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Editorial

Is It Me Or Is It Hot In Here? A Plea For More Research Into Hot Flushes

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Women who have been treated for breast cancer identify vasomotor symptoms, such as hot flushes and night sweats, as a serious problem. These symptoms can be unpleasant, with a significant impact on daily life and sleep quality:

> *It's as though somebody has built a furnace inside of you and it's your whole body. It starts almost at your feet and works up and you just feel as though you are literally on fire inside and it's trying to escape and you just want to escape but you can't escape, there's nowhere to go and nothing to do [1].*

The social consequences of this embarrassing experience can affect employment, personal relationships and quality of life:

> *Umm, when they were at their worst I would be yeah pretty much dripping in, in err, various places umm err from really from the nose downwards; the lips; the neck; umm chest and back; crooks of my arms. And I could, you know, often if I was sitting down I would get up and my trousers would be really wet and it would go right down to my toes [1].*

Oestrogen replacement remains the most effective treatment for hot flushes. However, this is contraindicated in the majority of women with oestrogen-dependent breast cancer. An estimated 550 000 people live in the UK today with a diagnosis of breast cancer and up to 70% experience hot flushes [2–5], which are exacerbated by a lack of safe and effective management strategies [4].

Although hot flushes may occur for a number of reasons, including natural or chemotherapy-induced menopause, they may also be side-effects of adjuvant hormonal therapies, such as tamoxifen and the aromatase inhibitors. Two recent clinical trials (aTTom [6] and ATLAS [7]) showed that 10 years of tamoxifen significantly reduces the risk of recurrence and breast cancer mortality. However, an increasing number of studies report that over 50% of women do not adhere to 5 years of endocrine treatment with an associated increase in mortality [8]. The lack of effective management of vasomotor symptoms may be an important contributory factor to this lack of adherence [9].

The pathophysiology of hot flushes is poorly understood. Proposed mechanisms include altered peripheral vascular reactivity and a narrowed thermoneutral zone [10], although how this relates to oestrogen deprivation is not understood. Without a fuller understanding of the physiology, mechanisms and triggers it will be difficult to develop new targeted therapies.

> *Adrienne Morgan says 'I was diagnosed with breast cancer eight years ago and continue to take anti-oestrogen drugs because my cancer has returned. I have had a hot flush every 45 minutes for the last eight years. It is difficult to convey to anyone who has never had a hot flush how awful they are; exhausting, embarrassing, agitating…. I am fatigued, unable to work, sleep is only possible with medication and every morning my bed is soaked. I have tried everything. Only the SSRIs have some effect by reducing the severity of the hot flushes (venlafaxine made me feel horrible so I take Citalopram) but they make me anorgasmic. It surprises me that there is not more basic research being done into the causes of hot flushes. After all, most women will have them at some stage in their lives – not just breast cancer patients – and now men with prostate cancer are getting them too'.*

National Cancer Research Institute Breast Clinical Studies Group Working Party on Hot Flushes

Patient members of the National Cancer Research Institute UK Breast Clinical Studies Group and UK Breast Intergroup identified that there is very little research into the management of symptoms after breast cancer treatment

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and that this constituted a lack in the current portfolio. Large clinical trials, such as the ATAC trial, tend to focus on serious adverse effects, such as cardiovascular events, endometrial cancer and fractures, but do not address common and debilitating symptoms, such as hot flushes [11]. As a response to this lack, a Working Party on Symptom Management has been established and agreed to work on the management of hot flushes in the first instance, due to its prevalence, distressing nature and intractability [12]. Members of the group all have a particular interest in the management of hot flushes and include patients, clinical and academic partners, representing oncology, psychology, gynaecology, complementary therapies and the voluntary sector.

What is Current Clinical Practice?

The Working Party gauged current clinical practice of management for hot flushes in cancer with a short questionnaire. This was circulated to the UK Breast Intergroup mailing list (about 800 breast cancer health professionals, including nurses, oncologists and surgeons). Respondents were asked to report which medical and complementary therapies they were prescribing or recommending.

There were 184 responses: 73% women and 27% men. Of these, 12% were surgeons, 39% were oncologists and 49% were nurses. Overall, 97% had direct clinical contact with patients. Most (94%) respondents agreed or strongly agreed that the management of hot flushes is an unmet need. Respondents' estimates of the percentage of their patients suffering from hot flushes ranged from 30 to 80%, with a mean of 60%.

A small number of respondents prescribed hormone replacement therapy (6.7%) or progesterone (megestrol acetate 4.7%). Non-hormonal treatments were more likely to be offered, particularly selective serotonin (and norepinephrine) reuptake inhibitors (58%), such as venlafaxine and citalopram. Gabapentin (36%) and clonidine (19%) were also used. The selective serotonin reuptake inhibitors seem to be the most effective non-hormonal medication in reducing the intensity of hot flushes [13] and help women to cope. However, they can have significant side-effects, including sexual dysfunction, in a group of women who are already having sexual problems due to the anti-oestrogen drugs.

The US Food and Drug Administration recently approved low-dose paroxetine for the treatment of hot flushes [14]. Sadly, this is not a popular option for breast cancer patients (only 8.2% prescribed in our survey) because of worries about its exceptionally potent inhibition of CYP2D6, a liver enzyme that converts tamoxifen into metabolites that are thought to be the active components [15,16]. Paroxetine (but not venlafaxine or citalopram) use during tamoxifen treatment has been associated with an increased risk of death from breast cancer [17].

The most popular complementary treatment was evening primrose oil, with almost half the respondents recommending it to their breast cancer patients, although evidence suggests that it offers no benefit over placebo [13,18]. About 12% recommended vitamin E and black cohosh. In a placebo-controlled trial, vitamin E reduced hot flushes by one a day, but was not preferred over placebo by patients [13,19]. There is evidence that black cohosh is more effective than placebo [13,20], but there are concerns about its phytoestrogenic effect in breast cancer [21]. Homeopathy, reflexology and Reiki were infrequently recommended (2.6, 7.5 and 5.4%, respectively). These findings are in line with those of a previous study of breast cancer patients' treatment preferences for treatments that often lacked evidence of their effectiveness [13,22].

Seventy per cent of responders recommended patients to psychological services, relaxation and exercise classes and 49% to acupuncture – treatments that have more evidence of effectiveness [23–26] – but there was considerable variation in the availability of these services. Only 16% of patients were often or frequently referred to a menopause clinic. In particular, nurses treating women with breast cancer reported their frustration in having so little to offer people – many of whom are in extreme distress.

Current Research

A brief review of clinical trials currently registered on the US National Cancer Institute and UK clinical trials databases revealed very few studies researching this area. Overall, there were 21 studies in the UK, Europe and the USA since 2006 (compared with over 120 currently open trials in the National Cancer Research Institute Breast Clinical Studies Group portfolio alone). Most current trials on hot flushes investigate non-pharmacological approaches or combinations and new versions of existing approaches. No research was identified testing new pharmacological agents.

What Do We Want?

Despite the size of this problem, there are no nationally agreed guidelines for managing hot flushes after breast cancer, which may limit the access and availability of currently available and appropriate interventions. There is limited evidence to support a variety of interventions, none of which are entirely effective at eliminating hot flushes, other than hormone replacement therapy, which is contraindicated. All the available pharmacological interventions can have severe side-effects and few are widely acceptable. As a result of the limited availability of effective interventions, it is clear from our survey that clinicians are left making individual decisions based on personal experience and availability of local services. There is patchy and inequitable management of this problem, which continues to be a cause of considerable distress to many women after breast cancer. There is an urgent need for research across the field to understand the physiology of flushing and to develop and test new interventions.

The aims of the Working Party are to highlight the poor management of vasomotor symptoms in breast cancer patients, to work towards agreed treatment and management standards and to encourage and stimulate research into this area.

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