Epidemiology in Europe

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Introduction

The topic 'Cancer in the elderly' will become increasingly important on the agendas of public health, clinical medicine and research, because the demand for oncological, medical and psychosocial care is rising steadily. Predictably, in most European countries, the peak will only be seen after 2030, resulting in more patients of an older age with more complex medical, psychological and social problems. The fact that there are less care providers because of the declining birth rates since the 1960's (earlier in some countries) could result in a critical situation, which can only be avoided by oncological and/or social breakthroughs.

This contribution deals with the major quantitative components and determinants of incidence and survival and, thus, also assesses the potential for primary and secondary prevention (as usual, in the long-term) and adequate management (in the short-term). The following questions will be addressed:

(1) which cancers occur mainly in the elderly?
(2) can they be prevented based on current knowledge of risk factors and when or on what terms?
(3) can the cancers (from question 1) be detected early enough to apply curative treatments?
(4) what are, in addition to stage and biological type, the major determinants of prognosis from a clinico-epidemiological viewpoint?

The emerging demographic situation in most European countries will be described briefly as being essential for an estimation of demand and the need for investments in supply of care, both 'caremanpower' and facilities.

Demographic characterisation

A demographic distribution of countries based on the current proportion of elderly in 2000 (high, medium, low) is shown in Fig. 1a and their growth potential in the near future (2015) (stable, marked increase, decrease) is shown in Fig. 1b; the changes to be expected in the generations born after 1960–70 (stable, minor or strong decrease) shows the discrepancy between supply and demand, in other words there is a decrease in the 'market' of manual labour, a market which is essential for adequate care provision, because health services are labour intensive. Europe is divided into Eastern, Northern, Southern and Western parts, although there is a lot variation within these geographical regions and even within the countries involved. This rough sketch is only intended to help oncologists to educate policymakers in demographics which should hopefully prompt them to provide for the needs of patients and their care providers. Investments in training may be most valuable here. No specific assumptions are made with respect to potentially marked changes in life-expectancy in the various birth cohorts, e.g. as a consequence of less smoking by males and more by females. When in third world countries the life-expectancy rises and the birth rates fall and the various cancer epidemics rage, sooner or later cancer in the elderly is likely to become a 'problem' with respect to discrepant care, demand and supply. On the Globocan 2000, CD-ROM calculations can be made for each country as a basis for deciding a variety of care prevalence scenarios [1].

Frequency

More than 25% of all new cancers in the world occurred in Europe during the 1990's, whereas its population comprises less than 10%. The reason for this is that more than a third of the elderly population of the world live in Europe. The first question on incidence can be answered with data from population-based cancer registries. There are now more than 150, covering more than 30% of Europe [2]. The most reliable ones send their data to Eurocim, a detailed database of which a new version has just appeared [3]. This Eurocim database, being

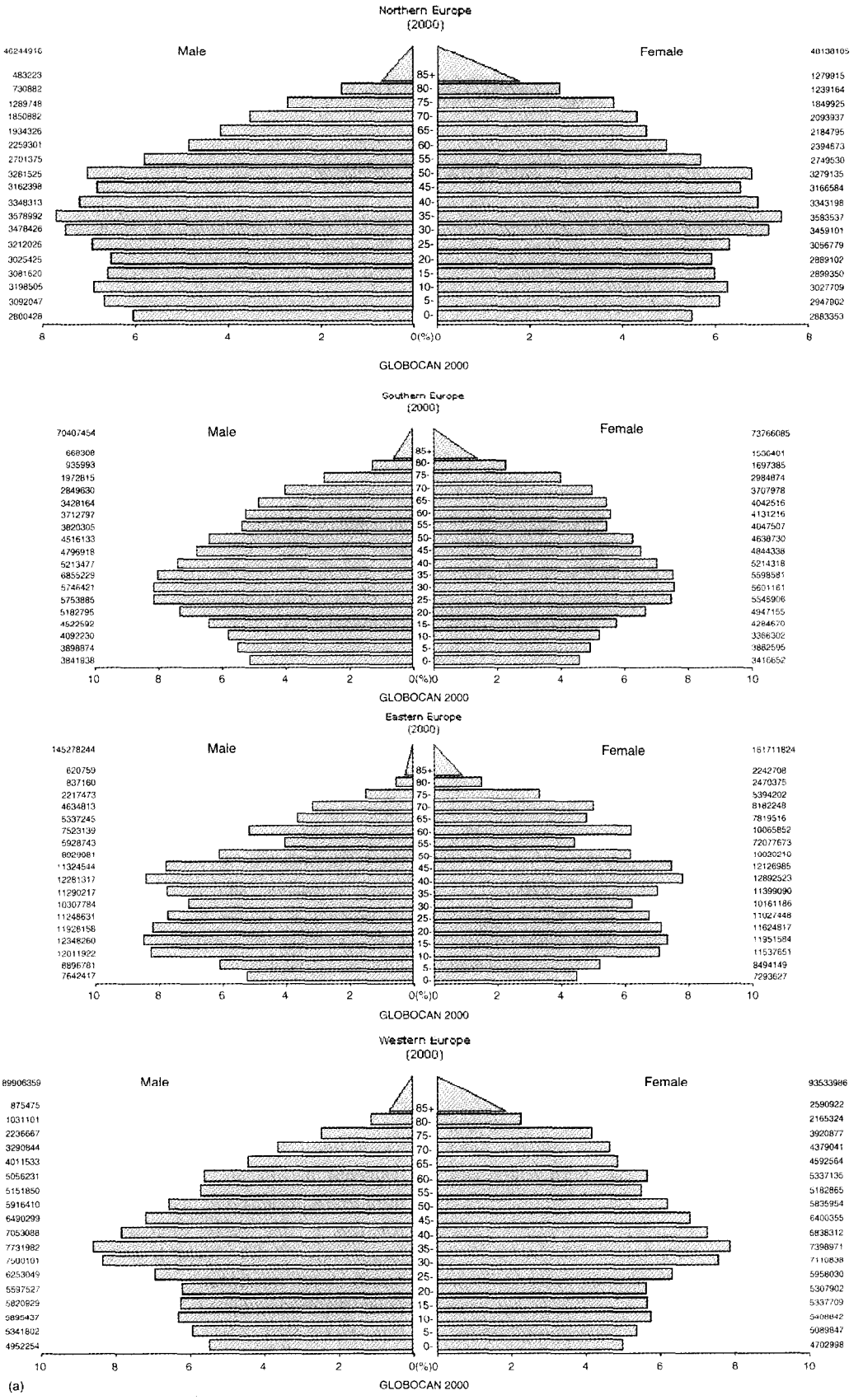

Fig. 1a. Proportion of the elderly in Europe in 2000.

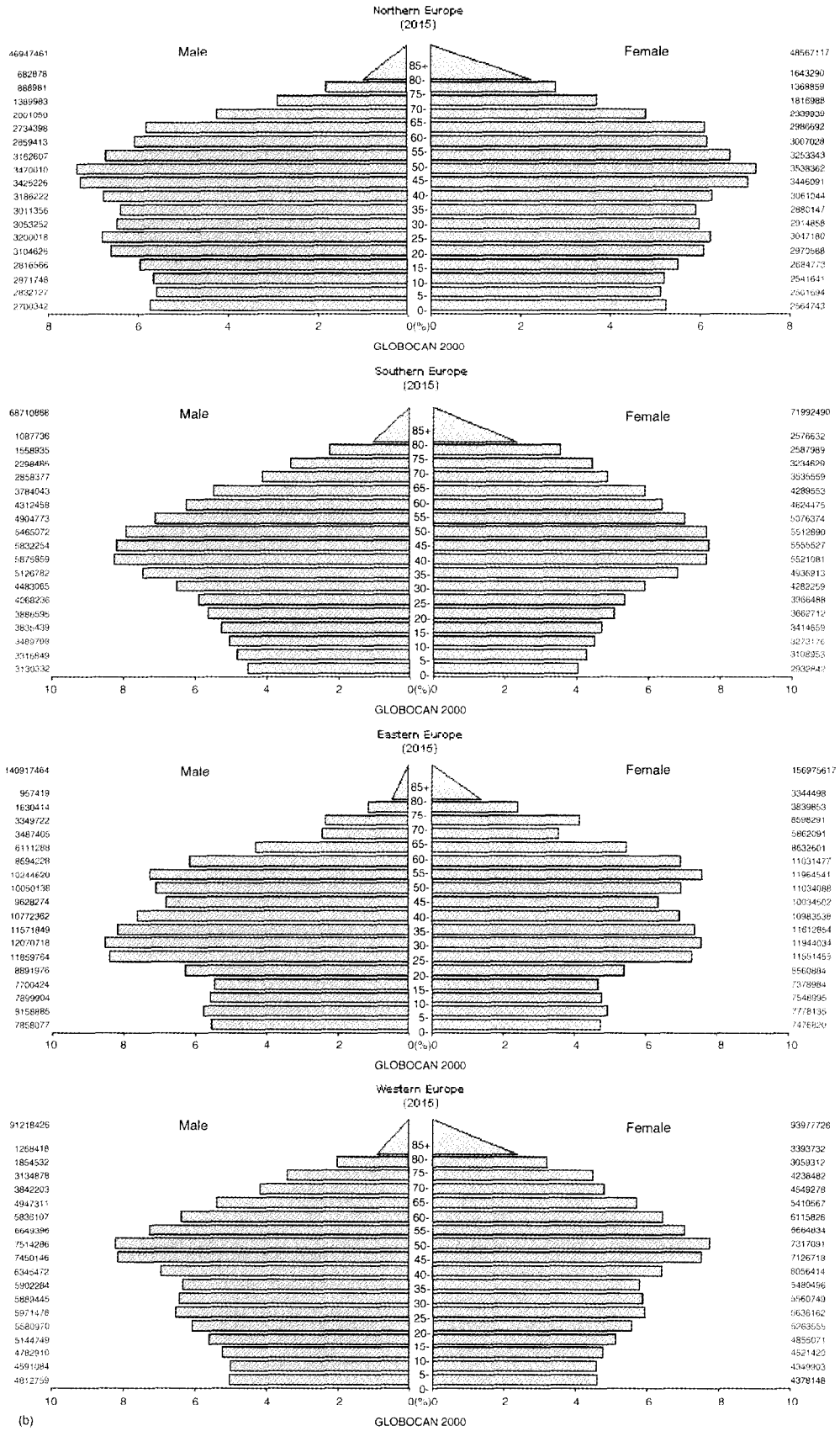

Fig. 1b. Expected proportion of elderly in Europe in 2015.

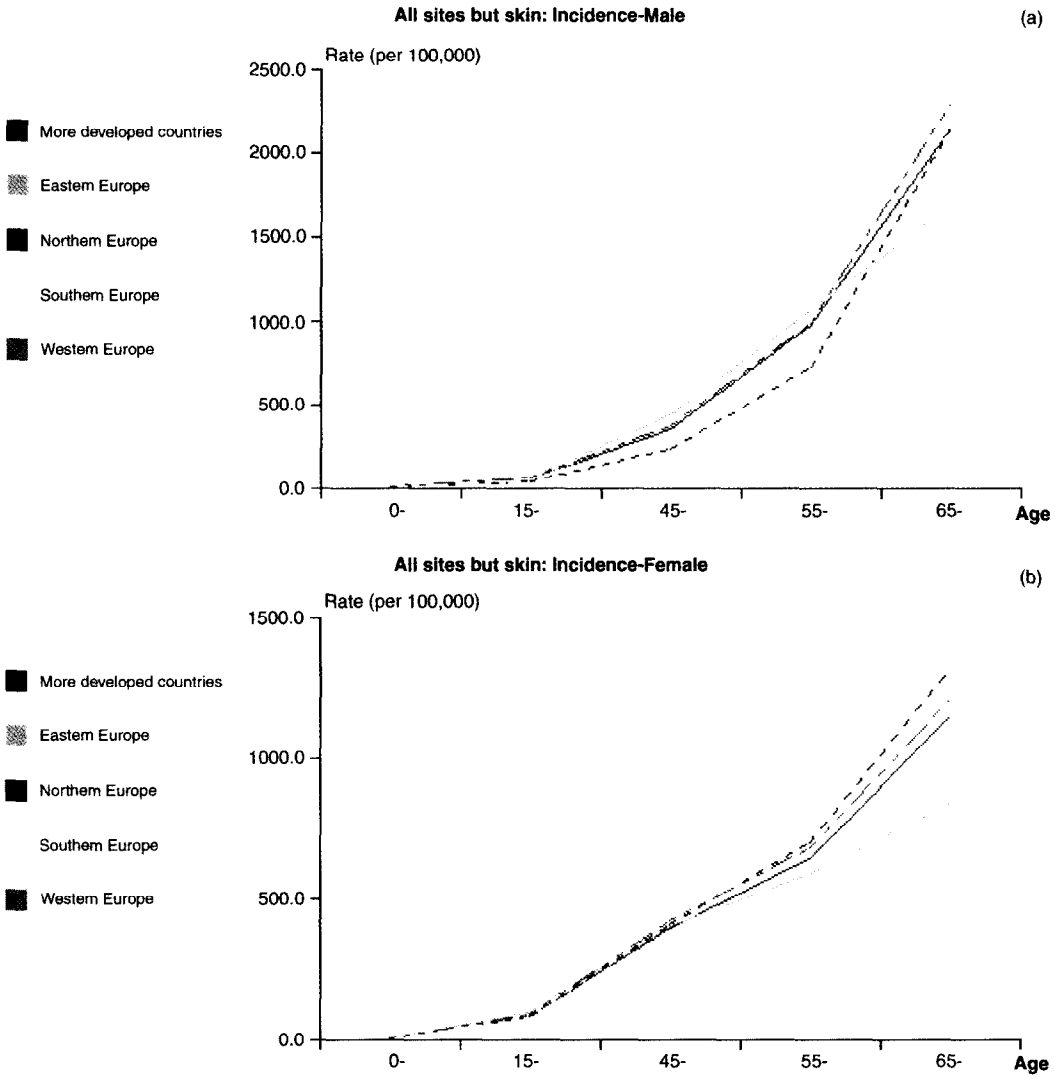

Fig. 2. Males (a) and Females (b): age-specific incidence of cancer in the various parts of Europe (source: Globocan 2000).

for contributing members only, is sustained by the European Network of Cancer Registries (ENCR) at the Unit of Descriptive Epidemiology of the International Agency for Research on Cancer (IARC) in Lyon (Fig. 2a).

It is clear that age-specific incidence rises much more steeply in males than in females, which would also be observed for the tumour-specific figures. Rates in Northern and Western Europe seem higher, but this is also a consequence of a higher average age in these populations. In most countries, the most frequent tumours in the elderly (>70 years) are either lung or prostate cancer in males which are highly prevalent with cumulative risks after the age of 70 years of between 5 and 10%. Colorectal cancer is usually the third most common cancer (CR <5%), followed by stomach and/or bladder cancers. In females, the most common cancer is of the breast (CR <5%) followed by colorectal cancer (CR <3%), and then either lung or the various gynaecological cancers.

Can primary prevention avoid the future increase in patients?

The application of primary prevention takes decades to implement and take effect. In fact, from the introduction of the exposure, we are dealing with epidemics of more than 100 years, usually related to combined changes in life habits rather than an environmental or occupational hazard, (note that the tobacco-related epidemic of lung cancer only started in the early 20th century to reach its peak in the

older generations, who were born before 1920, in the 1970s and 1980s). Most of the preventive measures (or the carcinogenic reverse) can be assumed to happen to birth cohorts; lifestyle changes in, for instance, smoking behaviour, alcohol use, sunbathing, sexual behaviour, drug use, dietary habits and physical activity are usually affected by a combination of parental and school influences, and, nowadays, increasingly by 'the media', especially television, music and film. The role of the physical environment, (e.g. opportunities to safely play outside the home and walk or bike to shops and schools), could play a larger part than we realise. As an example; the current endemic increase of obesity in the younger generations will increase the incidence of major cancers in the future, such as of the colorectum, (postmenopausal) breast, kidney, endometrium and the distal oesophagus [4]. However, our current awareness of obesity as a risk factor for cancer is probably taken as seriously as the risk of lung cancer was during the 1950's smoking epidemic, in part, because most relative risks seem to be in the order of less than 2 [5]. However, with the involvement of powerful industries, the predominance of obesity is increasing markedly among the young and middle-aged in many countries, whereas the 'counterforces' of awareness and action are still dispersed, partly because so many other chronic diseases are involved.

Although cancer patterns certainly differ in and within the various parts of Europe, which is often affected by socio-economic circumstances, a cumulatively growing demand for multidisciplinary care for elderly patients is to be expected in almost every European country in the next 10 years. This age-specific growth can be estimated to be between 20 and 40% (assuming that people do not die from other diseases like infections, vascular diseases, psychiatric problems, war or other disasters, food shortages or alcohol misuse). In fact, the reverse is more likely to happen: if less people die from those other causes mentioned above, especially cardiovascular diseases. Would they then be affected by or die from cancer? This is only true, if the type of preventive action, like stopping smoking, eating healthily, more exercise and less alcohol would have an immediate beneficial effect as for the other diseases. However, the long latency times of the initiation of cancer (10 to 30 years at least) may be a disadvantage in this respect.

A strategic view

An important point needs to be made here in relation to quality of care, which comprises both access and adequacy of care. Assuming that in most countries the demand for oncological care for the elderly keeps on rising by 1–3% annually during the next few decades, then the future provision of well trained health care personnel is absolutely essential. This, however, seems rather unlikely, because in most European countries the number of children has declined since the 1960's by 25 to 50%, accompanying the trend of smaller families and individualisation, and also caused by the greater mobility experienced by individuals. Increasingly, sick elders are not cared for within their families. Rough estimations of the need for health care personnel suggest that the proportion of those in the younger generations needed to work in the health service of the total workforce would have to rise from less than 10% to almost 20% of all school leavers. If this objective seems unattainable, then serious thoughts need to be given to new approaches such as increasing employment of the 55 to 70 years (third age) generation and of course immigration may have to become more important. It is vital that there is confidence in the health service, a prerequisite for the early detection of cancers on a large scale.

Is cancer in the elderly caused by ageing?

Fig. 2 clearly shows a marked increase in the incidence of most common tumours with age. Does this mean that the ageing process is (also) involved or is it a consequence of the same genetic alterations? Interestingly, the former hypothesis that aging is involved has been put forward by scientists from the former Soviet Union [6], despite the fact that the proportions of elderly are now traditionally low in these countries, having even declined in recent years because of deteriorating circumstances. By contrast, scientists in prosperous industrialised countries (with higher proportions of elderly) have generally upheld that the occurrence of cancer, especially the epithelial forms, in the elderly is not or is indirectly related to the ageing process [7], except for some lymphatic malignancies [8]. The reverse could even be true if deficient ageing of cells is partly responsible for an increased risk of cancer at old age [9]. Moreover, the incidence of most cancers decreases again at very old age, mostly after the age of 80 years (except prostate cancer), although underdiagnosis and underregistration may both play a role in these figures [10]. The discrepant views on the role of ageing may also be explained by research policy; if according to certain political views environmental risk factors cannot play any role, they should be ignored, whereas in

Table 1
Does ageing cause cancer or its promotion? Arguments in favour and against

In favour
Incidence rises steeply with age (and continously for some tumours)
Population-based autopsy studies show even higher cancer frequencies
Immune surveillance decreases with age
DNA-repair capacity decreases with age
Endocrine balance disturbed with increasing age
Against
Current knowledge of exogeneous causes of cancer dose response and importance of age at initiation, 80% avoidable and the epidemical course of the major cancers
Current knowledge on the genetic origin of cancer
Current knowledge on the pathogenesis: DNA-mutations, multistep process
Latency time of epithelial cancer development is more than 20–50 years
Higher frequency of similar cancers in males[a] and known association with previous exposures
Wide (more than 4-fold) differences in cancer incidence among older people
Decrease of cancer incidence after age 80 years (except prostate cancer)
Animal experiments suggest that the time of initiation is important (Peto)

[a] Except (and understandably) breast, thyroid and melanoma.

some cultures external causes must be found to be responsible and become 'sueable'.

The arguments against and in favour of age being an important cause of cancer are summarised in Table 1. The general conclusion that is often drawn is that the ageing process is most likely not related to the occurrence of epithelial cancer which can overwhelmingly be explained by external 'forces' given the genetic make-up, but for certain chronic lymphopoietic malignancies and prostate cancer a probably indirect association could exist through certain immunological and endocrine processes.

Thus, is cancer avoidable at old age, at least in the very long-term? Given the large differences in incidence over time and between populations it could be true, if the primary preventive measures mentioned above are followed.

Conclusion

Primary prevention of cancer in the elderly is possible and remains vital, but is only effective if implemented in the long-term. Besides continuing to target and reduce the smoking epidemic, an 'attack' should be made on the increasing epidemic of obesity. In both instances, collaboration is necessary with those who want to prevent other chronic conditions, especially cardiovascular disease.

Can cancers in the elderly be detected early?

As of now, most cancers in elderly people are detected later than in younger patients with a few exceptions: stomach and colorectal cancer and non-small cell lung cancer. This may be a matter of tumour biology, but also of subsite; e.g. in the stomach more cancer of the pylorus is observed at old age and cancer of the cardia at relatively young ages [11]. This also depends on proper access to specialised diagnostic services, like endoscopy, which in older generations can also be affected by educational status (awareness) and socio-economic circumstances (prosperity, current and also future prosperity), the latter also being dependent on equity through health insurance or tax-based financing systems. This matters especially at old age, when health care expenses become exponentially higher and premiums often come from taxes. Of course, distance to specialised care, financial barriers and incentives for delivery of a decent logistical service also matter. Before considering mass screening or high-risk strategies, we should realise that access to specialised care has appeared the strongest determinant for survival in the EUROCARE studies, especially for patients with solid tumours that are amenable to surgery or radiotherapy, [12,13].

With respect to mass screening, some, partly evidence-based, changes in health policy have occurred in the various countries in recent years [14,15]. They are summarised in Table 2. Unfortunately those who like to offer mass cancer screening policies seldom realise that this is only a responsible policy, when 'good' access to specialised care for every citizen is more or less guaranteed, a prerequisite for prompt and 'perfect' diagnostic and therapeutic 'aftercare'. Instead of dealing with sick patients, one now manages 'healthy', but very worried, consumers. In practice, cervical and breast cancer are the preferential tumour-sites for mass screening, prostate, colorectal, ovarian, lung and sometimes skin cancer are being considered. A tumour-specific view is given in Table 2.

The age limit for cervical cancer screening has increasingly included older women, but is still about 60 years of age in most countries, although women born between 1920 and 1930 (sexually active just after the second world war) could also benefit, if they have not already been screened before. Not only detectability, but also the possibility of alleviating the

Table 2
Overview of candidate tumour-sites for mass screening in Europe, recommended risk group(s), screening test(s), interval(s) and likely effect(s), costs and critical issues

Tumour site (% of all new cancers by gender)	High-risk group Age-range (years)	Cumulative rate (%) in age-range of high-risk group incidence mortality [b]	Proposed evidence-based mass-screening test (verifying procedures)	Interval between 2 tests	Maximum effect on incidence or mortality (RCT = randomised trial) (OB = observational)	Costs per – inhabitant [c] – life-year saved (Euros)	Issues, competing technologies, remarks (always: manpower shortages)
Cervix (3–6%)	30–60 years 20–29 (if high risk) 60+ years (if without previous screens)	<0.4% <0.2% <0.05% <0.002% <0.5% <0.4%	Pap-smear (colposcopy)	Every 5 years (3?) Prolonged in women with negative tests?	<90% incidence (OB) <70% mortality (OB) (3–5000 smears for 1 death)	3–5 [c] 10 000–20 000	Ever changing terminology Value of computerised cytology Follow-up of low grade lesions? HrHPV-screening in near future?
Breast (25–35%)	50–69 years	<5% <2%	Mammography:	Every 2 years	<30% mortality (RCT)	4–6 [c]	– Need for multidisciplinary aftercare by 'dedicated' breast teams
	70–75 years [a]	<1.5% <0.5%	– two-view,	(>2 years)	(1000 mammographies for 1 death)		
	40–49 years [a]	<1.5% <0.5%	– double reading (cytology, biopsy) Breast-(self) examination?	12–18 months every month (additive)	Up to 20% (OB, RCT) Small (rather psychological value)	5000–8000	– Digital mammography – Adjuvant systemic therapy – Familial cancer screening
Colorectal (10–15%)	50–74 years	M <5% <3%	Faecal Occult Blood Test (FOBT) (colonoscopy and polypectomy)	Every 2 years	Up to 16% (RCT) (3000 to 5000 FOBT for 1 death) (500 sigmoidoscopies)	About 5 [c]	Virtual colonoscopy
		F <4% <2%	Sigmoidoscopy (colonoscopy and polypectomy)	Once or every 5 years (discontinued after negative screen)	Up to 70% on incidence (OB); <on mortality	<5000	Distinction of high risk tissue? Chemoprevention? Role of familial screening? (Wo)manpower for endoscopy.
Prostate (10–25%)	55–74 years	<6% <3%	PSA-test Biopsy at >3–4 ng/l	Not yet known	Up to 20%? (>1000 biopsies)	Unknown >100 000	Adequate treatment of localised disease?

[a] only with adequate coverage of group 50–69 years.
[b] period of mortality 5 years later than incidence.
[c] attributed to gender.
PSA, prostate-specific antigen; Pap, Papanicolaou; HPV, human papilloma virus.

terrible suffering from advanced cancer are reasons for preventive action. Other risk profiles can be made in this respect. The so-called pill generation, women born after 1950 and especially after 1960, may also benefit from regular screening. It remains surprising that so little research activity has been spent on demonstrating the probably limited value of continued screening after two negative screens at age 40 years or so. Consensus increasingly exists on a screening interval of 5 years [16].

The age-limit for mass screening of breast cancer has recently been increased to 75 years of age in Sweden and the Netherlands, to 70 years of age in the UK, which only shifts the discussion on age-limits to even higher ages. Only observational data have supported this decision [17]. Although without equivocal evidence, the screening interval could safely become 3 years above 65 years of age or so. The official upper age-limit has become 75 years, but individualisation of choice increasingly matters in older people, both due to large variations in individual life expectancy and to personal circumstances and the perspective of the person, which can also be affected by other health problems or worries.

The efficacy of prostate cancer screening has not yet been assessed, but current screening programmes stop either at age 70 or 75 years. Given the often benevolent course of prostate cancer at older ages, the high frequency of subclinical cancer and the limited and uncertain therapeutical possibilities, it does not seem very likely that a mass screening programme (as proposed for men aged 55 to 74 years) will ever be put in place. Provision of enough urologists is needed, for the many other uropoietic conditions alone, as well as for radiotherapists who are increasingly treating patients with prostate cancer.

Mass screening for colorectal cancer by regular FOBT (faecal occult blood tests) or once sigmoidoscopy seems to be efficacious. Many problems of logistics and compliance remain, especially if endoscopy (coloscopy), is proposed as a screening modality, although the benefits could be substantial [18]. Many pilot studies and another set of locally adapted randomised trials will be necessary in the various populations before considering population-wide programmes. Access to endoscopy for every (suspected) patient may be easier to realise.

Mass screening for ovarian cancer through Ca-125 and echography is under study, but would seem to have a small effect on the death rate [19].

Plans for lung cancer screening with spiral computed tomography (CT)-scanning are currently in an early phase of consideration and pilot studies will probably be carried out in Europe [20].

With respect to non-melanoma skin cancer (both basal and squamous cell) that also increases markedly with age, it is clear that early detection is increasingly possible, again only with better awareness. Without enough dermatologists and (plastic) surgeons, mass screening is likely to have destructive effects on their practices. A rough calculation for the Netherlands shows that the demand for qualified skin advice in case of suspected pigmented lesions increases by 5 to 7% a year.

A recent report offers a framework for individualised decision-making with respect to cancer screening in elderly persons [21]. It is based on estimations of life-expectancy, risk of cancer death and screening outcomes, both positive and negative, and the information is presented as the number needed to screen to prevent one death (often more than 1000 persons); the authors estimate that screening is not useful when life-expectancy would be less than 5 years.

Conclusion

Given the rising numbers of new elderly cancer patients, the best strategy for early detection of the elderly with cancer is broad access to the specialised diagnostic teams. The better access to care, the less mass screening has to offer and the side-effects of screening can be avoided.

The contribution of epidemiology to quality of care: a study of co-morbidity

One of the major problems in treating cancer in elderly patients is the presence of co-morbidity, because it can complicate the course of the disease during and after treatment or the co-morbid condition itself can deteriorate. On the one hand, co-morbidity can obscure a diagnosis of cancer, but it can also enhance an early diagnosis, whereby screen-detected tumours may cause dilemmas for treatment, because it is often perceived that 'wait-and see' policies cannot be discussed in such circumstances.

Increasingly, knowledge on co-morbidity has become available from both clinical and population-based studies. Most of the data pertains to the often substantial prevalence of co-occurring diseases and the degree to which they affect the detection and treatment policy, rightly or wrongly. In the USA, extensive studies have been carried out [22] exhibiting a very high prevalence of a variety of chronic conditions, whereas quite a few registry-based studies in the south of the Netherlands [23] show a lower prevalence of serious conditions. However, from these

Table 3
Prevalence of co-morbidity, assessed through a population-based survey according to age and gender

Concomitant disease	Age-specific prevalence of serious concomitant diseases among newly diagnosed cancer patients in southeastern Netherlands, 1993–1999							
	Men				Women			
	Age (years)				Age (years)			
	<45 (%) (n = 1762)	45–59 (%) (n = 5196)	60–74 (%) (n = 13603)	75+ (%) (n = 7245)	<45 (%) (n = 3136)	45–59 (%) (n = 6893)	60–74 (%) (n = 9081)	75+ (%) (n = 6230)
Cancer [a]	2.0	7.0	12.0	17.0	2.9	7.1	11.3	14.4
Heart disease	0.5	6.8	17.4	20.9	0.4	1.8	8.1	15.7
Peripheral vascular disease	0.1	1.8	6.5	7.3	0.2	0.6	2.0	2.3
Hypertension	1.9	8.5	14.0	12.3	2.1	8.1	21.7	23.8
Pulmonary disease	2.2	6.9	14.9	18.4	3.0	4.3	7.1	7.4
Diabetes mellitus	0.6	3.6	7.7	9.3	1.0	2.9	10.7	15.8
Cerebrovascular	0.2	1.5	4.4	6.2	0.3	0.9	2.9	6.2
Autoimmune	0.1	0.5	0.8	0.8	0.3	0.6	1.0	1.6
Chronic infection	0.2	1.2	1.7	2.0	0.2	0.8	1.6	1.8
Central nervous system	–	0.1	0.3	1.7	–	–	0.2	2.6
Liver disease	0.9	1.0	0.6	0.5	0.4	0.6	0.6	0.4
Urinary	0.2	0.6	0.4	0.5	0.1	0.2	0.4	0.3
Digestive tract	0.9	2.9	5.1	5.6	0.8	0.9	2.0	2.3
Together [b]	9	32	55	62	12	24	47	59

[a] Also in same organ (but not metastasis of primary tumour).
[b] More conditions per patient are possible.
Source: Eindhoven Cancer Registry.

studies also it appears that the prevalence of serious co-morbidity at diagnosis is over 60% in people over 75 years of age. Furthermore, the problem occurs more frequently in males (Table 3). Moreover a marked socio-economic gradient occurs: cancer patients with a higher socio-economic status (SES) suffer less from co-existant diseases [24], which partially explains the large differences in relative survival among the elderly in the various countries of Europe [25]. Age-related differences in the medical care provided also contributes to this inequality [26].

The most important conclusion from all these studies is that quality of care (both access and concentration of certain treatments) matters, especially for the elderly who often need tailor made care, given their co-existing conditions.

Clinical research is directed at identifying frequently occurring clinical problems, mostly in the first few months (up to one year) after diagnosis. The purpose collect data to help lay a better foundation for anticipatory clinical strategies. One thing is sure: an increase in multidisciplinary care approaches needs to be developed within the framework of general hospitals which will have to take care of the largest proportions of these patients. Other interesting research of prognostic determinants helps in the recognition of weak features in frail patients, because they are so vulnerable, thereby focusing on concepts like sarcopenia (indicator of cardiovascular and insufficiency of the loco-motor tract). Also, early recognition of psychological weakness is important as this could lead to a deterioration in the general status of the older person.

Conclusions from epidemiology (and demography)

Cancer in the elderly is not only increasing, but also unlikely to go away. The most important factor affecting the provision of adequate care is the decrease in the number of people born since the 1960's in most countries. Moreover, prevention only works over a long period of time. Finally, early detection means there is good access to specialised care and therefore, this is of paramount importance.

References

1 Ferlay J, Bray F, Pisani P, Parkin DM. Globocan 2000: Cancer incidence, mortality and prevalence worldwide. IARC Scientific Publications, Lyon, 2001.

2 Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe, 1995. Eur J Cancer 2001, (in press).

3 Eurocim (version 4), Lyon, 2001.

4 Obesity and cancer. IARC Scientific Publications, Lyon, No 160, 2001.

5 Wolk A, Gridley G, Svensson M, Nyren O, McLaughlin JK, Fraumeni JF, Adami H-O. A prospective study of obesity and cancer risk (Sweden). Cancer Causes Control 2001, 12: 13–21.

6 Anisimov VN. Age-related mechanisms of susceptibility to cancer. In: Fentiman IS, Monfardini S. (Eds.), Cancer in the Elderly: Treatment and Research. Oxford University Press, 1994, pp. 1–10.

7 Peto R, Parish SE, Gray RG. There is no such thing as aging and cancer is not related to it. IARC Scientific Publications, Lyon, No 58, 1986, pp. 43–53.

8 Dix D. The role of ageing in cancer incidence: an epidemiological study. J Gerontol 1989, 44: 10–18.

9 Campisi J. The biology of replicative senescence. Eur J Cancer 1997, 33: 703–709 (special issue).

10 de Rijke JM, Schouten LJ, Hillen HF, Coebergh JWW, van den Brandt PA. Cancer in the very elderly Dutch population. Cancer 2000, 89: 1121–1133.

11 Pinheiro PS, van der Heijden LH, Coebergh JWW. Unchanged survival of gastric cancer in the southeastern Netherlands since 1982: result of differential trends in incidence according to Lauren type and subsite. Int J Cancer 1999, 84: 28–32.

12 Coebergh JWW. Summary and discussion of results. In: Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Estève J (Eds.), Survival of Cancer Patients in Europe: The Eurocare Study. IARC Scientific Publications, Lyon, No. 132, 1995, pp. 447–463.

13 Sant M, Berrino F et al. Trends in survival of cancer in Europe, 1978–1989. Eur J Cancer 2001, 37: (in press).

14 Recommendations on mass screening in Europe. Eur J Cancer 2000, 36: 1473–1478.

15 Coebergh JWW. Challenges and pitfalls of mass screening in the European Union. Eur J Cancer 2000, 36: 1469–1472.

16 Cervical cancer screening in the European Union. Linos A, Riza E, van Ballegooijen M, (Guest Eds) Eur J Cancer 2000, 36: 2175–2277 (special issue).

17 Van Dijck JA, Broeders MJ, Verbeek ALM. Breast cancer screening in older women. Is it worthwhile? Drugs Aging 1997, 10: 69–79.

18 Loeve F, Brown M, Boer R, van Ballegooijen M, van Oortmarssen G, Habbema JDF. Endoscopic colorectal screening: a cost-saving analysis. J Natl Cancer Inst 2000, 92: 557–563.

19 Jacobs IJ, Skates SJ, MacDonald N et al. Screening for ovarian cancer: a pilot randomised controlled trial. Lancet 1999, 353: 1207–1220.

20 Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS et al. Early lung cancer action project: overall design and findings from baseline screening. Lancet 1999, 354: 99–105.

21 Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. JAMA 2001, 285: 2776–2778.

22 Yancik R, Wesley MN, Ries LA, Havlik RJ, Long Sh, Edwards BK, Yates JW. Co-morbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients: a population-based study. Cancer 1998, 82: 2123–2134.

23 Coebergh JWW, Janssen-Heijnen MLG, Post PN, Razenberg PP. Serious co-morbidity among unselected cancer patients

newly diagnosed in the southeastern part of the Netherlands in 1993–1996. J Clin Epidemiol 1999, 52: 1131–1136.

24 Schrijvers CTM, Coebergh JWW, Mackenbach JP. Socio-economic variation and co-morbidity among newly diagnosed cancer patients. Cancer 1997, 80: 1482–1488.

25 Vercelli M, Capocaccia R, Quaglia A, Casella C, Puppo A, Coebergh JWW, the Eurocare Working Group. Relative survival in elderly European cancer patients: evidence for health care inequalities. Crit Rev Oncol/Hematol 2000, 35: 161–179.

26 De Rijcke JM, Schouten LJ, Schouten HC, Jager JJ, Koppejan AG, van den Brandt PA. Age-specific differences in the diagnostics and treatment of cancer aged 50 years and older in the province of Limburg, the Netherlands. Ann Oncol 1996, 7: 677–685.