EPIC Project

The European Prospective Investigation into Cancer (EPIC) is a prospective cohort of **521,468 men and women** enrolled from **ten countries**. When study participant recruitment began in 1992, detailed information on diet, comprehensive lifestyle characteristics, anthropometric measurements and medical history was collected. Biological samples including plasma, serum, leukocytes, and erythrocytes were collected from 387,889 individuals, and have been stored at the International Agency for Research on Cancer – World Health Organization (IARC-WHO) and EPIC collaborating centers. Overall, the EPIC biorepositories host over **9 million aliquots**, constituting **one of the largest biobanks in the world** for genetic, biochemical and epidemiologic investigations of cancer.

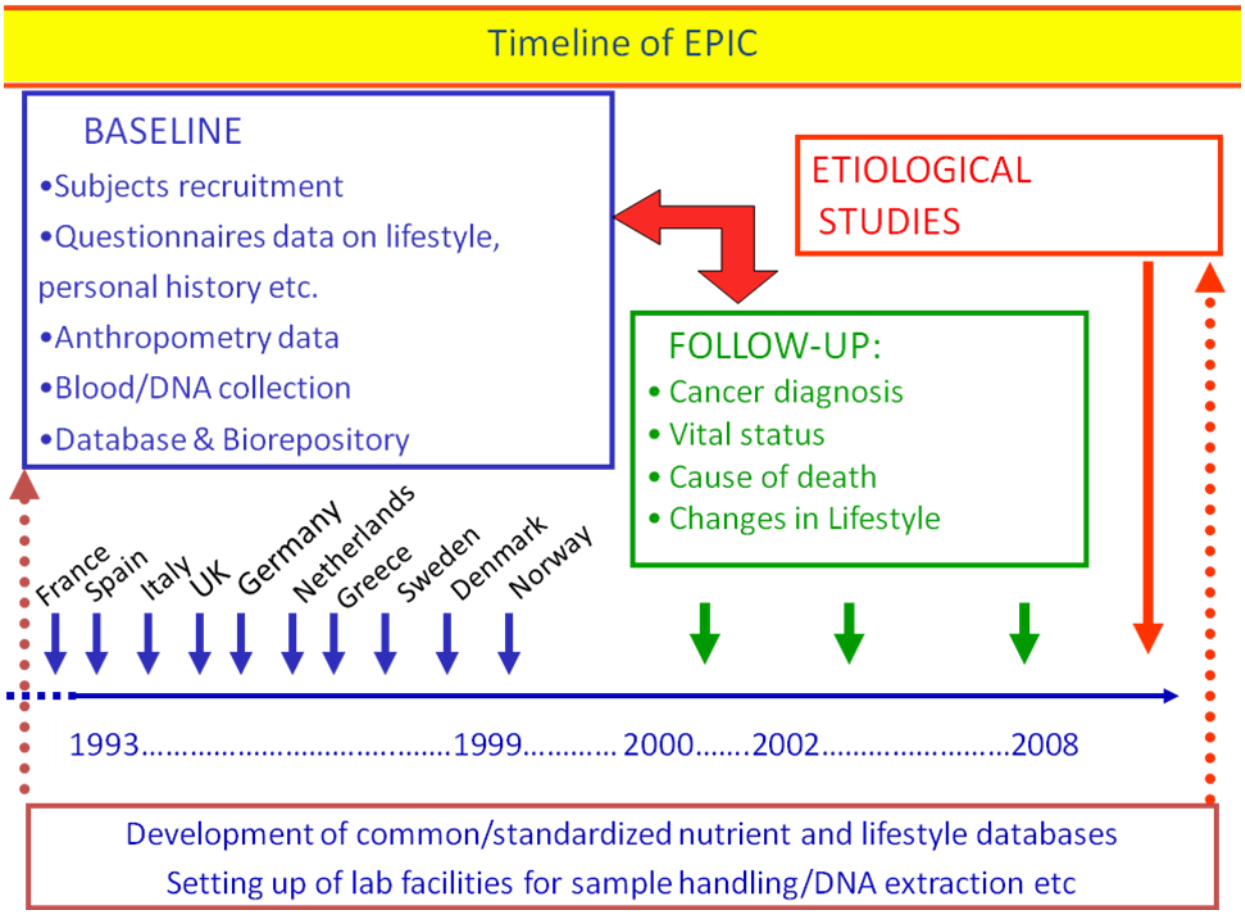
Centre	**Subjects Included**	
	Questionnaire	**Questionnaire and Blood Sample**
Denmark	57 054	56 131
France	74 524	21 053
Greece	28 555	28 483
Germany	53 091	50 678
Italy	47 749	47 725
Netherlands	40 072	36 318
Norway	37 215	11 000
Spain	41 440	39 579
Sweden	53 826	53 781
United Kingdom	87 942	43 141
TOTAL	521 468	387 889

From the baseline data collection through 2009, **more than 63,000 EPIC participants have been diagnosed with cancer**. It is anticipated that by 2020 this number will have risen to **90,000** and will include approximately 20,000 cases of breast, 8,000 prostate, 5,000 lung, 8,000 colorectal, 3,500 bladder, 2,500 pancreatic, 2,500 ovarian and 3,000 endometrial cancers. The large number of incident cancer cases with prospectively collected lifestyle data and blood specimens has allowed the EPIC investigators to conduct **state-of-the-art investigations into the etiology and prevention of several forms of cancer**.

In the last decade, EPIC has generated more than 300 dedicated articles in international peer-reviewed journals and has contributed data and biologic specimens to dozens of cancer-related research activities in Europe and the United States, particularly in studies of metabolic, nutritional and genetic risk factors.

History of EPIC

The planning and piloting of EPIC was initiated in 1990 by IARC-WHO and the participating centres, with support from the European Commission. The project started with a series of pilot studies to test the methodology for the establishment of a very large prospective cohort study with collection and storage of blood samples, as well as the feasibility of recruiting participants. As these methodological studies provided very encouraging results, the European Commission via its "Europe Against Cancer" programme decided to initiate the EPIC project and fund it with a shared cost mechanism by which approximately 50% of the funds would be provided by the EC and the remaining would be provided by national sources, either governments or charities. Recruitment of study participants and collection of data and biological samples started in 1993 in four countries (Spain, Italy, France and UK) and was extended between 1994 and 1996 to include six more countries (Greece, Germany, The Netherlands, Denmark, Sweden and Norway).



Recruitment of participants and data collection was completed in 1999. Follow-up of study subjects for disease endpoints, vital status and causes of death commenced in the mid-1990s. Additional follow-up to measure changes in lifestyle, health conditions, diagnosed diseases and related treatment was conducted a few years after baseline, at least once in all EPIC study centres.

Since its inception, the EPIC study has been coordinated by the EPIC Steering Committee, composed of the study coordinator (Elio Riboli), two representatives from IARC-WHO, and two representatives from each participating country. The governance of the project is regulated by a series of 'Collaborative Research Agreements' established between IARC-WHO and all national collaborating institutions. The EPIC Steering Committee meets monthly by teleconference and typically twice a year in person.

The study has been coordinated by the Unit of Nutrition and Cancer of IARC-WHO since its beginning. In 2006, certain coordinating activities shifted to Imperial College London, where Elio Riboli took up the appointment as Professor of Cancer Epidemiology and Prevention. EPIC's master database and main biobank resources are hosted at IARC-WHO's headquarters in Lyon, France. Coordination of the project is shared between the two organizations (ICL and IARC-WHO) under a Memorandum of Understanding.

FUNDING HISTORY

As outlined above, EPIC was originally funded under the European Commission's "Europe Against Cancer" programme (1992-2002) and subsequently by a DG-Research Coordination Action Grant from 2005-2009. For the period 2010-2012, EPIC's operations have been supported by country specific institutional funds and individual project grants, without a specific European central grant to support its core infrastructures. The total level of external investment in EPIC to date stands at approximately € 42.5 million, excluding support from EPIC participating institutions.

There are plans to submit an application to fund additional follow-up research activities including collection of additional blood samples and lifestyle/diet information when the Eighth Framework Programme or Horizon 2020 is launched. The EPIC Steering Committee now seeks funding to support the maintenance of EPIC's existing infrastructure, including the central database and the central biobank, and the core project management for the next 3-5 years (2012-2017).

European Commission Support under the "Europe Against Cancer" Programme
Contracts from the European Commission, Directorate General V, Division of Public Health, to support the establishment and implementation of EPIC, awarded to the International Agency for Research on Cancer, WHO, with Dr Elio Riboli as Principal Investigator and EPIC Coordinator:

1992	92-CV-v01-051-0	Planning Phase of the EPIC project + additional funds for field work provided directly to Centres	ECU $ 358,375 ECU $ 350,000 approx
1993	SOC93 102717 05E01	Coordination of the EPIC project + additional funds for field work provided directly to Centres	ECU $ 347,490 ECU $ 1,500,000 approx
1994	SOC94 201157 0F01	Coordination of the EPIC project + additional funds for field work provided directly to Centres	ECU$ 508,542 ECU $ 2,500,000 approx
1995	SOC95 200823 05F02	Coordination of the EPIC project	ECU $ 95,305
1996	SOC95 200416	Coordination of the EPIC project, including field work	ECU $ 3,653,482
1997	SOC97 200302 05F02	Coordination of the EPIC project, including field work	ECU $ 3,767,496
1998	SOC 98 200769 05F02	Coordination of the EPIC project, including field work	ECU $ 2,237,238
1999	SI2-195579	Coordination of the EPIC project, including	ECU $ 2,288,600

		field work	
2000	SI2-296584	Coordination of the EPIC project, including field work	Euro € 2,555,000
2001	SI2-326938	Coordination of the EPIC project, including field work	Euro € 2,060,000
2002	SPC.2002332	Coordination of the EPIC project, including field work	Euro € 2,224,300

Matched Funding from EC Member States 1992-2002	
DENMARK	Danish Cancer Society
FRANCE	Ligue contre le Cancer (France); Société 3M (France); Mutuelle Générale de l'Education Nationale; Institut National de la Santé et de la Recherche Médicale (INSERM)
GERMANY	German Cancer Aid; German Cancer Research Centre; German Federal Ministry of Education and Research
GREECE	Greek Ministry of Health; Greek Ministry of Education
ITALY	Italian Association for Research on Cancer; Italian National Research Council
THE NETHERLANDS	Dutch Ministry of Public Health, Welfare and Sports; Dutch Ministry of Health; Dutch Prevention Funds; LK Research Funds; Dutch ZON (Zorg Onderzoek Nederland)
NORWAY	Norwegian Cancer Society
SPAIN	Health Research Fund (FIS) of the Spanish Ministry of Health; the participating regional governments and institutions of Spain
SWEDEN	Swedish Cancer Society; Swedish Scientific Council; Regional Government of Skane and Västerbotten, Sweden
UK	Cancer Research UK; Medical Research Council ; the Stroke Association; British Heart Foundation; Department of Health; Food Standards Agency; the Wellcome Trust
International Agency for Research on Cancer	Financial support for infrastructure maintenance of data basis/personnel
Imperial College London	Financial support to scientific and managerial coordination of EPIC

Additional EC Funding by source		
DG-SANCO	Funding for PANACEA Project (PI: Petra Peeters)	€ 1,128,861 EURO
DG-RESEARCH	2004: EPIC Coordination Action Grant (SP23-CT-2005-006438) (PI Elio Riboli)	€ 999,000 EURO
	2005: InterAct Diabetes Project (PI: Nick Wareham)	€ 10,000,000 EURO
	2012: EPIC-CVD (PI: John Danesh)	€ 5,987,266 EURO

Research - Nutrition and Cancer

EPIC's research findings have been published in leading peer-reviewed journals as well as covered extensively by international media including Le Monde, Le Figaro, El Pais, The Guardian, The Telegraph, The Daily Mail, Corriere della Sera, la Repubblica, New York Times, BBC News, CNN, USA Today, The Times of India etc, and referenced by the National Health Service, World Health Organization and World Cancer Research Fund.

BREAST CANCER

Breast cancer is no longer treated as a single entity, and was therefore investigated in EPIC focusing on different subtypes within breast cancer.

Results from the EPIC study found a statistically significant though quantitatively modest increase in risk of breast cancer in relation to consumption of alcohol and saturated fat.

The association with saturated fat intake was more evident in postmenopausal women who never used hormone therapy.

- In postmenopausal women, overweight (expressed as Body Mass Index) was a significant predictor of breast cancer risk. Moderate and high levels of physical activity, combining recreational and household activities, were associated with a reduced risk, independently of the level of overweight.

- Results from EPIC showed that overall fruit and vegetable intake was not associated with a significant reduction in breast cancer risk; however, in postmenopausal women using exogenous hormones high intakes of beta-carotene and vitamin C were associated with lower risk.

- Data derived from EPIC have also shown that endogenous sex steroid hormones are associated with risk of hormone receptor positive [oestrogen receptor (ER) and progesterone receptor (PR)] breast cancer in postmenopausal women. This EPIC study focused on women not using Hormone Replacement Therapy to avoid any interfering effect of hormones taken as medication. Furthermore, in premenopausal women, elevated levels of androgens were associated with an increased risk of breast cancer.

COLORECTAL CANCER

Cancers of the colon and rectum are the third most common cancers in the EU in terms of both incidence and mortality. Thus, even small changes in overall colorectal cancer risks can have strong public health impact.

- The hypotheses that diets high in fibre reduce colorectal cancer risk, while those high in red and processed meats increase risk for the disease have been definitively confirmed by results from EPIC. These EPIC findings were published in high profile scientific journals, and were instrumental in guiding the recent World Cancer Research Fund (WCRF) recommendations for dietary and lifestyle cancer risk reduction strategies for these key dietary components.

- Recent EPIC findings show that adherence to the WCRF recommendations can in fact result in a 27% reduction in colorectal cancer incidence, highlighting the public health significance of dietary and lifestyle changes for colorectal cancer prevention.

- EPIC findings also show that lifestyle factors, particularly obesity (particularly abdominal fatness), physical inactivity, high intake of alcohol and smoking also contribute considerably to increased colorectal cancer risks.

- EPIC has published the largest study to date worldwide on blood vitamin D levels and risk of colorectal cancer. The findings show a strong dose response protective association with higher blood vitamin D and dietary calcium levels. Further analyses also show that higher vitamin D levels prior to diagnosis lead to longer survival from colorectal cancer.

GASTRIC CANCER

- The novel finding from EPIC-Eur-Gast on the association between dietary intake of heme iron and gastric cancer risk, together with the previous EPIC-Eur-Gast published results of the association with red and processed meat, and the endogenous formation of N-nitroso compounds, strongly support the hypothesis that high red meat consumption increases gastric cancer risk.

- The original findings from EPIC-Eur-Gast that adherence to a Mediterranean dietary pattern is associated with a significant reduction of gastric cancer risk, together with EPIC-Eur-Gast results in relation with vitamin C, citrus fruit, and total antioxidant capacity from plants foods, support the hypothesis of the role of a healthy dietary pattern for gastric cancer prevention.

- The EPIC-Eur-Gast results support the hypothesis that heavy alcohol consumption increases gastric cancer risk, and for individuals with specific alleles relevant for the metabolization of alcohol, the gastric cancer risk may be even greater.

LUNG CANCER

- The main risk factor for lung cancer is tobacco smoking, and this is clearly confirmed in the European populations enrolled in EPIC.

- A strong and consistent negative association between vitamin B6 and methionine levels in blood and the risk of lung cancer was observed, in both smokers and non-smokers.

- EPIC has shown that exposures to environmental tobacco smoke and traffic-related air pollution were associated with lung cancer in never and ex-smokers (current smokers were not investigated). We also found that biomarkers of DNA damage are associated with both air pollution and lung cancer, supporting the biological bases of the association with lung cancer risk.

- In addition to anti-smoking interventions, further decreases in lung cancer incidence could be obtained through reduction of air pollution levels and by improving dietary habits, particularly the intake of fruits and vegetables and of vitamins in the One-carbon metabolism pathway.

- In addition to smoking and air-pollution, there is great interest today into the large population of ex-smokers. The possible interactions between previous smoking and dietary or other exposures are of major public health interest for the identification of ways for further reducing lung cancer risk among subjects who have already stopped smoking.

PANCREATIC CANCER

- EPIC provided further evidence that active and passive smoking is associated with increased risk of pancreatic cancer and that this risk declines after smoking cessation. The association of tobacco with bladder cancer risk was corroborated by the finding that higher blood concentration of cotinine (a metabolite of nicotine and a biomarker of exposure to tobacco smoke) is a significant predictor of pancreatic cancer risk.

- The hypothesis that a larger waist-to-hip ratio and waist circumference, both reflecting abdominal or central fat distribution, increases the risk of pancreatic cancer was supported by EPIC results. This was later confirmed in the Pancreatic Cancer Cohort Consortium (PanScan) that includes EPIC.

- The hypothesis that people with blood group O may have a lower risk of pancreatic cancer than those with groups A or B was confirmed in PanScan. A further genome-wide association study in PanScan has identified three additional genetic susceptibility loci.

- Although research is still ongoing, our data thus far suggest that specific foods, drinking of alcohol, and menstrual and reproductive factors do not seem to play a major role in pancreatic cancer aetiology.

- EPIC provides further evidence that diabetes is a risk factor for pancreatic cancer, and also shows that moderately elevated blood glucose levels, even in the absence of clinically diagnosed diabetes are associated with increased risk.

BLADDER CANCER

Bladder cancer is not among the most frequent cancers, therefore large studies are needed in order to achieve enough statistical power to evaluate associations prospectively. To date, over 1,000 cases of bladder cancer have been identified within the EPIC study. Important contributions of the EPIC study to bladder cancer aetiology include:

- The strong association between tobacco smoking and bladder cancer, observed in several studies, was also found in EPIC, where it was possible to examine smoking patterns in detail, showing an increased bladder cancer risk with smoking intensity and duration, and even among occasional smokers, as well as

an increased risk with environmental tobacco smoke exposure in childhood (passive smoking).

- The association between dietary components and bladder cancer has been investigated extensively in EPIC, focusing on vegetable and fruit consumption and intake of meats and associated components, e.g. heme iron, nitrosamines and heterocyclic aromatic amines. The studies have shown no strong effect of these dietary components in bladder cancer etiology. However, an increased risk of bladder cancer with meat intake was detected among a specific genetically defined sub-group of carriers of the "rapid NAT2" genotype.

- The association between fluid intake and bladder cancer has been evaluated in several studies under the hypothesis that direct contact of bladder cells with urinary carcinogens may relate to the development of bladder cancer, and that a high consumption of fluids may dilute the urine and hereby reduce contact time between bladder cells and carcinogens. Analyses of EPIC data confirmed the lack of association between total fluid intake and bladder cancer.

PROSTATE CANCER

Prostate cancer is now the most common cancer in men in Europe, but its causes remain enigmatic. In a systematic programme of research, EPIC investigators have evaluated individual and combined possible roles of a wide range of dietary and hormonal factors including meat, fish, fruit, vegetables, vitamins, minerals and sex hormones. We have identified one clear risk factor: men with relatively high blood levels of the hormone Insulin-like Growth Factor I (IGF-I) have an increased risk for prostate cancer. Our research is now focused on examining whether dietary or other lifestyle factors can affect prostate cancer risk through IGF-I.

Research Findings in Other Disease Areas

Although EPIC was primarily established to study risk factors for cancer, its database and biological resources were designed with the view to provide the infrastructure for study of the determinants of other chronic diseases, to help advance scientific understanding and disease prevention and disease control strategies.

The prospective cohort study design of EPIC has the additional advantage of permitting the assessment and evaluation of risk factors involved in co-morbidity (i.e. lifestyle, metabolic or genetic factors associated with the risk of more than one chronic disease) and to investigate the risk factor's role in different populations. As a consequence, the EPIC design is very suitable to conduct research on ageing in European populations.

EPIC-HEART

EPIC-Heart has received funding from the EC, British Heart Foundation and UK Medical Research Council to investigate the interplay of genetic, biochemical and lifestyle factors on the risk of coronary heart disease, which is the single leading cause of death in Europe and worldwide. Over 10,000 of EPIC's participants have developed heart disease since the study began in the 1990s, providing a sufficiently large group of cases to allow reliable investigation of the joint effects of genes, biomarkers and lifestyles on heart disease risk.

AGEING/ AGE-RELATED NEURODEGENERATIVE DISORDERS/ ALZHEIMER'S DISEASE

Extending EPIC efforts to late onset dementias, such as Alzheimer's disease and other age-related neurodegenerative diseases, such as Parkinson's disease, will hopefully reduce some of the bottlenecks in clinical and pharmaceutical research on these disorders, and translate findings into reliable information of clinical, scientific and public health relevance.

A study investigating risk factors with an emphasis on the complex gene- environment interactions in Parkinson disease (PD) is ongoing, involving ~1200 PD incident cases and matched controls among EPIC participants.

Furthermore, with the wealth of its accumulated information, EPIC provides a unique opportunity to conduct prospective research on the aetiology of cognitive neurodegenerative diseases of ageing, to identify risk and protective factors (e.g. demographic, cardiovascular, lifestyle and genetic factors), and to identify and validate biomarkers of susceptibility. These associations will be investigated in relation to cognitive outcomes measured 15-20 years after the EPIC baseline. Comprehensive assessments and long duration of follow-up allows for classification of extreme phenotypes and exposures, reliable identification of populations at risk and detailed evaluation of risk and protective factors in the pre-symptomatic and symptomatic phases of dementia.

In an effort to address issues relevant to healthy ageing, EPIC researchers are currently seeking relevant funding sources. The ambitious project plans to bring together EPIC and other major European, American and Australian cohorts to explore and contrast different gradients towards healthy ageing, and how various factors (particularly diet and lifestyle, but also stress, sleep and socioeconomic status) can affect healthy ageing.

The promotion of successful ageing by prevention of major chronic diseases can be of great public health relevance for the ageing populations of Europe and worldwide.

INTERACT/DIABETES

Several studies have shown that the global prevalence of type 2 diabetes has a marked variability, suggesting that an interaction between genetic predisposition and lifestyles is central to determining diabetes risk. The geographical pattern of variation suggests that prevalence is lowest in rural areas of developing countries, is generally intermediate in developed countries, but is highest in certain ethnic groups who have adopted western lifestyle patterns. One explanation for this variation is the "thrifty genotype" hypothesis which postulates that genetic variation which was advantageous in times of food scarcity would become disadvantageous in times of food abundance. The human genome, tailored to function in a hostile environment with uncertain and variable food availability, now faces novel stressors, and depending on the genetic subgroup, copes variably with this challenge.

The InterAct project is aimed at investigating the basis of these interactions. EPIC contributed a case set of 10,000 individuals and a similarly sized control cohort free of diabetes to the project, and several members of EPIC's Steering Committee are actively involved in the study.

The Future of EPIC

FOLLOW-UP STUDY

Currently available data and biological samples from baseline and as well as those from follow-ups conducted during the past 10-15 years are of great value and have so far been only partially used.

There are tens of cases of cancer, cardiovascular diseases, diabetes, neurodegenerative diseases and other chronic diseases available for further studies that have so far been only partially utilized. Therefore there is great scope for conducting investigations on the exceptional resources that have been accumulated by EPIC between 1992 and the present day.

At the same time, looking to the next 10-20 years, it is important to plan for investigations based on disease cases which are yet to be diagnosed. From this perspective, it is critical for EPIC to plan for the standardized collection of a second harmonized round of blood samples, plus diet and lifestyle data across all EPIC centres. It is expected that the diet and lifestyle of EPIC participants will have changed in the 20 years since enrolment, and will likely change even further during the next decade, partly as a result of age-related variations and partly due to changes in environmental and lifestyle habits and the food market throughout Europe.

For example, major changes in the availability of new food products and changes in the living environment occurred during the past two decades, the extent of which likely differs between countries and between study participants. The vast majority of EPIC participants is now more than 60 years of age, and has undergone the transition from middle- to advanced-age during the past 20 years. Thus, this follow-up period may represent a critical time when diet, lifestyle and shifts in the metabolic and physiologic milieu could have had significant impact on future development of cancer and other chronic diseases. Measuring these changes will provide invaluable data that can be exploited to further characterize the etiology of specific cancers and other complex multifactorial chronic diseases, such as cardiovascular, Alzheimer's disease and other age- related dementias and type II diabetes, as well as multi-comorbidity among elderly.

Further, with respect to cancer, despite major improvements in cancer treatment, little is known of the host-specific factors that contribute to response to treatment, recurrence and survival. To study cancer survival, it is critical to collect more detailed clinical and pathological data on cancer diagnoses, treatment, recurrence and metastases than is routinely done in cancer cohorts, including EPIC. EPIC is well positioned to study cancer survival because of the large number of cancer cases with detailed pre-diagnostic biological samples and lifestyle data, and the potential availability of pathologic and treatment data from centralized hospital registries.

Selected Publications

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EPIC public website: www.epic.iarc.fr

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