop later. This is because preventive mastectomy may leave behind small amounts of breast tissue in the arm pit, near the collar bone, or in the abdominal wall.

If a woman is looking not to reduce the risk but just to have early detection, then surveillance is a good option. If she is looking to reduce the risk but does not want to go through such a radical procedure then an antiestrogen such as tamoxifen may be right. If she wants to minimize the

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risk down to the lowest level possible, which looks to be 90% or better, then a prophylactic mastectomy is the only option available to get to that level of risk reduction.

It is for this reason that between 1998 and 2003, rates of Contralateral Prophylactic Mastectomy in the United States more than doubled from 1.8% to 4.5%. And, among women having a mastectomy instead of lumpectomy, the rate of CPM increased from 4.2% to 11.0%. Women choosing CPM tend to be younger and have a higher educational level.<sup>[8]</sup>

In a prospective study of 139 women with a pathogenic BRCA1 or BRCA2 mutation, 76 underwent prophylactic mastectomy and the other 63 remained under regular surveillance. No cases of BC were observed after prophylactic mastectomy whereas eight BCs developed in women under regular surveillance after a mean follow-up of 3.0+/-1.5 years ( $P = 0.003$ ; hazard ratio, 0; 95% confidence interval, 0-0.36).<sup>[9]</sup>

Today, we have Total skin-sparing mastectomy (TSSM) with preservation of the nipple-areolar complex skin. It is now proven to be a cosmetically sound and oncologically safe procedure. A total of 53 BRCA-positive patients underwent bilateral TSSM for prophylactic (26 patients) or therapeutic indications (27 patients) from 2001 to 2011. Outcomes from 212 TSSM procedures in 53 cases and 53 controls were analyzed. At a mean follow-up of 51 months, no new cancers developed in either cohort.<sup>[10]</sup>

How does this compare to active surveillance for CBC? Can these be picked up early enough to prevent deaths? Women with UBC (UBC;  $N = 182,562$ ; 95 %) were compared to those who developed CBC (CBC;  $N = 8,912$ ; 5%) in the Netherlands Cancer Registry between 1989 and 2008 and were followed until 2010. Women with CBC exhibited a 30% increase in overall mortality. Women older than 50 years at CBC diagnosis and diagnosed 2-5 years after their first BC exhibited a 20% higher death risk. Women with CBC had a lower survival compared with women with UBC, especially those younger than 50 years at first BC diagnosis.<sup>[11-13]</sup>

3. Who is to decide whether surgery to prevent ovarian and BC on oneself is good or "hacking those organs"?

A factor that facilitates the decision to undergo a preventive mastectomy is that results of breast reconstructive surgery have improved. A 2004 Canadian study found that 70% of women were satisfied or extremely satisfied with the reconstruction after bilateral prophylactic mastectomy. In another study, 74 of the 76 women undergoing Bilateral Prophylactic Mastectomy had their breasts reconstructed with silicone prosthetics by a plastic surgeon in the same session, followed later by nipple reconstruction.<sup>[14,15]</sup>

4. What is the meaning of risk associated with certain genes?

Women who carry one of the so-called BC genes, BRCA1 or BRCA2, have a 55 to 85% chance of getting BC and a 15%-65% risk of ovarian cancer. The word "risk" here indicates the independent chance of having a particular

disease (cancer in this instance) during ones lifetime (or within a specified time period). This risk is not dependent on other factors (like lifestyle or environment).

5. Do patients have higher risk independent of that attributable to BRCA1 and BRCA2 genes?

Yes. It is possible that people will have other reasons to have high(er) risk independent of hereditary genes. The most common such factors are high fat diet, high caloric diet, sedentary life, alcohol, and tobacco consumption. All if these will add to the baseline risk that is imposed by genes like BRCA1 and BRCA2.

6. What is the implication of being diagnosed with BC? The diagnosis of BC has medical implications and those beyond simple medicine. The medical aspects include frequent visit to the hospital, a battery of investigations, invasive procedures and surgery, radiation therapy, and cancer-directed systemic therapy. This can require several months to several years.<sup>[16]</sup>

In one survey, opinion of cancer genetics specialists was studied in 1998 and compared to their view 14 years later (in 2012). The question asked was what they would do if they were at 50% risk of carrying a BRCA or Lynch syndrome mutation. There was a statistically significant increases in the percentage of specialists who: would undergo BRCA testing ( $P = 0.0006$ ), opt for PBM ( $P = 0.0001$ ) as well as opt for prophylactic removal of their uterus and ovaries for Lynch syndrome ( $P = 0.0057$  and  $P = 0.0090$ , respectively).<sup>[17]</sup>

Of the 163 members of the National Society of Genetic Counselors special interest group in cancer who responded, 85% predicted that if they had a 50% risk of carrying a BRCA1/BRCA2 mutation, they would pursue genetic testing. If they tested positive for a mutation at age 35, 25% predicted they would pursue prophylactic bilateral mastectomies and 68%, prophylactic oophorectomy and 26% would use an alias when undergoing testing. A total of 57% of counselors would seek professional psychologic support to help them cope with the results of testing.<sup>[18]</sup>

Another study included unaffected BRCA mutation carriers counseled at their center and who participated in a high-risk surveillance program from 1998 through 2010. Among the 136 unaffected women with BRCA mutations, risk-reducing mastectomy (RRM) was opted by 42% and risk-reducing bilateral salpingo-oophorectomy (RRBSO) selected by 52%. Thus, not all women at high risk for BC opt for such prophylactic surgeries. Family history of first- and second-degree relatives being deceased from BC was predictive of uptake of RRM and of RRBSO (odds ratio [OR], 11.0;  $P = 0.005$ ; and OR, 15.8;  $P = 0.023$ , respectively).<sup>[19]</sup>

Deciding whether to have such a prophylactic surgery is not simple. It is based on several patient, family, psychological, social, and economic factors. The risk-to-benefit ratio is part science and part psychological: Women have to weigh the surgical procedure and its

complications, discomfort, psychological issues, and self-image and sexual issues against the benefits of risk reduction. Some women have fears of developing BC in the remaining, healthy breast. These fears may be compounded by high levels of stress and anxiety related to future BC screening of the remaining breast. For such women, PBM is the choice that will give peace of mind.<sup>[20]</sup>

Celebrities are a beacon of hope. Their choice can influence others. However, they cannot be expected to make a “politically correct” choice or one that pleases their fans at the cost of their own health or lives. Respect their right to make their own choices and do not criticize them for the same. It is their life and choice. The only thing you can choose is whether you want to remain their fan or not.

Finally what about men, heightened risk of BC and PBM? Males are not immune to BC. Male carriers of BRCA1 and BRCA2 mutations have a higher risk of BC than other males, approximately 1.2% and 6.8%. But their risk is much lower than in female mutation carriers (about 60%) and lower than in the general female population (12%). Thus, preventive mastectomy has not been advocated or used for affected men.

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