

New frontiers in the fight against cancer : the revised hallmarks of cancer ; progress, innovation and clinical value. The role of the European Research

Intervento del Prof. Francesco Cognetti in occasione del Convegno “EU Research and Innovation in our daily life” che si terrà il 27.11.2018 presso il Parlamento Europeo (Brussels)

Europe contains 9% of the world population but has a 25% of the global cancer burden. The cancer incidence accounts for about (4 millions) European citizens and the mortality for about (2 millions).

The EU 28 countries account for 3 million cancer incidence and 1.5 million cancer deaths (specific mortality).

Cancer mortality has decreased in the western countries in the last 25 years (in almost all tumor types) mainly in woman than in males due more diffuse screening programs and better treatments. This reduction of mortality was inferior than for cardiovascular disease. Continuing falls in mortality rates from major cancer sites in Europe and its major countries, exceptions are pancreatic cancer and lung cancer in women. Improved treatment and organized screening may account for recent positive colorectal cancer trends in both sexes. Net survival at 5 and 10 years from cancer varies with age, sex and proportion of lethal cancer and has consistently increased during the last years being around 80-90% in thyroid, prostate, melanoma and breast cancers but much lower about 10-20% in brain, liver, lung, oesophagus and pancreatic cancer. There were constant improvements in cancer survival over time but persisting variations across countries with inequalities in cancer care related to several reasons: diagnostic intensity and screening leading to earlier or late stage at diagnosis, effective treatments, socioeconomic status, life style and and general health difference between population, cancer costs and organisation of care. Survival data are better in the Northern and Central Europe and in some countries of Southern Europe (Italy and Spain) and worse in UK and in Eastern Europe.

Health systems in the European Union aim to provide high-quality, cost-effective care. This is particularly difficult however, in cases of rare or low-prevalence complex diseases. European Reference Networks (ERNs) are virtual networks involving healthcare providers across Europe. They aim to facilitate discussion on complex or rare diseases and conditions that require highly specialized treatment, and concentrated knowledge and resources. To review a patient's diagnosis and treatment, ERN coordinators convene 'virtual' advisory panels of medical specialists across different disciplines, using a dedicated IT platforms and telemedicine tools. The ERN initiative receives support from several EU funding programmes, including

the Health Programme, the Connecting Europe Facility and Horizon 2020. RN initiative is mainly driven by EU countries.

New scientific insights and a spur of technological innovations make prospects for success greater than ever. There is a dramatic shift in our fundamental understanding and knowledge of cancer.

Each tumor is molecularly unique but certain pathways are repeatedly affected. This represents the revised hallmarks of cancer. Now the molecular circuitry of cancer cells is better understood.

There are new tools for cancer diagnosis and treatment that open a complete new prospective:

- Liquid biopsy represents the direct measurement of cancer DNA in the blood and can allow early detection and monitoring of minimal residual disease and also the detection of resistance mutations.
- Better imaging as SPION uptake of cancer. Lesions smaller than 300 millimicron in diameter are detectable and with further optimization, even single cancer cells.
- New anticancer strategies and therapies are being developed as multitargeted agents to precision individualised medicine and new immunotherapy which changed the outcome of many cancer disease that were incurable (malignant melanoma, non small cell lung cancer, kidney, cancer, et al.)

These new treatments were able to achieve a high rate of disease regression or stabilization and a long term survival in many cases.

In recognition of this development European and global research efforts to fight cancer have been ongoing since the last few years to turn this disease in to chronic disease.

A total of 252.000 papers were produced for 18 leading countries in Europe from 2002 to 2013. Germany, Italy and UK were the three leading European Countries for papers on cancer.

European cancer research funding in 2012-2013 amounted to 7.6 billion including Iceland, Norway and Switzerland.

Genetics was the dominant research domain, followed by prognosis and surgery.

There was very little research on quality of life, palliative care or screening and radiotherapy. Standard chemotherapy showed the slowest growth rate during the last few years, whereas targeted therapy showed the fastest annual growth in output. In 2013, the fractional European output was 30.000 research papers.

Government supported the largest share of European cancer research (30%), followed by the PNP (Private no profit) (19%), industrial (7%) and international sectors (3%). The European Commission was the largest single funder of European cancer research, with 2836 papers (2.4% of the total), amounting to approximately €147 million spent, with the number of research papers receiving its support increasing by 16% per year.

The French National Health and Medical Research Institute (INSERM) and the Italian Ministry of Health were the leading government bodies to support research, contributing to the equivalent of 2800 and 2468 papers, respectively, over the 5-year period. Therefore, collaborative research on cancer has been and remains a high priority in EU framework programme.

Certain European countries are underperforming in cancer research relative to their GDP (PIL) and need to do more to address the rising burden of cancer of the largest. Cancer research is a critical component of a country's performance in providing optimal cancer care for its citizens. Evidence confirms that the scale of private and public investment in research and innovation has a direct impact in enhancing productivity and boosting global competitiveness.

There is a particular need to encourage charitable and philanthropic funding in Eastern Europe, where cancer research support comes almost entirely from central government.

With regard to some of the European projects that are worthy to be mentioned these are the following:

-For primary prevention; The European Prospective Investigation into cancer and nutrition (Epic study) is actually running due to the efforts of 23 centres located in 10 European countries. The study was designed to investigate the relationship between nutrition and cancer.

-For translational research: the Transcan 2 on rare cancers it is going to be started has received funding of the European Union's Horizon 2010 research and innovation program

-For clinical research : the Italian GIM cooperative group on Breast Cancer that in the last 15 years carried out 19 clinical trials both in the adjuvant and metastatic setting achieving an accrual of about 15.000 patients. Part of these studies have been published and changed clinical practice in the treatment of this disease.

In Europe, most of the cancer clinical research dedicated to therapeutic innovations

aims primarily at regulatory approval. Once an anticancer drug enters the common market, each member state determines its real-world use based on its own criteria: pricing, reimbursement and clinical indications.

A gap exists in Europe between regulatory approval assessments and real-world application of anticancer treatment. Despite a centralized registration by EMA, the reimbursement of new drugs occurs at a national level, enabling the European member states to conduct independent public health policies.

Average market access time is very short in Germany and UK, medium in Netherland and Sweden, but very long delays occur also more than one year in Italy, Spain and France.

The time should be faster when the drug is reported as "highly innovative" because it involves a high benefit for the patients should be available to cancer patients before they are marketed. However, the variations in time from EMA to HTA (Health Technology Assessment) local decisional remained between different countries also for these high benefit drugs.

This should be a strong focus of the community. The urgency is related to the short-term lethal of the disease. This is very different from diabetes, hypertension or arthritis. Many lives are tragically ended by bureaucracy

In conclusion to help to reduce survival inequalities and to improve cancer care, all the European countries should pursue the reduction of the fragmentation of care services, the promotion of a comprehensive multidisciplinary cancer care centres, a better organisation and funding of health care system, the promotion and funding outcome research and finally the alliance and finally of the entire cancer fighting community. Intensive collaboration among scientific, medical, technological and pharmaceutical communities is thus indispensable.