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Personalized prevention in high risk individuals: Managing hormones and beyond

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ABSTRACT

Increasing numbers of women are being identified at 'high-risk' of breast cancer, defined by The National Institute of Health and Care Excellence (NICE) as a 10-year risk of ≥8%. Classically women have been so identified through family history based risk algorithms or genetic testing of high-risk genes. Recent research has shown that assessment of mammographic density and single nucleotide polymorphisms (SNPs), when combined with established risk factors, trebles the number of women reaching the high risk threshold. The options for risk reduction in such women include endocrine chemoprevention with the selective estrogen receptor modulators tamoxifen and raloxifene or the aromatase inhibitors anastrozole or exemestane. NICE recommends offering anastrozole to postmenopausal women at high-risk of breast cancer as cost effectiveness analysis showed this to be cost saving to the National Health Service. Overall uptake to chemoprevention has been disappointingly low but this may improve with the improved efficacy of aromatase inhibitors, particularly the lack of toxicity to the endometrium and thrombogenic risks. Novel approaches to chemoprevention under investigation include lower dose and topical tamoxifen, denosumab, anti-progestins and metformin.

Although oophorectomy is usually only recommended to women at increased risk of ovarian cancer it has been shown in numerous studies to reduce breast cancer risks in the general population and in those with mutations in *BRCA1/2*. However, recent evidence from studies that have confined analysis to true prospective follow up have cast doubt on the efficacy of oophorectomy to reduce breast cancer risk in *BRCA1* mutation carriers, at least in the short-term.

Introduction

The definition of high-risk in breast cancer usually means a lifetime risk of 30% or higher and can also be defined as a 10-year risk of 8% or more of developing the disease [1]. Until recently the main determination of high risk was from the presence of a significant family history using epidemiological data [2] or by identifying a high-risk breast cancer predisposition gene such as *BRCA1* or *BRCA2*. The advent of the use of additional information from mammographic density and common genetic variants (Single Nucleotide Polymorphisms-SNPs) means a much higher proportion of the population can be determined as high-risk and also facilitates more precise targeting of preventive measures. We review the patient pathways that can lead to a woman being defined as high risk.

- Assessment of family history ± other risk factors often with use of a risk algorithm such as Tyrer-Cuzick or Gail.
- Identification of a high-risk predisposition gene in the individual or close relative
- Use of additional risk measures such as mammographic density and SNPs

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Family history based risk estimation

Women at high-risk of breast cancer are most commonly identified through their family history with the strongest pedigrees undergoing genetic testing [3]. . High-risk can be defined with family history alone, using algorithms such as those in the NICE guidelines (two First Degree Relatives on the same side of the family with average age <50 or 3 <60) [1] or a lifetable approach [2]. Additional risk factors such as age at menarche and age at first childbirth can be incorporated into risk algorithms such as the Tyrer-Cuzick or Gail models. In a regional referral centre in Manchester, UK, the majority of women referred with a family history (1987-2017-n = 12,178) were below the age of 50 years (Fig. 1) with those at moderate (5–8% 10year risk) and high (>8%) risk approximately equally distributed (Fig. 2).

Common cancer non 'syndromic' breast cancer predisposition

There is clear epidemiological [1,2] and for some time genetic evidence that a minority of people who develop breast cancer have dominantly inherited gene mutations, which place them at high risk, but without other phenotypic features. There has been an enormous improvement in our understanding of the mechanisms of underlying hereditary predisposition during the last 28 years. Most cancers require a number of genetic mutations in a progenitor cell before an invasive tumour results. The combination and sequence in which these mutations occur may alter the histological as well as invasive nature of the cancer as seen with *BRCA1* mutations for breast and ovarian cancer [4,5]. Twin studies indicate that approximately 30% of breast cancers are associated with a substantial inherited component [6]. The discovery of germline inherited mutations in the *TP53* gene in rare families with Li Fraumeni syndrome (LFS) was the first major discovery in this area [7]. Whilst the condition is rare affecting around 1 in 5–40,000 people it is as common as *BRCA1* and *BRCA2* combined in very early-onset, apparently isolated breast cancers [8].

Breast/ovarian cancer syndromes

Breast cancer can occur as part of high-penetrance predisposition such as LFS and also through *BRCA1/2* mutation, the latter resulting in a breast/ovary syndrome., Pathogenic *BRCA1* and *BRCA2* mutations are each carried by approximately 0.15% of the population (rising to 2.5% combined for three founder mutations in the Ashkenazi Jewish population). Such mutations result in lifetime risks of 40–85% for breast cancer and 20–60% for ovarian cancer. In

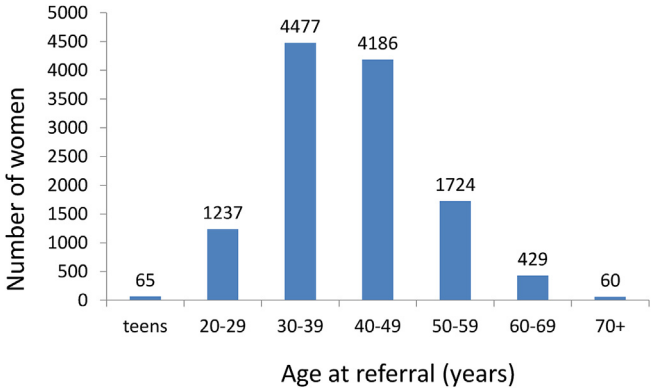

Fig. 1. Figure 1: Age of referrals of 12,178 women referred to the Manchester Family History Clinic.

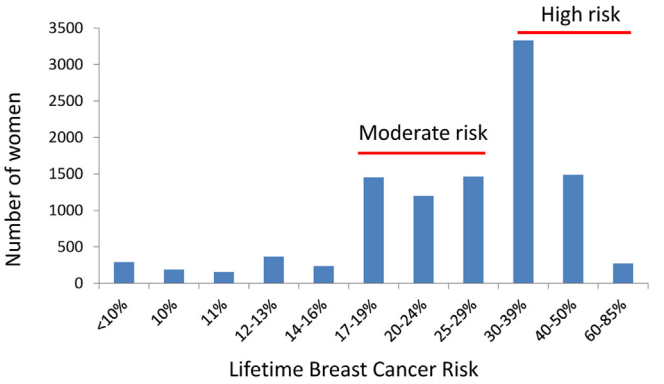

Fig. 2. Range of risks in 10,500 women on entry to the Manchester Family History Clinic.

the last few years much better risk prediction is possible even within BRCA families using information from mammographic density and multiple validated common SNPs [9–11].

Panel gene testing

Other high-risk genes have been identified such as *PTEN*, *STK11* and *CDH1*, and moderate risk genes such as *ATM, CHEK2*, and possibly *PALB2* (Table 1). Women carrying pathogenic variants in *BRCA1/2, PTEN, STK11, CDH1, TP53* and almost certainly *PALB2* are considered high-risk with lifetime risks of 30–90%. Until recently genetic testing for breast cancer predisposition mainly involved sequencing *BRCA1* and *BRCA2* and occasionally targeted testing of *TP53*. However, since 2013, many commercial companies and public health systems have moved to testing panels of known cancer predisposing genes, which may not even target the organs indicated from the family history [12,13]. Many of the remainder are genes that still have an unknown breast cancer risk that almost certainly does not reach a high risk definition (>30% lifetime risk). In reality the uplift of significant actionable high risk gene mutation from panel testing in high risk breast cancer families is small [14]. A great deal of caution is also required with interpretation of panel test findings [15]. Overall it is likely that <1% of the general population as a whole would be defined as high risk based on whole population testing without taking into account other factors.

Additional risk measures – mammographic density and breast cancer SNPs

In a mammographic screening population approximately 1% of individuals are at high risk (>8% 10 year risk) based on family history and standard risk factors used in models such as Tyrer-Cuzick [16]. Although not yet in widespread usage, this figure is increased to approximately 4% if either mammographic density or SNPs are added to the family history and up to 6% if family history, SNPs and density are used in risk determination [17,18].

The advent of Genome Wide Association Studies (GWAS) has provided very strong evidence for the existence of polygenic risk for many common cancers. The first major breakthrough occurred with breast cancer in 2007 [19] with 5 loci being identified with validated increases in risk of 1.1–1.4 fold. Individually these SNPs are very common, usually with population frequencies of 5–49% for the less common allele. Although they only confer a slight increase in risk individually evidence suggests that their effects are multiplicative even in the context of *BRCA1* and *BRCA2* [20–22]. By 2013, 77 validated SNPs had been published and their use in combination greatly improved risk stratification and prediction in the general

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