Conventional therapies are less efficient in prostate cancer patients carrying 'BRCA' mutations

November 14 2014

	3-year survival	5-year survival	10-year survival
Non-carriers (surgery)	99 %	97 %	91 %
Carriers (surgery)	96 %	89 %	67 %
Non-carriers (radiotherapy)	96 %	91 %	80 %
Carriers (radiotherapy)	85 %	57 %	39 %

This table shows 3-, 5- and 10-year metastasis-free survival according to the treatment and presence of BRCA mutations. Credit: CNIO

Prostate cancer patients carrying inherited mutations in the BRCA genes respond less well to conventional treatment, including surgery and/or radiotherapy - and they also have a lower survival rate than those who are non-carriers of these genetic mutations. Data from the study, which has been published in the journal *European Urology*, points to the need for new clinical trials aimed at targeting these mutations in order to tailor treatment for these patients.

The study has been led by David Olmos and Elena Castro at the Spanish

National Cancer Research Centre (CNIO) and Rosalind Eeles at the Institute of Cancer Research & Royal Marsden NHS Foundation Trust in the UK.

10-year survival reduced by half

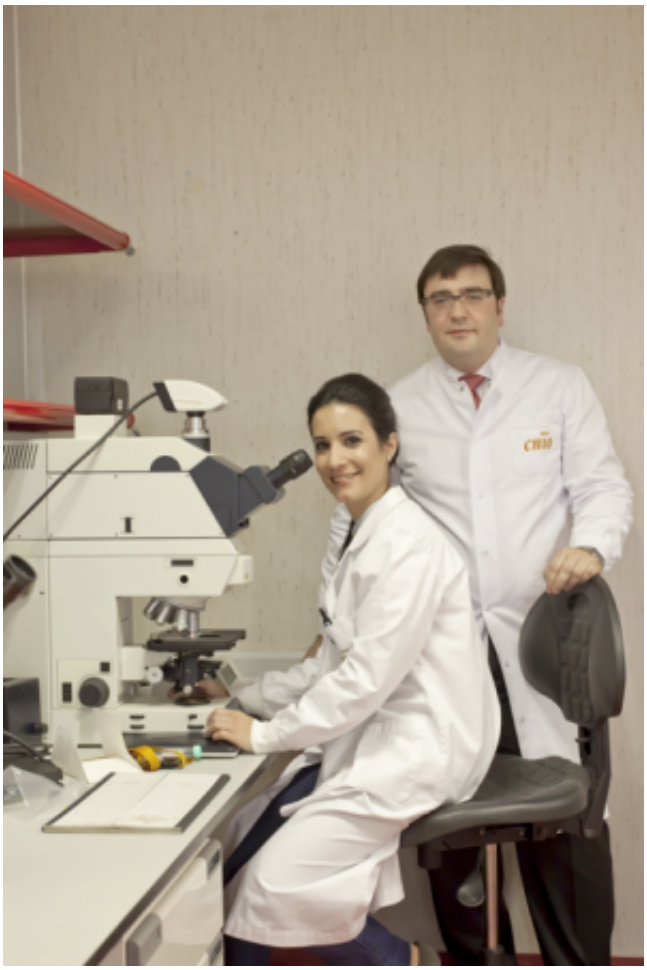
The findings originate from a 2013 study published by the same group of researchers in which they observed that patients carrying inherited mutations in the BRCA genes suffered from more aggressive tumours and died earlier. "That was when we found the first genetic factor associated with prostate cancer prognosis," explains Castro (for further information: http://www.cnio.es/es/news/docs/david-olmos-journal-clinical-oncology-9abr13-en.pdf)

It was then that the researchers decided to conduct a more in-depth study of patients with inherited BRCA mutations and the treatments applied to them, radiotherapy or surgery. According to the article, the results are unambiguous: regardless of the treatment received, patients with tumours at a localised stage (that is, non-metastatic tumours) do not respond as well to the current treatments as patients not carrying the mutations.

Over 1,300 patients participated in the study, 67 of whom were carriers of BRCA mutations. Patients carrying such mutations who had undergone radiotherapy showed 10-year survival rates of 39%, compared to 80% for non-carriers. Amongst patients who have undergone surgery the difference in 10-year survival rates is less pronounced (91% vs. 67%; see table); the smaller difference in survival rates among carriers and non-carriers who have undergone surgery shows that "these patients may require more long-term monitoring to establish whether or not this difference is significant," argues Castro.

Change of treatment strategy for these patients

Still to this day, the prognostic factors that would help determine a more personalised treatment are unknown. Smaller, less aggressive tumours are surgically removed; larger and/or more aggressive tumours are treated using surgery and radiation therapy. "An important issue is that during consultation we usually cannot predict which patients will evolve less favourably and which will live less time than others," the researcher explains. The team's objective is to identify the subgroup of patients with the least favourable prognosis and the treatments that best match their genetic characteristics.



CNIO researchers David Olmos and Elena Castro. Credit: CNIO

BRCA genes produce proteins that block tumour development, thereby guaranteeing the stability of the genetic material in cells; when the DNA gets damaged by environmental, hereditary or other factors, BRCA proteins come into play to fix it and therefore guarantee the survival of the cells. Specific mutations in these genes prevent damaged cells from repairing the DNA efficiently and have been associated with various types of cancer, including breast, ovarian and prostate cancer.

PARP inhibitors are used as tools for specifically targeting the destruction of tumour cells with BRCA mutations. These molecules, which are currently in clinical trials for the treatment of prostate cancer, are proving to be very effective in the treatment of breast and ovarian cancer when there are BRCA mutations. Furthermore, "prostate tumours with sporadic mutations [present only in the tumour, not inherited] in BRCA, also respond to these inhibitors, according to recent data presented during the ESMO [European Society for European Oncology] congress in Madrid," states Olmos.

The conclusions of this study underline the importance of launching clinical trials designed to assess new treatment strategies and the therapeutic potential of novel drugs for prostate cancer in these patients, such as PARP inhibitors.

Closer monitoring

This study has focused on prostate cancer patients with hereditary BRCA mutations. "We are investigating whether patients with sporadic mutations in these genes also show more aggressive and metastatic tumours, and whether or not they respond less well to conventional treatments than patients not carrying BRCA mutations."

If this hypothesis is confirmed "there would be a need for closer monitoring of patients with BRCA mutations, regardless of the origin

[hereditary or sporadic], in order to improve the clinical course of these patients."

Prostate cancer is the second most common form of cancer affecting men in the world - and the most common in some countries, including Spain, where 25,000 new cases are diagnosed every year. It is believed that 2% of these patients are carriers of hereditary BRCA mutations, while 12% of the patients have sporadic mutations in the same genes.

The relevance of this work and its implications for the improved care of prostate cancer patients were recognised last year at the Genitourinary Cancers Symposium organised by the American Society of Clinical Oncology (ASCO), which awarded the preliminary research work a Merit Award.

More information: Effect of BRCA mutations on metatastatic relapse and cause-specific survival after radical treatment for localized prostate cancer. Elena Castro, Chee Goh, Daniel Leongamornlert, Ed Saunders, Malgorzata Tymrakiewicz, Tokhir Dadaev, Koveela Govindasami, Michelle Guy, Steve Ellis, Debra Frost, Elizabeth Bancroft, Trevor Cole , Marc Tischkowitz, M. John Kennedy, Jacqueline Eason, Carole Brewer, D. Gareth Evans, Rosemarie Davidson, Diana Eccles, Mary E. Porteous, Fiona Douglas, Julian Adlard, Alan Donaldson, Antonis C. Antoniou, Zsofia Kote-Jarai, Douglas F. Easton, David Olmos, Rosalind Eeles. *European Urology* (2014). DOI: 10.1016/j.eururo.2014.10.022

Provided by Centro Nacional de Investigaciones Oncologicas