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**Economic progress as cancer risk factor**  
**I. Puzzling facts of cancer epidemiology**

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# Economic Progress as Cancer Risk Factor

## I. Puzzling Facts of Cancer Epidemiology

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### Abstract

The increase in cancer burden in developed countries refers to three major causes: population aging, an increase in the cancer incidence rate, and an improvement in the survival of cancer patients. Among these reasons, only the increase in the cancer incidence rate is a negative factor that could be really managed to decrease cancer burden; it, thus, urgently needs explanation and action to develop adequate cancer prophylactics. We have conducted a comparative analysis of cancer incidence and mortality rates in different countries of the world for different time periods. The typical age-trajectory of overall cancer incidence rate (for both sexes and all cancers combined) is characterized by a peak in early childhood, low risk in youth, increasing risk afterwards, and a leveling-out or even a decline in cancer risk for the oldest old. Patterns of age-specific cancer mortality resemble the incidence rate patterns; however, mortality is commonly lower and its curve shifts towards higher age. This shift could be due to a time lag between the age of cancer diagnosis and death from the disease. Analysis of time and place differences in the cancer incidence rate revealed that the overall cancer risk is higher in more developed regions as compared with less developed ones, and that until recently it increased over time along with economic progress. The proportions of separate cancer sites within the overall cancer morbidity differ between more and less developed regions, and their change over time is also linked to economic development. Surprisingly, cancer incidence and mortality rates exhibit different time trends. This divergence is most probably related to the substantial improvement in the survival of cancer patients observed in the last 50 years in developed countries. This improved survival has decreased cancer mortality but not its incidence, which has increased. This suggests that in developed countries cancer treatment has seen much more substantial progress than cancer prophylaxis, which has hardly seen positive results for the majority of human cancers (with a few exceptions). In our second paper we discuss possible explanations of the link between economic progress and the increase in the overall cancer risk.

*Key words: cancer incidence rate, age-patterns, time trends, place differences, economic progress*

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## 1 Introduction

The term "cancer" refers to a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. The initiation and promotion of cancer are influenced both by external factors (e.g., tobacco, radiation, some chemical and infectious agents) and internal ones (e.g., inherited mutations, the immune status, and aging). Despite substantial investments in cancer research (e.g, the 2004 budget of the USA National Cancer Institute (NCI) provides about six billion US dollars), and significant progress in the understanding of cancer biology, the exact causes of cancer remain a mystery in many cases, and the global cancer burden is increasing (Parkin et al., 2001). Worldwide, more than 10,000,000 people are diagnosed with cancer and more than 6,000,000 die of the disease every year. These figures emphasize the importance of understanding the factors responsible for time trends and place differences in cancer incidence, mortality, and survival rates worldwide.

*The cancer incidence rate.* The overall cancer risk dramatically increased in most countries of the world during the second half of the 20<sup>th</sup> century (IARC 1965-2003). In the United States, however, the overall cancer incidence rates dropped an average of 0.5 percent per year from 1991 to 2001 (Jemal et al. 2004a) owing to modest progress in cancer prevention as well as other developments, such as changes in the population structure over time. Still, about

1,368,030 new cancer cases are expected for the USA in 2004 (Jemal et al. 2004b); this figure excludes more than one million skin cancers. The majority of all cancers (about 80 percent) are diagnosed in people aged 55 and above (IARC 1965-2003). The populations of developed countries “age” over time (i.e., the proportion of elderly increases). Age-specific cancer rates, however, do not depend on population aging, and the reasons for higher cancer risks in elderly individuals from the more developed regions (compared to the less developed ones) remain largely unexplained.

***Cancer mortality.*** The death toll associated with cancer is high; cancer is the second most frequent cause of death in the United States. The American Cancer Society (ACS) predicts 563,700 deaths for 2004 (Jemal et al. 2004b). The National Institutes of Health (NIH) estimate indirect mortality costs alone at \$95.2 billion (the costs of lost productivity due to premature death). Three major factors contribute to cancer mortality: population aging, the cancer incidence rate, and the survival rates of cancer patients. The latter has been steadily improving, and is probably a major reason for the recent decline in cancer mortality. In the USA, death rates decreased (by 1.1 percent per year) for all cancers combined from 1993 to 2001 (Jemal et al. 2004a)

***Survival of cancer patients.*** In the past 50 years, we have seen a remarkable increase in the survival of cancer patients. For instance, five-year survival in the USA improved from an average of 35 percent over the period 1950-54 to 63 percent over the period 1989-97 (Ries et al. 2001). This increase has been due mainly to the rapid spread of new anti-cancer treatments, such as advanced chemotherapy. It is highly effective against several prevalent cancer sites (e.g., melanoma of the skin, prostate, breast, bladder, corpus uteri, and children’s leukemia). The five-year survival for these sites has been increasing during the last 50 years, reaching 80-97 percent (Ries et al. 2001). This positive achievement has negatively affected the global cancer burden, however: The number of individuals with cancer has drastically risen in the developed countries. At the same time, modern chemotherapy has failed to substantially improve survival from some other cancers (e.g., the pancreas, liver, lung, esophagus, stomach, and myeloma). It varies from 4 to 28 percent, depending on the site and country (Berrino et al. 1995, Ries et al. 2001). Unfortunately, some of the latter cancers are prevalent (e.g., of the lung and stomach) or rapidly increasing in prevalence (e.g., of the myeloma and liver), which means that the coming years may not see a rapid fall in cancer mortality. Together with cancer incidence and population aging, survival from cancer is a key factor that defines the values for cancer mortality and for the cancer burden in modern human populations.

***The cancer burden.*** A major outcome of the increasing cancer incidence, improved survival of cancer patients, and population aging is the increasing global burden of cancer. It is manifest in the total number of individuals with cancer within a population (cancer prevalence), as well as associated costs. Currently, there are over 22,400,000 cancer patients worldwide. The cancer burden is generally higher in the more developed countries despite a higher quality of medical help there. The NCI estimated that almost nine million Americans with a history of cancer were alive in 1999. The NIH estimated the overall cost for cancer in the year 2002 at \$171.6 billion, including \$60.9 billion for direct medical costs (total of all health expenditures), and \$15.5 billion for indirect morbidity costs (lost productivity due to illness). The total number of cancer cases is expected to double by 2050 if current incidence rates remain stable, solely due to population aging (Edwards et al. 2002). In case of continued improvement in cancer patient survival (which is highly probable), the increase in the cancer burden will be even more pronounced.

***Pivotal role of understanding trends in cancer incidence rates.*** As stated above, the increase in the global cancer burden can be attributed to three major factors: (1) an improvement in the survival of cancer patients, (2) an increase in the overall cancer risk, and (3) population aging. What steps can modern society take to meet these challenges?

Population aging is causally linked to fertility decline during the reproductive period and improvements in old age survival. The latter is, in fact, a positive social and medical achievement and it is thus unlikely that society will simply aim at reducing the number of old people in order to reduce the cancer burden. The development of new effective anti-aging interventions that diminish some of the negative effects of aging is a more realistic approach.

Improvement in the survival of cancer patients is another positive medical achievement with a negative effect in that it elevates the cancer burden. It is very likely that this effect will increase over time, due to promising new anti-cancer interventions. Again, it is unlikely that human society will favor increasing cancer fatality in order to reduce the cancer burden.

Thus, there is only one factor that is genuinely negative – increased cancer risks – and it is this factor that urgently needs attention to reduce the cancer burden. It is very important to further our understanding of the causes underlying the increases in cancer incidence rates over time as well as the higher cancer risks in the more developed regions.

Despite substantial progress in uncovering the biological mechanisms of cancer, the major factors responsible for determining trends in the cancer incidence rate remain unknown. Does an increase in carcinogenic load elevate cancer risks along with economic progress? Or is

this elevated risk just an effect of better diagnostics in the more developed countries, not caused by new cancer cases but simply not recognized before? Another possibility is that people in the more developed countries have higher vulnerability to cancer due to e.g., a relaxation in environmental selection.

In this paper (I. Facts), we analyze age-patterns, time trends, and place differences in cancer incidence and mortality rates in different countries around the world, focusing on an intriguing association between the overall cancer risk and economic development. We show that this association is widely observed phenomenon across human populations. In next paper (II. Explanations), we discuss factors of economic progress that could be largely responsible for higher cancer rates in more developed countries and pay special attention to the factors that elevate cancer risk increasing individual vulnerability to cancer rather than increasing carcinogenic load in populations.

## **2 Data Source and Definitions**

**Source of data.** For this analysis, we used data extracted from cancer registers published by the International Agency for Research on Cancer (IARC), part of the World Health Organization, in the book series “Cancer Incidence in Five Continents” (IARC 1965-1997), “Trends in Cancer Incidence and Mortality” (Coleman et al. 1993), the GLOBOCAN data bases (1998, 2001), and the EUCAN data base (1999), which altogether cover over 200 populations worldwide for the years 1957-2000. In addition, other sources were used, including the WHO Health for all Database (2000), the US National Cancer Institute (NCI) publications of SEER (The Surveillance, Epidemiology, and End Results) Program statistics on cancer incidence and survival, data from the Russian National Research Centre for Oncology, and other relevant materials that cover cancer history during recent time periods in different countries.

**Basic definitions.** The *age-specific cancer incidence rate* is defined as the number of new cancer cases (registered for the first time) per 100,000 people in a population of a given age in a particular year or time interval. *Age-specific cancer mortality rate* stands for the number of cancer deaths per 100,000 people in a population of a given age in a particular year or time interval. *Five-year survival from cancer* denotes the proportion of cancer patients who survived five years after diagnosis. *Cancer prevalence* is the proportion of individuals with diagnosed cancer (no matter when the diagnosis was made) relative to the general population of a given age. The prevalence characterizes the cancer burden.

### 3 Common Features of Cancer Rate Patterns

#### 3.1 Age-Specific Cancer Incidence Rates

*Various age-patterns of the cancer incidence rate.* There is a prevalent belief that the shape of the incidence rate pattern is an invariant characteristic of a particular cancer site. For instance, based on data from the USA population in the previous century, Rainsford et al. (1985) and Volpe and Dix (1986) held that male lung cancer exhibits an exponential rate increase until very old ages, regardless of time and place. They believed that the exponential nature of the lung cancer age-pattern is independent of environmental carcinogenicity and best attributed to some aspect of the intrinsic aging process. This view implies that such a shape is an inherent trait of the lung cancer pattern. Based on this prevalent view, we initially believed that specific traits in cancer incidence rate patterns (e.g., a peak or a plateau) depend in the main on the cancer site. However, a comparison of incidence rate curves showed that their shape depends not only on the cancer site and sex, but also on the timing, place, and the current prevalence of a cancer.

Fig.1-3 are about here

Figures 1-3 show three typical age-patterns for the cancer incidence rate: (1) an accelerated increase in the rate until very old age (85 and above), (2) a wave-like shape with a peak at middle-old ages (about 70), and (3) a linear or decelerated increase in the rate with a tendency to level off at old ages. However, these patterns are quite “plastic” and do not depend exclusively on a cancer site. Figures 4 and 5 show the age-specific rates for stomach and ovarian cancers. We see that the patterns for these cancers differ among countries. Sometimes, the incidence rate manifests a peak at old ages, and sometimes it does not.

Fig.4 and 5 are about here

Figure 6 shows examples of time and place differences in the incidence rate patterns for lung and breast cancers, which represent today’s most prevalent cancer sites. In the past, male lung cancer was less common in the USA and Japan. Its age-pattern in 1960-62 had a wave-like shape, with a peak at about 70-75 years of age. In 1980-92, the peak shifted to older ages. Female lung cancer did not exhibit a peak in the 1960s at all, but later began to resemble the male pattern.

Fig.6 is about here

In the UK, there is currently no peak in the male lung cancer curve (Figure 1 above), although a peak was evident during the 1930s and 40s – at the age of approx. 65 (Doll 1971). Breast cancer is less common in Russia (Moscow) than in the UK. It was also less prevalent in the Russia in the past than nowadays. The incidence rate curve for this cancer peaked in Russia in 1987, but not in the UK. In 1967 the peak shifted to younger ages. It can be said that the high incidence cancer sites of today (e.g., male lung, prostate, and colon) exhibit an age-related accelerated increase in the incidence rate until very old ages more often than do the sites with a low incidence (e.g., thyroid and eye cancers), while the latter sites more often exhibit a leveling off in the rate with age. The differences in the shape of the incidence rate pattern for the same cancer site may reflect time and place differences in carcinogenic exposures.

***Typical age-pattern of the overall cancer risk.*** Despite obvious differences, cancer rate patterns do have common features, which can be seen most clearly in the age-patterns of the overall cancer risk (i.e., for all sites combined) (Figure 7).

Fig. 7 is about here

These features include:

- (1) a peak in early childhood,
- (2) the lowest rate in youth,
- (3) an increase in the rate, starting in the reproductive period and more pronounced since its end, and
- (4) deceleration or decline in cancer risk at old ages (75 and over).

These features are recurrent over time and place (IARC 1965-97; see also the figures in Sections 4 and 6 below), and can be drawn not only from period data, but also cohort data (Figure 8).

Fig. 8 is about here

Animal experiments revealed similar features for cancer rate patterns in rodent species; in particular, an intriguing decline in cancer risks at old ages (Pompei et al. 2001). The latter is a very significant finding because many cancer researchers are not aware of the reality of such a decline in humans. They believe that it is spurious due to e.g., an underestimation of new cancer cases at old ages. However, a decline such as this in laboratory animals cannot be due to a



diagnostic bias, which in turn suggests that the decline in humans is also not artificial. Studies of random autopsies of older individuals also confirm diminishing cancer risks in advanced years (Kuramoto et al. 1993; Stanta et al. 1997). Several explanations for this phenomenon have been suggested. Firstly, differential selection that favors the survival of individuals without cancer (Vaupel and Yashin 1988). The possibility that older subjects are no longer exposed to certain prevalent carcinogens (e.g., the proportion of smoking people declines in advanced years) could also contribute to such a decline. Finally, some ambivalent effects of individual aging contribute to the deceleration in cancer rates at old ages (Ukrainitseva and Yashin 2001, 2003). We discuss these and other possible explanations for the typical features of the cancer incidence rate patterns in Chapter 1.2.

### **3.2 Age-Specific Cancer Mortality**

The overall cancer mortality rate exhibits a peak at oldest old ages (90 and over) and then declines. This peak is lower than the respective peak in the incidence rate, and shifts towards older ages (Figure 9).

Fig. 9 is about here

Such a shift is likely to be due to a time lag between the age at the clinical manifestation of cancer and death from the disease. The decline in overall cancer mortality after age 90 may have several reasons. First, cancer mortality in any particular year may reflect the cancer incidence rate observed in an earlier year. All explanations on the decline of the cancer incidence rate at old ages then are also applicable to the decline in cancer mortality at oldest old ages.

A second reason may be competing causes of death. Some data indicate that the share of deaths from cancer diminishes with advanced age to the benefit of deaths from acute pathological conditions. Bordin and co-authors (1999) reviewed the complete clinical and autopsy records of 114 patients aged 97-106 who died in Trieste, Italy; the patients represented 99 percent of all extreme-aged deaths in a particular hospital and 70 percent in the area. The control group included 151 younger patients (65-74) who died during the same period in the same hospital. The authors found that the most prevalent causes of death in the oldest old were pneumonia (35 percent) and pulmonary embolism (14 percent). Cancer was responsible for only 6 percent of deaths in the extreme aged, but for 42 percent in the younger group. The authors

concluded that the extreme aged died from *acute* events in most cases, while the middle-aged individuals died in most cases from chronic diseases (Figure 10).

Fig. 10 is about here

If a person with cancer dies from an acute pathological event (e.g., pneumonia, heart attack, or the flu), then this person will contribute statistically to cancer *incidence*, but not necessarily to cancer *mortality*. The competing deaths, thus, are masking part of the potential mortality from cancer in the oldest old.

In summary, the decline in cancer mortality at oldest old ages may reflect a respective decline in the cancer incidence rate at earlier ages, and/or it may be due to the impact of competing deaths from acute events.

## **4 Higher Overall Cancer Risk in the More Developed Countries**

### **4.1 Standardized Incidence and Mortality Rates**

Standardized cancer incidence and mortality rates for all sites combined show a clear association with economic development. Figure 11 illustrates these rates for selected regions of the world in 1990.

Fig.11 is about here

We see from this figure that the cancer incidence rate tends to be higher in more developed regions than in less developed ones. The United States exhibits the highest values of this index for both sexes. In almost all countries, except India and Columbia, the male incidence rate is higher than that for females. This difference seems to be larger in more developed countries.

Overall cancer mortality is also higher in more developed regions, and higher in males than in females. Surprisingly, however, the regions with a higher cancer incidence do not necessarily have correspondingly higher cancer mortality. For instance, the highest male cancer risks are observed in the United States, while male cancer mortality in the United States is not the highest among the countries represented. In fact, it is lower than in many other countries (e.g., the UK, Denmark, and Germany). The highest male cancer mortality is seen in Russia. In less developed regions, there is a closer relationship between cancer mortality and cancer

incidence than in more developed ones. In Mongolia, the incidence and mortality rates are almost the same.

Since cancer mortality reflects the contributions of both incidence and survival from cancer, the difference between cancer incidence and mortality rates observed in a country can partly be attributed to the rate of survival of cancer patients in that country. Less developed regions exhibit poor survival from cancer, the values of age-standardized incidence rates in these regions therefore are closer to the mortality values than in the more developed regions.

#### **4.2 Age-Specific Cancer Risk**

A comparison of the curves of age-specific cancer incidence rates in different countries (Figures 12-13) provides us with more information than we would get by simply looking at age-standardized values.

Fig. 12-13 are about here

The UK, the USA, West Germany, Sweden, Australia, and Denmark represent economically more developed regions from climatically different parts of the earth. Economically less developed regions (also from climatically different parts of the Earth) are China, Ecuador, Colombia, India, Thailand, and Belarus. Clear differences in age-specific cancer incidence rates can be seen between the more and less developed regions. The rates are commonly higher in more developed countries than in less developed ones, for both males and females.

Figure 13 shows the age-specific rates for intermediately developed regions (represented by East Germany, Poland, and Yugoslavia) in comparison with more and less developed ones (Canada and Thailand, respectively).

Fig. 13 is about here

It can be seen that the curves of the incidence rate for intermediately developed regions are located between the curves for the more and less developed ones.

Ethnic and climatic factors seem to contribute less substantially to the differences in the cancer incidence rates between countries than life styles linked to economic development. In countries with similar levels of economic development but a different climate (e.g., West

Germany vs. Australia), the cancer rate patterns look more similar than in countries with different levels of economic development but similar ethnic groups and climatic conditions (e.g., pre-unification East and West Germany) (Figure 14).

Fig. 14 is about here

Thus, the overall cancer risk is positively associated with economic progress. It is higher in more developed regions than in less developed ones. This can be observed not only for age-adjusted but also for age-specific values of the cancer incidence rate, particularly at ages above 40. Factors of economic progress that may be responsible for such an intriguing association are discussed in Chapter 2.2. .

## **5 Cancers that are More Common in Less Developed Regions**

A comparison of standardized incidence rates for different cancer sites in more and less developed regions reveals that, unlike the overall risk, a few cancers manifest higher rates in *less* developed countries. These include tumors of the cervix, liver, and oesophagus (Figure 15).

Fig. 15 (1, 2) is about here

The risk of these cancers has proven to be higher in the presence of infectious factors (IARC Monographs 1994, 1995).

***Liver cancer.*** A strong association has been established between chronic infection with hepatitis B and C viruses and liver cancer. This cancer is less common in western countries and has high rates in southern Africa and south-east Asia. The high rates may be linked to hepatitis B and C infection, with their occurrence being much higher in African and Asian populations than in Europe (Parsonnet, 1999; EstEve et al. 1993).

***Cervical cancer.*** Cervical cancer is caused by infection with HPV (*Human Papilloma Virus*), which is more common in less developed countries. This infection is transmitted most frequently by sexual intercourse, thus explaining an association that has been observed with the number of sexual partners and age at first intercourse. The HPV infection is probably responsible for the observed higher incidence of cervical cancer in less developed countries (Parsonnet, 1999; EstEve et al. 1993).

**Stomach cancer.** Differences in stomach cancer risks between more and less developed regions are not obvious when *standardized* rates are compared (Figure 15). Nevertheless, the cancer's *age-specific* incidence rate at old ages is often higher in less developed regions, especially in Eastern and Asian countries than in Western Europe and the USA (Figure 4 above). The contribution of *H. pilory* infections to the higher risk of stomach cancer was shown in a number of studies (Brenner et al., 2000; Parsonnet, 1999). The infection is thought to be more common in less developed countries, possibly because individuals in these countries do not have relevant antibiotics at their disposal to the same degree as their peers in more developed countries. Treatment with several antibiotics (e.g., metronidazole) has proven to protect against stomach cancer.

Dietary factors are also considered to be important causes of the disease, in particular high consumption of smoked, salted, and fried foods, and low consumption of green leafy vegetables and citrus fruits (EstEve et al. 1993). This accords with observations that smoked and salted food is prevalent in countries with high stomach cancer rates (e.g., China). However, the role of diet in stomach cancer risks is still questionable. For instance, the risks began to decrease in Japan immediately after changes in the food consumption patterns, reflecting “westernization”, towards increased consumption of meat, fat, and eggs, and a decreased ruder cereal (e.g., barley) intake (Kagawa et al. 1978). At the same time, the proportion of vegetables did not change significantly in the diet. In other words, the usual physician's recommendation to eat more grain and vegetables, and less fat, does not correspond to a true link between these food components and the risk of stomach cancer.

In summary, a few cancers exhibit a higher incidence rate in less developed regions. Infection is thought to be one of the main risk factors for these cancers. Successful treatments of the respective infectious conditions (e.g., gastritis, cervicitis, and hepatitis) provide an effective prophylaxis against stomach, cervical, and liver cancers and this has probably resulted in a commonly lower risk of these cancers in more developed countries. At the same time, the incidence rates for the majority of other cancer sites are higher in more developed regions. It is not clear which aspects of economic development are primarily responsible for these higher rates, but it is clear that prophylactic measures have not yet been effective enough for most human cancers.

*Leading cancer sites differ in more and less developed regions.* Differences in incidence rates of specific cancer sites between more and less developed countries result in different sets of the most common cancers (Figure 16).

Fig. 16 is about here

We see from Figure 16 that male lung and female breast cancers are the most common cancer sites in both more and less developed countries. However, the next two most common sites are different for the two groups. For males, these are stomach and liver cancer in the less developed regions, while prostate and colon cancer is more common in more developed ones. For females, they are cervical and stomach cancers in less developed regions and colon and lung cancers in more developed ones.

## **6 Overall Cancer Risk Increased Along with Economic Progress**

### **6.1 Increasing Overall Cancer Incidence Rate in the Second Half of the 20<sup>th</sup> Century**

*Age-standardized rates.* In most countries represented in the IARC reports, the standardized overall cancer incidence rates showed a tendency to increase during the second half of the last century, in parallel with economic progress. Figure 17 shows an example, with the time trajectories of the standardized rates in Denmark, Sweden, the UK, Kazakhstan, and Russia calculated for different time periods between 1980 and 1998.

Fig.17 is about here.

It can be seen from this figure that the overall cancer risk is higher in the more developed countries (Denmark, Sweden, and the UK) compared to the less developed ones (Kazakhstan and Russia). The risk increased over time in all countries. In other words, time trends in the standardized cancer incidence rate also show an association with economic progress. Changes in the standardized rate may mask changes in the age-specific rate. Indeed, a monotonic increase in the standardized rate may be accompanied by a decline in the age-specific rate for some ages. For this reason, the analysis of age-specific incidence rates may provide more information on the forces responsible for the observed changes.

*Age-specific rates.* Figures 18 and 19 show age-specific incidence rates and their time ratios for all cancers combined in the USA (1960-62 vs. 1988-92) and Japan (1962-64 vs. 1988-92) by sex.

Fig.18 (1, 2) and 19 (1, 2) are about here.

Figure 18 reveals that the cancer incidence rate in the USA increased between these two periods, particularly at ages 20-35 and above 50. Figure 19 shows that the cancer incidence rate in Japan increased mainly for ages below 10 and above 35. Time trends in cancer risks seem to differ for children and young adults in the USA and Japan. However, this effect is possibly spurious due to the relatively low number of cancer cases at these ages. As for older age morbidity, it can be seen that the increase in the cancer incidence rate was more pronounced in Japan than in the USA – a difference that needs explanation. It may be a reflection of e.g., the more rapid economic growth in Japan during this period and the fact that the changes in the set of prevalent carcinogens in Japan occurred more recently than in the USA.

An increase in the age-specific cancer rates over time has been observed not only in the period (cross-sectional) data (Figure 20) but also in the cohort data (Figure 21, Figures 6 and 9 above).

Fig. 20 and 21 are about here.

Thus, an analysis of time differences in cancer incidence rates shows that the increase in the overall cancer risk during the second half of the last century was positively associated with economic progress. The observed association, however, does not explain the mechanisms by which economic development influences cancer rates.

## **6.2 Decreasing Incidence Rates for Separate Cancer Sites**

The overall cancer incidence rate results from a combination of incidence rates for separate cancer sites. Their time trends respectively influence the time trend in the overall rate. The incidence rate for the majority of cancers has increased during the past century; only a few have seen a decline. Today's most prevalent cancer sites in the developed countries are that of the male lung, male prostate, female breast, and colon (both sexes). These cancers exhibited a clear increase in the incidence rate until the 1990s and are largely responsible for the steady growth in the overall cancer risk in the second half of the 20<sup>th</sup> century. The incidence of some other cancers

which were more prevalent in the past (e.g., stomach and cervical cancer) has decreased in many countries as the economic situation progressed. Figure 22 illustrates this, showing the standardized incidence rate for cervical cancer.

Fig. 22 is about here

Summing up, different time trends can be seen in the incidence rates for individual cancer sites and it is the balance between the cancers that are increasing and those that are decreasing in frequency which results in the time trend for the overall cancer risk. Until recently, this overall risk increased in most countries of the world. This indicates that factors associated with economic progress that promote cancer have been more influential than the factors that prevent cancer.

### **6.3 Declining Overall Cancer Risk in the 1990s in Some Developed Countries**

***Age-standardized rate.*** After a steady increase during the second half of the last century, the overall cancer risk (age-standardized) showed a deceleration or even a decline in the 1990s in several developed countries, such as the USA, Sweden, and Denmark (Ries et al. 2001, Holly et al. 2001, McKean-Cowdin 2000, Lynn et al. 2000, Health for all 2000). At the same time, intermediately developed countries (e.g., Russia) continue to see increases in the overall rate (see Figure 17 above). The decline in overall cancer risk was the most pronounced in the USA between 1992 and 1998 (Cole et al. 1996, Ries et al. 2001, Health in US 2001, Holly et al. 2001, Jemal et al. 2004a). It was largely due to decreasing incidence rates for some of the most prevalent cancer sites (e.g., of the male lung, male prostate, and colon in both sexes). The exact reasons for the decline in rates are not clear; reference is usually made to declining exposure to tobacco smoking. However, time trends in tobacco smoking do not seem to fit very well these trends (to be discussed in part II. Explanation).

***Incidence rates for separate cancer sites: alarming trends.*** At the same time, incidence rates for some other prevalent cancers (e.g., skin melanoma and female breast cancer) continue to increase. There has also been a deceleration in the long-term decline in the incidence rate of those cancers that showed an almost linear fall over the past decades in the USA and in other developed countries. These include stomach and cervical cancers (Ries et al. 2001, Health in US 2001, Holly et al. 2001, Health for all 2000, Levi et al. 1999).



A particularly important point is that while the incidence of some of today's most prevalent cancers is decreasing, the incidence of some other cancers that are less prevalent now is rising steeply and these may, in turn, in future become the more prevalent sites in developed countries. Examples include myeloma, non-Hodgkin's lymphoma, liver, thyroid, and kidney cancers. Rare in the past, they have seen an incident rate increase of more than 100 percent during a mere 50 years, meaning that they may replace today's most prevalent sites soon, if this trend continues (Table 1).

**Table 1.** Changes in incidence and survival rates for separate cancers during 1950-1998 in the USA (Source: Ries et al. 2001).

<b>Cancer</b>	<b>Change in incidence rate 1950 -1998 (%)</b>	<b>5-Year survival 1950</b>	<b>(%) 1997</b>
<b>*Melanoma</b>	<b>477</b>	<b>49</b>	<b>89</b>
<b>*Lung</b>	<b>248</b>	<b>6</b>	<b>15</b>
<b>Myeloma</b>	<b>222</b>	<b>6</b>	<b>28</b>
<b>*Prostate</b>	<b>194</b>	<b>43</b>	<b>97</b>
<b>Non-Hodgkin's lymphoma</b>	<b>185</b>	<b>33</b>	<b>54</b>
<b>Liver</b>	<b>180</b>	<b>1</b>	<b>6</b>
<b>Thyroid</b>	<b>155</b>	<b>80</b>	<b>95</b>
<b>Kidney</b>	<b>131</b>	<b>34</b>	<b>62</b>
<b>Brain</b>	<b>69</b>	<b>21</b>	<b>31</b>
<b>*Breast</b>	<b>63</b>	<b>60</b>	<b>87</b>
<b>Bladder</b>	<b>54</b>	<b>53</b>	<b>82</b>
<b>Childhood cancers</b>	<b>35</b>	<b>20</b>	<b>79</b>
<b>*Colon</b>	<b>15</b>	<b>41</b>	<b>62</b>
<b>Pancreas</b>	<b>14</b>	<b>1</b>	<b>4</b>
<b>Leukaemias</b>	<b>11</b>	<b>10</b>	<b>46</b>
<b>Corpus U</b>	<b>3.7</b>	<b>72</b>	<b>86</b>
<b>Ovarian</b>	<b>1</b>	<b>30</b>	<b>52</b>
<b>Esophagus</b>	<b>-3</b>	<b>4</b>	<b>15</b>

<b>*Stomach</b>	-79	<b>12</b>	<b>20</b>
<b>Cervix</b>	-79	<b>59</b>	<b>72</b>
<b>All sites</b>	<b>60</b>	<b>35</b>	<b>63</b>

\* - Most prevalent sites today; **red** - poor 5-year survival; **blue** - high 5-year survival; **green**- moderate 5-year survival; **pink** - rapid increase in the incidence rate during 50 years.

A similar development has occurred in the past. For instance, melanoma and female lung cancer were not among the most prevalent cancer sites in the USA 50 years ago, in contrast to stomach cancer (Ries et al. 2001). However, opposite trends in these cancers' incidence rates in the second half of the last century resulted in the fact that melanoma and female lung cancer are now among the 10 most prevalent cancer sites in the USA, while stomach cancer is not (Ries et al. 2001).

Thus, one should interpret recent positive trends in the overall cancer risk with caution, taking into account the speed of increase in the rates of today's less prevalent cancer sites. Cancers with both a rapidly increasing incidence rate and poor survival most urgently require prophylactic and therapeutic measures, even if these cancers are rare today. Myeloma, non-Hodgkin's lymphoma, liver, and brain cancers are examples (see Table 1 above).

## 7 Why Does Cancer Mortality Decline While the Incidence Rate Continues to Increase?

### 7.1 The Lag between Cancer Incidence and Mortality Increases

The age-pattern of the overall cancer mortality rate resembles that of the incidence rate (Figure 9 above). The values for mortality are usually lower than for incidence, however. The lag between cancer incidence and mortality rates increased over time for both sexes (Figure 23).

Fig. 23 is about here

One can see from this figure that cancer mortality in the UK of 1963-65 was closer to the incidence than in 1996, especially for males. The ratio of the age-specific cancer mortality to the incidence rate decreased over time at all ages. One reason may be the improvement in the survival of cancer patients observed in most developed countries during the past decades. For females, the ratio is lower than for males (except at old ages). Higher female survival from cancer certainly contributes to this difference. For instance, five-year survival from cancer in

countries of the EU varied in 1996 between 45-60 percent for females; this compares to 30-45 percent for males (EUCAN 1999).

## **7.2 Decline in Cancer Mortality: Competition Between Incidence and Survival**

### **7.2.1 Overall Cancer Mortality**

Despite the recent and slight decrease in the standardized incidence rate in some developed countries, the standardized mortality rates for all cancers combined showed a clear decline in many European countries and the USA before any decrease in the incidence rate was observed (Health for all 2000, McKean-Cowdin 2000, Levi et al. 1999, Cole et al. 1996). Figure 24 shows the trends in the standardized cancer mortality rate as compared to the trends in the incidence rate for all sites combined in the five countries discussed above.

Fig.24 is about here.

The figure shows a decline in overall cancer mortality in Sweden since 1976, the UK and Kazakhstan since 1990, and in Russia since 1994. The overall cancer incidence rate continued to increase during these years in all countries except Kazakhstan (the least developed region of the four). Interestingly, the cancer mortality rate was the lowest in Sweden, while the incidence rate in that country was one of the highest among the countries compared. To understand the reasons for such divergence, it has to be taken into account that cancer mortality does not result entirely from the cancer incidence rate. Improvements in the survival of cancer patients are likely to be the most important contributor to a decline in cancer mortality. This contribution is most significant in Sweden, where the survival of cancer patients is the highest in the EU.

### **7.2.2 Mortality for Individual Cancer Sites**

***Non-Hodgkin's lymphoma.*** The mortality for particular cancer sites continues to increase over time. The rise reflects the corresponding growth in the cancer incidence rate. For instance, the increase in mortality from Non-Hodgkin's lymphomas observed during previous decades in developed countries is related to a significant increase (almost twofold) in the respective incidence rate for the same period.

***Hodgkin's disease.*** Contrarily, a decline in cancer mortality over time does not necessarily result in a corresponding decline in the cancer incidence. Progress in the survival of cancer patients may also contribute to such a decline. This survival is commonly higher in more developed countries than in less developed ones (Sankaranarayanan et al. 1998, Berrino et al.

1995). For instance, a large decrease (about 75 percent) in Hodgkin's disease mortality during 1950-1997 in the USA is likely to be entirely due to a substantial increase in the 5-year survival from this cancer (from 30 percent in the 1950s to 84 percent in the 1990s). The incidence rate of Hodgkin's disease increased for the same period by 14 percent (Ries et al. 2001). This shows that this factor does not contribute to declining mortality.

**Cervical cancer.** Cervical cancer shows a decline in both incidence and mortality rates. Its incidence rate had already begun to decrease in the 1950s in the USA and Europe (Figure 20). The 5-year survival of patients with cervical cancer rose by about 10 percent over the same period (EstEve et al. 1993, Ries 2001, Health for all 2000). Under such favorable conditions, the observed decline in mortality from cervical cancer is to be expected (Ries 2001, Levi et al. 1999).

**Breast cancer.** Female breast cancer is an example of a cancer that exhibits an increase in the standardized incidence rate over time in most countries. Nonetheless, trends in breast cancer mortality vary considerably between the countries. Figure 25 shows time trends in breast cancer incidence and mortality for selected countries.

Fig. 25 is about here.

We see from this figure that breast cancer incidence and mortality rates are generally higher in the more developed countries (Denmark, Sweden, and the UK) than in the less developed ones (Kazakhstan and Russia). The breast cancer incidence rate increased over time in all countries, while the cancer's mortality rate rose in Russia and Kazakhstan only. The decline in the mortality rate from breast cancer has been observed in Sweden since 1975 and in the UK since 1990. It is surprising that the breast cancer incidence rate is higher in Sweden than in the UK, while mortality from this cancer is lower in Sweden than in the UK.

The variability in trends of breast cancer mortality cannot be explained without taking into account large differences in survival from this cancer among the countries compared. It differs significantly even between countries with a similar standard of medical assistance (e.g. the EU states). For instance, the 5-year survival of breast cancer patients in 1996 was about 81 percent in Sweden but only about 67 percent in the UK (EUCAN 1999). In Russia of 1999, it was even lower (about 54 percent) than in the UK of 1996 (Health in Russia 2000). The rise in breast cancer mortality in Russia reflects an increasing incidence rate on the grounds of poor survival

from this cancer. The differences in the survival of cancer patients are likely to be a major contributor to a divergence between incidence and mortality trends.

### 7.2.3 Why Does Survival From Cancer Differ Among Developed Countries?

Variability in survival of cancer patients can reasonably be expected when regions with clearly different levels of economic development and medical assistance are compared (e.g. Europe and Africa). Variability is not obvious in the case of countries with similar economic and health care conditions, however. The large difference between countries such as Sweden and the UK in the survival of cancer patients is surprising and requires explanation. Figure 26 shows the mean five-year-survival for all cancers combined in 1996 in European countries. It can be seen from this figure that survival varies among the countries, ranging from 37.5 percent in the UK to 53 percent in Sweden.

Fig 26 is about here

This difference appears puzzling. It is also unclear, why survival is highest in Sweden (53 percent), while neighboring Denmark (with a similar climate, economic system, and health service) has almost the lowest survival value among the EU countries (about 40 percent). As for individual cancer sites, the highest five-year survival rates are observed in different countries (e.g., prostate cancer in Sweden, lung cancer in France, colon cancer in the Netherlands). However, the lowest five-year-survival rates for almost all sites are found in only two countries (the UK and Denmark) (Table. 2).

**Table 2.** Differences in five-year survival from cancer among EU countries in 1996 (EUCAN 1996).

<b><u>Cancer</u></b>	<b><u>Highest Survival</u></b>	<b><u>Lowest Survival</u></b>
<b>Lung</b>	<i>France (20%)</i>	<i>UK, Denmark (7%)</i>
<b>Prostate</b>	<i>Germany (65%), Sweden (70 %)</i>	<i>Denmark (42%), UK (45%)</i>
<b>Breast</b>	<i>Sweden, France, Finland (80%)</i>	<i>Austria (63%), UK (67%)</i>
<b>Colon</b>	<i>Netherlands (56%)</i>	<i>UK (40 %), Denmark (43%)</i>
<b>Stomach</b>	<i>Austria, Spain, Germany (25-30%)</i>	<i>UK (12 %), Denmark (15%)</i>

This variability raises an important practical question: Which factors determine the differences in survival from cancer between countries with similar standards of medical assistance? Climatic, cultural, and ethnic differences may play a role, as may differences in medical care. For instance, access to medical specialists is limited in the UK compared to Sweden and this may lead to a higher proportion of patients in the UK being diagnosed with cancer at a late stage. This, in turn, will worsen prognosis and survival from cancer. The differences in treatment in a given country, such as preference of chemotherapy over surgery, or surgery over radiotherapy, may be important as well. Even a preference for a particular brand name of a drug in a country may influence the outcome of anti-cancer treatment. Pharmaceutical companies use slightly different technologies to manufacture drugs with presumably the same action. This may produce certain differences in the drug's efficiency. International differences in schemes of compensatory treatment (applied after the main course of cancer therapy) may be one more reason.

The exact causes of the large variability in survival from cancer therefore are not clear and require further study; their importance should not be underestimated. Understanding the reasons behind the differences in survival from cancer among equally developed countries could help improve survival even without additional investments in the development of new cancer therapeutics. In this chapter, we have only briefly shown that survival from cancer depends not only on standard anti-cancer treatment but also from other, hidden, factors.

In conclusion of this section, the contemporary decline in overall cancer mortality in developed countries results from time trends in both incidence rates and survival from cancer. These trends are different for individual cancer sites. Since the overall cancer risk increased during the second half of the 20<sup>th</sup> century in most countries studied, and the effectiveness of anti-cancer treatment has noticeably improved only in the last 20-30 years, it was relatively recent that the decline in overall cancer mortality began to be observed.

## **8 Concluding Remarks**

Comparison of cancer incidence and mortality rate curves as well as age-standardized values in different countries of the world for different time periods shows that:

(1) The overall cancer risk, until recently, has increased over time along with economic progress. It is also higher in the more developed regions than in the less developed ones for the same time point. The individual cancer sites' contributions to the overall rate also have changed in a way linked to economic development.

(2) Cancer incidence and mortality rates exhibit different time trends. While cancer incidence increased over time, mortality rates begun to decline. This divergence most probably reflects substantial progress in the survival of cancer patients during the last 50 years. Improved survival has decreased cancer mortality, but not its incidence. Both rising cancer incidence and falling mortality from cancer elevated the cancer burden in developed countries.

(3) The modest deceleration/decline in cancer incidence and significant decrease in mortality rates during the last decade in the USA, together, indicate that the progress in developing new effective cancer treatments has been more substantial than the progress in developing effective cancer prophylaxis.

(4) A comparative analysis of trends in incidence rate for separate cancer sites suggests that the recent positive tendency towards a decline in the overall cancer risk in the developed countries may be temporary. The decline was largely the result of the decreasing rates of a few prevalent cancer sites (e.g., male lung, male prostate, and colon). However, there are some other cancer sites (less prevalent now) with an incidence continuing to increase rapidly; these may become more prevalent in the near future and result in overall cancer risk elevation. Examples of cancers that are most worrying are myeloma, non-Hodgkin's lymphoma, and liver cancer. They not only have a continually increasing incidence, but also show poor 5-year survival rates. The development of effective prophylactics and treatments for these cancers is necessary in order to maintain the decline in cancer incidence and mortality rates in the future.

(5) Understanding the reasons behind increases in cancer incidence rate in the developed countries is of great importance. Three major processes contribute to the increase in the cancer burden worldwide: population aging, a rising cancer incidence rate, and an improving survival of cancer patients. Among these, only one factor – the increase in the cancer incidence rate – is genuinely negative. It is this factor that requires most attention, with the first step constituting an urgent search for explanations in order to develop adequate prophylactic measures. Which aspects of economic progress and western life style are primarily responsible for the elevated risks of the majority of cancers? Which aspects have influenced the changes in the proportions of individual cancer sites making up the overall rate? We address these questions and discuss possible explanations in the next paper (Economic Progress as Cancer Risk Factor II. Why is Overall Cancer Risk higher in More Developed Countries?).

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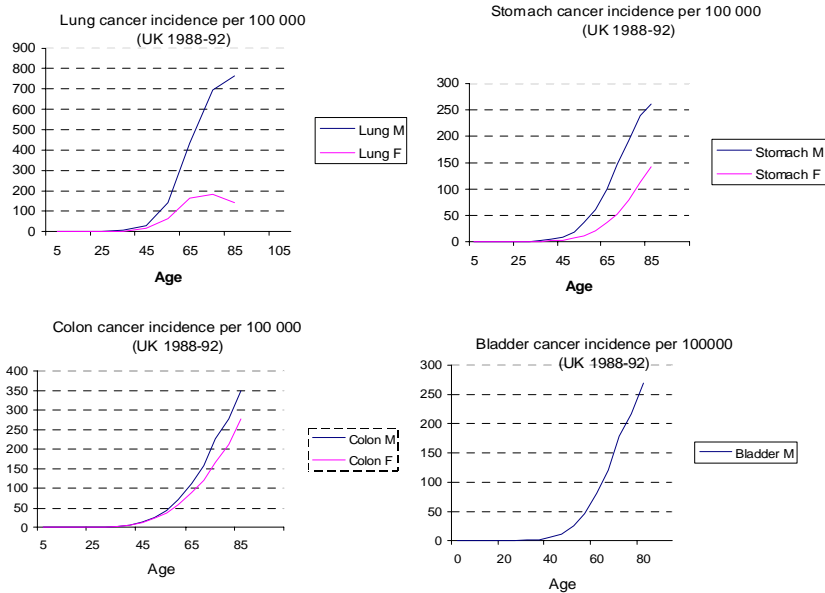
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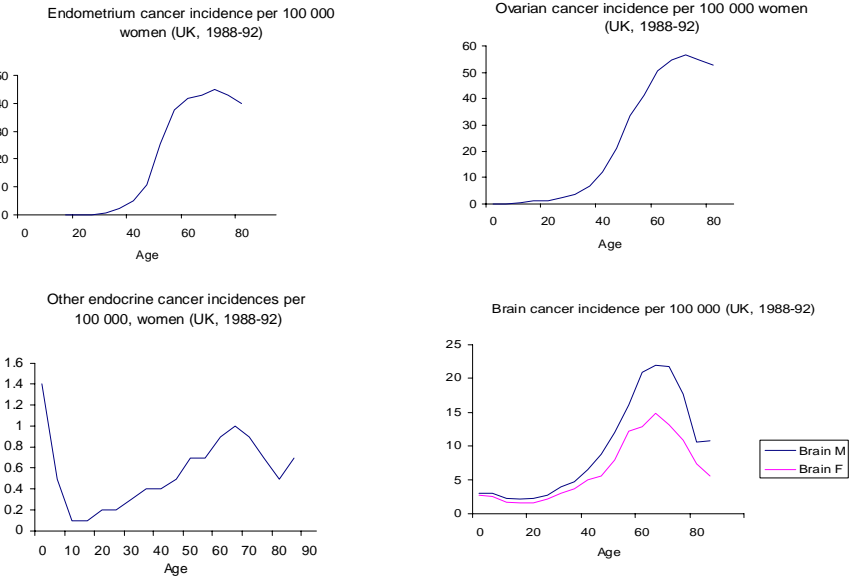
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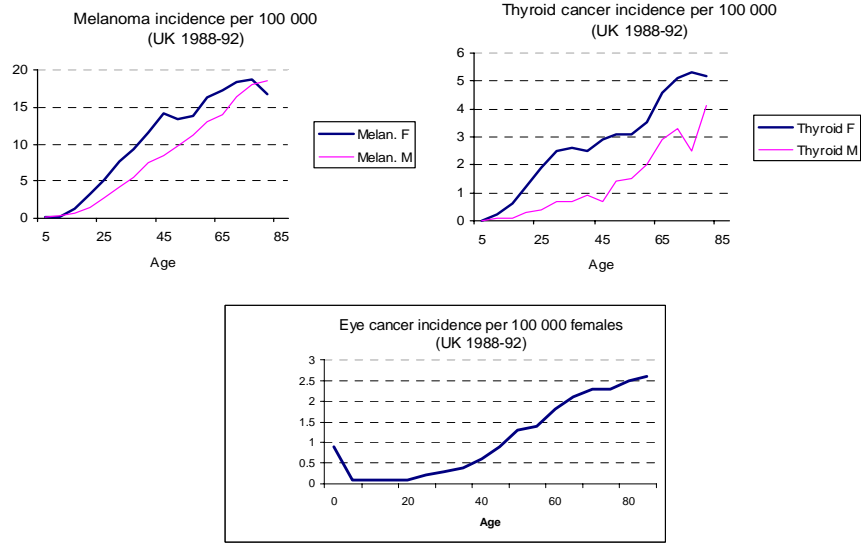


**Fig. 1.** Age-patterns of cancer incidence rate. Examples of accelerated increase in the rate until very old age (80+). The pattern of the female lung cancer incidence rate differs from that for males. The former manifests a wave-like shape with a peak at about age 70. The United Kingdom, 1988-92 (IARC 1997).

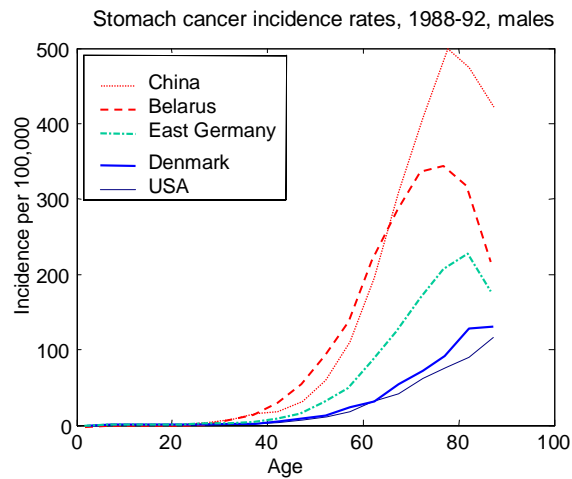


**Fig. 2.** Age-patterns of cancer incidence rate. Examples of a wave-like change in the rate with age. The United Kingdom, 1988-92 (IARC 1997).





**Fig. 3.** Age-patterns of cancer incidence rate. Examples of a linear or decelerated increase in the rate with age. The United Kingdom, 1988-92 (IARC 1997).



**Fig. 4.** Age-patterns of incidence rates for male stomach cancer, 1988-92, average annual. A comparison between more and less developed countries (IARC 1997).

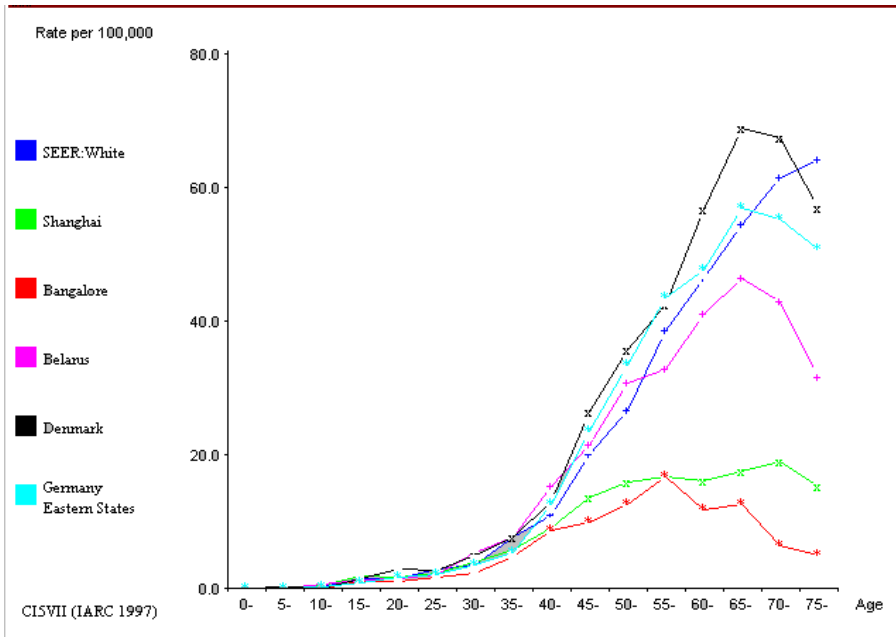


Fig. 5. Age-patterns of the incidence rates for ovarian cancer. A comparison between more and less developed countries (IARC 1997).

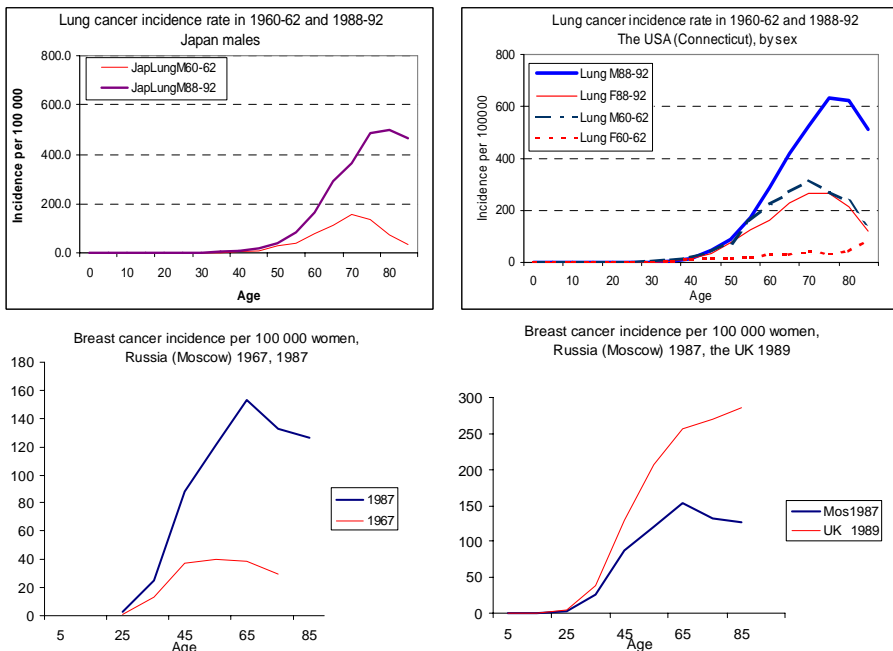
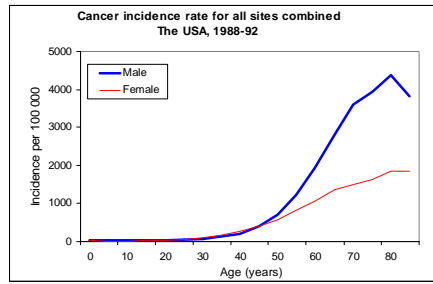
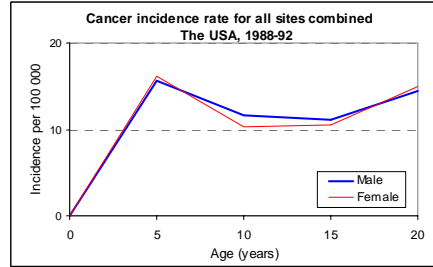


Fig. 6. Examples of time and place differences in age-patterns of the cancer incidence rate for today's most prevalent sites (Aksel and Dvoirin 1991, IARC 1965-1997).

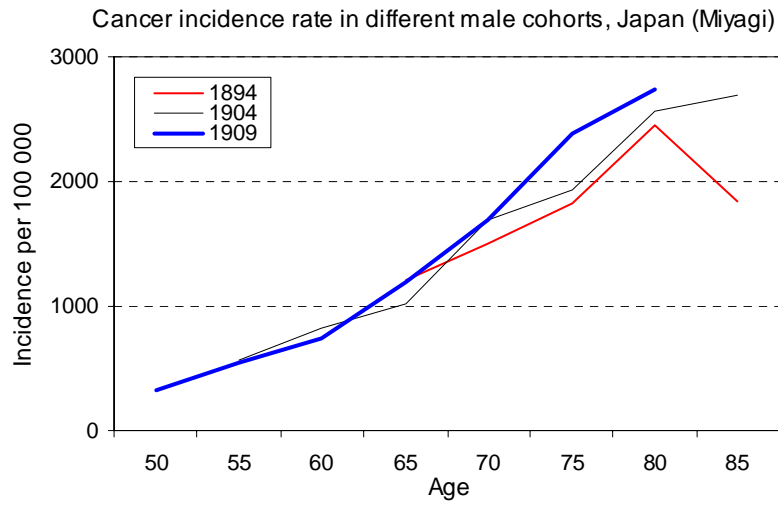


a. All ages

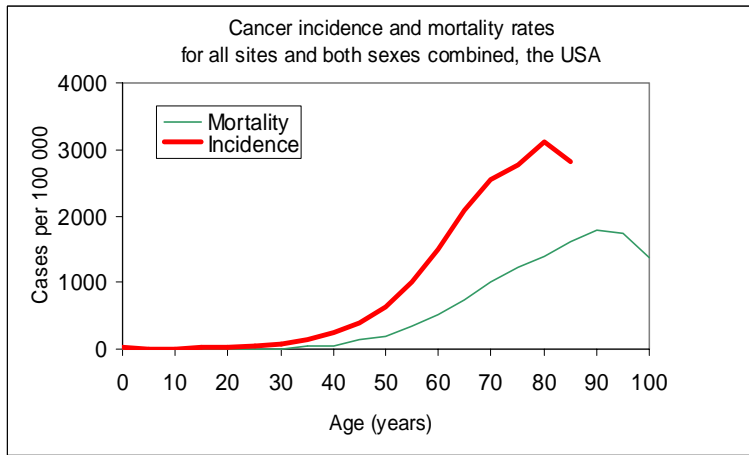


b. Children and teens

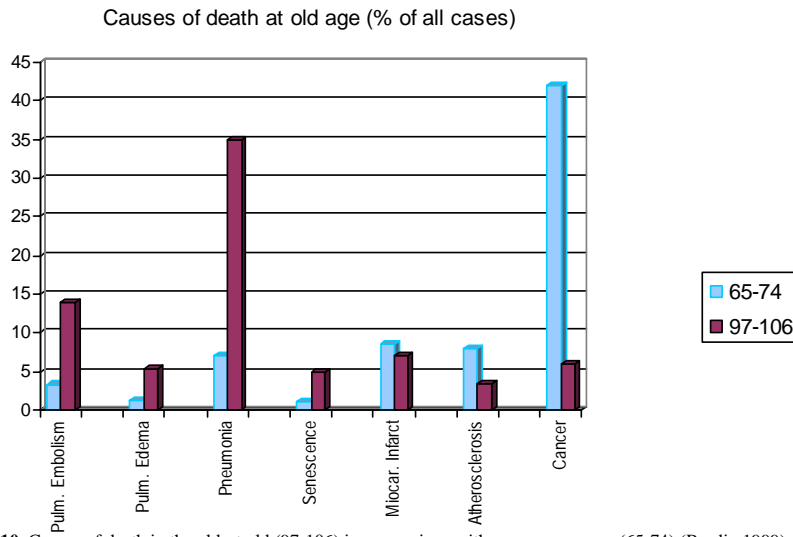
**Fig. 7.** Cancer incidence rate for all sites combined in the USA (1988-92), average annual (IARC 1997).



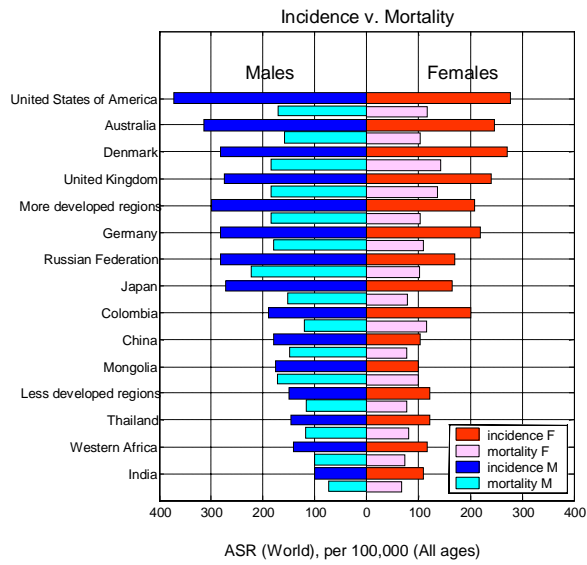
**Fig. 8.** Cancer incidence rate in different birth cohorts of Japanese men. The cohort rate is restored from period data for 1971-1997 (IARC 1965-1997). The rate decelerates (or decreases) with advanced age for all birth cohorts.



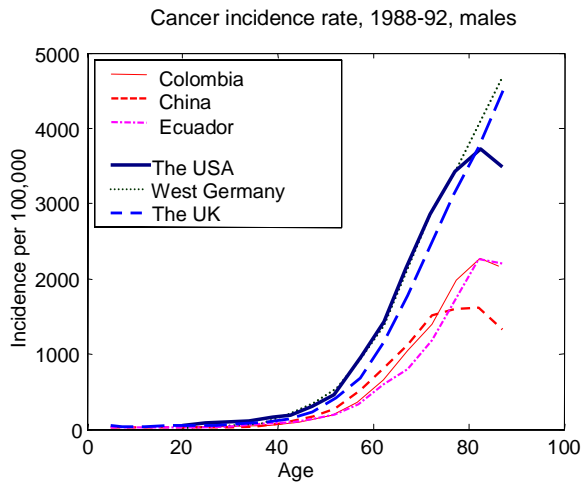
**Fig. 9.** Cancer incidence rate (1988-92), average annual, and mortality rate (1990) in the USA (combined from sources: IARC 1997, Health US 1996-1997, Smith 1996, 1999).



**Fig. 10.** Causes of death in the oldest old (97-106) in comparison with a younger group (65-74) (Bordin 1999).



**Fig. 11.** Age-standardized incidence and mortality rates for all cancer sites combined in 1990. A comparison between more and less developed countries, by sex (GLOBOCAN 1998).



**Fig. 12 (1).** Age-specific cancer incidence rate (all sites but skin) for males, 1988-92, average annual. Males. A comparison between more and less developed countries (IARC 1997).

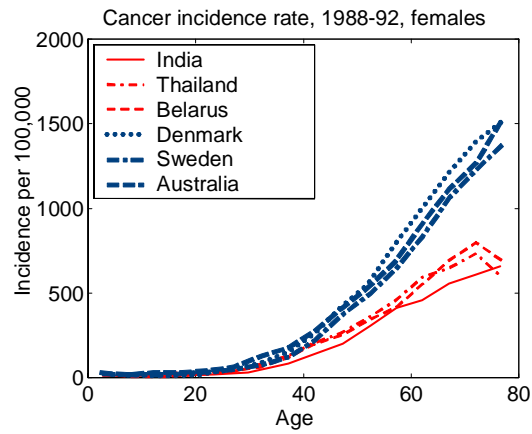


Fig. 12 (2). Age-specific cancer incidence rate (all sites, but skin), 1988-92, average annual. Females. A comparison between more and less developed countries (IARC 1997).

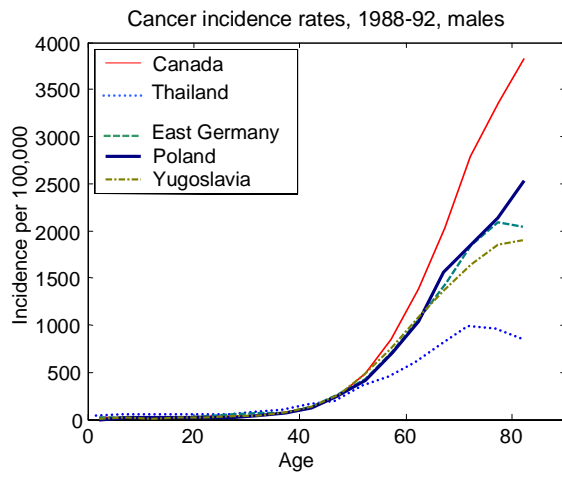
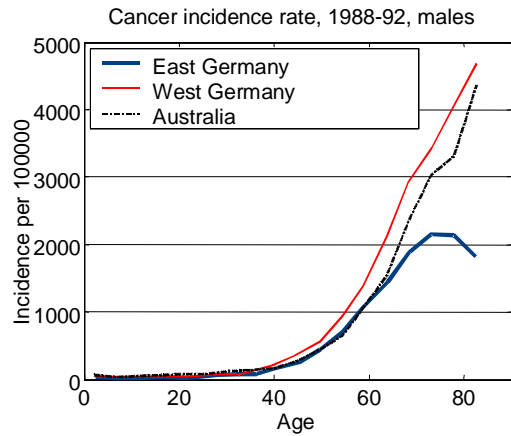
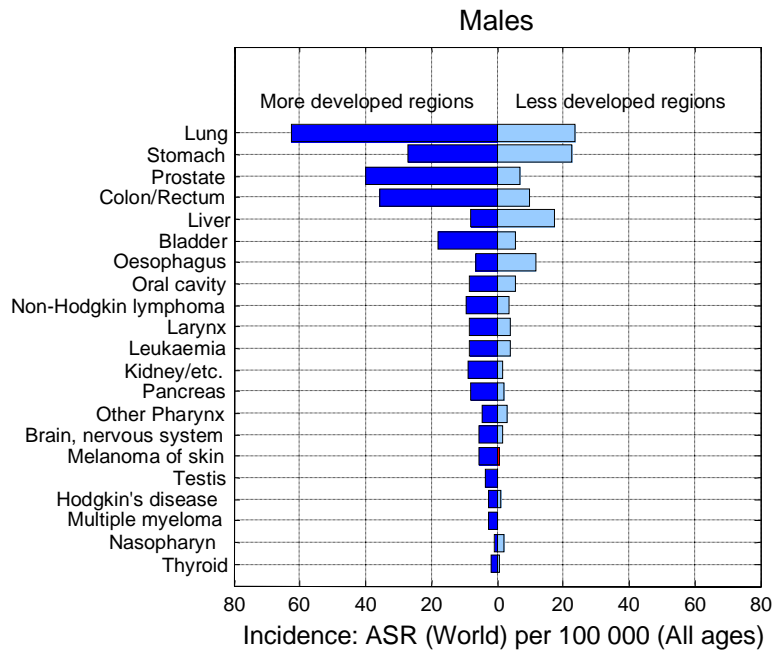


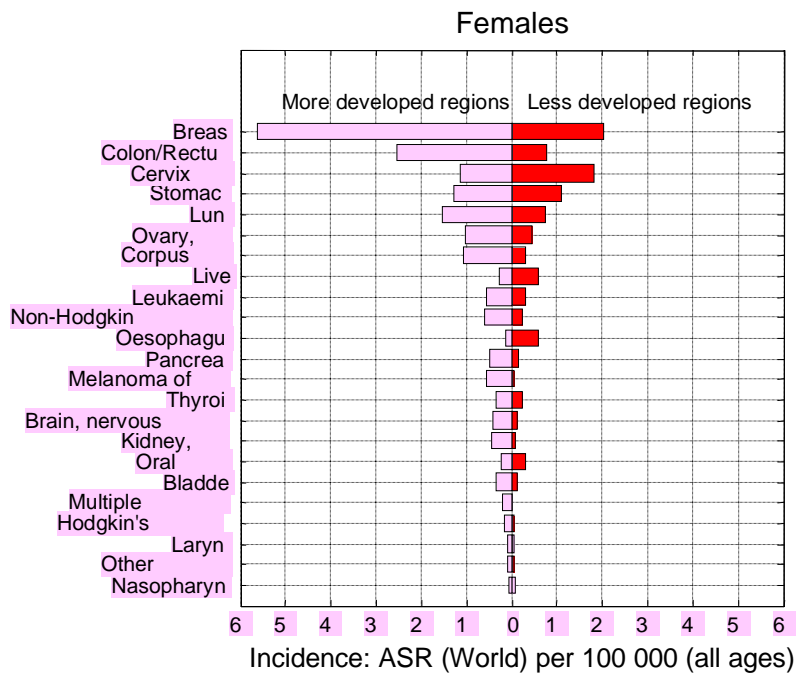
Fig. 13. Age-specific cancer incidence rate (all sites but skin), 1988-92, average annual. Intermediately developed regions in comparison with more and less developed ones (IARC 1997).



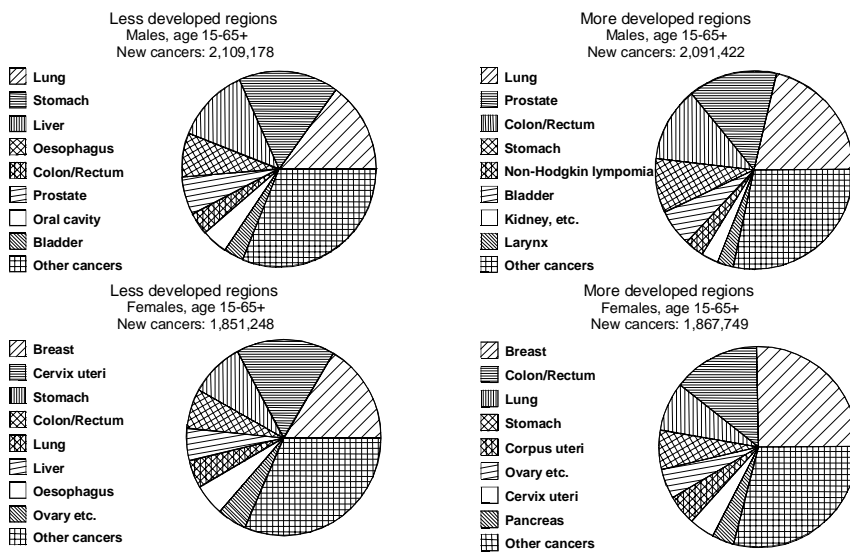
**Fig. 14.** Age-specific cancer incidence rate (all sites combined) by ethnicity and place, 1988-92, average annual (IARC 1997). Economic development produces more differences in age-patterns of cancer risk than ethnicity or climate.



**Fig. 15 (1).** Age-standardized incidence rates for separate cancer sites in 1990. More developed regions in comparison with less developed ones, males (GLOBOCAN 1998).



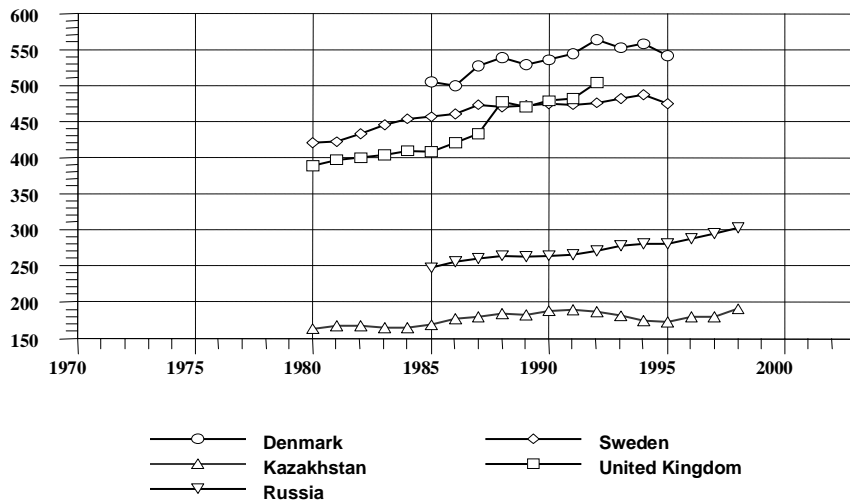
**Fig. 15 (2).** Age-standardized incidence rates for separate cancer sites in 1990. More developed regions in comparison with less developed ones, females (GLOBOCAN 1998).



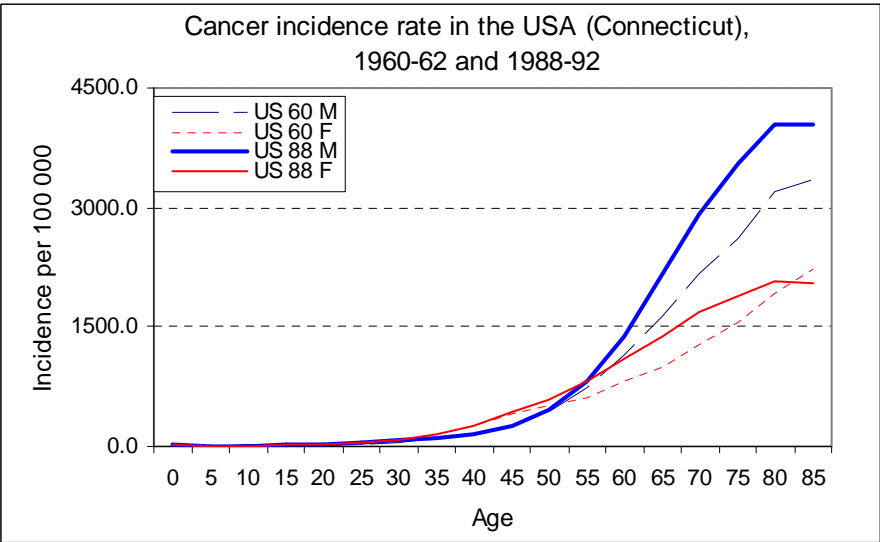
**Fig. 16.** Most common adult cancers in more and less developed regions in 1990 (GLOBOCAN 1998). Male lung and female breast cancers are the most common cancer sites in both more and less developed regions. However, the next two most common sites are different in these regions for each sex.



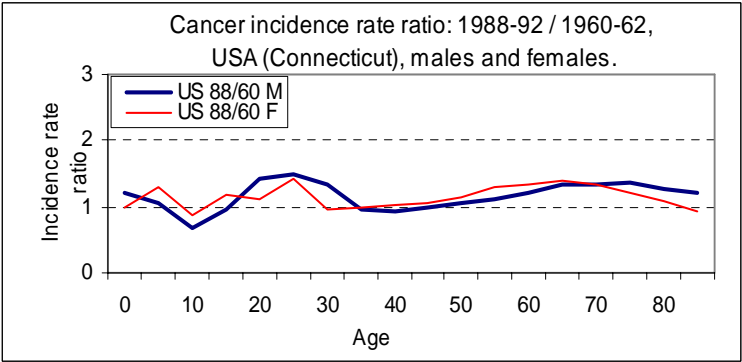
**Age-standardized cancer incidence rate (ASR), all sites (incidence per 100 000)**



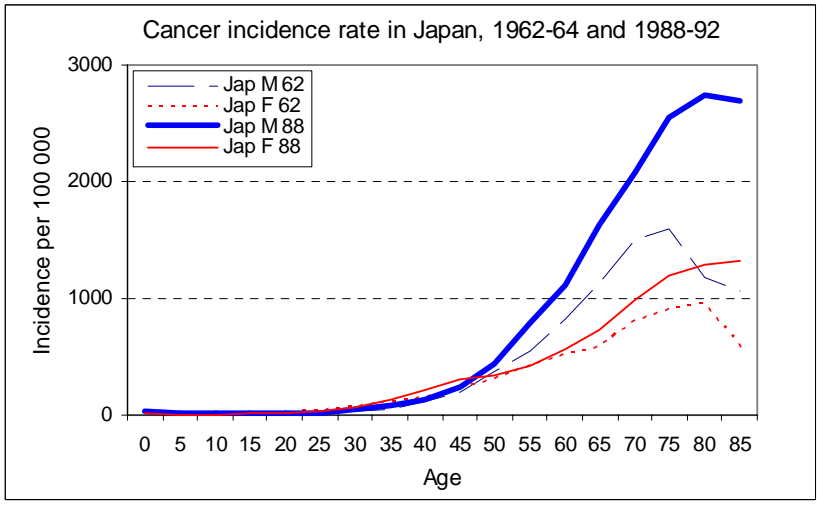
**Fig. 17.** Cancer incidence rate , age-standardized (ASR), in more and less developed countries at different years (Health for all 2000). Overall rate is higher in more developed countries (UK, Sweden, Denmark) than in less developed ones (Russia, Kazakhstan), and has increased over time.



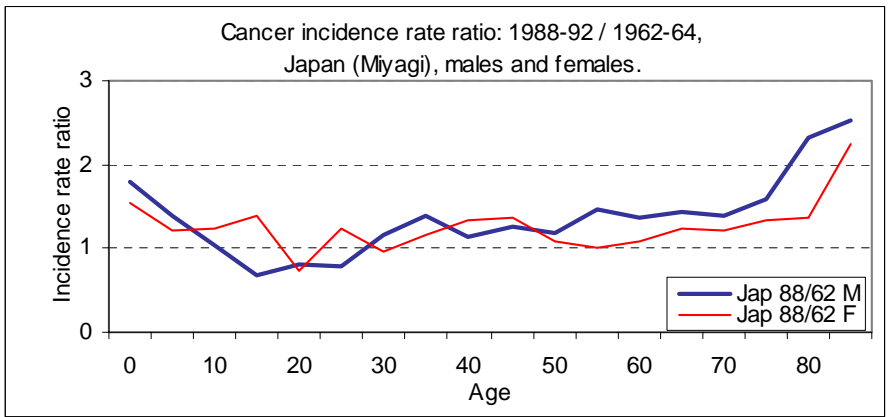
**Fig. 18 (1).** Overall cancer incidence rate in the United States, 1960-62 and 1988-92 (average annual), by sex (IARC 1965-1997). The rate increased over time both for males and females, beginning approximately at 50 years of age.



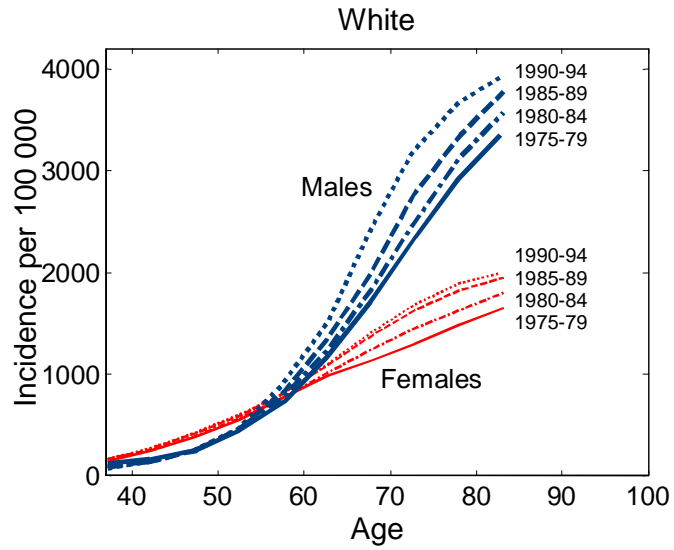
**Fig. 18(2).** Cancer incidence rate ratio 1988-92 to 1960-62 in the United States (IARC1965-1997). The rate increased over time largely at ages 20-40, and above age 50. The relative increase does not show a substantial sex difference.



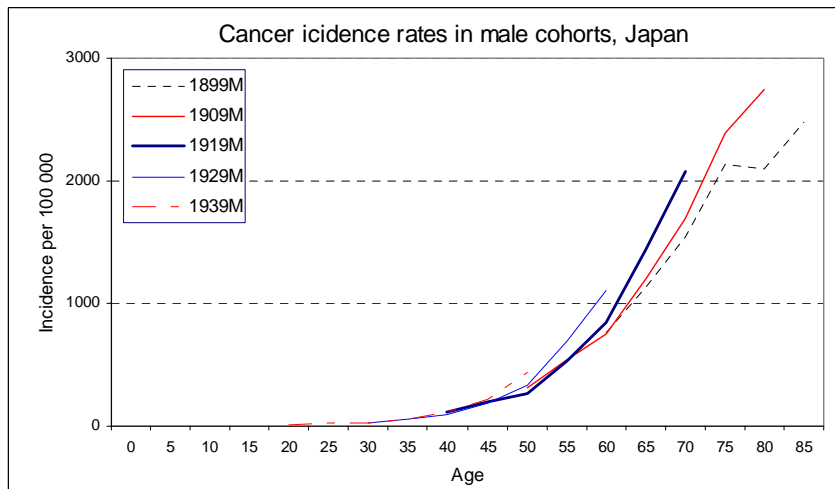
**Fig. 19(1).** Cancer Incidence rate in Japan 1962-64 and 1988-92, by sex (IARC 1965-1997). The rate increased over time both for males and females, beginning approximately at 35 years of age.



**Fig. 19(2).** Cancer incidence rate ratio 1988-92 to 1962-64 in Japan (IARC 1965-1997). The rate increased over time at ages 0-9, and after age 35. The relative increase seems to be higher for males than for females at old ages.

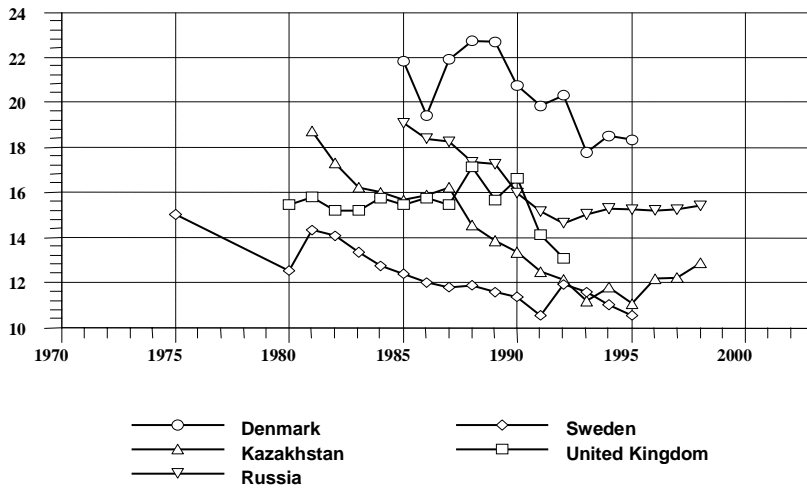


**Fig. 20.** Changes in period (cross-sectional) overall cancer incidence rate in the United States 1975-1994 (adapted from Dinse et al. 1999).

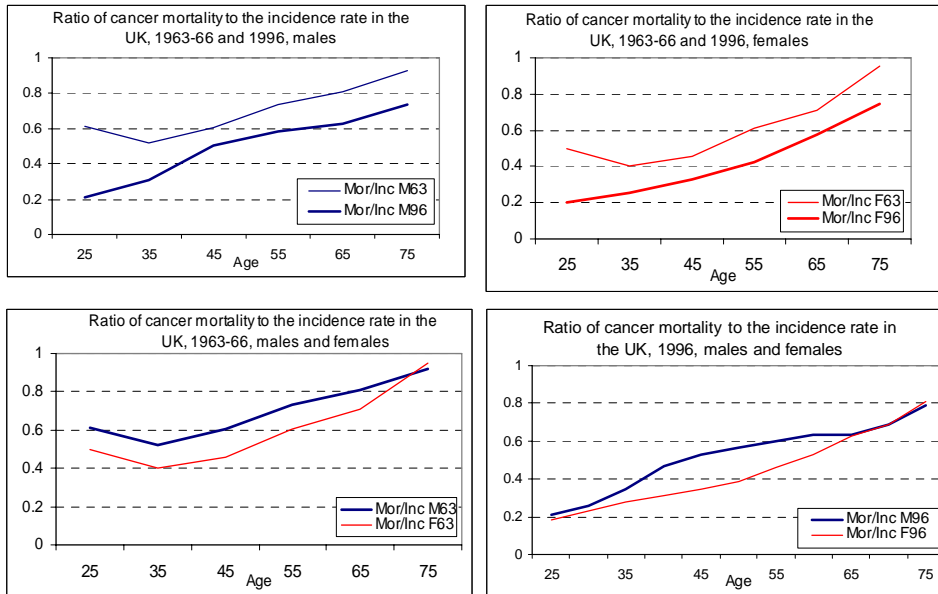


**Fig. 21.** Overall cancer incidence rate in different male cohorts in Japan (IARC1965-1997). One can see that the rate increased in successive generations of Japanese men.

**Age-standardized cancer incidence rate (ASR), Cervix uteri (incidence per 100 000)**

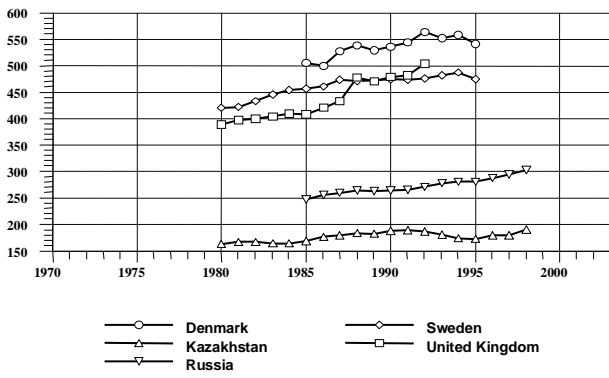


**Fig. 22.** Change in cervical cancer incidence rate, age-standardized (ASR), in more and less developed countries over time (Health for all 2000). Until recently, the rate declined in all countries compared.



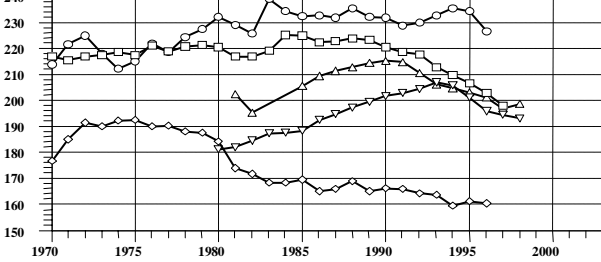
**Fig. 23.** The ratio of cancer mortality to the cancer incidence rate at different time periods in the UK (IARC 1965-1997, EUCAN 1999). The ratio decreased over time. It is higher for males than for females at all ages except old ages.

Age-standardized cancer incidence rate (ASR), all sites (rate per 100 000)



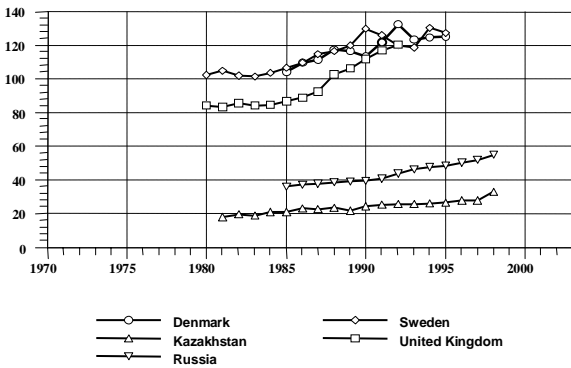
**Fig. 24(1).** Cancer incidence rate over time and place (ASR) (Health for all 2000). The overall rate is higher in more developed countries (UK, Sweden, Denmark) than in less developed ones (Russia, Kazakhstan). The cancer risk increased in more developed countries until recently. In less developed countries the increase continues.

Age-standardized death rate (SDR), malignant neoplasms (rate per 100 000)



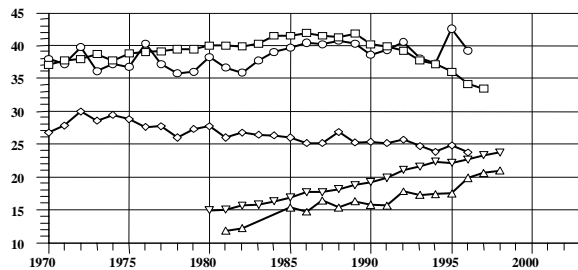
**Fig. 24(2).** Cancer mortality rate over time and place (SDR) (Health for all 2000). A decrease in cancer mortality in Sweden has been observed beginning from 1976. In other countries this decrease occurred approx. 15 years later. The high cancer risk in Sweden (Fig. 25 (1)) is accompanied by lowest cancer mortality. This fact reflects the highest in EU survival of cancer patients in Sweden.

Female breast cancer incidence per 100000 (ASR)

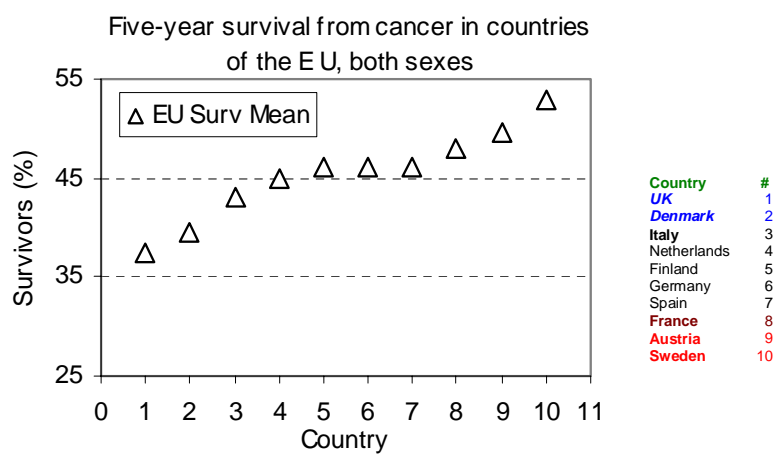


**Fig. 25(1).** Breast cancer incidence rate (ASR) over time and place (Health for all 2000). The rate is higher in more developed countries (UK, Sweden, Denmark) than in less developed ones (Russia and Kazakhstan). The increase in the rate appeared earlier in more developed countries than in less developed ones.

Standardized death rates (SDR) from female breast cancer (rate per 100000)



**Fig. 25(2).** Breast cancer mortality SDR over time and place (Health for all 2000). The mortality is higher in more developed countries. However, convergent time trends may change this situation soon. The rates increase in Russia and Kazakhstan but decline in Sweden and UK. An interpretation of these trends should take into account significant differences in survival from breast cancer between more and less developed regions.



**Fig. 26.** Survival of cancer patients in EU countries in 1996, both sexes and all sites combined (EUCAN 1999).