Surveillance report – Familial breast cancer (2013) NICE guideline CG164

November 2015

Surveillance decision

We will plan a partial update of the following sections of the guideline:

- The effectiveness of chemoprevention for the reduction of the incidence of breast cancer in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer.
- Referral to a specialist genetic clinic.

Reason for the decision

We found 11 new studies relevant to the guideline through the surveillance process. New evidence that could affect recommendations was identified.

Topic experts, including those who helped develop the guideline, advised us about whether the following sections of the guideline should be updated:

Risk reduction and treatment strategies

- What is the effectiveness of chemoprevention for the reduction of the incidence of breast cancer in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

From the surveillance review, 1 randomised controlled trial (RCT) was identified which reported that tamoxifen was more effective in preventing breast cancer compared to placebo, with a significant reduction in ductal carcinoma in situ (DCIS) breast cancer in the first 10 years of follow-up, but no significant effect on invasive oestrogen receptor-negative breast cancer. The study also reported that there was no significant difference in mortality between tamoxifen and placebo. A second RCT was identified which reported that after a median follow-up of 5 years, the aromatase inhibitor anastrozole was significantly more effective in preventing breast cancer compared to

placebo. The study also reported that no specific cause of death was more common in either the anastrozole or placebo group, however the risk of adverse effects such a musculoskeletal events and hypertension were higher in the anastrozole group.

The topic experts agreed that the recommendations on tamoxifen for chemoprevention need to be reviewed in an update to enable consideration of the new trial evidence in this area. The topic experts also agreed that an update should also include consideration of raloxifene as some recommendations include both tamoxifen and raloxifene as options for chemoprevention.

The topic experts felt that the use of aromatase inhibitors may also need to be considered for chemoprevention although opinion was divided. The IBIS-2 results published in 2014 were early results, in that median follow up was 5 years in a trial where treatment is for 5 years and the number of events (new cancers) was fairly low. In addition to the IBIS-2 trial, a recent report: 'Achieving world class cancer outcomes: a strategy for England 2015–2020' from the Independent Cancer Taskforce was identified. This report included a recommendation indicating that updated NICE guidelines should consider the use of aromatase inhibitors for untreated post-menopausal women at high risk. In light of the output of the Independent Cancer Taskforce report and the availability of data from the IBIS-2 trial, it was felt than an update of chemoprevention in the guideline should include consideration of aromatase inhibitors in addition to tamoxifen and raloxifene.

Decision: This review question should be updated.

Referral to a specialist genetic clinic

- For patients with an isolated breast cancer and no family history, what referral criteria are appropriate to decide referral to a specialist genetic clinic?

From the surveillance review, a study was identified which assessed the frequency of genetic mutations in individuals with triple-negative breast cancer

(TNBC) unselected for family history of breast or ovarian cancer. This new evidence shows that a small proportion of cases of TNBC are related to mutations in the BRCA1/2 genes, and that the average age of diagnosis of TNBC was under 50 years in women with a BRCA1/2 mutation, compared to 52 years for those with no mutations.

Topic experts advised that the results of this study may suggest that at the 10% threshold probability for detecting a germline mutation, even without a family history, patients with TNBC under 50 were close to the currently recommended threshold and, as such, may provide reasonable evidence that genetic testing should potentially be extended to those under 50 with TNBC regardless of family history.

Decision: This review question should be updated.

Other clinical areas

We also found new evidence relating to the following areas, but it was not deemed to have an effect on current recommendations. These areas were:

- Clinical significance of a family history of breast cancer
- Information and support
- Care of people in secondary care and specialist genetic clinics
- Genetic testing
- Risk reduction and treatment strategies (including risk reducing mastectomy and oophorectomy)

We did not find any new evidence related to:

- Care of people in primary care
- Surveillance and strategies for early detection of breast cancer

Overall decision

After considering all the new evidence and the views of topic experts, we decided that a partial update is necessary for this guideline.

See how we made the decision for further information.

Commentary on selected new evidence

With advice from topic experts we selected 2 studies for further commentary.

Risk reduction and treatment strategies – chemoprevention with tamoxifen

We selected the RCT by Cuzick et al. (2015) for a full commentary because this study reports long-term follow-up data from the International Breast Cancer Intervention Studies (IBIS)-I RCT. Results from IBIS-I were used to inform the current guideline recommendations in this area.

What the guideline recommends

The guideline recommends offering tamoxifen or raloxifene for 5 years to women at high risk of breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer. The guideline also states that tamoxifen or raloxifene should be considered for women at moderate risk.

Methods

Cuzick et al. (2015) reported on the long-term follow-up of the IBIS-I RCT which was conducted in 8 countries, including the UK. The trial compared oral tamoxifen 20 mg daily with placebo for 5 years in 7154 women. Between April 1992 and March 2001 women aged 35–70 who were judged to be at increased risk of developing breast cancer based on a family history of breast cancer or abnormal benign breast disease were recruited to the study. Exclusion criteria included a history of any invasive cancer (excluding skin cancer), deep vein thrombosis, pulmonary embolism, or women who wanted to become pregnant.

The primary outcome of the study was the occurrence of any type of breast cancer (including ductal carcinoma in situ).

Results

Over a median follow-up of 16 years, there was a significant reduction in the occurrence of all breast cancers in the tamoxifen group compared to the

placebo group (hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.60 to 0.83, p<0.0001).

The results for different types of breast cancer showed that tamoxifen had the most beneficial effect on preventing invasive oestrogen receptor-positive breast cancer, with a significant reduction in occurrence in the first 10 years of follow up (HR 0.68, 95% CI 0.53 to 0.88, p=0.0033) which was maintained in subsequent years (HR 0.63, 95% CI 0.45 to 0.87, p=0.0044). There was also a significant reduction in occurrence of ductal carcinoma in situ (HR 0.55, 95% CI 0.32 to 0.93, p=0.027) although only in the first 10 years of follow up. There was no overall significant effect with tamoxifen on invasive oestrogen receptor-negative breast cancer (HR 1.05, 95% CI 0.71 to 1.57, p=0.79).

In terms of breast cancer-specific mortality, there were more breast cancer deaths in the tamoxifen group, although this difference was not significant (31 deaths with tamoxifen vs 26 with placebo; Odds ratio [OR] 1.19, 95% CI 0.68 to 2.10, p=0.8).

The study also collected information about major thromboembolic, cerebrovascular, and cardiac events. Notably, in the first 10 years of follow up, there was an increased risk of deep vein thrombosis in women receiving tamoxifen (OR 1.87, 95% CI 1.11 to 3.18, p=0.011). There were no significant differences between treatment groups for major cardiovascular events (OR 0.76, 95% CI 0.34 to 1.67, p=0.46) or cerebrovascular accidents (OR 1.07, 95% CI 0.62 to 1.86, p=0.80).

Strengths and Limitations

Strengths

Strengths of the study included:

- Low risk of selection bias as randomisation was carried out centrally by non-consecutive allocation sequence generated by the IBIS-I research team before the study started.
- All IBIS-I researchers, participants in the trial and clinicians were masked to treatment allocation.

Limitations

Limitations of the study included:

- Selective reporting of effect measures for cause of death and inconsistent methods of follow up of participants, with varying methods of data collection used in different countries.
- The study was not sufficiently powered to assess a reduction in breast cancer specific mortality.

Impact on guideline

This study suggests that 5 years of tamoxifen treatment is effective in the longer term at reducing the incidence of breast cancer in high risk women. However, the increased number of deaths in the tamoxifen group, whilst not statistically significant, may need further consideration in relation to the current guideline recommendation to offer women tamoxifen for 5 years.

Risk reduction and treatment strategies* – *chemoprevention with aromatase inhibitors

We selected the RCT by Cuzick et al. (2014) for a full commentary because the guideline does not currently include recommendations on aromatase inhibitors for chemoprevention and topic experts highlighted this as an area of interest.

Methods

Cuzick et al. (2014) reported on results from the IBIS-II RCT on the use of anastrozole for prevention of breast cancer in postmenopausal women aged 40–70 years at increased risk of breast cancer. Women were considered to be at risk if they met one of the following criteria:

- Women aged 40–44 years who had a risk that was four times higher than in the general population;
- Women aged 45–60 years who had a relative risk of breast cancer that was at least 2 times higher;

- Women aged 60–70 years who had a risk that was at least 1·5 times higher.

Increased risk was based on specific criteria including: family history of breast or ovarian cancer; mammographic opacity covering at least 50% of the breast; age at menopause 55 years or more; nulliparous or age 30 or above at first birth.

The main exclusion criteria included: premenopausal status; any previous diagnosis of breast cancer; any invasive cancer in the previous 5 years; present or previous use of selective oestrogen receptor modulators for more than 6 months; intention to continue hormone replacement therapy; prophylactic mastectomy; evidence of severe osteoporosis; and life expectancy of fewer than 10 years.

Between February 2003 and January 2012, eligible women (n=3851) were recruited to the trial and randomised to receive 1 mg oral anastrozole, an aromatase inhibitor, or placebo for 5 years.

The primary outcome was histologically confirmed breast cancer (invasive cancers or non-invasive ductal carcinoma in situ).

Results

After a median follow up of 5 years, there were significantly fewer breast cancers in the anastrozole group compared to the placebo group (HR 0.47, 95% CI 0.32 to 0.68, p<0.0001). The results for different types of breast cancer showed a benefit from anastrozole on invasive oestrogen-receptor positive tumours (HR 0.42, 95% CI 0.25 to 0.71, p=0.001) and ductal carcinoma in situ (HR 0.30, 95% CI 0.12 to 0.74, p=0.009). However, there was no significant effect on invasive oestrogen-receptor-negative tumours (HR 0.78, 95% CI 0.35 to 1.72, p=0.538).

The study reported on a number of adverse advents. Notably, there was an increased risk of musculoskeletal adverse events (such as moderate arthralgia, carpal tunnel syndrome and joint stiffness) (Risk ratio [RR] 1.10, 95% CI 1.05 to 1.16), vasomotor symptoms (RR 1.15, 95% CI 1.08 to 1.22),

vaginal dryness (RR 1.19, 95% CI 1.03 to 1.37) and hypertension (RR 1.64, 95% CI 1.18 to 2.28) with anastrozole (no p values reported).

Strengths and Limitations

Strengths

Strengths of the study included:

- Randomisation by central computer allocation minimised the risk of selection bias.
- Low risk of performance bias as all IBIS-II researchers, trial participants and clinicians were masked to treatment allocation.

Limitations

Limitations of the study included:

- Selective reporting of effect measures, with no effect measures reported in the paper for causes of death.
- In addition, the study provides only short term results from a median follow up of 5 years. Further follow up is needed to determine the longer term impact of anastrozole, particularly on key outcomes such as mortality.

Impact on guideline

The results of the study show a reduction in the incidence of breast cancer after a median follow up of 5 years of follow-up in women at high risk of the disease. Feedback from topic experts suggests that the results are comparable with the results from the IBIS-I trial on tamoxifen and could therefore potentially impact on the guideline which does not currently include recommendations on the use of aromatase inhibitors for chemoprevention.

How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 2 years after the publication of Familial breast cancer (2013) NICE guideline CG164.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual'.

New evidence

We found 6 new studies in a search for RCTs published between 4 July 2012 to 26 January 2015. We also considered 5 additional studies identified by members of the Guideline Committee who originally worked on this guideline.

From all sources, 11 studies were considered to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See appendix A: decision matrix for summaries and references for all new evidence considered.

Views of topic experts

We considered the views of the topic experts, including those who helped to develop the guideline.

Views of stakeholders

Stakeholders are consulted only if we decide not to update the guideline following checks at 4 and 8 years after publication. Because this was a 2-year surveillance review, and the decision was to update, we did not consult on the decision.

See ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual' for more details on our consultation processes.

Date of next surveillance

Our next surveillance to decide if the guideline should be updated is scheduled for 2017.

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