Patient Access to Cancer Drugs in Nine Countries in the Middle East

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Summary

This study presents and compares the introduction of and access to new innovative cancer drug therapies in nine countries in the Middle East: Bahrain, Egypt, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia and United Arab Emirates (note: when "Middle East" is mentioned this only accounts for the nine countries include in this report). The uptake of new cancer drugs in these countries is compared to the uptake in the US, the UK, France and a group of 13 European countries that together constitute the majority of the European pharmaceutical market. The objective is to give an overview of oncology drug access in the nine Middle East countries, and discuss differences in the availability of new cancer drugs to patients and causes of the observed variations between countries.

Spending per capita on pharmaceuticals in general, and on cancer drugs, is considerably lower in the Middle East countries as compared to Europe/US; a major reason for this is demographic, since the population in the Middle East is younger than in Europe and the US and the incidence rate of cancer is considerably lower. However, this study indicates that spending on oncology drugs per cancer case in several of the nine Middle East countries is comparable to the spending per case in Europe and the US. Specific analyses of drug sales per cancer cases for the five recently introduced cancer drugs trastuzumab, capecitabine, bevacizumab, erlotinib and rituximab show that the drug uptake curves for these five products in most of the Middle East countries covered in this report are comparable to in Europe and in some cases also in line with the drug uptake in the US. The time lag until drug uptake was seen in the Middle East was one year after the 2004 FDA approvals of bevazicumab and erlotinib, while available sales data indicated that time lags until drug uptake were from one to three years for rituximab, trastuzumab, and capecitabine following approval by the FDA in 1997-1998.

Based on comparisons of incidence and burden of cancer in relation to oncology drugs sales this study indicates that health care expenditure per cancer case both in exchange rate € and PPP-adjusted € in the Middle East countries is comparable to the expenditure in France and the UK. (With the exclusion of Egypt that with the lowest GDP per capita of the countries compared has limited economical possibilities to provide advanced cancer treatment to the population.) Calculations based on total oncology drug sales in relation to cancer incidence assess the cost of cancer drugs in relation to the total cost of cancer care in the Middle East countries to be approximately 30%, compared to 12% in UK and 25-27% in France and in the US.

When interpreting the findings presented in this report, one must take into account the high number of expatriates in some of the Middle East countries that do not always have access to health care on the same premises as the national population, and the fact that parts of the populations may be treated outside their country of residence; this makes it problematic to define the relevant population encompassed by available data and to assess the actual access to treatment for cancer.

Up to date, health economic evaluation has limited influence on health care resource optimisation in the Middle East countries. Yet it can be expected that thorough analyses of the cost-effectiveness of new treatments and health care approaches will increasingly guide the development of the health care systems and optimal use of health care resources in the Middle East in the future since the Middle East countries will face a transition towards treatment of chronic diseases, which makes it important to consider how health care systems and especially hospital budgets should be organized to accommodate the introduction of new treatments.

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1. Introduction

Rapid progress in basic research in the field of oncology during the last decades has resulted in the identification of a number of molecule targets for drug therapies. The prospective to develop drugs that attack or block such targets, and thereby inhibit specific pathways in the growth and development of tumours, have spurred increased investments in cancer research by the pharmaceutical industry.

The pharmaceutical industry spends an estimated €5-6 billion on cancer research worldwide every year, mainly in Europe and the United States, which represents approximately 10-12% of today's total pharmaceutical industry research expenditure [1]. Additionally, total public spending on cancer research worldwide has been estimated at about €11 billion in 2004 of which €5 billion in the US [2].

The investments in oncology research and development have led to the market introduction of a number of new cancer drugs in recent years. With few exceptions these innovative drugs have come at high prices. This, in combination with better informed patients, has created a new situation what regards the demand for, and access to, cancer treatments. Economic factors have gained increasing importance, and there has been a growing interest in using cost-effectiveness as a criterion for reimbursement and funding of new treatments.

This study compares and discusses the introduction of and access to new innovative cancer drug therapies in nine countries in the Middle East: Bahrain, Egypt, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia and United Arab Emirates (ME-9). It is a complement to, and uses the same methodology, as previously published reports covering Europe and the US [1] and a few other countries e.g. Australia, Canada, Japan, and South Africa in unpublished studies. Market uptake of new cancer drugs in ME-9 is compared to the market uptake in the US, the UK, France and a group of 13 European countries that together constitute the majority of the European pharmaceutical market: Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, and United Kingdom (referred to in this study as E-13). The objective is to give an overview of oncology drug access in the nine Middle East countries, highlight the difference in patient access to new cancer drugs and discuss the causes of the observed variations between countries.

There were several specific challenges in undertaking a comparator study for the selected Middle East countries. The countries differ in many respects, for example regarding economic and social factors, the size of the population, and in the structure of the health care system. Data on cancer and its treatment are scarce and have been collected from several sources which make comparisons and interpretation difficult. It is also sometimes problematic to define the relevant population for the data available, since different populations within a country have different access to health care; the high number of expatriates in some of the countries and the fact that parts of the populations are treated outside the country of residence make it difficult to assess the actual access to treatments for cancer.

Table 1-1 Country economic indicators

	Population 2006 [3]		GDP per capita 2006 (€) [3]		Health care exp share of GDP 2005 [4]	Health care exp per capita (€)	
	Total	nationals (%) [5]	Exchange rate	PPP		Exchange rate	PPP
Bahrain	749,000	65%	16,337	19,182	3.7%	604	710
Kuwait	3,096,000	35%	24,695	16,647	2.2%	543	366
Oman	2,599,000	75%	11,035	14,743	2.8%	309	413
Qatar	838,000	20%	50,145	29,197	2.5%	1,254	730
Saudi Arabia	23,697,000	80%	11,743	13,155	3.8%	446	500
United Arab Emirates	4,229,000	20%	30,776	27,186	2.6%	800	707
Total ME-6	**35,208,000**	**67%**					
Egypt	72,131,000		1,186	3,902	6.1%	72	238
Jordan	5,599,000		2,007	4,472	9.7%	195	434
Lebanon	3,703,000		4,891	4,603	11.2%	548	516
France	61,354,000		29,258	25,366	10.4%	3,043	2,638
United Kingdom	60,533,000		31,587	28,283	8.3%	2,622	2,348
United States	299,715,000		35,089	34,450	15.3%	5,369	5,271

Note. Economic statistics are generally based on the full population, including expatriates. It should be remembered that the income level is different between national and expatriates, as well as access to health care and health care consumption. PPP conversion takes into account the purchasing power of the currency, and is less influenced by fluctuations in exchange rates. It is often complicated to calculate PPP, and data availability will affect the estimates. A PPP conversion generally shows the income and consumption in countries with low incomes as higher than when presented based only on the exchange rate, while the opposite is true for high income countries.

The studied countries will in some presentation be divided into two groups; the Gulf States (ME-6) and Egypt, Jordan and Lebanon (ME-3).

In the Gulf States, with a total resident population of about 35 million, whereof 23 million are nationals and 12 million expatriates (see table 1-1), the high expatriate share of the population has important consequences for health status and health care consumption. The expatriates are often young, and stay in the country for a limited time only. Their entitlement to and use of health care services is in most cases also different from that of the nationals. The Gulf States have GDPs per capita of the same range as found in Europe, €13,000-30,000 PPP per capita.

Egypt, with 72 million inhabitants, and Jordan and Lebanon with populations approaching 6 million and 4 million respectively, have GDPs per capita on the range of €4,000-5,000 PPP. Lebanon and Jordan, and to some extent also Egypt, have a relatively high share of GDP devoted to health care, considering their GDP per capita, 10-11% in Jordan and Lebanon and 6% in Egypt. The Gulf States spend a much smaller share of their GDP, 2-4%, on health care. Thus, the per capita spending on health care varies much less than the income levels between the two groups, ME-6 and ME-3. Nevertheless, in terms of affordability for new therapies, there is a major difference between the ME-6 countries and the ME-3 countries, which is one reason we have made this grouping.

One explanation for the low rate of spending in the Gulf States is that the countries are high-income countries with a relatively young population, that do not consume as much health care as the older populations. The average PPP-adjusted health care spending per capita in ME-6 is less than one fourth of that in France/the UK and just over 10% of the per capita expenditure on health care in the US. Another reason is probably the high proportion of expatriates in the

population. The population growths in some of the Gulf States are among the fastest in the world due to the large influx of expatriated workers. Therefore, different population estimates are used for the different calculations in the report in order to relate to the particular year of the other data analysed. In some cases the whole population is used and in other cases only nationals, this is in each case specified.

All currency values in the report are presented in € nominal values. Due the considerable fluctuation in the exchange rate of US$ to the € during the period covered in the report, the exchange rate for the year of the reported value has been used, e.g. the average exchange rate US$ - € for 2006 for any 2006 figure presented.

2. Cancer epidemiology

Each year there an estimated 11 million new cancer cases worldwide and approximately 7 million deaths due to cancer. Out of these cancer cases approximately 45% occur in Asia, 26% in Europe, 15% in North America, 7 % in Central/South America, 6 % in Africa and 1% in Oceania [6]. These estimates are based on Globocan 2002, which is the most recent assessment of worldwide cancer incidence. In this chapter, data on cancer incidence in the Middle East countries, based on local and regional cancer registries as well as Globocan 2002 will be presented. The national cancer registry data available are for most of the countries more recent than the Globocan estimates. However in some of the study countries (ME-6) it does not cover the entire population residing in the country: expatriates are not included in the statistics. Moreover, there are limited cancer incidence data available from Egypt, since registration of cancer cases has only been implemented in one region of the country, encompassing only 5% of the total population. Therefore both national registry data and Globocan estimates will be presented, and are use as basis for analyses in the study.

Table 1-2 presents an overview of the cancer incidence data. Lebanon has the highest cancer incidence in ME-9. The crude cancer incidence in Lebanon is approximately twice the average of the other countries. This can not be explained by demographic reason, since the Lebanon population is among those with the highest share of young people among the study countries (see demographic overviews figures 2-27 and 2-28). On the other hand, the considerably higher incidence rate of cancer in the comparator countries, France, the UK, and the US, may to a large extent be explained by demographic factors; the population in ME-9 is about the same as France and UK together, but the estimated total number of cases of cancer according to Globocan estimates is only about 80,000 compared to 550,000 in the two European countries. When comparing the national registry data, the average incidence rate in France, the UK and the US is more than six times as large as the average in ME-9.

As can be seen in the table below, the national estimates of total number of cancer cases are for the ME-6 countries considerably lower than the figures from Globocan. They are not directly comparable since the national registry data in most cases only take into account nationals while Globocan made estimations based on the entire population of the countries. For Saudi Arabia, the total number of cases according to the national cancer registry was 7,453 in 2001, including both Saudi nationals and expatriates, as compared to an estimate of 16,437 in Globocan. For Oman, the number of reported cancer cases was 930 in 2005, (6% of these cases were reported in expatriates), Globocan estimated 1,421 cases in Oman in 2002. National registries also report lower incidence rates than Globocan in some ME-6 countries, the difference is most pronounced in Saudia Arabia and United Arab Emirates. The cancer incidence rates in Bahrain and Qatar correspond fairly well to Globocan estimates while the incidence rate in nationals in Kuwait is higher than what Globocan estimates in the whole population.

On the other hand the cancer incidence rate of Egypt based on the population registry of the Gharbati region is considerable higher than the Globocan estimates. The national cancer registry of Lebanon includes Palestinians residing in Lebanon in the registry data, this may partly explains the higher estimates of total number of cases, as compared to Globocan however the incidence rate reported in the national registry is also significantly higher. It is unclear whether the inclusion of Palestinians residing in Lebanon is the reason the Lebanon cancer registry estimates the population of Lebanon to 4.4 million, while the World Bank (see table 1-1) and other sources consulted estimates the population to 3.7 million. The national estimates of cancer cases for Jordan are the only ones that correspond well with the Globocan estimates.

Table 2-1 Comparison of national cancer registries and Globocan 2002 estimates - cancer cases and total incidence rate in the study countries

	National/Regional sources				GLOBOCAN 2002	
	Source, Year	Total cases	Cases/ 100,000	Population basis	Total cases	Cases/ 100,000
Bahrain	Gulf Center for Cancer Registry[7], 1998-2002 average	379	95.2	nationals only: 398,221	612	90.0
Kuwait	Gulf Center for Cancer Registry [7], 1998-2002 average	594	71.9	nationals only: 826,083	1,393	57.6
Oman	Ministry of Health [8], Cancer Incidence in Oman 2005	nat:876 exp:54 tot:930	nat:45.7 exp:8.1 tot:35.6	nationals: 1,845,684+ expatriates: 666,153	1,421	58.1
Qatar	Gulf Center for Cancer Registry [7], 1998-2002 average	151	85.2	nationals only: 177,715	620	90.0
Saudi Arabia	Ministry of Health [9], Cancer Incidence Report Saudi Arabia 2001	nat:5,691 exp:1,762 tot:7,453	nat:35.4 exp:32.0 tot:34.6	nationals: 16,056,470+ expatriates: 5,505,209	16,437	75.0
United Arab Emirates	Gulf Center for Cancer Registry [7], 1998-2002 average	300	38.4	nationals only: 782,376	2,737	76.2
Total ME-6		**9,807**			**23,220**	
Egypt	Middle East Cancer Consortium [10], 1999-2001 average	*3,485*	99.8	Gharbiah region: 3,491,875	47,776	69.2
Jordan	Ministry of Health [11], Cancer Incidence in Jordan 2004	3,591	67.1	total population: 5,350,000	3,503	68.7
Lebanon	Ministry of Public Health [12], Cancer in Lebanon 2003	7,888	174.3	permanent residents+ Palestinian residents: 4,449,573	5,182	134.0
Total ME-9					**79,681**	
France	Institut de Veille Sanitaire [13], 2005	316,380	525.3	60,825,000	268,742	448.6
United Kingdom	Cancer Research UK [14], 2004	284,560	476.0	59,780,500	276,590	465.5
United States	United States Cancer Statistics [15], 2004	1,342,126	471.6	288,095,510	1,432,340	492.5

We will discuss the estimates further in the following sections of this paper. But the different estimates presented points to a general problem to document the actual number of diagnosed cases, and arrive at a good estimate of undiagnosed cases; a reason for the differing figures is that Globocan present estimates of the number of cancers occurring while cancer registries present the actual number of diagnosed cases, if there for example is no post-mortum diagnosis of cancer in a country this may lead many cases never being recorded and not taken into account in cancer registries.

2.1. Distribution of cancer incidence and mortality in ME-9, Europe (E-13) and the US

In the ME-9 countries the five cancer forms with highest estimated incidence rates are, according to Globocan: bladder, breast and lung cancer, leukaemia and colorectal cancer, with most deaths caused by bladder, breast, lung cancer, leukaemia and liver cancer in the order mentioned. Breast cancer, lung cancer and leukaemia are among the five most common cancer forms in eight of the nine countries, while bladder cancer and colorectal cancer are among the five cancer forms with highest incidence in six of the nine countries [6]. Particularly high relative incidence and mortality of bladder cancer were seen in Egypt. The high incidence of bladder cancer is due to infection of a parasitic worm, Schistosoma haematobium, common in the region.

The proportional distribution of incidence and mortality (total cases) in 2002 [6] of the most common cancers forms are presented for ME-9, ME-6, ME-3, E-13 and US (figures 2-1 to 2-5). Incidence and mortality are also presented for the nine Middle East countries separately (figures 2-6 to 2-14).

Figure 2-1 Cancer incidence and mortality - proportion of different cancer forms: ME-9

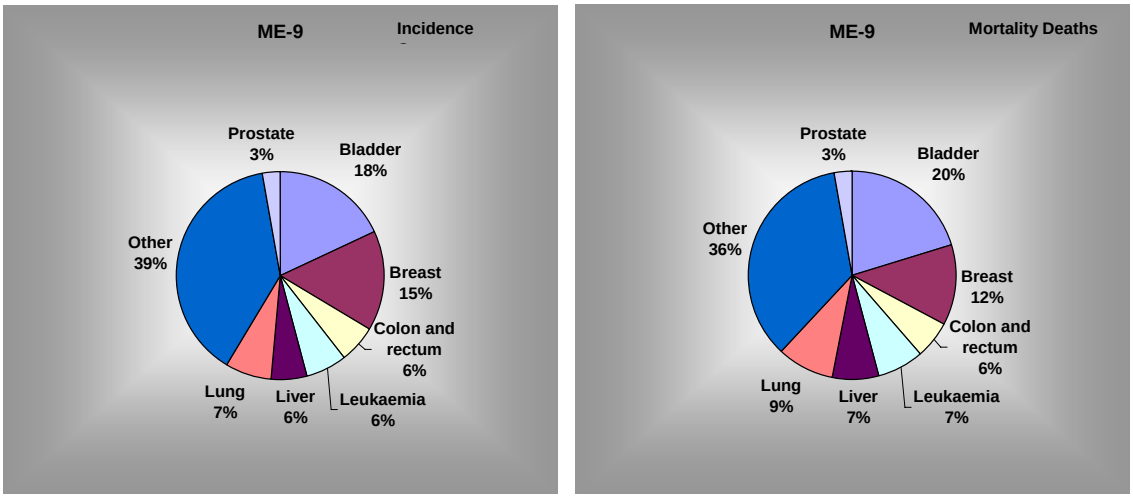


Figure 2-2 Cancer incidence and mortality - proportion of different cancer forms: ME-6

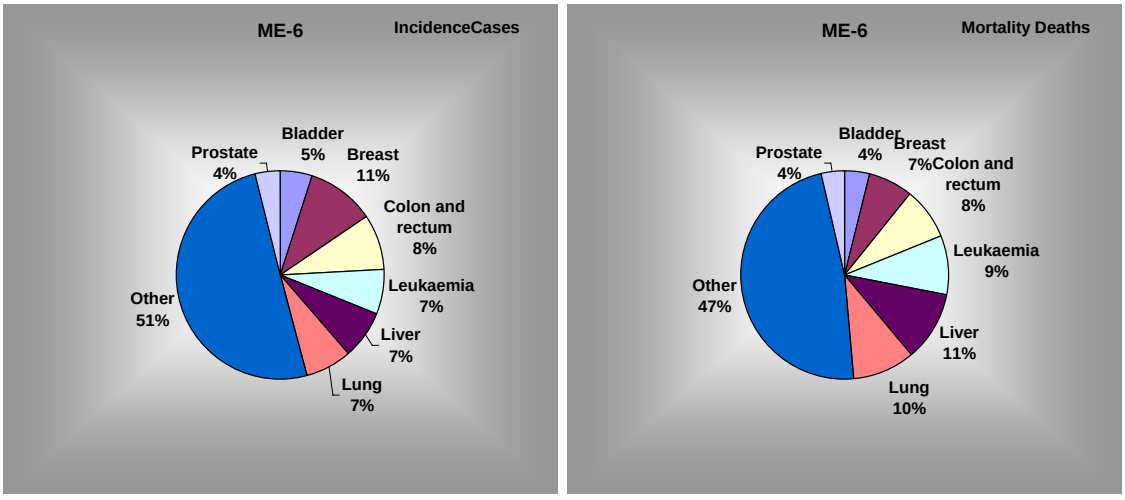


Figure 2-3 Cancer incidence and mortality - proportion of different cancer forms: ME-3

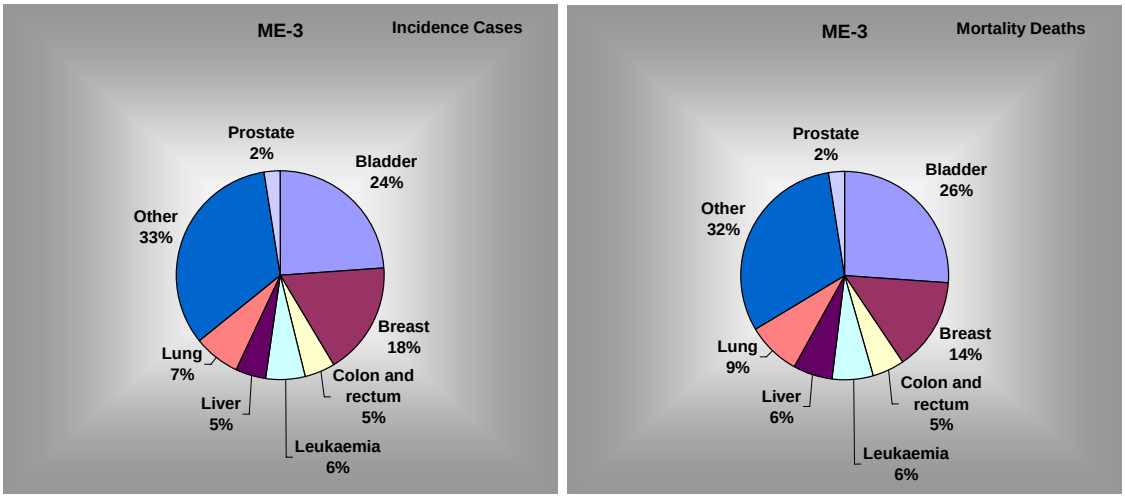


Figure 2-4 Cancer incidence and mortality - proportion of different cancer forms: E-13

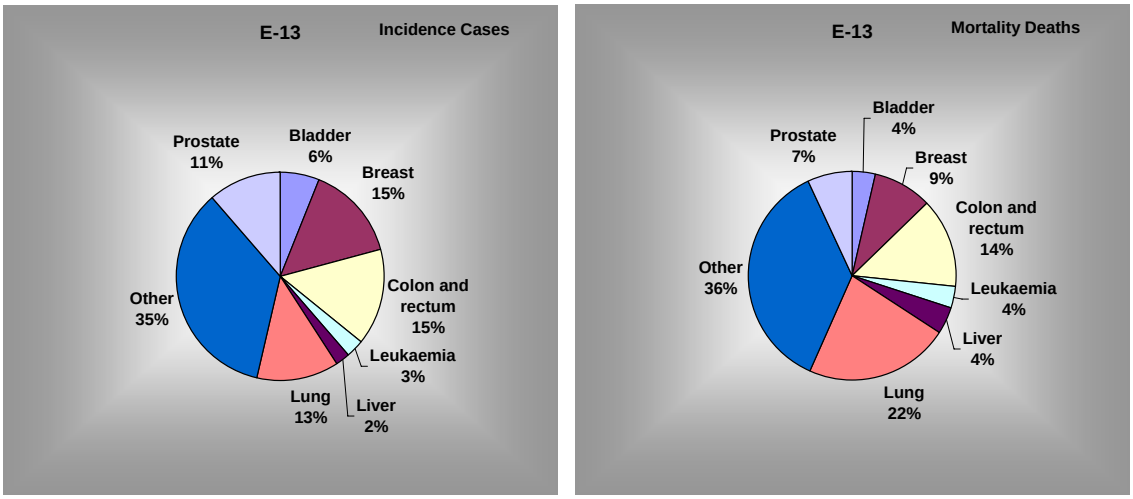
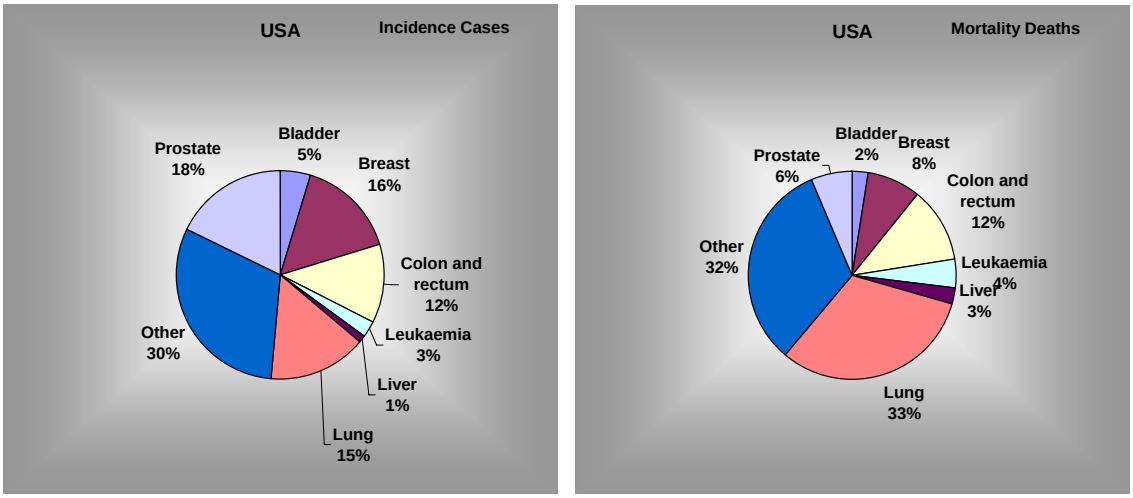


Figure 2-5 Cancer incidence and mortality - proportion of different cancer forms: US



The most marked differences between the Middle East countries and Europe/US are the lower rates of colorectal cancer and lung cancer in the ME-9 region as compared to in E-13 and in the US. Colorectal cancer and lung cancer are cancer forms that are mainly caused by lifestyle factors, they do affect middle age individuals although the great majority of cases are seen in individuals over 60-70 years of age. Thus demographic factors are probably the main explanation for the lower rate in the ME countries. In Europe most cases of colorectal cancer as seen in individuals over the age of 70 with a peak at 80-85 years, most cases of lung cancer occur in individuals older than 60 years with a peak at 70-80 years.

The share of breast cancer cases out of total cancer cases is the same in the ME-9 countries as in E-13 and the US, approximately 15%, the share is somewhat lower in ME-6 and higher in ME-3. Breast cancer generally occur in younger individuals than those affected by colorectal cancer and lung cancer, the risk of breast cancer increases significantly in women older than 55 years and thereafter remains relatively stable with a peak at. 60-70 years of age. As can be seen in the country-specific diagrams below, Globocan estimate breast cancer to be the most common cancer form in Bahrain, Kuwait, Jordan and Lebanon.

The high share of bladder cancer in the region is mainly due to the particularly high incidence of bladder cancer in Egypt (figure 2-12) which affects the overall distribution in the whole region due to the large population of Egypt.

In the ME-9 one third of cancer deaths are caused by bladder cancer and breast cancer, however this is to a great extent due to the dominance of these cancer forms in Egypt. When looking only at the ME-6 region, the three cancer forms causing the most deaths are liver cancer, lung cancer and leukemia, all together 30%. In E-13 one third of cancer deaths are due to colorectal cancer and lung cancer while in the US one third of deaths are caused by lung cancer alone.

Figure 2-6 Cancer incidence and mortality - proportion of different cancer forms: Bahrain

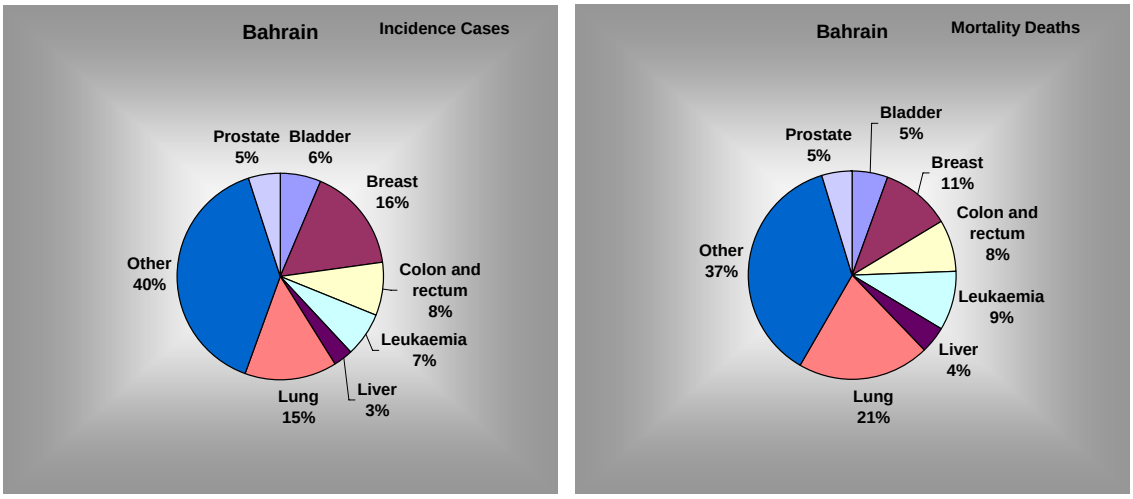


Figure 2-7 Cancer incidence and mortality - proportion of different cancer forms: Kuwait

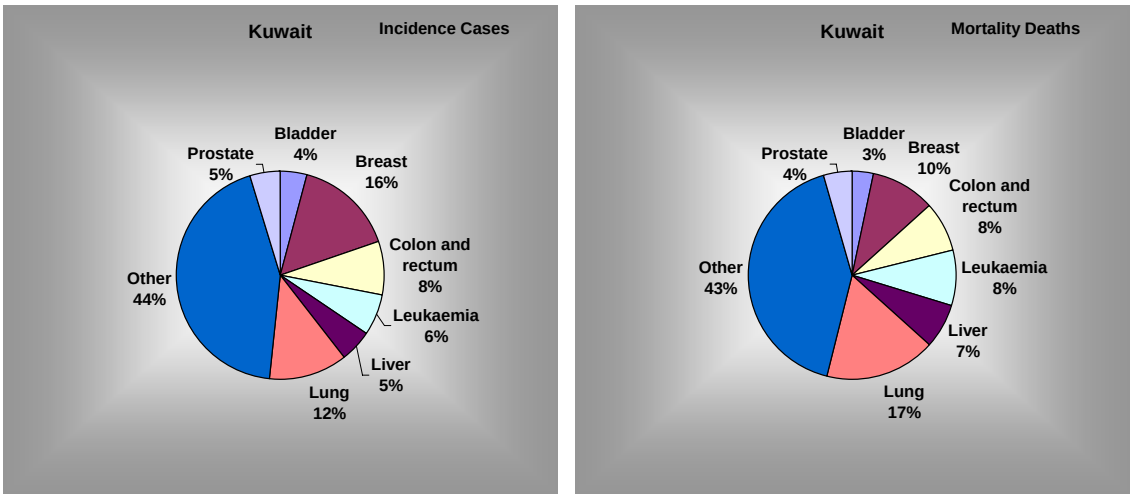


Figure 2-8 Cancer incidence and mortality - proportion of different cancer forms: Oman

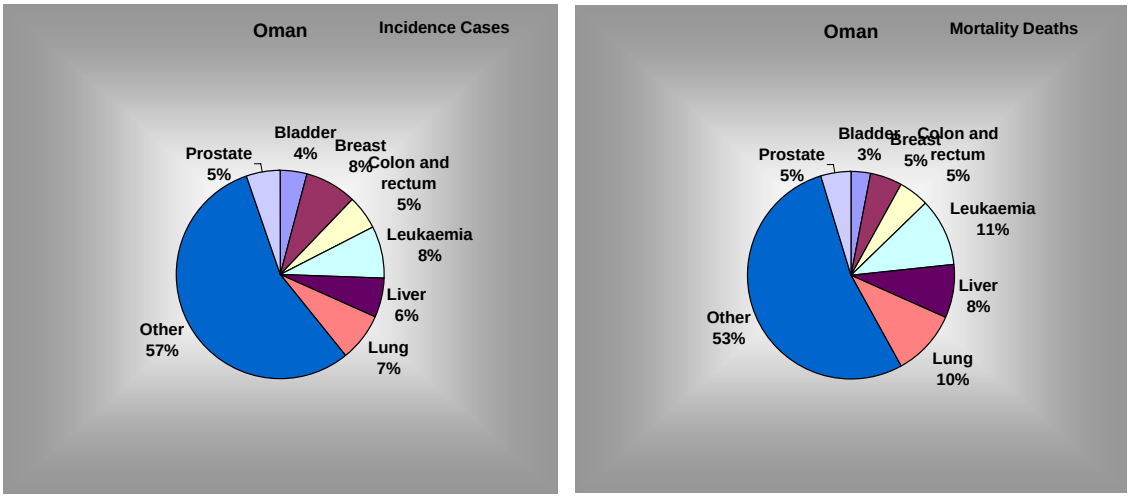


Figure 2-9 Cancer incidence and mortality - proportion of different cancer forms: Qatar

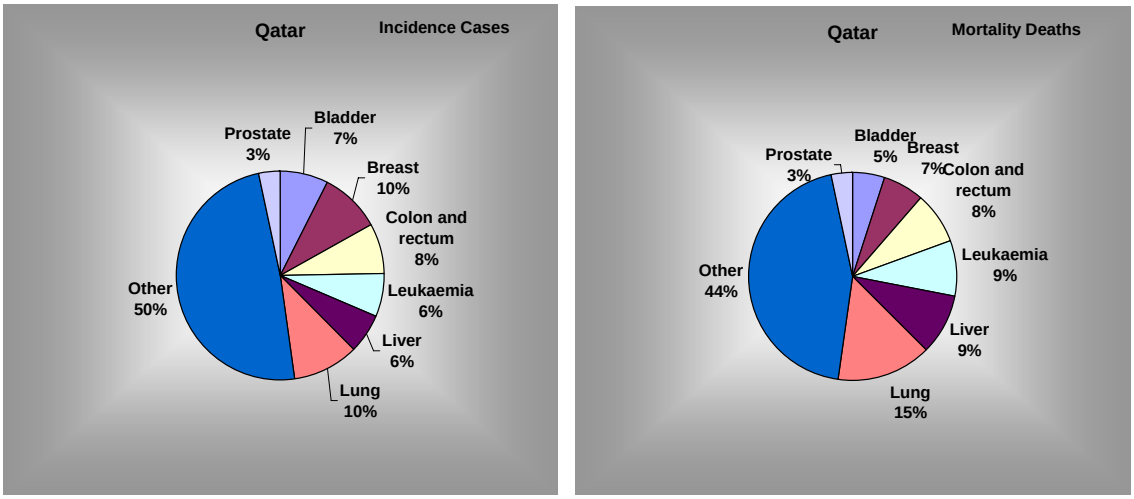


Figure 2-10 Cancer incidence and mortality - proportion of different cancer forms: Saudi Arabia

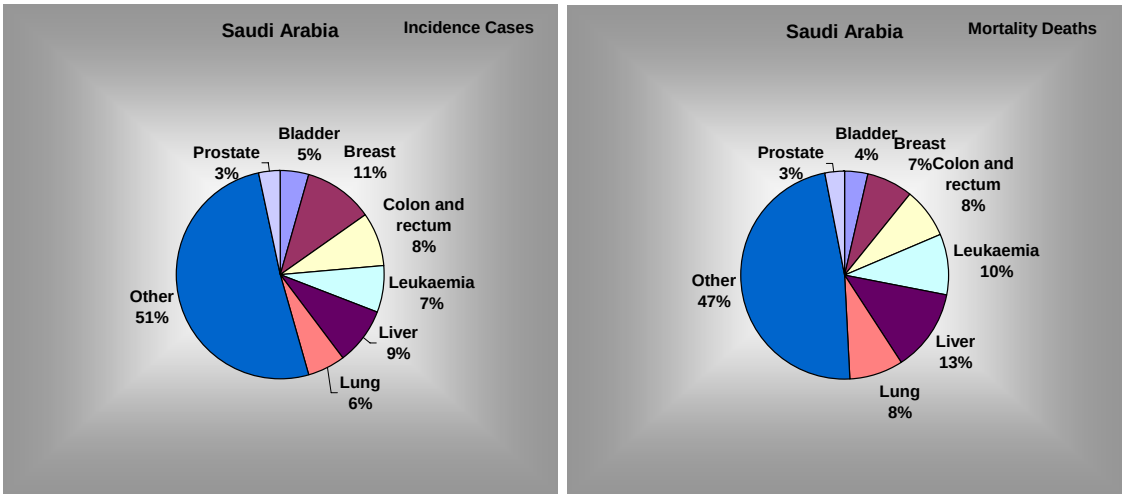


Figure 2-11 Cancer incidence and mortality - proportion of different cancer forms: United Arab Emirates

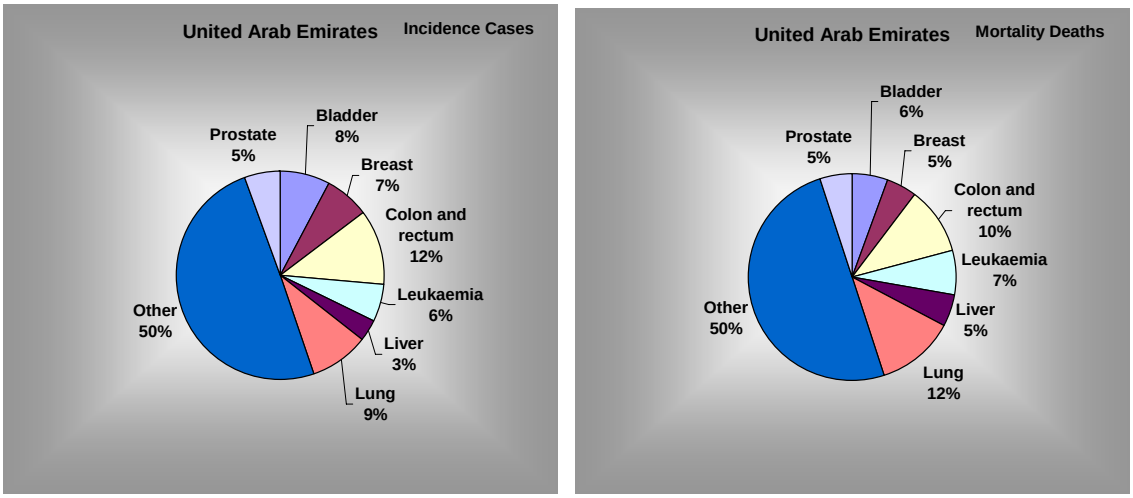


Figure 2-12 Cancer incidence and mortality - proportion of different cancer forms: Egypt

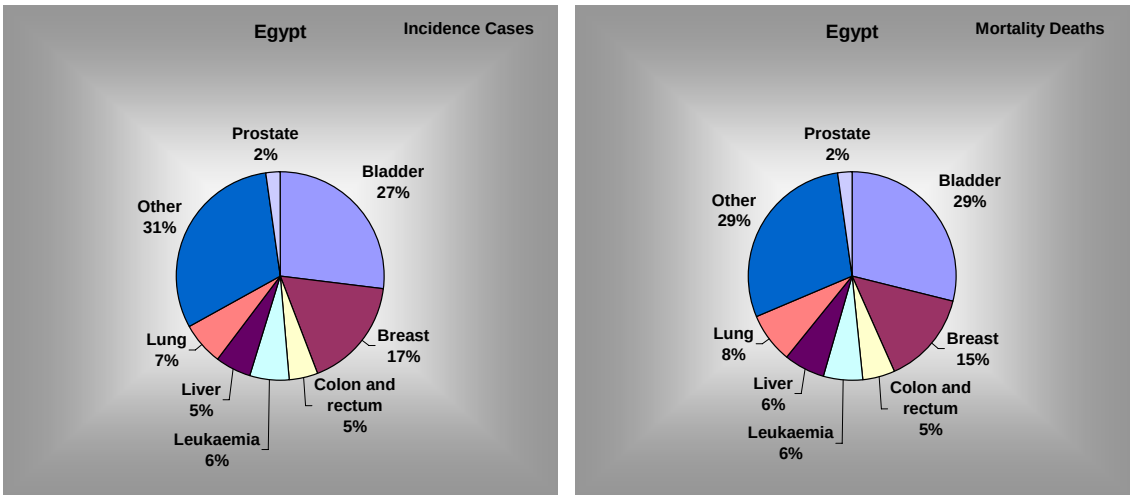


Figure 2-13 Cancer incidence and mortality - proportion of different cancer forms: Jordan

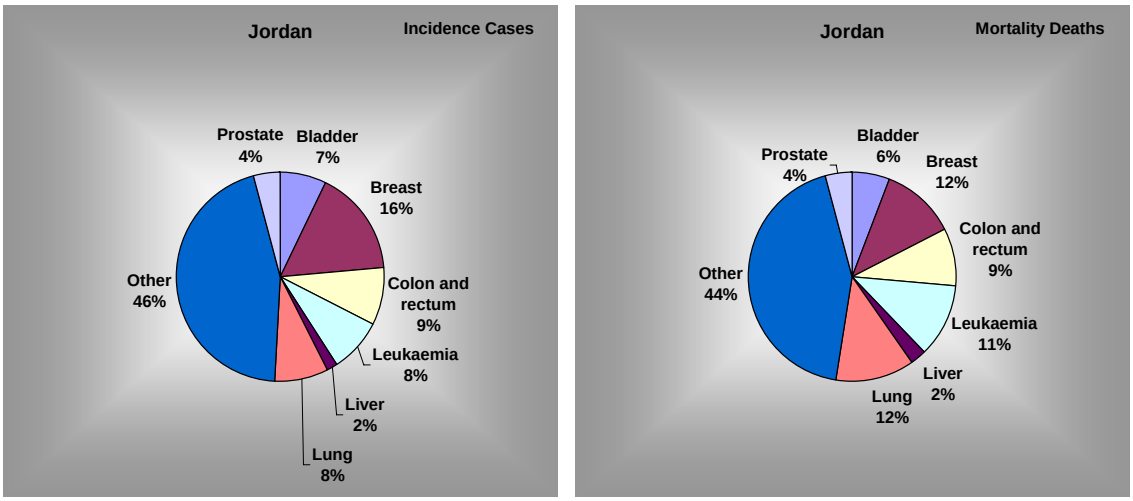
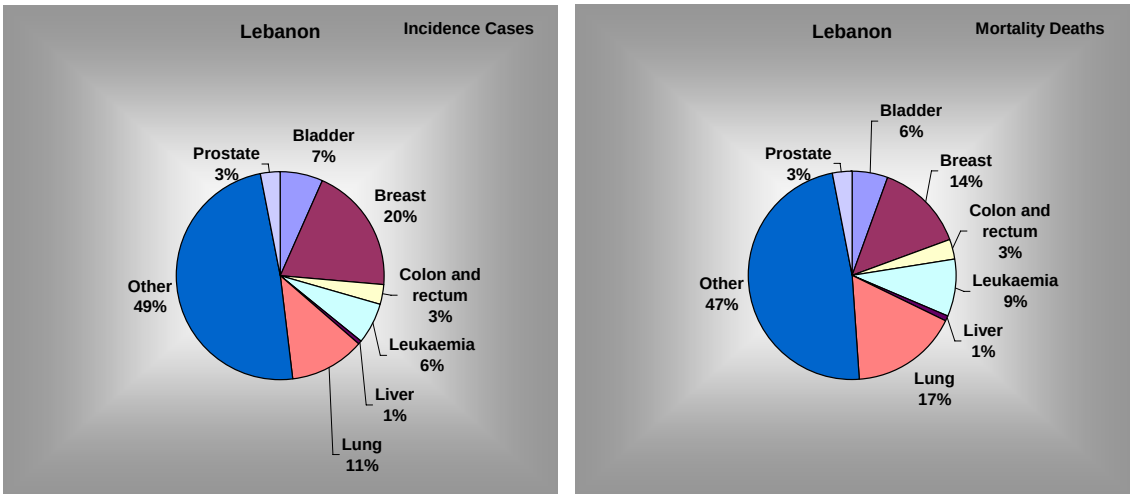


Figure 2-14 Cancer incidence and mortality - proportion of different cancer forms: Lebanon



The country specific diagrams show that the relative distribution of the seven major cancer forms presented in the diagrams are relatively evenly distributed in many of the ME-6 countries, with lung cancer and breast cancer dominating in Bahrain and Kuwait. As previously commented, bladder and breast cancer constitute close to half of cancer cases in Egypt, in Jordan breast cancer, colorectal cancer, leukemia and lung cancer are the dominating forms and in Lebanon, breast cancer, leukemia and lung cancer.

2.2. National cancer registry data

Incidence data from national and regional registries were found to be available to various extents in the study countries. For the Gulf region countries, the most complete data source identified was a report from 2006 by the Gulf Center for Cancer Registration presenting the five-year cancer incidence in the Gulf countries for the period 1998-2002 [16]. The data was complemented for some countries with estimates presented by the Eastern Mediterranean Regional Office (EMRO) of the World Health Organization for 1998, the fact that data was combined from different sources explains the inconsistency of some of the time-series graphs below, for example for Bahrain [11]. 1999-2001 data from Saudi Arabia was taken from National Cancer Incidence reports [9, 17]. The most complete incidence data were found for the Oman

population; Cancer Incidence in Oman is available for the period 1996-2005 [8]. The data from the Gulf Center for Cancer registration only covers nationals (approximately 67% of the total population in the Gulf countries). Saudi Arabia and Oman Cancer Incidence Report present the statistical data separately for national and non-nationals, with a higher level of detail for the nationals, therefore cancer incidence estimates in the Gulf countries presented below cover nationals only when not indicated otherwise.

Since there is no national cancer registry in Egypt, the 1999 age-adjusted incidence rate estimates are based on the Gharbiah region registry [18], which covers approximately 5.7% of the Egyptian population, and from an international comparative study that assessed the average age-adjusted cancer incidence rates in Egypt 1999-2001, based on extrapolation from the Gharbiah registry [10].

Data from Jordan were taken from the reports Incidence of Cancer in Jordan 2001-2004 [19] as well as from two publications comparing cancer Incidence in Jordan with other countries in the region [10, 20]. In Jordan, the national population-based cancer registry collects data on cancer from hospitals and pathology and haematology laboratories, all diagnosed malignancies have been registered nation-wide since 1996. Death certificates however are not used as an additional source of notification of cancer cases in Jordan. The Jordan Cancer registry also divide the cancer cases presented in Jordanians and non-Jordanians, however the non-Jordanians are not expatriates but non-residents referred from neighbouring countries to receive health care in Jordan. In 2004, 17% of the 4333 cancer cases registered in Jordan were in non-residents. The statistics presented above only take into account the cases that were registered in country residents.

Lebanon incidence data sources are the report Cancer in Lebanon 2003 [12], and publications from the American University of Beirut Medical Center Tumor Registry [21]. The cancer registry in Lebanon's first report covered cases captured in 2002 by passive routine surveillance procedures, while the report published for 2003 was based on passive data capturing and "active recapture" and extrapolation techniques.

2.3. Cancer incidence trends over time

Figures 2-15 to 2-22 summarise age-adjusted cancer incidence rates over time for some of the most common cancer forms based on data from national registries. Incidence of the most common cancer forms in the study countries given as crude incidence rates per 100.000 inhabitants. (All cancers women, all cancers men, lung women, lung men, breast women, bladder men, colorectal women, colorectal men, leukaemia women, leukaemia men). For Saudi Arabia data is presented for national and non-nationals separately, in most cases crude incidence rates did not differ considerably between nationals and non-nationals in Saudi Arabia.

Figure 2-15 All cancers women

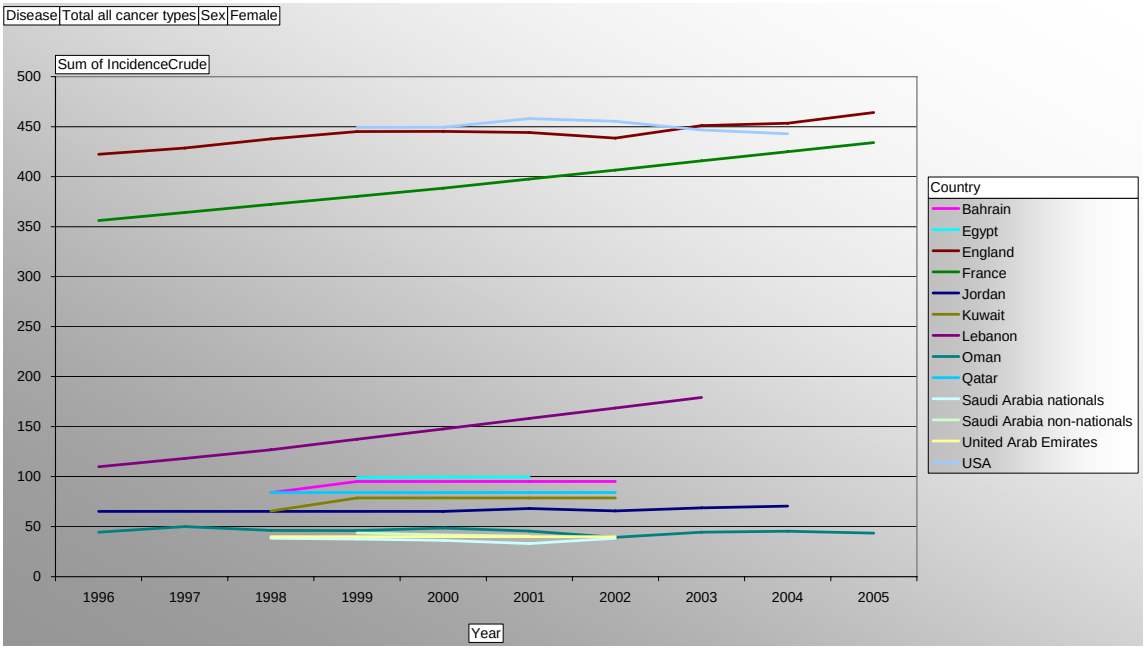


Figure 2-16 All cancers men

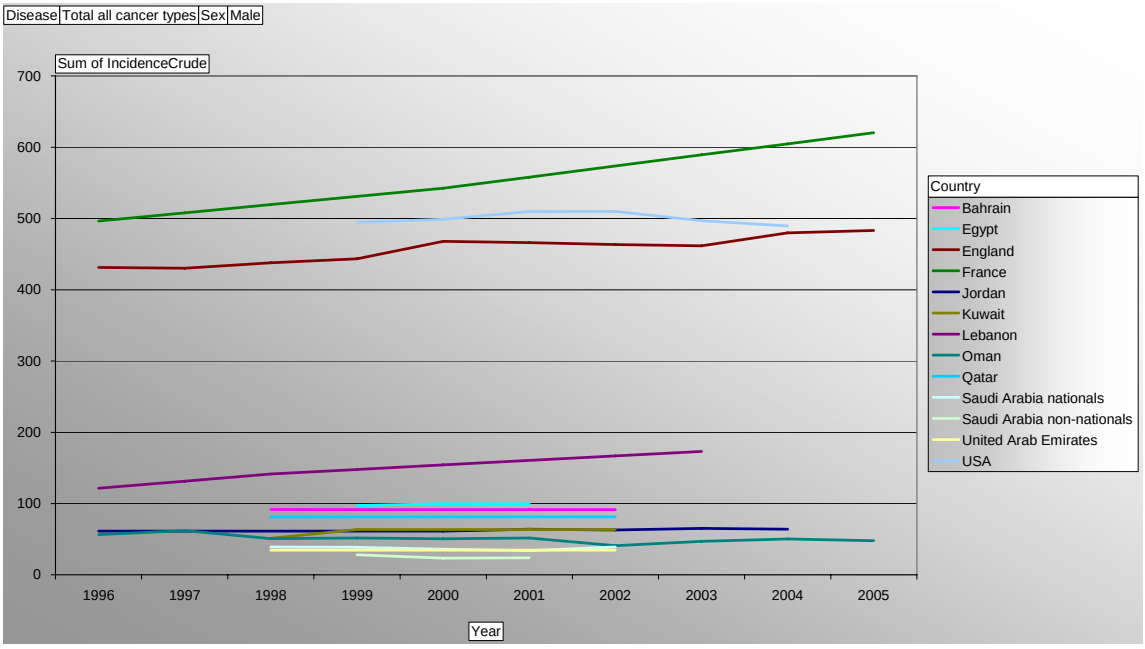


Figure 2-17 Breast cancer women

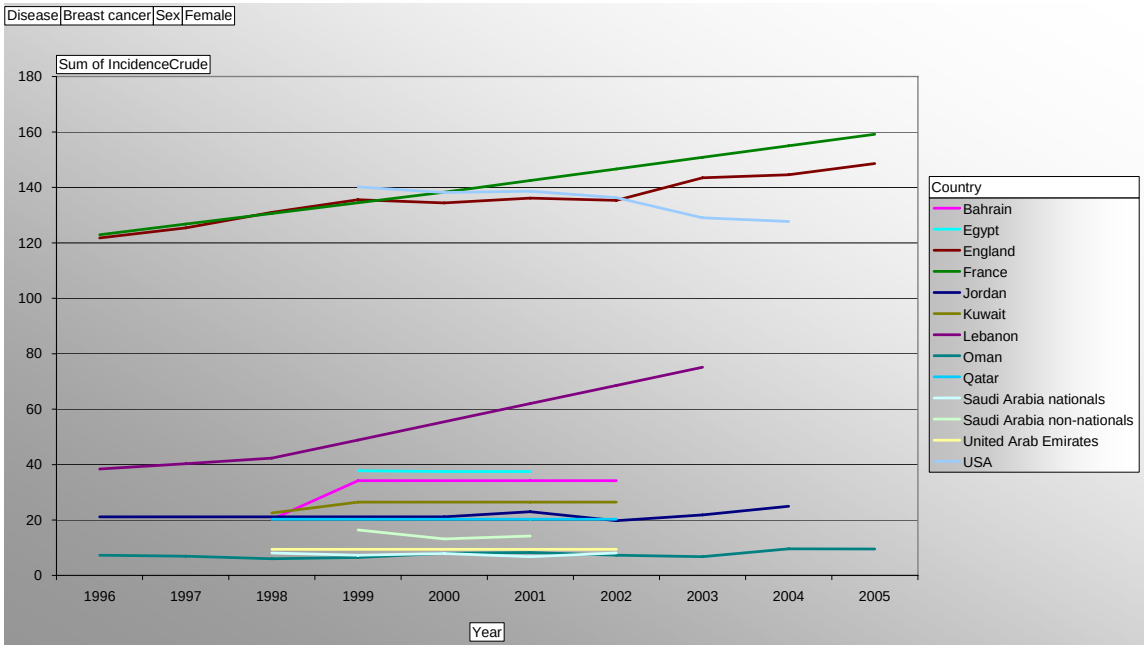


Figure 2-18 Bladder cancer men

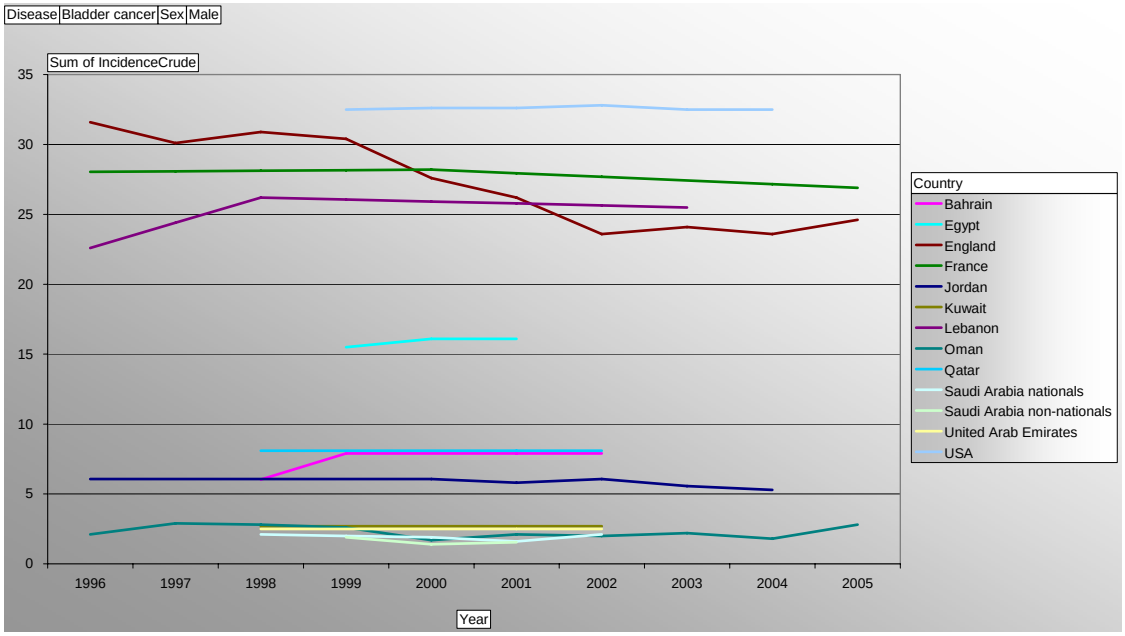


Figure 2-19 Lung cancer women

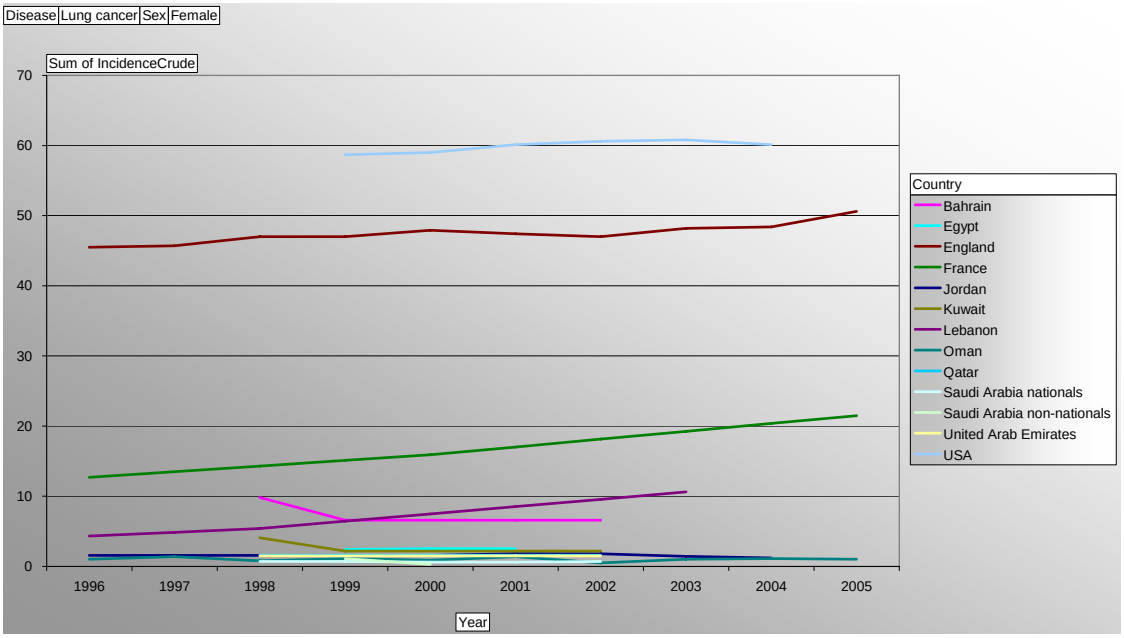


Figure 2-20 Lung cancer men

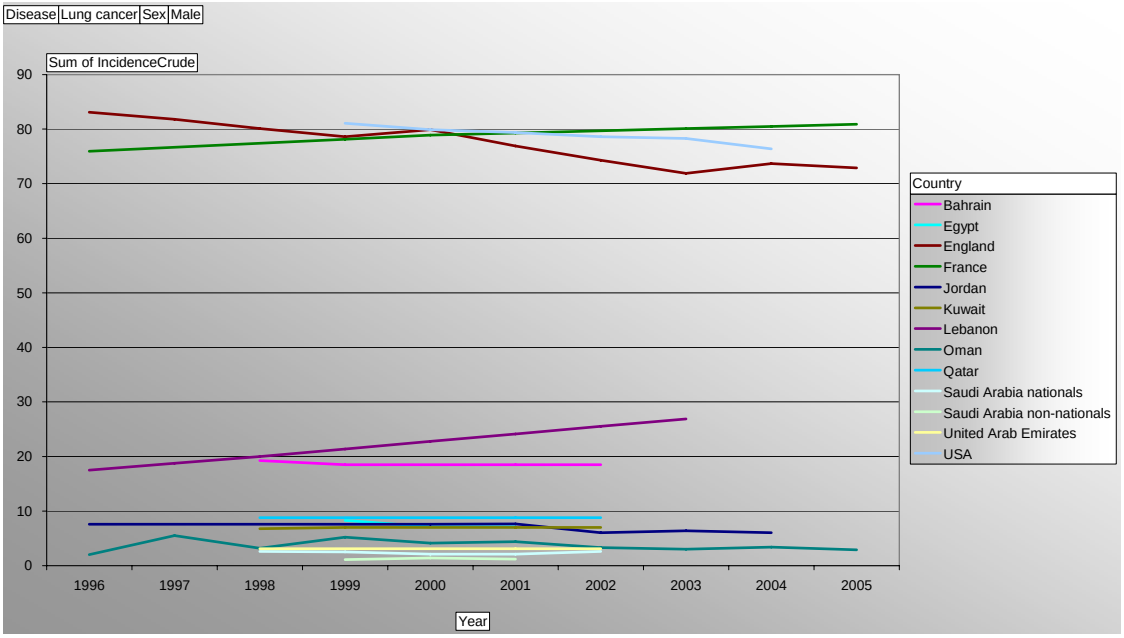


Figure 2-21 Colorectal cancer women

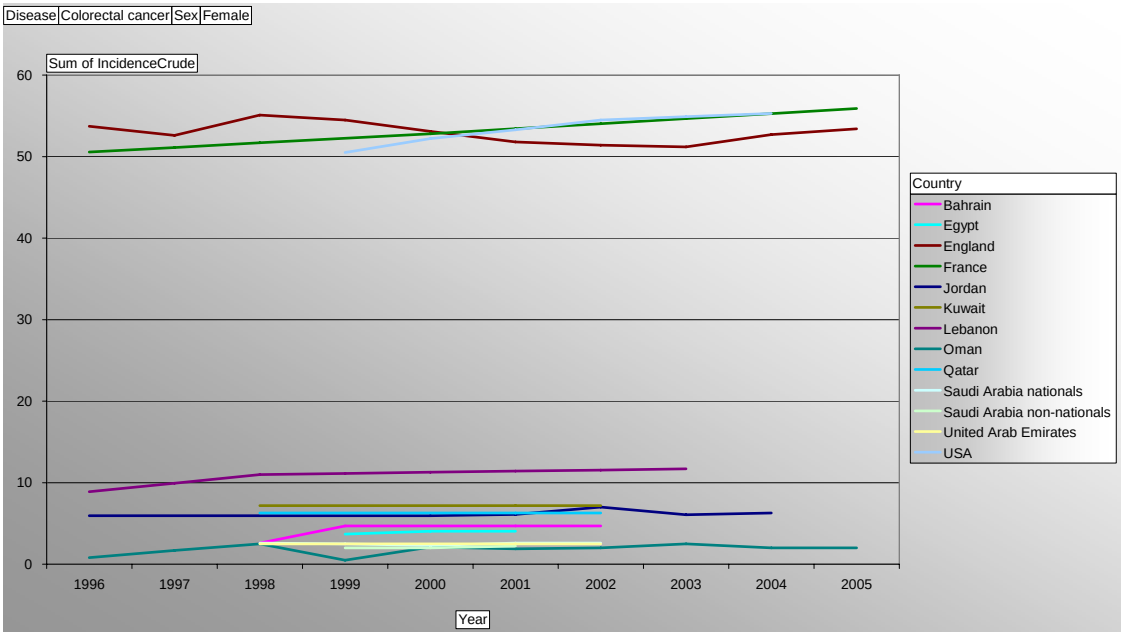


Figure 2-22 Colorectal cancer men

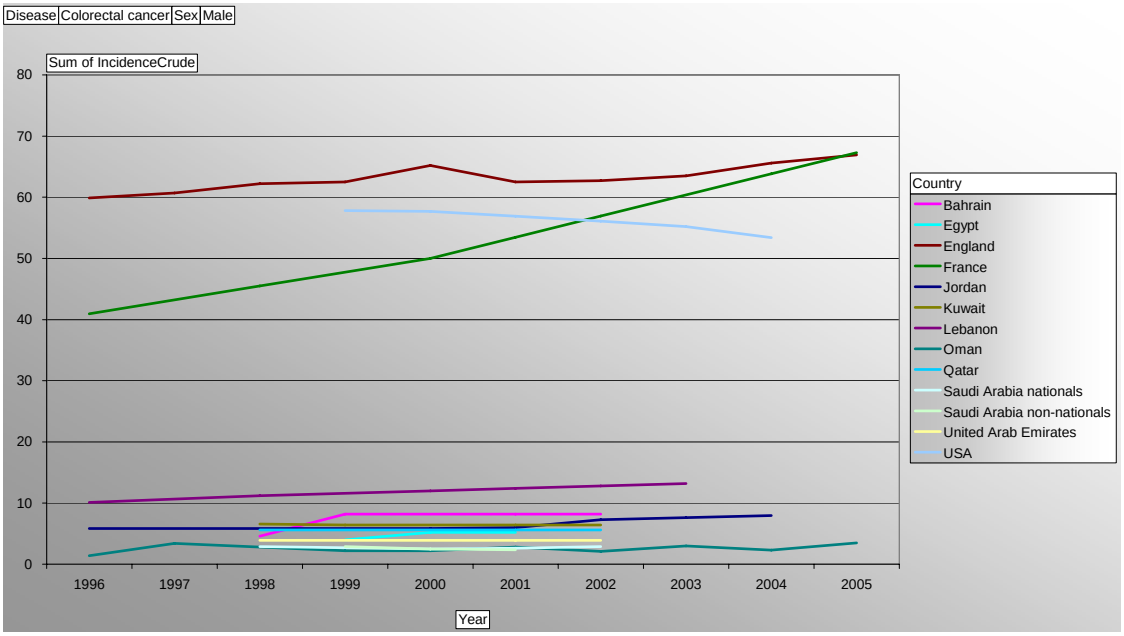


Figure 2-23 Leukemia women

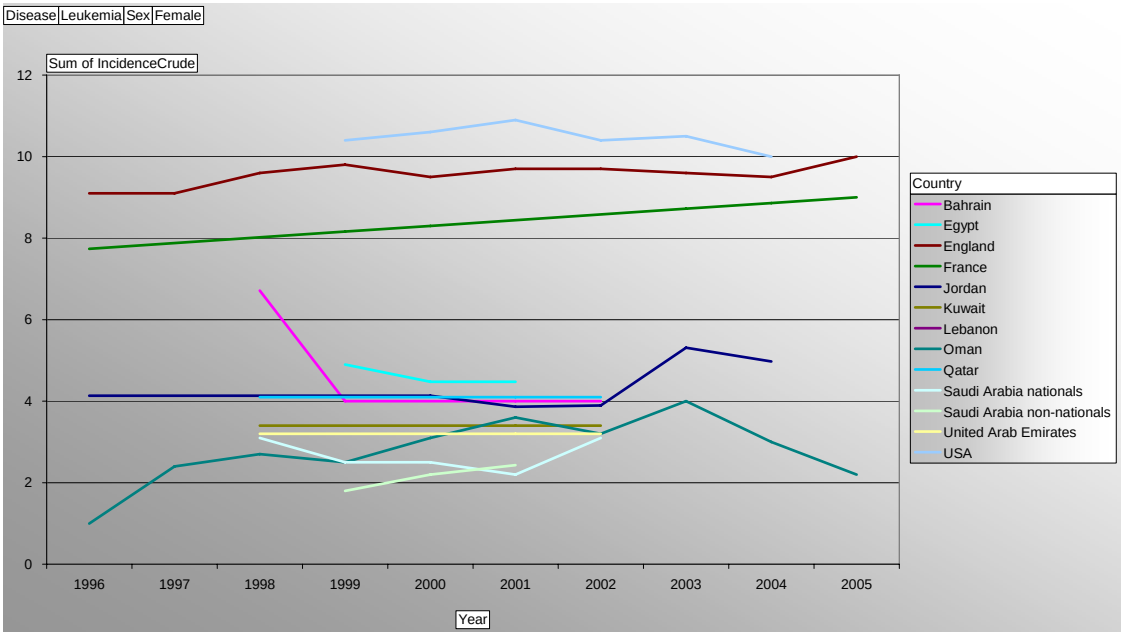


Figure 2-24 Leukemia men

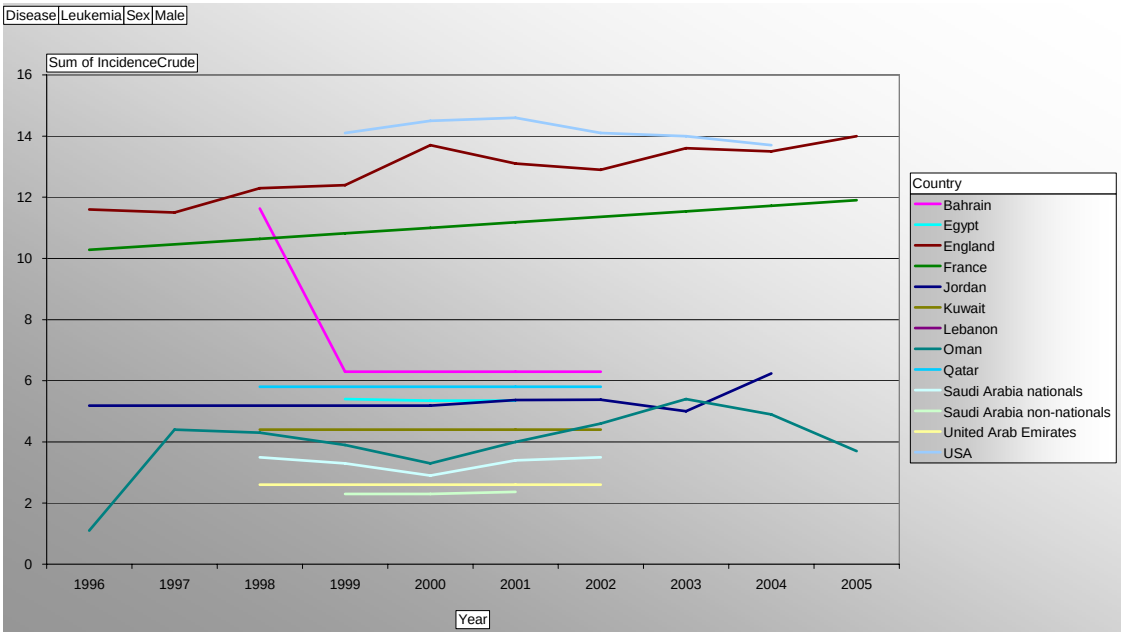
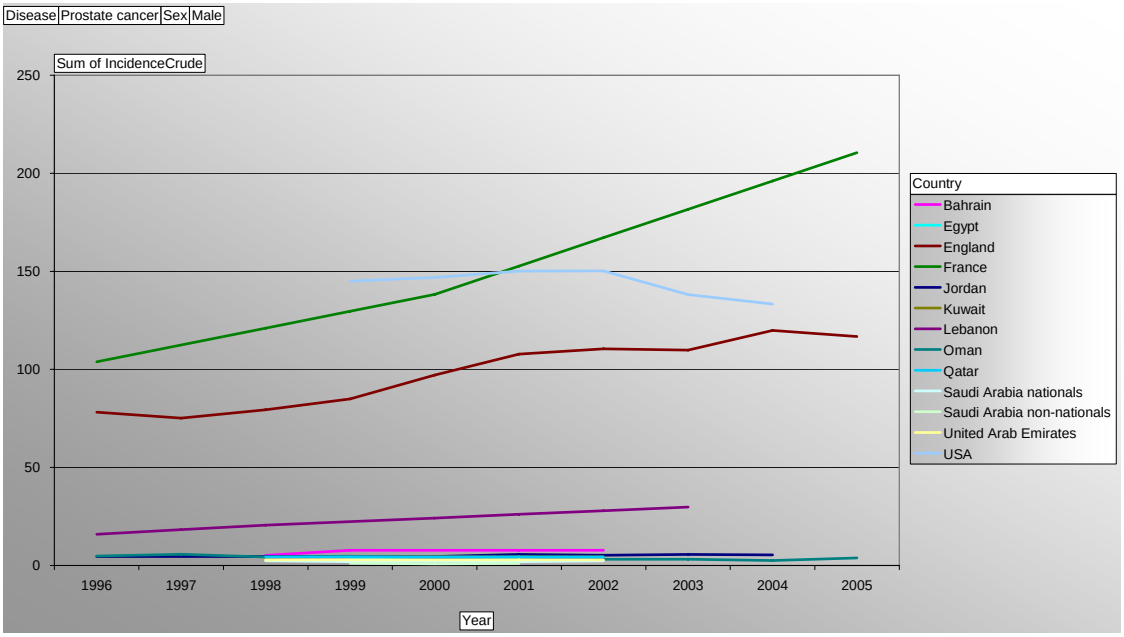


Figure 2-25 Prostate cancer men



In general, cancer incidence rates in the Middle East countries appear to have been rather constant over the up-to-10 year period presented, although for some countries (Bahrain, Kuwait, Qatar, United Arab Emirates, Egypt) it is difficult to draw conclusions about tendencies of decrease or increase in cancer incidence over time since data from these countries was only obtained as an average over several years. Yet, the curves for Jordan, Oman and Saudi Arabia are based on year-specific estimates and show likewise stable incidence trends over the time period. Lebanese incidence data show increased rates for some cancer forms, such a breast cancer and lung cancer in men over the period presented. It should be noted that in some cases rather steep shift are seen when data is combined from different sources but this may be due to other factors than an actual shift in incidence from one year to the next, such as the data coverage.

For most of the cancer forms presented above the differences are large between the Middle East countries and Europe/US. An important reason for this as already commented are the differing demographic structure of the countries (demographic structures for the study countries are presented in table 2-27).

Bladder cancer is the only cancer form where crude incidence rates in some Middle East countries, Lebanon and to a certain extent Egypt, approach those seen in Europe/US. Overall, according to national cancer registry data there are 10 times as many cancer cases per 100,000 individuals in the populations of France, England, the US as compared to in ME-9 (calculated as the sums and ratio of incidences rates per country, in order not to be dominated by the weight of the population). There are close to 10 times more cases of breast cancer in the populations in Europe/US and almost 20 times as many cases of colorectal and lung cancer. The rate of prostate cancer incidence is 30 times higher in France, England and the US as compared to in the ME-9. The incidence rates of leukaemia do not differ as much as the other cancer forms presented between Europe/US as compared to the Middle East countries, incidence rates are on average 3-5 times higher in Europe/US than in ME-9. Although leukaemia is one of few cancer forms that occur in children, the great majority of cases occur in individuals older than 65 years of age thus there seem to be a high incidence of leukaemia in the Middle East also when adjusting for demographic factors. Table 2-2 presents the age-adjusted incidence rate of the cancer forms presented in the diagrams above. Age-adjusted incidence rates have been adjusted

in order to exclude the demographic influence between countries in order to better be able to spot other epidemiological trends in cancer incidence. With age-adjusted rates, the incidence of leukaemia, bladder and breast cancer are 2-3 times higher in France/US as compared to ME-9, colorectal cancer and lung cancer in men 4 to 5 times higher, lung cancer in women 9 times higher and prostate cancer 12 times higher. Age adjusted incidence rates of all cancers are 4 to 5 times higher in France/US as compared to ME-9. Incidence rate for UK are not included since age-adjusted incidence rates for UK in relation to the world population were not found. Table 2.2 gives an overview of the age-adjusted incidence rates of cancer in the study countries.

Table 2-2 Age-adjusted annual incidence rates per 100,000 for the most common cancer forms in the study countries (Most recent estimate available for each country)

Country	Year	All cancers**		Breast	Bladder	Lung		Colorectal		Leukaemia		Prostate
		women	men	women	men	women	men	women	men	women	men	men
Bahrain	1998-2002*	140.2	154.6	46.4	14.4	12	34.2	7.3	13.5	4.4	8.7	14.1
Kuwait	1998-2002*	135.3	131.1	44.3	7	4.8	17	13.3	15.2	4	5.8	12.3
Oman	2005	93.4	110.0	19.9	7	2.4	7.5	3.6	8.6	2.9	4.8	10.7
Qatar	1998-2002*	159.3	151.7	35.5	16.2	4.2	18.8	14.1	11.6	5.4	9	9.4
Saudi Arabia	2001	58.2	59.0	11.8	2.9	1.4	4.1	5	4.9	2.8	3.9	9
Un. Arab Emir.	1998-2002*	79	66.9	19.2	5.3	3.7	7.2	5.5	8	3.7	2.7	6.4
Egypt	1999-2001*	135	152.6	49.6	27.5	3.7	11.9	5.1	6.9	5.3	6.7	7.5
Jordan	2004	112.6	112.5	24.9	5.3	1.2	1.8	6.5	8.2	5	6.2	5.3
Lebanon	2003	176.8	169.3	76.2	24.7	11.9	28.3	11.9	12.9	5.4	8.4	28.5
France	2005	434.2	620.4	101.5	14.6	37.4	50.5	24.5	37.7	5.5	8.1	121.2
United States	2004	419.0	568.0	117.7	37.3	54.2	85.3	42.7	58.2	9.1	15.2	145.3

**Annual average*
***Excluding ICD-10: C44 when specificed*

2.4. Deaths due to cancer

Cancer is estimated to be between the second and fourth cause of death in seven of the study countries. In Jordan and Lebanon cancer is second cause of death after circulatory disorders/ cardio-vascular diseases. Cancer is the third greatest cause of death in United Arab Emirates, after cardiovascular disease and accidental/injuries, likewise in Kuwait. In Oman, cancer is the third cause of death after diseases of circulatory system and infections and parasitic diseases, and in Bahrain cancer is the third cause of death following diseases of circulatory systems and "signs and ill-defined conditions". In Saudi Arabia, cancer comes fourth as cause of death following diseases of circulatory system, injury/poisoning and perinatal deaths, as well as in Qatar where cancer is the fourth cause of death following diseases of circulatory system, external causes of mortality, and endocrine, nutritional and metabolic diseases [13]. In Egypt cancer was not reported as among the top ten causes of mortality.

It should be remembered that mortality data are uncertain, since "post mortems" only rarely are performed in the Middle East. For deaths outside the hospital, the cause of death is thus not established with certainty. Oman Ministry of Health reported 282 in-hospital deaths due to cancer in 2006; the GLOBOCAN 2002 estimates of deaths due to cancer were 1,421. In Jordan the Ministry of Health reported 1,602 deaths due to cancer, as compared to the GLOBOCAN 2002 estimate of 3,503. Figure 2-26 is not complete since data was not found for the other countries.

Figure 2-26 Deaths due to cancer

	GLOBOCAN 2002	
	Deaths due to cancer	Death rate/100,000
Bahrain	612	90.0
Kuwait	1,393	57.6
Oman	1,421	58.1
Qatar	620	90.0
Saudi Arabia	16,437	75.0
United Arab Emirates	2,737	76.2
Egypt	47,776	69.2
Jordan	3,503	68.7
Lebanon	5,182	134.0
Total ME-9	**79,681**	**79.9**
France	268,742	448.6
United Kingdom	276,590	465.5
United States	1,432,340	492.5

2.5. The burden of cancer

Disease burden is a measurement of the health loss associated with diseases. The most commonly used measure of the burden of cancer is 'Disability Adjusted Life Years' (DALYs), which is an integrated measure of mortality and disability developed by the World Health Organization and the World Bank. One DALY can be thought of as one lost year of 'healthy' life.

Variations in the burden of cancer between countries are a consequence of demographic factors, life-style factors and hereditary factors. As can be seen in figures 2-27 and 2-28 the ME-9 countries have younger populations than the comparator countries France, the UK and the US, which, as previously discussed is an important reason for the change in incidence rates between the studies countries and the comparator countries.

Figure 2-27 Demographics of study countries for 2007 [22]

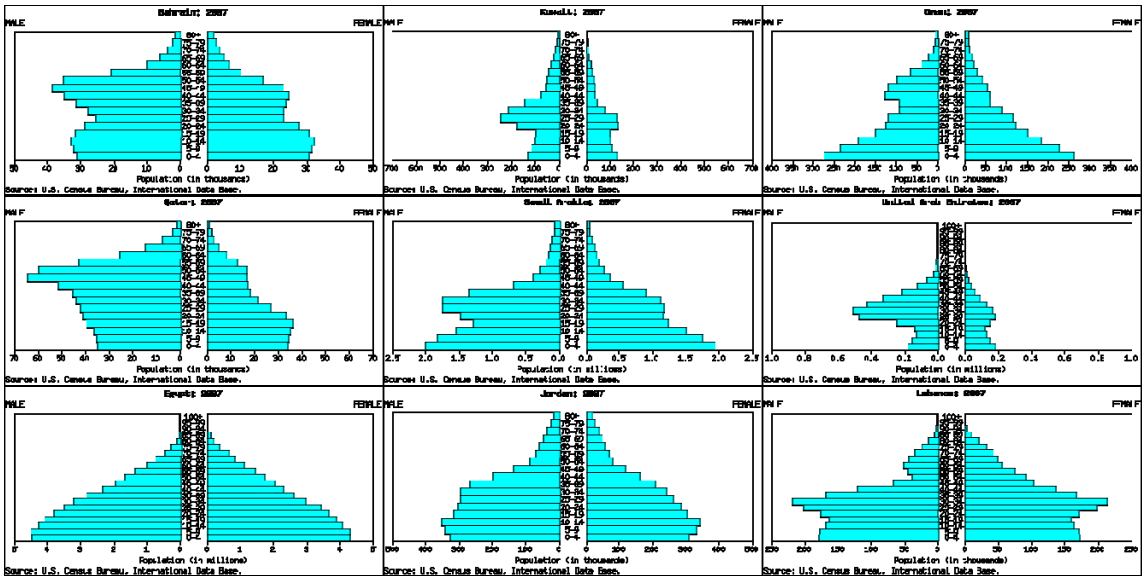
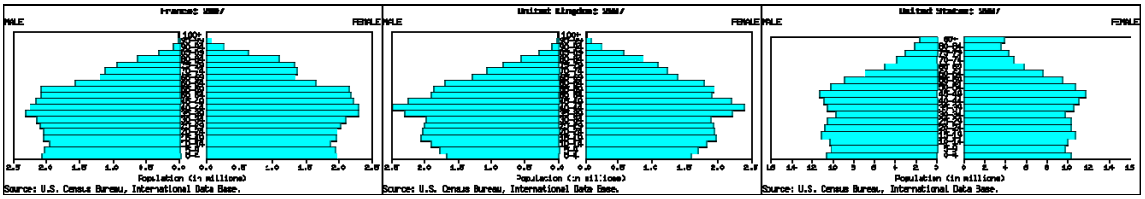


Figure 2-28 Demographics of comparator countries for 2007 [22]



One reason for the low median age of the population in the Gulf countries is the high amount of expatriate workers, a considerable part of the population that only live in the countries when they are of working age and not when they become older and run an increased risk of getting cancer - the population pyramids, as well as DALY statistics cover both nationals and expatriates residing in the countries. Yet, the burden of cancer in a particular country is evidently also a consequence of how the various cancers forms are diagnosed and what treatments are available. Moreover some of the differences may be due to variations in the reporting system. Table 2-3 shows DALYs lost for the 10 disease groups that cause the largest disease burden in the study countries in 2002. Cancer was estimated to represent between 2-5% of DALYs. The diseases causing the greatest burden in the countries were mental illness, injuries, and cardiovascular disease representing each between 15-23%, 8-20% and 8-16% of DALYs lost.

Table 2-3 The ten disease groups with largest total disease burden in the study countries in 2002 [23]

Population (million)	Bahrain *0.7*			Kuwait *2.4*			Oman *2.8*		
	Total DALYs	DALY/ 1000	%	Total DALYs	DALY/ 1000	%	Total DALYs	DALY/ 1000	%
All causes	**83,141**	**117.3**	**100.0**	**259,228**	**106.1**	**100.0**	**363,229**	**131.2**	**100.0**
Neuropsychiatric conditions	18,224	25.7	21.9	60,291	24.7	23.3	70,194	25.4	19.3
Injuries	10,403	14.7	12.5	29,914	12.2	11.5	46,330	16.7	12.8
Cardiovascular diseases	8,868	12.5	10.7	24,394	10.0	9.4	45,711	16.5	12.6
Sense organ diseases	11,645	16.4	14.0	40,534	16.6	15.6	36,464	13.2	10.0
Infectious and parasitic diseases	3,105	4.4	3.7	8,784	3.6	3.4	25,829	9.3	7.1
Respiratory infections & diseases	3,891	5.5	4.7	13,690	5.6	5.3	26,071	9.4	7.2
Congenital anomalies	2,983	4.2	3.6	16,122	6.6	6.2	17,075	6.2	4.7
Malignant neoplasms	**3,735**	**5.3**	**4.5**	**8,132**	**3.3**	**3.1**	**15,148**	**5.5**	**4.2**
Diabetes mellitus	3,968	5.6	4.8	10,405	4.3	4.0	10,138	3.7	2.8
Digestive diseases	3,178	4.5	3.8	5,377	2.2	2.1	10,639	3.8	2.9
Population (million)	Qatar *0.6*			Saudi Arabia *23.5*			United Arab Emirates *2.9*		
	Total DALYs	DALY/ 1000	%	Total DALYs	DALY/ 1000	%	Total DALYs	DALY/ 1000	%
All causes	**70,572**	**117.4**	**100.0**	**3,724,146**	**158.3**	**100.0**	**413,150**	**140.7**	**100.0**
Neuropsychiatric conditions	14,116	23.5	20.0	599,589	25.5	16.1	69,651	23.7	16.9
Injuries	8,011	13.3	11.4	732,281	31.1	19.7	73,898	25.2	17.9
Cardiovascular diseases	8,878	14.8	12.6	414,525	17.6	11.1	59,623	20.3	14.4
Sense organ diseases	11,359	18.9	16.1	316,843	13.5	8.5	51,696	17.6	12.5
Infectious and parasitic diseases	4,911	8.2	7.0	251,882	10.7	6.8	25,213	8.6	6.1
Respiratory infections & diseases	2,558	4.3	3.6	263,830	11.2	7.1	20,006	6.8	4.8
Congenital anomalies	2,639	4.4	3.7	327,127	13.9	8.8	14,441	4.9	3.5
Malignant neoplasms	**1,714**	**2.9**	**2.4**	**146,156**	**6.2**	**3.9**	**15,905**	**5.4**	**3.8**
Diabetes mellitus	3,631	6.0	5.1	91,412	3.9	2.5	28,104	9.6	6.8
Digestive diseases	1,600	2.7	2.3	97,987	4.2	2.6	6,483	2.2	1.6

Population (million)	Egypt *70.5*			Jordan *5.3*			Lebanon *3.6*		
	Total DALYs	DALY/ 1000	%	Total DALYs	DALY/ 1000	%	Total DALYs	DALY/ 1000	%
All causes	**13,692,210**	**194.2**	**100.0**	**842,978**	**158.2**	**100.0**	**652,513**	**181.5**	**100.0**
Neuropsychiatric conditions	2,037,757	28.9	14.9	145,483	27.3	17.3	98,652	27.4	15.1
Injuries	1,138,121	16.1	8.3	158,412	29.7	18.8	121,261	33.7	18.6
Cardiovascular diseases	2,201,645	31.2	16.1	70,155	13.2	8.3	99,108	27.6	15.2
Sense organ diseases	1,321,280	18.7	9.6	71,223	13.4	8.4	62,712	17.4	9.6
Infectious and parasitic diseases	1,262,544	17.9	9.2	86,476	16.2	10.3	35,619	9.9	5.5
Respiratory infections & diseases	1,229,738	17.4	9.0	57,474	10.8	6.8	55,743	15.5	8.5
Congenital anomalies	434,269	6.2	3.2	66,953	12.6	7.9	19,356	5.4	3.0
Malignant neoplasms	**572,360**	**8.1**	**4.2**	**41,158**	**7.7**	**4.9**	**30,726**	**8.5**	**4.7**
Diabetes mellitus	207,751	2.9	1.5	12,341	2.3	1.5	12,685	3.5	1.9
Digestive diseases	807,825	11.5	5.9	17,207	3.2	2.0	34,652	9.6	5.3

Table 2-4 compares the disease burden in the nine countries all together with the E-13 countries and US. The estimated total DALYs lost due to diseases is a bit higher in the ME-9 countries compared to E-13 and the US, 182 per 100 individuals versus, 123 and 143 in E-13 and US respectively. However, one must take into account that there may be a high degree of uncertainty in the conclusions to be drawn from DALY figures, since the morbidity and mortality assessments that constitute the basis for the DALY calculations are based on estimates of incidence and mortality due to disease, and as have been discussed previously such estimates may have significant range of uncertainty. Looking at individual countries we can see that Bahrain, Kuwait and Qatar haves a health status of the population that is similar or better than the E-13 countries. Oman, Saudi Arabia, the United Arab Emirates and Jordan are similar to US in terms of DALY lost per 1000 inhabitants. Egypt and Lebanon are significantly worse off in terms of disease burden or general health.

Table 2-4 The ten disease groups with largest total disease burden in the E-13 and US compared with the ME-9 countries (estimates for 2002)[23]

Population (million)	ME-9 *112.4*			E-13 *365.4*			US *291.0*		
	Total DALYs	DALY /1000	%	Total DALYs	DALY/ 1000	%	Total DALYs	DALY /1000	%
All Causes	**20,101,167**	**182.2**	**100.0**	**45,027,283**	**123.2**	**100.0**	**41,520,900**	**142.7**	**100.0**
Neuropsychiatric conditions	3,113,957	28.2	15.5	12,122,002	33.2	26.9	12,287,960	42.2	29.6
Malignant neoplasms	**835,034**	**7.6**	**4.2**	**7,507,887**	**20.5**	**16.7**	**5,076,683**	**17.4**	**12.2**
Cardiovascular diseases	2,932,907	26.6	14.6	7,447,825	20.4	16.5	6,156,359	21.2	14.8
Injuries	2,318,631	21.0	11.5	3,584,793	9.8	8.0	4,035,999	13.9	9.7
Respiratory infections & diseases	1,673,000	15.2	8.3	3,487,994	9.5	7.7	3,292,884	11.3	7.9
Sense organ diseases	1,923,755	17.4	9.6	2,169,834	5.9	4.8	1,628,248	5.6	3.9
Musculoskeletal diseases	402,387	3.6	2.0	2,120,871	5.8	4.7	1,513,961	5.2	3.6
Digestive diseases	984,947	8.9	4.9	1,946,146	5.3	4.3	1,437,266	4.9	3.5
Diabetes mellitus	380,436	3.4	1.9	952,852	2.6	2.1	1,280,198	4.4	3.1
Infectious & parasitic diseases	1,704,362	15.4	8.5	748,707	2.0	1.7	1,058,129	3.6	2.5

In the ME-9 countries, cancer is on average the 8th most prominent disease in terms of DALYs lost while in the E-13 countries and in the US and cancer is estimated to be the second and third most prominent disease in terms of overall disease burden. Cancer represented on average 4% of

DALYs lost in ME-9, compared to 17% and 12% respectively of all DALYs lost in E-13 and the US.

The total number of DALYs lost due to cancer in the ME-9 countries is 835,000, 190,000 in ME-6 and 645,000 in ME-3. Related to the estimated 80,000 cases, this amounts to a loss of about 10 DALY per case. If we compare with the US, the number of DALY lost per case of cancer is only about 3.5. Each case of cancer in the ME-9 countries thus creates a higher loss, probably mainly due to the fact that the individuals affected by cancer are, on average, younger that in the US.

2.6. Summary

The cancer incidence rate is much lower in the nine ME study countries as compared to Europe and the US. One major reason for this is the age distribution of the population, but there may also be significant under-diagnosis of cancer. This applies particular to the ME-6 countries, where the number of cases reported in national cancer registries covers only nationals which makes it difficult to relate to the total population. The low rate of post mortems, and thus the lack of reliable mortality statistics points in this direction. However an important reason for the difference in cancer burden between the Middle East region and Europe/US is the age-structure of the population; the changing age structure of the population, and the development of systems for diagnosis will probably lead to a rapid increase in the number of patients with some cancers, for example breast, lung, colorectal cancer, and non-Hodgkin's lymphoma.

3. Health care in the Middle East

As seen from the DALY statistics presented in the previous chapter, cancer is cause of a comparable less burden of disease in the ME countries compared to Europe and the US. However, in the Middle East and North Africa region, the burden of illness is expected to change from communicable diseases toward more expensive to treat non-communicable diseases and injuries over the next decades – it is estimated that these will account for 60% of the disease burden in 2020, compared to 45% today, which will have consequences for health system configurations and health spending [24]. Diagnosis and treatment of non-communicable diseases and acute injuries are often complex and costly, which will put increased pressure on health care budgets. It is therefore increasingly important that investments are well managed and directed towards cost-effective technologies. Challenges for the health systems in these countries are to analyse what the costs and benefits of treating non-communicable diseases are, and how to adopt the health care systems for treatment of such diseases in the optimal way [25].

The nine countries covered in this study are countries with rather different levels of economic and social development, which is reflected in their health systems. In a WHO ranking of the overall performance of worldwide health care systems from 2000, the health care system in Oman was ranked among the top 10 in the world; Saudi Arabia and United Arab Emirates were ranked among the 25-30 best overall performers, before for example, Canada, Denmark, Finland and the US; Bahrain, Qatar, and Kuwait were in the 40-45 range; while Egypt, Jordan and Lebanon were ranked, 63, 83 and 91 respectively. The ranking was based on a combination of goal attainment, disability-adjusted life expectancy and health equality in terms of child survival; and health system performance, responsiveness level and distribution and fairness of financial contribution, and can serve as an indication of the relative performance of health care in the countries analysed in this report [26].

Still, the total purchasing-power parity adjusted expenditure on health care per capita is considerable less in the Gulf countries compared with the US, France and the UK, as was illustrated in table 1-1. The Gulf countries spent between € 350-750 per capita in 2005, Egypt spent € 240, Jordan € 430 and Lebanon a bit more than € 520. In the US, more than € 5,000 was spend on health care per capita in 2006, and approximately € 2,600 in France and € 2,300 in the UK It should however be taken into account that in the Gulf countries health care is not always available for expatriate workers, they might go abroad for health services, but are included in the national expenditure data.

There are some problems and challenges applicable to the health systems in the Middle East region, although to various extents depending on the development of the health care sector in the country, including: dual (communicable and non-communicable) disease burdens; imbalances in the public-private mix in financing and lack of coordination between public and private delivery systems, which lead to access and equity problems, cost escalation and inefficient use of the combined delivery capacity. An issue is the growing private health sector in the region, it is largely unregulated and the role of the private health care sector is often not well defined in national health care plans. Moreover, there are significant gaps in health coverage in most countries in the region, particularly in rural areas and among informal sector workers and their families [24].

3.1. The Gulf States

According to the WHO health care ranking, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates all have health outcomes in parity with or approaching those of other high income economies. Available data suggest that further development should focus primarily on improving the efficiency and quality of the health systems and face the challenges of the

epidemiologic and demographic transition discussed above [24]. The six countries are the constituting parts of the Gulf Cooperation Council (GCC) an organisation that works to strengthen cooperation between the countries in, among other areas, health care. Access to health care is overall better for Gulf States citizens than for expatriate workers, which constitute rather large parts of the populations, between 25-80% (see table 1-1).

In Bahrain, comprehensive health care is provided free of charge to Bahrainis and heavily subsidised to the non-Bahraini population, including preventive, curative and rehabilitative services. Bahrain spends 4% of its gross domestic product on health. Public health services accounts for approximately 90% of health services in Bahrain. Private health care has been growing in an unregulated fashion, its current contribution to the overall health services is limited but the sector is growing very rapidly. The relationship and the interaction of public and private sectors are not well established. In 2004 private expenditure on health was estimated to account for 35% of total health care spending. The dependence on expatriate health workers is less in Bahrain than in other Gulf countries, since "Bahrainization" has been a government policy over the years. The health information system of Bahrain is rather well developed and there are detailed statistics available for primary and secondary care utilization [27].

All Kuwaitis have access to primary health care services. In Kuwait, health expenditure accounts for approximately 2.5% of GDP. During the Iraqi invasion, most medical facilities were destroyed; one of the government's primary tasks after liberation was to mount the health care system again in the shortest possible time. Kuwait is relying on non-Kuwaiti health professionals to support the expanding health system. Concerning further development of the health care sector, focus is on programs to expand hospital services in both public and private sector, and shift resources from curative to public health activities, including prevention of chronic diseases. Despite comprehensive services provided by the Ministry of Health, private hospitals and clinics flourish in Kuwait and are encored by the government. Private providers focus on curative services, and have little role in preventive interventions [28]. The country is a net donor of funds for supporting the health sector of other Islamic countries in the region.

In Oman the overall health care system is based on government provision. The private sector is limited. In 2004 there were three private hospitals in Oman. Total health expenditure in Oman was 3% of GDP in 2004. For nationals the provision of free health care includes health care services provided abroad, if services are not available in the country. Non-nationals working in the private sector in Oman are not entitled to free health care. A national drug policy has been initiated since July 2000, and in May 2000 a rational drug use policy introducing user fees for prescriptions was also put in place, which encourages prescription of generic drugs [29].

Over the past three decades Qatar has invested large amounts in the development of health services, which has resulted in significant improvements in delivery of services and in health status of the population and the quality of health care in Qatar is high even by the standards of the industrialized countries. Yet overall health expenditure constitutes only 2.5% of GDP. The government is reorganizing and developing the national health system with a strategic intent to be a regional centre of excellence for health care. Qatar previously provided free health care to all nationals and expatriates, but since 1999 the government requires expatriates to purchase health cards. However, costs for expatriates are still low and do not come close to meeting the actual cost of health provision [30].

In Saudi Arabia the Ministry of Health is the biggest provider of health care, providing more than 60% of health services, the rest is provided by other governmental and non governmental sectors. The total expenditure on health as percentage of GDP was 4% in 2004. There is a network of health centres distributed throughout the country, closely linked to the general

hospitals, that serve as the patient's first point of contact with the national health system [31]. Public sector health care expenditure represents 75% of total spending and about 80% of bed capacity and is provided by the Ministry of Health, the Ministry of Defence and state-owned companies. The Saudi government has however actively been encouraging and expanding health services in the private sector, approving loans for the construction of private hospitals and multi-disciplined health facilities [32].

The generally high standards of health care in the United Arab Emirates are a result of decades of high levels of public spending since the oil boom. There is a developing private health sector, several small private hospitals have been set up over the past few years, however wealthy people still tend to travel abroad for medical care. Health expenditure was almost 3% of GDP in 2004. Health care used to be free to all, but in 2001 the government introduced charges for expatriates, a move that partly sought to reduce the draw of health care on public funds, but also aimed to increase the employers' cost of expatriate labour (which now requires health insurance) and thus encourage the employment of local staff. Since the policy was introduced, visits to government hospitals have fallen sharply, with some reports suggesting a 50% reduction [33].

Table 3-1 Health care resource estimates for 2006 in the ME-9 countries [32]

	Hospitals	Beds per '000 pop	Doctors per '000 pop
Bahrain	17	3.0	2.0
Kuwait	25	2.5	-
Oman	58	2.3	1.6
Qatar*	9	2.0	2.8
Saudia Arabia	241	2.4	1.4
United Arab Emirates	63	2.3	2.0
Egypt	1054	2.2	0.6
Jordan	101	1.9	2.1
Lebanon	186	4.1	2.7

**Data from 2004* [13]

3.2. Lebanon, Jordan and Egypt

Lebanon, Jordan, and Egypt are middle/lower-middle income countries. The countries have made progress in improving the health outcomes of the population during the last two decades. Lebanon is spending over 11% of GDP on health, which is a larger share than most European countries spend. Yet, due to conflicts, Lebanon has seen a recent decrease in health status of the population, and the country must tackle urgent health needs and reconstruction efforts at the same time as building a sustainable health care system. Lebanon has a rather well developed network of private providers available to the wealthier part of the population in urban areas, whereas the poor have more limited access to care [34].

Jordan has a relatively advanced health care system, health care services are however highly concentrated to the capital Amman. The WHO estimated total health expenditure in Jordan in 2004 to be almost 10% of GDP. The public sector accounts for approximately two thirds of all hospital beds in the country, there are more than 50 private hospitals providing for the rest of hospital beds [35]. Sixty-nine percent of Jordanians receive free health care, due to their status as public sector employees or their dependents. Jordan has the ambition to become a medical hub for the Middle East. The country is already attracting patients from other parts of the Arab world by offering quality care at reasonable rates [36].

The health system in Egypt is complex, with various public and private providers. The public financing of health care is fragmented, with a great number of agencies involved; the Egyptian

government is currently undertaking a health care sector reform programme aiming to improve the financing system and make the country's health care system more effective. Compared to other countries at its level of income, Egypt's health indicators are poor. More than 50% of health care expenditures are out-of-pocket payments directly to providers. Spending on health care amounted to 6% of GDP in 2004 according to WHO estimates [37]. Prior to the 1990s, health care in Egypt was predominantly state-controlled, but there is a growing trend of privatisation within the Egyptian health care sector, stimulated by inefficiency of public sector health care and the private sector now plays an increasingly important role in health care provision.

3.3. Summary

The health care systems in the ME-6 countries are considered among the best in the world, despite a much lower spending on health care per capita than other high-income economies. The high level despite such low per capita spending is to a great extent a consequence of demographic factors. This is expected to change in the next decades in the Middle East countries due to demographic transition and will put increased pressure on the health care systems due to increasing rates of non-communicable diseases, such a cancer. Private actors are gaining increased influence in health care in many of the Middle East countries and as in all countries where this trend is seen it is important to regulate and define the role of private actors in the national health care system.

4. The pharmaceutical market in the Middle East

The pharmaceutical market in the six Gulf States grows at approximately 10% per year and had an annual turnover of almost €2.3 billion in 2006 [32]. The total estimated value of the ME-9 market is €3.7 billion with the largest markets being Saudi Arabia, Egypt, and United Arab Emirates. The largest figures of per capita spending on pharmaceuticals are seen in United Arab Emirates, Lebanon, Kuwait and Qatar. PPP-adjusted per capita spending is highest in Lebanon, Jordan and United Arab Emirates. The price levels of drugs in the study countries, which influence the per capita spending, are further discussed in chapter 7.7.

Table 4-1 Total value of nation pharmaceutical markets (€ million) in 2006 [32]

Country	Pharma-ceutical market 2006 (€ million)	Drug expenditure per capita (€)	Drug expenditure per capita (€ PPP)	% prescription drugs	- whereof share generic drugs [32, 38-40]	Drug expenditure as percentage of total health expenditure
Bahrain	43	57	74	95%	-	12%
Kuwait	306	99	69	90%	-	16%
Oman	79	30	38	90%	5%	13%
Qatar*	64	76	45	-	-	11%
Saudi Arabia	1,180	50	65	89%	6%	8%
United Arab Emirates	646	153	96	86%	10%	22%
ME-3	**2,318**	**66**				
Egypt	765	11	38	86%	17%	26%
Jordan	243	43	108	82%	68%	21%
Lebanon	379	102	124	88%	4%	30%
ME-9	**3,705**	**32**				
France**	30,013	489	437		9%	17%
UK**	17,944	296	263		26%	12%
US**	215,995	721	721		10%	14%

**Data from 2002 [41] **Data from 2005 [4]*

In the Gulf States, there has previously been a strong dominance of governments as the main purchasers of drugs through tenders. An increased importance of the private market in recent years is mainly due to two reasons: the considerable expatriate labour force in the Gulf States that increasingly are being excluded from state health care, and the expansion of high-class private clinics and hospitals operated by expatriate doctors and surgeons with high qualifications from Europe or North America which leads to the well-off population previously seeking treatment abroad in Europe or in the US, now seeking treatment in the region. The expansion of the private sector has led to an increased market uptake of medicines for diabetes, cardiovascular diseases and oncology [41].

In 2002 it was estimated that Jordan and Egypt were over 90% self-sufficient in terms of pharmaceutical products, while the rest of the ME-9 countries were producing less than 20% of their requirements. This can be seen from the higher market share for generic products in these two countries as compared to the other ME-9 countries. The Egyptian drug industry is the largest producer of pharmaceuticals in the Middle East and North Africa region. Jordan is the only country in the Middle East with a positive pharmaceutical trade balance, 70%, in value terms, of Jordanian pharmaceutical production is exported. The pharmaceutical industry is second only to the mining industry in terms of export earnings for the country. National pharmaceutical companies take the top three places in terms of market share, although in principle limited to the manufacture of basic generics. In Lebanon the pharmaceutical market remains almost entirely on imports, which account for more than 95% of spending. Despite considerable generic production in the Middle East region, pharmaceutical research and development is very limited [41].

5. The cost of cancer

The costs to society of cancer can be divided into direct costs, for medical treatment, prevention, etc., and indirect costs, including cost of morbidity (productivity loss due to sick-leave and early retirement) and cost of mortality. Available international studies show that indirect costs are twice as high as the direct costs and thus account for about two thirds of the total costs of cancer [42, 43]. Indirect costs are dominated by the cost of mortality in persons of working age. Yet, as the survival of cancer patients improves with earlier detection and improvements in cancer treatment, the share of indirect costs due to morbidity can be expected to increase and the share due to mortality to drop over time [44].

Cancer is a disease group that has gotten less recognition in the Middle East compared to in Europe and in the US, partly because cancer is a less prominent disease in these countries, due to demographic and lifestyle factors as reflected in the previously shown data on the burden of disease. It is difficult to find good estimates on the resources used for treating cancer in the ME-9 countries. Therefore, the cost of cancer care in the ME-9 countries will be estimated based on data from US and European studies linked to health expenditure data, oncology drug sales, and disease burden estimates from the ME countries.

5.1. Direct costs of cancer

In the US, cancer costs have consistently, from 1963 to 2004, been reported to constitute approximately 5% of total health care expenditure [45]. A recent French study estimated that 6.1% of the total French health care budget was spent on cancer in 2004 [46]. In a recent study for 2004, the share for cancer of total NHS expenditures in England has been estimated to 5.6% [47]. Since it is not always easy to estimate the fraction of overall health care costs that is attributable to a particular disease some assumptions have to be made, which, together with variations in treatment practices in different countries, may explain some of the discrepancies between study estimates.

Table 5-1 presents estimated total costs for cancer care, in 2005 Euro. The figures for France, the UK and the US are based on data from WHO National Health Accounts on total health care expenditure in the study countries [4] and estimates of the share of total expenditure spent on cancer as reported in the studies reviewed above. Since no studies have been found previously assessing the cost of cancer care in the ME-9 countries, the following approaches were taken to estimate the cost of cancer care in the study countries:

1) The burden of cancer for respective country in relation to the burden of cancer in the European countries and the US and the estimated cost of cancer care in these countries: The ratio between cancer as a percentage of total burden of disease and cost of cancer care as a percentage of total health care expenditure was approximately 2.5 in both E-13 and in the US. DALYs due to cancer were 16.7% and 12.2% of total DALYs and cost of cancer care out of total health care expenditure were, as stated above, 6.6% and 5% respectively. In ME-9, the percentage burden of cancer was on average 4% (2.4%-4.9%) of total disease burden, which directly applied leads to an assumption that the proportional cost of cancer care out of total health care expenditure would be in the range of 1-3%.

2) A second basis for calculation is the incidence of cancer in the study countries, related to the incidence and cost of cancer care in France, the UK and the US: The DALYs are based on incidence so these two estimates correlate. However, based only on incidence the resulting calculated costs of cancer care in relation become even lower, as previously

commented, on average each cancer case leads to 10 DALYs lost in ME-9 as compared to 3 years in Europe/US.

3) Data on the oncology drug markets in the countries, as presented below in table 5-2, divide by the share of total health care expenditure that is spent on drugs, leads to much higher estimates of the total cost of cancer care in the Middle East countries. (It should be noted that some of the Gulf countries may source pharmaceuticals for neighbour countries through bulk tenders and that parallel importation and counterfeit drugs has been reported as common in some of the countries, which may explain incoherence between countries in the results. Moreover it is possible that patients go to neighbour countries for treatment.)

Table 5-1 Calculation of the direct costs for cancer care in 2005, based on three different sources: DALYs due to cancer, Globocan 2002 cancer incidence, and oncology drugs sales in 2006

	Total health care expenditure (€ million) [48]	**1) Cancer costs as % of total health care costs** (proportion of DALYs due to cancer)	Cost cancer (€ million)	Cost per cancer case	**2) Cancer costs as % of total health care costs** (proportional to Globocan estimated cancer incidence)	Cost cancer (€ million)	Cost per cancer case	**3) Cancer costs as % of total health care costs** (based on oncology drug sales & % drug exp of THE)	Cost cancer (€ million)	Cost per cancer case
Bahrain	399	1.8%	7	11,818	1.0%	4	6,563	8%	33	54,466
Kuwait	1,455	1.3%	19	13,870	0.6%	9	6,722	8%	113	80,761
Oman	702	1.7%	12	8,344	0.6%	5	3,205	5%	38	27,067
Qatar	838	1.0%	8	13,048	1.0%	8	13,587	4%	36	58,651
Saudi Arabia	9,490	1.6%	149	9,061	0.8%	80	4,838	11%	1,063	64,641
UAE	2,788	1.5%	43	15,575	0.9%	24	8,672	11%	295	107,948
Egypt	4,591	1.7%	78	1,624	0.8%	35	743	1%	42	886
Jordan	996	3.1%	31	8,810	0.8%	8	2,183	11%	114	32,625
Lebanon	1,995	1.9%	38	7,280	1.5%	30	5,763	4%	77	14,795
France	178,868	6.1%	10,911	40,600						
UK	148,486	5.6%	8,315	30,063						
US	1,526,347	4.7%	71,738	50,085						

Based on the three different methods of calculating cancer incidence presented in Table 5-1, an estimate was derived that the cost of cancer out of total health care expenditure could be in the range of 4%, due to large fluctuations between the estimates for individual countries with the somewhat imprecise calculations the same average was assumed for all countries but Egypt, which had a considerably lower spend on cancer drugs than the other countries. For Egypt it was assumed that expenditure on cancer represents approximately 1% of health care expenditure. The resulting estimates of the cost of cancer as a percentage of total health care expenditure per country is presented in table 5-2.

Table 5-2 presents the resulting estimates for cost of cancer in the region, and compares this with what would be the cost per cancer case in each country.

Table 5-2 Direct cost of cancer in study countries (estimates are based on calculations above)

	Cancer costs as % of total health care expenditure (estimated share)	Cost of cancer care (€ million)	Cost per cancer case (Globocan estimate) (€)	Cost per cancer case (€ PPP)	Cost per cancer case (National Cancer Registry) (€)
Bahrain	*4%*	16	26,106	33,467	42,156
Kuwait	*4%*	58	41,781	29,114	97,980
Oman	*4%*	28	19,750	24,712	33,370
Qatar	*4%*	34	54,044	31,596	221,903
Saudi Arabia	*4%*	380	23,095	29,998	50,933
UAE	*4%*	112	40,743	25,634	371,709
ME-6		**627**			
Egypt	*1%*	46	961	3,444	638
Jordan	*4%*	40	11,374	28,188	11,095
Lebanon	*4%*	80	15,396	18,664	10,115
ME-9		**792**			
France	6.1%	10911	40,600	36,274	34,487
UK	5.6%	8315	30,063	26,669	29,221
US	4.7%	71738	50,085	50,085	53,451

The total cost of cancer care in ME-9 is estimated to €800 million, of which €630 million in the Gulf countries.

The direct costs of cancer per cancer case in ME-6 were under the assumptions explained above estimated to €20-40,000, PPP-adjusted to €24-34,000.

If cost of cancer are related to nationals only, according to cancer cases reported in the national cancer registries instead of the Globocan estimates, the cost per cancer cases increases in all the ME-6 countries, most significantly in Qatar and United Arab Emirates. This indicates that according to oncology drug sales in these countries and what may be considered a reasonable share of total health expenditure spend on cancer, a great deal more cancer patients are treated in these two countries than those reported in the national cancer registries. Therefore the Globocan estimates seem to give a more realistic picture of the cost per cancer case. The high resulting cost per cancer case in UAE when using National Cancer Incidence reporting is partly due to the fact that the annual rate of 300 cancer cases being reported in 1998-2002 only applies to the national population (800,000 of 4,200,000).

In Egypt the cost per cancer case was estimated to €1,000, PPP-adjusted €4,000, in Jordan €11,000, PPP-adjusted €28,000 and in Lebanon, €15,000, PPP-adjusted €18,500.

Opposite to ME-6, in Egypt, Jordan, and Lebanon the costs per cancer cases decreases slightly when relating the assumed total expenditure on cancer to cases reported in national cancer registries, since these present higher rates of cancer cases than Globocan estimates.

The PPP-adjusted cost per cancer cases is in line with the estimates for the UK and France, in all ME-6 countries and in Jordan. The resulting costs per cancer case are somewhat lower in Lebanon and Egypt, and higher in the US.

5.2. The costs of cancer drugs

Pharmaceuticals account for a high share of total health spending in general the Middle East and North African countries, approximately 25% on average, which is much larger share of total health expenditure than in the E-13 countries and the US, where pharmaceuticals account for 10-17% of total health expenditure. However in the ME-6 countries the share of total health care expenditure spent on pharmaceuticals is similar to what is seen in Europe and the US. Estimates from 2006 indicate that in all ME-6 countries but United Arab Emirates, the share is 8-16%. In Jordan and UAE 21-22% of total health care expenditure is spend to pharmaceutical, in Egypt and Lebanon the shares are 26% and 30% respectively, see table 4-1. Table 5-3 below presents the share of cancer drugs out of total drug costs, which varies between 1-10% in the countries for which data were available. The total oncology market in the ME-6 countries summed up to €180 in 2006, which is 29% of the total cost of cancer in ME-6, €630, estimated in table 5-2. For ME-9 the share of cancer drugs out of total expenditure of cancer would be an estimated 30% (240/800). Based on the calculations in tables 5-2 and 5-3 cancer drugs constitute approximately 25% or of total directs costs of cancer care in France, 12% in the UK and 27% in the US.

Table 5-3 Estimated cost for cancer drugs in the study countries

	Oncology drug market 2006 (€ million) [32, 49]	**Cancer drug expenditure as share of total drug expenditure [4, 32]**	**Cancer drug expenditure per cancer case (€)** *Total number of cases as reported in Globocan 2002 (See Table 2-1)*	**Cancer drug expenditure per cancer case (€ PPP)** *Total number of cases as reported in Globocan 2002 (See Table 2-1)*	**Cancer drug expenditure per cancer case (€)** *Total number of cases as reported in National Cancer Registries (See Table 2-1)*
Bahrain	4	9%	6,536	8,379	10,554
Kuwait	18	6%	12,922	9,004	30,303
Oman	5	6%	3,519	4,403	5,945
Qatar*	*4*	*7%*	7,226	4,224	29,669
Saudi Arabia	85	7%	5,171	6,717	11,560
United Arab Emirates	65	10%	23,749	14,942	216,667
ME-6	**181**				
Egypt	11	1%	230	825	153
Jordan	24	10%	6,851	16,980	6,683
Lebanon	23	6%	4,438	5,380	2,916
ME-9	**239**				
France	2,754	9%	10,247	9,155	8,704
UK	1,086	6%	3,926	3,483	3,816
US	19,160	9%	13,377	13,377	14,276

** Estimate of total sales of oncology drugs in Qatar were not found for 2006, the presented estimate is based on the assumption that oncology drugs represent 7% of the total pharmaceutical market which is the average share of the other ME-6 countries. This was applied to the total pharmaceutical market in Qatar in 2002, the latest identified estimate.*

The high rates of oncology drug expenditure out of total drug expenditure in some of the ME-9 countries, such as Jordan and the United Arab Emirates, may reflect that patients come from other countries to receive cancer care. For example, the Jordan Cancer Registry reports that 17% of cancer patients treated in the country did not live in Jordan. Thus an additional 742 patient

come to Jordan for treatment in addition to the nationals reported with cancer that were used as basis for the calculation of drug cost per cancer case above. Taking this into account when calculating the cost of cancer drugs per cancer cases in Jordan, the estimate based on cases reported in National cancer registries, would be lowered to approximately €5,539. However, it is likely that in some cases patients registered with cancer leave to receive cancer care abroad. Therefore it may be more relevant to look at the average estimate of oncology drugs spending per cancer in the region than at estimates from individual countries. The average expenditure on oncology drugs per cancer case in the ME-6 countries would in that case be approximately €10,000 (PPP €8,000) and in Jordan/Lebanon €5,000 (PPP €10,000) (using the estimated expenditure per cancer case of €5,539 for Jordan that includes patients coming from abroad to receive treatment) and for Egypt €250 (PPP €850).

Another factor that influences the uncertainty of estimates of the total value of the oncology drug market is that definitions of oncology drugs may vary, for example supportive care treatments may be included in some estimates and not in others. When there are several steps in the distribution chain it might be impossible to obtain information on final customer prices, especially in countries when large parts of drug purchase are based on tenders. This must be taken into account when assessing the validity of the calculated estimates presented above.

5.3. Indirect costs of cancer

The indirect cost of a specific cancer form depends to a large extent on the age distribution of the patients, since patients above retirement age do not incur cost of production loss. This means that there are great differences in the distribution of the indirect costs between different types of cancer. Breast and lung cancer are the cancer forms that cause the greatest indirect costs due to being common in relatively young individuals, followed by leukaemia [50]. Conversely, prostate cancer is not as important in terms of lost working years despite a high incidence since it mainly occurs in elderly.

Data from the US, France and Sweden, presented in table 5-4, estimate the indirect cost for cancer to constitute about 50-60% of the total cost, and that the majority of the indirect cost is due to cost of mortality. Data is not available to estimate the indirect costs due to cancer in the ME-9 countries, however, the DALY calculations previously presented showed that number of DALYs lost per cancer case are three times higher in the ME-region compared to Europe/US since the a larger share of total cancer cases are such forms that affect younger individuals. Therefore, it can be assumed the share of indirect cost out of the total cost of cancer in ME-9 is even larger than the 50-60% estimated in the studies from the US, France and Sweden.

Table 5-4 Assessment of the direct and indirect cost of cancer from year 2002 in the US and year 2004 in France and Sweden (million €)

	US[51]		France [46]		Sweden [52]	
	Cost 2002	*Share of total cost*	*Cost 2004*	*Share of total cost*	*Cost 2004*	*Share of total cost*
Direct costs	64,600	**35%**	11,134	**39%**	1,812	**50%**
- Drug costs			895	3%	218	6%
Indirect costs	117,500	**65%**	17,449	**61%**	1,799	**50%**
- Morbidity	16,500	9%	528	2%	387	11%
- Mortality	101,000	55%	16,921	59%	1,412	39%
Total costs	182,200	100%	28,583	100%	3,611	100%

5.4. Summary

The calculations on the direct costs of cancer presented in this chapter, indicates that despite a much lower total spend on cancer in the Middle East, the cost per cancer case may be in line with the spending in Europe. Since the health care systems of the ME-6 countries are to some extent integrated, both when it comes to procurement of pharmaceuticals and outsourcing of care, and the populations constitute many expatriates that may go abroad for care, it may be more relevant to look at ME-6 as a group instead of the individual countries. The average cost per cancer case for the ME-6 countries was estimated to €34,000 (not weighted by population) and the drug cost per cancer case was estimated to €10,000, 29% of total care costs.

Direct health care costs per cancer cases in Jordan and Lebanon were estimated to on average €13,000, with cost of drugs augmenting to €5,000.

Egypt has a much lower health care expenditure per capita than the other countries and based on estimates of total oncology drug sales it is estimated that the share of cancer spending out of total health care spent on cancer is lower in Egypt than in the other ME-9 countries. Our calculations estimated the cost per cancer case to €1,000 and the cost of cancer drugs per case to €250.

In France and the US direct health care costs per cancer case are an estimated €40,000 and €50,000 respectively. Drug costs per case were calculated to 25-27%, in line with the estimates for the ME countries. In the UK the costs per cancer case was estimated to €30,000 whereof the cost of oncology drugs was estimated to constitute 12%.

6. Medical review

6.1. Introduction

Agents that inhibit cancer growth (chemotherapy) were first developed in the 1940s based on the discovery of alkylating agents and anti metabolites - two groups of agents still in use in oncology [53, 54]. During the 1950-70s further classes of cell toxic agents were discovered and it became clear that chemotherapy could cure some haematological malignancies. The introduction of platinum compounds was a major breakthrough since it resulted in a high cure rate in metastatic testicular cancer, a previously untreatable solid tumour form. These results confirmed that chemotherapy could potentially cure cancer and provided a rationale for introducing chemotherapy, in combination with surgery and radiotherapy, to decrease the risk of recurrence of the disease. The potential value of adjuvant chemotherapy after surgery was first demonstrated in 1974 in osteosarcomas [55].

Gradually, chemotherapy has been introduced in various tumour forms, as palliative treatment to relieve symptoms and increase the quality of life in late stages of the disease, or in conjunction with surgery and/or radiotherapy, in order to increase cure rates. Cancer treatment has become a multimodality treatment requiring multidisciplinary teams in order to achieve optimal results. As for chemotherapy, there has been a trend towards using combinations of agents with different mechanisms of action in order to achieve maxim efficacy. Major obstacles for maxim efficacy using conventional chemotherapeutic agents have been severe side effects and the development of drug resistance in tumours.

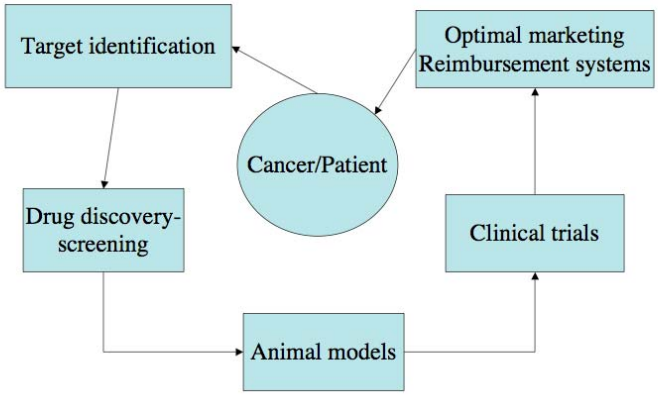
As cancer patients live longer there has been an increased demand for supportive care and a development of a wide range of drugs aimed at improving quality of life and reducing chemotherapy side effects. The development of potent anti-emetic agents, erythropoietin analogues, G-CSF and improved broad spectrum antibiotics has enabled both intensified treatment schedules with increased efficacy but has also led to a shift in cancer care from mainly in-hospital treatments in the 1980s to a continuously increasing proportion of out patient treatments making patients less hospital bound.

Until the 1980ies, drug discovery in oncology was dominated by academia and publicly sponsored institutions like the NCI in the US. Screening programs of potential drug candidates were initiated from the mid 1950s at the NCI and over the coming decades several groups of agents with anti-tumour effects were found. The last decade has seen a dramatic change in drug discovery and advances in biological research has enabled the identification of more specific targets of intervention and efforts can be concentrated on finding agents that act on these targets. The improved techniques in molecular medicine and increased investments in the oncology area, have led to a transformation from publicly funded (NIH/NCI in the US) screening programs in the 70 and 80s to a major international industrial effort increasing the impetus of drug discovery and drug development in oncology. Of biotech companies in the US today, half are focussing on cancer and according to a recent review there are about 400 new agents in clinical trials [56].

Oncology has entered an exciting new phase with a rapidly expanding arsenal of new active agents. In the light of recent advances it is relevant to evaluate to what extent these advances reach their full clinical usefulness and what obstacles and factors there may be that affect the speed of uptake of new treatments after they prove clinical efficacy and acceptable safety.

The following sections review some of the more significant advances seen in the management of cancer patients from improvements in diagnostic techniques to advances in the medical treatment of cancer.

Figure 6-1 The five vital steps in improving outcome for cancer patients- from target identification in cancer cells and the development of agents that interact with those targets to fast patient access to new agents



6.2. Advances in diagnostic techniques

Diagnostic radiology has come to play a key role in oncology, not only as a diagnostic tool, but also as a method of evaluating the efficacy of treatment by measuring progression or regression of tumours and metastatic lesions. The introduction of new radiological methods in the 1980s and 1990s such as computer tomography (CT) and magnetic resonance imaging (MRI) have greatly improved the diagnostic accuracy and evaluations of the effects of treatment. Other methods such as ultrasound and scintigraphy also play an important role as diagnostic tools and can help in directing local therapy such as radiotherapy. Currently, positron emission tomography (PET) in combination with CT (PET/CT) is being introduced in clinical practice with the advantage of being more sensitive than earlier alternatives in differentiating between viable and non-viable tumour tissue. The development of improved radiological techniques with the ability to accurately identify responders from non responders after only a brief treatment time or perhaps even before onset of treatment (tracers, probes etc) will be pivotal in decreasing the number of patients that receive treatment that they don't benefit from. Advances in molecular medicine such as gene and protein profiling techniques have contributed to increased understanding of cell and cancer biology but also to more accurate classification of various tumour forms. We now know that different sets of genes are expressed in different cell populations and at different stages of life. It is estimated that, of the 30,000 genes in our genome, only one tenth are expressed in each cell. Cancer tumour cells are characterised by genetic instability and altered gene expression. By analysing the gene expression of a wide range of tumours, it has been possible to identify genes that are responsible for tumour-specific characteristics. In some cases it is also possible to predict if an individual tumour will respond to certain treatments [57]. Pharmacogenomics has become an important field in cancer research and drug development. Soon, pharmacogenomics, together with analyses performed on sampled tumour material to determine the potential for a response to treatment (chemosensitivity tests), will be available on a larger scale in the clinical setting and promise a much more individualised approach to treatment, with better chances for improved outcomes.

Although mapping the entire genome in less than 50 years after the DNA helix was first described has been an immense achievement, it has also become apparent that genes tell us far from everything. Less than 2% of human diseases are caused by one gene (monogenic), the rest are caused by multiple genes in combination or by changes in the proteins they encode. The deciphering of the entire human proteome is underway and will undoubtedly shed new light on disease mechanisms and possible points of intervention. Already, the individual protein patterns of different types of tumours are being mapped and it has been demonstrated that patients with a specific type of cancer have certain protein patterns in the blood indicating a potential for diagnostic purposes [58].

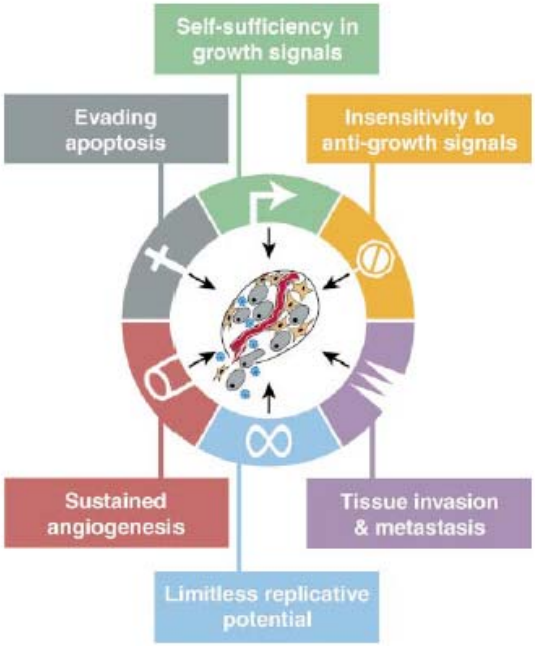
6.3. Cell biology, tumour cells and their microenvironment

Progress in molecular medicine has led to increased understanding of how cancer evolves and how cancer cells are characterised by defects in their DNA repair mechanisms, leading to an increased accumulation of genetic defects, fuelling tumour development but also increasing the risk of for instance acquired drug resistance.

Some individuals are genetically predisposed to developing cancer due to the existence of altered genes that normally act as gatekeepers against cancer (tumour suppressor genes). The development of invasive cancer (Figure 6-2) is a process with many steps that includes an accumulation of genetic changes thought to occur over a prolonged time period (5-20 years) [59].

Cancer treatments in the 20th century started as chance observations of effect. Intense research during the last century has increased knowledge about the human cell and the molecular mechanisms that govern it which has led medical oncology in the 21st century to a new phase. Increased knowledge of cancer biology has led to a clear trend where highly cell-toxic treatments are starting to give way to more disease-specific agents targeting particular weaknesses in tumour development and progression.

Figure 6-2 The six hallmarks of cancer (Adapted from Hanahan & Weinberger 2000 [59])



The main areas where new agents have been developed and now are used in clinical practice:

- Targeting of the cell cycle and apoptosis, DNA replication/transcription and repair
- Inhibition of hormones, growth factors and cell signaling pathways
- Inhibition of angiogenesis
- Biotherapy

Most chemotherapeutic agents developed until the 1990s act by inhibiting DNA replication in some way and in many cases the main mechanism of action has been elucidated long after the introduction of the agents in the clinical setting. In some cases the mechanisms of action of older chemotherapeutic agents still remain unclear. In 1984, it was shown that anthracyclines, one of the most efficient class of compounds in conventional chemotherapy at the time, worked by affecting topoisomerase activity [60], fuelling the interest in finding other agents with similar mechanisms of action. In the 1990s, the topoisomerase inhibitors irinotecan and topotecan were introduced with significant clinical impact in, for instance, colon cancer. During the 90s the central role of microtubules in cell division, proliferation and chemotaxis was evident and several agents, taxanes (paclitaxel and docetaxel), and vinca alkaloids (vinblastine, vincristine, and vinorelbine) derived from plant toxins were developed that affect microtubule dynamics. Since their introduction in the 1990s, these agents have had an important impact on the treatment of cancer, with impressive responses in a wide variety of tumour forms. There are also several new agents in clinical trials with similar anti tumour mechanisms, for instance a group of compounds called epothilones [61].

New antimetabolite agents have also been introduced the last decade with an important clinical impact-gemcitabine with efficacy in pancreatic cancer [62] and non-small cell lung cancer, pemetrexed with a efficacy in non-small cell lung cancer [63] and capecitabine, a drug similar to 5-FU with a wide range of indications but in an oral form enabling many patients to take their treatment at home, resulting in increased cost effectiveness.

However, the main group of recently introduced anti-tumoural substances belong to a group of agents often referred to as targeted agents. They represent an important shift in drug development in oncology since they have been developed in order to interfere with specific molecules identified as specifically important in driving tumour development and progression.

6.4. Targeting hormones, growth factors and cell signalling pathways

Cells are not static, independent units but are interacting components that must be able to respond to a wealth of stimuli, ranging from nerve signals and hormones to signals of local tissue damage. Intracellular signal transduction pathways have evolved to respond to proteins, amino acids, lipids, gases and even light. Binding to the receptors activates various enzyme systems, ultimately resulting in changes in cellular behaviour or growth. Signalling pathways that are critical in cancer growth have been investigated as therapeutic targets.

6.5. Endocrine therapy

In many ways, the introduction of endocrine agents represents the first steps from highly toxic agents to treatments focused on well-defined molecular targets. Tamoxifen, which acts by blocking oestrogen stimulation, was the first hormonal agent to be widely used in breast cancer. Since its introduction in the 1970s, tamoxifen has proved valuable in the treatment of metastatic breast cancer, as an adjuvant treatment after surgery, decreasing the risk of relapse and as a preventive agent in high risk populations. The efficacy and relatively low toxicity of tamoxifen has led to the development of a large number of similar drugs, and increased knowledge of hormone synthesis and metabolism has led to the development of several new classes of

hormonal agents. Interfering with the production of hormones or blocking their action through drug therapies have become cornerstones in the treatment of both breast and prostate cancer.

In breast cancer, a number of aromatase inhibitors (eg anastrozole, letrozole and exemestane) have been introduced in the last decade and, together with other agents with similar mechanisms of action (eg fulvestrant, megestrol), they constitute valuable therapeutic options in metastatic breast cancer. Aromatase inhibitors are also gaining acceptance as adjuvant treatment in postmenopausal women. In prostate cancer, anti-androgens (eg flutamide, bicalutamide and nilutamide) have been developed as an alternative to testicular ablation. Additionally, gonadotropin releasing hormone analogues (eg goserelin, leuprolide), which block the production of testosterone, have been developed to achieve chemical castration. Recent research has also focused on the potential for hormonal agents to prevent cancer.

6.6. Inhibiting growth factors and signal transduction systems

Growth factors play an important role in stimulating cell growth during development and in cell populations where constant proliferation and tissue renewal is required (eg the skin, bone marrow and intestines). Growth factors stimulate cell growth by binding to cell surface receptors and starting a cascade of activity of specific enzymes in the cell. Many cancers over express growth factor receptors or have mutations that lead to defective growth signal transduction, resulting in abnormal growth as well as invasion of normal tissue.

There are two main groups of agents that have demonstrated efficacy in interfering with growth factor signalling. Monoclonal antibodies against growth factors and/or their receptors and small molecular drugs that block the tyrosine kinases which most growth factors exert their effects through. Most research efforts have focused on families of growth factors that are known to be over expressed in various tumour types, such as the epidermal growth factor receptor (EGFR aka HER1/erbB), vascular endothelial growth factor (VEGF) receptor, platelet-derived growth factor (PDGF) receptor and insulin-like growth factor (IGF-1) receptor.

Cetuximab, a monoclonal antibody developed against EGFR, has demonstrated efficacy in metastatic colorectal cancer by increasing the time to disease progression [64]. In combination with radiotherapy, cetuximab has also demonstrated efficacy in patients with advanced head and neck tumours [65] Tyrosine kinase inhibitors against the EGFR pathway have also been introduced. Erlotinib [66] has demonstrated efficacy and positive survival data as monotherapy in non-small-cell lung cancer, and gefitinib [67] has demonstrated efficacy in a subset of patients with the same disease. Several clinical trials are ongoing in other tumour types.

Approximately 20-30% of all breast cancer tumours over express the HER2 receptor, and treatment with the monoclonal antibody trastuzumab directed against the receptor has led to markedly prolonged survival in metastatic disease [68]. HER2 status is determined through a diagnostic test, thereby making testing of patients an important step in determining eligibility for trastuzumab treatment. Adjuvant treatment with trastuzumab results in approximately 50% reduction in recurrence of the disease after a median follow-up of 1-2.4 years of treatment in patients with HER2-positive disease [69, 70].

Chronic myeloid leukaemia was the first malignant disease for which a characteristic genetic abnormality, the Philadelphia chromosome (1960), was described [71]. In the 1980s, the genetic alteration was identified as the BCR-ABL fusion gene and the protein it encodes was established as the cause of the initial phase of chronic myeloid leukaemia. In the late 1990s, imatinib, an agent inhibiting BCR-ABL activity, was developed [72]. Treatment with imatinib results in complete responses in 80% of patients [73]. Unfortunately, resistance to imatinib occurs, but the

mechanisms of resistance have been clarified and an agent that restores sensitivity to imatinib in 14 of the 15 resistance mechanisms described has already been developed [74]. Imatinib also inhibits another cell enzyme, C-KIT, which is mutated in 95% of patients with gastrointestinal stromal tumours. Treatment with imatinib results in long-lasting tumour regression [75] and has been an enormous step forward, since the disease does not respond to conventional chemotherapy.

These agents that inhibit growth factors and their signal transduction systems represent a new class of anti-tumour agents and their place in the clinical setting continues to evolve. In some cases like gastrointestinal stromal tumours and renal cancer, for which there are no active chemotherapy alternatives they are first-line options. In other tumour forms it remains to be seen if these agents will replace conventional chemotherapy as first-line treatment. Present data seem to support the concept of combining these agents with radiotherapy and chemotherapy and combining agents inhibiting different pathways (eg bevacizumab [targeting VEGF] in combination with erlotinib [targeting EGFR] in both renal and non-small-cell lung cancer) [76, 77]. The additive value of combining drug therapies that target the same pathway or sequential use of these drug therapies does, however, need to be determined. Currently, data is indicating increased efficacy but also increased side effects when combining some of these agents.

Another key issue with these agents, as with conventional chemotherapy, is the ability to predict responders. The clinical trials and initial introduction of gefitinib (outside the EU) may serve to illustrate the complexity of clinical trials in different patient populations, the value of post-marketing surveillance but also the potential of today's biological research. The first studies of gefitinib indicated high response rates in the Japanese population that subsequently were not consistently seen in other patient populations. Further analysis indicated that certain subgroups (non-smokers, women and patients whose tumours had particular histological characteristics) were more likely to respond to treatment [78]. Genetic analysis has also led to the identification of mutations in the EGFR that correlate to response to gefitinib [79].

Table 6-1 Agents inhibiting tyrosine kinases that have been approved for use in oncology

Generic name/Trade name	Drug class	Target	Year of approval
Trastuzumab/Herceptin	Antibody	HER2	1998
Imatinib/Glivec	small molecular drug	bcr-abl, ckit	2001
Cetuximab/Erbitux	Antibody	EGFR	2003
Erlotinib/Tarceva	small molecular drug	EGFR	2004
Bevacizumab/Avastin	Antibody	VEGF	2004
Sorafenib/Nexavar	small molecular drug	VEGFR, PDGFR	2005
Sunitinib/Sutent	small molecular drug	VEGFR, PDGFR	2005

6.7. Inhibiting angiogenesis

The development of new blood vessels, angiogenesis, is an important normal physiological function, especially during pregnancy, growth, inflammation and wound healing. The regulation of angiogenesis is complex, with stimulating and inhibiting factors that, under normal conditions, strike a fine balance. It has long been recognised that some tumours are highly vascularised. However, it was not until the 1970s that Judah Folkman hypothesised that tumours need angiogenesis for their continued growth [80]. We now know that tumours will not grow beyond 1-2 mm3 if they are unable to develop blood vessels of their own. In addition, autopsies have shown that many elderly have small, early-stage cancers (such as of the thyroid gland, breast and prostate) that were not previously known [81]. The point at which the tumour starts producing

pro-angiogenic factors (angiogenic switch) is believed to be one of the most important steps in transforming these 'dormant' tumours into rapidly growing tumours with metastatic potential [82].

Several growth factors are involved in angiogenesis but VEGF has been identified as the most important in many tumour forms. Both monoclonal antibodies against VEGF and tyrosine kinase inhibitors targeting the VEGF receptor pathway have been developed. Bevacizumab, a monoclonal antibody against VEGF, has demonstrated increased survival in patients with metastatic colon, breast and lung cancer [83-85].

In renal cancer that does not respond to conventional chemotherapy, bevacizumab has extended the period of time over which the cancer is stable [86]. Bevacizumab represents an important breakthrough in cancer therapy because it is the first agent in this new class of drugs that show impressive response and efficacy over a range of tumours. Several studies are ongoing to investigate the effects of bevacizumab on other tumour forms, in earlier stages of disease and as an adjuvant agent, both as monotherapy and in combination with other agents. Two agents, sorafenib and sunitinib malate, inhibiting tyrosine kinase inhibitors targeting the VEGF receptor pathway have recently been approved and have demonstrated efficacy in a variety of tumour forms, such as renal cancer [87, 88]. Several new agents are also in late clinical trials. It has also been shown that continuous low-dose chemotherapy (rather than the conventional high-dose intermittent dosing) has an effect on tumour angiogenesis, thereby inhibiting tumour growth [89].

As with other new classes of agents, the final place for anti-angiogenesis treatment in the management of cancer remains to be seen. The ability to predict which patients will benefit from this type of treatment is an interesting question. Initial studies using anti-angiogenesis treatment combined with conventional chemotherapy have led to varied results, but mostly indicate the additive value of such a combination. Trials are also ongoing to determine the role of angiogenesis inhibition in disease prevention and in early disease stages.

6.8. Biotherapy

Several of the anti tumour agents that have been introduced in recent years are antibodies and thus belong to the class of drugs referred to as biotherapeutic agents. As key problems have been identified and overcome the development of a large number of new antibodies may however be very rapid.

In the 1970s, the hybridoma technique [90] enabled mass production of antibodies with the same binding sites (monoclonal antibodies). The first clinical trials were conducted using murine antibodies (from mice) targeting tumour cell surface structures (antigens). Unfortunately, the results did not meet expectations, largely because of inefficiency of the antibodies and the development of human antibodies against murine antibodies, leading to increased elimination. The development of antibodies where the majority of the molecule is of human origin and only the binding fraction is murine (humanised antibody) has overcome these problems. The high specificity and, in general, low toxicity of antibodies makes them attractive therapeutic options, with a number on the market (Table 6-2) and more than a dozen in late-phase clinical trials.

Table 6-2 Monoclonal antibodies approved for use in oncology

Generic name/Trade name	Indication	Year of first approval	Country of first approval
Rituximab/Mabthera	Non-Hodgkin's lymphoma	1997	US
Trastuzumab/Herceptin	Breast cancer	1998	US
Gemtuzumab /Mylotarg	Acute myeloid leukaemia	2000	US
Alemtuzumab/Campath/MabCampath	Chronic lymphocytic leukaemia	2001	EU
Ibritumomab tiuxetan/Zevalin	Non-Hodgkin's lymphoma	2002	US
Tositumomab/Bexxar	Non-Hodgkin's lymphoma	2003	US
Cetuximab/Erbitux	Colorectal cancer	2003	Switzerland
Bevacizumab/Avastin	Colorectal cancer	2004	US

In 1997, the first monoclonal antibody (rituximab) was introduced in oncology and approved for the treatment of non-Hodgkin's lymphoma, fuelling renewed belief in antibodies as a treatment option in oncology. It was not long before the first antibody for solid tumours, trastuzumab, was approved which has demonstrated impressive results in metastatic disease and as adjuvant treatment in breast cancer [68-70].

One of the challenges in developing efficient antibody therapies is finding parts of the tumour cell that can be targeted that differ from normal cells. Targets other than tumour cell surface structures have, however, proven successful as bevacizumab demonstrates its efficacy in a broad range of solid tumour forms (colon, breast, lung and renal cancer) [83-86]

The binding of radionuclides, immunotoxins or chemotherapeutic agents to the antibody may also enhance the effect of antibodies. Ibritumomab tiuxetan, an antibody targeting CD20 with an attached radionuclide is one example.

6.9. Advances in supportive drug treatment

As survival rates of cancer patients have increased, the development of new classes of 'supportive drugs' has been essential. These drugs enable intensified treatment schedules but also an increase in the quality of life for patients suffering from adverse symptoms of cancer or its treatment. Patients with metastatic disease and those treated with chemotherapy often develop fatigue, low levels of red blood cells (anaemia), decreased white blood cell counts (neutropenia) and nausea, all of which can be ameliorated by supportive drug treatment.

The fatigue of cancer patients is often multi-factorial: it may be related to side effects of treatment and psychological stress; many tumours also secrete substances (cytokines) that may cause fatigue. However, in many cases fatigue is primarily caused by anaemia. Traditionally, anaemia has been treated with blood transfusions, but new drugs (eg epoetin alpha, epoetin beta, erythropoetin) that increase the production of red blood cells have now been developed. In addition, chemotherapy treatment is often associated with bone marrow depression leading to anemia, neutropenia and thrombocytopenia which in turn may delay further chemotherapy treatment. The development of erythropoietin, G-CSF (filgrastim, pegfilgrastim), broad spectrum antibiotics and platelet transfusion techniques has decreased morbidity and mortality in conjunction with intensive treatment and also enabled intensified treatment schedules increasing cure rates.

During the last 10 years, several new agents have been developed to prevent nausea (eg ondansetron, granisetron). Bone metastasis is another field where new drugs have been introduced. Bisphosphonates delay the risk of skeletal events (fractures) as well as providing relief from the pain caused by skeletal metastases.

6.10. Advances towards curing cancer

Although cancer is a common disease affecting roughly every third person during their lifetime, approximately 50-60% of patients diagnosed with cancer will either be 'cured' or will die from other causes. Progress in the medical treatment of cancer has been made in almost every area of oncology. In most tumours, stepwise and relatively modest improvements in oncology management have, over time, resulted in impressive increases in the proportion of patients considered 'cured' of their cancer. For instance, overall breast cancer mortality in the US and UK has been reduced by 25% from the 1980s to 2000 [91]. This progress is to some extent the result of screening programs enabling earlier detection of the disease but also a true reduction in mortality due to improvements in adjuvant treatment - for instance, anthracycline based poly-chemotherapy reduces the annual breast cancer death rate by about 38% for women younger than 50 years of age when diagnosed and by about 20% for those of age 50-69 years when diagnosed. Additional use of 5 years of tamoxifen treatment in ER-positive disease results in a reduction of the annual breast cancer death rate by 31% [92]. Improved chemotherapeutic regimes have increased survival further and recently, adjuvant treatment with trastuzumab in patients with HER2 positive disease have indicated a 50% decreased relapse risk and a 33% reduced mortality risk after 3 years [69, 70].

Considerable progress has also been made in other major tumours, like colon cancer where adjuvant chemotherapy have reduced mortality with 20-30% [93-95] and chemotherapy in the metastatic setting has increased average survival four fold, from 5 to 20 months in 15 years [83]. In other diseases like aggressive non-Hodgkins lymphoma (NHL), the combination of CHOP plus rituximab results in a five year survival rate of 58% in patients over 60 years [96] and a 2-year overall survival of 95% in patients below 61 years [97].

In other areas of oncology, such as testicular cancer and Hodgkin's disease, the changes in 'cure' rates have been sudden and dramatic. With the introduction of the MOPP regimen (nitrogen mustard, vincristine, procarbazine and prednisone) in 1967, cure rates of over 50% were obtained in patients with advanced Hodgkin's disease [98]. This was a milestone in medical oncology, proving the ability of chemotherapy to cure even in advanced stages of disease. Since then, even higher cure rates (90%) have been obtained using new combinations of chemotherapy [99]. In testicular cancer, the prognosis has turned from one of the worst to one of the best among cancer diagnosis. The introduction of a cisplatin in the 1970s was an immediate breakthrough in the treatment of testicular cancer [100]. The addition of further chemotherapy agents to surgery and local radiotherapy has further increased curative rates in patients with metastatic testicular cancer disease to approximately 90-95%.

However, it's important to note that since breast cancer is a much more common disease, the number of patients cured of breast cancer far exceeds that of those cured of testicular cancer and Hodgkin's disease, in absolute terms.

6.11. Advances towards the prevention of cancer

A number of agents that cause cancer have been brought to light. Epidemiological research has shown that cancer risk is associated with various external and lifestyle factors such as smoking,

alcohol consumption, obesity, exercise habits and exposure to certain viruses. Cancer can be prevented. For example, it has been known for more than 50 years that smoking increases the risk of developing many cancers, especially lung cancer. Very little has been done in order to change smoking habits, which has resulted in the global epidemic of lung cancer we now see. The strong relationship between hormone exposure and breast cancer was the rationale for the first chemoprevention trials in women with an increased genetic risk of breast cancer who were found to benefit from treatment with tamoxifen (50% risk reduction) [101]. In the US, the Food and Drug Administration (FDA) has approved the use of tamoxifen as a preventive agent in high-risk patients. However, no such license exists in Europe.

Recently, raloxifene (an agent similar to tamoxifen) has proved as efficient as tamoxifen as a preventive agent but with less side effects [102]. There are also several ongoing studies with aromatase inhibitors, which lower the production of oestrogen, as preventive agents for breast cancer. Other agents that have indicated their effect as preventive agents are non-steroidal anti-inflammatory drugs in colon cancer [103], finasteride in prostate cancer [104] and recently statins in breast cancer [105]. The fact that there are agents that can be used for prevention of cancer is in itself an important milestone in oncology.

The first vaccines against human papilloma virus [106] - the causative agent of the vast majority of cervical cancer in women are on the market, but their full potential will require politicians and those responsible for reimbursement decision to realize the importance and full value of preventive measures.

The area of cancer prevention is complex and involves political as well as medical measures. From a medical perspective, the main challenge is finding preventative agents/measures that are non-toxic and well tolerated. As costs for cancer treatments continue to increase, the value of preventive measures will become more pronounced.

6.12. Summary

Oncology has entered an exciting phase in which extensive research is paying dividends in the form of new treatments designed to target disease-specific mechanisms. It is clear that in some tumour forms that these agents will replace generally cytotoxic agents as first line treatment whereas in other tumour forms their final place in the therapeutic arsenal is still unclear. The number of new agents with anti tumour effects has accelerated during the last 10 years and, judging from the number of ongoing trials and pipelines of pharmaceutical companies, there is every reason to believe that this trend will continue in years to come. Intense research in molecular medicine and tumour biology will also lead to the identification of more potential targets of intervention. The dividends mentioned above are, however, only realised once these drugs are adopted into routine clinical practice and reach the patients that may benefit from them. The following section looks at the speed of uptake of a number of new agents that have recently become licensed in the selected countries. Within the report, we then go on to look at factors that impact the availability of innovative treatments to patients.

7. Uptake of oncology drugs in the Middle East region

During the past 15 years (1990-2004) on average two new oncology drugs have been introduced per year worldwide. In order to give an idea of the market uptake of new oncology products in the Middle East the market introduction and total sales of five recent and innovative oncology products were analysed.

For each drug, uptake is presented as sales (€) from the time of local introduction or first period of sales (a drug could have been sold under special license prior to national authorization). Data are given for sales per cancer case in the main indication of the drug. The Middle East data are also put in relation to the uptake in France, representing a high European uptake and the UK, representing a low European uptake and to E-13 representing the average uptake of the drug in the following European countries: Austria, Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland and the UK. In addition to this European comparison the uptake in the US is also illustrated.

The drugs presented are the products for which we were able to obtain sales data for a relevant period of time in the countries. They are all Roche products due to the availability of such data to us, and the difficulty of obtaining complete data on sales of other oncology drugs in the Middle East region; however they are also characterised as being breakthrough products for their respective indication. The annual sale statistics in the period 2000-2006 were obtained from Roche Middle East offices. Sales data are presented as trade prices (wholesaler selling price). Data are presented in nominal prices and have been converted to Euros, using the average market exchange rate for each year. Since the sales are presented in nominal values, consumer price index rates for the study countries are presented as reference for the total period 2000-2006 rates were slightly negative (0.92-0.99) in Lebanon, Bahrain, Oman, and Saudi Arabia, in Kuwait, Jordan and Qatar CPI for the six-year period was 1.09-1.15, it was 1.21 in United Arab Emirates, and as much as 1.41 in Egypt; the Egyptian pound was considerably devaluated during the period [107].

Drug sales per cancer case are first presented for all countries combined based on cancer incidence estimates from Globocan 2002. Thereafter drug uptake per cancer case as reported in national cancer registries are presented for the countries divided in three groups in order to better illustrate the uptake in the individual countries. Due to the low number of cancer cases reported in national registries in some of the ME-6 countries, especially in the United Arab Emirates and Qatar, where only 20% of the populations are nationals and cancer cases reported in national cancer registries amount to only 10% and 24% respectively of what Globocan estimates, the drug uptake curves for these countries based on national cancer registry data express extremely high drug expenditure per cancer case, up to €70,000 for some drugs in United Arab Emirates. In Saudi Arabia and Kuwait cancer cases in national registries are 45% and 43% respectively of what Globocan reports, in Bahrain and Oman 62% and 65% or what Globocan reports, these differences have to be taken into account when interpreting the uptake curves in the various graphs. For Lebanon the total number of cancer cases reported by national registry is 1.5 times higher than what Globocan estimates, and in particular the Globocan estimates for colorectal cancer cases appears to be too low, set to 125 cases in Lebanon as compared to 622 cases reported by the national registry, this explain the unrealistically high resulting expenditure per cancer case in Lebanon on the drugs capecitabine and bevacizumab that are seen in figures 7-5 and 7-9. Due to the lack of a national cancer registry in Egypt, cancer cases in Egypt are based on Globocan estimates in all curves.

7.1. Breast cancer

Breast cancer represents the most drug-intensive area when it comes to treatment of solid tumours. Tamoxifen, launched in 1975 and once also considered a costly treatment with limited effects, has established itself as the most cost-effective cancer treatment to date. Its broad indication for the treatment of advanced disease and adjuvant treatment (and prevention in the US) represents a major breakthrough in the treatment of breast cancer. Newer, innovative drugs (aromatase inhibitors; anastrozole, exemestane and letrozole) are now replacing, fully or in part, tamoxifen, both in the treatment of advanced disease but also in the adjuvant setting. In addition, anthracyclines and taxanes have established themselves as very valuable palliative and adjuvant treatments.

Trastuzumab, a HER2 receptor antibody, has become a cornerstone of treatment for patients with advanced breast cancer over-expressing HER2, and has now been approved in many countries, based on strong clinical data (2005), in the adjuvant setting. Diagnostic testing of women diagnosed with breast cancer determines whether a patient is a candidate for hormonal treatment as well as for trastuzumab treatment. We have illustrated the adoption of new drugs in breast cancer with the uptake of trastuzumab.

Figure 7-1 Illustrates the use of trastuzumab per cancer case as estimated in Globocan 2002

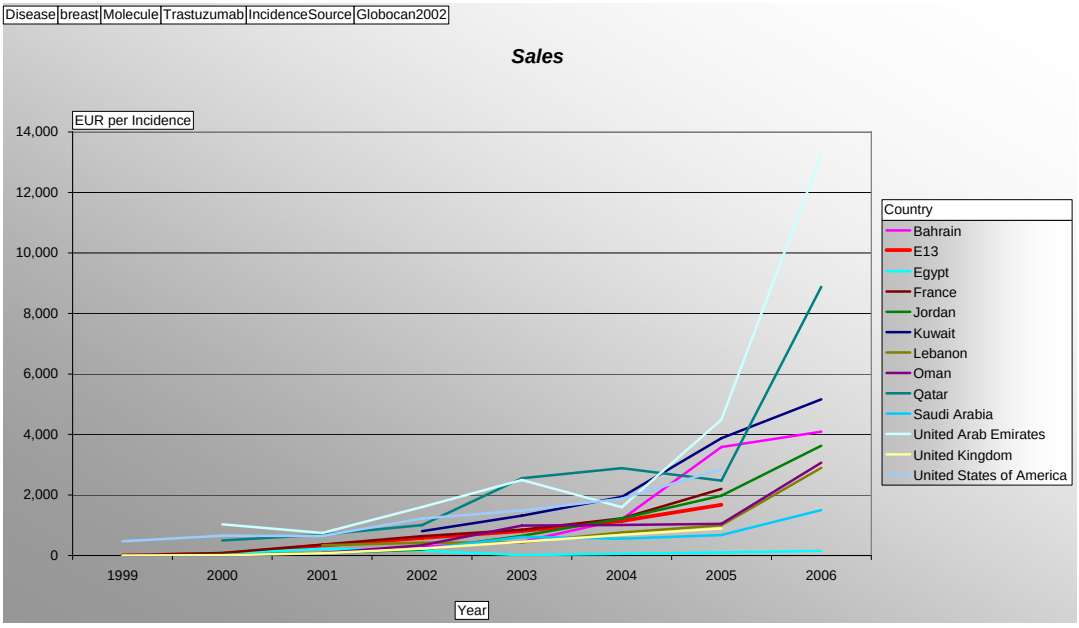


Figure 7-2 Illustrates the use of trastuzumab per cancer case as most recently reported in National Cancer Registries in Egypt, Jordan, Lebanon, United Kingdom and E-13

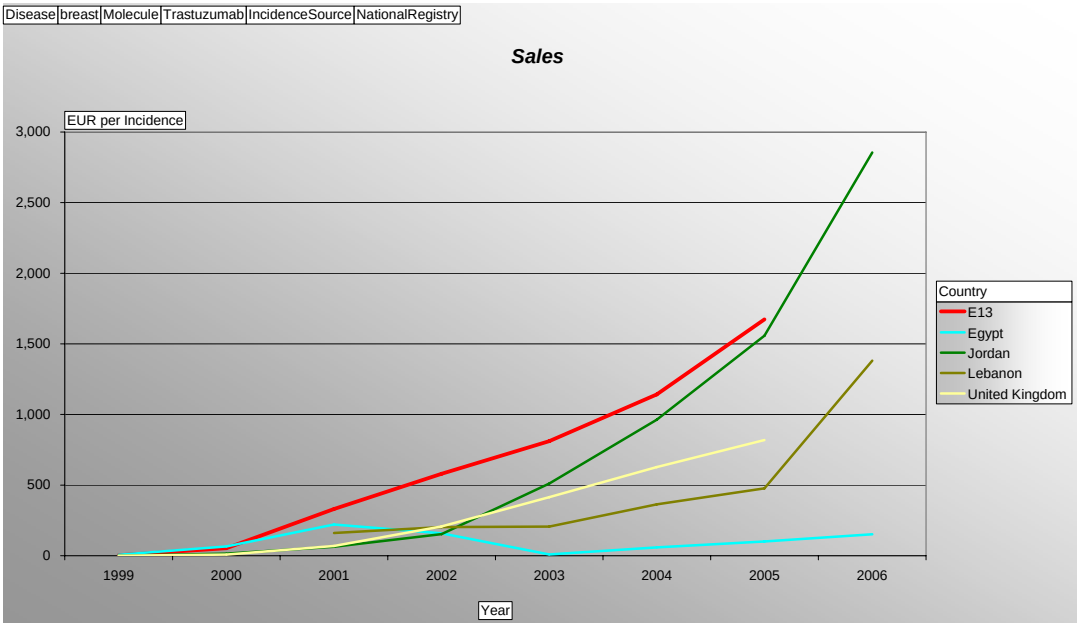


Figure 7-3 Illustrates the use of trastuzumab per cancer case as most recently reported in National Cancer Registries in Bahrain, Oman, Saudi Arabia, France and E-13

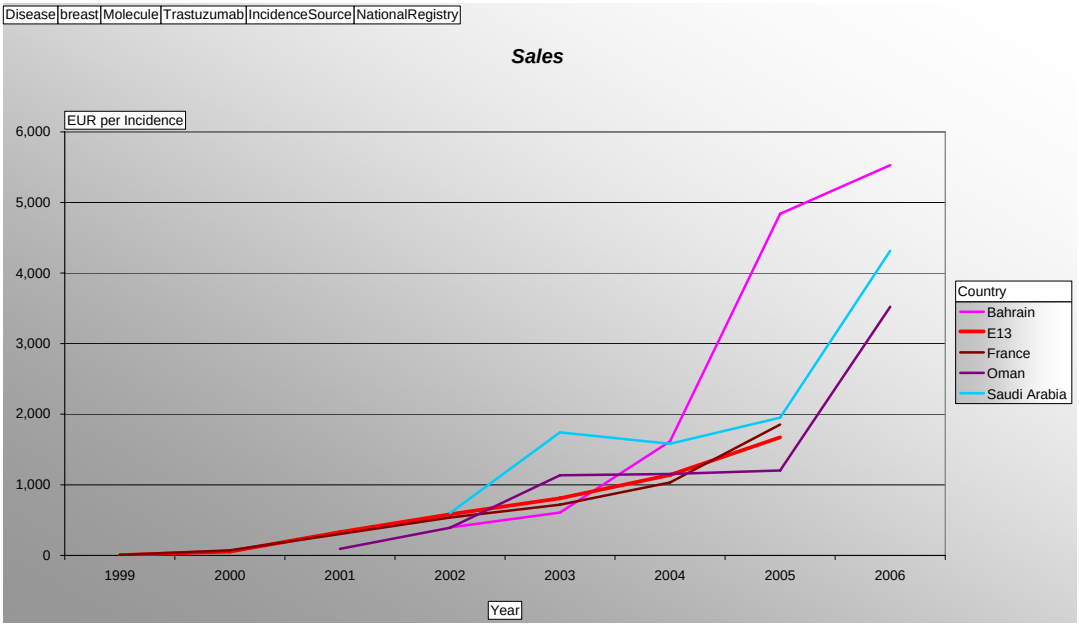
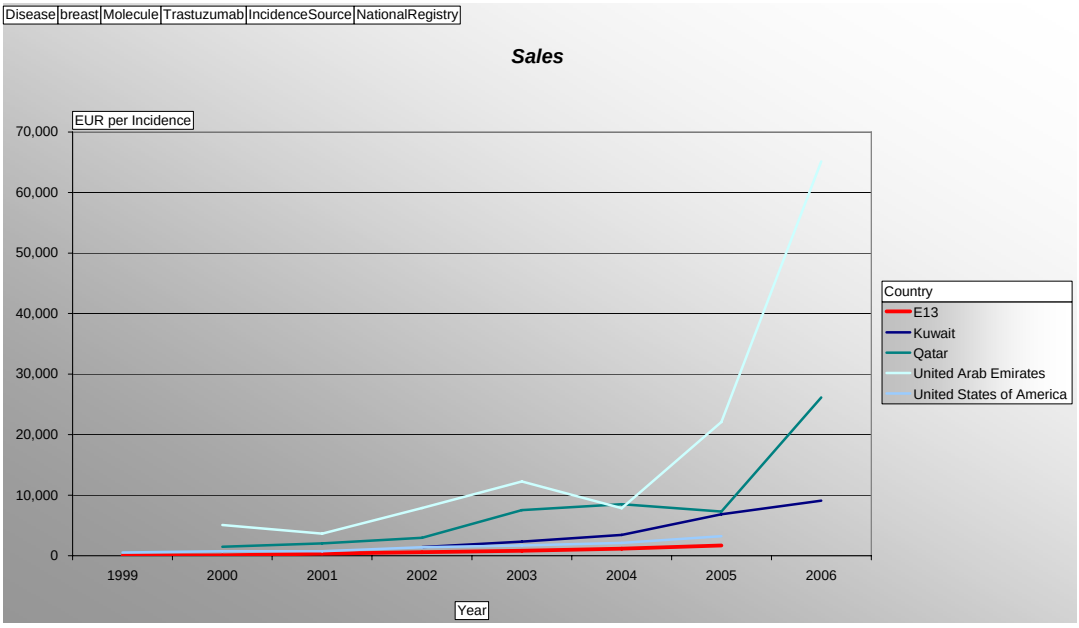


Figure 7-4 Illustrates the use of trastuzumab per cancer case as most recently reported in National Cancer Registries in Kuwait, Qatar, United Arab Emirates, United States and E-13



The drug uptake curves for trastuzumab indicate that the uptake profile of the drug in the ME is in line with that of Europe and the US. The estimates of drug expenditure per case are dependant on the price level of the drugs as well as the uncertainties in cancer incidence that prevail in the incidence estimates available that have been presented previously in this report therefore it is more relevant to look at the trends of the uptake curves from a holistic perspective than comparing the spending per case in an individual country. Another factor influencing the cost per case is the diagnostic patterns of breast cancer, the share of metastatic cases out of total breast cancer cases, since until 2006 trastuzumab was indicated only for metastatic disease. There are clear tendencies of increased uptake of the drug as a consequence of the new indication for adjuvant treatment in early breast cancer from 2005 in most of the ME-9 countries. Unfortunately we did not have access to data from E-13 and the US for 2006 to be able to compare the trends in these countries.

7.2. Colorectal cancer

Until the end of the 1980s, colorectal cancer remained a therapeutic area in which medical treatment was considered to have little or no effect. Developments in diagnostic and surgical techniques were major contributors to outcome improvement. With the publication of the adjuvant data on modulated 5-fluorouracil (5-FU)-based therapy in the late 1980s and mid 1990s, colorectal cancer rapidly became an area of focus for further drug development. In the mid 1990s, both irinotecan and oxaliplatin became established additive agents to modulated 5-FU, which was still the cornerstone of treatment for both early and advanced colorectal cancer. Recently two new innovative drugs, bevacizumab and cetuximab, have also been approved for the treatment of advanced colorectal cancer; representing a new breakthrough in the treatment of the disease. Bevacizumab is an anti-angiogenesis drug with its indication in the first line treatment of advanced colorectal cancer. Cetuximab, which interacts with the epidermal growth factor (EGF) receptor, is indicated in the 2nd or 3rd line treatment of metastatic disease.

Here we illustrate drug uptake in colorectal cancer through the sales of oral 5-FU; capecitabine and bevacizumab. Capecitabine is also approved for breast cancer and bevacizumab is now also approved (during 2007) for use in breast, lung and renal cancer in some countries.

Figure 7-5 Illustrates the use of capecitabine per cancer case as estimated in Globocan 2002

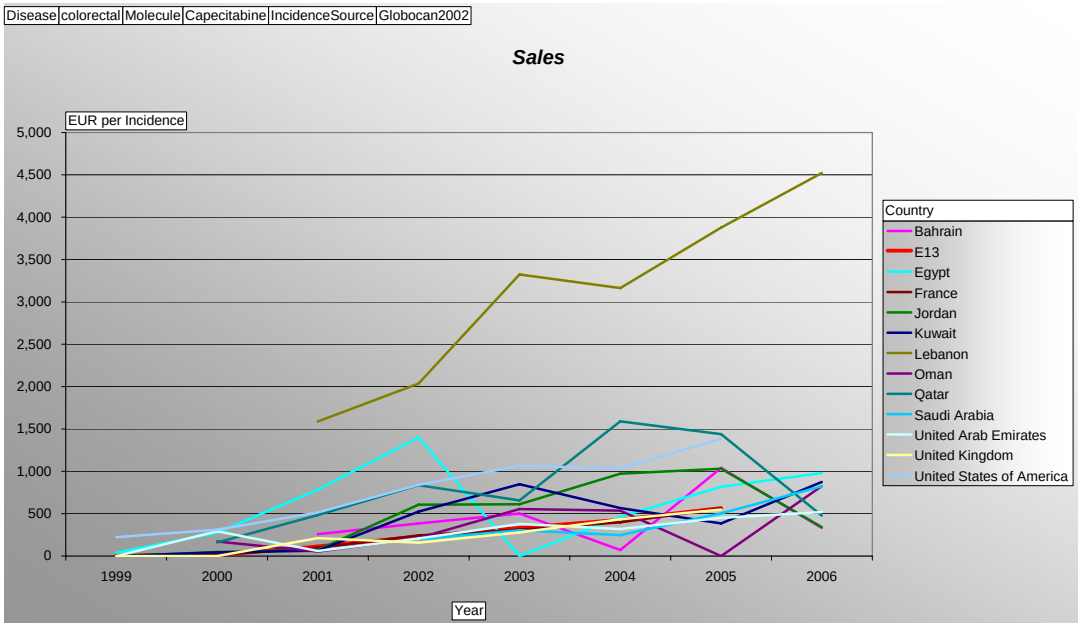


Figure 7-6 Illustrates the use of capecitabine per cancer case as most recently reported in National Cancer Registries in Egypt, Jordan, Lebanon, United Kingdom and E-13

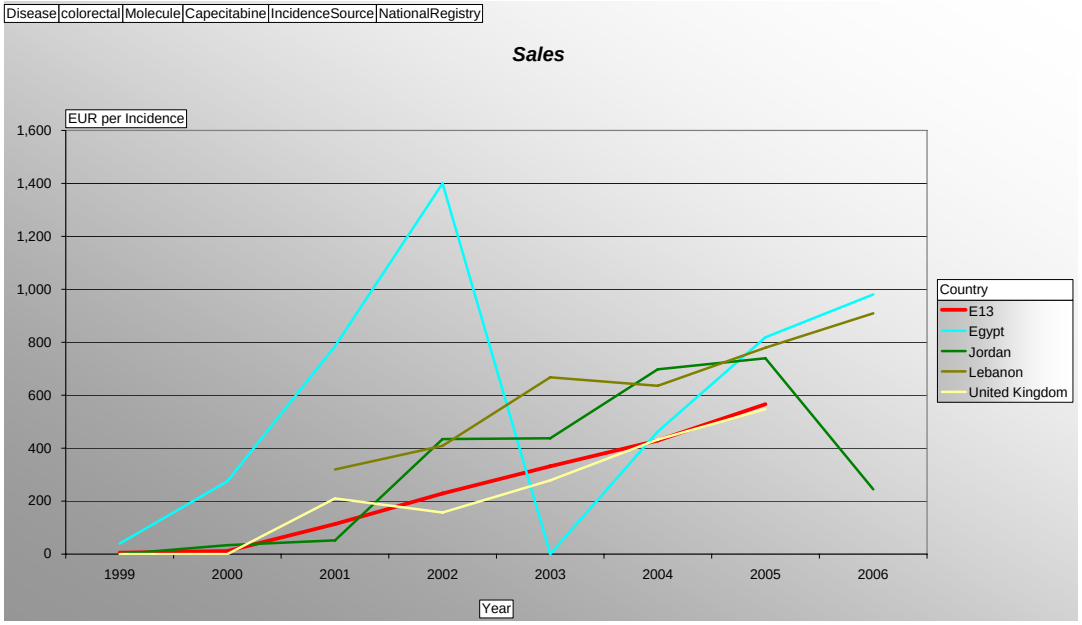


Figure 7-7 Illustrates the use of capecitabine per cancer case as most recently reported in National Cancer Registries in Bahrain, Oman, Saudi Arabia, France and E-13

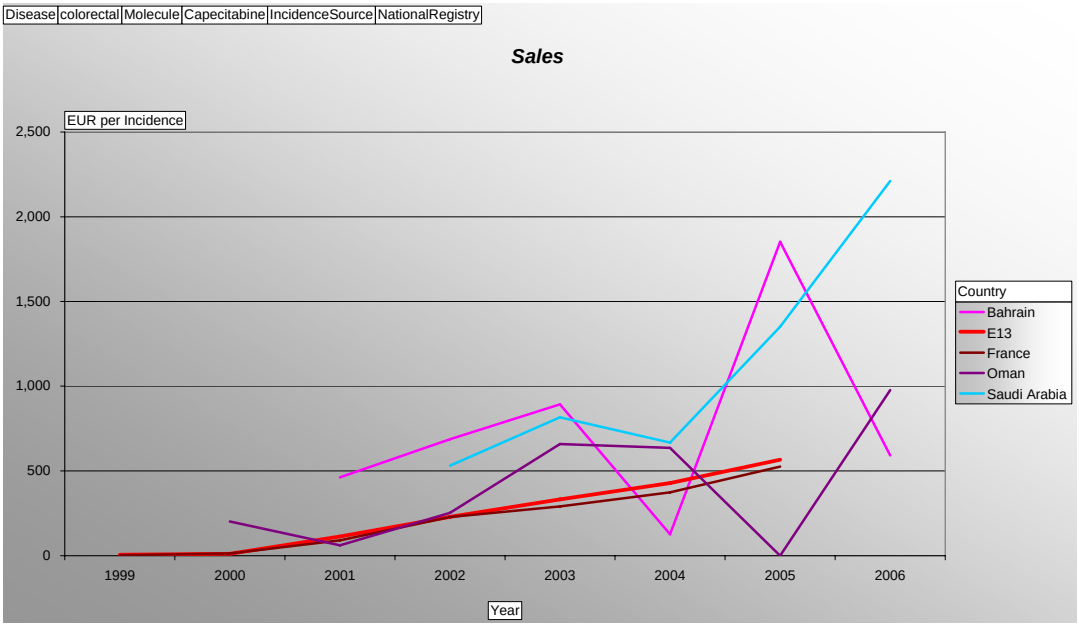
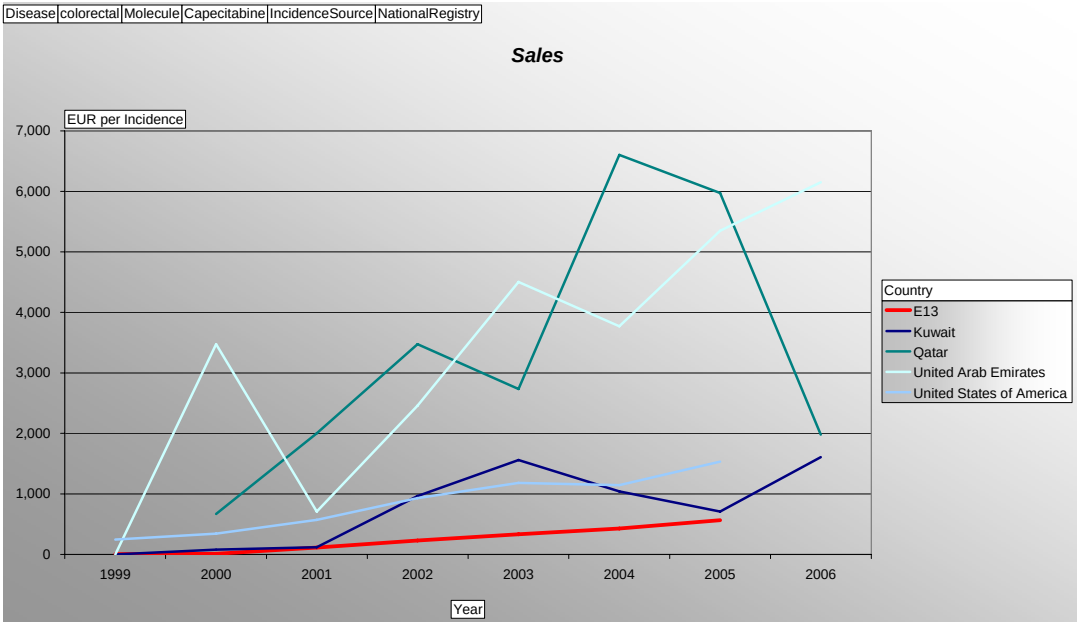


Figure 7-8 Illustrates the use of capecitabine per cancer case as most recently reported in National Cancer Registries in Kuwait, Qatar, United Arab Emirates, United States and E-13



Also for capecitabine, drug sales per cancer case for capecitabine appears to be in line with or higher than the sales per case in the comparator countries in Europe and the US. The big fluctuations in drug uptake for some of the ME-6 countries indicate that bulk purchasing was made of the drug for longer time periods. The sales per cancer case of capecitabine in Egypt was very high in 2002 falling to nothing in 2003, due to foreign currency issues in 2002 in Egypt, nevertheless, it is notable that the uptake of capecitabine per cancer cases in Egypt is higher than

in the other countries presented in figure 7-6 also when looking at the average of the eight-year period due to the relatively low spending on cancer drugs overall in Egypt as compared to the other countries.

Figure 7-9 Illustrates the use of bevacizumab per cancer case as estimated in Globocan 2002

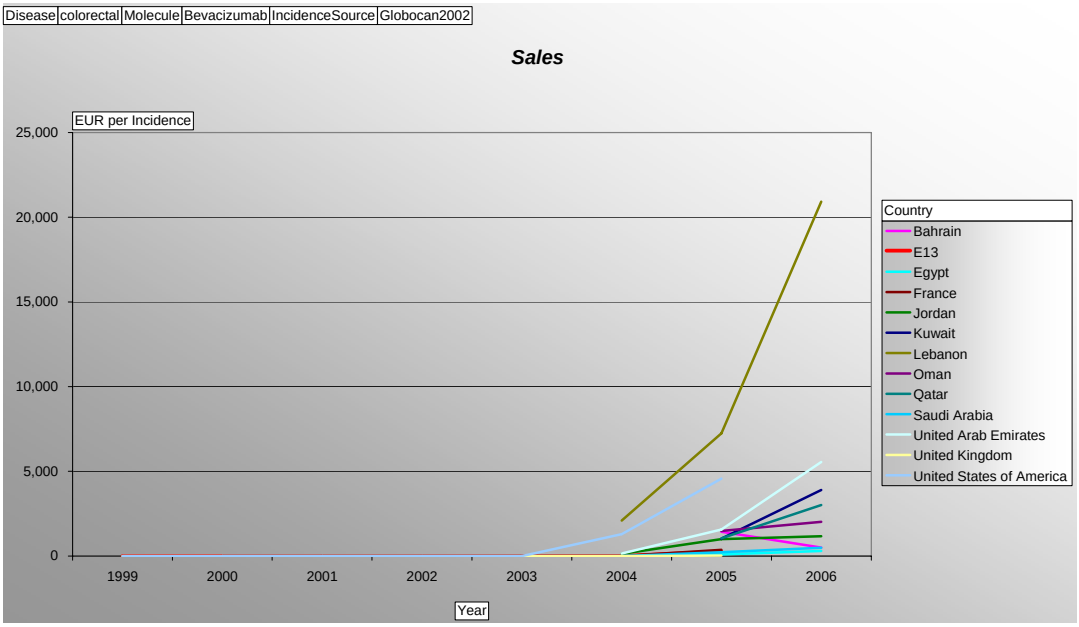


Figure 7-10 Illustrates the use of bevacizumab per cancer case as most recently reported in National Cancer Registries in Egypt, Jordan, Lebanon, United Kingdom and E-13

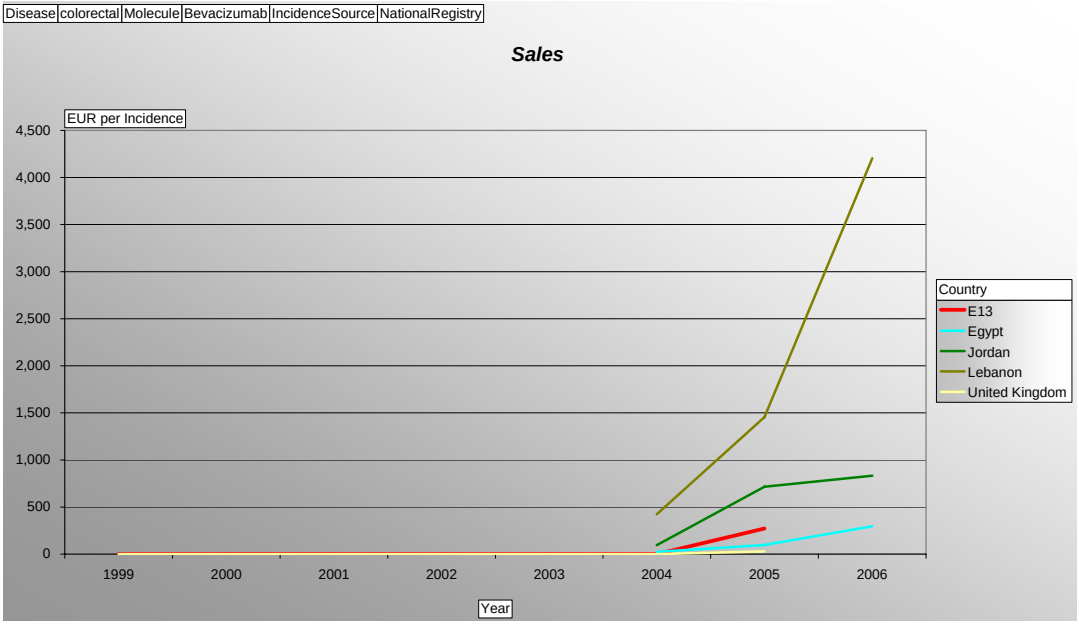


Figure 7-11 Illustrates the use of bevacizumab per cancer case as most recently reported in National Cancer Registries in Bahrain, Oman, Saudi Arabia, France and E-13

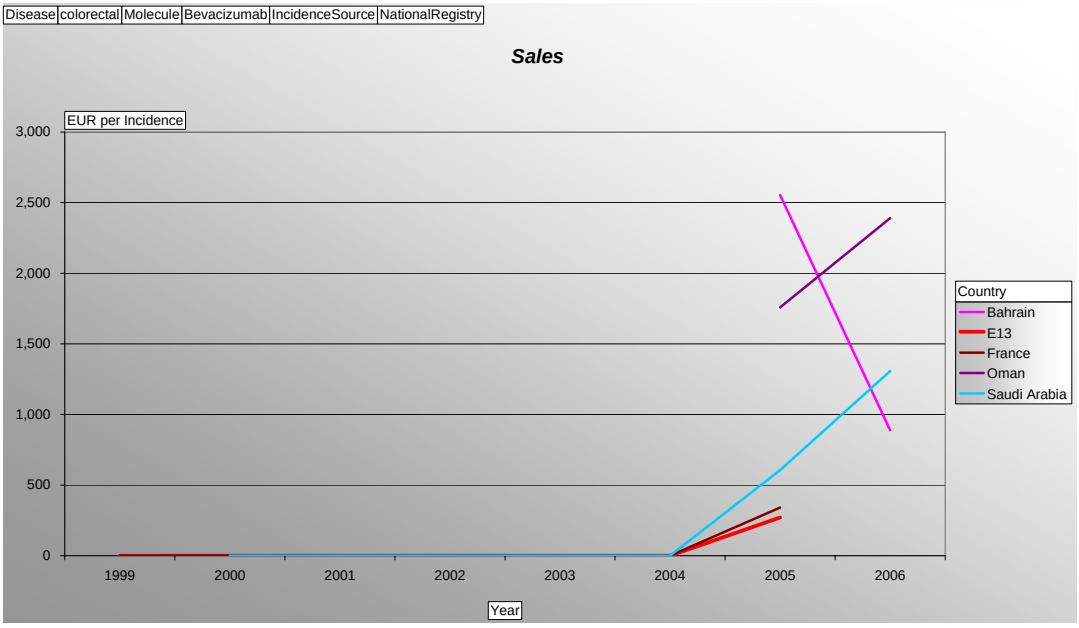
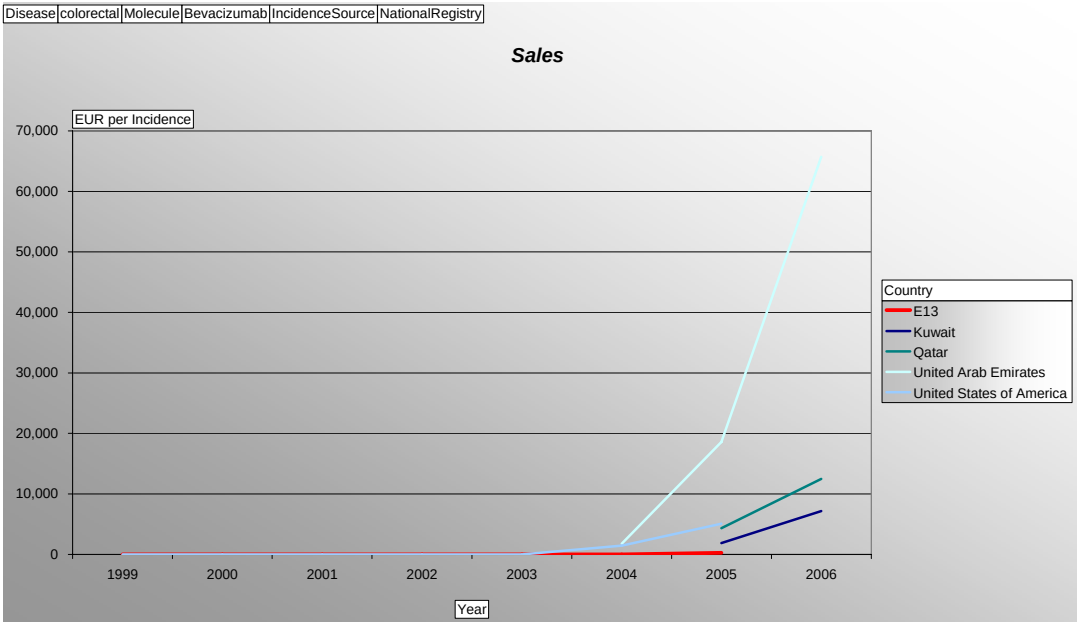


Figure 7-12 Illustrates the use of bevacizumab per cancer case as most recently reported in National Cancer Registries Kuwait, Qatar, United Arab Emirates, United States and E-13



The unrealistic estimate of colorectal cancer cases in Lebanon is reflected also in graph 7-9, however the sales per cancer case of bevacizumab is considerably higher in Lebanon than in Europe also as related to cancer cases reported in the national registry. €1,500 per colorectal cancer case in 2005 and increasing to €4000 in 2006 as compared to €300 per case in E-13 and even less in the UK, see figure 7-10. The uptake in the European countries remained low up until 2005, the last year data was available, as compared also to the ME-6 countries.

7.3. Non-small cell lung cancer

NSCLC has for long been an area of therapeutic nihilism in many countries. It was not until a decade ago, when platinum-based chemotherapy was shown to provide a clear benefit for patients with advanced disease, that the development of modern chemotherapy in this area of oncology escalated. We now also have solid clinical evidence that adjuvant chemotherapy will also give substantial benefit in selected patients. During the 1990s new chemotherapy agents like taxanes (docetaxel, paclitaxel), gemcitabine and vinorelbine came into use in the combination with cis- or carboplatin.

There are now new therapeutic options in NSCLC, including EGFR-targeting agents such as cetuximab and erlotinib and chemotherapy with pemetrexed. In the following graphs we illustrate the uptake of erlotinib.

Figure 7-13 Illustrates the use of erlotinib per cancer case as estimated in Globocan 2002

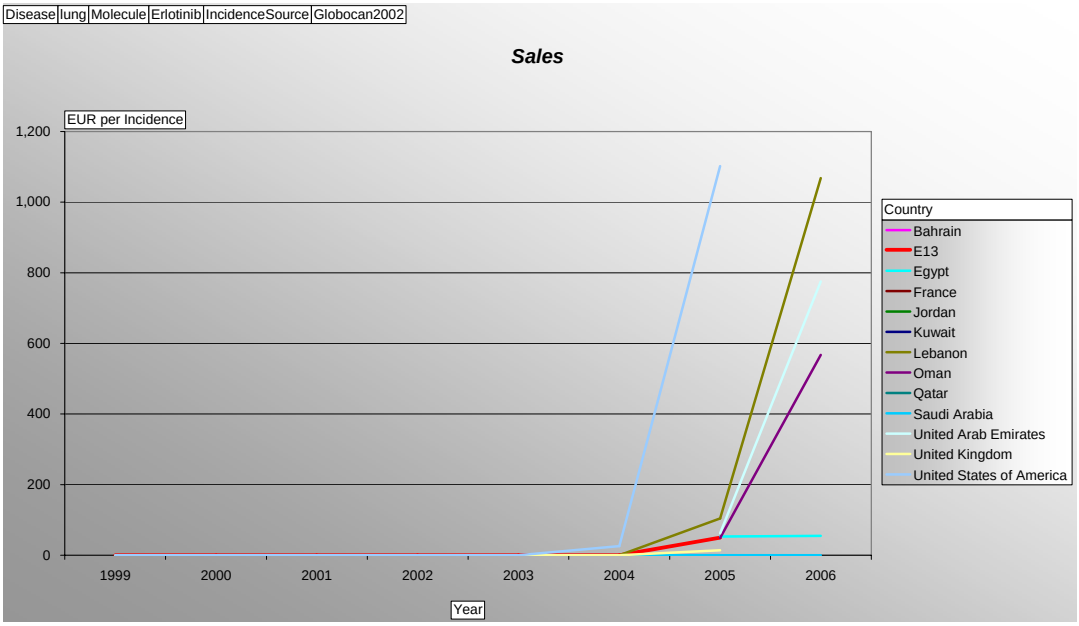


Figure 7-14 Illustrates the use of erlotinib per cancer case as most recently reported in National Cancer Registries in Egypt, Jordan, Lebanon, United Kingdom and E-13

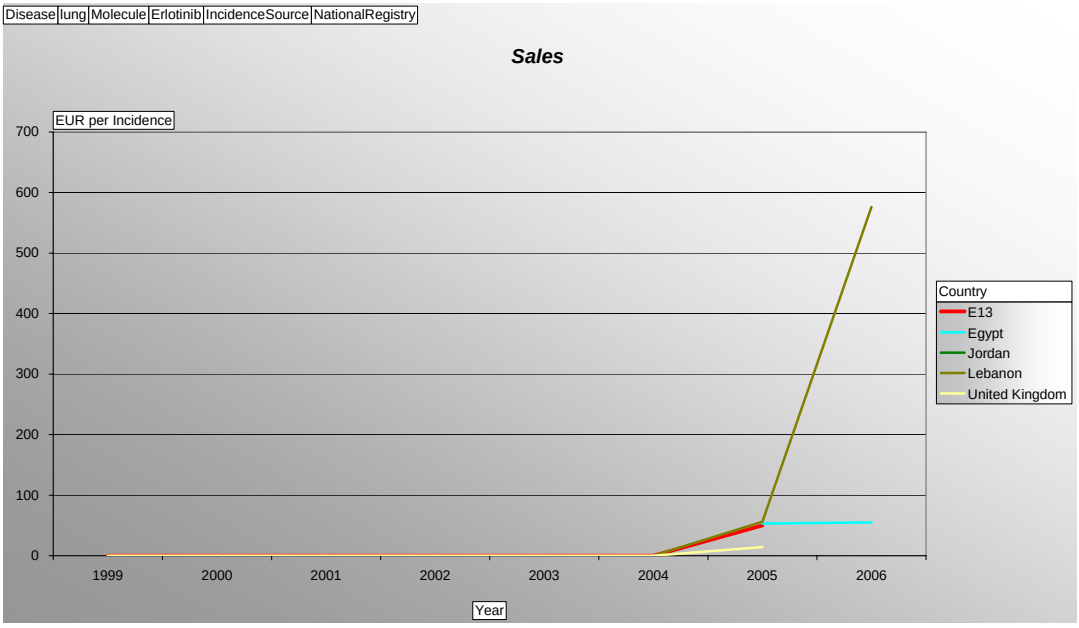


Figure 7-15 Illustrates the use of erlotinib per cancer case as most recently reported in National Cancer Registries in Bahrain, Oman, Saudi Arabia, France and E-13

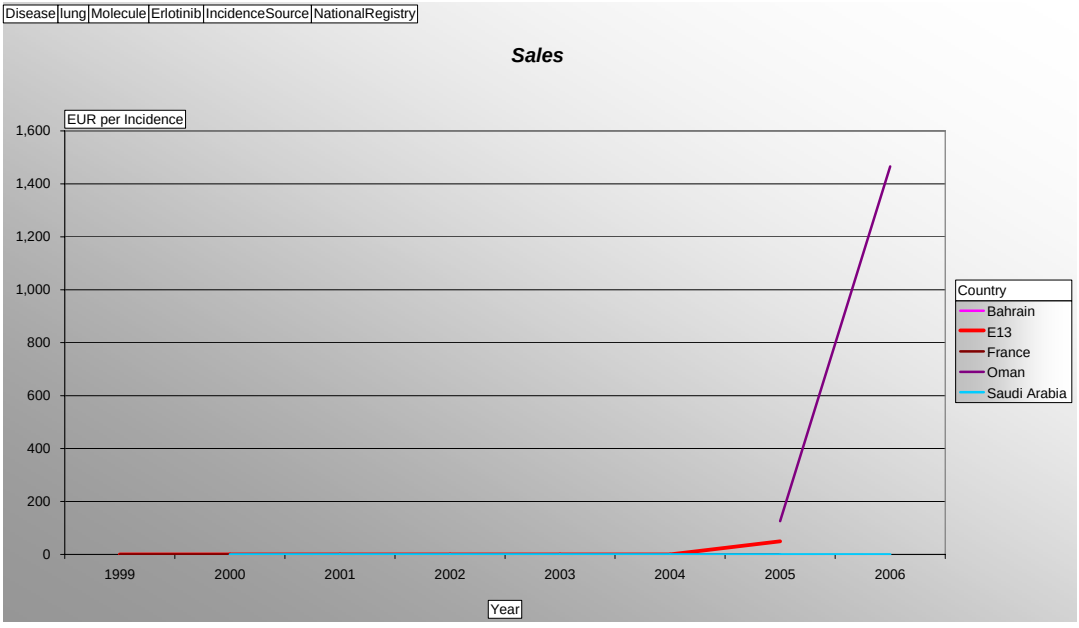
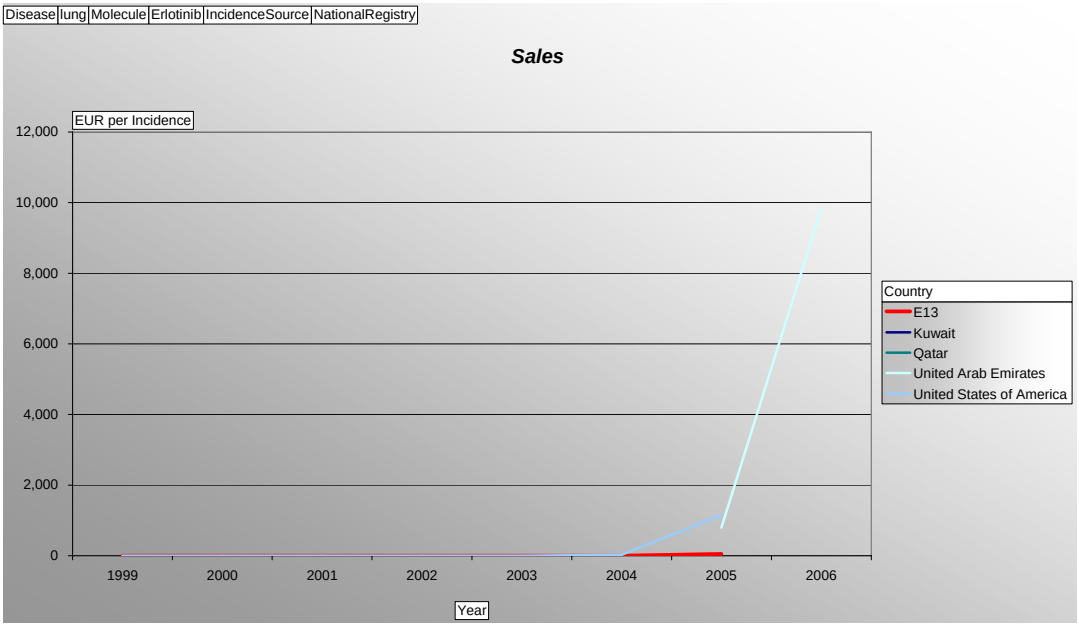


Figure 7-16 Illustrates the use of erlotinib per cancer case as most recently reported in National Cancer Registries in Kuwait, Qatar, United Arab Emirates, United States and E-13



In figure 7-13, the uptake curves for erlotibin in Lebanon, United Arab Emirates and Oman show similar trends as in the US one year before. Sales in E-13 remained low in 2005.

7.4. Non-Hodgkin's lymphoma (NHL)

NHL represents a malignant disease in which major breakthroughs have been seen. Rituximab has become an important treatment option and has, with expanding indications, become a standard component in the treatment of NHL.

Figure 7-17 Illustrates the use of rituximab per cancer case as estimated in Globocan 2002

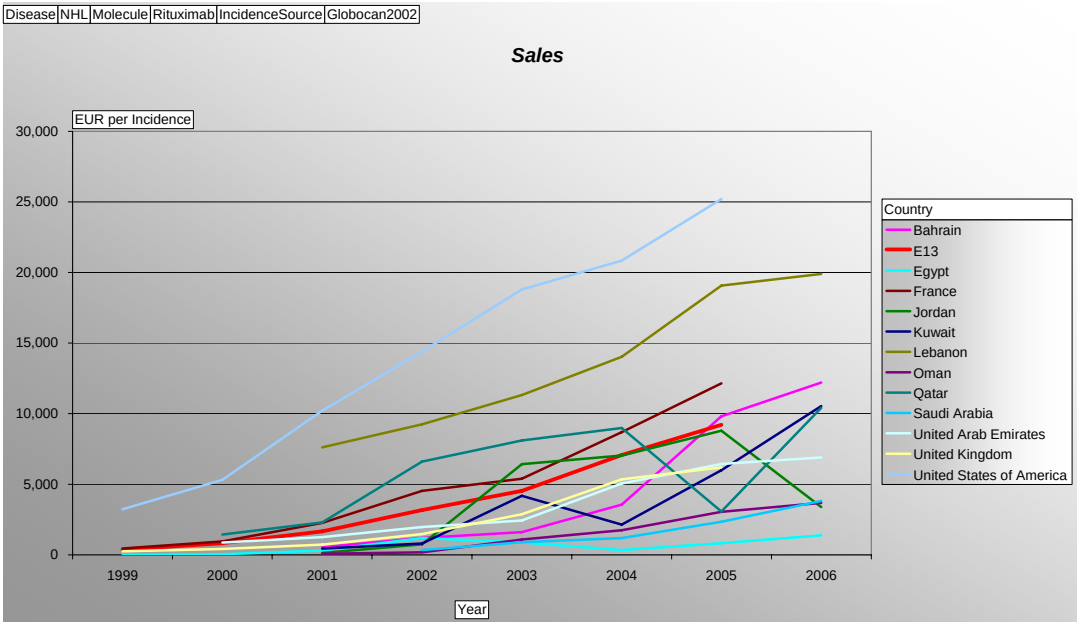


Figure 7-18 Illustrates the use of rituximab per cancer case as most recently reported in National Cancer Registries in Egypt, Jordan, Lebanon, United Kingdom and E-13

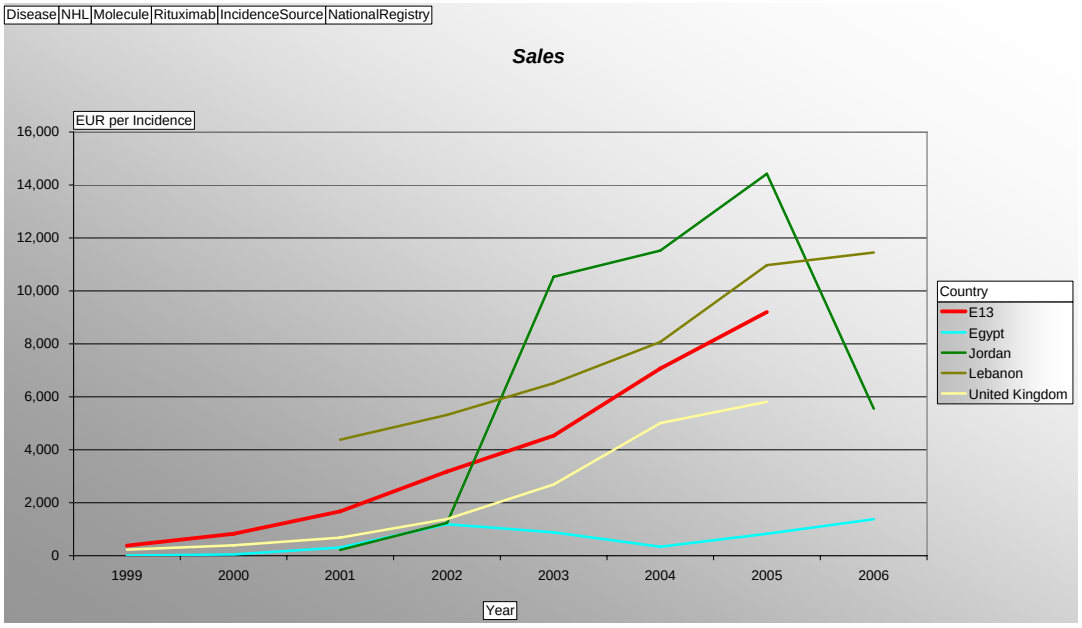


Figure 7-19 Illustrates the use of rituximab per cancer case as most recently reported in National Cancer Registries in Bahrain, Oman, Saudi Arabia, France and E-13

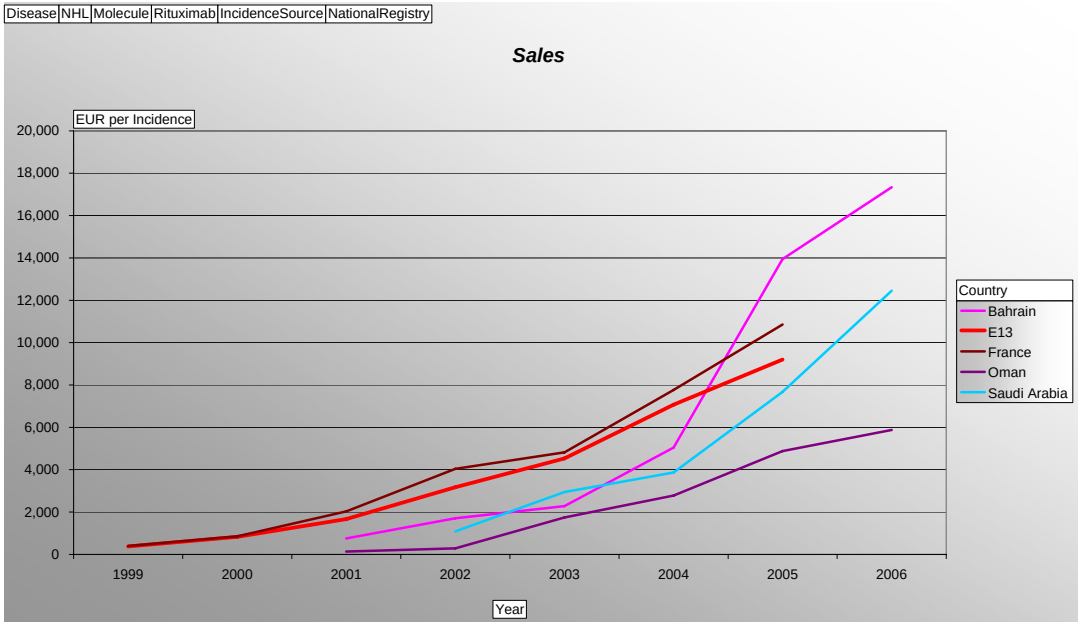
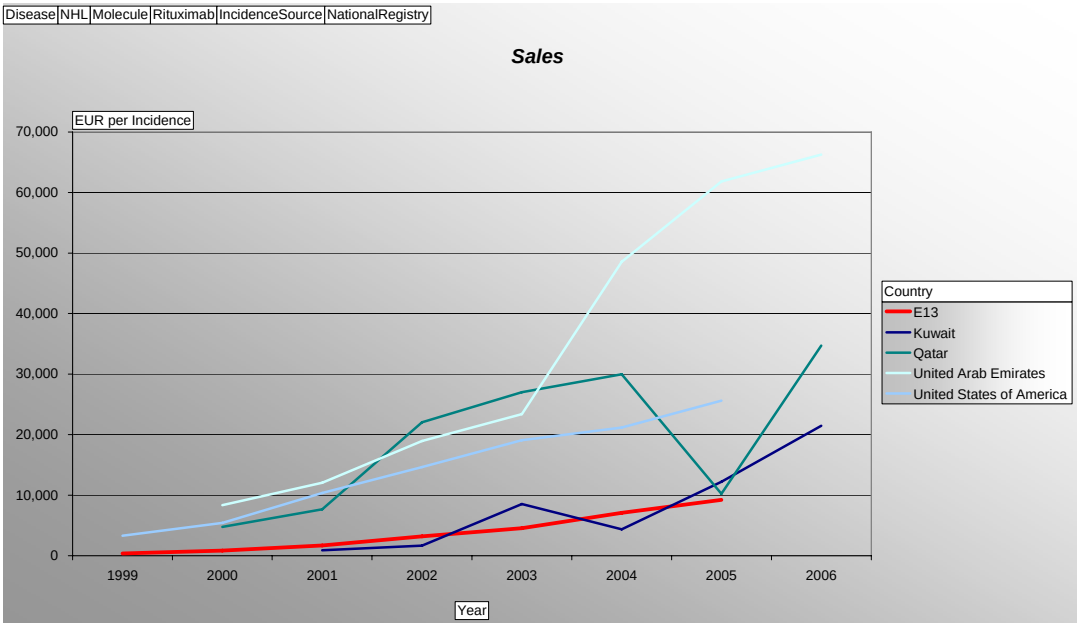


Figure 7-20 Illustrates the use of rituximab per cancer case as most recently reported in National Cancer Registries in Kuwait, Qatar, United Arab Emirates, United States and E-13



In figure 7-17, the US shows the greatest sales per NHL case of rituximab, however Jordan and Lebanon show sales that are above the European average in both figures 7-17 and 7-18. However, the Globocan estimates for NHL in Lebanon appears to be unrealistically low like for colorectal cancer since the number of cases reported in the national cancer registry results in a level more in line with that of the other countries. Rituximab sales in Bahrain increased considerably between 2004 and 2005.

7.5. The approval process of new cancer drugs

The assessment of a new drug's safety, efficacy, and quality before the granting of market authorisation or licence is a complicated and often time consuming regulatory process. Most countries have national medicine agencies responsible for authorising new pharmaceuticals for sale. In ME-9, it is generally the Ministry of Health that is responsible for the drug authorisation process. Since 2004, the Gulf countries are harmonising the marketing application process in the countries, under the coordination of the Gulf Central Committee for Drug Registration. However national applications are still made in the Gulf countries. Dossiers are then usually prepared to a standard acceptable in Saudi Arabia, since the review system of Saudi Arabia is considered the most rigorous [108].

The registration process of pharmaceutical products in the Middle East countries differs from other regions in the world in the sense that a company registration, including documentation for each manufacturing site and all relevant company subsidiaries, is required in addition to individual product applications and in some countries this company registration must be approved before product registration (Bahrain, Oman, Saudi Arabia). In other countries the company and product registration can be filed in parallel (Egypt, Jordan, Kuwait, Lebanon, Qatar, United Arab Emirates). There are no time limits for the review of company registration, and that may considerably delay the product registration process in some countries [108]. There is also requirement for a Certificate of Pharmaceutical Product (CPP) at the time of marketing authorisation application or at authorisation. A CPP is a certificate issued by the national health authorities upon request from the manufacturer, the customer, or the authorities in the importing

country. The certificate is issued for a specific product and states whether or not the product is marketed in the country of origin. Furthermore, it states that the manufacturer of the product complies with Good Manufacturing Practice and is inspected regularly by the national health authorities.

A 2001 study by Centre for Medicines Research International assessed the regulatory and health care environment in the Middle East; data was collected on companies' pharmaceutical registration and authorisation activities in the Middle East between 1999 – July 2001 [109]. Comparing this information with previously collected data, from 1995 – 1998, revealed decreases in review time in some of the countries, most notably in Qatar. Review times remained relatively short over the entire period in Bahrain and Kuwait, at less than six months, but remained static at or increased to over 1.5 years in Saudi Arabia and Egypt during the measurement period. (See figure 7-21.)

The health ministries in the study countries assessed that the main reason for delayed access to new medicines for patients in the region was lack of internal resources within the ministries of health. They requested educational workshops with pharmaceutical companies concerning the drug development process and a harmonisation of regulatory requirements. An initiative that has been successful in promoting dialogue between the pharmaceutical industry and Middle East ministries of health is the Middle East Regulatory Conferences (MERC), established in the mid 1990s, that has helped ministries throughout the Middle East require pricing information from the country of origin and other countries in the region upon Marketing Authorisation Application (MAA).

In Bahrain, the drug registration system is generally considered efficient. The average approval time for new drugs is three to six months. However the country has a policy that requires that new pharmaceutical products should be marketed in another country for a minimum of two years as a condition for local marketing authorisation to ensure adequate pharmacological efficacy and safety. Although exceptions are frequently granted, this regulation is a hurdle to technology transfer and slows down access to hi-tech drugs. For pharmaceutical imports, the product should be licensed in Saudi Arabia and in one other GCC country before it can be placed on the Bahraini market [32].

Kuwait's registration system is one of the most efficient in the region, there is a streamlined process for the registration of new drugs provided that the drugs have been approved in a "major" reference country, e.g. products with US, EU or Japanese approval usually experience little difficulty in gaining access to the market. Registration takes six to 24 months, with a fast-track process for life-saving medicines [32].

In Oman, product registrations generally take between six and 12 months, but if a drug is not imported within a year of approval, it may be de-registered and the process has to be repeated. Registration must also be renewed every five years. Like in Bahrain, regulation requires products to be marketed in the source country for at least two years before they can be registered in Oman, with the motive to ensure pharmacological efficacy and safety [32].

Jordan has recently restructured its product registration process and reduced delays from several years to 180 days. Moreover, the country's intellectual property environment has improved rapidly over the past decade. Since the US signed a Free Trade Agreement with Jordan in 2000 - which included provisions covering data protection - there have been 32 new innovative products launched in the country [32]. Registration fees differ in Jordan between originator brands and generic, as well as between imported and locally produced medicines, with generics and locally produced products having lower registration fees [110].

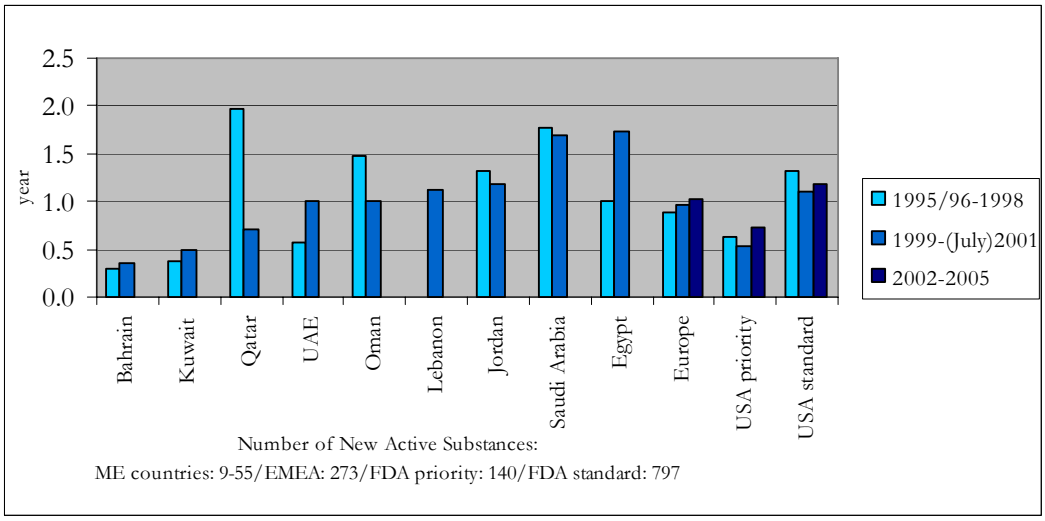
In Lebanon, the Drug Registration Technical Committee of the Ministry of Health is to spend a maximum of three months revising the drug files if requirement are meet, thereafter drug samples are tested in laboratory and based on the results the drug can be approved. In practice the approval process can be longer, up to two years, with a median time of just over one year according to the study results presented in figure 7-21 [109]. All products must be registered under the product name used in the country of origin. There is no fast-track approval process for new chemical entities [32].

Registering a new drug in Egypt can involve multiple committees and applications reviews. Foreign companies wishing to register a drug must submit a legalized CPP, also required are the drug's clinical and pre-clinical data, its worldwide registration status and its price statement. 20 samples of packaging material have to be submitted, while 20 samples of the finished product must be submitted for analysis. However, the Ministry of Health is proposing to take away the requirement for bioavailability testing provided the drug has already been approved by either the in the FDA or the European Medicines Evaluation Agency (EMEA). Until recently it could take up to five years for foreign companies to register a new product in Egypt, although regulators now claim to have streamlined the process to take as little as six months [32].

In the US, the assessment of the safety, efficacy and quality of new therapeutic products is performed by the Food and Drug Administration (FDA) and the Center for Drug Evaluation and Research (CDER). Statistics from FDA show that the median review time for all standard drugs approved in 2004 was 387 days, while the median review time for priority drugs was 180 days [111]. The successful development of the US pharmaceutical industry, the FDA's comparably short drug approval process, as well as the economic attractiveness of the country's health care market have made US the first country of launch for close to half of the oncology drugs brought to market in the last 11 years. There has then usually been a lag time before market authorisation is granted in other countries.

The EMEA coordinates the evaluation and supervision of medicinal products throughout the EU [50]. Since November 2005, all new oncology drugs in EU will have to be authorised via the Centralized Procedure of EMEA and will thus be reviewed by the CHMP (Committee for Medicinal Products for Human Use). 20 anticancer agents were authorised via the EMEA Centralized Procedure since its implementation in 1995 until mid 2004 [112]. The mean and median total times for regulatory approval were 429 and 418 days, respectively. The total time till approval ranges from 225 days to 734 days among the 20 drugs.

Figure 7-21 Median time* in years from MAA to authorisation for pharmaceuticals that were granted MA



**In the Middle East countries median time between 1995–1998 and 1999–July 2001 [109], in Europe (EMEA), average total time 1996-2005 [113] and in the US (FDA) median total approval time 1995-2005 of Priority New Molecular Entities and Biologics/Standard New drug Applications and Biologics [114]*

Figure 7-21 shows the median time from market access application to authorisation in the ME study countries, compared with the average/median time respectively for Europe and the US. In the mid 1990s the EU was the market most commonly chosen for the first submission of a new drug application, but this changed in the late 1990s and early 2000s when the US FDA instead became the most common authority for first application submission [115]. A reason for this is that approval times for new drugs are shortest in the US, as can be seen in the figure, approximately seven months for new drug applications.

Delay in uptake of new treatments may be explained by several factors. The first step in the introduction of new drugs is the market authorisation. The second step in the introduction is the pricing/reimbursement decisions, which is necessary in most countries and the third step is the acceptance and use of the drugs by the treating physician. The time from first global market launch to the first sale in a country may be seen as an indication of the total delay in uptake of new drugs. However comparisons of approval times may be uncertain due to differences in the national regulatory systems. According the data presented in figure 7-21, the ME region has a median approval time comparable to the average in European countries and the median approval time in the US for non-priority products.

It is important to minimize the time for approval of new drugs, without reducing the quality of the evaluation and decision process, in order not to delay the access of new treatments. Although the regulatory approval time has been reduced during the last years in some countries, there seem to be opportunities to further reduce the administrative time in the approval process. In the EU, the mean time for administration, i.e. the time needed for translation, approval of the national product information, and publication of the Commission decision, is, according to EU legislation, foreseen to be 90 days, but is on average 117 days (range 92 to 173), which constitute approximately 30% of the total regulatory time.

7.6. Sales of new oncology drugs

In the following section is presented the sale over time for a selection of important cancer drugs in E-13 and the US, to illustrate how the value of the oncology market has evolved over time, as well as the impact of new drugs in terms of sales. Sales are presented in nominal prices. Unfortunately sales data obtained from the ME-9 countries was not sufficiently complete to allow such comprehensive analysis of the uptake of cancer drugs in the region.

Figure 7-22 Total cancer drug sales (€'000s) in US and E-13 2000-2006 by year of first worldwide launch (Source: IMS Health)

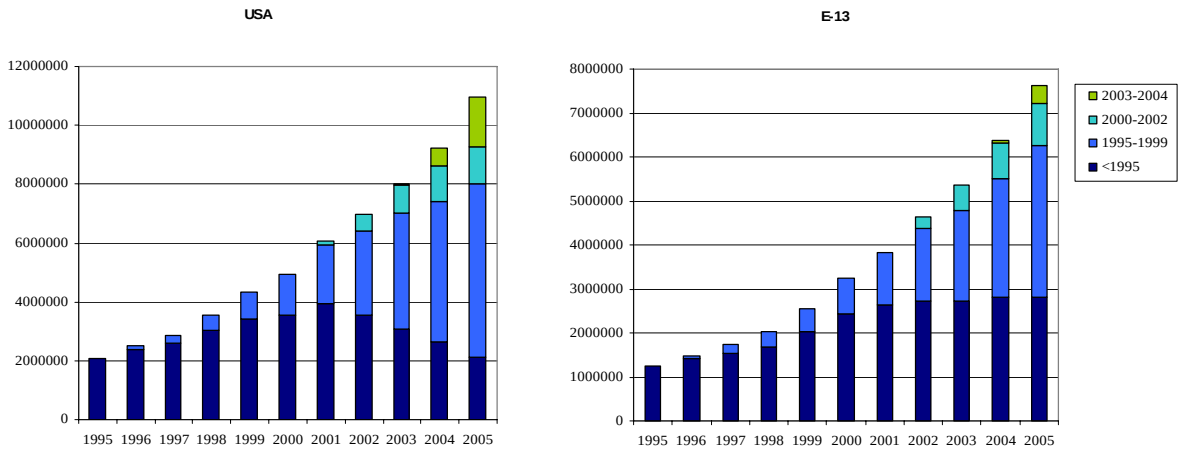


Figure 7-22 shows the total annual sale of oncology drugs over the period 1995-2005. In the US annual sales have increased from €2 billion in 1995 to €11 billion in 2005 while in the E-13 countries the increase in annual sales has been from €1.3 billion in 1995 to €7.6 billion in 2005. The increased sales of oncology products over the period can, to a great extent, be explained by the introduction of new innovative drugs. The number of active substances available in the beginning of 2005 had increased by 70% compared to 1995. Sales of new drugs introduced in the period 1995-2005 have continuously increased both in absolute terms and in terms of their share of total sales. However, it should also be noted that in E-13, drugs introduced before 1995 had higher sales in 2005 than in 1995. This reflects a significant increase in the use of these "older" drugs, as many of them have become generic and subject to price competition.

Figure 7-23 PPP-adjusted per capita cancer drug sales (€) in 2005

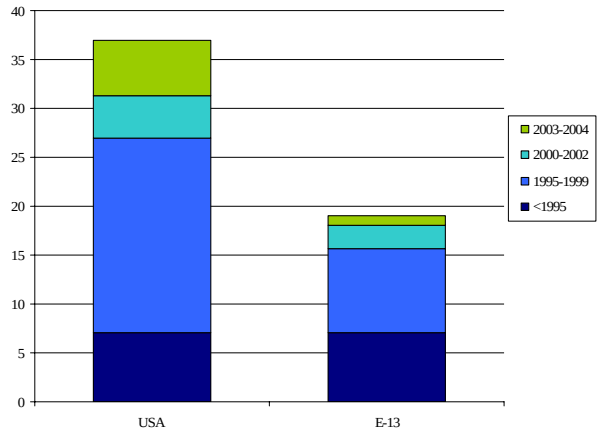


Figure 7-23 shows the PPP-adjusted per capita sale in 2005 in E-13 countries and US. The sale is divided in shares based on year of introduction of the drugs. The faster uptake of new drugs in the US; is clearly illustrated by the relative proportional spend on drugs that were introduced after 2000, which is considerably larger in the US. Data was not available to illustrate the share of oncology drug sales in relation to year of introduction in ME-9.

7.7. Pricing of pharmaceuticals

Pricing of pharmaceuticals is influenced by a number of factors. The complexity of pharmaceutical pricing is a result of the large expense associated with pharmaceutical R&D; the considerable investment in drug development is a sunk cost at the time the product is launched and drug prices are negotiated, and thus in strong contrast with the marginal cost of producing additional units, which is generally very low. Patent protection is one of the regulations of the pharmaceutical market aiming at providing incentives for research and development and at the same time controlling society's costs for drug treatments. The patent system provides a mean for pharmaceutical companies to gain a monopoly-like position on the market during a certain time period following the launch of a new drug, which allows the recuperation of R&D investments before allowing competitors to enter the market with generic copies of the drug. In addition, various other methods may be used to control and regulate drug prices. A study comparing pharmaceutical price controls of eleven OECD countries to the US [116], found that principal methods of price control in the countries studied were reference pricing, procedural barriers, restrictions on dispensing and prescribing, and reimbursement. In countries with strict price regulations, generic penetration of the market tend to be lower than in less regulated markets[117]. In price-regulated markets, original products might be priced lower while on patent, but are able to better defend their market share after patent expiry since generic competition is weaker.

In Middle East countries, a price fixation is generally required for all prescription products and some over-the-counter products. A requirement for the pricing decision is a certificate including information about, among other, the wholesale price in the country of origin and the registered price in neighbour countries if available. Recently, reference pricing based on the average of the three lowest prices in neighbour countries has been adopted by some countries. Innovative products will normally receive a higher price than follow-on products.

GCC (Gulf Cooperation Council) members have attempted to align their drug pricing policies in recent years, with the approval of a unified pricing mechanism for the public and private sectors in the member countries and the submission of joint tenders [118]. In 2005, the GCC approved a mechanism for unifying the prices of medicines in the private-sector market of each member state (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates). While drug supply in the GCC region has traditionally taken place through the extensive public health care systems, the private-sector market for drugs is growing rapidly, to a great extent due to compulsory private health-insurance packages for non-nationals. Public sector drug procurement is carried out through closed international tenders, GCC bulk procurement and direct purchasing.

In Saudi Arabia, prices are set based on ex-factory price, proposed export price to Saudi Arabia, and export price of approximately 30 other countries; whereof the lowest price found will be approved [108]. The Saudi government plays a prominent role in the purchase of pharmaceuticals, negotiating with the leading drug companies to buy large quantities of product and deciding upon the supply schedule the other GCC members collectively purchase pharmaceuticals and vaccines through these tenders that allow the smaller countries to buy in bulk and gain significant cost savings from multinational drug makers [32].

In Bahrain, as basis for pricing a price certificate authenticated by the health authorities in country of origin stating the ex-factory price, the wholesale and public sale price in the country of origin, the CIF (cost- insurance-freight) price in the GCC countries, and the suggested CIF price in Bahrain shall be provided [119]. Cost-containment policies in the pharmaceutical sector in Bahrain include a policy of price controls on pharmaceuticals [32].

The Kuwaiti government operates a system of price and profit controls - medicine price regulation was introduced in Kuwait in 1993 - and has a fixed margin for wholesalers and retailers. Medicine prices in private retail pharmacies are set by the Ministry of Health. Multinational companies are required by law to register at the price of the source country [32]. The government central medical stores buy drugs through competitive tender (there is no special privilege for local of regional manufacturers) and through the GCC bulk purchasing scheme [120].

In the United Arab Emirates, a government measure to bring drug prices more in line with other GCC states was introduced in 2005, and reduced average final selling prices by 7%; a subsequent cut lowered selling prices by 11%. The cost containment policies are explained by the government's desire to find a balance between affordable health care and international obligations to uphold patent and product quality standards[32]. There are wide differentials in pricing between the private health care sector and the public sector in United Arab Emirates.

In 2002, the Ministry of Health in Oman implemented price controls for all medicines available in the country before 2002 [121]. As a result, the percentage of drug expenditure from the health budget has fallen in recent years, from 10.4% in 1995 to 8.7% in 2004. The price control has negatively affected pharmaceutical companies' revenues, but arguably benefited both local citizens and expatriates, who are dependent on the private sector for their medicines, since the price control regulates the prices of essential medicines in the private sector. Government purchasing is predominantly branded-product based, but the share of generics is increasing [32].

In Jordan, a new pricing regime for imported medicines was recently developed. The new structure includes a decrease in the value of about 2,000 drugs sold in pharmacies and close to 200 used in hospitals, an increase in the prices of about 750 medicines used in hospitals and pharmacies, while the cost of only some 60 medicines remained unchanged. The decision on the new pricing structure was made after a comparison of the drug prices in Jordan to those of manufacturing countries such as the UK, France, as well as regional neighbours such as Saudi Arabia [32]. As a basis for pricing decision is now required a certificate from the manufacturing company showing manufacturer prices and public prices of the drug in France, Germany, Greece, Italy, the Netherlands, Spain, and the UK as well as the export price of the drug to Saudi Arabia [122].

In Lebanon, after a new drug has been approved, the pricing committee under the Ministry of Health is to make a pricing decision within one month. The prices of imported drugs are based on the cost in the country of origin. A recent government proposal to implement a new pricing system based on the reference prices of drugs in similar markets around the world will likely lead to reductions in prices over the coming years in Lebanon [32].

The Egyptian government has attempted to create an affordable health care system through drug price controls, and the strict price controls have resulted in some of the lowest drug prices in the region. The government line is that international drug companies make large profits and can therefore afford to sell their products for less in poorer countries [32]. The price fixation of pharmaceutical prices has been an issue to pharmaceutical companies, since the pricing system does not allow price increases to compensate for inflation. Due to a period of considerable

devaluation of the Egyptian currency, in 2004 the Ministry of Health increased prices of 11 new pharmaceutical product by 10-70% including medications for cancer [123].

Currency fluctuations following the pricing of certain pharmaceuticals may indeed greatly contribute to price differences between countries. Yet, studies [116, 117] have shown that the international variance in pharmaceutical prices are lower than price variances for other medical interventions and that variations in drug prices are approximately in line with the income differences between high-income countries This is however usually not the case in low-income countries the prices of pharmaceutical products are often comparable to those of high-income countries and not relative to the per capital income of the population. Medicine price, availability and affordability comparator surveys - using a standard survey methodology developed by the World Health Organization (WHO) and Health Action International (HAI), based on a group of 30 medicines that are relevant to the global burden of disease plus selected medicines of national importance – were carried out in some of the ME-9 countries: Jordan, Kuwait, Lebanon, and, partly using the HAI standard survey methodology, Egypt, in 2003/2004. The results of the national surveys in these countries are briefly presented below. Generally, across the WHO Eastern Mediterranean Region, the WHO/HAI assessed public sector procurement to be reasonably efficient; however the availability of essential medicines in the public sector was unreliable, resulting in patients often having to pay for their own medicines in the private sector, then often at high and frequently unaffordable prices. It was concluded that there was a need for stronger government action to introduce or improve national medicines policies and effective pricing policies [124].

The WHO/HAI assessment in Jordan, covering 23 drugs for the treatment of chronic and acute diseases from the core WHO/HAI assessment list and 6 drugs specific Jordan concluded that in the public sector in Jordan procurement prices were close to international reference prices, generic medicines were generally sold to patients at prices close to procurement prices. However, the overall availability of essential medicines in the public sector was low, and original brand medicines were rarely found in the public sector even though such products were procured in tenders. Thus many patients must purchase medicines in the public sector. For the listed drugs, generics were available to a greater extent than brand products also in the private sector, but here priced approximately 10 times higher than international reference prices [110].

The survey conducted in Lebanon, covering 32 medicines, showed the drug procurement in the Lebanese public health sector to be relatively efficient. The Lebanon Ministry of Health supplies drugs by tenders or agreements; drugs are divided into two categories, very important and less important, where anti HIV/AIDS drugs, cancer drugs, and mental illness medicines, etc. are considered very important drugs and to be delivered to patients free of charge. Medicines were purchased at reasonable prices. Yet as availability in the public sector was very low and far from optimal, poor patients were often forced to buy expensive medicines from private pharmacies. Availability of medicines was very good in private sector especially for branded drugs, but in the private sector almost all the surveyed medicines were higher priced than the international reference price. Taxes, tariffs and mark-ups on pharmaceuticals in Lebanon are relatively high and contribute to making many medicines unaffordable for the majority of patients [125].

The survey of the availability and prices of 35 medicines undertaken in the public and private sector pharmacies in Kuwait showed that generic medicines are overpriced with little price differential between innovator brand and generic medicines in Kuwait. When generic pharmaceuticals were available they were often priced only 10-15% below the innovator brand price due to lack of competition and the pricing regulation system; referred to a desire in Kuwait not to price generics too far below innovator brands in order to not excessively reduce the margins of the pharmaceutical agent. The retail price ratio in the private sector for the core HAI

list medicines assessed was about 17 times the reference prices. (75% of the 21 core drugs compared were generic products, thus the high pricing of generics in Kuwait was a contributing factor to the large discrepancy between Kuwaiti and reference prices.) Public sector procurement of medicines in Kuwait was considered efficient however in some cases with a unnecessary reliance on brand products [120].

In Egypt the medicine price and availability survey, covering 35 drugs, concluded that drug prices obtained in governmental procurement were reasonable, and in the public sector medicines were dispensed to patients for free or at the procurement price. However, since only a limited number of products were available through the public sector it was not uncommon that public sector doctors prescribed medicines that were only available in private pharmacies. Private sector prices were considerably higher. Thus the prescribed treatments often resulted unaffordable for patients, in particular when innovator brands were prescribed, since the prices of innovator brands are considerably higher than the prices of their generic equivalents. The survey report recommended the implementation of a generic substitution policy and incentives for pharmacists to comply with such a policy, such as fixed mark-ups for brand products [126].

7.8. Summary

As shown by the uptake curves presented in this chapter, sales of the selected oncology drugs per cancer cases are, in most of the ME-9 countries, comparable with those in Europe and in some cases also in line with those in the US. The lag in drug uptake appear to be one year as compared to the US for capecitabine, bevacizumab and erlotibin, until the uptake is comparable in some of the Middle East countries and one to three years for trastuzumab that was approved in the US in 1998. The exact time lag for rituximab is difficult to estimate, rituximab was approved by the FDA in 1997 and sales data from the Middle East countries were not available for 1999-2000 to show the uptake trends in the study countries in these years.

The overview of pharmaceutical prices in the ME-9 countries indicates that the drug procurement prices in the public sector are generally comparable to international levels but that retail prices in the private sector can be considerably higher than international reference prices, leading to high treatment costs for patients in need of treatments not provided or readily available to them from the public health care system.

8. Market access for cancer drugs and the role of health economics

The variations in uptake of new treatments lead to inequitable patient access to cancer drugs between countries and/or regions. To overcome this problem, various countries have introduced different methods to fund and introduce new cancer drugs. Cost-effectiveness is one of several factors guiding different types of decisions related to the introduction and uptake of new drugs.

8.1. The role of cost-effectiveness as basis for reimbursement decisions

In the ME-9 countries, price negotiations are often based on reference pricing and the basis for inclusion of drugs on national formularies is generally not cost-effectiveness criteria. Lebanon is the only of the countries with a reimbursement system.

In Kuwait, the public-sector health care covers basic medical care and drugs, but high-cost specialist treatments are of limited access. The public list of approved drugs comprises about 70 active ingredients and drugs are prescribed in the public sector only on the basis of a valid prescription from a medical practitioner. Since many expensive foreign-made drugs are excluded from the approved drug list in Kuwait, likewise in Bahrain and Oman, patients may be forced to purchase such high-priced medicines on the private market or in neighbouring countries. Expatriates in Kuwait have only limited cover from the approved drug list. In Bahrain the government is reported to be planning to introduce a medicine fund to enable low-income citizens to afford some expensive medicines [32]. The Oman National Drug Policy of 2000 covers initiatives to promote rational drug use, prompted by surveys of prescription habits indicating limited use of generics, polypharmacy and a liberal prescription of antibiotics [121]. In Saudi Arabia the inclusion of new drugs in the hospital formulary once approved for sale in the country is relatively fast, similar in the United Arab Emirates.

In Lebanon, there are two public reimbursement institutions, the National Social Security Fund (reimburses 80% of the drug healthcare bill) and the Cooperative of Civil Servants (reimburses 75% of the drug bill), which cover private sector and public sector employees, respectively. Moreover the Ministry of Health aims to provide, free of charge, expensive drugs to uninsured citizens suffering from HIV/AIDS, cancer, etc, as well as vaccines and essential drugs to public health care centres and hospitals. However the Ministry of Health budget is insufficient to provide all needed medicines. NGOs and UNICEF assist in drug provision in Lebanon; the YMCA Medical Assistance Program, set up in 1988, provides chronically ill patients, suffering from acute poverty or refugees due to the war situation, with required and necessary drugs on a regular basis. Government contribution to this programme in 2003 was approximately 11% of the total public drug budget [125].

In Jordan, a national medicines policy has been in place since 2002, a second review of the drug formulary listing was done the same year and a third revision in 2006. In 2006 a joint drug procurement administration the three public tender offices, the Ministry of Health, the Royal Medical Services and the Jordan University Hospital, was established in Jordan [110].

The formulary listing of new drugs in Egypt is lengthy and favours national producers. The Ministry of Health and Population has developed "essential" and "non-essential" drug lists. Egypt's authorities are under pressure to establish a universal reimbursement system, requiring higher payments for wealthier individuals, that would replace the current system [32].

In certain European countries (for example Belgium, Finland, the Netherlands, Norway, and Sweden) there is a formalised decision-making process where economic evaluation and the issue of cost-effectiveness influence national reimbursement decisions and the reimbursement decision process includes a discussion of the price and often the expected sales. In other countries (such

as the UK, Germany, Denmark, and Switzerland) cost-effectiveness evidence is not a formalized part of reimbursement decisions [127]. Countries that in different ways have led the development of introducing cost-effectiveness as a criterion for reimbursement and/or treatment guidelines include Canada, Australia and Northern European countries (the UK, Scandinavian and Benelux countries). Australia and the Canadian provinces of Ontario and British Columbia were pioneers; they have demanded health economic evaluations as part of manufacturer submissions for reimbursement since the early 1990s [128]. In some countries, it is not necessary to apply for reimbursement if the drug is used only for hospital in-patients. The rationale for this is that drug costs are part of the overall hospital costs and the hospital pays for the drug costs from its budget which takes into consideration the number and type of patients treated. In these situations it is the hospital that makes decisions regarding availability of new cancer drugs. If drugs used in hospitals are financed outside the regular hospital budget system administrative rules and regulations for price and volume may apply. Since new cancer drugs may be used in the hospital setting initially, but later transferred to ambulatory use, it is sometimes unclear how they should be handled in the reimbursement process.

In the US, there are no requirements for the submission of cost-effectiveness data for new and existing medicines to obtain formulary listing under the US national health insurance programmes (Medicare and Medicaid). In the private sector, the demand for such evidence by managed care organisations is growing, but the impact of such information, particularly cost-per-QALY data, is not widely or consistently accepted by decision-makers and third-party payers. Thus there is no parallel in the US to the European tendency to use health economic evidence for national guidance or control, and even if private health plans in the US make use of cost-effectiveness analysis the decision-makers are still accountable to their members, which is not the case with a centralized decision system. Since health care in the United States is delivered through a combination of public- and private-sector entities, among the most important are employer-based health insurance programmes and government-run programmes for specific patient groups including Medicare, Medicaid, and Tricare, pharmaceuticals are purchased by many different independent entities, including health plans, pharmacy benefit managers (PBMs), and the state programmes, which use a wide range of tools to manage pharmaceutical spending, for example price negotiations, tiered co-pays, and prior authorization requirements, various payers have different requirements for information there is no single central reimbursement procedure or formulary listing. The US leadership in global innovation in the pharmaceutical and biotechnology industries is rooted in the predominantly "market" system of US health care. There is a debate on what role, if any, economic evaluations should play in coverage and payment decisions by public and private payers with some debating that the US innovative lead in pharmaceuticals and biotech would suffer if cost-effectiveness scrutiny in the public sector was mandatory also in the US[129]. Yet, it is expected that the influence and requirement for economic evaluations will increase among health care payers in the United States.

8.2. The influence of health technology assessment on treatment recommendations

Cost-effectiveness information is becoming an important part of Health Technology Assessment (HTA) reports published by HTA agencies. The increased interest in cost-effectiveness information for health-care decision making has led to a growing number of published economic evaluations. Such reports support different types of decision-making in health care related to the choice of interventions. In many cases there is a direct link between the assessment by the HTA agency and funding for the technology appraised. A study comparing the use and impact of HTA in the G-7 countries found that the impact of HTA agencies was strongest in the UK, France and Canada. In Italy and Germany, HTA impact on policy making seemed to be limited, while little evidence was found of HTAs impact on policy making in the US and Japan, where interest in HTA has been relatively limited [130].

Nevertheless, in the US a considerable number of HTAs are produced by various public and private agencies: the Agency for Health care Research and Quality (AHRQ), the health services research arm of the U.S. Department of Health and Human Services, provides technology assessments for the Centers for Medicare & Medicaid Services (CMS) to inform national coverage decisions; the Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC) is one of 13 Evidence-based Practice Centers (EPC) under AHRQ that assess the clinical effectiveness of medical technologies for clients in both the private and public sectors; another EPC is ECRI (formerly the Emergency Care Research Institute) a non-profit health services research agency which provides information services and technical assistance to more than 5,000 hospitals, health care organizations, etc. worldwide regarding e.g. the cost-effectiveness in health care; Veterans Affairs' Technology Assessment Program (VATAP) is a national program within the Office of Patient Care Services dedicated to advancing evidence-based decision making in veterans affairs.

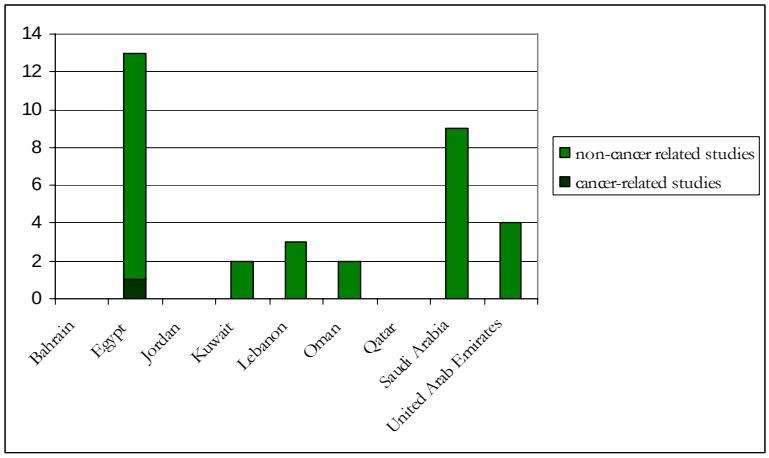
In the E-13 countries, HTA activity is at differing stages of development. England, the Netherlands, Norway, and Sweden have well established groups and economic evaluations have a certain influence on prescription patterns and treatment guidelines, although the groups differ in their sphere of activity, methods used, and relationship with government [127, 131]. In particular in the UK, economic evaluations have played a very important role in the work by the National Institute for Health and Clinical Excellence (NICE), the All Wales Medicines Strategy Group and the Scottish Medicines Consortium. In France, Italy and Spain, health-economic evidence is of relatively low significance for decision making in medical care in general, although in France, as well as in Germany, economic evidence is considered to be of importance when taking decisions on expensive innovative drugs such as new cancer drugs. It is expected that in the future the influence of health economic data will increase in these countries [127].

8.3. The increasing availability of health economic evidence

The activity in the health economics area is steadily increasing. However health economic assessments have yet little impact on health care decision making in the ME countries. Searches in three health economics databases were performed to assess what health economic evidence is available for the study countries.

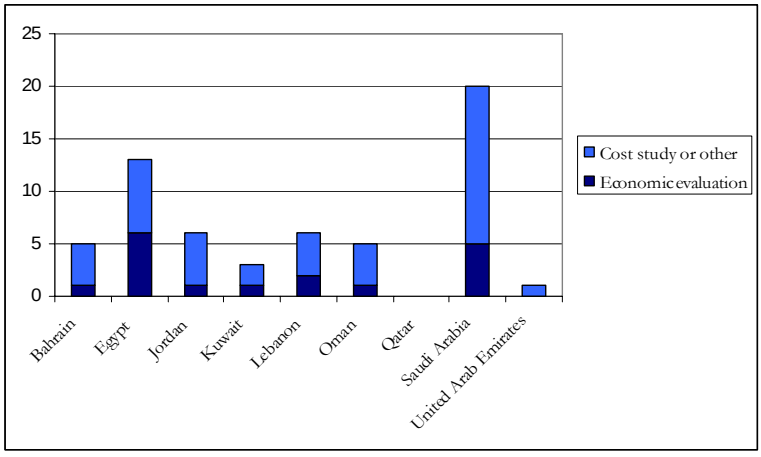
The Health Economic Evaluations Database (HEED) is an online source of health economic information and evaluations that was developed as a joint initiative between the Office of Health Economics (OHE) and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). HEED contains more records and content than any other health economics database. It also includes publications in non-English journals. Studies were included when the study was applicable to the specific country or when the authors were based in the country although the study was of international applicability. The studies were cost-effectiveness analyses, cost consequence analyses, or cost analyses. Twelve Egyptian studies and nine studies from Saudi Arabia were identified. United Arab Emirates, Lebanon, Kuwait and Oman were represented by two to four studies respectively. No studies for Bahrain, Jordan or Qatar were identified. Figure 8-1 shows the number of studies from respective study country identified in the HEED database. Only one of the studies identified related to cancer, it was an Egyptian study from 1996 assessing the costs, benefits and operational implications of using a filtrating technique to screen for schistosomiasis haematobium (the worm that causes the high incidence of bladder cancer) in Egypt as compared to concurrent filtering practices [132].

Figure 8-1 Health economics studies for ME-9 countries in the HEED database



The NHS EED database is funded by the UK National Health Services. The database aims to assist decision-makers by systematically identifying, describing and appraising the quality of economic evaluations. The database includes over 23,000 entries. Hits in relation to the study countries are presented in figure 8-2.

Figure 8-2 Health economics studies for ME-9 countries in the NHS EED database



Another database of health economics studies is the ISPOR Research Digest, an electronic database of research papers presented at ISPOR (International Society for Pharmacoeconomics and Outcomes Research) Conferences from 1998 to date. Over 8700 abstracts are included to date. Four abstracts were found that directly related to Saudi Arabia and one concerning Oman. No abstracts were found for the other seven ME countries. An additional two abstracts including Saudi Arabia and two abstracts including Egypt in studies of multinational coverage were identified.

8.4. Summary

Health economic evaluation, as a basis for making priorities in health care, or from a scientific point of view, seems to be limited in the Middle East countries. With the increased introduction of expensive treatments it is likely that this will become an increasingly important method to make priorities in health care in the region.

9. Discussion

Analysis of the uptake of new cancer drugs show that the spending per capita on pharmaceuticals in general, and on cancer drugs, is considerably lower in the ME-9 countries compared to Europe/US. A major reason for this is demographic, since the ME-9 population is younger than the population in Europe and the US and the incidence rate of cancer is lower. In the ME-9 countries, reported cancer incidence rates in national registries varies between 35 and 175 cases per 100,000 individuals (lowest in Saudi Arabia and highest in Lebanon) as compared to a cancer incidence rate in the US, the UK and France of between 470 and 525 cases per 100,000 individuals.

However, the spending on oncology drugs per cancer case in several of the ME-9 countries seem to be comparable to the spending per case in Europe and the US. The oncology drug share of the total drug market also appears to be similar in the ME-9 countries and in France, the UK and the US, between 6-10%, with the exception of Egypt where the share was calculated to around 1%.

Data on the cost of inpatient and outpatient cancer care were not available for the ME-9 countries. However, based on incidence and burden of cancer in relation to oncology drugs sales and national health care expenditure, the average health expenditure per cancer case in respective country was estimated. The results indicate that the cost per cancer case, in both exchange rate € and PPP-adjusted €, in the six Gulf States is comparable to that of France and the UK. With PPP-adjustment, so also the cost per cancer case in Jordan. The calculated cost per cancer case was considerably lower for Egypt; the lower GDP in Egypt as compared to in the other study countries limits the economical possibilities to provide advanced cancer treatment for the population. Based on this, the cost of cancer drugs in relation to total cost of cancer care in ME-9 would be approximately 30%, as compared to 12% in the UK and 25-27% in France and the US.

Health economics, in particular economic evaluation, has emerged as a method to evaluate the trade-off between the costs and benefits of new drug therapies by those making decisions on reimbursement and market access. Health technology assessments and economic evaluations are sometimes referred to as the 'fourth hurdle' (after safety, efficacy and quality) with regard to patient access to new therapies. The incorporation of health economic evidence in optimisation of health care resources is limited in the Middle East countries today. However, it can be expected that thorough analyses of the cost-effectiveness of new treatments and health care approaches will increasingly guide the development of the health care systems and optimal use of health care resources in the Middle East in the future. The majority of the Middle East countries analysed in this report have well-developed public-financed health systems, that will need to face a transition towards treatment of chronic diseases, which makes it important to consider how health care systems and especially hospital budgets should be organized to accommodate the introduction of new cancer drug therapies.

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