Prophylactic Mastectomy and BRCA1 or BRCA2 Gene Mutations

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When, within a family, there are several members with cancers of the breast or ovary a genetic predisposition (GP) to these cancers should be considered. Faced with a suggestive family history (Table 10.1), an oncogenetic consultation must be offered. This may confirm a constitutional mutation to the BRCA1 and BRCA2 genes within that family.

Mutation identified in a woman, termed the "index" case, becomes the basis for testing the whole family. Even though the initial test takes a long time (several months) and may be difficult, further investigations are simplified once a target has been identified in the index case. If no mutation is identified in the relatives, they may be reassured. On the other hand, if mutation is present, the latter are at high risk of developing breast and ovarian cancer. A meta-analysis of 22 population studies summarised the risks as shown in Tables 10.2 and 10.3.

What management of the breast can be suggested to women with a GP today? We consider first prophylactic mastectomy, and then the different strategies available, according to whether the particular woman has a diagnosed breast cancer or not (see also Chapter 8).

Prophylactic Mastectomy: Principles and Efficacy of Prevention

Prophylactic mastectomy (PM) consists of removal of the mammary gland, nipple and areola and is generally accompanied by immediate breast reconstruction.

The principle behind this strategy is based on the hypothesis that breast ablation, if carried out sufficiently early in life, significantly reduces the risk of breast cancer.

Early PMs were performed in "high risk" women due to a suspicious breast cancer family history, prior to the availability of molecular diagnosis (Hartmann et al. 1999, 2001; Meijers-Heijboer et al. 2001; Rebbeck et al. 2004).

Table 10.1 Situations in which a familial genetic inquiry may be suggested generally (commencing with the affected person)

1. At least three cases of breast or ovarian cancer appearing in the same parental branch and occurring in first- or second-degree relatives
2. Two cases of breast cancer in first-degree relatives where the age of diagnosis is 40 years or below
3. Two cases of breast cancer in first-degree relatives where at least one case is male
4. Two cases in first-degree relatives with at least one case of ovarian cancer
5. The association of breast cancer with primary ovarian cancer

Table 10.2 Breast cancer risk with mutations*

	BRCA1 (%)	BRCA2 (%)
Cumulative risk to 50 years	38 (30–50)	16 (11–21)
Cumulative risk to 70 years	65 (51–75)	45 (33–54)

*95% confidence interval

Table 10.3 Ovarian cancer risk with mutations*

	BRCA1 (%)	BRCA2 (%)
Cumulative risk to 50 years	13 (8–18)	1 (0–3)
Cumulative risk to 70 years	39 (22–51)	11 (4–18)

*95% confidence interval

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A recent literature review (Bermejo-Perez et al. 2007) concluded that there was a reduction in the risk of breast cancer after PM of 91–100% with a 3–7-year follow up. This limited follow up is as yet insufficient to draw any conclusions about the effect of PM on mortality.

Balancing the preventive efficacy of PM, are risks from both anaesthesia and surgery (haematoma, infection, implant-related problems and subsequent interventions) about which the patients must be carefully informed.

Several studies evaluated the social and psychological consequences of PM (Stefanek et al. 1995; Borgen et al. 1998; Frost et al. 2000; Hatcher et al. 2001; van Oostrom et al. 2003; Metcalfe et al. 2004a; Bresser et al. 2006) and concluded that satisfaction with the prophylaxis must be dissociated from satisfaction with the reconstruction itself (which depends specifically on complications and aesthetic outcomes).

Although the majority of women report a clear reduction in anxiety levels after intervention, the long-term adverse consequences, particularly sexuality (loss of erogenous sensibility secondary to nipple–areola complex ablation, body image and reactions of partners), must not be underestimated.

Management of Women Carrying BRCA1/2 Mutations Without Cancer

Two main strategies of management are currently proposed:

- MRI surveillance
- Preventative surgical or medical methods

The first strategy comprises attentive screening in order to detect small cancers that are potentially curable with early diagnosis. The American Cancer Society recently recommended that mammography be supplemented with MRI in those electing for surveillance (Saslow et al. 2007). Several prospective studies of MRI in high-risk women showed a significantly improved sensitivity (between 71 and 100%) over mammography alone (Kriege et al. 2004; Kuhl et al. 2005; MARIBS 2005; Lehman et al. 2005; Warner et al. 2004) and a lower rate of interval cancers (10% vs. 50%), although with a lower specificity. The recall rate for supplementary imaging varied between 8 and 17%, and biopsy between 3 and 15%.

The second strategy relies on prevention. The choice of a prophylactic mastectomy may only be considered if the woman concerned is completely informed of the options and associated risks. In genetically predisposed women, a prophylactic oophorectomy is recommended in order to prevent the development of ovarian cancer. In addition to the considerable reduction (of the order of 95%) of ovarian cancer risk (Rebbeck et al. 2002), there is also a reduction in breast cancer risk of approximately 50% (Rebbeck et al. 2002). Acceptance with this strategy in young women is, however, often poor.

Regarding chemoprevention, there are several arguments suggesting that tumourigenesis in these GP women is, at least initially, responsive to oestrogens and anti-oestrogens (Pujol et al. 2004) even if the majority of cancers occurring in mutated cases are not hormone-receptor positive. To date, several anti-oestrogens have been tested in women at risk of breast cancer: tamoxifen (Fisher et al. 2005; Cuzick et al. 2003, 2007; Powles et al. 2007), raloxifen (Vogel et al. 2006) and anti-aromatases.

In France, these compounds are neither licensed for this condition nor can they be used in clinical trials.

The management of mammary risk in GP women has been the subject of two collective reports (Eisinger et al. 1998, 2004), and it is based on these that the Institut Curie offers patients carrying either a mutation or a suggestive family history the specific therapeutic pathway. In addition to the geneticist, all patients are routinely offered consultations with a gynaecologist, psychologist, and an oncoplastic surgeon.

The final decision is made after multidisciplinary discussion with all parties.

Importantly, the advice and participation of the partner in any decision is recommended as is a delay of at least four months for reflection.

Diagnosis of a Breast Cancer in a Woman with BRCA1/2 Mutation

When a primary breast cancer is diagnosed during surveillance of a GP woman, the therapeutic strategy must take account of the gene mutation.

The prognosis of tumours occurring in the context of BRCA1 or BRCA2 remains the source of discussion: poor according to some (Stoppa-Lyonnet et al. 2000),

and no different according to others (Bonadona et al. 2007; Brekelmans et al. 2007).

On the other hand, it is well established that the risk of contralateral breast cancer is increased: of the order of 2–3% per annum with BRCA2 and 3–4% for BRCA1 (Metcalfe et al. 2004b), compared to 0.7% for the population in general.

In breast cancer amenable to conservative treatment, two options may be discussed: either conservative treatment, for which we aim as standard, or nonconservative treatment; the latter involving delayed breast reconstruction, after adjuvant chemotherapy and/or radiotherapy, which may be combined with contralateral prophylactic mastectomy and immediate reconstruction to reduce the risk of contralateral tumour development (Vansprundel et al. 2005).

Discovery of BRCA1/2 Mutation After Diagnosis of Breast Cancer

BRCA1/2 mutation may also be diagnosed in a woman already treated for breast cancer.

In the case of mastectomy, one may offer at the time of any secondary surgery, a contralateral prophylactic mastectomy with IBR. Another option is surveillance of the contralateral breast with MRI.

If the initial treatment is conservative, the discussion is more delicate. In fact, it appears that the risk of ipsilateral recurrence will be no different to that of anyone else with cancer in the following ten years (Kirova et al. 2005; Pierce et al. 2006), which suggests a protective effect of irradiation. The increased risk of contralateral cancer, however, remains.

Women who do not wish to risk a second cancer may thus opt for a contralateral PM with IBR, or even for bilateral mastectomy, considering the potential problems involved in reconstructing an already irradiated breast.

High Family Risk Without Identified Mutation

Even with a high familial incidence of breast cancer, BRCA1/2 mutation is sometimes not identified genetically and statistical methods of predicting tumour risk may be used instead (Eisinger et al. 2004). These differ between teams. In an unaffected woman, or one presenting with breast cancer, a request for PM may be considered whilst awaiting validation, taking note of the family history. This indication for PM will only therefore be accepted in the setting of a multidisciplinary decision.

Conclusion

In conclusion, the management of breast and ovarian risk in GP is delicate. It is currently only possible in a specialist environment. Certain questions—such as the management of breast cancer in a GP woman, or the strategy suggested to a woman who has been already treated in a conservative fashion—remain sources of discussion, and require prospective research.

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