The Eve Appeal funds research into the earlier diagnosis, risk prediction and developing screening for gynaecological cancers. Genetic Cancer Prediction through Population Screening Study (GCaPPS) has been wholly funded by The Eve Appeal. The research study explored the effects of offering genetic tests to everyone in the UK Ashkenazi Jewish population, a group known to have a higher proportion of people carrying BRCA gene mutations. The research study provides valuable evidence for reviewing the national screening process for cancers within specific populations which currently relies on assessing someone's family history.

Population testing for cancer-promoting BRCA genes

25 November 2014

Introduction

Testing for mutations in the BRCA genes that increase the risk of certain cancers is becoming increasingly affordable as the technology becomes more powerful and more widely available. Within the NHS in the UK, this testing is only offered to people on the basis of well defined criteria involving a personal or family history of breast and ovarian cancer. However, a number of people carrying the gene mutations do not fulfil these criteria, are not aware of their family history or do not understand the significance of their family history.

In GCaPPS (Genetic Cancer Prediction through Population Screening Study) researchers explored the effects of offering genetic tests to everyone in the UK Ashkenazi Jewish population, a group known to have a higher proportion of people carrying these gene mutations. They compared testing everyone in this population (population screening) with testing only those who fulfilled the current family history criteria (family history testing)[1]. They also carried out a cost-effectiveness analysis, published separately.[2] Results from both papers will be published in the Journal of the National Cancer Institute (30.11.14).

Key findings

- The researchers found that 2.45% of people in this population carried one of the known cancer-linked mutations (alterations) in the BRCA1 or BRCA2 genes.
- More than half (56%) of the people carrying a BRCA mutation would not have been tested under the existing family history criteria.
- The researchers assessed study participants for the psychological impact of testing for these mutations. They found no significant differences in anxiety, depression, health anxiety, distress, uncertainty and quality of life between those in the family history testing group and those in the population screening group.
- The researchers used an economic model to estimate the cost-effectiveness of screening all Ashkenazi Jewish women aged 30 and over, compared with family history testing. They found that screening this population would reduce the number of ovarian and breast cancers that occur and could save the NHS £3.7 million. .
- The model estimated that if 71% of the 114,400 eligible women were tested, there would be 276 fewer cases of ovarian cancer and 508 fewer breast cancers in this group. This would increase average life expectancy by 33 days per woman.

Background
Certain mutations in the BRCA genes are strongly linked to an increased chance of getting cancer. Women carrying these altered genes have a 45% to 65%% chance of getting breast cancer in their lifetime, and a 15% to 45% chance of getting ovarian cancer. Men carrying these mutations also have an increased risk of breast cancer and prostate cancer.

Women who are found to be carrying these altered genes are offered treatment to reduce their risk of cancer. Treatment options include having the ovaries and fallopian tubes removed (salpingo-oophorectomy), having the breasts removed (mastectomy) or having annual breast screening by MRI or mammography.

The BRCA genes are inherited, which is why a family history of breast or ovarian cancer is seen as an important marker for cancer risk. People with a strong family history of breast and ovarian cancer can be tested to see if they carry these gene mutations. Criteria for testing include assessment of how many relations developed cancer before certain ages, and the closeness of the relationship. (For more, see the NICE guidelines on familial breast cancer at http://www.nice.org.uk/guidance/cg164/informationforpublic)

However, not everyone who carries the genes gets cancer. Many people are not aware of their family history or its significance and do not seek advice. In addition, it is possible to carry these genes without having a close relation who has had cancer, which means some people who would not be eligible for genetic testing will nevertheless carry faulty BRCA genes.

The Ashkenazi Jewish population is known to have a high rate of carriers of BRCA mutations. About 1 in 40 people in this population carry BRCA mutations, compared to 1 in 800 in the general population.[3]

What was the aim of the research?
The GCaPPS researchers wanted to know whether it would be better to offer genetic testing to the whole of the Ashkenazi Jewish population, rather than just those people who have a strong family history of cancer. The trial was designed to show the benefits and harms of population-based screening of this group.

The researchers also wanted to compare the cost effectiveness of screening all Ashkenazi Jewish women (because women can then be offered preventive treatment) with the current system of family history testing.

How was the research done?
The researchers recruited people from the north London Jewish community after an information campaign which involved community charities, religious groups, the Boots pharmacy chain and a website. Everyone who volunteered received pre-test genetic counselling. After counselling, people who agreed to testing were randomly assigned to either the family history group or the population screening group.

Everyone in the population screening group (530 people) had genetic testing. People in the family history group had testing only if they met the family history criteria (66 out of 504 people). At the end of the study, those in the family history group who had not been tested because they didn't have a strong family history were also offered testing if they still wanted it.

The researchers used questionnaires to assess people's levels of depression and anxiety, quality of life, health anxiety, distress and uncertainty before counselling, after counselling, then seven days and three months after having the test results.

Researchers used estimates from their study as well as data from previous studies about cancer risk, benefits of prevention, and costs of cancer treatment to assess what would happen, if all women aged 30 and over in the Ashkenazi Jewish population of the UK were offered screening.

They designed a decision analytical model to compare the cost-effectiveness of population screening, compared to testing based on family history. The model used estimated lifetime costs and effects of different strategies, and the known probabilities of each potential outcome, to calculate the overall effect.

Results
A total of 1615 people registered an interest in the study and 1168 attended for genetic counselling, between August 2008 and July 2010. Of these, 89% consented to have genetic testing and were randomly allocated to family history (504 people) or population screening (530 people). The average age of participants was 54. One third (33%) were men and two thirds (67%) women. Of the 1034 participants, 128 (12%) would have been eligible for testing using family history criteria.

The study found 13 people carrying the altered genes in the population screening group (2.45%) and 9 people carrying the altered genes in the family history testing group (1.79%). Five more people in the family history group who were not eligible for testing on family history criteria but who chose to be tested later were found to be carrying the altered gene.

Only three of the 13 people with altered genes in the population group would have been eligible for testing under family history criteria. When the researchers added the people in the family history testing group who later tested positive, they calculated that 2.03% of people in this population without a strong family history of cancer were nevertheless carriers of the altered genes. This means that more than half (56%) of people carrying the altered genes in this population were not identified using the family history testing approach.

When introducing a new screening test, it is important to know whether the harms outweigh the benefits. Possible harms include the psychological impact of having the test, such as worry and anxiety about cancer. It is possible that people with a strong family history of cancer will have spent more time thinking about their cancer risk, and so the worry of the test might affect them differently. But the researchers didn't find any significant differences in psychological impact between the family history testing group and the population screening group in this study.

The cost-effectiveness study predicted what would happen if all Ashkenazi Jewish women aged 30 and over were offered genetic testing. The model predicted that compared to family history testing, offering population screening to these women would increase the average time they lived adjusted for their quality of life by 0.1 year.
The researchers also calculated that a population based approach to screening in these women was likely to save the NHS money, by reducing the costs of cancer treatment. The researchers assumed that 71% of women would accept testing (as happened in the study) and that a proportion of those found to have gene mutations would have risk-reducing surgery. They

estimated that this would prevent 276 ovarian cancers and 508 breast cancers among the women screened. The researchers calculated that population screening compared to family history testing saved £2079 per Quality Adjusted Life Year, meaning it saves the NHS money compared to the current testing strategy and that screening this population would save around £3.7 million.[4]

Conclusions

The researchers say they have shown that offering testing to the whole population of Ashkenazi Jews can detect 56% more people carrying known cancer-related BRCA mutations, compared to the existing family history based testing (even if all people with a family history seek advice), and that population screening in this group did not have an adverse affect on people's quality of life or psychological state.

In addition, they say that their economic model demonstrated that offering screening to all Ashkenazi Jewish women aged 30 and over for BRCA mutations would be highly cost effective and would be likely to save the NHS money, as well as increasing length of life and reducing the numbers of cancers among women in this group.

Notes

1: R Manchanda, K Loggenberg, S Sanderson et al. Population testing for cancer predisposing BRCA1/BRCA2 mutations in the Ashkenazi-Jewish Community: A randomized controlled trial. J Natl Cancer Inst 2014 107(1): dju379
2: R Manchanda, R Legood, M Burnell et al. Cost-effectiveness of population screening for BRCA mutations in Ashkenazi Jewish women compared with family history-based testing. J Natl Cancer Inst 2014 107(1): dju:380
3: NHS Choices 2013. Predictive genetic tests for cancer risk genes. http://www.nhs.uk/Conditions/predictive-genetic-tests-cancer/Pages/Introduction.aspx
4: The standard way to assess the cost effectiveness of a treatment or diagnostic test is to calculate the incremental cost effectiveness ratio (ICER) per quality-adjusted life year (QALY). The guideline set by the National Institute for Health and Care Excellence is that an ICER should be below £20,000 to £30,000 per QALY. The researchers calculated the likely ICER for population screening compared to family history testing was minus £2079 per QALY, meaning it saves the NHS money compared to the current testing strategy. When they adjusted the model to allow for the lowest prevalence of BRCA alterations, the ICER was £3,877, which would not be cost saving but is still well under the NICE threshold and extremely cost effective.

Published: 1st December 2014
Charity number: 1091708