Abstract – Globally cancer will increase greatly over the next 20 years because of ageing populations. Minimally invasive surgery will reduce the need for routine organ resection. The application of sophisticated computer systems to radiotherapy planning will allow the precise shaping of beam delivery conforming exactly to the shape of the tumour. The most promising advances will come from the rapidly increasing understanding of the molecular genetics of cancer. This will have considerable impact on prevention, screening, diagnosis, and treatment and lead to a golden age of drug discovery. Individual cancer risk assessment will provide messages tailored for individual prevention and have far-reaching public health consequences. Increased consumerism in medicine will produce increasingly informed and assertive patients seeking out novel therapies, bypassing traditional referral pathways through global information networks. This will bring new ethical and moral dilemmas. The cancer future will be created by the interaction of four complex factors: technological success, society’s willingness to pay, future healthcare delivery systems and the financial mechanisms that underpin them.

KEY WORDS: biomarkers, cancer, chemoprevention, chemotherapy, surrogate endpoints

Epidemiology

The global cancer burden is set to double over the next twenty years. The World Health Organisation estimates that there are currently 10 million new cancer patients a year with 6 million deaths. By 2020 there will be a modest increase in the world’s population but a doubling of new cancer patients to an incidence of 20 million a year with 12 million deaths. Seventy-five percent of these patients will live in the developing world which can ill afford the rising costs of high technology medical care. A map of the world shows that cancer is indeed a disease of the wealthy (Fig 1).

North America, Europe, Japan and Australasia are the main areas of high cancer incidence and prevalence. Poorer countries such as those of Africa and Asia have a much lower incidence. This is simply a reflection of longevity: people in rich countries live well into their 70s on average, whereas until now people in poorer countries have only lived into their 40s and 50s. This is set to change thanks to better medical care, sanitation, housing and other sociological phenomena around the world. It is this increase in longevity that brings more and more of the world’s population into the cancer age group. There is a striking correlation between cancer incidence and the per capita gross national product as an index of wealth. However, the biggest change over the next 20 years will actually occur in poorer countries where longevity will dramatically increase the number of patients entering into the cancer age group.

Cancer and society

There are several trends in the way in which people of all cultures are dealing with cancer (Table 1). We now live in a global village crammed full of information; national boundaries are no hindrance to the power of the Internet. The ongoing revolution in wireless telephones without reliance on a creaking telecommunications infrastructure means that people in some of the world’s remotest places can connect to remarkable cancer information websites. In an increasingly politically centrist Europe there is tremendous interest in being seen to do something to improve cancer care. The policies of most political parties are becoming extremely difficult to differentiate, and therefore doing something about cancer is a natural vote winner. This is reflected in the priority attached to Britain’s recent National Cancer Plan, even though it was known that Britain was lagging behind the rest of Europe in cancer survival more than a decade ago.
The integrity of conventional religious structures and families is declining due to greater mobility, divorce, single parenthood and the break-up of traditional caring patterns for older people. This means that when a life-threatening illness such as cancer strikes, patients have fewer psychological crutches to lean on today than in the more structured society of 20 years ago. Better psychosocial care is therefore needed alongside the technology-based service doctors are traditionally trained to provide. Offering patients more informed choice may well cause uncertainty and psychological confusion. As the costs of technology increase, state systems find themselves increasingly unable to pay for all the new therapies that could possibly be used. This is especially so in a society that wishes to reduce its taxation burden, putting more and more of the decision-making and consequent funding responsibility onto the consumer. This creates increasing distrust in state healthcare systems and sparks a search for alternative mechanisms to fund cancer care. Politicians of all persuasions try to fudge the rationing issue and consistently discount co-payment mechanisms for high-cost but low-value treatments. But inequity is inevitable — the assertive and educated are more effective users of complex healthcare systems, whatever their structure or funding. And the rich can simply use the private sector to buy what they want.

Causes and prevention

Tobacco

Cancer has many causes. We can identify the cause of three-quarters of the world’s cancers (Fig 2). Tobacco products, both smoked and chewed, cause approximately 3 million new patients with cancer a year. The majority will have lung cancer but other types associated with smoking are those of the oropharynx, pancreas, kidney and bladder. The message is simple: stop smoking. However, this is an extremely complex area entwined in politics, taxation, corruption and big business. The media have been manipulated by the tobacco industry through advertising muscle, with good evidence of suppression of the true risk. Although in Europe there have been considerable inroads into curtailing tobacco use, the developing world is now suffering the brunt with a dramatic increase in teenage smoking and the likelihood of an epidemic of lung cancer over the next 20 years. Manufacturers have bought up local factories and are now producing cheap, globally branded cigarettes with their image of success, wealth and sexual prowess.

Table 1. Cancer and society: projected trends to 2022.

- More awareness and information
- Greater political interest
- Decline in integrity of family and religious structures
- Increased demand for psychosocial care
- More informed choice
- Difficulty in paying for new therapies
- Increasing consumerism in medicine
- Co-payment for therapies gains ethical acceptance

Fig 1. Global incidence of cancer. Incidence per 100,000 is colour coded and is high in wealthier countries (from Globocan programme accessible through www.iarc.fr).
Diet

The second major cause of cancer is poor diet. This is estimated to cause another 3 million cancer patients per year. Cancers with a clear relationship to diet include those of the colon, breast, stomach and liver. The problem with diet is that, unlike smoking, we have to eat. The relationship between diet and cancer is extremely complex. It is not just the food that we eat but also the way in which the contents are digested, interact with each other and cause changes in hormone levels. We know certain foods protect against cancer whilst others stimulate. Thus high-fibre low-fat diets with a high content of fresh fruit and vegetables are protective. Conversely low-fibre high-fat diets, common in northern Europe, carry significant cancer risks. The perception that organic, vegetarian diets reduce cancer incidence has never been validated. There is no biological reason why organic food should be less carcinogenic than normal farm produce: plants contain far more potent natural cancer-causing agents than traces of pesticides.

Infection

Infection causes a surprising 1.5 million cancers globally each year. Papilloma virus infection induces cervical cancer, the hepatitis virus causes hepatoma, and the Epstein Barr virus, lymphoma. All these cancers are potentially preventable using vaccines. The difficulty is in persuading politicians to invest now for the benefit of future generations. The commonest cancer in West Africa is hepatoma. For $2 extra per child at the time of childhood vaccination, hepatitis immunisation will reduce the incidence of hepatoma by 90%. Yet politicians avoid tackling this issue as they see no gain until well beyond the end of their own careers. Instead they aspire to unrealistic but highly visible projects such as new cancer centres, screening units and bone marrow transplantation facilities.

Risk assessment

The public perception of cancer risk is heavily swayed by interesting but negligible or non-existent risk factors. These are fanned by good media stories and the desire to find scapegoats for our unhealthy lifestyle. Cellphones, radiation from power lines, plastic films for food packaging and stress figure large in public surveys on causes of cancer, even though their risks are so low so as to be nearly impossible to measure. Public education is the key to the future.

Over the next 20 years, novel programmes of individual cancer risk assessment will be established. From the newly sequenced human genome we will learn about the complex interplay of our genes and the environment. Tailored cancer prevention programmes will be available. New screening technology coupled with drugs and vaccines that prevent cancer will come into routine use.

Cancer preventive drugs and hormones are already available for certain high-risk situations: tamoxifen for breast cancer and the cox 2 inhibitors for familial polyposis, which if untreated...
will inevitably lead to colon cancer. These drugs were developed and marketed for indications other than cancer prevention. The identification of effective biomarkers of cancer risk is essential if novel drug discovery programmes are to be created. The ability to prevent cancer will dramatically increase the number of people who will need to attend clinics regularly. Few countries have anticipated this potential tripling of people with a cancer label and Britain’s NHS has no contingency plan in place. Table 2 lists likely changes in cancer prevention.

Diagnosis

*Imaging and biomarkers*

Cancer presents with a myriad of symptoms depending on the site, size and growth pattern of the tumour. Although some symptoms alarm patients more than others there is tremendous variability in the speed at which cancer can be diagnosed. A lump can be biopsied, but many deep-seated tumours present late, long after they have already spread. Most patients have actually been harbouring the cancer for several years before it becomes apparent.

The two drivers of improvement in cancer diagnosis are imaging and biomarkers. The last two decades have seen a massive rise in the use of computed tomography (CT) and magnetic resonance imaging (MRI) scans to outline in beautiful detail the anatomy of a cancer and its surrounding normal structures. Positron emission tomography, in which a molecule is labelled with a radioactive marker, allows us to examine the living biochemistry of the body. The future of imaging will be the coupling of high-definition structural information to real-time functional change. This will allow the precise effects of drug or other treatment to be monitored in three dimensions. It is also likely that the telecom revolution will produce new devices for examining the function of interior compartments of the body without causing distress to the patient.

Biomarkers are biochemical changes produced by the presence of a cancer (see box below for definition). They may be

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**Table 2. Cancer prevention to 2022.**

- Genetic risk assessment
- Lifestyle risk assessment
- Cancer preventive drugs and vaccines
- Increased health awareness
- Novel healthcare provider systems for healthy populations

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**Definitions**

There is a lack of consistency in how certain terms are used despite several attempts to formalise definitions13.

A *surrogate endpoint* is defined as a substitute measurement of benefit, derived from the Latin *surrogare*, to substitute. Tumour shrinkage is an effective surrogate for clinical efficacy as measured by long-term survival. The complete disappearance of tumour on an x-ray image carries a better prognosis than only a minor effect after giving chemotherapy or radiation14. Similarly, the generation of data showing a long average time to disease progression with therapy can in some cases be a surrogate for long-term survival. In addition, the decline of a serum biochemical tumour marker suggests a tumour response that may lead to a better outcome. Although some tumour markers are reliable surrogates for ultimate outcome (human chorionic gonadotropin (HCG) in choriocarcinoma and testicular teratoma), changes in others such as prostate specific antigen (PSA) or carcinoembryonic antigen (CEA) are less tightly linked with subsequent survival15.

A *biomarker* can be defined as a biological marker of target effect. By definition, it will always be a surrogate for the effect of a drug on its molecular target. In certain cases it may also be a surrogate for tumour response and subsequent prolonged survival, although this will need verification. A biomarker may be biochemical or reflect a physiological by-product such as hypotension or platelet aggregation. It may involve a complex imaging process such as positron emission tomography or the genomic analysis of tumour biopsies before and after therapy. Tumour markers are just a subset of biomarkers that are sometimes useful in predicting prognosis. Biomarkers are commonly used outside oncology to monitor the effectiveness of a therapy. Serum cholesterol, glycated haemoglobin and blood pressure are biomarkers for statin therapy, control of diabetes and anti-hypertensive treatment respectively. They are also effective surrogates for the likely long-term consequences of the relevant disease. Unfortunately, we currently lack such tightly correlated biomarkers which will become essential if we are to make cancer a chronic illness controlled by long-term medication.
synthesised directly by the cancer, for example prostate specific antigen (PSA), or represent a complex change in an organ system, for example abnormal liver function tests caused by liver metastases. As we understand more about the molecular abnormalities that lead to cancer through the science of genomics and proteomics, novel biomarkers will be identified. These will not only enable us to diagnose cancer at an earlier stage but also to predict the likely natural history of the cancer – whether it will spread rapidly or invade neighbouring structures. This information will be essential for planning optimal care. It is likely that a cancer screening kit for the four major cancers (lung, breast, colorectal and prostate) will be on sale within the next decade in pharmacies, fitness centres and health food shops, so increasing consumerism. There will be a rise in cancer screening and prevention clinics in the private sector, almost certainly attached to the ‘cancer hotels’ of the future.

Genomic monitoring

Looking further forward it is likely that continuous monitoring for potentially dangerous mutations will be possible. Up-market car engines have systems to measure performance against baseline, sending a signal to the driver if a problem arises. Implanted devices to identify genomic change and signal abnormalities to a home computer may well allow the detection of cancer long before any metastasis. It will be essential to carry out careful outcome research on such new diagnostic and screening techniques to validate their benefits.

Projected developments in future cancer diagnosis are shown in Table 3.

Surgery

Cancer surgery has been a dramatic success. Effective cancer surgery began in the late nineteenth century when it was realised that tumours could be removed along with their regional lymph nodes. This enhanced the chances of complete cure as it had the greatest possibility of avoiding any spread of the cancer. Surgery still remains the single most effective modality for cancer treatment. It has become increasingly conservative, able to retain organs and structures. Breast cancer is an excellent example. The radical mastectomy performed until 30 years ago left women with severe deformity on the chest wall. This was replaced first by the less mutilating simple mastectomy, and now excision biopsy followed by radiotherapy, where the breast remains fully intact. New technology permits minimally invasive (keyhole) surgery for many other cancer types. The science of robotics will allow completely automated surgical approaches with enhanced effects and minimal damage to surrounding structures. Ultimately, it is likely surgery will disappear as an important treatment and become confined simply to biopsy performed under local anaesthetic with image guidance to check that the correct site is identified (Table 4).

Radiotherapy

Radiotherapy was first used for cancer treatment over 100 years ago. Originally crude radium was used as the radiation source, but we now have a variety of sophisticated techniques available. Modern linear accelerators – the workhorse for radiotherapy – allow dose delivery to the precise shape of the tumour. Conformal therapy aims to deliver high dose just to the tumour volume in three dimensions, killing the cancer cells and avoiding sensitive normal surrounding tissue. Novel computer-based imaging techniques have revolutionised our ability to understand the precise anatomy of cancer in a patient and therefore to deliver far more effective radiotherapy. Future developments will combine computerisation with multimedia imaging and optimised conformal planning. We have also learnt to understand the biological differences between different tumours in patients and can begin to plan individualised treatment courses to optimise selective destruction (Table 5).

Chemotherapy

Chemotherapy began after the sinking of an American battleship in Bari Harbour, Italy, in 1943. It was noticed that leucopenia developed in many of the injured. Although shrouded in secrecy at the time, alkylating agents for use as chemical warfare agents were being carried on the ship. This led naval physicians to treat patients with lymphoma and leukaemia with nitrogen mustard. In 1946, 67 patients were reported as having had good but brief responses to injections of this drug. A new era of cancer care had begun.

Table 4. Cancer surgery to 2022.

| Further organ conservation |
| Minimally invasive and robotic surgery |
| Image-guided biopsy only for most cancers |
| Fast-tracked, next day service |
| Tailored adjuvant systemic therapy |

Table 5. Radiotherapy to 2022.

| Multimedia imaging |
| Robotic set-up |
| Optimised conformal planning |
| Biological optimisation of planning volume based on tissue radiosensitivity |
| Designer fractionation to increase selectivity |
There are now three groups of cancers in terms of chemosensitivity. In the first we can achieve a high complete response rate and a high cure rate. These include Hodgkin’s disease, childhood leukaemia and other cancers such as choriocarcinoma and testicular cancer. Unfortunately, this group of successfully treated cancers represents less than 5% of the global cancer burden. At the other end, we have a group with a low complete response and low cure rate, such as lung, colon and stomach cancer. So far chemotherapy has made little inroads, although some useful palliation and prolongation of survival, sometimes for months, can be achieved. In the middle, there are cancers with a high complete response but a low cure rate. These cause problems in resource allocation. The use of taxanes in breast and ovarian cancer is a classic example. Here, high-cost drugs can achieve extension of life by several months for many patients. When deciding on priorities we have to assess how much we are willing to pay for a month of reasonable quality life. The NHS currently limits this to about £1,000 for cancer, although nowhere is this figure openly discussed. Rationing is deplored by patients, support groups and politicians but also is used relentlessly by the media to demonstrate the inadequacies of the system.

Drug discovery and development

Cancer drug development is entering a remarkable new phase. Recent advances in molecular biology have led to a host of new validated targets. In silico drug design allows the construction of thousands of virtual compounds, the most promising of which can be rapidly synthesised. This complements robotic high throughput screening of well organised chemical and natural compound libraries. This has led to a platform approach to drug discovery – the creation of specific inhibitors for each member of a gene family such as the protein kinases. This approach has been remarkably successful and a range of small molecules are now available which affect processes as diverse as cell cycle control, mitotic spindle separation, apoptosis, signal transduction, angiogenesis and tumour invasion. Over the last five years there has been a shift away from the search for new cytotoxic drugs to drugs acting through defined molecular mechanisms known to be aberrant in cancer. Nearly 500 molecules are currently undergoing clinical study and this may well reach 1,000 by 2004. Clearly, new methods to identify and prioritise the most promising candidates are necessary as there are only limited resources to take these compounds into expensive and time-consuming phase III studies. Figure 3 shows the potential timeline for the introduction of new technology to the marketplace. The critical years are predicted to be 2005–10.

The traditional approach to cytotoxic drug development is not appropriate for many of these new agents for several reasons. Firstly, as their precise molecular mechanism is known it should be possible to develop a pharmacodynamic assay for their molecular effectiveness in patients. This can be used to determine the maximally effective dose for use in further studies. This approach will replace the classical phase I study which has in the past been used to evaluate the maximal tolerated dose. Second, it may not be possible to rely on tumour response in phase II as a guide to survival benefit. Many of the new agents will cause disease stabilisation and not shrinkage. Thus it will be necessary to commit to expensive randomised phase III studies without having the confidence generated by a successful phase II programme. The key to success in this mechanistically based future will be the collection of far more data in the early phase of drug development by the use of surrogates of both molecular target effects and clinical efficacy.

A toolkit for early cancer drug development

Biomarkers, surrogate endpoints, functional imaging and predictive markers can be developed to form an essential toolkit
for early drug development. The target molecules for novel anti-cancer agents can be grouped by their function, and a set of biomarkers developed for each function (Fig 4). The practical value of each component can be evaluated in cell lines and animal tumours to determine its effectiveness in producing accurate dose-response information – a prerequisite for determining pharmacodynamic endpoints. For safety, an escalating dose scale will still be necessary when a compound first enters the clinic. However, the toolkit can be used to avoid the need to determine the maximal tolerated dose (MTD).

Conventionally the safe starting dose is one-tenth of the LD 10 in the most sensitive of three species. This can then be increased using an accelerated titration method until the maximal molecular effect can be obtained on the drug’s target. This dose may produce no toxic effects whatsoever. Choosing the correct dose based on pharmacodynamic data permits proof of principle studies to proceed with confidence. It reduces the number of patients required for a phase I study, speeding up this phase and avoiding many patients receiving a sub-therapeutic dose. Furthermore, it reduces the risk of operating at a dose higher than peak effectiveness if the effect of the drug peaks at a certain concentration. It also avoids a later potential commercial disaster if the drug priced for a high dose close to toxicity is demonstrated to work just as well at a much lower one.

For most novel agents the toolkit for measuring biomarkers of cell function can be validated in healthy volunteer subjects. This is a radical departure for trials of cancer agents and an area where oncologists traditionally have no expertise. It enhances the speed of data acquisition by forward planning and avoiding the need to identify cancer patients in real time, as stacking for a defined future time-point would be unethical given the likely progress of the disease.

The different components of the early development toolkit have different costs, risks and potential information yield. The investment payback will depend on how critical the information is to the successful development of drugs against a defined target. Thus biomarkers of molecular effect are a requirement for all drugs. Surrogate endpoints of clinical benefit are particularly important for drugs whose long-term administration is necessary to achieve either tumour stabilisation, such as anti-angiogenic agents, or prevention of metastasis where the cost in both time and effort of pivotal studies is immense. Success in achieving surrogate benefit here gives the confidence to commit long-term financial resources by effectively reducing the risk of failure. Functional imaging studies are particularly helpful where optimising the effect of a drug requires precise scheduling, for example with cell cycle inhibitors and pro-apoptotic agents. By obtaining real-time images of mitosis and apoptosis in patients, logical decisions about enhancing selectivity can be made more easily.

### Supportive care

Table 6 charts the likely direction of supportive care in the future. The hospice movement has injected a much needed sense of reality into the hype-up world of cancer drug development. Immortality is simply unachievable. We need to encourage society to provide novel care structures within the community, as close to patients’ homes as possible. Mood control drugs may remove the depression sometimes associated with terminal illness. In seeking to achieve compressed morbidity it is likely that euthanasia will become formalised. Seamlessness between cancer treatment and supportive care will become emphasised as part of a far more integrated, holistic and patient-focused package delivered in attractive hotel-like environments that deliberately downplay technology.

### Technology and society – alternative futures

Medicine is undergoing a technological explosion that will continue to prolong survival. The aim must be not only to prolong life but also to enhance its quality. Cancer care, like much of medicine, is in transition. Achieving good quality of life for the majority of people with cancer is on the horizon. The cancer future is made up of four components – the technology to control cancer, the willingness of society to pay for that technology, the mode of its delivery and the method of its financing (Fig 5). There are four alternative futures with many possibilities for overlap (Fig 6). Increasing numbers of cancer patients, a rise of patient power, and increased competition between those discovering and providing the technology, are common to each. In the most favourable scenario, technological

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success is delivered rapidly and society is willing to pay for it, making cancer a chronic, controllable disease. In the second, society is not willing to pay; this leads to increasing inequity with the rich getting more effective care than the poor. This scenario would be similar to the current situation with HIV disease in Africa. The remaining alternatives assume little technological advance. Here quality of life improvements arising from effective palliation dominate in therapy choice, as long as society is willing to pay. In poor environments, a fourth future of rigid prioritisation to maximise therapeutic gain will become essential, although inequity abounds.

How will cancer services in Britain evolve? The National Cancer Plan is delivering increasing funding and significant improvements in infrastructure. However, it can never keep up with demand. Complex assessments of cost-effectiveness fail to reassure patients seeking cure at any price. Organisations such as the National Institute for Clinical Excellence (NICE) will never convince determined and organised patient groups that in the end NICE’s deliberations are not a form of rationing. The pressures to expand demand are driven by potential financial gain by the pharmaceutical and healthcare industry and fanned by the media’s insatiable appetite for controversy. What politician can be seen to condone the refusal a new drug for a young woman with breast cancer pictured with her two beautiful children on the front of a national newspaper? Figure 7 illustrates the dilemma of the cancer demand pyramid. However
generous the core services, there will be an increase in demand-led services which will remain outside the core package. These demands may be for new high-cost drugs with marginal benefit, more precise radiotherapy technology, complementary medicines, or simply better hotel facilities in hospital. Some form of co-payment model is inevitable in their provision. The private sector can provide many demand-led services that are not available in the NHS. As public and private services move closer to a unified provider model, a more transparent allocation of resources is now needed to avoid the pressures imposed by postcode prescribing and other geographic inconsistencies. As we move through the next 20 years it is likely that the treatment of cancer will significantly improve (Table 7). But we urgently need to ensure open and mature debate about the best way to deal with the financial consequences.

Table 7. Providing cancer care to 2022.

- Cancer becomes a chronic controllable disease
- Cancer ‘hotels’ in most towns
- New roles for cancer professionals
- Negotiators to help with options
- Black box near-patient testing systems to guide therapy
- Novel financial, insurance and delivery systems
- Global provider franchises