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Patient and medical barriers preclude uptake of tamoxifen preventative therapy in women with a strong family history

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ABSTRACT

Aims: To assess the eligibility, uptake and impediments to tamoxifen use in high-risk women attending a risk management clinic due to family history.
Patients and methods: All patients with a germline mutation in a cancer predisposing gene or at high genetic risk (based on family history) attending a Breast and Ovarian cancer risk management clinic from February 2014 to May 2015 received both verbal and written evidence-based information on preventive therapy and were recommended to consider endocrine prevention if not contraindicated. Endocrine therapy initiation, use and cessation were captured. Patient eligibility was analysed and reasons for declining, ceasing or contraindications for medication use were recorded.
Results: During the study period, 237 women were seen over 305 consultations for breast surveillance and preventative therapy discussion. They comprised 38 BRCA1 and 42 BRCA2 mutation carriers, 4 with Peutz-Jegher syndrome, 153 with a strong family history. Their median age was 39.4 years. Endocrine preventative was considered and discussed with all but 19 women. Of the remaining 218, 34 chose bilateral prophylactic mastectomy, while endocrine preventative was not recommended in 50 women due to contraindications and 25 women declined treatment due to their intention to fall pregnant. In 118 patients who remained eligible, 18.6% (22) tried prevention and 9.4% (14) remained on therapy.
Conclusions: Physician-reluctance is not a dominant reason for poor uptake of endocrine prevention even by high-risk premenopausal women in a specialised risk management clinic. Many women are not eligible, and most elect for alternative options.

1. Introduction

Prevention strategies for women who are at high risk of developing breast cancer include bilateral mastectomy, bilateral salpingo-oophorectomy and risk reduction with selective oestrogen receptors modulators or aromatase inhibitors [1–4] [5,6]. A recent meta-analysis of 83,399 women with a median follow-up was 65 months demonstrated a 38% reduction (hazard ratio [HR] 0·62, 95% CI 0·56–0·69) in breast cancer incidence [2]. The IBIS-1 prevention trial of tamoxifen versus placebo for 5 years has the longest follow-up with a 34% reduction in oestrogen-receptor positive breast cancer and ductal carcinoma *in situ* incidence at 16 years (HR 0·66 [95% CI 0·54–0·81], $p < 0·0001$) [1].

Tamoxifen was approved for primary endocrine prevention in 1998 in the US, followed by raloxifene in 2007. The US NCCN [7], ASCO [8], UK NICE [9] and Cancer Australia guidelines [10] recommend endocrine preventive therapy be considered for women at high risk based on a strong family history and/or the presence of a *BRCA1* or *BRCA2* mutation. The evidence for tamoxifen as a prevention therapy for *BRCA1* mutation carriers is less clear [3,6,11]. In a broader setting, tamoxifen does not appear to prevent oestrogen-receptor negative cancer [2]. However, based on the reduction in contralateral breast cancers risk seen in observational

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studies, endocrine prevention was initially recommended for all mutation carriers [12]. Guidelines were adapted due the long-term follow-up of nine large randomised clinical trials [1,3,13–20].

The uptake of tamoxifen in high-risk patients remains low at 8–10% of eligible women [21,22] and physician reluctance and ignorance has been considered a major underlying factor [23–25]. Other perceived barriers include time constraints [26] and the lack of an interim biomarkers to monitor efficacy.

We established a Breast and Ovarian Cancer Risk Management Clinic (RMC) in 2010 at our institution to provide surveillance and prevention strategies for women at high lifetime risk of developing breast cancer based on family history (>25–30%, Familial Risk Assessment – Breast and Ovarian Cancer (FRA-BOC) [27] or gene mutation status). These patients were recruited from the familial cancer centres, GP referrals, public and private breast clinics to centralise the management of high-risk women. Any patients who had not had a formal risk assessment through the familial cancer clinic, had a risk assessment performed my genetic counsellors at the first consultation to ensure they were high risk. In 2014 we introduced a policy of routine discussion of endocrine preventative therapy with all women attending the clinic. The study period was prior to government funding for preventative therapy.

The aim of this study is to analyse the number of suitable women for endocrine prevention within these clinics, to assess the uptake of and compliance with endocrine prevention, and reasons for declining and factors for not recommending endocrine prevention.

2. Patients and methods

All patients attending the RMC at The Royal Melbourne Hospital between February 2014 and May 2015 received both verbal and written evidence-based information on endocrine preventive therapy and were registered prospectively in the risk management database (FAMBIS, Cancer Council Victoria, version 3.8.1) and a separate study database (Microsoft®Excel® version14.5.9) after institutional ethics approval. The written information was tailored to menopausal status and contained a summary of the randomised trials and side effects of the different drugs. Demographic, family history and mutation testing details were collected. Endocrine preventive therapy was routinely considered in all patients and eligibility, use and cessation were captured. Reasons for medical prevention being considered inappropriate by the physician were recorded. Reasons for declining treatment were determined by the physician during a consultation, or by personal contact from the clinic nurse with the patient after the consultation and recorded. This was captured by the simple standardised question, “Can you tell me why you are not interested in taking the preventative medication?” and reasons were captured as free text. Patients ceasing treatment were identified at a subsequent clinic appointment or by telephone contact, and the reasons were determined and recorded.

The analysis was performed using Stata12 (StataCorp, TX, USA. Any associations between participants' age and their willingness to accept the prevention were assessed using two-sample Student T-test, while the association between willingness and categorical variables were assessed using Fisher's exact test. Level of significance for the study was set at $p < 0.05$. Overall uptake was analysed for all patients and uptake in those patients with no medically valid reason to decline endocrine prevention was assessed separately.

3. Results

During the study period, 237 women had 305 consultations. There were 38 *BRCA1* and 42 *BRCA2* mutation carriers, 4 Peutz-Jegher syndrome patients, 153 women with a strong family history (>25–30% lifetime risk). The median age was 39.4 years (range: 21–70). Fifty-four women presented for their first risk management clinic consultation during this time. Ninety-five percent of the women attending were pre-menopausal and hence tamoxifen was the mainstay of endocrine preventive therapy.

Of the 237 women, endocrine preventive therapy was considered and discussed for all except 5 women who had no record of discussion and was actively deferred in 14 women who required biopsy for suspicious lesions, with one diagnosis of invasive breast cancer (Fig. 1). In 50 women, tamoxifen was not recommended for the following reasons: 27 too young (<30 years and >10 years younger than index case in family), 2 patients had previous DCIS and received endocrine prevention, 2 patients were on the IBIS II trial, 2 patients were breastfeeding, 8 were currently pregnant, 1 patients had current treatment for lymphoma, 1 patient had a new cancer diagnosis, one patient was considered too old at age 69 years (Table 1).

Of 168 women, 146 patients (87%) declined preventive therapy (Table 2). The main reasons for declining therapy were intention to fall pregnant ($n = 25$, 15%), preference for prophylactic mastectomy ($n = 34$, 20%), and concerns regarding the side effects ($n = 15$, 9%). Forty-seven ‘were just not interested’ (28%) and when probed, were unable to attribute a reason for declining. Fifteen were concerned about the side effects profile, and 10 did not want to take tablets. Other reasons included wishing to wait until they could assess the effects of their prophylactic bilateral salpingo-oophorectomy before considering any further endocrine blockade, active menopausal symptoms and fear of increased symptoms, risk reduction not great enough, and low priority given a history of ovarian cancer.

Upon exclusion of medically valid reasons such as planned conception and preferring mastectomy to decline tamoxifen, 118 patients remained suitable of which 22 tried tamoxifen (18.6%) and 14 remained on it during the study period (9.4%). All patients who tried tamoxifen did so after a review appointment rather than at the first visit. Four patients were *BRCA2* mutation carriers, two were *BRCA1* mutation carriers and eight had strong family history only. The median duration of tamoxifen use was 12 months (range 1–20 months). Six of the 14 patients were experiencing side effects at the time of consultation. Two patients had hot flashes, of which one was on venlafaxine to manage the vasomotor symptoms. One patient had fluid retention, one patient had panic attacks and two reported increased vaginal dryness. Eight patients who had commenced endocrine prevention prior to the study period had ceased due to side effects (3 had hypersensitivity reactions, rash and angioedema and the remaining 5 had intolerable vasomotor symptoms). Those who tried tamoxifen were more likely to be older (43.5 ± 7.2 vs 38.8 ± 9.1, $p = 0.002$). There was no association between gene status and uptake (9% of carriers, 8% of non-carriers).

4. Discussion

Our clinic was established to manage young women at high risk of developing breast cancer due to family history. In the US, 15% of US women are reported as high risk using the Gail model ≥ 1.66 [28]. The Gail model [28] was validated in the P1 [3] and P2 [29] study to determine 5 year and lifetime risk of developing breast cancer [3]. It includes first degree family history and benign non-proliferative biopsies but does not include menopausal status, second degree relatives and ovarian cancer history or body mass index which are included in the Tyler-Cuzick (IBIS) models [1,30]. For those with a strong history of breast and/or ovarian cancer, other risk models such as Claus [31] and BRCAPRO [32] were developed to assess the likelihood of carrying a BRCA1 or BRCA2 risk [33]. More recently, BOADICEA [33–35] has been validated and