Cancer Epidemiology – Cases, Causes, Challenges

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Cancer is one of the major health threats to populations worldwide. While in the past cancer and other chronic diseases were seen to be problems mainly of industrialized countries, there is increasing certainty that populations in less developed countries are carrying an ever larger part of the global disease burden from cancer.

This presentation gives an overview of the exciting field of cancer epidemiology, defined as the study of distribution and determinants of cancer and the application of this knowledge to cancer control. In particular issues of cancer case registration, of established cancer causes and of challenges lying ahead of cancer epidemiologists will be discussed.

The presentation entertains an international perspectives but at times aspects particular to Germany and Europe will be pointed out so as to allow comparisons with and reflections on the situation found in Japan and Asia.

Overview

- Cancer background, milestones
- Cancer registries (Germany)
- Cancer epidemiology today
  - New agenda
  - Unfinished agenda
- Screening for early cancer
- Some challenges of cancer epidemiology

The presentation consists of five parts:

After a rather short overview about cancer data and some milestones of research in cancer epidemiology the important role of cancer registries for epidemiologic research will be pointed out, noting in particular some recent developments in Germany.

The current themes of cancer epidemiology - some longstanding, some more recent - will be discussed, and the issue of cancer screening described as an example of the complexities cancer epidemiologists and public health practitioners face when considering appropriate ways of preventing cancer.

Finally some challenges of cancer epidemiology are identified and discussed.

Epidemiology – basics

- **How many cancer cases/deaths are there? (per year, sex, age group etc.)**
- **Is cancer more frequent around nuclear installations?**
- **What are the causes of stomach cancer?**
- **What is the association between tobacco smoke and (lung) cancer?**
- **Should screening for prostate cancer be recommended?**
- **Does cancer prevention work?**

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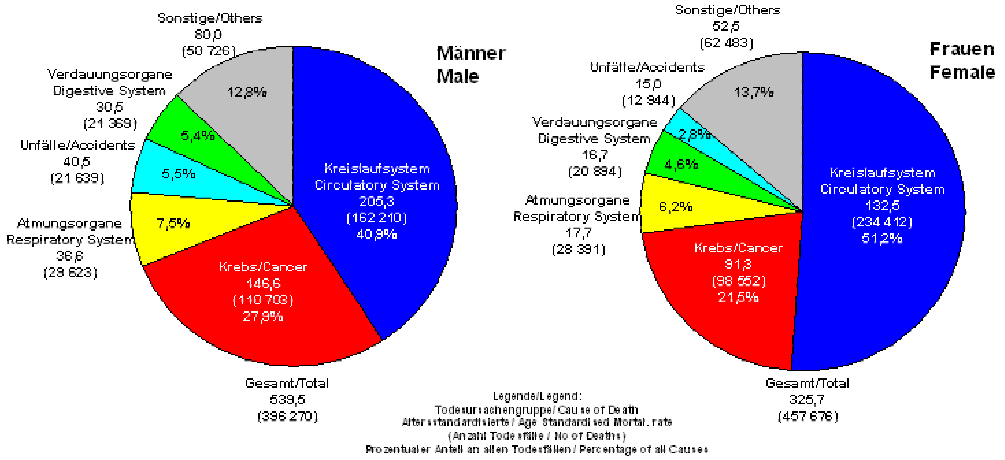
Not everyone is familiar with the science and practice of epidemiology. There are formal definitions and longer introductory explanations available, but a more pragmatic approach may be to look at some research questions that epidemiology deals with.

The question of disease frequency, specified for time, person and place, is central to many research efforts and also to inform researchers and policy makers about time trends, groups or areas that deserve specific attention etc. For example, in order to assess whether cancer around nuclear installations is more frequent than elsewhere, quality data on new and existing cancer cases and deaths have to be available.

Analytical cancer epidemiology aims at identifying cancer causes in population studies. For example, in countries with high stomach cancer rates there have been major research efforts to identify risk factors for stomach cancer that can be modified and thus help prevent the cancer. These studies are often extended to look in detail at the risk in relation to the factors such as age at first exposure, the intensity of the exposure (e.g. amount of smoking over time) and to many other factors.

An important approach in cancer prevention is screening, i.e. the early detection and subsequent treatment of cancer. However, such programmes are costly and therefore need to be well justified. Epidemiology helps to assess whether screening works in principle and whether screening programmes that put the chosen screening approach into practice show the desired effect.

Die häufigsten Todesursachengruppen in Deutschland 2003
The Most Frequent Causes of Death in Germany in 2003



100,000 cancer deaths among women, 110,000 among men

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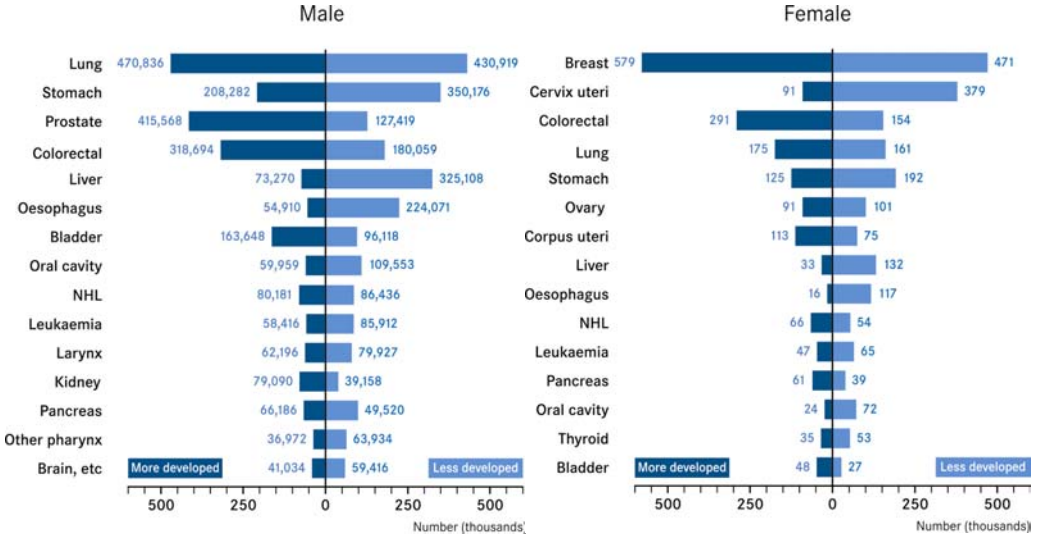
In Germany cancer ranks highly on the chart of frequent causes of death. Among men there were 110,000 cancer deaths in 2003, representing almost 28% of all deaths, second only to cardiovascular system deaths. Similarily, among women there were 100,000 cancer deaths, representing 22% of all deaths in 2003. Cardiovascular and cancer deaths together are responsible for close to three quarters of all deaths in Germany. A comparable situation exists in many rich countries.

The most common cancers worldwide



World cancer report, IARC 2003

Among the individual cancer sites lung cancer dominates among men globally in terms of mortality. Prostate, stomach and colorectal cancer are also among the leading cancer causes of deaths, but there are some differences between developed and less developed countries. Liver cancer is a major cause of death in developing countries, mainly due to infectious causes, and causes less deaths among men in developed countries.

Breast cancer is now the most frequent cancer cause of death globally while cervical cancer shows large differences between developed and less developed countries. Colorectal, lung and stomach cancer are also major sites among women, with lung cancer steadily increasing in many countries due to higher smoking rates among women.

Cancer Epidemiology milestones

Richard Doll and Austin Bradford Hill, 1964

Mortality in relation to smoking: ten years´ observations of British doctors

Risk of Lung cancer death / 1000

Smokers (+ 25 cig/day):

- 2.27 (Men) — 0.22 (Women) — RR 7

Nonsmoker: — RR 32

- 0.07 (Men) — 0.03 (Women)

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BMJ 1: 1399-1410 & 1460-67

The research on tobacco as a major cancer causing factor is of pivotal importance to epidemiology and public health for many reasons. *Richard Doll and Austin Bradford-Hill* conducted one of the most influential investigations in the history of epidemiology, using an elegant and simple design and putting much stress on the quality of their data and the methods employed. In their prospective cohort of British doctors they could show the massively increased lung cancer risk among smokers as compared to non-smokers (Relative risk RR = 32). They also noted a much larger risks among women than among men which is an observation still puzzling today to some extent. This study recently celebrated its 50th anniversary, shortly before the sad death of Sir Richard Doll in 2005. One of the developments associated with these research efforts is the marked drop in smoking among British citizens, from around 80% in the 1950s to 26% today.

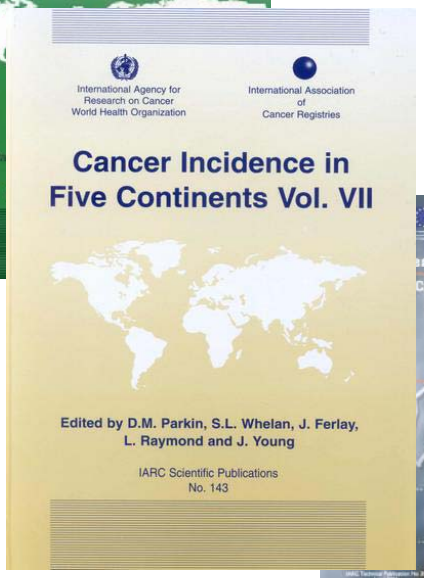
Migrant studies: cancer in a changing environment

Cause of death (M)	Japan	Americans of Japanese Descent: non US born	Americans of Japanese Descent: US born	Americans (white)
Stomach-Ca	100	72	38	17
Colon-Ca	100	374	288	489
Cause of death (F)				
Stomach-Ca	100	55	48	18
Colon-Ca	100	218	209	483
Breast-Ca	100	166	136	591

Haenszel W, Kurihara M*: Studies of Japanese Migrants. I. Mortality from Cancer and other diseases among Japanese in the United States* J. Nat Cancer Inst. 1968: 43-68

Studies of migrants also contributed significantly to cancer epidemiology. Such studies allow to assess how risk changes when people enter a new environment and are exposed to the risk and preventive factors. *Haenszel and Kurihara* reported on causes of death among Japanese migrants to the United States. They could demonstrate a number of interesting findings, notably the marked risk changes in stomach cancer from high death rates among the Japanese comparison population towards the low risks among white Americans. Conversely colon cancer death risk increased among the migrants. These finding point to the importance of environmental and life-style habits for these diseases, whereas the much less dramatic changes in breast cancer among women of Japanese descent lead to the conclusion that genetic factors or those active in early life may be of relatively greater importance for breast cancer. These studies were later extended to look at details such as timing of and age at migration in much more detail. Transitions in cancer patterns among migrants continue to attract the interest of cancer epidemiologists, and the challenge is to assess individual exposures, behaviours and socio-economic environments to better understand these findings and use them in cancer prevention.

Cancer registration



… an important tool for epidemiologic cancer research

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Among cancer epidemiologists there is consensus that functioning cancer registries form an important basis for research work in this field. Cancer registries aim at timely, accurate and complete registration of new cancer cases. Registries allow not only to assess the numbers and trends concerning cancer occurrence but also serve for linkage with other data bases and for identifying cases for specific epidemiologic designs such as case-control studies.

Around the world many local, regional and national cancer registries operate, and the ongoing international collaboration between many registries aims at ensuring comparability, good data quality and consistency between registries and over time. However, good registries require appropriate and continuous funding which is an obstacle to establishing or maintaining comprehensive registries even in many rich countries.

Cancer registries in Germany:

Population coverage is improving

Recent addition: North Rhine Westfalia

Opportunities for research

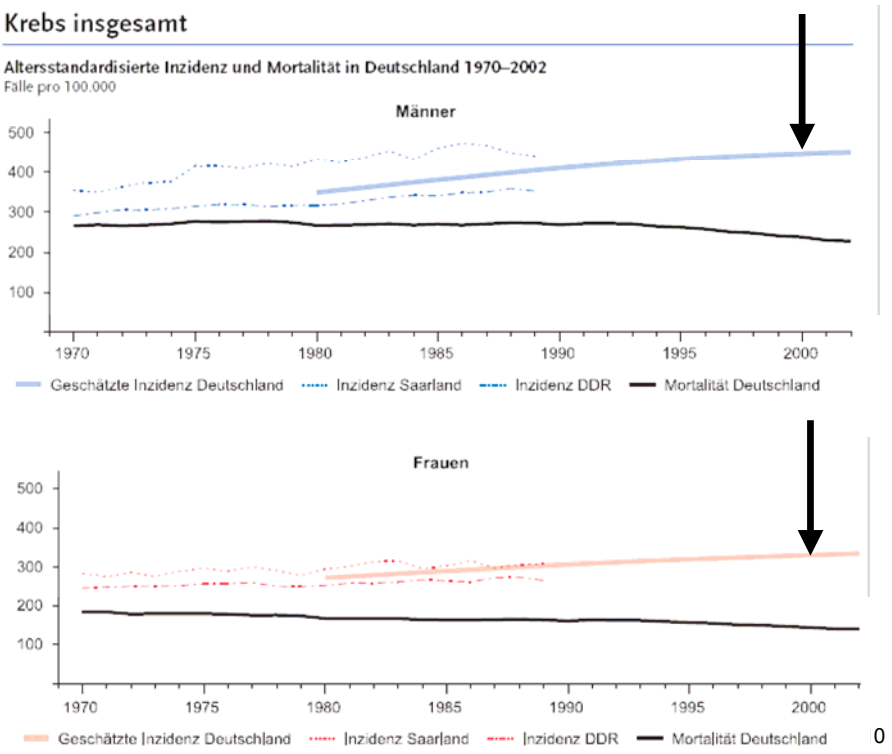
Examples:

- **Cohort studies on second primary cancers**
- **Case-control study on leukemia risk factors**
- **Cancer trends over time**

+ German Childhood Cancer Registry

Germany has seen a surge in the establishment of comprehensive cancer registries in recent years. Most recently a cancer registry covering the more than 22 Mill. inhabitants of Germany´s most populous federal state, North Rhine – Westphalia was approved. Currently only a few white spots on the "cancer registry map" of Germany remain, although some of the registries will only provide high quality data in a few years time.

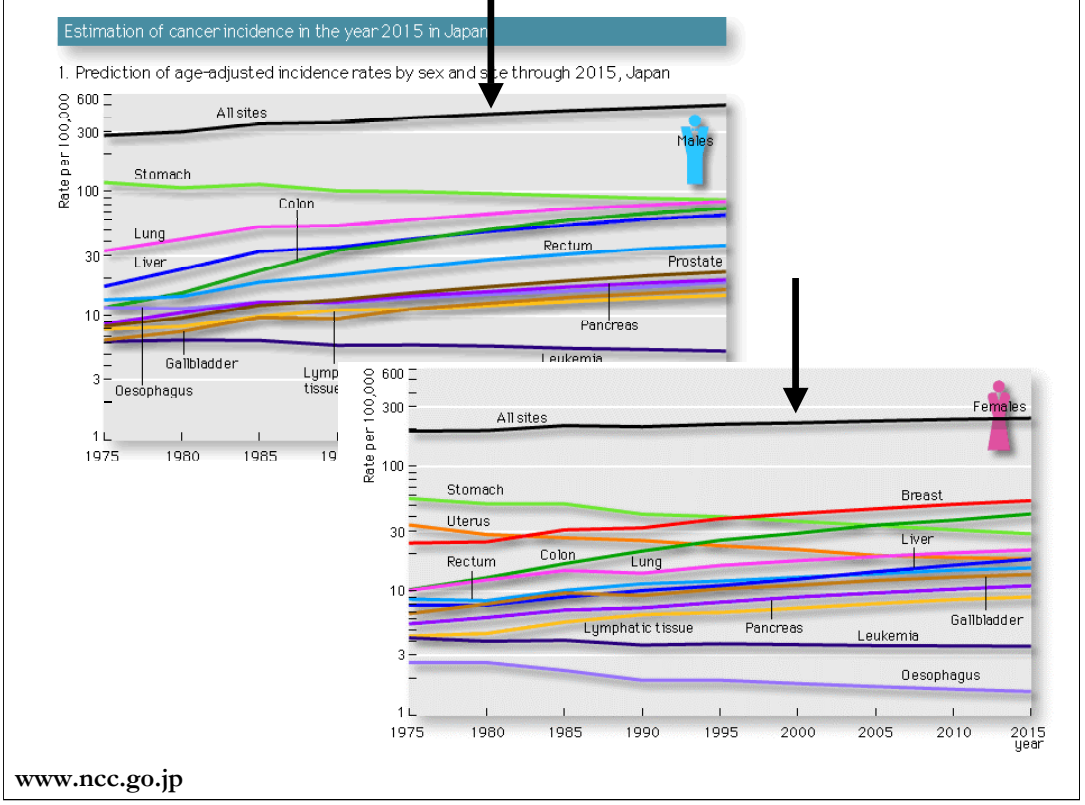
The German Childhood Cancer Registry is the largest registry of its kind worldwide and has been a highly valuable research resource for many years. All incident cancer cases among children under age 15 in Germany are included in the registry; the completeness is about 95% for all cancers except for central nervous system tumours.



www.rki.de

Cancer trends:

German cancer registry data demonstrate that cancer incidence has been increasing slightly over the past years among men and women when changes in age structure are taken into account. However, the rise appears to level off recently, while mortality has been decreasing in both genders since about 1990. These trends can be interpreted in several ways, but may indicate that therapeutic advances and perhaps earlier detection of some cancers help to decrease cancer mortality to some extent.



Comparing German with Japanese data there are little differences in the age-adjusted overall cancer incidence rates among German and Japanese men (taking 2000 as reference year, see arrow). Japanese women, however, have lower overall cancer rates (Germany: 300/100,000 – Japan: ~ 200/100,000) to which lower breast cancer rates among Japanese women probably contribute significantly.

All in all, the parallels between Germany and Japan in terms of cancer frequency and trends are rather obvious, which suggests that close collaboration in cancer control could be an aim of common interest.

Cancer epidemiology today

Some major issues of analytic research:

- **Diet and cancer**
- **Lifestyle issues (physical activity etc.)**
- **Infections and cancer**
- **Genetic epidemiology**
  - **Interplay of genes and environment**
- **Environment and cancer**

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Modern cancer epidemiology puts a focus on investigating cancer causes through population studies, using more and more advanced methods and attempting to integrate the increasingly obvious complexities of cancer causation into study design and analyses.

The issues in modern cancer epidemiology are manifold. The association of diet and cancer and of lifestyle issues such as physical activity have been at the core of many epidemiological studies. The discovery of cancer-causing infectious agents has generated widespread interest in recent years, as has the genetic basis of cancer, with one important research branch focussing on the interplay between genes and environmental factors.

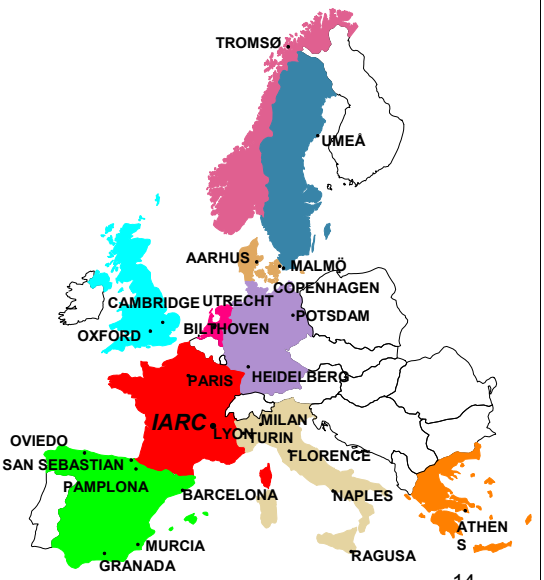
Environmental including occupational cancer causes continue to attract attention since they are generally modifiable and therefore entry points for cancer prevention.

Diet and cancer

Diet and cancer is the theme of a large European epidemiologic research collaboration that I will shortly describe here in order to point out study approaches and some particularities that are important to understand when discussing large-scale epidemiologic studies.

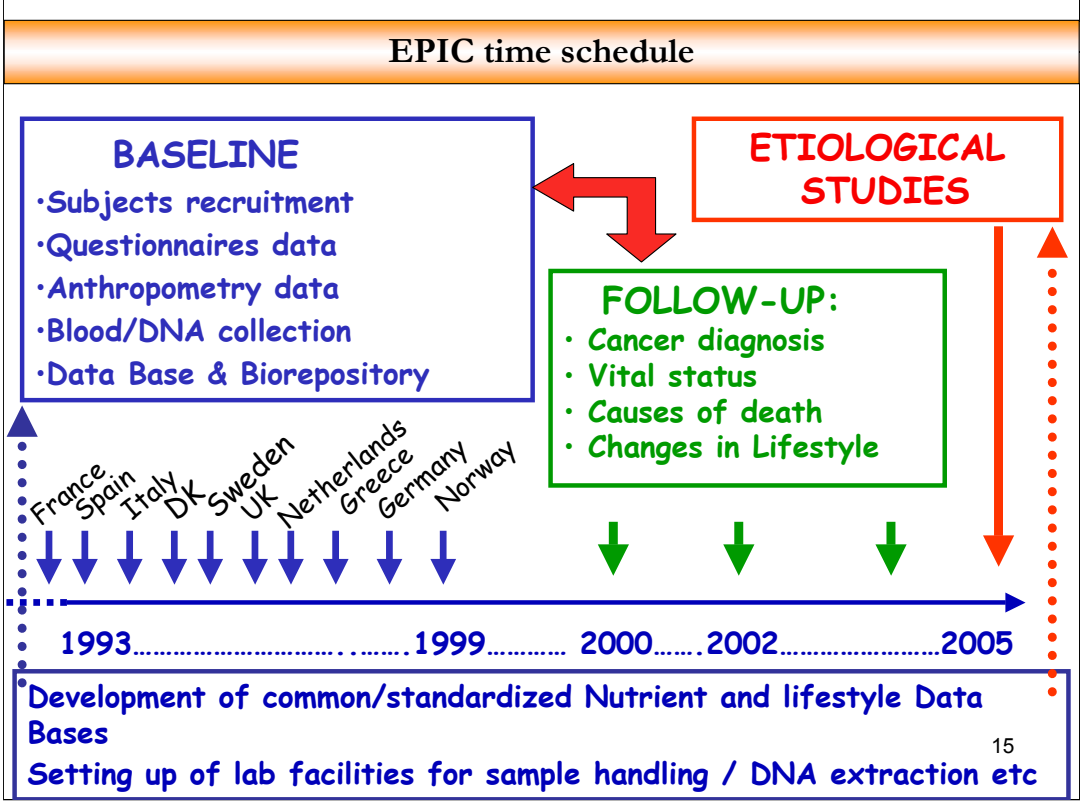
EPIC European Prospective Investigation into Cancer

	Participating Subjects	
	Questionnaire	Q + Blood
France	74 524	28 053
Italy	47 749	47 725
Spain	41 440	39 579
U.K.	87 942	43 141
Netherlands	40 072	36 318
Greece	28 555	28 483
Germany	53 091	50 678
Sweden	53 826	53 781
Denmark	57 054	56 131
Norway	37 215	31 000
Total	521 468	414 889



The EPIC study is a prospective cohort study involving several hundred thousand adult subjects from 10 European countries. The large majority of them has provided personal data on a wide range of health and nutrition issues through questionnaires, as well as providing a blood sample for analyses.

EPIC has been coordinated by the International Agency for Research on Cancer (IARC), the WHO Cancer Research Agency in Lyon, France.



Prospective studies such as EPIC often are long-term activities. Countries joined the collaboration at different years, and standardized data collection instruments and data bases were developed in the first years of the study.

After the initial recruitment of persons into the study regular follow-ups were organized in order to obtain updated information about the health and nutritional status of study participants. In particular, all new cancers are registered in order to allow etiologic analyses investigating the association between dietary and lifestyle variables and cancer.

The large size of the EPIC cohort allows to look not only at common diseases and risk factors but also at rare diseases and associated risks. In addition, there is a good degree of variability of exposure in the cohort through the inclusion of populations from different countries, another advantage of this study.

Challenges obviously lie in the sheer size of the cohort and the need to obtain relatively homogeneous data (quality) from the different contributors. The storage of biological samples from hundreds of thousands of people is a major technical challenge as well.

EPIC first results

Large and very variable cohort
Methodological advances (e.g. nutrition assessment)

Intake of fibres and colon cancer:

- **40% reduced risk if intake is doubled (legumes, fruits)**
- **Particularly effective in persons with high meat consumption**

Meat and colon cancer:

- **Processed & red meat increases risk**
- **Fish reduces risk, poultry +-**

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Bingham et al 2003, Norat et al 2005

In the last few years, first results from the EPIC cohort have started to be published in the international scientific literature. For example, EPIC contributed to the longstanding issue of the effect of fibres on colon cancer risk, reconfirming a protective effect through high fibre consumption.

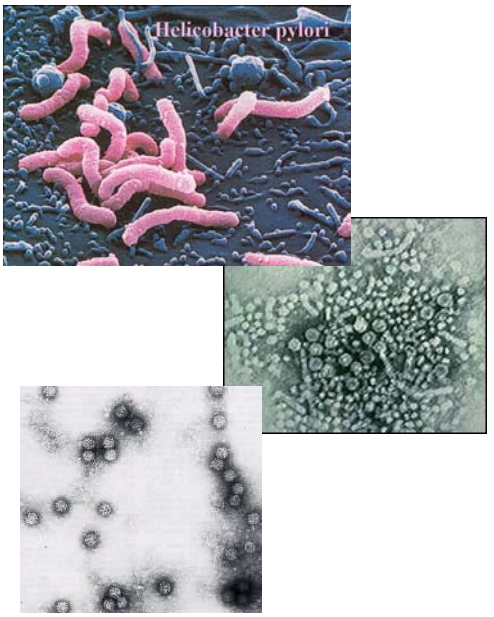
Recent analyses also found that processed and red meat increase colon cancer risk whereas fish consumption was associated with reduced colon cancer incidence.

Many of these issues are not entirely new but have previously been discussed on the basis of inconsistent results. EPIC hopes to provide more definite answers on these questions.

Infections and cancer

Infections and cancer are the topic of a further presentation; this paper only touches briefly on the issue.

- **Helicobacter pylori**
  - Gastric cancer
  - 490,000 cases/year
  - 5.4% of all cancers globally
- **Hepatitis B/C**
  - Liver cancer
  - 390.000 cases/year
  - 4.3%
- **Human papilloma**
  - Cervical cancer (+)
  - 550,000 cases/year
  - 6.1%



Uneven distribution of burden between developing and developed countries

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World Cancer Report 2003

The number of viruses, bacteria and parasites that are recognized cancer causing agents is growing. The World Cancer Report 2003 estimated that around 1.5 Mill cases annually are caused by helicobacter pylori, hepatitis viruses and human papilloma viruses alone. The report notes that the cancer burden associated with these agents rests heavily on the developing countries where primary prevention, e.g. through immunization, early recognition e.g. through screening for early cervical cancer, or treatment e.g. for helicobacter through antibiotic drugs may not or less easily be available.

Cervical Cancer in Germany

- **Incidence still high in Germany compared to other European countries (13.8/100,000)**
- **6,500 Women are diagnosed each year, often young**
- **Cervical cancer screening in place, but not as organized programme**
- **Participation unsatisfactory**
- **HPV prevalence in general population not known (most studies among patients)**

- **Ongoing study (MARZY) among 5000 women in Germany**
  - **Testing an organized invitational system**
  - **Assess usefulness of different types of cytology (PAP versus liquid based)**
  - **Assess HPV- status including genotyping**

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There are some epidemiological projects in Germany focussing on infectious causes of cancer.

Cervical cancer, though clearly on the decline over many years, still affects more than 6,500 women in Germany annually. Cervical cancer screening is part of the early recognition package offered to all Germans insured through the health insurance system. However, the screening is rather individualized and the activities do not fulfil criteria of an organized screening programme. This may partly explain why the participation is considered unsatisfactory, and new approaches are being tested.

As an example, the ongoing MARZY study includes about 5000 women from the Rhine-Main area and aims at testing an organized invitational system as well as assessing the usefulness of new approaches to cytology and the HPV status of participants. This study is expected to yield interesting data that will inform the future preventive efforts in cervical cancer in Germany.

Immunization against cervical cancer

- **Randomized trials of vaccines ongoing**
- **HPV16 L1 VLP – 48 months results**
  - **Vaccine group: 0 of 755 developed CIN**
  - **Placebo group: 11 of 750**

Persistent HPV infection

- **Vaccine group: 7 of 755**
- **Placebo group: 111 of 750**

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Mao et al 2006

Immunization against the viruses causing cervical cancer would open an entirely new way of cancer prevention. There are promising results from several trials, one of the most recent (Mao et al, 2006) demonstrating an excellent efficacy of the tested vaccine against cervical intraepithelial neoplasia (CIN 2-3), a lesion where precancerous cells are found in the tissue of the cervix which may turn into cancer.

The recent results also indicate that HPV persistence can also be markedly reduced through the vaccination. The US Food and Drug Administration has recently licensed the use of a cervical cancer vaccine for the first time.

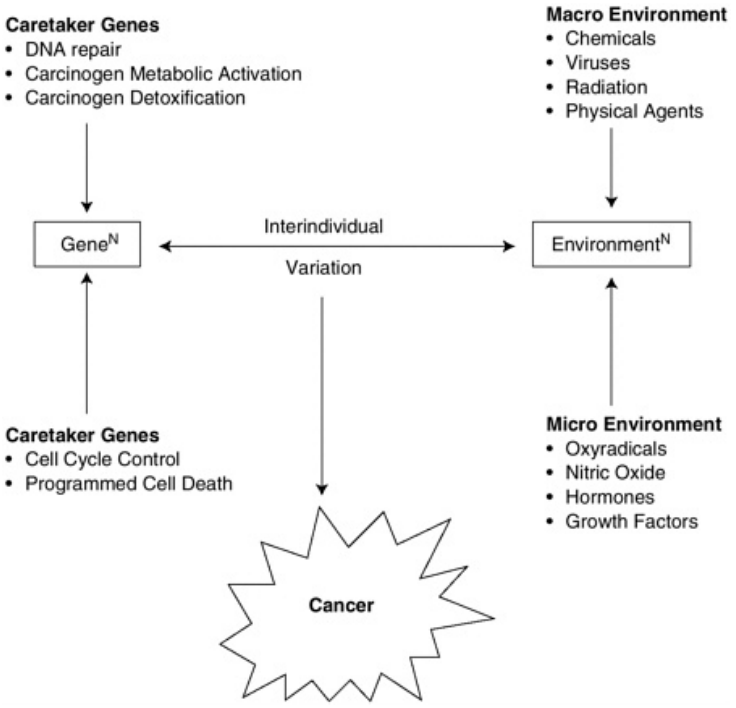
Genetic epidemiology

Another area of major current research activity is genetic epidemiology on which I will also touch briefly. The issue of gene-environment interactions is particularly interesting, looking at links between the genetic basis and environmental risks of disease.

Gene – environment interactions

- **Genes affect the way some mutagens/cancerogens are metabolized, activated or inactivated**

Genes control the way(s) our body deals with agents that increase the rate of mutations or are indeed cancerogenic. For example, they influence the metabolization, activation or inactivation of these agents once they have entered the body.



Caretaker genes also regulate DNA repair and other important cellular mechanisms such as the programmed cell death.

There is much inter-individual and population variation in the extent that environmental exposures with carcinogenic potential – such as chemicals and viruses – actually affect the individual. In conjunction with the specific genetic make-up of the individual these exposures may lead to the eventual development of clinical cancer.

Gene – environment interactions

- **Genes affect the way some mutagens/cancerogens are metabolized, activated or inactivated**
- **The aim: identify candidate genes (or polymorphisms of these) that alter cancer risk substantially**

- **Example:**
  - **workers exposed to aromatic amines**
  - **Markedly higher bladder cancer risk among those of a particular phenotype (NAT 2 slow acetylator)**

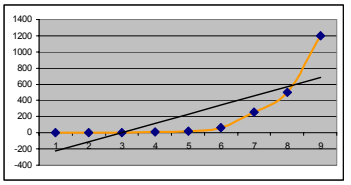
Epidemiologic studies try to identify patterns in this interaction. They aim at the identification of candidate genes or their polymorphisms that alter the risk from given environmental exposures. As an example, among industry workers exposed to aromatic amines, those with a particular genetically determined phenotype have been shown to have markedly higher bladder cancer risks than those with alternative phenotypes. Apart from revealing molecular mechanisms of cancer induction and learning about basic biological principles, such results can be of potential use in identifying individuals who are particularly sensitive to occupational hazards. However, the application of such knowledge brings along serious ethical and societal questions which epidemiologists must be aware of.

Gene – environment interactions

- **However: most candidate genes identified so far confer only small risks**

Major statistical issue(s):

- **high number of gene-environment or gene-gene interactions examined: chance findings increase**



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More and more candidate genes are being identified, most, however, confer only small risks in no way comparable to the major risk increases associated with classical environmental or life-style exposures such as tobacco smoke.

There are also several statistical issues that are emerging in this field, among them the fact that simply through investigating more and more potential interactions the number of chance findings increases. The task is here – as in all serious science - to use the highest scientific standards and to critically assess the validity and implications of these investigations.

Target: breast cancer

- **Familial aggregation well known**
- **BRCA-1 and -2 as "classical breast cancer genes" responsible for a small percentage of cases (2-5%)**
- **Other genes of low penetrance (and probably many of those) contribute importantly to breast cancer risk**

Large study of familial breast cancer in Germany (DKFZ):

- **Some known protective factors (high parity, late menarche) are modulated by genetic susceptibility to breast cancer**

Becher et al IJE 2003

In Germany genetic epidemiology studies conducted at the German Cancer Research Centre DKFZ have centred on breast cancer. It is clear that the by now "classical" breast cancer genes BRCA-1 and -2 are directly responsible only for a small percentage of all cases. The role of other genes of low penetrance therefore is of interest. Becher and colleagues have recently shown that genetic susceptibility modulates some of the known protective factors for breast cancer such as high parity and late menarche. Further investigations are ongoing.

The unfinished agenda
- some examples -

While much current epidemiological cancer research focuses on these and other new developments and research issues, there is a large unfinished agenda in cancer epidemiology where research results await better translation into public health practice or where some issues remain contested in spite of large research efforts.

Smoking

- Still the major cancer risk in many countries
- Smoking popular among (young) women
- Smoking epidemics in China, India, with consequences to come
- Passive smoking

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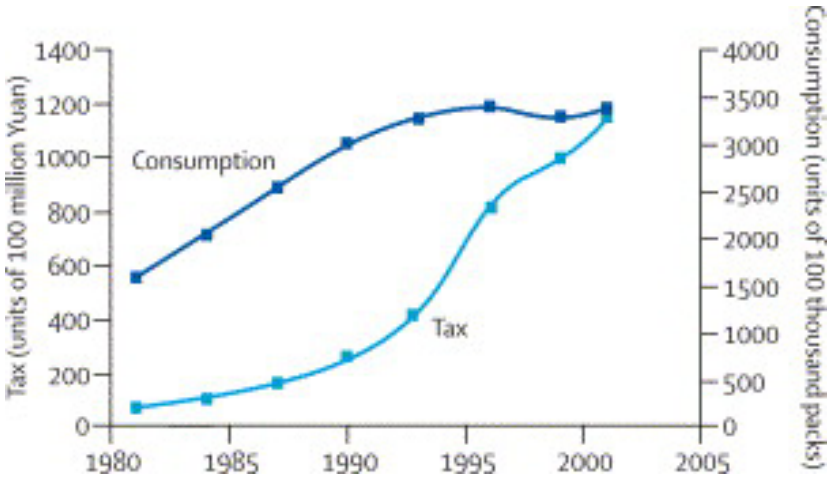
Smoking is such a case. Epidemiology – as previously pointed out – has contributed importantly to the hazard identification and forms the basis for public health action in tobacco control. Also, the risks of passive smoking have been characterized more precisely. Still, tobacco consumption has been rising in many countries, often particularly so among women.

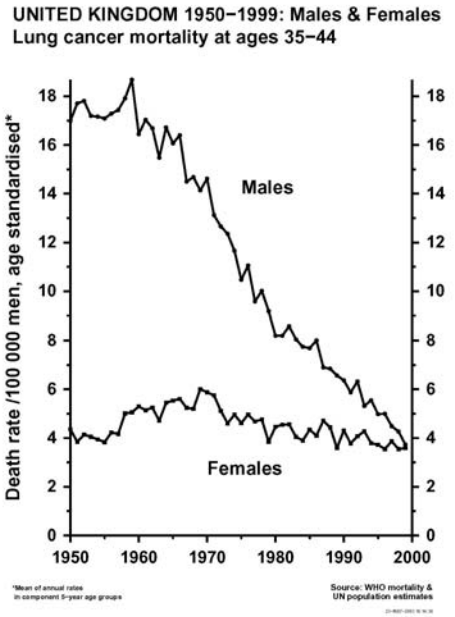
Epidemics of smoking-attributable disease and death are foreseen for countries like India and China. Global estimates predict around 10 Mill tobacco-related deaths annually for the next decades.

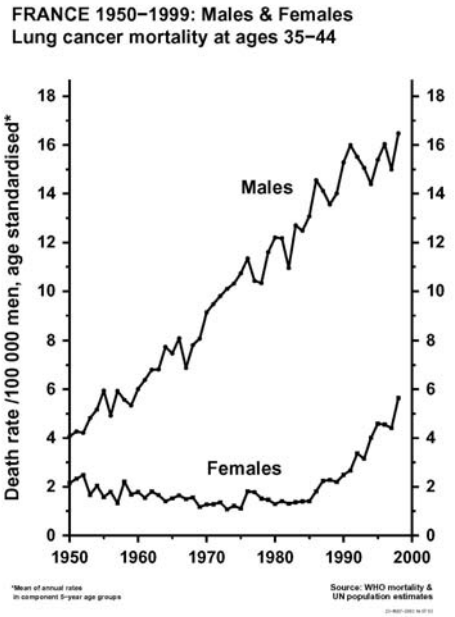
China – tobacco consumption



China has witnessed a marked increase in tobacco consumption in the last decades. Tax increases imposed by the government can be correlated with a levelling-off of overall consumption levels. However, public health activities have to be intensified further in order to control the tobacco epidemic.

With the long latency of chronic diseases such as lung cancer, the consequences of the consumption patterns of the past decades are only beginning to appear now.





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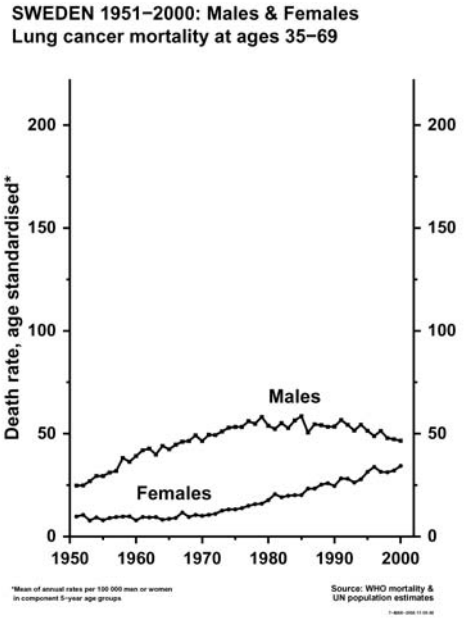
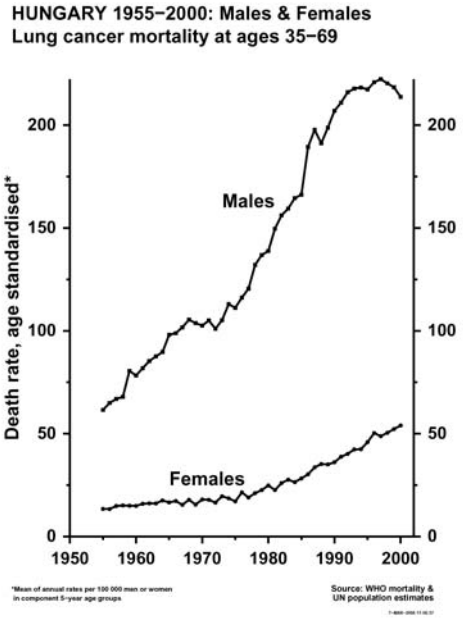
In developed countries, surprising variations are seem in today's lung cancer mortality rate. Lung cancer can be attributed to smoking to a large extent. In the United Kingdom, for example, lung cancer among males aged 35-44 has decreased rapidly since the 1960s, whereas exactly the opposite trend is obvious in France. France has now reached male lung cancer rates seen in the UK 40 years ago. The sharp increase of lung cancer deaths among women is equally worrying and reflects the increase in smoking among women several years prior to this period.





Even more striking differences can be seen when comparing European countries such as Sweden and Hungary. Sweden has enjoyed one of the lowest smoking prevalences in Europe for many years, and accordingly lung cancer death rates have been low (displayed are age groups 35-69). Women have taken up smoking also in Sweden such that their lung cancer mortality is now approaching that of Swedish males. Hungarian women have only slightly higher rates than Swedish women. However, Hungarian men have one of the highest lung cancer mortality rates in the world, with very marked increases during the second half of the last century. Only recently a deceleration of the mortality increase has become obvious.

Ionizing Radiation

- **Hiroshima & Nagasaki LSS**
- **Chernobyl - 26.4.1986**

- **Studies on populations exposed to low doses**
  - **Nuclear power workers**
  - **Flight crew**
  - **Miners**
  - **Populations living around nuclear installations**
  - **General population (radon)**

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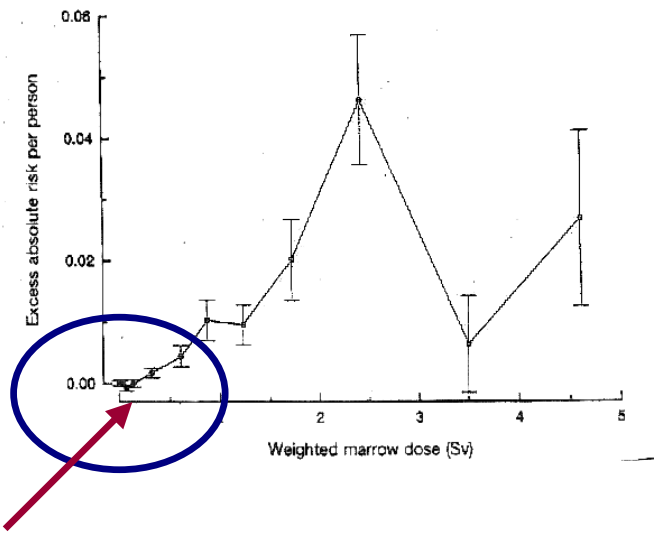
Another issue of longstanding epidemiologic research and continued public interest is radiation. The recent 20th anniversary of the Chernobyl catastrophe has reminded many people of the health and environmental consequences that radiation may have particularly in accidents or even warfare. In fact, much of what we know about ionizing radiation health effects is based on the studies among survivors of the Hiroshima and Nagasaki bombings in 1945.

For the public and the workforce, low dose exposures are generally most relevant. The main concern is an increased risk of cancer and of hereditary effects in exposed persons. Many populations have been studied, among them nuclear power workers, flight crew (cosmic radiation), mine workers, populations living near nuclear installations, and also the general public. The latter is exposed to indoor radon, a radioactive gas from the ground, and in some parts of the world to other sources of high background radiation. Also, the question of adverse effects of medical radiation exposures – such as trough normal x-ray or CT investigations – is being studied.

Life Span Study – leukaemia dose response



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Just to exemplify the problem of assessing health effects of low radiation doses, some data on leukaemia among participants of the Life Span Study (LSS) are presented. In this cohort, people were exposed to a wide range of doses, from low to very high. As mentioned, for radiation protection purposes today the major interest lies in the dose area indicated by the red arrow, between 1 and perhaps 100 milliSievert. Unfortunately, the risk estimations from this and other cohorts for this low dose area are pretty uncertain. A linear extrapolation from high to low dose ranges has therefore been applied and investigated extensively, but critical voices question this approach, claiming that perhaps there is a dose threshold somewhere below 100 mSv below which no measurable health effects occur.

Apart from using evidence from radiobiological studies, epidemiologists have tried to find answers to this controversy by directly studying populations who are only exposed to comparatively low radiation doses.

Recent examples of studies in Germany

- **Two large case-control studies on radon and lung cancer**
- **Cohort study among 60.000 former uranium miners (Wismut)**
- **Northern German lymphoma and leukemia study (region around nuclear power plant)**
- **(European) Cohort study among aircrew**

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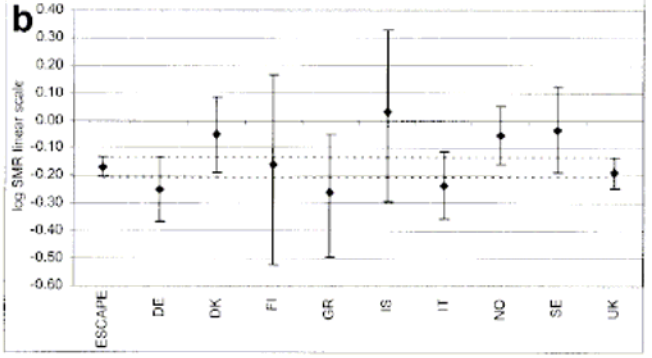
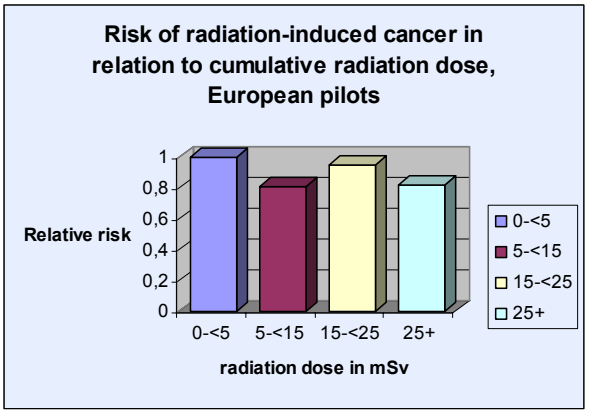
In Germany, such studies have recently focussed on the issue of lung cancer from radon in homes and among miners in the former East German uranium mines that provided uranium for the atomic weapons programme of the (then) USSR. In fact, some of these workers incurred rather high doses from radon gas in the mines.

An extensive series of studies was also conducted to investigate a cluster of leukaemia around a nuclear power plant in Northern Germany, similar to investigations around Sellafield in the UK and other nuclear installations worldwide. No clear link of leukaemia occurrence to environmental radiation could be found in these investigations.

Own studies have focussed on aircrew who – through their occupation – are exposed to radiation from the cosmos, in markedly higher doses than found on the Earth.

All cancer, cockpit crew in Europe





Low dose studies: tremenduous benefit if appropriate markers of risk were at hand

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In this large pooled cohort study involving crews from nine European countries, we could not show links between the estimated radiation dose and cancer mortality; some methodological limitations and the young average age of cohort members cause problems in the interpretation, however.

Risks of melanoma skin cancer and breast cancer in female cabin crew are increased in this cohort, but the links to ionizing radiation are not clear. In general, studies of low dose would benefit very much from improved biological markers of risk, especially those that would highlight past exposures to low doses. The search for such markers and other, improved means of assessing ionizing radiation doses and their relevance for health outcomes, is ongoing.

Screening for early cancer

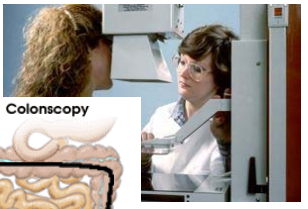
As a final topic, screening for early cancer will be discussed, in particular the way epidemiologic studies can help to guide decisions of societies whether to implement such programmes or not.

Screening

- Try to find early stages of cancer
- ... with the hope of a better cure chance when found early

Targets:

- Cervical cancer
- Breast cancer
- Colon cancer
- Skin cancer
- Prostate cancer
- Childhood cancer



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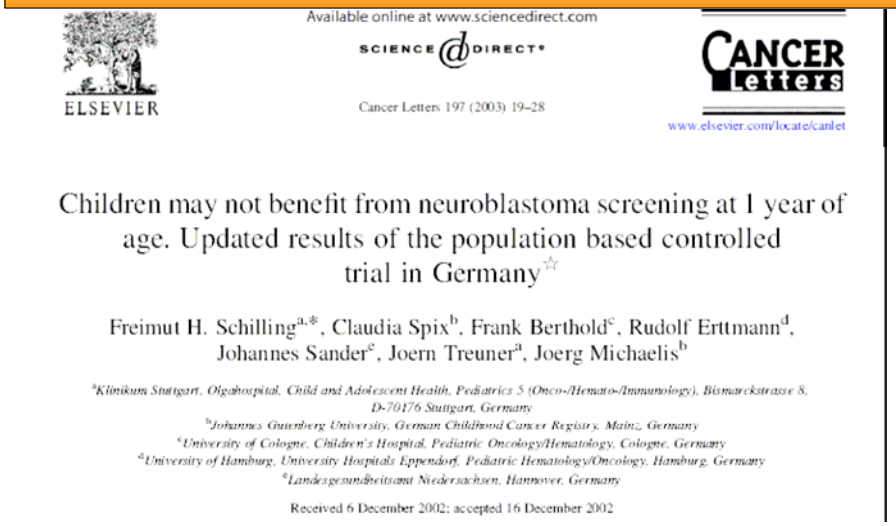
Through screening, we try to find early stages of cancer that offer better chances for cure when found early. This is important because simply finding early stages without any resulting gains would not be useful.

There are several target cancers where screening programmes have been implemented or are being evaluated. Most experiences exist with cervical and breast cancer screening, but colon cancer screening is also being implemented in several countries while screening for other cancers is being evaluated.

Cancer in childhood causes great suffering for the children and their families, and the effectiveness of screening for the main childhood cancers has been investigated.

Screening for Neuroblastoma



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Children may not benefit from neuroblastoma screening at 1 year of age. Updated results of the population based controlled trial in Germany☆

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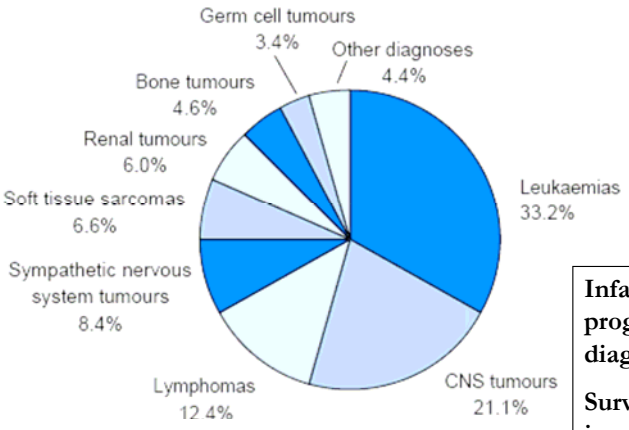
As an example for the importance of such investigations before starting to implement full programmes, I will present a large trial conducted in Germany using the German childhood cancer registry. The topic is screening for neuroblastoma, a frequent childhood tumour, and the title of one of the central papers on this trial reveals the main – and perhaps disappointing – outcome of the study. What lies behind this headline?

Neuroblastoma - Backgrounder



Infants have best prognosis, esp. when diagnosed early

Survival – little improvement in recent years

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Neuroblastomas are amongst the most common types of childhood tumours. They are solid cancers of the sympathetic nervous system and can be cured well when localized. Some neuroblastomas regress spontaneously from malignant into benign, which is very rare with other cancers.

Infants have the best prognosis, especially when diagnosed early. Overall, survival has not been changing much over the past years.

Even early neuroblastomas produce catecholamines which can be measured in the urine. This has been used to study whether screening reduces metastatic disease or mortality from neuroblastoma.

The study

- **Children * 1993-2000 (age 9-18 months) in 6 German states were offered screening (+ 2 Mill.)**
- **Children from the other 10 states served as controls (+ 2 Mill.)**
- **Simple urine test for catecholamines (from nappies)**
- **Linkage to Childhood Cancer registry**

In a large German-wide study, more than 2 Mill. children aged 9-18 months from 6 federal states were offered a simple urine test, and a similar number of children from the remaining ten states served as controls. Through a linkage to the German childhood registry, new cases of neuroblastoma were identified and parameters such as incidence of metastatic neuroblastoma and mortality from that disease were compared between screened and non-screened groups.

Main results

- **Total incidence of advanced neuroblastoma similar in screening and control area [3.9 (5.6) vs. 4.6 per 10^5]**
- **Total mortality similarily unchanged [1.6 (2.0) vs. 1.8 per 10^5]**
- **Significant overdiagnosis – many cases detected by screening that were likely to have regressed spontaneously**
- **Overall: screening at age 1 year not advisable**

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The results of this large trial showed no significant differences between screened and unscreened group for incidence and mortality. In fact, among screened cases there was an indication of overdiagnosis, likely due to the fact that a number of cases detected by active screening might have regressed spontaneously later and would therefore never be detected clinically.

The overall interpretation of this trial was therefore clear: screening at age 1 seemed not advisable as benefits could not be proven.

As demonstrated here, thorough scientific investigations of proposed screening programmes can be very useful to inform health policy, in this case giving guidance to not invest in such a – presumably rather expensive – population-wide programme. Evidence-based approaches should be the basis for such important decisions, in particular in times of spiralling health service costs.

Challenges and developments

This paper concludes with a few thoughts about challenges for cancer epidemiology in the future.

Cancer risk factors (USA) [Peto, Nature 2001]

	Deaths avoidable after removing preceding causes	
Risk factor	Smokers	Non-smokers
Smoking	**60**	**-**
Known Infection	**2**	**5**
Alcohol	**0.4**	**1**
UV-Light	**0.4**	**1**
Air pollution	**0.4**	**1**
Occupation	**0.4**	**1**
Lack of exercise	**0.4**	**1**
Diet		
Obesity	**4**	**10**
Other dietary factors	**4-12 ?**	**10-30**
Presently unavoidable	**~ 25%**	**+ 50%**

First of all it is obvious that the main known cancer causes still need to be successfully tackled on a population scale. Taking US data, for example, cancer prevention based on epidemiological evidence could help to prevent up to 75% of cancers among smokers, and around 50% in non-smokers.

However, so far there are very few convincing signs that these aims are truly going to be achieved: the resources for prevention are simply too limited and the motivation of individuals and the society at large to take part in the fight against cancer could be much stronger.

Challenges

- **Many causes of individual cancers remain unknown**
- **Intriguing observations**
  - **Increased cancer risk among patients with depressed immunity**
  - **Role of immune system ?**
- **Observations from genetic and molecular studies will lead to better understanding of cancer development, and to identification of high risk groups**

Even though we know many main cancer risk factors, it is equally true that for many individual cancers the causes remain unclear or only partially known.

Novel approaches are constantly needed, and an intriguing observation relates to the role of the immune system: patients with depressed immunity have a markedly increased cancer risk, as also seen in the context of the AIDS epidemic. Increasing knowledge about how the immune system controls abnormal cell growth and conversion of cells from normal to malignant will be important both for prevention and therapy of cancer. Epidemiology, perhaps particularly that line of work concerned with genetic and molecular developments, may well lead to improved understanding of these processes and subsequent applications in cancer prevention.

Challenges II

- **For small risks**
  - **increasing use of pooling studies across populations and exposures**
  - **More differentiated assessment of exposures and susceptibility**
- **For large risks – improving the applicability of cancer epidemiology results so that population benefits can be achieved**
  - **Risk communication**
  - **Contribution to cancer control**

Many currently studied factors only confer rather small risks to those exposed. Nevertheless, when large proportions of populations are exposed, even small risks can lead to considerable disease burden. To better study such small risks, epidemiology increasingly turns to large pooled studies, involving different populations and exposure situations. This work poses many challenges e.g. in ensuring data comparability from different substudies.

Much work in epidemiology also focuses on better and more differentiated assessment of exposures (and outcomes) and on establishing susceptibility to particular risks.

Concerning those cancer risk factors that carry well - known and large risks for the population (e.g. smoking), epidemiologists will have to work towards ensuring that the results are applicable and are indeed used for effective cancer control.

Thank you !

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