

## S13. Prophylactic Mastectomy or Pharmacologic Prevention

J. Klijn

*Daniel den Hoed Cancer Center Erasmus MC, Erasmus Medical Center, Rotterdam, The Netherlands*

Current risk-reduction strategies aimed at prevention of breast cancer and death by cancer include changes in lifestyle, early detection of cancer by regular surveillance, prophylactic mastectomy (PM), prophylactic oophorectomy (PO) and chemoprevention [1]. Early studies on the possible interest in PM in untested high-risk women showed a wide range of outcomes. At our family cancer clinic 51% of unaffected women with a proven gene mutation choose PM, and 64% PO [2]. Predictive factors for PM are young age and parenthood. In our clinical practice, women increasingly base their decision for prophylactic surgery on proven susceptibility by a DNA-test. Until recently, only case reports and retrospective studies of the outcome of prophylactic mastectomy (mainly subcutaneous, and thus often incomplete) have been published. Hartmann and colleagues reported an approximate 90% risk reduction by PM in 639 women with a family history of breast cancer after a median follow-up of 14 years [3]. In a very small group of 18 women with a confirmed BRCA1 or BRCA2 mutation no breast cancers were observed after PM after a median follow-up of 13 years. After these retrospective studies, we performed the first prospective comparative study in 139 BRCA1/2 mutation carriers [4]. No cases of breast cancer were observed after bilateral total PM after a mean follow-up of 2.9 year in 76 BRCA1/2 mutation carriers (mean age 37.7 yr) in contrast to 8 breast cancers in the surveillance group (n = 63, mean age 39.5 yr, mean follow-up 3.0 year) resulting in a hazard ratio of 0 (95% CI: 0 - 0.36; p = 0.003). After a recent preliminary update at 5.2 yr of follow-up this risk reduction ( $\pm 95\%$ ) was still highly significant (p < 0.004), also after adjustment for PO (p < 0.005). In our affected BRCA1/2 mutation carriers with primary breast cancer, 35% of the patients opted for prophylactic bilateral/contralateral

mastectomy [5], also resulting in a strong risk reduction for a second primary breast cancer, but until thus far without a significant effect on overall survival (Seynaeve et al, SABCS 2003). The strong protective effect of PM must be weighed against possible surgical complications by breast reconstruction [6], psychological problems and quality of life [7]. In our experience only 5% did regret PM, but at 3 years of follow-up a significant number of women reported some negative effects on body image and sexuality. Endocrine prevention by PO or pharmacological intervention (chemoprevention) resulted in a risk reduction of about 50% for breast cancer. In postmenopausal women mainly tamoxifen and raloxifen have been used, while aromatase inhibitors will be tested in ongoing trials. In premenopausal high risk women a pharmacological alternative for PO is chemical castration by LHRH analogues, in combination with other drugs such as raloxifen, tibolone or bisphosphonates. However the accrual rate in such trials appeared to be low (about 10%). In conclusion: thus far prophylactic bilateral total mastectomy is the most effective way of prevention, but PO is a reasonable alternative, while chemoprevention has to be preferably applied in clinical trials.

### References

- [1] Klijn and Meijers-Heijboer. EJC Supplements Vol 1, No. 1; 13-23 (2003).
- [2] Meijers-Heijboer et al. Lancet 355:2015-20 (2000).
- [3] Hartmann et al. New Engl. J. Med. 340:77-84 (1999).
- [4] Meijers-Heijboer et al. New Eng. J. Med. 345:159-65 (2001).
- [5] Meijers-Heijboer et al. J. Clin. Oncol. 21:1675-81 (2003).
- [6] Contant et al. Eur. J. Surg. Oncol. 28:627-32 (2002).
- [7] Van Oostrom et al. J. Clin. Oncol. 21:3867-74 (2003).