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E8. Prevention of breast and gynaecological tumours when there is a proven genetic risk: a review

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As genetic testing for cancer risk assessment enters the clinical mainstream, gynaecologists are increasingly required to provide guidance to women with a proven genetic risk, specifically regarding risk-reduction management. We reviewed the current status of knowledge on this topic for women diagnosed with pathogenic germline mutations, *BRCA1*/*BRCA2* mutation carriers being at risk for breast and ovarian cancer, and MLH1/MSH6 mutation carriers (hereditary non-polyposis colorectal cancer syndrome or HNPCC) at risk for endometrial and ovarian cancers.

Risk-reduction options include increased surveillance, chemoprevention, and prophylactic surgery. In HNPCC, the benefit of screening for endometrial and ovarian cancer is uncertain and of secondary importance to regular colonoscopy [1]. Expert opinion recommends to discuss the option of a prophylactic hysterectomy and bilateral salpingo-oophorectomy at the time of colonic resection for women with HNPCC-associated colorectal cancer [2].

Breast cancers in *BRCA1*/*BRCA2* mutation carriers are characterised by early onset [3,4] and risk of second primary breast cancer [5]. Screening recommendations for ovarian cancer using an algorithm of CA125 and transvaginal ultrasound are based on expert opinion only, without evidence of an improved early detection rate or effect on mortality. The same goes for breast cancer screening where it is recommend that yearly mammo-echography should start not later than age 30 years [6]. However, mammography in this setting has a low sensitivity and poor compliance, but the promising results with magnetic resonance imaging (MRI) should be explored further [7]. As a strategy, surveillance remains inferior to other risk-reduction measures in *BRCA1*/*BRCA2* mutation carriers [8,9].

Arguments to promote chemoprevention with tamoxifen in *BRCA1*/*BRCA2* mutation carriers are hard to find: the results of a sub-analysis of *BRCA1*/*BRCA2* mutation carriers in the National Surgical Adjuvant Breast and Bowel Project (NSABP)-P1 trial were inconclusive [10]. One case-controlled study showed a 50% reduction of contralateral breast cancer [11]. Moreover 70–80% of breast cancers in *BRCA1*/*BRCA2* mutation carriers are oestrogen-receptor-negative. The results of the chemoprevention study with raloxifene are awaited.

The risk-benefit effect of oral contraceptives in *BRCA1*/*BRCA2* mutation carriers is controversial and has remained unexplored so far in HNPCC women with regard to the ovarian cancer risk [12,13].

Clinical data on prophylactic surgery in asymptomatic *BRCA1*/*BRCA2* mutation carriers are more reliable, though the level of evidence is largely limited to results from retrospective and case-control studies. Prophylactic bilateral mastectomy (PBM) is most effective (>90% risk-reduction), but remains controversial not least because the prevention strategy is more radical than the cure [3,4]. However, prophylactic salpingo-oophorectomy (PSO) is more acceptable and able to reduce the risk of both breast and ovarian cancer (53–75% and 85–96%. respectively) [14,15].

Survival estimates, expressed as years in life expectancy gained, obtained from decision analysis models, help physicians to communicate the anticipated effects of various cancer prevention strategies on health outcomes for *BRCA1*/*BRCA*2 mutation carriers. They learn that prophylactic surgery for breast cancer has a significant effect on survival that is influenced by procedure (PBM plus PSO > PBM > PSO), by age at intervention, the level of mutation penetrance, and prior PSO. The absolute gain in life expectancy by PBM was more pronounced if performed at an early

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age and in women with a high phenotypic mutation penetrance, tailed off after prior PSO and disappeared when performed after the age of 50 years [8,9]. However, PSO may be delayed until age 40 years or completion of childbearing without loss of life-expectancy [9]. The acceptance of prophylactic surgery is study-dependent, but generally low, with PSO being more acceptable than PBM [3]. A specific group of young women with a high personal cancer risk estimate and who reported high levels of cancer worry were more likely to consider PBM. Quality of life-adjusted survival estimates taking into consideration the disfiguring effects of prophylactic surgery, promote PSO followed by hormonal replacement therapy until the age of 50 years rather than PBM [8,9]. Women with a *BRCA*1/*BRCA*2 gene mutation who have developed breast cancer have a 12–20% risk of subsequent contralateral breast cancer [5]. Few data are available on the efficacy of interventions to reduce the risk of contralateral breast cancer in *BRCA*1/*BRCA*2 mutation carriers. However, their impact on gain in life expectancy was less than in asymptomatic *BRCA*1/*BRCA*2 mutation carriers and depended on the prognosis of the primary breast cancer they were treated for [16].

It has been pointed out that specific methodological problems associated with research evaluating the efficacy of prophylactic surgery results in an overestimation of its benefit [17]. A similar overestimation is noted in decision analysis models as the gains in life expectancy projected only apply to women destined to die from their cancer, while the more favourable outcomes (asymptomatic or recurrence-free life) are not taken into account [18]. Further research therefore does not only require prospective cohort studies to eliminate various selection biases, but also a refining and validation of the risk estimates which we develop in decision analysis models is needed. This will ultimately enable the clinician to counsel his patients more accurately.

References

1. Lawes DA, SenGupta SB, Boulos PB. Pathogenesis and clinical management of hereditary non-polyposis colorectal cancer. *Br J Surg* 2002, **89**, 1357–1369.
2. Burke W, Petersen G, Lynch P, *et al.* Recommendations for follow-up care of individuals with an inherited predisposition to cancer I. Hereditary non-polyposis colon cancer. *JAMA* 1997, **277**, 915–919.
3. Meijers-Heijboer H, van Geel B, van Putten WLJ, *et al.* Breast cancer after prophylactic bilateral mastectomy in women with BRCA1 or BRCA2 mutation. *N Engl J Med* 2001, **345**, 159–164.
4. Hartmann LC, Sellers TA, Schaid DJ, *et al.* Efficacy of bilateral prophylactic mastectomy in BRCA1 or BRCA2 gene mutation carriers. *J Natl Cancer Inst* 2001, **93**, 1633–1637.
5. Haffty BG, Harrold E, Khan AJ, *et al.* Outcome of conservatively managed early-onset breast cancer by BRCA1/2 status. *Lancet* 2002, **359**, 1471–1477.
6. Burke W, Daly M, Garber J, *et al.* Recommendations for follow-up care of individuals with an inherited predisposition to cancer II. BRCA1 and BRCA2. *JAMA* 1997, **277**, 997–1003.
7. Brekelmans CTM, Seynaeve C, Bartels CCM, *et al.* Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. *J Clin Oncol* 2001, **19**, 924–930.
8. Grann VR, Jacobson JS, Thomason D, *et al.* Effect of prevention strategies on survival and quality-adjusted survival of women with BRCA1/2 mutations: an updated decision analysis. *J Clin Oncol* 2002, **20**, 2520–2529.
9. van Roosmalen MS, Verhoef LCG, Stalmeier PFM, Hoogerbrugge N, van Daal WAJ. Decision analysis of prophylactic surgery or screening for BRCA1 mutation carriers: a more prominent role for oophorectomy. *J Clin Oncol* 2002, **20**, 2092–2100.
10. King MC, Wienand S, Hale K, *et al.* Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *JAMA* 2001, **286**, 2251–2256.
11. Narod SA, Brunet JS, Ghadirian P, *et al.* Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. *Lancet* 2000, **356**, 1876–1881.
12. Narod SA, Rich H, Moslehi R, *et al.* Oral contraceptives and the risk of hereditary ovarian cancer. *N Engl J Med* 1998, **339**, 424–428.
13. Modan B, Hartge P, Hirsch-Yechezkel G, *et al.* Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. *N Engl J Med* 2001, **345**, 235–240.
14. Rebbeck TR, Lynch HT, Neuhausen SL, *et al.* Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med* 2002, **346**, 1616–1622.
15. Kauff ND, Satagopan JM, Robson ME, *et al.* Risk-reducing salpingo-oophorectomy in women with BRCA1 or BRCA2 mutation. *N Engl J Med* 2002, **346**, 1609–1615.
16. Schrag D, Kuntz KM, Garber JE, Weeks JC. Life expectancy gains from cancer prevention strategies for women with breast cancer and BRCA1 or BRCA2 mutations. *JAMA* 2000, **283**, 617–624.
17. Klaren HM, van't Veer LJ, van Leeuwen FE, Rookus MA. Potential bias in studies on efficacy of prophylactic surgery for BRCA1and BRCA2 mutation. *J Natl Cancer Inst* 2003, **95**, 941–947.
18. Miller L, Singer ME. Benefit of prophylactic mastectomy for women with BRCA1 or BRCA2 mutations. *JAMA* 2000, **283**, 3070.